METFORMIN

A 3-IN-1 MEDICAL REFERENCE

Medical Dictionary

Bibliography &

Annotated Research Guide

TO INTERNET REFERENCES

ICON Group International, Inc.

METFORMIN

A MEDICAL DICTIONARY, BIBLIOGRAPHY,
AND ANNOTATED RESEARCH GUIDE TO
INTERNET REFERENCES

JAMES N. PARKER, M.D.
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FORWARD

In March 2001, the National Institutes of Health issued the following warning: "The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading."[1] Furthermore, because of the rapid increase in Internet-based information, many hours can be wasted searching, selecting, and printing. Since only the smallest fraction of information dealing with metformin is indexed in search engines, such as **www.google.com** or others, a non-systematic approach to Internet research can be not only time consuming, but also incomplete. This book was created for medical professionals, students, and members of the general public who want to know as much as possible about metformin, using the most advanced research tools available and spending the least amount of time doing so.

In addition to offering a structured and comprehensive bibliography, the pages that follow will tell you where and how to find reliable information covering virtually all topics related to metformin, from the essentials to the most advanced areas of research. Public, academic, government, and peer-reviewed research studies are emphasized. Various abstracts are reproduced to give you some of the latest official information available to date on metformin. Abundant guidance is given on how to obtain free-of-charge primary research results via the Internet. **While this book focuses on the field of medicine, when some sources provide access to non-medical information relating to metformin, these are noted in the text.**

E-book and electronic versions of this book are fully interactive with each of the Internet sites mentioned (clicking on a hyperlink automatically opens your browser to the site indicated). If you are using the hard copy version of this book, you can access a cited Web site by typing the provided Web address directly into your Internet browser. You may find it useful to refer to synonyms or related terms when accessing these Internet databases. **NOTE:** At the time of publication, the Web addresses were functional. However, some links may fail due to URL address changes, which is a common occurrence on the Internet.

For readers unfamiliar with the Internet, detailed instructions are offered on how to access electronic resources. For readers unfamiliar with medical terminology, a comprehensive glossary is provided. For readers without access to Internet resources, a directory of medical libraries, that have or can locate references cited here, is given. We hope these resources will prove useful to the widest possible audience seeking information on metformin.

The Editors

[1] From the NIH, National Cancer Institute (NCI): **http://www.cancer.gov/cancerinfo/ten-things-to-know**.

CHAPTER 1. STUDIES ON METFORMIN

Overview

In this chapter, we will show you how to locate peer-reviewed references and studies on metformin.

The Combined Health Information Database

The Combined Health Information Database summarizes studies across numerous federal agencies. To limit your investigation to research studies and metformin, you will need to use the advanced search options. First, go to **http://chid.nih.gov/index.html**. From there, select the "Detailed Search" option (or go directly to that page with the following hyperlink: **http://chid.nih.gov/detail/detail.html**). The trick in extracting studies is found in the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Journal Article." At the top of the search form, select the number of records you would like to see (we recommend 100) and check the box to display "whole records." We recommend that you type "metformin" (or synonyms) into the "For these words:" box. Consider using the option "anywhere in record" to make your search as broad as possible. If you want to limit the search to only a particular field, such as the title of the journal, then select this option in the "Search in these fields" drop box. The following is what you can expect from this type of search:

- **Effects of Withdrawal From Metformin on the Development of Diabetes in the Diabetes Prevention Program**

  Source: Diabetes Care. 26(4): 977-980. April 2003.

  Contact: Available from American Diabetes Association. 1701 North Beauregard Street, Alexandria, VA 22311. (800) 232-3472. Website: www.diabetes.org.

  Summary: In the Diabetes Prevention Program (DPP), metformin significantly reduced the risk of diabetes in individuals with impaired glucose tolerance (IGT). This article reports on a study in which diabetes status was assessed by oral glucose tolerance tests (OGTTs) performed while participants were still taking metformin or placebo. To determine whether the observed benefit was a transient pharmacological effect or more sustained, the authors performed a repeat OGTT after a short 'washout' period during

which medications (metformin or placebo) were withheld. There were 1,274 participants who underwent the washout study and 529 who did not because they had already developed diabetes. Before the washout, the odds of diabetes in the metformin group was lower than that in the placebo group. After the washout, diabetes was somewhat more frequently diagnosed in the metformin participants. Combining diabetes conversions during the DPP and during the washout, diabetes was diagnosed significantly less frequently in the metformin than the placebo group. The primary analysis of the DPP demonstrated that metformin decreased the risk of diabetes by 31 percent. The washout study shows that 26 percent of this effect can be accounted for by a pharmacological effect of metformin that did not persist when the drug was stopped. After the washout, the incidence of diabetes was still reduced by 25 percent. 2 figures. 2 tables. 8 references.

- **Effect of Metformin in Pediatric Patients with Type 2 Diabetes: A Randomized Controlled Trial**

  Source: Diabetes Care. 25(1): 89-94. January 2002.

  Contact: Available from American Diabetes Association. 1701 North Beauregard Street, Alexandria, VA 22311. (800) 232-3472. Website: www.diabetes.org.

  Summary: Metformin is the most commonly prescribed oral antidiabetic agent in the United States for adults with type 2 diabetes. The incidence of type 2 diabetes in children has increased dramatically over the past 10 years, and yet, metformin has never been formally studied in children with type 2 diabetes. This study evaluated the safety and efficacy of metformin at doses up to 1,000 milligrams twice daily in 82 subjects aged 10 to 16 years for up to 16 weeks in a randomized double blind placebo controlled trial from September 1998 to November 1999. Metformin significantly improved glycemic control. Mean HbA1c (glycosylated hemoglobin, a measure of blood glucose levels over time) values, adjusted for baseline levels, were also significantly lower for metformin compared with placebo. Improvement in fasting plasma glucose (FPG) was seen in both sexes and in all race subgroups. Metformin did not have a negative impact on body weight or lipid profile. Adverse events were similar to those reported in adults treated with metformin. The authors conclude that metformin was shown to be safe and effective for treatment of type 2 diabetes in pediatric patients. 1 figure. 2 tables. 15 references.

- **Metformin: A Biguanide**

  Source: Diabetes Educator. 21(6): 509-514. November-December 1995.

  Contact: Available from American Association of Diabetes Educators. 100 West Monroe, 4th floor, Chicago, IL 60603. (800) 338-3633 or (312) 424-2426. Fax (312) 424-2427.

  Summary: This article brings diabetes educators up to date on the use of metformin, a biguanide, to treat type 2 diabetes. After a brief review of the history of biguanide use, the authors discuss the drug's chemistry, pharmacology, pharmacokinetics, indications, warnings and contraindications, adverse drug reactions, and dosage. An additional section describes the benefits and disadvantages of combination therapy using metformin and sulfonylurea compounds. The authors conclude that metformin is safe, provided the cautions and contraindications are followed and the patient is monitored for hepatic and renal function. 24 references.

- **Glycemic Control with Diet, Sulfonylurea, Metformin, or Insulin in Patients with Type 2 Diabetes Mellitus: Progressive Requirement for Multiple Therapies (UKPDS 49)**

  Source: JAMA. Journal of the American Medical Association. 281(21): 2005-2012. June 2, 1999.

  Summary: This article describes a study that assessed glycemic control with diet alone, insulin, sulfonylurea, or metformin in patients who have type 2 diabetes. A total of 4,075 patients newly diagnosed as having type 2 diabetes, aged 25 to 65 years, were recruited between 1977 and 1991 in the first 15 United Kingdom Prospective Diabetes Study (UKPDS) centers established. The median fasting plasma glucose (FPG) concentration was 11.5 mmol/L, and glycosylated hemoglobin (HbA1c) was 9.1 percent. After 3 months on a low fat, high carbohydrate, high fiber diet, patients were randomized to therapy with diet alone, insulin, sulfonylurea, or metformin. Patients were seen at clinic visits every 3 months with the aim of achieving an FPG level of less than 6 mmol/L with the allocated therapies. The study found that the proportion of patients who maintained target glycemic levels declined markedly over 9 years of followup. After 9 years of monotherapy with diet, insulin, or sulfonylurea, 8 percent, 42 percent, and 24 percent, respectively, achieved FPG levels of less than 7.8 mmol/L, and 9 percent, 28 percent, and 24 percent achieved HbA1c levels below 7 percent. In obese patients randomized to metformin, 18 percent attained FPG levels of less than 7.8 mmol/L, and 13 percent attained HbA1c levels below 7 percent. Patients less likely to achieve target levels were younger, more obese, or more hyperglycemic than others. The article concludes that each therapeutic agent, as monotherapy, increased two to threefold the proportion of patients who attained HbA1c below 7 percent compared with diet alone. However, the progressive deterioration of diabetes control was such that after 3 years, some 50 percent of patients could attain the goal with monotherapy, but by 9 years this declined to approximately 25 percent. In the long term, most patients need multiple therapies to attain target glycemic levels. 3 figures. 3 tables. 30 references. (AA-M).

- **Metformin: A New Treatment Option for Non-Insulin-Dependent Diabetes Mellitus**

  Source: Journal of Family Practice. 42(6): 612-618. June 1996.

  Contact: Available from Educational Services Division, American Journal of Nursing Company. 555 West 57th Street, New York, NY 10019-2961. (800) 627-0484 or (303) 604-1464.

  Summary: This article describes metformin, a biguanide that can be used alone or in conjunction with sulfonylureas or insulin in the treatment of noninsulin-dependent diabetes mellitus (NIDDM). Biguanides reduce hyperglycemia by increasing insulin sensitivity, decreasing glucose absorption, and inhibiting hepatic gluconeogenesis. Advantages of metformin include achieving glycemic control without exacerbating weight gain or hyperinsulinemia and beneficially affecting serum cholesterol concentrations. Risk factors for lactic acidosis associated with metformin including renal serum creatinine levels greater than 1.5 mg per dL and cardiovascular, pulmonary, or hepatic disease. The authors note that metformin should be temporarily discontinued prior to surgery and before administration of radiologic intravenous contrast, and in patients with sepsis, severe gastrointestinal disease, trauma, and acute cardiovascular events. 3 tables. 52 references. (AA-M).

- **Glucophage: How It Works**

  Source: Diabetes Self-Management. 16(4): 41, 44-47. July-August 1999.

Contact: Available from R.A. Rapaport Publishing, Inc. 150 West 22nd Street, New York, NY 10011. (800) 234-0923.

Summary: This article describes the features of type 2 diabetes and provides an overview of the drug metformin. Metformin, the first drug in a class called biguanides to be sold in the United States since 1977, became available for the treatment of type 2 diabetes in 1995. Unlike older diabetes drugs such as sulfonylureas and insulin, metformin does not increase the amount of insulin circulating in the blood. Instead it lowers blood glucose by enabling the body to better use its own insulin, that is, it makes muscle and fat cells more sensitive to insulin and better able to take in glucose following a meal. Metformin works mainly by preventing the liver from overproducing glucose and reducing the amount of fat and cholesterol produced by the liver. Numerous studies have shown that maintaining blood glucose levels as close to normal as possible reduces the risk of microvascular complications associated with diabetes, including the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study (UKPDS). In the UKPDS, metformin was shown to lower the risk of heart attacks and strokes when given as initial therapy to overweight people who had type 2 diabetes. Another study showed that participants taking metformin had reductions in fasting blood sugar and glycosylated hemoglobin concentrations. In addition, metformin has beneficial effects on blood lipids and body weight. Studies have shown that it lowers blood levels of triglycerides and cholesterol. In the UKPDS, participants treated with metformin gained only slightly more than 2 pounds compared with 11 pounds gained by people treated with sulfonylureas and over 15 pounds gained by people treated with insulin. The most common side effects of metformin are nausea and diarrhea, and the most serious side effect associated with metformin is lactic acidosis. The drug may be used in combination with drugs that increase insulin release and with insulin.

- **Glucophage (Metformin Hydrochloride)**

  Source: Gastroenterology Nursing. 19(3): 113-116. May-June 1996.

  Contact: Available from Williams and Wilkins. 351 West Camden Street, Baltimore, MD 21201-2436. (800) 638-6423 or (410) 528-8555.

  Summary: This article familiarizes nurses with the use of Glucophage (metformin hydrochloride), an antihyperglycemic agent that improves glucose tolerance in patients with noninsulin-dependent diabetes. Topics include a description of the drug, indications and recommended uses, contraindications, precautions, adverse reactions, dosage and administration, and nursing interventions. The article concludes with a series of questions commonly asked by patients, with recommended answers. The author emphasizes that the patient on Glucophage and his or her family require intense education regarding the use of alcohol, dehydration, and the role of lactic acidosis from fever, infection, or surgery.

- **Metformin: Good News for Type II's**

  Source: Diabetes Self-Management. 12(2): 52, 54. March-April 1995.

  Contact: Available from R.A. Rapaport Publishing, Inc. 150 West 22nd Street, New York, NY 10011. (800) 234-0923.

  Summary: This article familiarizes readers with a recently approved drug called metformin that effectively controls blood glucose levels in people with noninsulin-dependent diabetes (NIDDM) without the side effects of the diabetes drugs presently

used. The author describes metformin and how it works; sulfonylurea compounds and how they work; insulin therapy; the benefits of metformin therapy; and patient selection for metformin. The author stresses that, whether metformin is used alone or with sulfonylureas, it can keep the blood glucose levels steady while lowering the levels of circulating insulin and triglycerides, thereby reducing the patient's risk of heart disease.

- **Metformin Improves Glucose, Lipid Metabolism,and Reduces Blood Pressure in Hypertensive, Obese Women**

  Source: Diabetes Care. 16(10): 1387-1390. October 1993.

  Summary: This article presents a short report on research conducted to determine the effects of metformin on blood pressure, left ventricular mass, and some metabolic and endocrine parameters in nondiabetic, obese, hypertensive women (n=12). The women received 850 mg metformin 2 times/day for 12 weeks and placebo for another 12 weeks, according to a double-blind, cross-over, randomized design. All patients were hospitalized 4 times: before randomization and after each treatment (metformin or placebo), to conduct metabolic and cardiovascular investigations (oral glucose tolerance test, euglycemic clamp associated with indirect calorimetry, and echocardiography). Fasting glucose, glycosylated hemoglobin, fasting and glucose-stimulated insulin, blood pressure and left ventricular mass, cholesterol, triglycerides, and fibrinogen decreased significantly after metformin treatment, whereas high-density lipoprotein cholesterol increased. 2 figures. 1 table. 20 references. (AA-M).

- **Use of Metformin to Prevent Complications**

  Source: Practical Diabetology. 18(3): 6-13. September 1999.

  Contact: Available from R.A. Rapaport Publishing, Inc. 150 West 22nd Street, New York, NY 10011. (800) 234-0923.

  Summary: This article provides guidelines for the use of metformin in patients who have type 2 diabetes. This form of diabetes is characterized by insulin resistance and lack of insulin secretion. People who have insulin resistance have high blood sugar levels and are likely to have other abnormalities that are referred to as components of the insulin resistance syndrome. Each component of the syndrome is a risk factor for macrovascular disease. Both the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that maintaining blood sugar levels as close to normal as possible reduces the microvascular complications associated with diabetes in people who have type 1 and type 2 diabetes. The UKPDS also confirmed the benefits of metformin in reducing macrovascular complications in people who have type 2 diabetes. The largest study designed to test the ability of metformin to lower glucose found that there was a reduction in fasting blood glucose and glycosylated hemoglobin concentrations in metformin treated patients compared with those receiving placebo. Metformin has also been found to lower triglycerides and cholesterol. Both the glucose lowering and lipid lowering effect of metformin are dose dependent. The most common adverse effects of metformin therapy are gastrointestinal effects. Lactic acidosis is the most serious adverse effect associated with the drug. Metformin may be combined with sulfonylureas, repaglinide, rosiglitazone, or insulin. 5 figures. 2 tables. 11 references.

- **Effect of Orlistat in Overweight and Obese Patients with Type 2 Diabetes Treated with Metformin**

  Source: Diabetes Care. 25(7): 1123-1128. July 2002.

Contact: Available from American Diabetes Association. 1701 North Beauregard Street, Alexandria, VA 22311. (800) 232-3472. Website: www.diabetes.org.

Summary: This article reports on a study of the effect of orlistat, a gastrointestinal lipase inhibitor, on body weight, glycemic control, and cardiovascular risk factors in metformin-treated patients with type 2 diabetes. The 1 year, multicenter, randomized, double blind, placebo controlled trial of 120 milligrams orlistat (n = 249) or placebo (n = 254) combined with a reduced calorie diet was conducted in overweight and obese patients with suboptimal control of type 2 diabetes. After 1 year of treatment, mean weight loss was greater in the orlistat than in the placebo group (minus 4.6 percent of baseline weight versus minus 1.7 percent of baseline weight, respectively). Orlistat treatment caused a greater improvement in glycemic control than placebo, as evidenced by a greater reduction in serum HbA1c (glycosylated hemoglobin, a measure of blood glucose over time), adjusted for changes in metformin and sulfonylurea therapy. Compared with the placebo group, patients treated with orlistat also had greater decreases in total cholesterol, LDL cholesterol, and systolic blood pressure. Although more subjects treated with orlistat experienced gastrointestinal side effects than placebo, more subjects in the placebo group withdrew prematurely from the study than in the orlistat group (44 percent versus 35 percent). The authors conclude that orlistat is a useful adjunctive treatment for producing weight loss and improving glycemic control, serum lipid levels, and blood pressure in obese patients with type 2 diabetes who are being treated with metformin. 1 figure. 2 tables. 31 references.

- **Metformin as an Adjunct Therapy in Adolescents with Type 1 Diabetes and Insulin Resistance**

  Source: Diabetes Care. 26(1): 138-143. January 2003.

  Contact: Available from American Diabetes Association. 1701 North Beauregard Street, Alexandria, VA 22311. (800) 232-3472. Website: www.diabetes.org.

  Summary: This article reports on a study that evaluated whether, in adolescents with type 1 diabetes, the addition of metformin to insulin and standard diabetes management results in higher insulin sensitivity and lower HbA1c (glycosylated hemoglobin, a measure of blood glucose levels over time), fasting glucose, insulin dosage, and body mass index (BMI). This randomized, placebo-controlled 3 month trial of metformin therapy included 27 adolescents with type 1 diabetes, high insulin dosage, and HbA1c greater than 8 percent. Results showed that metformin treatment lowered HbA1c and decreased insulin dosage with no weight gain in teens with type 1 diabetes in poor metabolic control. Changes in insulin sensitivity were not documented in this study. 1 figure. 2 tables. 32 references.

- **Acarbose Improves Glycemic Control in Overweight Type 2 Diabetic Patients Insufficiently Treated with Metformin**

  Source: Diabetes Care. 26(2): 269-273. February 2003.

  Contact: Available from American Diabetes Association. 1701 North Beauregard Street, Alexandria, VA 22311. (800) 232-3472. Website: www.diabetes.org.

  Summary: This article reports on a study undertaken to investigate the efficacy and safety of acarbose as add-on therapy in overweight patients with type 2 diabetes inadequately controlled by metformin. After a 4 week placebo run-in period, subjects were randomized to either acarbose or placebo. The primary efficacy variable was the change in HbA1c (glycosylated hemoglobin, a measure of blood glucose over time) from

baseline to the end of the 24 week treatment period. The intention to treat analysis from baseline to week 24 (81 patients for HbA1c and 82 for fasting blood glucose) showed statistically significant differences between acarbose and placebo treatment in HbA1c and fasting blood glucose. In all, 18 patients (47 percent) in the acarbose group were classified as responders with a greater than 5 percent reduction in HbA1c (relative to baseline) at the end point compared to 6 (14 percent) in the placebo group. The safety profiles were similar for both treatment groups except for the higher incidence of gastrointestinal side effects during acarbose therapy. The authors conclude that the addition of acarbose to metformin monotherapy provides an efficacious and safe alternative for glycemic improvement in overweight type 2 patients inadequately controlled by metformin alone. 1 figure. 2 tables. 27 references.

- **Metformin: A 'New' Drug for Type II Diabetes**

  Source: Practical Diabetology. 14(2): 8-12. June 1995.

  Contact: Available from R.A. Rapaport Publishing, Inc. 150 West 22nd Street, New York, NY 10011. (800) 234-0923.

  Summary: This article reviews the basis of metformin pharmacology and its use for noninsulin-dependent diabetes mellitus (NIDDM). Topic include the introduction and approval of metformin in the United States, its clinical pharmacology, mechanism of action, the effect of metformin on insulin and counterregulatory hormones, the effects on hepatic glucose production and on glucose utilization, the effects on the stomach and intestine and on lipid metabolism, the clinical use of metformin, concerns about lactic acidosis, and drug monitoring particularly for renal toxicity. The author concludes that, used with appropriate caution, metformin is an important addition to the drugs available to treat diabetes. One sidebar summarizes the Glucophage package insert information for metformin. 4 references.

- **Coming to America: Used For Three Decades Around the World, Metformin in Finally Nearing Approval in the United States**

  Source: Diabetes Forecast. 47(8): 20, 22. August 1994.

  Contact: Available from American Diabetes Association. 1701 North Beauregard Street, Alexandria, VA 22311. (800) 232-3472. Website: www.diabetes.org.

  Summary: This brief article familiarizes readers with a long-awaited drug for noninsulin-dependent diabetes mellitus (NIDDM), metformin. Metformin, with the trade name Glucophage, is expected to be available in the United States within a year. The author describes how metformin lowers blood glucose by slowing the liver's release of stored glucose and by hindering the absorption of glucose from food being digested in the small intestine; it may also lower insulin resistance. Other topics covered include patient selection for the drug; side effects of metformin, including the potential risk of lactic acidosis; and expected availability of the drug.

- **'Can I Use Metformin?'**

  Source: Diabetes Forecast. 49(11): 28, 30-31. November 1996.

  Contact: Available from American Diabetes Association. 1701 North Beauregard Street, Alexandria, VA 22311. (800) 232-3472. Website: www.diabetes.org.

  Summary: This patient education article explores common questions that readers may have about metformin (Glucophage) a drug recently made available in the United States

to treat diabetes and other blood glucose problems. Topics include how metformin works in blocking the production of glucose by the liver and possibly in improving the body's response to insulin; metformin as one member of the triad of exercise, nutrition, and drug therapy in controlling diabetes; switching from glyburide to metformin; the use of metformin as an adjunct to insulin in people with insulin-dependent diabetes mellitus (IDDM); safety concerns about metformin and the development of lactic acidosis; and the potential side effects of metformin, including abdominal pain, bloating, diarrhea, nausea, and vomiting. The article is written in question and answer format.

- **Metformin: Effects on Cardiovascular Risk Factors in Patients with Non-Insulin-Dependent Diabetes Mellitus**

  Source: Journal of Diabetes and Its Complications. 12(2): 110-119. March-April 1998.

  Contact: Available from Elsevier Science Inc. 655 Avenue of the Americas, New York, NY 10010.

  Summary: This review article addresses the effects of metformin, a biguanide, on cardiovascular risk factors in people with type 2 diabetes. The author points out that cardiovascular disease is the primary cause of death in people with type 2 diabetes. Factors such as obesity, dyslipidemia, atherosclerotic vascular disease, and hypertension, all of which contribute to morbidity and mortality, frequently coexist with type 2 diabetes. Even when hyperglycemia is adequately controlled, risk factors for coronary heart disease may remain unchanged. Treatment with metformin controls hyperglycemia in type 2 diabetes and may also have positive effects on cardiovascular risk factors. When used alone or in combination with sulfonylureas, metformin tends to stabilize or decrease weight, maintains or reduces insulin levels, has beneficial effects on plasma lipid profiles, and may also have beneficial effects on blood pressure and the fibrinolytic system. 2 figures. 3 tables. 66 references. (AA-M).

- **Metformin: A Review of Its Metabolic Effects**

  Source: Diabetes Reviews. 6(2): 89-131. 1998.

  Contact: Available from American Diabetes Association. 1701 North Beauregard Street, Alexandria, VA 22311. (800) 232-3472. Website: www.diabetes.org.

  Summary: This review article, which focuses on recently published studies, presents the most relevant information on the pharmacology, mechanism of action, and clinical efficacy of the biguanide known as metformin. Metformin has been used worldwide to treat type 2 diabetes for the past 40 years. It improves glycemic control by enhancing insulin sensitivity in liver and muscle. Metformin does not stimulate insulin secretion and therefore is not associated with hypoglycemia. Improved metabolic control with metformin does not induce weight gain and may even cause weight loss. Metformin also has a beneficial effect on several cardiovascular risk factors, including dyslipidemia, elevated plasminogen activator inhibitor 1 levels, other fibrinolytic abnormalities, hyperinsulinemia, and insulin resistance. Although metformin reduces insulin resistance, the cellular mechanism of action is incompletely understood. Metformin enhances muscle and adipocyte insulin receptor number or affinity, increases insulin receptor tyrosine kinase activity, stimulates glucose transport and glycogen synthesis, and reduces both hepatic gluconeogenesis and glycogenolysis. In addition, metformin has been reported to decrease lipid oxidation and plasma free fatty acid levels, thus leading to an inhibition of an overactive Randle cycle. In patients with type 2 diabetes, metformin monotherapy decreases the fasting plasma glucose concentration by approximately 60 to 70 milligrams per deciliter and glycosylated hemoglobin by 1.5 to

2.0 percent. The biguanide is completely additive to sulfonylureas and vice versa, as well as to acarbose and probably troglitazone. In people who take insulin for type 2 diabetes, the addition of metformin improves insulin sensitivity and glycemic control and allows a reduction in the daily insulin dose. Side effects of metformin are primarily confined to the gastrointestinal tract. Lactic acidosis is rare, with most reported cases occurring in patients with contraindications. The ability of metformin to improve insulin sensitivity and the cardiovascular risk profile of people who have type 2 diabetes has enhanced its clinical use as first-line therapy. In the future, its indications may expand to insulin resistant patients at a high risk of developing type 2 diabetes or patients with other components of the insulin resistance syndrome. 17 figures. 13 tables. 461 references. (AA-M).

- **Contraindications to Metformin Therapy in Patients With NIDDM**

  Source: Diabetes Care. 20(6): 925-928. June 1997.

  Summary: This study addresses the contraindications to the biguanide, metformin (dimethybiguanide) therapy in patients with noninsulin-dependent diabetes (NIDDM, or Type II). In 1995, metformin was approved by the Food and Drug Administration (FDA) for use in patients with NIDDM as an adjunct to diet or in combination with sulfonylureas. Although recent studies have confirmed the safety of metformin, the importance of observing contraindications to metformin has recently been reemphasized. Treatment with metformin is occasionally associated with the development of severe lactic acidosis, but this is usually observed just in patients with major contraindications to the drug. The authors attempt to determine the prevalence of conditions currently regarded as either contraindications or cautions to the use of metformin in patients with NIDDM. More than half of the patients in their survey of metformin-treated patients attending a United Kingdom university hospital diabetes clinic had at least one condition currently regarded as a caution or contraindication to metformin therapy. Concomitant chronic disorders associated with a potentially increased risk of hyperlactatemia were renal impairment, cardiac failure, and chronic liver disease. Other potentially relevant disorders include ischemic heart disease, clinical proteinuria, peripheral vascular disease, and pulmonary disease. The authors conclude that regular surveillance is necessary to detect the development of complications such as renal impairment. In cases where major intercurrent illnesses independently disturb lactate metabolism in patients with NIDDM, metformin should be withdrawn promptly. 2 tables. 24 references. (AA-M).

- **Efficacy and Metabolic Effects of Metformin and Troglitazone in Type II Diabetes Mellitus**

  Source: New England Journal of Medicine. 338(13): 867-872. March 26, 1998.

  Summary: This study examines the effectiveness and metabolic effects of metformin and troglitazone in type 2 diabetes. The authors note that combination therapy is logical for people with type 2 diabetes, because they often have poor responses to single-drug therapy. Twenty-nine participants were randomly assigned to receive either metformin or troglitazone for three months, and then they were given both drugs for another three months. During metformin therapy, fasting and postprandial plasma glucose concentrations decreased by 20 percent and 25 percent, respectively. The corresponding decreases during troglitazone therapy were also 20 percent and 25 percent. While it was unchanged by troglitazone therapy, endogenous glucose production decreased by a mean of 19 percent during metformin therapy. The mean rate of glucose disposal increased by 54 percent during troglitazone therapy and 13 percent during metformin

therapy. In combination, metformin and troglitazone further lowered fasting and postprandial plasma glucose concentrations by 18 percent and 21 percent, respectively. The mean glycosylated hemoglobin value decreased 1.2 percentage points. The authors conclude that metformin and troglitazone have equal and additive beneficial effects on glycemic control in people with type 2 diabetes. Troglitazone acts primarily by increasing the rate of peripheral glucose disposal, and metformin acts primarily by decreasing endogenous glucose production. 3 figures. 1 table. 29 references. (AA-M).

- **Differential Effects of Metformin and Troglitazone on Cardiovascular Risk Factors in Patients with Type 2 Diabetes**

  Source: Diabetes Care. 25(3): 542-549. March 2002.

  Contact: Available from American Diabetes Association. 1701 North Beauregard Street, Alexandria, VA 22311. (800) 232-3472. Website: www.diabetes.org.

  Summary: Traditional cardiovascular risk factors (CVRF) only partly explain the excessive risk of cardiovascular disease in patients with type 2 diabetes. There is now an increasing appreciation for many novel CVRF that occur largely as a result of insulin resistance and hyperinsulinemia. This article reports on a study that investigated whether diabetes medications that vary in their mechanism of action and ability to reduce insulin resistance may differ in their effects on both traditional and novel CVRF. The authors compared the addition of metformin or troglitazone therapy on CVRF in 22 subjects with type 2 diabetes who remained in poor glycemic control while taking glyburide 10 milligrams twice daily. After 4 months of treatment, both metformin and troglitazone led to similar decreases in fasting plasma glucose and HbA1c (glycosylated hemoglobin, a measure of blood glucose levels over time). The reduction in insulin resistance was nearly twofold greater with troglitazone than metformin. The authors conclude that for patients with type 2 diabetes in whom maximal sulfonylurea therapy failed, the addition of the insulin sensitizer troglitazone seemed to have greater benefits on several traditional and novel CVRF than metformin therapy. These data suggest that medications that more effectively address this underlying metabolic defect may be more beneficial in reducing cardiovascular risk in type 2 diabetes. 1 figure. 4 tables. 56 references.

- **Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin**

  Source: New England Journal of Medicine. 346(6): 393-403. February 07, 2002.

  Summary: Type 2 diabetes affects approximately 8 percent of adults in the United States. Some risk factors (elevated blood glucose levels in the fasting state and after an oral glucose load, overweight, and sedentary lifestyle) are potentially reversible. This article reports on a study undertaken to determine if modifying these factors with a lifestyle intervention program or with the drug metformin would prevent or delay the development of diabetes. The authors randomly assigned 3,234 nondiabetic persons with elevated fasting and post-load blood glucose concentrations to placebo, metformin (850 milligrams twice daily) or a lifestyle modification program with the goals of at least a 7 percent weight loss and at least 150 minutes of physical activity per week. The mean age of the participants was 51 years, and the mean body mass index 9BMI) was 34; 68 percent were women, and 45 percent were members of minority groups. The average follow up was 2.8 years. The incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person years in the placebo, metformin, and lifestyle groups, respectively. The lifestyle intervention reduced the incidence by 58 percent and metformin reduced the incidence

by 31 percent, as compared with placebo. The lifestyle intervention was significantly more effective than metformin. 4 figures. 3 tables. 27 references.

Federally Funded Research on Metformin

The U.S. Government supports a variety of research studies relating to metformin. These studies are tracked by the Office of Extramural Research at the National Institutes of Health.[2] CRISP (Computerized Retrieval of Information on Scientific Projects) is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other institutions.

Search the CRISP Web site at **http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen**. You will have the option to perform targeted searches by various criteria, including geography, date, and topics related to metformin.

For most of the studies, the agencies reporting into CRISP provide summaries or abstracts. As opposed to clinical trial research using patients, many federally funded studies use animals or simulated models to explore metformin. The following is typical of the type of information found when searching the CRISP database for metformin:

- **Project Title: ANTIHYPERTENSIVE MECHANISMS OF METFORMIN**

  Principal Investigator & Institution: Muntzel, Martin S.; Herbert H. Lehman College Bedford Park Blvd W New York, Ny 10468

  Timing: Fiscal Year 2001

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ARTERIAL BAROREFLEX CONTROL OF BLOOD PRESSURE (EXERCISE)**

  Principal Investigator & Institution: Raven, Peter B.; Professor and Chairman; Integrative Physiology; University of North Texas Hlth Sci Ctr Fort Worth, Tx 761072699

  Timing: Fiscal Year 2003; Project Start 01-JUN-1996; Project End 30-JUN-2007

  Summary: (provided by applicant): A number of investigations have demonstrated that arterial baroreflex (CBR) control of blood pressure has a primary role in providing the necessary regulation of the sympathetic neural outflow to active and inactive tissue beds associated with dynamic exercise. In addition, we have documented a reduced vasoconstrictive response to hypotension of the highly trained endurance athlete despite an augmented CBR mediated increase in MSNA. A growing body of evidence suggests that the regulatory role of sympathetic neural outflow to the vasculature is modulated by metabolic by-products released within the active tissue and involve mechanisms of functional sympatholysis. A suggested mechanism of functional sympatholysis is that contraction induced metabolites within the active muscle open ATP-sensitive potassium (KATP) channels and thereby partially inhibit sympathetic vasoconstriction. However, it has recently been demonstrated that the CBR mediated vasoconstriction within the

[2] Healthcare projects are funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Healthcare Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH).

active muscle provides the greatest reflex vasoconstrictor response to hypotension during exercise. Therefore, we hypothesize that the CBR has a fundamental role in the control of MSNA and skeletal muscle vasculature at rest and during exercise. Furthermore, we contend that the CBR regulation of vasomotor function in exercising muscle is altered by local metabolic by-products and their interaction with other vasoactive substances and the KATP channels of the vascular smooth muscle within the active tissue. In addition, these mechanisms of CBR control of the vasculature are modulated by endurance exercise training. To address these hypotheses: Comparisons of carotid baroreflex function curves of blood pressure (BP), MSNA and leg vascular conductance (LVC) will be made between rest, the non-exercising leg (NEL) and the exercising leg (EL) using the classic one-legged exercise protocol performed by humans. Carotid baroreflex function will be assessed using our well established modeling technique. Comparisons of CBR function curves of BP, MSNA and LVC will be made at rest, in the NEL and the EL (except MSNA) between average fit, high fit endurance trained athletes and NIDDM patients treated with glibenclamide and NIDDM patients treated with **Metformin.** We anticipate that the findings obtained from this project will provide a comprehensive understanding of the fundamental mechanisms involved in the regulation of arterial blood pressure by the arterial baroreflex and its influence on the regulation of vasomotion in active muscle tissue and inactive muscular tissue in matching blood flow to oxygen demand during exercise in humans. These findings will have implications for the care of patients suffering from non-insulin dependent diabetes mellitus (NIDDM), hypertension and cardiac failure.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: BRL 49653C--26 WK STUDY COMBINED WI/METFORMIN IN NIDDM**

  Principal Investigator & Institution: Wittlin, Steven; University of Rochester Orpa - Rc Box 270140 Rochester, Ny 14627

  Timing: Fiscal Year 2001

  Summary: The purpose of this study is to find out whether BRL 49653C when combined with another antidiabetic drug **metformin,** is effective in treating patients who have non-insulin dependent diabetes mellitus.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CARBOHYDRATE AND LIPID METABOLIC PATHWAYS**

  Principal Investigator & Institution: Landau, Bernard R.; Professor of Medicine and Biochemistry; Medicine; Case Western Reserve University 10900 Euclid Ave Cleveland, Oh 44106

  Timing: Fiscal Year 2001; Project Start 01-MAY-1978; Project End 31-MAR-2002

  Summary: Our long-term objective is to develop and apply novel methods that will significantly advance our understanding of carbohydrate and lipid metabolism in physiological and pathological states, in particular diabetes. These methods have in common the safe 2H- enrichment of body water with 2H20. We plan to achieve the following seven interrelated specific aims. 1. To quantitate glycogen hydrolysis, cycling, and turnover as a function of liver glycogen content. 2. To measure the rate of de novo glycerol formation via labeling from 2H20, and to define: (i)the role of liver and kidney in glycerol production, fatty acid reesterification, and lipolysis quantitation., and (ii) the source of carbon of glycerol-3-P used by adipose tissue to reesterify fatty acids. 3. To determine the pathway(s) by which 2H20 labels H on C1 of glucose, and to define how

this labeling affects calculations of gluconeogenesis and glycogenolysis. 4. To develop a method for quantitating glyconeogenesis, based on 2H-enrichment of body water. 5. To evaluate to what extent the transaldolase reactions affect quantitations of gluconeogenesis and glycogenolysis 6. To apply these techniques to measurements of gluconeogenesis (i) in subjects who are at high risk for NIDDM. (ii) in NIDDM patients, and (iii) in the NIDDM patients then treated with **metformin.** 7. To apply these techniques to measurements of gluconeogenesis in obese patients. The subjects will ingest 2H2O (to measure the contribution of gluconeogenesis to glucose production from the C5/C2 2H-labeling ratio in glucose), and will be infused with (6,6-2H2) glucose (to measure glucose turnover). The 2H-enrichment at the glucose carbons will be amplified six-fold by incorporating them into hexamethylenetetramine for assay. The contribution of gluconeogenesis will be related to hepatic glycogen content measured by 13C-NMR spectroscopy. Our studies will define the role of gluconeogenesis (i) in diabetic hyperglycemia, (ii) as a possible etiologic factor in the onset of NIDDM, and (iii) in the mechanism of metformin's action. They will help establish whether the propensity of upper body obese subjects to insulin resistance, NlDDM, and cardiovascular disease is related to increased gluconeogenesis. Also, the direct conversion of glycogen to glucose may prove to be an important regulator of glycogen content. Our studies will shed new light on how glucose and lipid metabolism in adipose tissue adapts to fasting.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CELLULAR MECHANISMS OF DRUG ELIMINATION**

  Principal Investigator & Institution: Giacomini, Kathleen M.; Professor of Pharmacy; Biopharmaceutical Sciences; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 94122

  Timing: Fiscal Year 2003; Project Start 04-APR-1986; Project End 31-JAN-2007

  Summary: (provided by applicant): Organic cation transporters in the kidney play key roles in the body's defense against foreign substances including drugs and other xenobiotics. Many clinically used drugs (e.g., **metformin**), hormones (e.g., dopamine) as well as toxic substances (e.g., MPP+ (1-methyl-4-phenylpyridinium)) are organic amines and are eliminated in the kidney by secretory transporters. The working hypothesis of the proposed studies is that the organic cation transporter, OCT2, is localized to the basolateral membrane of the proximal tubule and is the key transporter responsible for the first step in the renal secretion of many organic cations. To test this hypothesis, comprehensive studies, ranging from molecular analysis of specificity through studies of an OCT2 knockout mouse and genetic studies in humans, are proposed. The specific aims are to: (1) Determine the specificity of OCT2 in heterologous expression systems; (2) Construct a humanized cell culture model to localize the transporter to the apical or basolateral membrane and localize the transporter along the nephron; (3) Determine the role of OCT2 in renal secretion by studying renal elimination and accumulation in an OCT2 knockout mouse that will be provided by our collaborator, A. Schinkel; and (4) Determine whether genetic variation in OCT2 contributes to variation in renal clearance of the model organic cation, **metformin,** an anti-diabetic drug, in humans. Methods used in analysis of specificity of OCT2 include two-electrode voltage clamp methods in oocytes. Confocal microscopy, in situ hybridization techniques and immunohistochemistry will be used to localize OCT2 to the apical or basolateral membrane and to ascertain the regional specific distribution of the transporter along the nephron. Pharmacokinetic studies in mice will be used to determine the role of the transporter in in vivo renal elimination. Finally, clinical studies in normal volunteers with particular OCT2 genotypes and haplotypes including OCT2*1, OCT*3D and three

missense mutations (M1651, R400C, K432Q) will be performed to determine whether genetic variation in OCT2 contributes to variation in renal clearance of **metformin.** These variants have been shown in cells to have altered function in comparison to the common form of OCT2. These studies are significant to our basic understanding of the mechanisms involved in renal drug elimination and will enhance our ability to predict renal clearance, toxicities and drug response.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CLINICAL RESEARCH ON NON-ALCOHOLIC STEATOHEPATITIS**

  Principal Investigator & Institution: Chalasani, Naga P.; Associate Professor of Medicine; Medicine; Indiana Univ-Purdue Univ at Indianapolis 620 Union Drive, Room 618 Indianapolis, in 462025167

  Timing: Fiscal Year 2002; Project Start 20-MAY-2002; Project End 30-APR-2007

  Summary: Non-alcoholic steatohepatitis (NASH) is a chronic liver disease that occurs in individuals without significant alcohol consumption and histologically it resembles alcoholic liver disease with macorvesicular steatosis, spotty necrosis, inflammation, Mallory bodies, and fibrosis. It is increasingly being recognized as a predominant type of chronic liver disease in the United States; however, its prevalence, pathogenesis, and natural history have not been adequately studied. In order to better understand the epidemiology and pathogenesis and to identify optimal therapy for NASH, we propose to conduct NASH-related clinical research in the following specific aims: Specific Aim 1: The objective is to create a database of patients with fatty liver and NASH that will enable us to perform multi-disciplinary and multi-centered studies on the epidemiology, pathogenesis, and therapy of NASH. The subgroups of patients included in this database are adults with fatty liver and NASH, women with polycystic ovary syndrome, and appropriately matched controls. The cohort will be characterized clinically, anthropometrically, through laboratory tests, and histologically. A repository containing liver tissue, blood samples, and DNA from subjects with disease and controls will be developed; Specific Aim 2: The overall goal of this specific aim is to derive and validate risk equations that measure and stratify the risk for advanced histology in patients with non-alcoholic fatty liver disease. To this end, we will conduct a multi-center, nested case-control study of patients with simple fatty-liver, non-cirrhotic NASH, and cirrhotic NASH to identify risk factors for advanced histology; Specific Aim 3: We hypothesize that insulin resistance is pivotal in the pathogenesis of NASH and measures that improve insulin resistance would lead to an improvement in liver histology in non-diabetic NASH. Here, we propose to conduct a multi-center, randomized, double-blind, placebo-controlled study of moderate weight reduction with or without **metformin** for 12- months. The primary end-point is the change in liver histology measured by comparing biopsy findings at baseline at the end of 12-months. The primary end-point is the change in liver histology measured by comparing biopsy findings at baseline and at the end of 12-month treatment period. The secondary end-points are changes in insulin resistance, lipid peroxidation, determination of oxidative stress, anthropometric measurements, liver biochemistry, and the measures of quality of life.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: COMPARE COMBINED SUBMAXIMAL SULFONYLUREA AND METFORMIN THERAPY IN NIDDM**

  Principal Investigator & Institution: Bryer-Ash, Michael; University of Tennessee Health Sci Ctr Memphis, Tn 38163

Timing: Fiscal Year 2001

Summary: It is hypothesized that patients with NIDDM, who have failed to respond adequately to initial sulfonylurea treatment, will have a superior glycemic response to combination therapy employing the addition of **metformin,** with a lower incidence of adverse effects in comparison to therapy with sulfonylureas alone in maximum dosage."

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: COOPERATIVE MULTICENTER REPRODUCTIVE MEDICINE NETWORK**

  Principal Investigator & Institution: Legro, Richard S.; Associate Professor; Obstetrics-Gynecology; Pennsylvania State Univ Hershey Med Ctr 500 University Dr Hershey, Pa 17033

  Timing: Fiscal Year 2001; Project Start 30-JUN-2000; Project End 31-MAR-2005

  Summary: The overall hypothesis of this proposal is that insulin resistance is the fundamental pathophysiologic defect in women with polycystic ovary syndrome (PCOS), and therefore interventions to improve it are most likely to result in spontaneous ovulation and a singleton term pregnancy in infertile PCOS women. The primary aim is to identify the most effective form of ovulation induction in PCOS women that will result in a full term singleton intrauterine pregnancy with the safest profile. We propose to perform a multicenter-randomized trial of two methods of ovulation induction in clomiphene-resistant PCOS women (failure to either ovulate or conceive after an adequate trial of clomiphene). The women will be randomized to either gonadotropin or **metformin** treatment. Gonadotropins are the current standard method of ovulation induction in clomiphene resistant PCOS women and directly stimulate ovarian follicular development. The large cohort of arrested antral follicles and the unique pathophysiology of insulin resistance in PCOS places these women at particular risk for ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy with this form of therapy. **Metformin** achieves ovulation through improvement in insulin sensitivity and suppression of hepatic gluconeogenesis. These changes induce secondary effects of decreased circulating insulin, androgens and gonadotropins, increased sex hormone binding globulin, and increased ovulatory function. PCOS women will be identified on the basis of unexplained hyperandrogenemic chronic anovulation, without other health problems, and no other major infertility factor. We hypothesize that the treatment arm that improves insulin sensitivity will be more likely to result in monofollicular ovulation and thus singleton pregnancy, and less likely to result in the complications of ovulation induction including multiple pregnancy and OHSS. This study could have a major impact on infertility in PCOS women while avoiding the risks and costly burden of OHSS and multiple pregnancy.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CORE--DIETARY ASSESSMENT AND BODY COMPOSITION FACILITY**

  Principal Investigator & Institution: Woods, Margo N.; Associate Professor; Tufts University Boston Boston, Ma 02111

  Timing: Fiscal Year 2002

  Summary: The role of Core D is to perform dietary assessments, anthropometric measurements, body composition/energy metabolism measurements, and nutrition counseling and support. A complete list of the study parameters is presented in Table 1. Project 1 conducts the continuing surveillance of the "Nutrition for Life" (NFL) cohort

that has currently been followed from one to three years and involves comprehensive longitudinal data on each subject. This Core will continue to set the protocols, quality control, training, and analyses on the cohort data. This cohort data includes dietary assessments (3-day food record (3DFR) and food frequency questionnaire (FFQ)), anthropometric measurements (weight, height, skin folds, hand grip, and circumferences), body composition measurements (bioelectrical impedance (BIA) and dual energy x-ray absorptiometry (DEXA)), and energy expenditure and metabolism measurements. This core will also provide nutrition counseling and support for the cohort. Project 1 will now include use of DEXA for determinations of body composition (yearly). Project 2 will utilize most of the services and measurements listed in this Core. This project has a population study group of 100 with each participant enrolled for one year. An average of 20 persons per year will be enrolled in the study. Individual nutrition counseling will be used for this study due to the specific nature of the nutrition interventions and the staggering of enrollment. Use of this Core?s services by Project 2 is delineated in the table on Page 381. Project 3 will contain three studies and will utilize many of the services and measurements offered in this Core (table on page 381). Study 1 will include only NFL participants and will not require any additional measurements for the NFL participants. Study 2, cohort sub-study with intensive metabolic measurements, will have 50 participants with each participant enrolled for one year. Study 3, **Metformin** for abdominal adiposity, will have 30 participants and will last for six months. Individual nutrition counseling will be utilized for this project because of the more detailed and instructional nature of the nutrition intervention and the importance of tracking. Staggered recruitment also necessitates individual counseling. Project 4 will be carried out at two sites (Children?s Hospital, Boston, MA; and Rochester Medical Center, Rochester, NY) by Tracie Miller, M.D. Procedures and protocols for the methods cited in this Core have already been adapted for this special population of infants and children.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DETERMINE EFFECTS OF DOSES OF METFORMIN IN PATIENTS W/ TYPE 2 DIABETE**

  Principal Investigator & Institution: Fonseca, Vivian; Tulane University of Louisiana New Orleans, La New Orleans, La 70112

  Timing: Fiscal Year 2001

  Summary: The results of a recently completed diabetes complications and control trial showed that good glycemic control resulted in slower progression of the chronic complications of diabetes. These beneficial effects apply to patients with type 1 and type 2 diabetes. The goal of therapy today is to achieve good glycemic control to prevent the long-term complications of elevated glucose levels. **Metformin** hydrochloride has been successfully used for many years as an antihyperglycemic agent for type 2 diabetes. **Metformin** acts to lower glycemia primarily by inhibiting hepatic glucose production and also by enhancing peripheral glucose uptake. A once daily dosing of **metformin** would be more desirable than multiple daily dosings. The novel biphasic oral dosage form is designed to slow the release of the drug, and to prolong its residence time in the upper GI tract. This new formulation provides the opportunity for decreased frequency of dosing. Decreased frequency of dosing results in the benefit of increased patient convenience and increased compliance. The purpose of this study is to determine the effects on glycemic control of several doses of the novel oral **metformin** administered once or twice per day versus placebo in patients with type 2 diabetes mellitus who have inadequate glycemic control with diet and exercise.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DIABETES PREVENTION PROGRAM**

  Principal Investigator & Institution: Orchard, Trevor J.; Professor; Epidemiology; University of Pittsburgh at Pittsburgh 350 Thackeray Hall Pittsburgh, Pa 15260

  Timing: Fiscal Year 2003; Project Start 15-AUG-1994; Project End 31-JAN-2008

  Summary: (provided by applicant): The Diabetes Prevention Program is a multicenter controlled clinical trial examining the efficacy of an intensive life-style intervention or **metformin** to prevent or delay the development of diabetes in a population selected to be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 ADA criteria, is the primary outcome while cardiovascular disease and its risk factors are important secondary outcomes. The DPP began recruitment in mid-1996. At the time of this application, total study exposure is a mean of approximately 3 years (range 2 to 5) with a total of approximately 10,000 patient years in the 3,234 volunteers in the 3-arm study. On the basis of a statistically significant and clinically compelling decrease in the development of diabetes in the life-style intervention and metformin-treated groups (58% and 31% reductions, respectively) compared with the placebo treated group, the DPP Data Monitoring Board and NIDDK ended the masked treatment phase of the study in May, 2001, one year earlier than originally planned. This application is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of data collected during the study. The highly compliant DPP cohort, including 45% minorities, is the largest IGT population ever studied. Moreover, the subcohort that has developed diabetes (n approximately 700) has been followed from near the exact time of diabetes onset. Clinically important research questions remain in the wake of the DPP. The carefully collected, centrally measured and graded data in this cohort should help to answer, definitively, a number of important questions regarding the clinical course of IGT and early onset type 2 diabetes. Specific aims include: 1. Examine the long-term effects and durability of prior DPP intervention on the major DPP outcomes including diabetes, clinical cardiovascular disease, atherosclerosis, CVD risk factors, quality of life and cost-benefit; 2. Determine the clinical course of new onset type 2 diabetes and IGT, in particular regarding microvascular and neurologic complications; 3. Determine the incidence of cardiovascular disease (CVD), CVD risk factors and atherosclerosis in new onset type 2 diabetes and IGT; and 4. Examine topics 1-3 in minority populations, men vs. women, and in older subjects in the DPP. The current application is for 5 years of funding, although the some of the goals of the projects described will require a 10-year study.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DIABETES PREVENTION PROGRAM**

  Principal Investigator & Institution: Wing, Rena R.; Professor of Psychiatry; Psychiatry; University of Pittsburgh at Pittsburgh 350 Thackeray Hall Pittsburgh, Pa 15260

  Timing: Fiscal Year 2001; Project Start 15-AUG-1994; Project End 30-JUN-2003

  Summary: Diabetes mellitus is a major cause of morbidity and mortality in the United States, and individuals with impaired glucose tolerance (IGT) or a history of gestational diabetes (GDM) are at increased risk of developing this disease. Research to test whether it is possible to prevent the occurrence of NIDDM is a national priority. The University of Pittsburgh proposes a primary prevention trial that optimally tests the hypothesis that NIDDM is preventable through weight loss and physical activity and

simultaneously addresses whether an intervention that is more easily adopted by the health care system is of benefit. Targeted advertisement and chart review will be used to identify 100 subjects with IGT (confirmed on repeat OGTT and with at least one 2-hour BS>170); 100 GDM subjects will be identified from a registry of over 1000 women with GDM; we aim for 40% of participants to be African American. These 200 high risk subjects will be randomized to a control group, a standard life-style intervention (SLI), or an enhanced life-style intervention (ELSI). The goals for the two intervention groups will be a 10% weight loss and 3 hours/week of physical activity. To achieve these goals, the SLI group will participate in a standard diet/exercise program that could be easily implemented by the health system; community-led exercise groups will also be available. The ELSI group will be given enhanced treatment to optimally test the prevention hypothesis; these subjects will be seen individually on a monthly basis; intervention will be prescribed as needed to achieve and maintain the weight and exercise goal. The primary outcome will be development of NIDDM (WHO criteria; confirmed by second test). Other endpoints will be changes in glucose, insulin resistance, insulin secretion, and the cardiovascular risk profile. During screening, some subjects will be identified as having non-fasting diabetes (NFD; FBS 200). These subjects will participate in a secondary prevention trial using a 2 x 2 factorial design with the two life-style conditions (SLI vs ESLI) crossed with 2 drug conditions (metformin vs placebo). The primary outcome measures for this secondary prevention study will be development of fasting hyperglycemia and incidence or progression of diabetic complications. The University of Pittsburgh is well qualified to participate in this trial as we have extensive experience in life-style interventions, exercise, clinical trials, diabetic complications, and in the medical management of diabetes.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DIABETES PREVENTION PROGRAM**

  Principal Investigator & Institution: Olefsky, Jerrold M.; University of California San Diego 9500 Gilman Dr, Dept. 0934 La Jolla, Ca 92093

  Timing: Fiscal Year 2001

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DIABETES PREVENTION PROGRAM (DPP)**

  Principal Investigator & Institution: Shamoon, Harry; Professor and Dcrc Program Director; Medicine; Yeshiva University 500 W 185Th St New York, Ny 10033

  Timing: Fiscal Year 2001; Project Start 15-AUG-1994; Project End 30-JUN-2003

  Summary: There is increasing evidence that the development of noninsulin dependent diabetes mellitus (NIDDM) is presaged many years earlier by the presence of biochemical and other phenotypic features in susceptible individuals. Earlier intervention in such individuals may prevent or slow the occurrence of overt hyperglycemia which, in turn, may limit the morbidity and mortality associated with diabetes. By selecting populations at higher than average risk for the ultimate development of NIDDM, we propose to be able to practically test the following hypothesis: The reduction in risk of developing NIDDM in persons at high risk for the development of diabetes will be dependent on treatment which affects insulin resistance, islet B-cell dysfunction, and/or hepatic glucose production. Interventions which include diet, exercise sulfonylurea drugs, and **metformin** in a factorial design can address this hypothesis. The Diabetes Center at the Albert Einstein College of Medicine

is a multidisciplinary aggregation of scientists and clinicians actively involved in various aspects of diabetes. With the resources and expertise available among individuals in the Center, we will participate in a multicenter NIDDM Prevention Trial. The Albert Einstein Center would be able to contribute to the success of such a Trial for the following reasons: l) a Diabetes Research and Training Center underpinning and the Institutional commitment to addressing issues in underserved populations of New York City; 2) our participation in the Diabetes Control and Complications Trial as a clinical center; 3) the availability of a large, identified population of individuals from racial and ethnic minority groups in the Bronx and Westchester Counties who receive their medical care in Einstein-affiliated programs; 4) an identified and well characterized population of women who had gestational diabetes diagnosed between 1988 and the present, and an annual accrual of an additional cohort of women with gestational diabetes; 5) expertise in the design and implementation of clinical trials; 6) strong research foci of the principal and co-investigators in areas such as pathophysiology and diagnosis as well as nutritional and pharmacologic treatment of NIDDM; 7) members of the treatment team with specific competence in diabetes in Hispanic and in African-American individuals; 8) a new outpatient facility in which to conduct a clinical trial; 9) expertise in related areas such as hypertension control, cardiovascular risk reduction, and behavioral techniques intended to achieve therapeutic goals; and lO) a track record of participating in constructive collaborative efforts to achieve the goals of NIH-initiated multicenter projects. We will participate in the Trial by providing personnel, resources, and study volunteers to achieve the aims of the planning, implementation, and data analysis phases of the proposed 7-year study.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DIABETES PREVENTION PROGRAM (DPP)**

  Principal Investigator & Institution: Metzger, Boyd E.; Professor; Northwestern University Office of Sponsored Programs Chicago, Il 60611

  Timing: Fiscal Year 2001

  Summary: Impaired glucose tolerance represents a category of results from glucose tolerance tests that is not completely normal nor meets criteria for NIDDM. About half of all subjects found to have IGT progress to NIDDM over time with a rate of about 5% per year. The purpose of this randomized, prospective multicenter clinical trial is to determine whether the progression from IGT to NIDDM in high risk populations can be prevented or delayed with specific interventions, including intensive lifestyle change and **metformin.**

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DIABETES PREVENTION PROGRAM LONG-TERM FOLLOW-UP STUDY**

  Principal Investigator & Institution: Pi-Sunyer, F. Xavier.; Director; St. Luke's-Roosevelt Inst for Hlth Scis Health Sciences New York, Ny 10019

  Timing: Fiscal Year 2003; Project Start 15-AUG-1994; Project End 31-JAN-2008

  Summary: (provided by applicant): The Diabetes Prevention Program is a multicenter controlled clinical trial examining the efficacy of an intensive life-style intervention or **metformin** to prevent or delay the development of diabetes in a population selected to be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 ADA criteria, is the primary outcome while cardiovascular disease and its risk factors are important secondary outcomes. The DPP began

recruitment in mid-1996. At the time of this application, total study exposure is a mean of approximately 3 years (range 2 to 5) with a total of approximately 10,000 patient years in the 3,234 volunteers in the 3-arm study. On the basis of a statistically significant and clinically compelling decrease in the development of diabetes in the life-style intervention and metformin-treated groups (58% and 31% reductions, respectively) compared with the placebo treated group, the DPP Data Monitoring Board and NIDDK ended the masked treatment phase of the study in May, 2001, one year earlier than originally planned. This application is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of data collected during the study. The highly compliant DPP cohort, including 45% minorities, is the largest IGT population ever studied. Moreover, the subcohort that has developed diabetes (n approximately 700) has been followed from near the exact time of diabetes onset. Clinically important research questions remain in the wake of the DPP. The carefully collected, centrally measured and graded data in this cohort should help to answer, definitively, a number of important questions regarding the clinical course of IGT and early onset type 2 diabetes. Specific aims include: 1. Examine the long-term effects and durability of prior DPP intervention on the major DPP outcomes including diabetes, clinical cardiovascular disease, atherosclerosis, CVD risk factors, quality of life and cost-benefit; 2. Determine the clinical course of new onset type 2 diabetes and IGT, in particular regarding microvascular and neurologic complications; 3. Determine the incidence of cardiovascular disease (CVD), CVD risk factors and atherosclerosis in new onset type 2 diabetes and IGT; and 4. Examine topics 1-3 in minority populations, men vs. women, and in older subjects in the DPP. The current application is for 5 years of funding, although the some of the goals of the projects described will require a 10-year study.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DIABETES PREVENTION PROGRAM PHASE 1,2,3 AND 4**

  Principal Investigator & Institution: Dagogo-Jack, Samuel E.; Professor of Medicine; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2001

  Summary: As part of a multicenter study, 4,000 patients with IGT will be identified and randomly assigned to (a) an intensive lifestyle intervention of diet and exercise (b) troglitazone (c) **metformin** or (d) placebo to determine if any of the three interventions prevent progression NIDDM over a period of 3-6 years.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: EFFECTS CHRONIC INSULIN REDUCTION SPONTANEOUS AND INDUCED OVULATION**

  Principal Investigator & Institution: Ratts, Valerie; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2001

  Summary: There is no text on file for this abstract.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: EFFECTS OF ETHANOL ON LIPID METABOLISM**

  Principal Investigator & Institution: You, Min; Medicine; Indiana Univ-Purdue Univ at Indianapolis 620 Union Drive, Room 618 Indianapolis, in 462025167

Timing: Fiscal Year 2003; Project Start 01-MAR-2003; Project End 29-FEB-2008

Summary: (provided by applicant): This project is designed to investigate the effects of ethanol on the activities of peroxisome proliferator activated receptor (PPARs) and sterol regulatory element (SRE)-binding protein (SREBPs). We have determined that ethanol treatment of hepatoma cells or hepatocytes decreases the ability of PPAR? to activate a PPAR responsive reporter plasmid. This effect of ethanol depends on ethanol metabolism and is mediated by acetaldehyde. Further, in nuclear extracts from ethanol-treated cells, we have noted decreased binding of the PPAR?/RXR? heterodimer to an oligonucleotide containing the PPAR response element. We have also found that ethanol treatment increases SREBP-regulated transcription of a SRE reporter in a dose-dependent manner in two hepatoma cell lines but not in CV-I cells, suggesting that ethanol metabolism is also required for this effect. This effect is mediated via the SREBP proteolytic maturation cascade and is blocked by increasing concentration of sterols. We hypothesize that ethanol causes the development and maintenance of fatty liver by effects on these transcription factors, in addition to its well known effects on redox state and oxidative stress. This will be tested in both animals and cell culture models. We will examine the effect of alcohol feeding on levels of PPARs, their DNA-binding activity, levels of PPAR-regulated mRNAs, and responsiveness to WY14643. We will examine the l effects of alcohol feeding on levels of SREBP-regulated mRNAs, and responsiveness of the system to cholesterol and **metformin.** The activities of these transcription factors and the genes they regulate will be correlated with hepatic histology, lipid content, and measures of total body lipid metabolism. Mechanisms for these activities of alcohol will be tested in hepatoma cells to better understand the molecular basis for the effects. Since these pathways can be manipulated by pharmacological agents, this hypothesis suggests possible new therapies for alcoholic fatty liver and possibly steatohepatitis.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: EFFECTS OF METFORMIN & INSULIN ON GLUCONEOGENESIS IN NIDDM**

  Principal Investigator & Institution: Boden, Guenther; Professor of Medicine; Temple University 406 Usb, 083-45 Philadelphia, Pa 19122

  Timing: Fiscal Year 2001

  Summary: The objectives of this investigation are 1) to compare effects of **Metformin** and NPH insulin on overnight rates of gluconeogenesis, glycogenolysis and hepatic glucose production in patients with T2DM and 2) to evaluate whether **Metformin,** given at bedtime, can be used clinically to control nocturnal hepatic glucose production in patients with T2DM.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: EFFECTS OF METFORMIN ON LIPOPROTEIN (A) CONCENTRATIONS AND METABOLISM**

  Principal Investigator & Institution: Ginsberg, Henry; Columbia University Health Sciences New York, Ny 10032

  Timing: Fiscal Year 2001

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: EFFICACY, SAFETY & TOLERABILITY OF BRL 996536C IN NIDDM**

  Principal Investigator & Institution: Greenberg, Andrew; New England Medical Center Hospitals 750 Washington St Boston, Ma 021111533

  Timing: Fiscal Year 2001

  Summary: The primary objective in this 26 week study is to evaluate the efficacy of a new investigational antidiabetic drug, BRL 49653C, in reducing hyperglycemia when added to the therapy of NIDDM patients who are inadequately controlled on a maintenance dose (2.5g/day) of **metformin.** The primary endpoint will be the reduction from baseline in HBA1c after 26 weeks of treatment in BRL 49653C/metformin combination groups (BRL 49653C 4 mg or 8 mg qd plus **metformin** 2.5g/day) in comparison with the **metformin** monotherapy group (BRL 49653C placebo plus **metformin** 2.5g/day). Secondary objectives include defining the clinical safety and tolerability of the monotherapy and combination groups. Also the **metformin** monotherapy group will be compared with the BRL 49653C **metformin** combination groups in terms of their efficacy in reducing fasting plasma glucose (FPG), fructosamine, C-peptide, immunoreactive insulin and serum lipids including total cholesterol, HDL-cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides and free fatty acids at week 26.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ETIOLOGY OF OVARIAN HYPERANDROGENEMIA IN PCOS**

  Principal Investigator & Institution: Mccartney, Christopher R.; Physiology; University of Virginia Charlottesville Box 400195 Charlottesville, Va 22904

  Timing: Fiscal Year 2001; Project Start 01-SEP-2001

  Summary: (provided by applicant): PCOS is a disorder marked by excessive ovarian androgen production, but its etiology is unknown. Provocative ovarian testing involving markedly supraphysiologic LH stimuli have produced abnormal steroid responses in PCOS, leading to the theory that inherent abnormalities of ovarian steroidogenesis underlie PCOS. We propose to further explore this hypothesis in specific aim 1 by delineating ovarian steroid responses to physiologic LH stimuli, thus allowing the construction of LH-steroid dose-response curves in both normal women and women with PCOS. Consistent features of PCOS include persistent LH hypersecretion, insulin resistance/hyperinsulinemia, and hyperandrogenemia, and some or all of these factors may play a role in causing and/or perpetuating the abnormalities of ovarian steroidogenesis. In specific aim 2, studies will investigate the relative roles of persistent LH hypersecretion, hyperinsulinemia, and ovarian hyperandrogenemia in the maintenance of abnormal ovarian steroid responses to LH in PCOS. The ovarian steroid response to physiologic LH stimulation will be examined 6 weeks after reduction of LH using the gonadotropin-releasing hormone agonist leuprolide; 6 weeks after reduction of hyperinsulinemia using **metformin** or rosiglitazone; and 6 weeks after androgen receptor blockade using flutamide. The results of these studies will help elucidate mechanisms involved in ovarian hyperandrogenemia in women with PCOS.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: EXERCISE, DENERVATION AND INSULIN RESISTANCE IN MUSCLE**

  Principal Investigator & Institution: Pilch, Paul F.; Professor; Biochemistry; Boston University Medical Campus 715 Albany St, 560 Boston, Ma 02118

Timing: Fiscal Year 2002; Project Start 01-AUG-1996; Project End 31-MAR-2006

Summary: (provided by applicant): AMP-activated protein kinase (AMPK) plays a major role in the response of many cells to stresses that alter their energy state. In skeletal muscle, AMPK activity is increased during exercise (contraction), and a large body of evidence indicates that this regulates observed increases in glucose transport, fatty acid oxidation and UCP3 expression. Much of this knowledge has been obtained utilizing AICAR, an AMPK activator whose specificity has been questioned. Here, we will make use of AICAR and alternative approaches to modulate AMPK activity, to explore the physiological roles of AMPK in muscle and the biochemical basis for its effects on glucose transport, glycogen synthesis and UCP3 expression. The following are our aims: (1) To characterize pharmacological and other means for increasing AMPK activity in incubated muscles and to determine if they stimulate glucose transport via nitric oxide. The effects of prior hypoxia, incubation with a glucose-free medium, **metformin** and alpha-adrenergic stimulation, all of which increase AMPK activity, will be compared with that of AICAR. In addition, we will assess the specificity of a new small molecular weight AMPK inhibitor. (2) To determine the biochemical pathway(s) by which AMPK activation in skeletal muscle leads to GLUT4 translocation and UCP-3 gene transcription. In vitro phosphorylation assays and metabolic labeling of isolated muscle will be used to identify the phosphoprotein targets of AMPK related to glucose transporter translocation. We will also introduce constitutively active and dominant negative AMPK constructs into cultured myocytes to ascertain the AMPK-dependency of the UCP3 mRNA induction, and we will attempt to identify the transcription factors that modify this process. (3) To explore the basis for the inhibition of insulin-stimulated glycogen synthesis in the denervated extensor digitorum longus (EDL) muscle and its restoration by incubation with AICAR. We will determine whether the effects of AICAR are mimicked by other AMPK activators, what processes AMPK activation restores and why AICAR does not have a similar effect in the denervated soleus. (4) To determine whether treatment with AICAR or **metformin** in vivo prevents or attenuates the alterations in gene expression (e.g. GLUT4, UCP-3, myogenin, etc.), and lipids that occur in rat muscle 6-72 hrs after denervation. We will also assess if treatment with these agents stimulates GLUT4 recruitment, and we will use new methodology to test the hypothesis that exercise/contraction/AMPK responsive glucose transporter pools differ from insulin-responsive pools in their biochemical composition and ability to associate with glycogen particles.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: FITNESS,GROWTH HORMONE IGF1 AXIS, METFORMIN THERAPY IN NIDDM CHILDREN**

  Principal Investigator & Institution: Estrada, Elizabeth; University of Connecticut Sch of Med/Dnt Bb20, Mc 2806 Farmington, Ct 060302806

  Timing: Fiscal Year 2001

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: GENETIC, IMMUNOLOGIC AND BETA CELL FUNCTION MARKERS IN TYPE 1.5 DIABETES**

  Principal Investigator & Institution: Palmer, Jerry P.; Professor; University of Washington Seattle, Wa 98195

  Timing: Fiscal Year 2001

Summary: A large amount of clinical and basic research supports our current understanding that there are two major types of diabetes, termed IDDM and NIDDM. The disease process in classical IDDM patients is believed to be autoimmune in nature because of a strong association with certain HLA genes, the presence of humoral and cellular immune responses against islet antigens, and inflammatory infiltrate termed insulitis, the ability of T- cells to transfer IDDM, and the observation that immunotherapy alters the natural history of IDDM. In contrast, the disease process in NIDDM patients is not auto-immune in nature; a decreased sensitivity to insulin action is central to the disease process, and a poorly understood but non- inflammatory beta cell lesion occurs which diminished insulin secretory ability. The clinical distinction where NIDDM is very common, can have diabetes pathophysiologically similar to classical NIDDM, and some of the antibodies characteristic of IDDM can occur in older, obese individuals with phenotypic NIDDM. The main hypothesis to be tested in this project is that the pathophysiologic mechanism causing hyperglycemia in ICA and/or IAA, and/or GAD Ab, and/or ICA-512 positive, phenotypic NIDDM patients over the age of 40 (antibody positive NIDDM) is a combination of the Type I and Type II diabetes disease processes. The specific aims to be tested are: I. To compare the relative frequency of Type I diabetes susceptibility and protective genes (and gene loci) in Ab(+) NIDDM with relative frequency of the same genes in Ab(-) NIDDM, childhood IDDM, and normal controls. II. To compare the frequency of Type II diabetes susceptibility genes (and gene loci) in Ab(+) NIDDM with the frequency of these same genes in Ab(-) NIDDM, childhood IDDM, and normal controls. III. To compare ICA, GAD Ab, IAA, and ICA-512 frequency and levels, individually and in combination, in Ab(+) NIDDM with antibody frequency in childhood IDDM and to compare T-cell responses to islet antigens by cellular immunoblotting in Ab(+) NIDDM, Ab(-) childhood IDDM, and normal controls. IV. To compare T-cell Th2-type cytokine production with Th1-type cytokine production in Ab(=) NIDDM, childhood IDDM, Ab(-) NIDDM, and normal controls. V. To compare AIRmax, slope of glucose potentiation, and insulin sensitivity in Ab(+) NIDDM with these measures of beta cell function and insulin sensitivity in Ab(-) NIDDM, childhood IDDM, and normal controls. VI. To determine whether insulin treatment of recently diagnosed Ab(+) NIDDM results in greater preservation of residual beta cell function compared to treatment with glyburide or **metformin.**

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: GINKGO BILOBA EXTRACT & THE INSULIN RESISTANCE SYNDROME**

  Principal Investigator & Institution: Kudolo, George B.; Associate Professor; Clinical Laboratory Sciences; University of Texas Hlth Sci Ctr San Ant 7703 Floyd Curl Dr San Antonio, Tx 78229

  Timing: Fiscal Year 2001; Project Start 12-SEP-2001; Project End 31-MAY-2004

  Summary: (provided by applicant):Herbal remedy is popular among those with chronic diseases, who may already be taking several prescription medications, thereby increasing the risk of drug-herb interactions. Ginkgo biloba extract is a popular dietary supplement that is ingested by the general population to enhance mental focus and by the elderly to delay onset of age-acquired loss of cognitive function. In subjects with non-insulin dependent diabetes (NIDDM), ingestion of Ginkgo biloba significantly increases pancreatic beta-cell function. The increased plasma C-peptide levels in response to glucose loading is accompanied by decreased plasma insulin levels and no significant changes in plasma glucose levels. The central hypothesisof this application is that ingestion of Ginkgo biloba produces the dissimilar plasma C-peptide/insulin ratios

by increasing the metabolic clearance rates of insulin and the antidiabetic medications. The underlying mechanism may involve the alteration of drug pharmacokinetics resulting in decreased efficacy of the hypoglycemic agents and increased whole body insulin resistance. The primary objective-of this study is to determine the mechanism by which Ginkgo biloba may accelerate pancreatic function and reduce glucose metabolism. The specific aims of this projects are to determine (a) the effect of ingesting Ginkgo biloba on the pharmacokinetics of glipizide, pioglitazone and **metformin** and (b) how the interaction between Ginkgo biloba and the three hypoglycemic agents affect the three homeostatic variables that control blood glucose levels: insulin synthesis, insulin action and hepatic glucose production. Because aging is a significant risk factor for the development of NIDDM as a result of a progressive decline in pancreatic function, and because the elderly chronically take multiple prescription medications, the increased use of Ginkgo biloba in this population may increase drug-herb interactions. Therefore, we shall examine the effect of Ginkgo biloba on the pancreatic function in the elderly to determine whether it may produce pancreatic dysfunction and a potential for the development of insulinopenia. The results of this study, when taken together should provide very important information on balancing the risk of accelerating pancreatic beta-cell dysfunction, with its beneficial effects on delaying the onset of cognitive function. The results of this study should also provide valuable information for designing new therapeutic strategies for the treatment of diseases in the insulin resistance syndrome.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: GLYCATION AND MU DICARBONYLS IN DIABETIC COMPLICATIONS**

  Principal Investigator & Institution: Beisswenger, Paul J.; Professor; Medicine; Dartmouth College 11 Rope Ferry Rd. #6210 Hanover, Nh 03755

  Timing: Fiscal Year 2002; Project Start 30-SEP-2002; Project End 31-AUG-2007

  Summary: (provided by applicant): My objective is to combine my expertise in the biochemical basis of diabetic complications with my clinical research to develop new approaches for understanding the pathogenesis of this devastating cluster of diseases. My career has had several phases, including basic science, clinical endocrinologist, and educator, but over the past 10 years I have become fully committed to the continued development of a strong clinical research program. I believe that such a program could be a model for those considering a career in clinical investigation. Funding is being sought through this K-24 program to continue this transition and achieve blocks of protected time to focus on my research and develop a mentoring program for the training of clinical investigators. Over the longer term, my objectives are to create a stable and productive research program which will span the hitherto neglected gap between clinical and basic science and provide a fertile training ground for new investigators. The research and mentoring will take place at Dartmouth Medical School (DMS) and its two major clinical facilities, the Dartmouth-Hitchcock Medical Center (DHMC) and the White River Junction Veterans Hospital (VAH). This institution offers a rich milieu for one seeking well educated and highly motivated trainees, and has all of the required facilities for clinical research program. I have carefully prepared a comprehensive mentoring program which can be immediately implemented if this award is granted. This program is designed to give the trainees proficiency in the planning, execution and completion of study projects that provide a model combining powerful analytical tools with carefully selected clinical populations to solve important diabetes related questions. Over the 5 years of the granting period I propose to spend

my time on three concurrent projects evaluating the role of nonenzymatic glycation, dicarbonyls, and AGEs in the pathogenesis of diabetic complications. The projects currently in progress or planned include. a. Effect and mechanism of action of binding agents on the production, detoxification, and scavenging of alpha-dicarbonyls and the progression of diabetic macrovascular complications, b. The role of post-prandial hyperglycemia on alpha-dicarbonyls, tissue glycation, and diabetic macrovascular complications. c. Methylglyoxal production and the role of Fructosamine 3 Kinase (FN3K) deglycation in the control of glucose-mediated nonenzymatic glycation and predisposition to diabetic nephropathy. Additional clinical projects will be added as selected basic research projects in my laboratory "mature" and as other study populations present improved models to test our hypotheses. These exciting research projects, and new ones on the horizon, combined with the proposed mentoring/training program offers real opportunities of attracting and rewarding a new generation of clinical investigators.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: HIGH MONO FAT DIET VERSUS LOW FAT DIET FOR DIABETIC PATIENTS**

  Principal Investigator & Institution: Ahmann, Andrew; Oregon Health & Science University Portland, or 972393098

  Timing: Fiscal Year 2001

  Summary: Participants in this research study have Type 2 diabetes mellitus (also called adult-onset diabetes, Type II Diabetes, or non-insulin dependent diabetes mellitus). Type 2 diabetes mellitus is the most common form of diabetes. It can lead to diseases of the eyes, nerves and kidneys, but heart disease is the major disease risk. Diet plays an important role in treatment of this kind of diabetes in several ways. The main goal of diet therapy is improvement in blood glucose levels. Glucose levels may be improved by the type of food eaten and also by weight loss. Fat levels in the blood (e.g. cholesterol and triglycerides) represent other important factors that can be affected by diet in diabetes. Generally, high fats in the blood are associated with increased risk of heart disease. Dietary advice for people with diabetes has changed over the past 30 years. Recently a diet high in carbohydrates with no more than 30% of calories from fat has been recommended. However, there has also been significant interest in using a diet higher in monounsaturated fats (special types of fat that you eat, like olive oil and canola oil) and lower in carbohydrates (fruits, vegetables and starches). Some studies have shown that a diet high "mono" (monounsaturated fats) results in lower sugars and improved fat levels in the blood. Several questions about the best diet for diabetes are still not clearly answered. The purpose of this study is to measure the glucose, insulin and lipid responses to a low fat, high carbohydrate diet compared to a high mono-unsaturated fat, low carbohydrate diet. In addition, the study will evaluate how each diet affects how much of the foods are eaten. We will also give nutrition questionnaires during each diet and also questionnaires which measure sense of well-being.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: HOE490 & T&E& COST OF AMARYL , METFORMIN IN DM TYPE II**

  Principal Investigator & Institution: Harrison, Robert; University of Rochester Orpa - Rc Box 270140 Rochester, Ny 14627

  Timing: Fiscal Year 2002

  Summary: This abstract is not available.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: HYPERINSULINEMIA AND THE PATHOGENESIS OF NASH**

  Principal Investigator & Institution: Neuschwander-Tetri, Brent A.; Internal Medicine; St. Louis University St. Louis, Mo 63110

  Timing: Fiscal Year 2002; Project Start 20-MAY-2002; Project End 30-APR-2007

  Summary: Non-alcoholic fatty liver disease (NAFL or NAFLD) and its subset, non-alcoholic steatohepatitis (NASH) are increasingly recognized as common forms of liver disease. In the absence of concomitant cellular injury, fatty liver is a benign condition that may cause elevated liver enzymes, fatigue and abdominal pain. MASH is identified by the presence of fat in the liver plus hepatocellular injury, inflammation and varying degrees of liver fibrosis. It afflicts up to 3% of adults n the United States and one third of these people may be at risk for developing cirrhosis. NASH also affects children, although its prevalence in the pediatric population is less well defined. Currently 2% of liver transplants performed in the United States are performed because of known diagnosis of NASH. Insulin resistance, with its major associated diseases of obesity and Type 2 diabetes, is emerging as a major coexisting condition. This application proposes two clinical studies to be performed in the context of a cooperative clinical research network to achieve the long-term goals of establishing the role of hyperinsulinemia in the pathogenesis of NASH and identifying rational and effect strategies to prevent and cure NASH. These goals will be addressed by specific aims of this proposal that seek to better understand the prevalence of NASH in hyperinsulinemic patients and establish whether reducing insulin levels pharmacologically improves the necroinflammatory changes associated with NASH. Two clinical studies are proposed. The first study establishes the prevalence of NASH in patients with hyprinsulinemia and imaging evidence of fatty liver. A secondary goal of the prevalence study is to establish racial differences in the risk for developing NASH because NASH may be underrepresented or underdiagnosed in African Americans. Enrollment will include adequate African Americans to allow subgroup analysis. The second proposed study is to a 48 week treatment trail of patients with NASH using the PPAR-gamma ligand rosiglitazone and, if needed to control hyperinsulinemia, **metformin.** Liver biopsies of patients recruited from all Clinical Centers will be compared to liver biopsies of patients treated with the standard recommendation of weight reduction. The primary endpoint will be improvement in the liver biopsy necroinflammatory score.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: INDUCTION OF OVULATION IN PCOS**

  Principal Investigator & Institution: Nestler, John E.; University of Virginia Charlottesville Box 400195 Charlottesville, Va 22904

  Timing: Fiscal Year 2003; Project Start 23-APR-2003; Project End 31-MAR-2008

  Summary: The polycystic ovary syndrome (PCOS) is the major cause of female factor infertility in the United States. This is in part related to chronic anovulation, and is likely further aggravated by other factors which produce an increased rate of early (i.e., first trimester) pregnancy loss (EPL). It is now recognized that insulin resistance is a prominent feature of PCOS and that it contributes to the anovulation of PCOS, as evidenced by a marked increase in frequency of ovulation with the administration of **metformin.** In PCOS **metformin** i) increases frequency of spontaneous ovulation, ii) increases success of induction of ovulation, and iii) increases rate of clinical pregnancy. Studies suggest that insulin resistance also contributes to infertility in PCOS by

producing an unfavorable endometrial milieu, and administration of **metformin** to women with PCOS throughout pregnancy is associated with a 79% reduction in the rate of EPL. The focus of this U54 Subproject is the role of insulin resistance in the infertility of PCOS. The present application proposes two clinical research studies. The first study is a collaborative trial the Reproductive Medicine Network to determine what represents the optimal pharmacologic intervention for initial induction of ovulation in PCOS: **metformin** monotherapy, clomiphene monotherapy, or simultaneous administration of both **metformin** and clomiphene. The second study explores the effects of **metformin** on the reproductive system of both healthy women and women with PCOS, assessing the effects of **metformin** on i) dynamics of pituitary gonadotropin secretion, ii) adequacy of luteal phase progesterone and other circulating sex steroids, and iii) anatomic endometrial maturation as well as endometrial expression of receptors for sex steroids and integrins. Obtaining this information is critical since physicians are increasingly administering **metformin** to women with PCOS to facilitate ovulation and pregnancy. In summary, the proposed studies will provide both important translational and mechanistic information. They promise to enhance our understanding of the relationship of insulin resistance to the infertility of PCOS, and to provide useful information that can be directly translated into the clinical care of women with PCOS.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: INHALED HUMAN INSULIN AS ADJUNCTIVE THERAPY IN SUBJECTS WITH TYPE 2 DIABETES**

  Principal Investigator & Institution: Werbel, Sandra S.; Wake Forest University 2240 Reynolda Rd Winston-Salem, Nc 27106

  Timing: Fiscal Year 2002

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: INHALED HUMAN INSULIN IN TYPE 2 DM ON SULFONYLUREA AND/OR METFORMIN**

  Principal Investigator & Institution: Feinglos, Mark N.; Duke University Durham, Nc 27706

  Timing: Fiscal Year 2001

  Summary: PURPOSE: The purpose of this study is to determine, in subjects with type 2 diabetes mellitus currently receiving a sulfonylurea and /or **metformin** as therapy (1) whether glycemic control can be improved, as measured by a decrease of at least 1% in the glycosylated hemoglobin, by the addition of a regimen of pre-meal inhaled insulin and (2) the toleration and safety of inhaled insulin therapy and its effects after 3 months, if any, on measures of pulmonary function. METHODS: In total, 60 subjects will participate in this trial, with approximately 6 being evaluated at this site. During this three-month comparative trial, half of the subjects will be randomized to receive an inhaled insulin regimen plus pre-study oral agent while the other half will continue pre-study oral agent. Patients who successfully complete this three-month trial will be eligible for a one-year, open-label protocol extension. Prior to study entry, subjects undergo a screening session, including a history and physical exam, EKG, CXR, and lab studies to verify that the patient is eligible for participation. This is followed by a 4 week baseline lead-in period, during which patients continue their pre-study oral agent. Subjects undergo pulmonary function tests (PFTs), dietary instruction, and home blood glucose monitoring instruction during this time. All patients are provided with a

glucose meter and supplies and are required to perform blood glucose checks 4 times/day, to record doses and meter readings, and to document any hypoglycemic or adverse events which occur. At the end of the baseline period, subjects are admitted for a 2 day inpatient session, during which they are instructed in the use of the device and dosing with inhaled insulin. At the end of the admission, subjects are randomized to one of two treatment groups (premeal inhaled insulin plus oral hypoglycemic agent vs premeal inhaled placebo plus oral agent). Randomization is double-blinded and is stratified based on HbA1c. During the treatment period, patients are followed at weekly intervals. For the first 4 weeks of treatment, patients must return to the clinic for evaluation every week. After that, patients may return once every other week. Meal challenge studies will be performed at weeks 0,4,8, and 12, during which a patient will be asked to consume 16 oz of Sustacal beverage and timed blood draws measuring blood glucose and free insulin levels will be collected. Also at clinic visits, blood samples will be collected to evaluate HbA1c, fasting blood glucose, fructosamine, and lipids. Spirometry will be performed at week 6, and a full PFT battery will be repeated at week 12. In the optional one year extension, patients are required to return for monthly clinic visits. PFT's will be performed every 3 months. RESULTS AND CONCLUSIONS: The study is ongoing, and results are not available to date. SIGNIFICANCE: The Diabetes Control and Complications Trial (DCCT) demonstrated the long-term benefits of tight glycemic control. However, the clinical realization of the benefits of aggressive insulin therapy has been limited by the shortcomings of available SC delivery methods. In particular, multiple injection therapy has had poor patient acceptance. This study aims to determine whether the addition of a pre-meal inhaled insulin regimen can provide improved glycemic control to patients poorly controlled on oral agents. This system is designed to permit safe, non-invasive delivery of rapid-acting insulin in 1-2 inhalations per dose. If proven to be safe and effective, inhaled insulin, which is easy to administer and provides a predictable pattern of insulin action, may be more acceptable to patients requiring insulin therapy and may provide better overall glycemic control thereby possibly reducing the incidence of diabetic complications. Plans for phase III studies of inhaled insulin are currently underway by the study sponsor, Pfizer, Inc.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: INSULIN REDUCTION AND OVULATION IN WOMEN WITH PCOS**

  Principal Investigator & Institution: Evans, William S.; University of Virginia Charlottesville Box 400195 Charlottesville, Va 22904

  Timing: Fiscal Year 2001

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: INSULIN RESISTANCE IN THE HIV LIPODYSTROPHY SYNDROME**

  Principal Investigator & Institution: Hadigan, Colleen M.; Assistant Professor; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114

  Timing: Fiscal Year 2001; Project Start 01-JUL-2000; Project End 30-JUN-2005

  Summary: (Applicant's abstract) The lipodystrophy syndrome is a newly recognized complication of HIV disease, which affects up to half of all HIV-infected patients on potent antiretroviral therapy, and for which there is no effective therapy. The syndrome is characterized primarily by fat redistribution, including truncal obesity, as well as peripheral fat loss. Although the mechanism of the syndrome is unknown, and may relate in part to protease inhibitor therapy, preliminary data suggest that the syndrome

is characterized by fasting hyperinsulinemia. However, detailed evaluation of insulin dynamics in affected patients has not previously been performed, and it is unknown whether the syndrome is characterized by insulin resistance per se. If insulin resistance is shown, it is not known whether the defect is central, due to central hepatic insulin resistance and excessive glucose production or peripheral, related to diminished glucose utilization. This determination is critical for the establishment of appropriate therapy for insulin resistance in this population. One hypothesis in this proposal is that significant insulin resistance exists in the HIV-lipodystrophy syndrome and is closely associated with visceral abdominal fat and increased fatty acid production in such patients. Furthermore, truncal adiposity and increased free fatty acid (FFA) production is hypothesized to result in primarily hepatic insulin resistance, compared to peripheral resistance. To investigate these hypotheses, insulin dynamics and visceral adiposity will be compared in both HIV-infected patients with and without lipodystrophy and healthy controls. Acute intervention with acipimox will be investigated to determine the role of FFA in the insulin resistance, and euglycemic clamp will be used to differentiate between hepatic and peripheral insulin resistance in patients with HIV lipodystrophy. Furthermore, insulin dynamics, body composition and sex steroid levels will be compared in men and women to determine gender differences in this syndrome. The second aim of this proposal will be to investigate whether the use of an insulin sensitizing agent, **metformin,** will effectively reduce insulin resistance in HIV-infected patients with the lipodystrophy syndrome. The potential benefits of **metformin** therapy in the HIV lipodystrophy syndrome are two-fold and include reduction in long-term cardiovascular complications and reversal in the changes in body fat distribution in the HIV lipodystrophy syndrome. In summary, this proposal will investigate the potential pathophysiologic mechanisms of insulin resistance in the HIV lipodystrophy syndrome and will evaluate a novel therapeutic strategy to reverse insulin resistance in patients affected by this syndrome. As HIV patients are living longer, development of successful therapies to prevent potential long-term morbidity associated with insulin resistance is critical for the emerging population of chronically infected, but immunologically stable, population of patients.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: INSULIN RESISTANCE/SEX HORMONE BINDING GLOBULIN IN PCS**

  Principal Investigator & Institution: Santoro, Nanette F.; Professor; Yeshiva University 500 W 185Th St New York, Ny 10033

  Timing: Fiscal Year 2001

  Summary: There is no text on file for this abstract.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: LINKING GENOMICS TO FUNCTION VIA METABOLIC PHENOTYPING**

  Principal Investigator & Institution: Stephanopoulos, Gregory N.; Bayer Professor of Chemical Engineering; Chemical Engineering; Massachusetts Institute of Technology Cambridge, Ma 02139

  Timing: Fiscal Year 2001; Project Start 30-SEP-2000; Project End 31-AUG-2003

  Summary: Recombinant strains with well defined genetic backgrounds are often found to exhibit small functional differences despite specific changes at the genetic level while in other cases, single gene alterations result in profound phenotypic variations.

Although a first step in explaining such macroscopic differences is to probe the full detail of the expression phenotype by genome-wide expression measurements, transcription data alone are insufficient to elucidate the actual metabolic state of a cell and its functions. The latter require information about intracellular metabolic fluxes, which constitute fundamental determinants of cell physiology and excellent metrics of cell function. "Metabolic phenotyping" is the process and methods of determining intracellular fluxes as determinants of the cellular metabolic state. Combined with transcription data, the investigators provide a complete framework for analyzing the effect of drugs and studying disease. This application integrates the expertise of three participating laboratories for the purpose of combining metabolic and expression phenotyping to elucidate central carbon and lipid metabolism in model mouse hepatoma and hepatocyte cultures. Determination of intracellular fluxes will follow a systems approach termed metabolic reconstruction whereby the entire metabolic network is configured such as to best represent macroscopic rate and isotopic label distribution measurements made by GC-MS. Of particular attention are issues of observability, redundancy, and solution stability to ensure method feasibility and accuracy of the results. Differential transcription data will be obtained by DNA microarrays for mouse genes involved in central carbon metabolic, gluconeogenic and lipid biosynthetic pathways, as well as for other genes with particular expression variability that will be identified in the course of the research. Bioinformatics methods and programs, developed over the past 12 years will be deployed for this purpose. The general goal of the research is to identify relationships between the metabolic phenotype as defined above and the transcriptional state as defined by expression data of consequence in pathways important to diabetes. Specific aims will focus on flux quantification in mouse hepatoma and hepatocyte cultures to elucidate glutamine metabolism and lipogenesis, other central metabolic pathways and cholesterol synthesis, the effect of nutrients, hormones and drugs like **Metformin** and finally, pleiotrophic effects generated by altering the normal expression of a single gene, such as over-expressing the truncated verion of sterol-regulatory element binding protein-1a in transgenic mice. The broader contribution of this research is to extend the paradigm of holistic transcriptional investigation introduced by DNA microarray technologies to the study of metabolic level processes by metabolic phenotyping. As such, it holds the promise of identifying most, if not all points in metabolism affected by the action of drugs or genetic modifications thus guiding future programs of drug development and gene therapy.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: LONG TERM DPP FOLLOW-UP STUDY**

  Principal Investigator & Institution: Ratner, Robert E.; Vice-President; Medstar Research Institute Hyattsville, Md 20783

  Timing: Fiscal Year 2003; Project Start 20-AUG-1994; Project End 31-JAN-2008

  Summary: (provided by applicant): The Diabetes Prevention Program is a multicenter controlled clinical trial examining the efficacy of an intensive life-style intervention or **metformin** to prevent or delay the development of diabetes in a population selected to be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 ADA criteria, is the primary outcome while cardiovascular disease and its risk factors are important secondary outcomes. The DPP began recruitment in mid-1996. At the time of this application, total study exposure is a mean of approximately 3 years (range 2 to 5) with a total of approximately 10,000 patient years in the 3,234 volunteers in the 3-arm study. On the basis of a statistically significant and

clinically compelling decrease in the development of diabetes in the life-style intervention and metformin-treated groups (58% and 31% reductions, respectively) compared with the placebo treated group, the DPP Data Monitoring Board and NIDDK ended the masked treatment phase of the study in May, 2001, one year earlier than originally planned. This application is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of data collected during the study. The highly compliant DPP cohort, including 45% minorities, is the largest IGT population ever studied. Moreover, the subcohort that has developed diabetes (n approximately 700) has been followed from near the exact time of diabetes onset. Clinically important research questions remain in the wake of the DPP. The carefully collected, centrally measured and graded data in this cohort should help to answer, definitively, a number of important questions regarding the clinical course of IGT and early onset type 2 diabetes. Specific aims include: 1. Examine the long-term effects and durability of prior DPP intervention on the major DPP outcomes including diabetes, clinical cardiovascular disease, atherosclerosis, CVD risk factors, quality of life and cost-benefit; 2. Determine the clinical course of new onset type 2 diabetes and IGT, in particular regarding microvascular and neurologic complications; 3. Determine the incidence of cardiovascular disease (CVD), CVD risk factors and atherosclerosis in new onset type 2 diabetes and IGT; and 4. Examine topics 1-3 in minority populations, men vs. women, and in older subjects in the DPP. The current application is for 5 years of funding, although the some of the goals of the projects described will require a 10-year study.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: MANAGEMENT OF PEDIATRIC TYPE 2 DIABETES MELLITUS**

  Principal Investigator & Institution: Stanley, Charles A.; Chief; Children's Hospital of Philadelphia 34Th St and Civic Ctr Blvd Philadelphia, Pa 19104

  Timing: Fiscal Year 2001; Project Start 30-SEP-2001; Project End 28-FEB-2009

  Summary: (provided by applicant): Recently, an increasing number of cases of type 2 diabetes (T2DM) in children have become evident, a phenomenon which is thought to be related to widespread obesity, decreased physical activity, and other factors. The rising rates of diabetes among children represent a disturbing trend with significant implications for future health care costs to society. Currently, there are no widely accepted clinical recommendations for screening or managing this condition in the pediatric population. A program is being established by the NIH to address this emerging health problem by implementing an intervention trial to identify appropriate treatment of childhood T2DM. The Children?s Hospital of Philadelphia (CHOP) proposes to be a clinical site. Philadelphia is representative of urban America and has a large proportion of African-American and Hispanic high-risk minorities. The Diabetes Care Center (DCC) at CHOP currently follows over 1100 children with diabetes and diagnoses 30 new cases per year of T2DM. Given that the majority of children with T2DM suffer from obesity, with resultant insulin resistance, we hypothesize that improvement of peripheral insulin sensitivity will be the most effective treatment, both for glucose control and for the preservation of insulin secretion. The aims of this proposal are: 1) To evaluate glucose control of pediatric Type 2 diabetes patients on monotherapy with either a thiazolidinedione, a biguanide, or a sulfonylurea in a prospective double blind randomized trial. 2) To evaluate secondary outcome measures including insulin secretory function, insulin sensitivity glucose tolerance and body composition over time, in relation to treatment interventions, glucose control, and psychosocial functioning. 3) To evaluate glucose control on combination therapy with 2

oral agents in pediatric subjects with T2DM who have demonstrated inadequate glucose control (hemoglobin A1c>6.5) after 6 months on a single oral agent; 4) To establish and sustain a local network of partnerships with health care providers, health care systems, and community agencies in Philadelphia to support effective implementation of lifestyle changes critical to the management of childhood T2DM. and finally 5) To evaluates the impact of the local network on lifestyle modification on specific patient?s outcomes over time such as weight and BMI, psychological function, diet, and physical fitness. Aim 1 is completed after 6 months of the monotherapy. Subsequently, the patients are followed for 5 years. To achieve these aims, CHOP will build upon its existing resources within the DCC, the Nutrition Section, and Department of Psychiatry. New and existing partnerships will be forged and reinforced with members of the Philadelphia community to implement lifestyle changes.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: MECHANISMS AND STRATEGIES FOR INSULIN RESISTANCE IN AIDS**

  Principal Investigator & Institution: Grinspoon, Steven K.; Associate Professor of Medicine; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114

  Timing: Fiscal Year 2001; Project Start 15-SEP-2000; Project End 31-AUG-2005

  Summary: (Adapted from the applicant's abstract) The lipodystrophy syndrome is a newly recognized syndrome among HIV-infected men and women. The investigator has shown in a recent collaboration with the Framingham Heart Study that patients with lipodystrophy demonstrate a significant insulin resistance syndrome , characterized by hyperinsulinemia, dyslipidemia and increased diastolic blood pressure. Insulin resistance associated with the HIV lipodystrophy syndrome poses a considerable risk for long-term increased cardiovascular disease, but little is known of its mechanism nor has treatment been established. Fat redistribution is strikingly abnormal in affected female patients, but the gender-specific cardiovascular consequences of the insulin resistant phenotype are not known. In this grant proposal this project will determine the gender-specific characteristics of the insulin resistant phenotype in HIV-infected men and women. The investigator will test the hypothesis that truncal fat gain and subcutaneous fat loss contribute independently to the insulin resistant phenotype, and furthermore, that hyperinsulinemia impairs fibrinolysis and disrupts endothelial function leading to increased carotid intimal medial thickness and stenosis. The investigator will test the hypothesis that increased circulating free fatty acids (FFA) resulting from fat redistribution contribute to insulin resistance and increased endogenous hepatic glucose production. Simultaneously, a novel approach to the treatment of insulin resistance in patients with the lipodystrophy syndrome, in which there was shown an effect of **metformin** to lower insulin levels in preliminary studies. In the final aim of the proposal, the project will investigate in vitro, the independent and combined effects of PI's and nucleoside analogues on human subcutaneous and visceral adipocytes. These studies will allow us to determine for the first time the depot-specific mechanisms by which these agents may lead to subcutaneous fat loss and visceral fat gain and thereby promote insulin resistance. This project will study the effects of these agent on adipogensis, differentiation, insulin sensitivity and expression of PPAR and other adipocyte regulatory genes using thiazolidinediones to determine whether PPAR gamma activation can rescue the differentiated phenotype. The novel studies in this grant proposal will provide important new information on mechanisms, cardiovascular effects and optimal treatments for insulin resistance in the HIV-lipodystrophy syndrome. The proposed studies represent a significant collaborative effort between

clinical researchers, adipocyte biologists, epidemiologists and nutritional biochemists in satisfaction of the mandate of the RFA.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: MECHANISMS FOR ALTERED GLUCOSE HOMEOSTASIS DURING HAART**

  Principal Investigator & Institution: Hruz, Paul W.; Pediatrics; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2003; Project Start 01-APR-2003; Project End 31-JAN-2007

  Summary: (provided by applicant): The long-term objective of this project is to understand the molecular mechanisms responsible for altered glucose homeostasis during highly active antiretroviral therapy. The studies in this proposal are intended to identify the cellular targets of HIV protease inhibitors that lead to impaired beta-cell function and alterations in hepatic glucose production and to elucidate the molecular mechanism of this inhibition. We hypothesize that the peptide structure within all currently available HIV protease inhibitors is responsible for acute and reversible inhibition of the insulin-responsive glucose transporter GLUT4 and the liver/pancreas transporter GLUT2. To test this hypothesis, the acute effects of HIV protease inhibitors on the glucose-stimulated insulin secretory pathway in freshly isolated rodent and human islets as well as cultured MIN6 cells will be determined. Euglycemic hyperinsulinemic clamp experiments will also be performed in rats to determine the acute effects of HIV protease inhibitors on hepatic glucose production. The ability of the biguanide **metformin** to prevent protease inhibitor mediated inhibition of GLUT4 activity will be tested in Xenopus oocytes heterologously expressing this transporter isoform. Finally, the structural determinants involved in PI-induced GLUT4 inhibition will be determined by testing a family of synthetic aromatic peptides for their ability to inhibit 2-deoxyglucose uptake in GLUT4 expressing oocytes. Taken together, these studies will provide new insights into the molecular mechanism(s) leading to insulin resistance in patients treated with HIV protease inhibitors. This may facilitate the design of newer HIV protease inhibitors that maintain their clinical efficacy while avoiding their adverse effects on glucose homeostasis and will assist efforts to develop more effective treatment strategies.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: MECHANISMS OF ACTION IN DPP INTERVENTIONS**

  Principal Investigator & Institution: Kitabchi, Abbas E.; Professor; Medicine; University of Tennessee Health Sci Ctr Memphis, Tn 38163

  Timing: Fiscal Year 2001; Project Start 05-AUG-1998; Project End 30-JUN-2004

  Summary: (adapted from the application) The Diabetes Prevention Program (DPP) is an NIH-sponsored multicenter study with the specific objective of comparing, in high risk individuals, the efficacy of three intervention methods (intensive behavior modification, **metformin,** and troglitazone) vs control placebo group in preventing or delaying conversion of impaired glucose tolerance (IGT) to non-insulin dependent diabetes mellitus (NIDDM). A total of 4000 subjects (from 26 clinical centers) of whom 50% will consist of minority groups, will be randomly assigned to one of the four groups. Since the DPP is not designed to study the mechanism of action of these interventions, the present proposal is an ancillary study to the DPP to investigate the mechanisms by which the three interventions affect glucose intolerance and insulin resistance. Other rationales for the proposed study are that: (a) hyperandrogenism and decreased sex

hormone binding globulin (SHBG) are known to be additional risk factors for development of NIDDM in certain female populations, (b) hyperandrogenism of gonadal origin [i.e. testosterone(T), and androstenedione(A)] is believed to be more deleterious to glucose tolerance and insulin sensitivity than adrenal androgens [i.e. DHEA(D) DHEAS(DS)] and c) recent preliminary studies suggest that **metformin,** troglitazone and exercise plus dietary modification alter androgenic profiles and improve glucose intolerance, possibly by three different mechanisms. Therefore, the DPP offers a unique opportunity to study the mechanism of action of these three interventions. We hypothesize that those modalities which most improve glucose intolerance and insulin resistance will be associated with more favorable androgenic profiles (i.e. lower T/D ratio) and CV risk factors. The specific aim of this ancillary study is to recruit 200 pre- and perimenospausal women from eight of the DPP centers (equally distributed among the four treatment groups) and among three ethnic groups (Caucasians, Hispanics and African-Americans) to: (a) assess insulin secretion by OGTT, (b) measure androgenic profiles, (c) measure body fat distribution by CT Scan, and lean body mass (LBM) and fat content by DEXA and (d) study glucose and insulin metabolism and clearance, and insulin sensitivity by the use of modified frequently sampled iv glucose tolerance test (FSIGT). These studies will be done at baseline, and at the end of the 1st and 3rd year of intervention. The proposed ancillary study should, therefore, enable us to assess the correlation between glucose intolerance, insulin resistance, and androgenic profile, as well as the effect of various treatment modalities on them and the mechanism of action, in a setting of multiethnic diabetes prevention program.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: MECHANISMS OF INSULIN/LH SYNERGY IN THECAL CELLS**

  Principal Investigator & Institution: Veldhuis, Johannes D.; University of Virginia Charlottesville Box 400195 Charlottesville, Va 22904

  Timing: Fiscal Year 2001

  Summary: The polycystic ovarian syndrome (PCOS) represents the most common reproductive pathophysiology in pre-menopausal women. Hallmarks of PCOS are increased LH secretion, altered insulin action, and augment ovarian androgen biosynthesis. Overall working hypothesis is that LH and insulin synergize at the level of the ovarian theca cell to drive excessive androgen secretion. Although LH and insulin (or IGF-1) can synergistically amplify ovarian androgen biosynthesis in vivo and by human, hen, rat and pig theca cells in vitro (present data), how LH and insulin collaborate in this fashion is not known. This project will investigate the clinical and molecular mechanisms of lH and insulin synergy in PCOS patients in vivo and on (pig) theca cells in vitro. Our individual aims arise from the following specific hypotheses: I. Preferential suppression of hyperinsulinism (via **metformin** treatment) of LH hypersecretion (via leuprolide down-regulation) alters the testosterone secretory response to human recombinant LH infusions in PCOS patients; II. In vitro, in pig theca-cell populations, LH and insulin synergistically up-regulate the molecular expression of critical genes that control sterol commitment to androgen biosynthesis; namely, the low-density lipoprotein (LDL) receptor, the steroidogenic acute responsive protein (StAR), and the 17-alpha hydroxylase enzyme; III. In situ, at the single-theca-cell level, LH and insulin synergize by coordinately enhancing multiple sterol-regulatory gene co-expression in individual theca cells; and IV. There are pivotal cis-DNA promoter elements in the StAR and LDL receptor genes that mediate responses to the intracellular signals generated by insulin and LH, acting singly and synergistically. The preceding

clinical and basic-science hypotheses and corresponding experiments should help identify novel clinical and molecular mechanisms that govern theca-cell androgen biosynthesis, and thereby offer new insights into the basic pathobiology of PCOS.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: METABOLIC ADAPTIONS TO DIABETES**

  Principal Investigator & Institution: Carlson, Michael G.; Assistant Professor of Medicine; Vanderbilt University 3319 West End Ave. Nashville, Tn 372036917

  Timing: Fiscal Year 2001

  Summary: Intensive insulin treatment in individuals w/IDDM attenuates the neuroendocrine and lipolytic responses to acute exercise. Rigorous metabolic control significantly enhances exercise capacity and the cardiovascular and metabolic adaptations to endurance training in IDDM, compared to the blunted training response seen in conventionally treated IDDM. Intensive pharmacologic treatment w/sulfonylureas, but not w/metformin, blunts the neuroendocrine and lipolytic responses to acute exercise in NIDDM and contributes to the increased risk of exercise-induced hypoglycemia in sulfonylurea-treated NIDDM patients. Sulfonylureas and **metformin** exert differential effects on the energy cost of physical activity and/or fuel utilization patterns during exercise in intensively treated NIDDM patients. Compared w/metformin treatment, intensive treatment w/sulfonylureas reduces energy expenditure and/or decreases fat utilization during equivalent physical activity, contributing to the propensity for weight gain and increased adiposity in sulfonylurea-treated NIDDM patients.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: METABOLIC REGULATION OF GENE EXPRESSION BY AMP-KINASE**

  Principal Investigator & Institution: Leff, Todd A.; Pathology; Wayne State University 656 W. Kirby Detroit, Mi 48202

  Timing: Fiscal Year 2003; Project Start 01-JUN-2003; Project End 31-MAY-2006

  Summary: (provided by applicant): AMP activated protein kinase (AMPK) is the central component of a signaling system that functions to maintain cellular energy balance in response to stresses that deplete intracellular ATP. It is often referred to as a "metabolic master switch" because of the central role that it plays in the maintenance of metabolic homeostasis. AMPK activity has a strong influence on the regulation of whole body glucose metabolism and it may also play a role in the development of type-2 diabetes. It has recently been reported that some of the antidiabetic activities of the drug **metformin** and the hormone adiponectin may be mediated by activation of AMPK in the liver, suggesting a potential link between AMPK and hepatic glucose metabolism. We have recently demonstrated that the transcription factor HNF4alpha, a well-characterized regulator of metabolic gene expression in the liver, is inhibited by AMPK mediated phosphorylation on serine-304. HNF4alpha is known to play an important role in the expression of liver genes involved in regulating hepatic glucose production, a key contributor to normal and diabetic whole body glucose homeostasis. The central hypothesis of the work proposed here is that an AMPK-HNF4alpha signaling pathway in the liver mediates important metabolic effects of AMPK. The overall goals of this proposal are to characterize the molecular details of this proposed AMPK-HNF4alpha signaling pathway and to determine the extent to which it influences gene expression and metabolism in normal and diabetic liver. In addition, the possibility that AMPK

mediated phosphorylation of HNF4alpha contributes to the hepatic effects of **metformin** and adiponectin will be explored. Results from these studies will provide a clearer understanding of the functional relationship between HNF4alpha and AMPK and a more complete picture of the physiological role that these two important proteins play in the liver.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: METABOLIC STRESS, AMPK AND THE ENDOTHELIUM IN DIABETES**

  Principal Investigator & Institution: Ruderman, Neil B.; Professor and Unit Director; Boston Medical Center Gambro Bldg, 2Nd Fl, 660 Harrison Ave, Ste a Boston, Ma 02118

  Timing: Fiscal Year 2003; Project Start 01-MAY-2003; Project End 30-APR-2008

  Summary: Endothelial cell damage and dysfunction are early events in the pathogenesis of atherosclerosis. Although they both have been observed in patients with diabetes, the mechanisms responsible for their occurrence is unclear. This project examines the hypothesis that an imbalance between intracellular fatty acid availability and oxidation induced by hyperglycemia, elevated plasma free fatty acids (FFA) and the two in combination is a key pathogenetic event. In support of this notion, we have shown that hyperglycemia (30mM glucose)-induced apoptosis in human umbilical vein endothelial cells (HUVEC) is preceded by inhibition of fatty acid oxidation, an increase in the synthesis of diacylglycerol, and an impaired ability of insulin to activate Akt. We have also found that all of these changes are prevented by adding to the incubation medium, AICAR, an activator of AMP-activated protein kinase. Furthermore, incubation with the fatty acid palmitate (0.5mM) in a normoglycemic medium also caused apoptosis, and this too was prevented by AICAR. To assess our basic hypothesis, studies will be carried out in HUVEC and/or human aortic endothelial cells with the following aims: (1) To characterize glucose and fatty acid metabolism in endothelium and determine how they are altered when AMPK is activated by **metformin,** AICAR or infection with a constitutively active AMPK linked to adenovirus; (2) To determine whether sustained hyperglycemia causes endothelial cell damage (apoptosis) and impairs insulin signaling by altering DAG-PKC signaling, ceramide synthesis and/or oxidative stress; (3) To prove that AMPK activation is responsible for the protective effect of AICAR and to determine how it works; and (4) To evaluate whether excess FFA (palmitate) causes cell damage by a similar mechanism and if its effects are additive to those of hyperglycemia. These studies will provide novel information as to how the metabolic stresses associated with diabetes cause damage to the endothelium. They should also yield insights into how the endothelial cell attempts to protect itself against these stresses and whether AMPK is a potential target for therapy.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: METFORMIN & INSULIN FOR TREATMENT OF ADOLESCENT NIDDM**

  Principal Investigator & Institution: Dahms, William T.; Professor; Case Western Reserve University 10900 Euclid Ave Cleveland, Oh 44106

  Timing: Fiscal Year 2001

  Summary: Clinicians and researchers now agree that type 2 diabetes is a condition that can affect the pediatric population. The incidence of type 2 diabetes in children has increased dramatically over the past ten years, especially in African American, American Indian, and Hispanic populations. This increased incidence has been linked to

the increasing prevalence of childhood obesity and sedentary lifestyle. Type 2 diabetes in children represents an emerging epidemic in which African American, American Indian, and Hispanic children are disproportionately represented. There is a need for controlled clinical studies to evaluate the safety and utility of **metformin** in children with type 2 diabetes since the standard of care for children with all types of diabetes has previously been considered to be insulin as the sole FDA approved agent. This study will serve to assess **metformin** plus insulin in comparison to insulin monotherapy for the care of children with type 2 diabetes of moderate severity. It will also serve to show the safety of adding **metformin** to insulin in adolescents with type 2 diabetes. In addition, this study will provide pharacokinetic data for **metformin** therapy in adolescents.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: METFORMIN AND GLYBURIDE COMBINATION PRODUCTS IN DIABETES PATIENTS**

  Principal Investigator & Institution: Mcgill, Janet; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2001

  Summary: There is no text on file for this abstract.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: METFORMIN AND METABOLISM/BODY COMPOSITION IN HIV/AIDS**

  Principal Investigator & Institution: Hellerstein, Marc H.; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 94122

  Timing: Fiscal Year 2001

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: METFORMIN AND PRAVACHOL IN TREATMENT OF DIABETIC DISLIPIDEMIA**

  Principal Investigator & Institution: Crouse, John; Wake Forest University 2240 Reynolda Rd Winston-Salem, Nc 27106

  Timing: Fiscal Year 2002

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: METFORMIN EFFECTS ON LEPTIN LEVELS AND BODY COMPOSITION IN OBESE CHILDREN**

  Principal Investigator & Institution: Rogol, Alan D.; University of Virginia Charlottesville Box 400195 Charlottesville, Va 22904

  Timing: Fiscal Year 2001

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: METFORMIN HYDROCHLORIDE FOR TREATMENT OF ADOLESCENTS WITH TYPE 2 DIABETES**

  Principal Investigator & Institution: Tamborlane, William V.; Professor of Pediatrics; Yale University 47 College Street, Suite 203 New Haven, Ct 065208047

  Timing: Fiscal Year 2001

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: METFORMIN HYDROCHLORIDE IN LIPODYSTROPHY IN HIV POSITIVE PATIENTS**

  Principal Investigator & Institution: Shevitz, Abby H.; New England Medical Center Hospitals 750 Washington St Boston, Ma 021111533

  Timing: Fiscal Year 2001

  Summary: An emerging syndrome of fat redistribution called lipodystrophy (LD) which consists, in part, of abdominal obesity is being reported with increasing frequency in persons with HIV infection. Although it is usually noted in association with the class of antiretroviral drugs, protease inhibitors, the cause and mechanism of this syndrome are unclear. Subclinical insulin resistance also occurs frequently with the protease inhibitors, and has been found relatively soon after these medications are begun. Therefore, insulin resistance may be causing or contributing to the development of LD. Because protease inhibitores should usually not be discontinued in the presence of virologic success, and because chronic consequences of abdominal obesity are well-established, other treatment for LD is needed. This is a 6-month placebo-controlled randomized clinical trial of **metformin** hydrochloride, an oral diabetic medication, 1.5 grams daily, for HIV-associated LD. All participants will also receive individual nutritional counseling to reduce the glycemic index of their diets. The primarily endpoint is the reduction of abdominal adiposity measured by CT scan; secondary endpoints include improvements in serum triglycerides and HDL cholesterol levels.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: METFORMIN IN OBESE ADOLESCENTS PREDISPOSED TO TYPE II DIABETES**

  Principal Investigator & Institution: Freemark, Michael S.; Duke University Durham, Nc 27706

  Timing: Fiscal Year 2001

  Summary: Obese adolescents with insulin resistance are predisposed to the development of Type II diabetes mellitus in adulthood. This study examines the effects of **Metformin** on insulin sensitivity in obese adolescents with elevated fasting insulin levels and first degree relatives with Type II diabetes. The trial is double-blind and placebo controlled. In the study, obese adolescents undergo a rapid intravenous glucose tolerance test, permitting baseline assessment of insulin sensitivity using the Bergman minimal model. Patients are then assigned to drug or placebo groups for a total of six months, with monitoring of fasting plasma glucose, insulin, glycosylated hemoglobin, plasma lipids and weight, blood pressure and total body fat. Insulin sensitivity is assessed at the end of the trial by repeating the intravenous glucose tolerance test. Enrollment of patients and all testing have now been completed. We are currently in the initial phases on analyzing the data. The results of these studies may provide a new approach to the prevention of diabetes mellitus in patients predisposed to the disease.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: METFORMIN IN TREATMENT OF ADOLESCENTS WITH NIDDM**

  Principal Investigator & Institution: Jones, Kenneth L.; Professsor of Pediatrics; University of California San Diego 9500 Gilman Dr, Dept. 0934 La Jolla, Ca 92093

  Timing: Fiscal Year 2001

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: METFORMIN TITRATION BEFORE METFORMIN THERAPY IN NIDDM**

  Principal Investigator & Institution: Connor, James D.; Professor; University of California San Diego 9500 Gilman Dr, Dept. 0934 La Jolla, Ca 92093

  Timing: Fiscal Year 2001

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: METFORMIN/GLYBURIDE AS 1ST LINE THERAPY IN TYPE 2 DIABETES**

  Principal Investigator & Institution: Buse, John B.; Associate Professor; University of North Carolina Chapel Hill Office of Sponsored Research Chapel Hill, Nc 27599

  Timing: Fiscal Year 2001

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: MULTI-CENTER STUDY OF THE TREATMENT OF T2DM IN YOUTH**

  Principal Investigator & Institution: Caprio, Sonia; Associate Professor of Endocrinology And; Pediatrics; Yale University 47 College Street, Suite 203 New Haven, Ct 065208047

  Timing: Fiscal Year 2001; Project Start 30-SEP-2001; Project End 28-FEB-2009

  Summary: (provided by applicant): The rising prevalence of type 2 diabetes mellitus (T2DM) in obese children, particularly in minority ethnic groups, is an enormous public health problem. The early age of onset of T2DM in youth may particularly increase the risk of devastating complications which are known to be directly related to the degree and duration of hyperglycemia. There is strong evidence from studies in adults (UKPDS) that normalization of glucose greatly decreases the frequency of microvascular complications of T2DM. It is, therefore, imperative to aggressively treat T2DM in order to reach long-term glycemic control in youths. The UKPDS also showed that life style intervention or monotherapy with insulin or **metformin** alone is usually insufficient to maintain long-term diabetes control. We, hereby, propose to test the hypothesis that the combined use of therapeutic agents that reverses or improves insulin resistance and restores first phase insulin secretion VS monotherapy with **metformin** alone will serve to preserve B-cell function in youth with new onset T2DM and increase the likelihood of achieving and maintaining strict metabolic control of diabetes. We seek to serve for a clinical site for a multi center trial site for the treatment of T2DM in children and adolescents of different ethnic groups. At randomization patients will be allocated to 4 treatment strategies: 1) **metformin** alone; 2) **metformin** plus inhaled insulin; 3) **metformin** plus nateglinide and 4) piozlitazone plus **metformin.** The primary efficacy

aim is: To examine and compare the effects of the treatments on overall diabetes control, as assessed by sequential HbA1c level less than or equal to 7.0 percent. Furthermore, to determine differences in the ability of treatments regimens to achieve and maintain target HbA1c levels less than or equal to 7 percent. Secondary efficacy aims: To examine and compare the effects of the treatment on macrovascular risk factors (lipid profiles, post-prandial hyperglycemia etc.); preservation of B-cell function as assessed by the C-peptide stimulation test; development and progression of microvascular complications and psychosocial well being. Safety aims are hypoglycemia; accelerated weight gain and known potential adverse effects of pharmacological agents. To accomplish these goals and to best perform as a clinical site in the multi center treatment trial of T2DM in youth, we have brought together a team of researchers with expertise in childhood obesity, T1 and T2DM in youth, pharmacological studies in children (Pediatric Pharmacology Research Unit, PPRU) and community based interventions.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: NEUROENDOCRINE REGULATION OF OVULATION--STUDIES IN PCOS**

  Principal Investigator & Institution: Marshall, John C.; Arthur and Margaret Ebbert; University of Virginia Charlottesville Box 400195 Charlottesville, Va 22904

  Timing: Fiscal Year 2001

  Summary: This proposal will explore the concept that the ability to change the frequency of GnRH secretion is critical for the maintenance of regular cyclic ovulation in women. Different patterns (frequency and amplitude) of GnRH stimuli differentially regulate synthesis and secretion of pituitary LH and FSH in rats. Thus GnRH secretory patterns may exert similar actions in women, in part effecting the cycle of predominant FSH followed by LH secretion leading to ovulation. Studies will examine regulation of GnRH secretion in normal women and polycystic ovarian syndrome (PCOS)-proposed to be a disorder of GnRH secretion. We hypothesize that: -a GnRH pulse frequency of approximately 1/h is the basal frequency in postpubertal women in the absence of ovarian regulation; the regulatory event needed to maintain ovulatory cycles may be suppression of this rapid frequency by the combined effects of luteal E/2 and P, P playing the predominant role. In normal women we will assess if follicular E2 is required to regain a GnRH frequency of 1/h after slowing is initially attained by E/2 and P administration. PCOS may in part reflect the effects of unremitting rapid (1/h) GnRH secretion, due to an abnormal high hypothalamic threshold for slowing of GnRH by E/2 and P. Initial studies have shown that E/2 and P suppress GnRH pulses to a greater degree in normal women than in PCOS. In dose response studies slowing the frequency of GnRH secretion required a higher P conc/n in PCOS compared to normals. We aim to determine if this reflects an inherent hypothalamic abnormality in PCOS, or is secondary to the effects of elevated androgens or to insulin resistance. Dose response studies of P suppression of GnRH will be performed before and after 4 weeks of blockade of androgen action by flutamide, and after reduction of plasma insulin by **metformin.** The possibility of applying these principles to induce follicular maturation and ovulation in PCOS will be explored. After long term (6 weeks) suppression of GnRH secretion by luteal conc/n of E/2 and P, we will assess if the preferential FSH secretion which follows E/2 and P withdrawal is adequate to induce ovulation.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: OBESITY, HYPERINSULINEMIA AND COLON CANCER**

  Principal Investigator & Institution: Fleming, Sharon E.; Professor; Nutritional Scis & Toxicology; University of California Berkeley Berkeley, Ca 94720

  Timing: Fiscal Year 2002; Project Start 30-SEP-2002; Project End 31-AUG-2004

  Summary: (provided by applicant): There is substantial epidemiological evidence that being overweight or obese increases risk of colonic cancer. The data are stronger for men than for women and stronger for cancer of the left than right colon, with an overall doubling of risk. Data from two studies using Zucker rats support this notion. Diabetes is associated also with increased risk of colonic cancer, and this is directly supported by one animal study. Insulin and insulin-like growth factors are known to affect biological processes such as proliferation and apoptosis in vitro. Since obesity and hyperinsulinemia often co-exist in animal models and in humans, it has been difficult to determine their separate contributions to disease risk. In this application, we hypothesize that hyperinsulinemia is responsible for increased susceptibility of the overweight and obese to colonic cancer. We will use C57BL/6J mice to determine whether obese animals are more susceptible than their lean littermates to carcinogen-induced colon tumorigenesis. Initially, this will be done by comparing responses of wild-type versus Lepob mutants. In a second study, responses of lean, wild-type mice with normal weight and insulin levels will be compared to responses of mice that are both obese and hyperinsulinemic (induced by feeding a diet high in coconut oil) or hyperinsulinemic but not obese (induced by feeding a high-fructose diet). To determine the contribution that obesity in the absence of hyperinsulinemia makes to colonic tumorigenesis, plasma insulin levels will be reduced in Lepob mutants using **metformin.** Susceptibility to colonic tumorigenesis will be assessed by measuring aberrant crypt foci, crypt cell proliferation, and tumor incidence and multiplicity. We expect that hyperinsulinemia will stimulate colon tumorigenesis, whereas obesity in the absence of hyperinsulinemia will not. These studies will provide new knowledge that will be used to support a follow-up R01 application.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: PATHOGENESIS, PROGNOSIS, AND TREATMENT OF NAFLD PATIENTS**

  Principal Investigator & Institution: Diehl, Anna M.; Professor; Medicine; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2002; Project Start 01-MAY-2002; Project End 30-APR-2007

  Summary: (provided by the applicant) Non-Alcoholic Fatty Liver Disease (NAFLD) is defined histologically as a spectrum of liver diseases, ranging from steatosis to steatohepatitis (NASH), and cirrhosis. There is tremendous inter-individual variability in the tendency to develop cirrhosis, the stage of NAFLD that is associated with the greatest liver-related morbidity and mortality. The variable progression of NAFLD may be explained by the "multiple hit hypothesis". According to this hypothesis, a primary insult (i.e., "hit") causes normal livers to accumulate fat. Evidence suggests that the first "hit" that causes fat to accumulate in the liver is insulin resistance, which may be either primary or secondary to obesity. Fatty livers are unusually vulnerable to damage from various secondary insults and NASH develops when fatty livers experience a second "hit", such as exposure to intestinal bacterial products that induce inflammatory cytokines, which cause oxidative stress and further mitochondrial dysfunction. Because NASH does not always culminate in cirrhosis, it is likely that additional "hits" may be required for hepatic fibrosis to occur. Progression from clinically-compensated to

decompensated cirrhosis may require further insults. If this "multiple-hit hypothesis" explains the histological and clinical progression of NAFLD, then interventions which remove the vulnerability state by reversing hepatic steatosis, or which prevent the superimposition of the secondary "hits" should be effective treatments. To test the validity of these therapeutic strategies, we propose 3 SPECIFIC AIMS. Aim #1 is to create and maintain a NAFLD registry. This will be accomplished by screening various populations that have a high risk of NAFLD to determine if there are host or environmental factors (i.e., "hits") that distinguish subjects without fatty liver from those with fatty livers, as well as factors that distinguish among the various histologic stages of NAFLD. Aim #2 is to identify promising treatments that may prevent the progression of NAFLD by improving one or more of the "hits". This will be accomplished y retrospective analysis of trials that have already tried to improve the putative, primary "hit" (Aim #2a) and by a prospective valuation of the importance of intestinal bacterial overgrowth, which may generate putative secondary "hits"(Aim #2b). Aim #3 is to design and conduct a Network-wide randomized, controlled trial in patients with NAFLD. Assuming that insulin resistance emerges as a promising target for therapy, we will test the hypothesis that a 12-month course of **metformin** therapy will produce significant improvement in hepatic steatosis and in NAFLD-related metabolic factors without adverse effects. Completion of these Aims will provide important information about host and environmental factors that promote NAFLD and is likely to identify treatments that prevent the progression from steatosis to NASH and more advanced stages of liver damage.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: PHYSICAL & METABOLIC CHARACTERISTICS OF HAIR AN & PCOS IN CHILDREN**

  Principal Investigator & Institution: Arslanian, Silva; Children's Hosp Pittsburgh/Upmc Hlth Sys of Upmc Health Systems Pittsburgh, Pa 15213

  Timing: Fiscal Year 2001

  Summary: There is no text on file for this abstract.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: POLYCYSTIC OVARIAN SYNDROME IN OVERWEIGHT ADOLESCENTS**

  Principal Investigator & Institution: Hoeger, Kathleen M.; Obstetrics and Gynecology; University of Rochester Orpa - Rc Box 270140 Rochester, Ny 14627

  Timing: Fiscal Year 2002; Project Start 01-APR-2002; Project End 31-MAR-2004

  Summary: (provided by applicant): Polycystic Overy Syndrome (PCOS) is a broad-spectrum disease characterized by chronic anovulation and androgen excess, affecting 4-8% of women. Onset of the disorder is recognized to occur around the time of puberty but is often not diagnosed until adulthood. More than half of women with PCOS are obese, and insulin resistance appears to be an important part of its underlying pathophysiology. Long-term consequences in PCOS are now recognized to include increased risk of development of type 2 diabetes mellitus and cardiovascular disease. This has led to an interest in reduction of insulin resistance as a long-term treatment strategy. This reduction in insulin resistance can be accomplished by weight reduction or by insulin sensitizers such as **metformin.** To date, however, there are limited data on the effectiveness of insulin sensitizers and no data on the impact of weight reduction in adolescents with PCOS. Adolescence is a time of tremendous physical and psychosocial

change. Obesity in adolescence is often predictive of lifelong obesity. The constellation of hirsutism, irregular bleeding, and obesity, often seen in adolescents with PCOS, could potentially have lifelong social and health consequences. A successful weight reduction strategy with improvement in insulin sensitivity at the onset of the symptoms of PCOS could have substantial long-term health benefits. The applicant hypothesizes that weight loss and **metformin** in the overweight adolescent with PCOS can reduce insulin resistance and improve the symptoms and metabolic profile associated with PCOS. Accordingly, a randomized, placebo-controlled, parallel-group trial comparing **metformin** and intensive lifestyle modification is proposed to gather preliminary data on the rate of ovulation, changes in testosterone and insulin and impact on cardiovascular risk of weight reduction and **metformin** as compared to placebo in a total of 30 subjects. Data obtained from this pilot trial on recruitment rates, drop-out, compliance, and estimated treatment effect sizes will be used to refine power calculations for a large-scale randomized trial focused on a comparison of **metformin** and weight reduction in obese adolescents.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: POST DPP (DIABETES PREVENTION PROGRAM)**

  Principal Investigator & Institution: Barrett-Connor, Elizabeth L.; Professor and Chair; Medicine; University of California San Diego 9500 Gilman Dr, Dept. 0934 La Jolla, Ca 92093

  Timing: Fiscal Year 2003; Project Start 10-SEP-1994; Project End 31-JAN-2008

  Summary: (provided by applicant): The Diabetes Prevention Program is a multicenter controlled clinical trial examining the efficacy of an intensive life-style intervention or **metformin** to prevent or delay the development of diabetes in a population selected to be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 ADA criteria, is the primary outcome while cardiovascular disease and its risk factors are important secondary outcomes. The DPP began recruitment in mid-1996. At the time of this application, total study exposure is a mean of approximately 3 years (range 2 to 5) with a total of approximately 10,000 patient years in the 3,234 volunteers in the 3-arm study. On the basis of a statistically significant and clinically compelling decrease in the development of diabetes in the life-style intervention and metformin-treated groups (58% and 31% reductions, respectively) compared with the placebo treated group, the DPP Data Monitoring Board and NIDDK ended the masked treatment phase of the study in May, 2001, one year earlier than originally planned. This application is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of data collected during the study. The highly compliant DPP cohort, including 45% minorities, is the largest IGT population ever studied. Moreover, the subcohort that has developed diabetes (n approximately 700) has been followed from near the exact time of diabetes onset. Clinically important research questions remain in the wake of the DPP. The carefully collected, centrally measured and graded data in this cohort should help to answer, definitively, a number of important questions regarding the clinical course of IGT and early onset type 2 diabetes. Specific aims include: 1. Examine the long-term effects and durability of prior DPP intervention on the major DPP outcomes including diabetes, clinical cardiovascular disease, atherosclerosis, CVD risk factors,quality of life and cost-benefit; 2. Determine the clinical course of new onset type 2 diabetes and IGT, in particular regarding microvascular and neurologic complications; 3. Determine the incidence of cardiovascular disease (CVD), CVD risk factors and atherosclerosis in new onset type 2 diabetes and IGT; and 4. Examine topics 1-3 in minority populations, men

vs. women, and in older subjects in the DPP. The current application is for 5 years of funding, although the some of the goals of the projects described will require a 10-year study.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: POST DPP FOLLOW UP STUDY: DATA COORDINATING CENTER**

  Principal Investigator & Institution: Fowler, Sarah E.; Research Professor; Statistics; George Washington University 2121 I St Nw Washington, Dc 20052

  Timing: Fiscal Year 2003; Project Start 20-AUG-1994; Project End 31-JAN-2008

  Summary: (provided by applicant): The Diabetes Prevention Program is a multicenter controlled clinical trial examining the efficacy of an intensive life-style intervention or **metformin** to prevent or delay the development of diabetes in a population selected to be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 ADA criteria, is the primary outcome while cardiovascular disease and its risk factors are important secondary outcomes. The DPP began recruitment in mid-1996. At the time of this application, total study exposure is a mean of approximately 3 years (range 2 to 5) with a total of approximately 10,000 patient years in the 3,234 volunteers in the 3-arm study. On the basis of a statistically significant and clinically compelling decrease in the development of diabetes in the life-style intervention and metformin-treated groups (58% and 31% reductions, respectively) compared with the placebo treated group, the DPP Data Monitoring Board and NIDDK ended the masked treatment phase of the study in May, 2001, one year earlier than originally planned. This application is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of data collected during the study. The highly compliant DPP cohort, including 45% minorities, is the largest IGT population ever studied. Moreover, the subcohort that has developed diabetes (n approximately 700) has been followed from near the exact time of diabetes onset. Clinically important research questions remain in the wake of the DPP. The carefully collected, centrally measured andgraded data in this cohort should help to answer, definitively, a number of important questions regarding the clinical course of IGT and early onset type 2 diabetes. Specific aims include: 1. Examine the long-term effects and durability of prior DPP intervention on the major DPP outcomes including diabetes, clinical cardiovascular disease, atherosclerosis, CVD risk factors, quality of life and cost-benefit; 2. Determine the clinical course of new onset type 2 diabetes and IGT, in particular regarding microvascular and neurologic complications; 3. Determine the incidence of cardiovascular disease (CVD), CVD risk factors and atherosclerosis in new onset type 2 diabetes and IGT; and 4. Examine topics 1-3 in minority populations, men vs. women, and in older subjects in the DPP. The current application is for 5 years of funding, although the some of the goals of the projects described will require a 10-year study.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: POST DPP FOLLOWUP STUDY**

  Principal Investigator & Institution: Marrero, David G.; Professor of Medicine; Medicine; Indiana Univ-Purdue Univ at Indianapolis 620 Union Drive, Room 618 Indianapolis, in 462025167

  Timing: Fiscal Year 2003; Project Start 15-AUG-1994; Project End 31-JAN-2008

  Summary: (provided by applicant): The Diabetes Prevention Program is a multicenter controlled clinical trial examining the efficacy of an intensive life-style intervention or

metformin to prevent or delay the development of diabetes in a population selected to be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 ADA criteria, is the primary outcome while cardiovascular disease and its risk factors are important secondary outcomes. The DPP began recruitment in mid-1996. At the time of this application, total study exposure is a mean of approximately 3 years (range 2 to 5) with a total of approximately 10,000 patient years in the 3,234 volunteers in the 3-arm study. On the basis of a statistically significant and clinically compelling decrease in the development of diabetes in the life-style intervention and metformin-treated groups (58% and 31% reductions, respectively) compared with the placebo treated group, the DPP Data Monitoring Board and NIDDK ended the masked treatment phase of the study in May, 2001, one year earlier than originally planned. This application is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of data collected during the study. The highly compliant DPP cohort, including 45% minorities, is the largest IGT population ever studied. Moreover, the subcohort that has developed diabetes (n approximately 700) has been followed from near the exact time of diabetes onset. Clinically important research questions remain in the wake of the DPP. The carefully collected, centrally measured and graded data in this cohort should help to answer, definitively, a number of important questions regarding the clinical course of IGT and early onset type 2 diabetes. Specific aims include: 1. Examine the long-term effects and durability of prior DPP intervention on the major DPP outcomes including diabetes, clinical cardiovascular disease, atherosclerosis, CVD risk factors, quality of life and cost-benefit; 2. Determine the clinical course of new onset type 2 diabetes and IGT, in particular regarding microvascular and neurologic complications; 3. Determine the incidence of cardiovascular disease (CVD), CVD risk factors and atherosclerosis in new onset type 2 diabetes and IGT; and 4. Examine topics 1-3 in minority populations, men vs. women, and in older subjects in the DPP. The current application is for 5 years of funding, although the some of the goals of the projects described will require a 10-year study.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: POST DPP FOLLOW-UP STUDY**

  Principal Investigator & Institution: Goldberg, Ronald B.; Chief, Division of Diabetes and Metaboli; Medicine; University of Miami-Medical Box 248293 Coral Gables, Fl 33124

  Timing: Fiscal Year 2003; Project Start 20-AUG-1994; Project End 31-JAN-2008

  Summary: (provided by applicant): The Diabetes Prevention Program is a multicenter controlled clinical trial examining the efficacy of an intensive life-style intervention or **metformin** to prevent or delay the development of diabetes in a population selected to be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 ADA criteria, is the primary outcome while cardiovascular disease and its risk factors are important secondary outcomes. The DPP began recruitment in mid-1996. At the time of this application, total study exposure is a mean of approximately 3 years (range 2 to 5) with a total of approximately 10,000 patient years in the 3,234 volunteers in the 3-arm study. On the basis of a statistically significant and clinically compelling decrease in the development of diabetes in the life-style intervention and metformin-treated groups (58% and 31% reductions, respectively) compared with the placebo treated group, the DPP Data Monitoring Board and NIDDK ended the masked treatment phase of the study in May, 2001, one year earlier than originally planned. This application is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of

data collected during the study. The highly compliant DPP cohort, including 45% minorities, is the largest IGT population ever studied. Moreover, the subcohort that has developed diabetes (n approximately 700) has been followed from near the exact time of diabetes onset. Clinically important research questions remain in the wake of the DPP. The carefully collected, centrally measured and graded data in this cohort should help to answer, definitively, a number of important questions regarding the clinical course of IGT and early onset type 2 diabetes. Specific aims include: 1. Examine the long-term effects and durability of prior DPP intervention on the major DPP outcomes including diabetes, clinical cardiovascular disease, atherosclerosis, CVD risk factors, quality of life and cost-benefit; 2. Determine the clinical course of new onset type 2 diabetes and IGT, in particular regarding microvascular and neurologic complications; 3. Determine the incidence of cardiovascular disease (CVD), CVD risk factors and atherosclerosis in new onset type 2 diabetes and IGT; and 4. Examine topics 1-3 in minority populations, men vs. women, and in older subjects in the DPP. The current application is for 5 years of funding, although the some of the goals of the projects described will require a 10-year study.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: POST-DDP FOLLOW-UP STUDY**

  Principal Investigator & Institution: Kahn, Steven E.; Medicine; University of Washington Seattle, Wa 98195

  Timing: Fiscal Year 2003; Project Start 20-AUG-1994; Project End 31-JAN-2008

  Summary: (provided by applicant): The Diabetes Prevention Program is a multicenter controlled clinical trial examining the efficacy of an intensive life-style intervention or **metformin** to prevent or delay the development of diabetes in a population selected to be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 ADA criteria, is the primary outcome while cardiovascular disease and its risk factors are important secondary outcomes. The DPP began recruitment in mid-1996. At the time of this application, total study exposure is a mean of approximately 3 years (range 2 to 5) with a total of approximately 10,000 patient years in the 3,234 volunteers in the 3-arm study. On the basis of a statistically significant and clinically compelling decrease in the development of diabetes in the life-style intervention and metformin-treated groups (58% and 31% reductions, respectively) compared with the placebo treated group, the DPP Data Monitoring Board and NIDDK ended the masked treatment phase of the study in May, 2001, one year earlier than originally planned. This application is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of data collected during the study. The highly compliant DPP cohort, including 45% minorities, is the largest IGT population ever studied. Moreover, the subcohort that has developed diabetes (n approximately 700) has been followed from near the exact time of diabetes onset. Clinically important research questions remain in the wake of the DPP. The carefully collected, centrally measured and graded data in this cohort should help to answer, definitively, a number of important questions regarding the clinical course of IGT and early onset type 2 diabetes. Specific aims include: 1. Examine the long-term effects and durability of prior DPP intervention on the major DPP outcomes including diabetes, clinical cardiovascular disease, atherosclerosis, CVD risk factors, quality of life and cost-benefit; 2. Determine the clinical course of new onset type 2 diabetes and IGT, in particular regarding microvascular and neurologic complications; 3. Determine the incidence of cardiovascular disease (CVD), CVD risk factors and atherosclerosis in new onset type 2 diabetes and IGT; and 4. Examine topics 1-3 in minority populations, men

vs. women, and in older subjects in the DPP. The current application is for 5 years of funding, although the some of the goals of the projects described will require a 10-year study.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: POST-DIABETES PREVENTION PROGRAM (DPP)**

  Principal Investigator & Institution: Ehrmann, David A.; Associate Professor; Medicine; University of Chicago 5801 S Ellis Ave Chicago, Il 60637

  Timing: Fiscal Year 2003; Project Start 20-AUG-1994; Project End 31-JAN-2008

  Summary: (provided by applicant): The Diabetes Prevention Program is a multicenter controlled clinical trial examining the efficacy of an intensive life-style intervention or **metformin** to prevent or delay the development of diabetes in a population selected to be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 ADA criteria, is the primary outcome while cardiovascular disease and its risk factors are important secondary outcomes. The DPP began recruitment in mid-1996. At the time of this application, total study exposure is a mean of approximately 3 years (range 2 to 5) with a total of approximately 10,000 patient years in the 3,234 volunteers in the 3-arm study. On the basis of a statistically significant and clinically compelling decrease in the development of diabetes in the life-style intervention and metformin-treated groups (58% and 31% reductions, respectively) compared with the placebo treated group, the DPP Data Monitoring Board and NIDDK ended the masked treatment phase of the study in May, 2001, one year earlier than originally planned. This application is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of data collected during the study. The highly compliant DPP cohort, including 45% minorities, is the largest IGT population ever studied. Moreover, the subcohort that has developed diabetes (n approximately 700) has been followed from near the exact time of diabetes onset. Clinically important research questions remain in the wake of the DPP. The carefully collected, centrally measured and graded data in this cohort should help to answer, definitively, a number of important questions regarding the clinical course of IGT and early onset type 2 diabetes. Specific aims include: 1. Examine the long-term effects and durability of prior DPP intervention on the major DPP outcomes including diabetes, clinical cardiovascular disease, atherosclerosis, CVD risk factors, quality of life and cost-benefit; 2. Determine the clinical course of new onset type 2 diabetes and IGT, in particular regarding microvascular and neurologic complications; 3. Determine the incidence of cardiovascular disease (CVD), CVD risk factors and atherosclerosis in new onset type 2 diabetes and IGT; and 4. Examine topics 1-3 in minority populations, men vs. women, and in older subjects in the DPP. The current application is for 5 years of funding, although the some of the goals of the projects described will require a 10-year study.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: POST-DPP FOLLOWUP STUDY**

  Principal Investigator & Institution: Nathan, David M.; Principal Investigator; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114

  Timing: Fiscal Year 2003; Project Start 20-AUG-1994; Project End 31-JAN-2008

  Summary: (provided by applicant): The Diabetes Prevention Program is a multicenter controlled clinical trial examining the efficacy of an intensive life-style intervention or **metformin** to prevent or delay the development of diabetes in a population selected to

be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 ADA criteria, is the primary outcome while cardiovascular disease and its risk factors are important secondary outcomes. The DPP began recruitment in mid-1996. At the time of this application, total study exposure is a mean of approximately 3 years (range 2 to 5) with a total of approximately 10,000 patient years in the 3,234 volunteers in the 3-arm study. On the basis of a statistically significant and clinically compelling decrease in the development of diabetes in the life-style intervention and metformin-treated groups (58% and 31% reductions, respectively) compared with the placebo treated group, the DPP Data Monitoring Board and NIDDK ended the masked treatment phase of the study in May, 2001, one year earlier than originally planned. This application is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of data collected during the study. The highly compliant DPP cohort, including 45% minorities, is the largest IGT population ever studied. Moreover, the subcohort that has developed diabetes (n approximately 700) has been followed from near the exact time of diabetes onset. Clinically important research questions remain in the wake of the DPP. The carefully collected, centrally measured and graded data in this cohort should help to answer, definitively, a number of important questions regarding the clinical course of IGT and early onset type 2 diabetes. Specific aims include: 1. Examine the long-term effects and durability of prior DPP intervention on the major DPP outcomes including diabetes, clinical cardiovascular disease, atherosclerosis, CVD risk factors, quality of life and cost-benefit; 2. Determine the clinical course of new onset type 2 diabetes and IGT, in particular regarding microvascular and neurologic complications; 3. Determine the incidence of cardiovascular disease (CVD), CVD risk factors and atherosclerosis in new onset type 2 diabetes and IGT; and 4. Examine topics 1-3 in minority populations, men vs. women, and in older subjects in the DPP. The current application is for 5 years of funding, although the some of the goals of the projects described will require a 10-year study.

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- **Project Title: POST-DPP FOLLOW-UP STUDY**

  Principal Investigator & Institution: Haffner, Steven M.; Professor of Medicine; Medicine; University of Texas Hlth Sci Ctr San Ant 7703 Floyd Curl Dr San Antonio, Tx 78229

  Timing: Fiscal Year 2003; Project Start 22-SEP-1994; Project End 31-JAN-2008

  Summary: (provided by applicant): The Diabetes Prevention Program is a multicenter controlled clinical trial examining the efficacy of an intensive life-style intervention or **metformin** to prevent or delay the development of diabetes in a population selected to be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 ADA criteria, is the primary outcome while cardiovascular disease and its risk factors are important secondary outcomes. The DPP began recruitment in mid-1996. At the time of this application, total study exposure is a mean of approximately 3 years (range 2 to 5) with a total of approximately 10,000 patient years in the 3,234 volunteers in the 3-arm study. On the basis of a statistically significant and clinically compelling decrease in the development of diabetes in the life-style intervention and metformin-treated groups (58% and 31% reductions, respectively) compared with the placebo treated group, the DPP Data Monitoring Board and NIDDK ended the masked treatment phase of the study in May, 2001, one year earlier than originally planned. This application is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of

data collected during the study. The highly compliant DPP cohort, including 45% minorities, is the largest IGT population ever studied. Moreover, the subcohort that has developed diabetes (n approximately 700) has been followed from near the exact time of diabetes onset. Clinically important research questions remain in the wake of the DPP. The carefully collected, centrally measured and graded data in this cohort should help to answer, definitively, a number of important questions regarding the clinical course of IGT and early onset type 2 diabetes. Specific aims include: 1. Examine the long-term effects and durability of prior DPP intervention on the major DPP outcomes including diabetes, clinical cardiovascular disease, atherosclerosis, CVD risk factors, quality of life and cost-benefit; 2. Determine the clinical course of new onset type 2 diabetes and IGT, in particular regarding microvascular and neurologic complications; 3. Determine the incidence of cardiovascular disease (CVD), CVD risk factors and atherosclerosis in new onset type 2 diabetes and IGT; and 4. Examine topics 1-3 in minority populations, men vs. women, and in older subjects in the DPP. The current application is for 5 years of funding, although the some of the goals of the projects described will require a 10-year study.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: POST-DPP FOLLOW-UP-STUDY**

  Principal Investigator & Institution: Bray, George A.; Director; None; Lsu Pennington Biomedical Research Ctr 6400 Perkins Rd Baton Rouge, La 70808

  Timing: Fiscal Year 2003; Project Start 01-OCT-1994; Project End 31-JAN-2008

  Summary: (provided by applicant): The Diabetes Prevention Program is a multicenter controlled clinical trial examining the efficacy of an intensive life-style intervention or **metformin** to prevent or delay the development of diabetes in a population selected to be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 ADA criteria, is the primary outcome while cardiovascular disease and its risk factors are important secondary outcomes. The DPP began recruitment in mid-1996. At the time of this application, total study exposure is a mean of approximately 3 years (range 2 to 5) with a total of approximately 10,000 patient years in the 3,234 volunteers in the 3-arm study. On the basis of a statistically significant and clinically compelling decrease in the development of diabetes in the life-style intervention and metformin-treated groups (58% and 31% reductions, respectively) compared with the placebo treated group, the DPP Data Monitoring Board and NIDDK ended the masked treatment phase of the study in May, 2001, one year earlier than originally planned. This application is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of data collected during the study. The highly compliant DPP cohort, including 45% minorities, is the largest IGT population ever studied. Moreover, the subcohort that has developed diabetes (n approximately 700) has been followed from near the exact time of diabetes onset. Clinically important research questions remain in the wake of the DPP. The carefully collected, centrally measured and graded data in this cohort should help to answer, definitively, a number of important questions regarding the clinical course of IGT and early onset type 2 diabetes. Specific aims include: 1. Examine the long-term effects and durability of prior DPP intervention on the major DPP outcomes including diabetes, clinical cardiovascular disease, atherosclerosis, CVD risk factors, quality of life and cost-benefit; 2. Determine the clinical course of new onset type 2 diabetes and IGT, in particular regarding microvascular and neurologic complications; 3. Determine the incidence of cardiovascular disease (CVD), CVD risk factors and atherosclerosis in new onset type 2 diabetes and IGT; and 4. Examine topics 1-3 in minority populations, men

vs. women, and in older subjects in the DPP. The current application is for 5 years of funding, although the some of the goals of the projects described will require a 10-year study.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: PROTEASE INHIBITOR RELATED ADIPOGENESIS IN HIV INFECTION**

  Principal Investigator & Institution: Agrawal, Krishna C.; Regents Professor and Chairperson; Pharmacology; Tulane University of Louisiana New Orleans, La New Orleans, La 70112

  Timing: Fiscal Year 2001; Project Start 01-AUG-2001; Project End 31-MAY-2004

  Summary: (Provided by applicant) The clinical use of HIV-1 protease inhibitors (PIs) in highly active anti-retroviral therapy (HART) has led to significant improvements in the prognosis and quality of life in HIV-1 infected patients. However, long-term use of PIs has resulted in side effects such as peripheral lipodystrophy, hyperlipidemia, insulin resistance, and disruption of the adipogenic process. Our preliminary studies have shown that PIs suppress adipogenic differentiation in 3T3-L1 cells and the addition of TNFalpha further suppressed the rate of adipogenesis. In contrast, the insulin sensitizing agent, troglitazone, blocked this suppression even in TNFalpha sensitized cells. The primary goal of the proposed research is to investigate the molecular mechanisms involved in the PI-induced modulation of adipogenesis and to test the hypothesis that preadipocytes are sensitized by HIV-1 induced inflammatory cytokine TNFalpha and/or HIV-1 Tat protein, to PI-induced disruption of adipogenesis. This will be achieved by the following specific aims: 1.) To determine the in vitro effects of PIs on adipogenic differentiation in human bone marrow stromal progenitor cells. Transcripts of early, middle and late genetic markers i.e., pref-1, lipoprotein lipase (LPL) and GAPDH, respectively will be determined. Levels of nuclear transcription factors, PPAR-gamma and C/EBP-alpha will be determined by transient transfection assays and gel mobility shift assays. 2.) to determine the sensitizing effect of the HIV-1 induced inflammatory cytokine, TNFalpha and/or HIV-1 Tat protein on PI-induced inhibition of adipogenic differentiation in human bone marrow stromal progenitor cells. 3.) To determine the in vitro effects of PIs on the activity of ECM degrading proteases in human stromal adipogenic progenitor cells. Fibrinolytic activity in undifferentiated and differentiated cells will be monitored by using a chromogenic plasmin substrate. The ECM production at different stages of differentiation will be determined by SDS-PAGE electrophoresis and the activation of ECM degrading proteolytic enzymes (MMPs) will be monitored by gelatin zymography. Real time RT-PCR studies will monitor gene expression of tPA, PAI-1/2 and MMPs/TIMPs which are involved in the fibrinolytic cascade. 4.) To investigate the ameliorative effects of insulin sensitizers on PI-induced lipodystrophy. We will investigate the efficacy of thiazolidinediones (rosiglitazone and pioglitazone) and biguanides (metformin) in suppressing the effects of PI-induced inhibition of adipogenic differentiation. These studies will delineate the molecular mechanisms that may be responsible for the adipogenic side effects induced by the PIs in the presence of HIV infection.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: QUANTITAION OF NET HEPATIC GLYCOGENOLYSIS AND GLUCONEOGENESIS WITH METFORMIN**

  Principal Investigator & Institution: Shulman, Gerald I.; Yale University 47 College Street, Suite 203 New Haven, Ct 065208047

Timing: Fiscal Year 2001

Summary: To study the effect of **metformin** on hepatic glycogenolysis and gluconeogenesis in non-insulin dependent diabetic subjects using magnetic resonance imaging and spectroscopy in combination with glucose turnover technique.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: QUANTITATION OF FACTORS REGULATING GLUCOSE TOLERANCE**

  Principal Investigator & Institution: Bergman, Richard N.; Professor of Physiology and Biophysics; Physiology and Biophysics; University of Southern California 2250 Alcazar Street, Csc-219 Los Angeles, Ca 90033

  Timing: Fiscal Year 2003; Project Start 01-AUG-1981; Project End 30-NOV-2007

  Summary: (provided by applicant): Normal glucose tolerance is maintained by a balance between insulin secretion and insulin action to enhance glucose disposal and regulate glucose output. In normal individuals basal and postprandial insulinemia increases so that glycemia does not exceed the normal range at basal and with meals. This compensation is due to upregulation of beta cell sensitivity to secretagogues, as well as downregulation of first-pass liver insulin clearance. Impaired glucose tolerance results when there is inadequate compensation for insulin resistance, and as this dysfunction progresses, diabetes develops. The precise mechanisms by which resistance results in beta-cell upregulation are not known. We are examining several mechanisms which may play a role in hyperinsulinemic compensation for insulin resistance. We exploit the isocaloric or hypercaloric fat-fed dog model, which develops visceral adiposity, insulin resistance and a well-defined pattern of compensation. We will determine whether postprandial or nocturnal glucose or free fatty acids explain upregulation of beta-cell function. We will counter increases in postprandial nutrients with pharmacological agents (acarbose and/or metformin). We examine the relationship between cortisol and growth hormone and metabolic compensation, and disrupt the secretion/action of these hormones with antagonists infused systemically or into the third ventricle of the brain. We consider whether gastrointestinal peptide GLP-1 is an important mediator of the compensatory response to insulin resistance. We hypothesize that GLP-1 is stimulated in the fat-fed model and acts via specific receptors in the portal vein. The putative GLP-1 reflex will be blocked by denervation of the portal vein, or with portal infusion of GLP-1 antagonists. We will examine whether portal GLP-1 plays a vital role in the putative action of the peptide to upregulate islets in the insulin resistant state. Failure of "compensatrins" to upregulate may be the earliest change in the pathogenesis of Type 2 diabetes. Identification of the origin and metabolic actions of such molecules should lead to more accurate identification of those at risk for diabetes, and allow for prevention of the disease.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: RACE AND LONG-TERM DIABETES SELF-MANAGEMENT IN AN HMO**

  Principal Investigator & Institution: Ross-Degnan, Dennis; Harvard Pilgrim Health Care, Inc. 93 Worcester St Wellesley, Ma 02481

  Timing: Fiscal Year 2002; Project Start 15-JAN-2002; Project End 31-DEC-2004

  Summary: (provided by applicant): This project will examine the complex relationships between race, diabetes self-management (including self-monitoring of blood glucose and diabetes drug therapy), glycemic control, and diabetes complications in a managed

care setting over a nine-year period. African Americans with diabetes are less likely to be in glycemic control, a major risk factor for development of complications, including nephropathy, retinopathy, and peripheral vascular disease. Randomized controlled trials suggest that diabetes self-management including patient education, drug therapy, changes in diet, and regular exercise can improve glycemic control in the African American population. However, there is little epidemiological evidence regarding the role of race/ethnicity as a determinant of adherence to recommended diabetes self-management practices, or regarding the relationship between self-management, glycemic control, and subsequent clinical outcomes. Further, previous studies of race and diabetes self-management have been limited by short study periods, inadequate sample size, and reliance on self-reported measures of self-monitoring of blood glucose. The clinical setting for this study is Harvard Vanguard Medical Associates (HVMA), a large multi-site, multi-specialty group affiliated with Harvard Pilgrim Health Care. HVMA consists of 14 health centers serving over 300,000 people in the Boston area. We will use an open cohort design to enroll all adult (l8 years) patients between 1991 and 1999 who have 24 months or more of uninterrupted enrollment in HVMA following ascertainment of non-gestational diabetes, defined by (1) hospital discharge diagnosis of diabetes mellitus, (2) outpatient diagnoses of diabetes mellitus, HbAlc lab test result 8.0, or use of a diabetes drug (insulin, sulfonylurea, or metformin). We estimate that the cohort will include approximately 1,800 adults identified as African American and 5,000 identified as Caucasian. Access to HVMA computerized medical records, hospital emergency room and inpatient claims, lab, and pharmacy data will allow us to create reliable, objective measures of self-monitoring (home glucose monitor test strip use), drug therapy. glycemic control (HbAlc lab results), and diabetes complications (as measured in outpatient visits, emergency room visits, and hospitalizations). Stratifying by type of drug therapy (insulin/combined therapy vs. oral therapy), we will use descriptive analyses, generalized linear mixed models, and proportional hazards models to (1) identify racial differences in self-management practices and diabetes-related health outcomes over time; (2) assess whether African American race is an independent predictor of self-monitoring practice or adherence to drug regimen; and (3) whether there are racial/ethnic differences in the association between self-management and specific clinical endpoints, including glycemic control (HbAlc<8.0) and the incidence of diabetes-related complications over the nine-year study period.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: REGULATION OF HEPATIC INSULIN EXTRACTION**

  Principal Investigator & Institution: Polonsky, Kenneth S.; Chief, Section of Endocrinology; Internal Medicine; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2001; Project Start 01-JAN-1983; Project End 31-DEC-2001

  Summary: (Adapted from Applicant's Abstract): The overall goal of this project is to study the effects of specific diabetes susceptibility genes on insulin secretion and to define clinical protocols which describe the altered pattern of secretion associated with expression of these genes. Since susceptibility genes for the common form of late-onset NIDDM have not yet been identified, MODY will be used as an experimental model. Three genetic subtypes of this condition (MODY1, MODY2, and MODY 3) have been identified each being linked to a separate susceptibility locus. Studies will be performed in subjects with the three forms of MODY to further define the insulin secretory responses to glucose and non-glucose stimuli on physiological testing. A specific attempt will be made to determine whether defects in insulin secretion are present in

subjects genetically predisposed to MODY prior to the onset of overt hyperglycemia. Complementary studies will be performed in a mouse model in which one allele of the glucokinase gene has been knocked out. Heterozygous animals have reduced expression of glucokinase in the B-cell and liver and in this respect resemble subjects with MODY2 in which the mutation in the enzyme glucokinase results in production of an inactive enzyme. Using the isolated perifused pancreas and isolated perfused islets we propose to study responses to non-glucose stimuli in these animals, alterations in oscillatory insulin secretion and the ability of animals lacking one glucokinase allele to compensate for mild hyperglycemia and insulin resistance. It is proposed to explore the mechanisms associated with altered insulin secretion in subjects with impaired glucose tolerance by determining if they are reversible by treatment with **metformin,** a biguanide which lowers glucose levels by suppressing hepatic glucose production and troglitazone, a novel agent which appears to reduce peripheral insulin resistance. We will also determine whether subjects with impaired glucose tolerance are able to increase insulin secretion in response to infusion of a triglyceride emulsion and heparin, a combination which increases insulin resistance by increasing the concentrations of free fatty acids. It is anticipated that these studies will provide mechanistic insights into the role of abnormal B-cell function in the pathophysiology of NIDDM. By allowing the manifestations of the insulin secretory defects present in subjects with impaired glucose tolerance to be compared with those present in MODY, these studies should define experimental approaches which will uncover B-cell dysfunction at an early stage in the development of NIDDM even before the onset of overt hyperglycemia.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: REVERSAL OF DECLINE OF GH SECRETION OF AGING**

  Principal Investigator & Institution: Thorner, Michael O.; Professor of Medicine; Medicine; University of Virginia Charlottesville Box 400195 Charlottesville, Va 22904

  Timing: Fiscal Year 2001; Project Start 01-DEC-1992; Project End 30-NOV-2002

  Summary: The decline in GH secretion with age may play a major role in the increasing morbidity and frailty, and the reduced quality of life of the aging population. Recent studies by this group demonstrate that the decline in GH secretion can be reversed by taking a daily oral dose of the GHRP mimetic MK-677 and these results are compatible with the focus of this grant: the decline of GH secretion with age is mediated by decreased secretion of the natural ligand for GHRP. Diminished GHRP natural ligand production may decrease GHRH release, increase SRIH release and reduce the effectiveness of GHRH on somatotroph function. Decreased GH secretion likely promotes reduction of lean tissue (sarcopenia) and accumulation of abdominal (visceral) fat as occurs in GH deficient adults, resulting in insulin resistance and increased cardiovascular risk. Recent developments offer new possibilities to investigate the regulation of GH secretion. Both human and animal experiments are proposed to explore our central hypothesis. Specific Aim 1. Hypothesis: Long term administration (2 yr) of an oral GHRP mimetic (MK-677) in the elderly will restore GH secretion to that observed in young adults. The restoration of GH secretion will alter body composition, metabolic rate, aerobic exercise capacity, proximal muscle strength and bone density toward that of young adults. Specific Aim 2. Hypothesis: The decline of GH secretion with aging is mediated by a reduced hypothalamic stimulation of somatotrophs. Blockade of GH feedback with a GH receptor antagonist (opening the negative feedback loop) will augment GH secretion more in young than in older adults. Studies will be performed in young and older adults and in young and old rats. Specific Aim 3. Hypothesis: Enhanced SRIH secretion and/or action contributes to the decline of GH

secretion with increasing age. Administration of the somatostatin receptor-2 (SSTR2) antagonist (to block the primary SRIH receptor subtype mediating inhibition of GH secretion) will lead to increased GH secretion. Increased SRIH secretion inhibits GH secretion directly and possibly indirectly by also decreasing GHRH release. The recent development of a SSTR2 antagonist now permits evaluation of the critical role of this receptor in pulsatile GH secretion in animals and man and will also allow determination of the relative role of SRIH in the regulation of GH secretion in the young versus the old. Specific Aim 4. Hypothesis: IGFBP-1 is pivotal in regulating IGF-1 feedback by modulating circulating free IGF-1 concentrations. IGFBP-1 inhibits IGF-1 action and circulation levels are correlated inversely with serum insulin concentrations. Since IGFBP-1 is low in older adults with increased visceral fat, administration of **metformin,** a biguanide, for 4 weeks will lower insulin levels without changing blood glucose, will increase circulating IGFBP1 levels and thus enhance GH secretion in older adults.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ROSIGLITAZONE IN POLYCYSTIC OVARY SYNDROME**

  Principal Investigator & Institution: Cataldo, Nicholas A.; Assistant Professor of Obstetrics and Gy; Gynecology and Obstetrics; Stanford University Stanford, Ca 94305

  Timing: Fiscal Year 2001; Project Start 01-APR-2001; Project End 31-MAR-2003

  Summary: (Adapted from applicant's description): Polycystic ovary syndrome (PCOS) is a disorder affecting about 5% of reproductive-age women characterized by anovulation and excess production of androgens by the ovary. Anovulation causes menstrual irregularity and infertility, while excess androgens cause unwanted hair growth and may promote acne. Traditional treatments for PCOS have consisted of medication to stimulate ovulation if fertility is desired, or medication to suppress or block androgents or restore regular menstrual cycles if fertility is not an immediate goal, but these treatments are often mutually exclusive PCOS is frequently associated with a common metabolic disorder, insulin resistance, and like insulin resistance alone carries an increased risk of non-reproductive health problems such as the development of diabetes or atherosclerosis. Insulin resistance leads to excessive insulin secretion, and this may stimulate the ovary to hypersecrete androgens. In the last few years, published reports have described the treatment of PCOS with insulin sensitizers, medications developed to treat diabetes which can improve insulin resistance. These drugs can improve the hormonal abnormalities in PCOS and in some cases can restore regular menses and/or ovulation. Of the two marketed drugs tested to date, **metformin** has not been consistently effective, while troglitazone is effective but has been found to have an unacceptable risk of liver toxicity. This project will study rosiglitazone, a newly approved drug closely related to troglitazone in structure and action but without apparent toxicity, in an open-label, Phase II format. Subjects with PCOS wiII have insulin resistance identified by dynamic testing using the octreotide insulin suppression test, and after further evaluation of provoked insulin secretion will receive rosiglitazone daily in one of three doses for 12 weeks. Insulin resistance and insulin secretion, glucose tolerance, serum total and free testosterone, LH, and circulating lipids will be measured on rosiglitazone and compared to subjects' pretreatment values. The occurrence of ovulation will be evaluated by weekly serum progesterone levels. The dose of rosiglitazone and the time needed for its effect to develop will be determined. Associations between effects on metabolic parameters and effects on reproductive ones will be sought. The hypothesis of this study is that rosiglitazone can improve insulin sensitivity and lower circulating insulin, and thereby restore ovulation as well as correct

elevated LH and testosterone. Rosiglitazone is potentially an appropriate and beneficial treatment for all women with PCOS and insulin resistance regardless of goals.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: SAFETY & EFFICACY OF METFORMINBLYBURIDE COMBINATION PRODUCTS IN NIDDM**

  Principal Investigator & Institution: O'shaughnessy, Irene; Medical College of Wisconsin Po Box26509 Milwaukee, Wi 532264801

  Timing: Fiscal Year 2001

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: TREATMENT ALTERNATIVES IN PEDIATRIC TYPE 2 DIABETES**

  Principal Investigator & Institution: Zeitler, Philip S.; Pediatrics; University of Colorado Hlth Sciences Ctr P.O. Box 6508, Grants and Contracts Aurora, Co 800450508

  Timing: Fiscal Year 2001; Project Start 30-SEP-2001; Project End 28-FEB-2009

  Summary: (provided by applicant): In recent years, type 2 diabetes has been recognized as increasingly common among children and adolescents and data from diabetes referral centers indicate that type 2 diabetes now accounts for approximately 40 percent of patients diagnosed with diabetes between the ages of 10-19 years. A number of large epidemiological studies are currently underway to address the question of the true incidence of type 2 diabetes in the pediatric age population. However, despite this increasing incidence of type 2 diabetes among children and adolescents, there have been no large published studies examining the efficacy of potential treatment interventions. Rather, pediatric diabetologists have had to rely on treatment approaches based on the understanding of the pathophysiology of type 2 diabetes, and the results from treatment studies in adult patients. However, the relevance of adult studies to the treatment of type 2 diabetes in adolescents and children is unclear. This proposal aims to address the lack of such studies. Our intent is to participate in a multi-center, randomized, clinical trial to assess the efficacy and safety of potential treatment options for this disorder. We propose a four-arm trial, where participants are randomized to one of the following initial interventions: 1) **metformin;** 2) intensive lifestyle intervention to promote weight loss and alter diet, physical activity; and behavior patterns; 3) intensive lifestyle intervention plus **metformin;** 4) insulin. We also propose an approach for stepped-care for patients failing to meet minimum goals for glycemic control in their initial assigned treatment arm. This four-year study will assess the relative efficacy and safety of each of the experimental interventions, examining the primary outcomes of glycemic control and changes in insulin sensitivity and secretion. Associated secondary outcomes will include effects of treatment alternatives on body composition, cardiovascular fitness, cardiovascular risk factors, incidence of diabetes-related complications, as well as patient quality of life. It is anticipated that this trial will provide critical information to guide practitioners in the effective care of these patients, as well as establishing the infrastructure for an ongoing consortium of centers interested in the coordinated study of pediatric type 2 diabetes.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: TROGLITAZONE COMBO W/ SULFONYLUREA OR METFORMIN IN NIDDM**

  Principal Investigator & Institution: Jacobs, Laurence S.; Professor; University of Rochester Orpa - Rc Box 270140 Rochester, Ny 14627

  Timing: Fiscal Year 2002

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: TROGLITAZONE ON SUBSTRATE METABOLISM AND BODY COMPOSITION IN DIABETES**

  Principal Investigator & Institution: Klein, Samuel; Professor of Medicine and Director; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2001

  Summary: There is no text on file for this abstract.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: TROGLITAZONE, METFORMIN, & SULFONYLUREA IN INSULIN STIMULATED GLUCOSE**

  Principal Investigator & Institution: Kelley, David; University of Pittsburgh at Pittsburgh 350 Thackeray Hall Pittsburgh, Pa 15260

  Timing: Fiscal Year 2001

  Summary: The objective of this study is to assess the potential mechanism by which Troglitazone improves skeletal muscle insulin sensitivity in patients with Non-Insulin Dependent Diabetes Mellitus (NIDDM) and compare these to the effects of **Metformin** and sulfonylurea treatments. The hypothesis to be tested is that troglitazone has a greater effect to improve skeletal muscle insulin sensitivity than does **metformin** or sulfonylurea therapy.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: USE OF METFORMIN TO TREAT INSULIN RESISTANCE AND OBESITY**

  Principal Investigator & Institution: Hardin, Dana S.; Associate Professor; University of Texas Hlth Sci Ctr Houston Box 20036 Houston, Tx 77225

  Timing: Fiscal Year 2001; Project Start 01-APR-2001; Project End 28-FEB-2002

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

E-Journals: PubMed Central[3]

PubMed Central (PMC) is a digital archive of life sciences journal literature developed and managed by the National Center for Biotechnology Information (NCBI) at the U.S. National

[3] Adapted from the National Library of Medicine: **http://www.pubmedcentral.nih.gov/about/intro.html**.

Library of Medicine (NLM).[4] Access to this growing archive of e-journals is free and unrestricted.[5] To search, go to **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Pmc**, and type "metformin" (or synonyms) into the search box. This search gives you access to full-text articles. The following is a sample of items found for metformin in the PubMed Central database:

- **Metformin in polycystic ovary syndrome: systematic review and meta-analysis.** by Lord JM, Flight IH, Norman RJ.; 2003 Oct 25;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=259161

The National Library of Medicine: PubMed

One of the quickest and most comprehensive ways to find academic studies in both English and other languages is to use PubMed, maintained by the National Library of Medicine.[6] The advantage of PubMed over previously mentioned sources is that it covers a greater number of domestic and foreign references. It is also free to use. If the publisher has a Web site that offers full text of its journals, PubMed will provide links to that site, as well as to sites offering other related data. User registration, a subscription fee, or some other type of fee may be required to access the full text of articles in some journals.

To generate your own bibliography of studies dealing with metformin, simply go to the PubMed Web site at **http://www.ncbi.nlm.nih.gov/pubmed**. Type "metformin" (or synonyms) into the search box, and click "Go." The following is the type of output you can expect from PubMed for metformin (hyperlinks lead to article summaries):

- **A 67-year-old female with a 4-year history of type 2 diabetes, treated with metformin, presented with unstable angina.**
  Author(s): Waksman R.
  Source: Cardiovascular Radiation Medicine. 2002 April-June; 3(2): 121.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12741407&dopt=Abstract

- **A cautionary tale: fatal lactic acidosis complicating nucleoside analogue and metformin therapy.**
  Author(s): Worth L, Elliott J, Anderson J, Sasadeusz J, Street A, Lewin S.
  Source: Clinical Infectious Diseases : an Official Publication of the Infectious Diseases Society of America. 2003 July 15; 37(2): 315-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12856228&dopt=Abstract

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[4] With PubMed Central, NCBI is taking the lead in preservation and maintenance of open access to electronic literature, just as NLM has done for decades with printed biomedical literature. PubMed Central aims to become a world-class library of the digital age.

[5] The value of PubMed Central, in addition to its role as an archive, lies in the availability of data from diverse sources stored in a common format in a single repository. Many journals already have online publishing operations, and there is a growing tendency to publish material online only, to the exclusion of print.

[6] PubMed was developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM) at the National Institutes of Health (NIH). The PubMed database was developed in conjunction with publishers of biomedical literature as a search tool for accessing literature citations and linking to full-text journal articles at Web sites of participating publishers. Publishers that participate in PubMed supply NLM with their citations electronically prior to or at the time of publication.

- **A comparison of acarbose versus metformin as an adjuvant therapy in sulfonylurea-treated NIDDM patients.**
  Author(s): Bayraktar M, Van Thiel DH, Adalar N.
  Source: Diabetes Care. 1996 March; 19(3): 252-4.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8742572&dopt=Abstract

- **A comparison of metformin versus guar in combination with sulphonylureas in the treatment of non insulin dependent diabetes.**
  Author(s): Wilson JA, Scott MM, Gray RS.
  Source: Hormone and Metabolic Research. Hormon- Und Stoffwechselforschung. Hormones Et Metabolisme. 1989 June; 21(6): 317-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2777189&dopt=Abstract

- **A comparison of preconstituted, fixed combinations of low-dose glyburide plus metformin versus high-dose glyburide alone in the treatment of type 2 diabetic patients.**
  Author(s): Erle G, Lovise S, Stocchiero C, Lora L, Coppini A, Marchetti P, Merante D.
  Source: Acta Diabetologica. 1999 June; 36(1-2): 61-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10436254&dopt=Abstract

- **A comparison of troglitazone and metformin on insulin requirements in euglycemic intensively insulin-treated type 2 diabetic patients.**
  Author(s): Yu JG, Kruszynska YT, Mulford MI, Olefsky JM.
  Source: Diabetes. 1999 December; 48(12): 2414-21.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10580431&dopt=Abstract

- **A diabetes outcome progression trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes.**
  Author(s): Viberti G, Kahn SE, Greene DA, Herman WH, Zinman B, Holman RR, Haffner SM, Levy D, Lachin JM, Berry RA, Heise MA, Jones NP, Freed MI.
  Source: Diabetes Care. 2002 October; 25(10): 1737-43.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12351470&dopt=Abstract

- **A proposal for the locus of metformin's clinical action: potentiation of the activation of pyruvate kinase by fructose-1,6-diphosphate.**
  Author(s): McCarty MF.
  Source: Medical Hypotheses. 1999 February; 52(2): 89-93. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10340287&dopt=Abstract

- **A randomized trial of sibutramine in the management of obese type 2 diabetic patients treated with metformin.**
  Author(s): McNulty SJ, Ur E, Williams G; Multicenter Sibutramine Study Group.
  Source: Diabetes Care. 2003 January; 26(1): 125-31.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12502668&dopt=Abstract

- **A retrospective analysis of the efficacy and safety of metformin in the African-American patient.**
  Author(s): Briscoe TA, Anderson D, Usifo OS, Cooper GS.
  Source: Journal of the National Medical Association. 1997 November; 89(11): 728-30. Erratum In: J Natl Med Assoc 1998 July; 90(7): 389.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9375476&dopt=Abstract

- **A retrospective chart review of uncontrolled use of metformin as an add-on therapy in type 2 diabetes.**
  Author(s): Johnson M, Krosnick A, Carson P, McDade AM, Laraway K.
  Source: Clinical Therapeutics. 1998 July-August; 20(4): 691-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9737829&dopt=Abstract

- **A risk-benefit assessment of metformin in type 2 diabetes mellitus.**
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  Author(s): Klein W.
  Source: Diabete Metab. 1991 May; 17(1 Pt 2): 235-40.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1936483&dopt=Abstract

- **Sulphonylureas and metformin overdose: clinical features and management.**
  Author(s): Bates N.
  Source: Emergency Nurse : the Journal of the Rcn Accident and Emergency Nursing Association. 2001 May; 9(2): 18-22. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11935618&dopt=Abstract

- **Survival after metformin-associated lactic acidosis in peritoneal dialysis--dependent renal failure.**
  Author(s): Schmidt R, Horn E, Richards J, Stamatakis M.
  Source: The American Journal of Medicine. 1997 May; 102(5): 486-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9217647&dopt=Abstract

- **Sustained benefits of metformin therapy on markers of cardiovascular risk in human immunodeficiency virus-infected patients with fat redistribution and insulin resistance.**
  Author(s): Hadigan C, Rabe J, Grinspoon S.
  Source: The Journal of Clinical Endocrinology and Metabolism. 2002 October; 87(10): 4611-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12364443&dopt=Abstract

- **The comparison of clinical and hormonal parameters in PCOS patients treated with metformin and GnRH analogue.**
  Author(s): Cicek MN, Bala A, Celik C, Akyurek C.
  Source: Archives of Gynecology and Obstetrics. 2003 June; 268(2): 107-12. Epub 2002 September 26.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12768300&dopt=Abstract

- **The contribution of metformin to glycaemic control in patients with Type 2 diabetes mellitus receiving combination therapy with insulin.**
  Author(s): Tong PC, Chow CC, Jorgensen LN, Cockram CS.
  Source: Diabetes Research and Clinical Practice. 2002 August; 57(2): 93-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12062853&dopt=Abstract

- **The effect of a thiazolidinedione drug, troglitazone, on glycemia in patients with type 2 diabetes mellitus poorly controlled with sulfonylurea and metformin. A multicenter, randomized, double-blind, placebo-controlled trial.**
  Author(s): Yale JF, Valiquett TR, Ghazzi MN, Owens-Grillo JK, Whitcomb RW, Foyt HL.
  Source: Annals of Internal Medicine. 2001 May 1; 134(9 Pt 1): 737-45.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11329231&dopt=Abstract

- **The effect of intravenous metformin on glucose metabolism during hyperglycaemia in type 2 diabetes.**
  Author(s): Sum CF, Webster JM, Johnson AB, Catalano C, Cooper BG, Taylor R.
  Source: Diabetic Medicine : a Journal of the British Diabetic Association. 1992 January-February; 9(1): 61-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1551312&dopt=Abstract

- **The effect of metformin on glycemic control, serum lipids and lipoproteins in diet alone and sulfonylurea-treated type 2 diabetic patients with sub-optimal metabolic control.**
  Author(s): Mughal MA, Jan M, Maheri WM, Memon MY, Ali M.
  Source: J Pak Med Assoc. 2000 November; 50(11): 381-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11126815&dopt=Abstract

- **The effect of metformin on hirsutism in polycystic ovary syndrome.**
  Author(s): Kelly CJ, Gordon D.
  Source: European Journal of Endocrinology / European Federation of Endocrine Societies. 2002 August; 147(2): 217-21.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12153743&dopt=Abstract

- **The effect of metformin on ovarian stimulation and in vitro fertilization in insulin-resistant women with polycystic ovary syndrome: an open-label randomized cross-over trial.**
  Author(s): Fedorcsak P, Dale PO, Storeng R, Abyholm T, Tanbo T.
  Source: Gynecological Endocrinology : the Official Journal of the International Society of Gynecological Endocrinology. 2003 June; 17(3): 207-14.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12857428&dopt=Abstract

- **The effect of metformin plus clomiphene citrate on ovulation and pregnancy rates in clomiphene-resistant women with polycystic ovary syndrome.**
  Author(s): Cochrane Database Syst Rev. 2003;(2):CD002967
  Source: Saudi Med J. 2002 June; 23(6): 663-6.
  /entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12804446

- **The effects of long-term metformin treatment on adrenal and ovarian steroidogenesis in women with polycystic ovary syndrome.**
  Author(s): Vrbikova J, Hill M, Starka L, Cibula D, Bendlova B, Vondra K, Sulcova J, Snajderova M.
  Source: European Journal of Endocrinology / European Federation of Endocrine Societies. 2001 June; 144(6): 619-28.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11375796&dopt=Abstract

- **The effects of metformin and diet on plasma testosterone and leptin levels in obese men.**
  Author(s): Ozata M, Oktenli C, Bingol N, Ozdemir IC.
  Source: Obesity Research. 2001 November; 9(11): 662-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11707532&dopt=Abstract

- **The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes.**
  Author(s): Freemark M, Bursey D.
  Source: Pediatrics. 2001 April; 107(4): E55.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11335776&dopt=Abstract

- **The potential of metformin for diabetes prevention.**
  Author(s): Slama G.
  Source: Diabetes & Metabolism. 2003 September; 29(4 Pt 2): 6S104-11. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14502107&dopt=Abstract

- **The short-term effect of a switch from glibenclamide to metformin on blood pressure and microalbuminuria in patients with type 2 diabetes mellitus.**
  Author(s): Amador-Licona N, Guizar-Mendoza J, Vargas E, Sanchez-Camargo G, Zamora-Mata L.
  Source: Archives of Medical Research. 2000 November-December; 31(6): 571-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11257323&dopt=Abstract

- **The synergistic effect of miglitol plus metformin combination therapy in the treatment of type 2 diabetes.**
  Author(s): Chiasson JL, Naditch L; Miglitol Canadian University Investigator Group.
  Source: Diabetes Care. 2001 June; 24(6): 989-94.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11375358&dopt=Abstract

- **Thiazolidinediones but not metformin directly inhibit the steroidogenic enzymes P450c17 and 3beta -hydroxysteroid dehydrogenase.**
  Author(s): Arlt W, Auchus RJ, Miller WL.
  Source: The Journal of Biological Chemistry. 2001 May 18; 276(20): 16767-71. Epub 2001 February 07.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11278997&dopt=Abstract

- **Transfer of metformin into human milk.**
  Author(s): Gardiner SJ, Kirkpatrick CM, Begg EJ, Zhang M, Moore MP, Saville DJ.
  Source: Clinical Pharmacology and Therapeutics. 2003 January; 73(1): 71-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12545145&dopt=Abstract

- **Transitioning patients with type 2 diabetes to a fixed combination > glyburide/metformin tablet.**
  Author(s): Blonde L, Sandberg MI.
  Source: Diabetes Technology & Therapeutics. 2000 Autumn; 2(3): 479-80.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11467351&dopt=Abstract

- **Treatment with metformin of non-diabetic men with hypertension, hypertriglyceridaemia and central fat distribution: the BIGPRO 1.2 trial.**
  Author(s): Charles MA, Eschwege E, Grandmottet P, Isnard F, Cohen JM, Bensoussan JL, Berche H, Chapiro O, Andre P, Vague P, Juhan-Vague I, Bard JM, Safar M.
  Source: Diabetes/Metabolism Research and Reviews. 2000 January-February; 16(1): 2-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10707032&dopt=Abstract

- **Troglitazone add-on therapy to a combination of sulfonylureas plus metformin achieved and sustained effective diabetes control.**
  Author(s): Gavin LA, Barth J, Arnold D, Shaw R.
  Source: Endocrine Practice : Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2000 July-August; 6(4): 305-10.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11242607&dopt=Abstract

- **Troglitazone but not metformin restores insulin-stimulated phosphoinositide 3-kinase activity and increases p110beta protein levels in skeletal muscle of type 2 diabetic subjects.**
  Author(s): Kim YB, Ciaraldi TP, Kong A, Kim D, Chu N, Mohideen P, Mudaliar S, Henry RR, Kahn BB.
  Source: Diabetes. 2002 February; 51(2): 443-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11812753&dopt=Abstract

- **Use of intravenous contrast agents in patients receiving metformin.**
  Author(s): Gupta R.
  Source: Radiology. 2002 October; 225(1): 311-2; Author Reply 312.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12355024&dopt=Abstract

- **Use of metformin in polycystic ovary syndrome.**
  Author(s): De Sloover Koch Y, Ernst ME.
  Source: The Annals of Pharmacotherapy. 2001 December; 35(12): 1644-7. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11793635&dopt=Abstract

- **Use of urea containing dialysate to avoid disequilibrium syndrome, enabling intensive dialysis treatment of a diabetic patient with renal failure and severe metformin induced lactic acidosis.**
  Author(s): Doorenbos CJ, Bosma RJ, Lamberts PJ.
  Source: Nephrology, Dialysis, Transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association. 2001 June; 16(6): 1303-4.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11390747&dopt=Abstract

- **Utility of metformin as an adjunct to hydroxycitrate/carnitine for reducing body fat in diabetics.**
  Author(s): McCarty MF.
  Source: Medical Hypotheses. 1998 November; 51(5): 399-403.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9848468&dopt=Abstract

- **Vascular effects of glibenclamide vs. glimepiride and metformin in Type 2 diabetic patients.**
  Author(s): Abbink EJ, Pickkers P, Jansen van Rosendaal A, Lutterman JA, Tack CJ, Russel FG, Smits P.
  Source: Diabetic Medicine : a Journal of the British Diabetic Association. 2002 February; 19(2): 136-43.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11874430&dopt=Abstract

- **Vitamin B 12 and metformin.**
  Author(s): Stowers JM, Smith OA.
  Source: British Medical Journal. 1971 July 24; 3(768): 246-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=5559051&dopt=Abstract

CHAPTER 2. NUTRITION AND METFORMIN

Overview

In this chapter, we will show you how to find studies dedicated specifically to nutrition and metformin.

Finding Nutrition Studies on Metformin

The National Institutes of Health's Office of Dietary Supplements (ODS) offers a searchable bibliographic database called the IBIDS (International Bibliographic Information on Dietary Supplements; National Institutes of Health, Building 31, Room 1B29, 31 Center Drive, MSC 2086, Bethesda, Maryland 20892-2086, Tel: 301-435-2920, Fax: 301-480-1845, E-mail: ods@nih.gov). The IBIDS contains over 460,000 scientific citations and summaries about dietary supplements and nutrition as well as references to published international, scientific literature on dietary supplements such as vitamins, minerals, and botanicals.[7] The IBIDS includes references and citations to both human and animal research studies.

As a service of the ODS, access to the IBIDS database is available free of charge at the following Web address: **http://ods.od.nih.gov/databases/ibids.html**. After entering the search area, you have three choices: (1) IBIDS Consumer Database, (2) Full IBIDS Database, or (3) Peer Reviewed Citations Only.

Now that you have selected a database, click on the "Advanced" tab. An advanced search allows you to retrieve up to 100 fully explained references in a comprehensive format. Type "metformin" (or synonyms) into the search box, and click "Go." To narrow the search, you can also select the "Title" field.

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[7] Adapted from **http://ods.od.nih.gov**. IBIDS is produced by the Office of Dietary Supplements (ODS) at the National Institutes of Health to assist the public, healthcare providers, educators, and researchers in locating credible, scientific information on dietary supplements. IBIDS was developed and will be maintained through an interagency partnership with the Food and Nutrition Information Center of the National Agricultural Library, U.S. Department of Agriculture.

The following is a typical result when searching for recently indexed consumer information on metformin:

- **A comparison of acarbose versus metformin as an adjuvant therapy in sulfonylurea-treated NIDDM patients.**
  Author(s): Department of Endocrinology, Hacettepe University, Ankara, Turkey.
  Source: Bayraktar, M Van Thiel, D H Adalar, N Diabetes-Care. 1996 March; 19(3): 252-4 0149-5992
- **Additive glucose-lowering effects of glucagon-like peptide-1 and metformin in type 2 diabetes.**
  Author(s): Department of Endocrinology, Hvidovre Hospital, Denmark.
  Source: Zander, M Taskiran, M Toft Nielsen, M B Madsbad, S Holst, J J Diabetes-Care. 2001 April; 24(4): 720-5 0149-5992
- **Double-blind evaluation of efficacy and tolerability of metformin in NIDDM.**
  Author(s): Nottingham University and City Hospitals, United Kingdom.
  Source: Dornan, T L Heller, S R Peck, G M Tattersall, R B Diabetes-Care. 1991 April; 14(4): 342-4 0149-5992
- **Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin.**
  Author(s): Lipid and Diabetes Research Center, St. Lukes Hospital, Kansas City, Missouri, USA. miles.john@mayo.edu
  Source: Miles, J M Leiter, L Hollander, P Wadden, T Anderson, J W Doyle, M Foreyt, J Aronne, L Klein, S Diabetes-Care. 2002 July; 25(7): 1123-8 0149-5992
- **Effect of weight change and metformin on fibrinolysis and the von Willebrand factor in obese nondiabetic subjects: the BIGPRO1 Study. Biguanides and the Prevention of the Risk of Obesity.**
  Author(s): INSERM (National Institute of Health and Medical Research) Unit 21, Villejuif, France. charles@vjf.inserm.fr
  Source: Charles, M A Morange, P Eschwege, E Andre, P Vague, P Juhan Vague, I Diabetes-Care. 1998 November; 21(11): 1967-72 0149-5992
- **Efficacy and safety of acarbose in metformin-treated patients with type 2 diabetes.**
  Author(s): Dallas Diabetes and Endocrine Center, TX 75230, USA.
  Source: Rosenstock, J Brown, A Fischer, J Jain, A Littlejohn, T Nadeau, D Sussman, A Taylor, T Krol, A Magner, J Diabetes-Care. 1998 December; 21(12): 2050-5 0149-5992
- **Further evidence for a central role of adipose tissue in the antihyperglycemic effect of metformin.**
  Author(s): Department of Medicine, Stanford University School of Medicine, California, USA.
  Source: Abbasi, F Carantoni, M Chen, Y D Reaven, G M Diabetes-Care. 1998 August; 21(8): 1301-5 0149-5992
- **Improved control of mealtime glucose excursions with coadministration of nateglinide and metformin.**
  Author(s): Department of Clinical Pharmacology, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936, USA.
  Source: Hirschberg, Y Karara, A H Pietri, A O McLeod, J F Diabetes-Care. 2000 March; 23(3): 349-53 0149-5992

- **Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin.**
  Author(s): Department of Medicine, Mount Sinai School of Medicine, New York, USA. bauman.william@bronx.va.gov
  Source: Bauman, W A Shaw, S Jayatilleke, E Spungen, A M Herbert, V Diabetes-Care. 2000 September; 23(9): 1227-31 0149-5992

- **Irreversibility of the defect in glycogen synthase activity in skeletal muscle from obese patients with NIDDM treated with diet and metformin.**
  Author(s): Hvidore Hospital, Klampenborg, Denmark.
  Source: Damsbo, P Hermann, L S Vaag, A Hother Nielsen, O Beck Nielsen, H Diabetes-Care. 1998 September; 21(9): 1489-94 0149-5992

- **Metabolic and hemodynamic effects of metformin and glibenclamide in normotensive NIDDM patients.**
  Author(s): Department of Clinical Pharmacology, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, N.T.
  Source: Chan, J C Tomlinson, B Critchley, J A Cockram, C S Walden, R J Diabetes-Care. 1993 July; 16(7): 1035-8 0149-5992

- **Metformin enhances clearance of chylomicrons and chylomicron remnants in nondiabetic mildly overweight glucose-intolerant subjects.**
  Author(s): Department of Internal Medicine C Tel Aviv Sourasky Medical Center, Tel Aviv University, Israel.
  Source: Grosskopf, I Ringel, Y Charach, G Maharshak, N Mor, R Iaina, A Weintraub, M Diabetes-Care. 1997 October; 20(10): 1598-602 0149-5992

- **Metformin's effects on glucose and lipid metabolism in patients with secondary failure to sulfonylureas.**
  Author(s): Endocrinology Service, General Hospital of Mexico, Mexico City.
  Source: Fanghanel, G Sanchez Reyes, L Trujillo, C Sotres, D Espinosa Campos, J Diabetes-Care. 1996 November; 19(11): 1185-9 0149-5992

- **Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes.**
  Author(s): Joslin Diabetes Center, Boston, Massachusetts 02215, USA. edward.horton@joslin.harvard.edu
  Source: Horton, E S Clinkingbeard, C Gatlin, M Foley, J Mallows, S Shen, S Diabetes-Care. 2000 November; 23(11): 1660-5 0149-5992

- **Results of a placebo-controlled study of the metabolic effects of the addition of metformin to sulfonylurea-treated patients: evidence for a central role of adipose tissue.**
  Author(s): Stanford University School of Medicine, Stanford.
  Source: Abbasi, F. Kamath, V. Rizvi, A.A. Carantoni, M. Chen, Y.D.I. Reaven, G.M. Diabetes-care (USA). (December 1997). volume 20(12) page 1863-1869. diabetes sulphonamides amides drug therapy blood sugar fatty acids blood lipids men women 0149-5992

- **The effects of metformin on glycemic control and serum lipids in insulin-treated NIDDM patients with suboptimal metabolic control.**
  Author(s): Imperial College of Medicine, St. Mary' s, Norfolk Place, London.
  Source: Robinson, A.C. Burke, J. Robinson, S. Johnston, D.G. Elkeles, R.S. Diabetes-care (USA). (May 1998). volume 21(5) page 701-705. diabetes insulin drug therapy amides blood sugar blood lipids men women 0149-5992

- **The synergistic effect of miglitol plus metformin combination therapy in the treatment of type 2 diabetes.**
  Author(s): Research Group on Diabetes and Metabolic Regulation, Research Center, Centre Hospitalier de l'Universite de Montreal, 3850 St. Urbain, 8-202, Montreal, Quebec, Canada H2W 1T8. jean.louis.chiasson@umontreal.ca
  Source: Chiasson, J L Naditch, L Diabetes-Care. 2001 June; 24(6): 989-94 0149-5992

- **Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations. A double-blind controlled study.**
  Author(s): Department of Community Health Sciences, Lund University, Dalby, Sweden.
  Source: Hermann, L S Schersten, B Bitzen, P O Kjellstrom, T Lindgarde, F Melander, A Diabetes-Care. 1994 October; 17(10): 1100-9 0149-5992

The following information is typical of that found when using the "Full IBIDS Database" to search for "metformin" (or a synonym):

- **A comparison of metformin versus guar in combination with sulphonylureas in the treatment of non insulin dependent diabetes.**
  Author(s): Bangour General Hospital, Broxburn, West Lothian, United Kingdom.
  Source: Wilson, J A Scott, M M Gray, R S Horm-Metab-Res. 1989 June; 21(6): 317-9 0018-5043

- **A comparison of treatment with metformin and gliclazide in patients with non-insulin-dependent diabetes.**
  Author(s): Diabetic Department, Gartnavel General Hospital, Glasgow, U.K.
  Source: McAlpine, L G McAlpine, C H Waclawski, E R Storer, A M Kay, J W Frier, B M Eur-J-Clin-Pharmacol. 1988; 34(2): 129-32 0031-6970

- **A short-term cost-of-treatment model for type 2 diabetes: comparison of glipizide gastrointestinal therapeutic system, metformin, and acarbose.**
  Author(s): Department of Medicine, University of California, San Diego, USA.
  Source: Ramsdell, J W Grossman, J A Stephens, J M Botteman, M F Arocho, R Am-J-Manag-Care. 1999 August; 5(8): 1007-24 1096-1860

- **Acarbose vs. bedtime NPH insulin in the treatment of secondary failures to sulphonylurea-metformin therapy in type 2 diabetes mellitus.**
  Author(s): Departamento de Diabetes y Metabolismo de Lipidos, Instituto Nacional de la Nutricion, Vasco de Quiroga, Mexico City, Mexico.
  Source: Lopez Alvarenga, J C Aguilar Salinas, C A Velasco Perez, M L Arita Melzer, O Guillen, L E Wong, B Brito, G Mercado, V Gomez Perez, F J Rull Rodrigo, J A Diabetes-Obes-Metab. 1999 January; 1(1): 29-35 1462-8902

- **Bicarbonate haemodialysis: an adequate treatment for lactic acidosis in diabetics treated by metformin.**
  Author(s): Service de Medicine Interne-Endocrinologie, Centre Hospitalier Regional et Universitaire, Amiens, France.
  Source: Lalau, J D Westeel, P F Debussche, X Dkissi, H Tolani, M Coevoet, B Temperville, B Fournier, A Quichaud, J Intensive-Care-Med. 1987; 13(6): 383-7 0342-4642

- **BIGPRO (biguanides and the prevention of the risk of obesity): study design. A randomized trial of metformin versus placebo in the correction of the metabolic abnormalities associated with insulin resistance.**
  Author(s): INSERM U21, Villejuif, France.
  Source: Fontbonne, A Andre, P Eschwege, E Diabete-Metab. 1991 May; 17(1 Pt 2): 249-54 0338-1684

- **Causes of weight gain during insulin therapy with and without metformin in patients with Type II diabetes mellitus.**
  Author(s): Department of Medicine, Helsinki University Central Hospital, Finland.
  Source: Makimattila, S Nikkila, K Yki Jarvinen, H Diabetologia. 1999 April; 42(4): 406-12 0012-186X

- **Combination daytime chlorpropamide-metformin/bedtime insulin in the treatment of secondary failures in non insulin dependent diabetes.**
  Author(s): Departamento de Diabetes y Metabolismo de Lipidos, Instituto Nacional de la Nutricion Salvador Zubiran, Mexico, D.F.
  Source: Aguilar, C A Wong, B Gomez Perez, F J Rull, J A Rev-Invest-Clin. 1992 Jan-March; 44(1): 71-6 0034-8376

- **Comparative efficacy of metformin and glibenclamide in patients with non-insulin-dependent diabetes mellitus.**
  Author(s): Department of Community Health Sciences, Dalby, Sweden.
  Source: Hermann, L S Bitzen, P O Kjellstrom, T Lindgarde, F Schersten, B Diabete-Metab. 1991 May; 17(1 Pt 2): 201-8 0338-1684

- **Comparative three-month study of the efficacies of metformin and gliclazide in the treatment of NIDD.**
  Author(s): Innopharm, Boulogne, France.
  Source: Noury, J Nandeuil, A Diabete-Metab. 1991 May; 17(1 Pt 2): 209-12 0338-1684

- **Comparison of bedtime NPH insulin or metformin combined with glibenclamide in secondary sulphonylurea failure in obese type II (NIDDM) patients.**
  Author(s): Department of Medicine, Pakistan Institute of Medical Sciences, Islamabad.
  Source: Niazi, R Muzaffar, Z J-Pak-Med-Assoc. 1998 November; 48(11): 336-8 0030-9982

- **Cost-effectiveness analysis of intensive blood-glucose control with metformin in overweight patients with type II diabetes (UKPDS No. 51).**
  Author(s): Health Economics Research Centre, Department of Public Health, University of Oxford, Institute of Health Sciences, Headington, Oxford OX3 7LF, UK.
  Source: Clarke, P Gray, A Adler, A Stevens, R Raikou, M Cull, C Stratton, I Holman, R Diabetologia. 2001 March; 44(3): 298-304 0012-186X

- **Diurnal pattern of plasma metformin concentrations and its relation to metabolic effects in type 2 (non-insulin-dependent) diabetic patients.**
  Author(s): Istituto di Clinica Medica Generale e Terapia Medica II, University of Pisa, Italy.
  Source: Marchetti, P Gregorio, F Benzi, L Giannarelli, R Cecchetti, P Villani, G Di Cianni, G Di Carlo, A Brunetti, P Navalesi, R Diabete-Metab. 1990 December; 16(6): 473-8 0338-1684

- **Do metformin and phenformin potentiate differently B-cell response to high glucose? An in vitro study on isolated rat pancreas.**
  Author(s): Instituti di Clinia Medica I, Universita di Perugia, Italy.
  Source: Gregorio, F Ambrosi, F Cristallini, S Marchetti, P Navalesi, R Brunetti, P Filipponi, P Diabete-Metab. 1991 Jan-February; 17(1): 19-28 0338-1684

- **Effect of glycaemic control, metformin and gliclazide on platelet density and aggregability in recently diagnosed type 2 (non-insulin-dependent) diabetic patients.**
  Author(s): Diabetic and Dietetic Department, Royal Infirmary, Edinburgh.
  Source: Collier, A Watson, H H Patrick, A W Ludlam, C A Clarke, B F Diabete-Metab. 1989 Nov-December; 15(6): 420-5 0338-1684

- **Effects of metformin on fibrinogen levels in obese patients with type 2 diabetes.**
  Author(s): Department of Endocrinology, General Hospital of Mexico, Mexico City, Mexico. gfangh@yahoo.com
  Source: Fanghanel, G Silva, U Sanchez Reyes, L Sisson, D Sotres, D Torres, E M Rev-Invest-Clin. 1998 Sep-October; 50(5): 389-94 0034-8376

- **Energy metabolism and substrates oxidative patterns in type 2 diabetic patients treated with sulphonylurea alone or in combination with metformin.**
  Author(s): Department of Metabolic Diseases, Lapeyronie Hospital, Montpellier, France. a-avignon@chu-montpellier.fr
  Source: Avignon, A Lapinski, H Rabasa Lhoret, R Caubel, C Boniface, H Monnier, L Diabetes-Obes-Metab. 2000 August; 2(4): 229-35 1462-8902

- **Evidence that metformin increases insulin-stimulated glucose transport by potentiating insulin-induced translocation of glucose transporters from an intracellular pool to the cell surface in rat adipocytes.**
  Author(s): Department of Medicine, University-Hospital of Hamburg, Germany.
  Source: Matthaei, S Hamann, A Klein, H H Benecke, H Kreymann, G Flier, J S Greten, H Horm-Metab-Res-Suppl. 1992; 2634-41 0170-5903

- **Glucose and lipid metabolism in non-insulin-dependent diabetes. Effect of metformin.**
  Author(s): Cattedra di Malattie del Ricambio, University of Padova, Italy.
  Source: Riccio, A Del Prato, S Vigili de Kreutzenberg, S Tiengo, A Diabete-Metab. 1991 May; 17(1 Pt 2): 180-4 0338-1684

- **Glyburide/metformin combination product is safe and efficacious in patients with type 2 diabetes failing sulphonylurea therapy.**
  Author(s): Ochsner Clinic Foundation, New Orleans, LA 70121, USA. lblonde@ochsner.org
  Source: Blonde, L Rosenstock, J Mooradian, A D Piper, B A Henry, D Diabetes-Obes-Metab. 2002 November; 4(6): 368-75 1462-8902

- **Inhibition of carbohydrate-induced hyperglyceridemia by metformin [Fructose-induced].**
  Source: Zavaroni, I. Dall'Aglio, E. Bruschi, F. Alpi, O. Coscelli, C. Horm-Metab-Res. Stuttgart, W. Ger. : Georg Thieme. February 1984. volume 16 (2) page 85-87. 0018-5043

- **Insulin, glibenclamide or metformin treatment for non insulin dependent diabetes: heterogenous responses of standard measures of insulin action and insulin secretion before and after differing hypoglycaemic therapy.**
  Author(s): Sir George E Clark Metabolic Unit, Royal Victoria Hospital, Belfast, UK.
  Source: Boyd, K Rogers, C Boreham, C Andrews, W J Hadden, D R Diabetes-Res. 1992 February; 19(2): 69-76 0265-5985

- **Interleukin-8 production in human adipose tissue. inhibitory effects of anti-diabetic compounds, the thiazolidinedione ciglitazone and the biguanide metformin.**
  Author(s): Department of Endocrinology and Metabolism C, Aarhus Amtssygehus, Aarhus University Hospital and Faculty of Health Sciences, Aarhus University, Denmark. jmb@mail-online.dk
  Source: Bruun, J M Pedersen, S B Richelsen, B Horm-Metab-Res. 2000 Nov-December; 32(11-12): 537-41 0018-5043

- **Long-term glycaemic improvement after addition of metformin to insulin in insulin-treated obese type 2 diabetes patients.**
  Author(s): The Swedish Network for Pharmacoepidemiology, Malmo, Sweden.

Source: Hermann, L S Kalen, J Katzman, P Lager, I Nilsson, A Norrhamn, O Sartor, G Ugander, L Diabetes-Obes-Metab. 2001 December; 3(6): 428-34 1462-8902

- **Metformin & lifestyle intervention prevent Type 2 diabetes: lifestyle intervention has the greater effect.**
  Author(s): Department of Physiology and Pharmacology, School of Biomedical Sciences, University of Queensland, 4072 Australia. s_doggrell@yahoo.com
  Source: Doggrell, S A Expert-Opin-Pharmacother. 2002 July; 3(7): 1011-3 1465-6566

- **Metformin and carbohydrate-modified diet: a novel obesity treatment protocol: preliminary findings from a case series of nondiabetic women with midlife weight gain and hyperinsulinemia.**
  Author(s): Division of Endocrinology, New York Medical College, Valhalla, New York, USA. hrmogul@nymc.edu
  Source: Mogul, H R Peterson, S J Weinstein, B I Zhang, S Southren, A L Heart-Dis. 2001 Sep-October; 3(5): 285-92 1521-737X

- **Metformin decreases platelet superoxide anion production in diabetic patients.**
  Author(s): Department of Endocrinology, University of Rome La Sapienza, Rome, Italy.
  Source: Gargiulo, P Caccese, D Pignatelli, P Brufani, C De Vito, F Marino, R Lauro, R Violi, F Di Mario, U Sanguigni, V Diabetes-Metab-Res-Revolume 2002 Mar-April; 18(2): 156-9 1520-7552

- **Metformin enhances certain insulin actions in cultured rat hepatoma cells.**
  Author(s): Cattedra di Endocrinologia e Patologia Costituzionale, University of Catania, Italy.
  Source: Purrello, F Gullo, D Buscema, M Pezzino, V Vigneri, R Goldfine, I D Diabetologia. 1988 June; 31(6): 385-9 0012-186X

- **Metformin improves lipid metabolism and attenuates lipid peroxidation in high fructose-fed rats.**
  Author(s): Department of Biochemistry, Annamalai University, Tamil Nadu, India.
  Source: Anurag, P Anuradha, C V Diabetes-Obes-Metab. 2002 January; 4(1): 36-42 1462-8902

- **Metformin increases circulating tumour necrosis factor-alpha levels in non-obese non-diabetic patients with coronary heart disease.**
  Author(s): Section of Endocrinology, University Hospital of Trondheim, Norway.
  Source: Carlsen, S M Waage, A Grill, V Folling, I Cytokine. 1998 January; 10(1): 66-9 1043-4666

- **Metformin potentiates B-cell response to high glucose: an in vitro study on isolated perfused pancreas from normal rats.**
  Author(s): Istituti di Clinica Medica Ie, Universita di Perugia, Italy.
  Source: Gregorio, F Filipponi, P Ambrosi, F Cristallini, S Marchetti, P Calafiore, R Navalesi, R Brunetti, P Diabete-Metab. 1989 May-June; 15(3): 111-7 0338-1684

- **Metformin-like effects of quei fu di huang wan, a chinese herbal mixture, on streptozotocin-induced diabetic rat.**
  Author(s): Department of Pharmacology, College of Medicine, National Cheng Kung University, Tainan City, Taiwan, R.O.C.
  Source: Cheng, J T Liu, I M Chi, T C Su, H C Chang, C G Horm-Metab-Res. 2001 December; 33(12): 727-32 0018-5043

- **Miglitol combined with metformin improves glycaemic control in type 2 diabetes.**
  Author(s): Department of Endocrinology, Metabolism and Clinical Nutrition, Faculty of Medicine, Universitaire Instelling Antwerpen, Wilrijkstraat 10, B-2650 Antwerp, Belgium. luc.van.gaal@uza.uia.ac.be
  Source: Van Gaal, L Maislos, M Schernthaner, G Rybka, J Segal, P Diabetes-Obes-Metab. 2001 October; 3(5): 326-31 1462-8902

- **Nateglinide improves glycaemic control when added to metformin monotherapy: results of a randomized trial with type 2 diabetes patients.**
  Author(s): Department of Diabetology, Hospital Bichat-Claude Bernard, Paris, France. michel.marre@bch.ap-hop-paris.fr
  Source: Marre, M Van Gaal, L Usadel, K H Ball, M Whatmough, I Guitard, C Diabetes-Obes-Metab. 2002 May; 4(3): 177-86 1462-8902

- **Oral antidiabetic combination therapy with sulphonylureas and metformin.**
  Author(s): Saale Hospital, Bad Kissingen, Germany.
  Source: Haupt, E Knick, B Koschinsky, T Liebermeister, H Schneider, J Hirche, H Diabete-Metab. 1991 May; 17(1 Pt 2): 224-31 0338-1684

- **Prospective randomized two-years clinical study comparing additional metformin treatment with reducing diet in type 2 diabetes.**
  Author(s): Diabetes Clinic Bad Mergentheim, Germany.
  Source: Teupe, B Bergis, K Diabete-Metab. 1991 May; 17(1 Pt 2): 213-7 0338-1684

- **Results of use of metformin and replacement of starch with saturated fat in diets of patients with type 2 diabetes.**
  Author(s): Christiana Care Health Services, Inc., Cardiology Research, Newark, Delaware 19718, USA.,
  Source: Hays, J H Gorman, R T Shakir, K M Endocr-Pract. 2002 May-June; 8(3): 177-83 1530-891X

- **Reversal of increased lymphocyte PC-1 activity in patients with type 2 diabetes treated with metformin.**
  Author(s): Institute of Nephrology and Hemodialysis, Faculty of Medicine, Nis, Yugoslavia. stefanovic@cent.co.yu
  Source: Stefanovic, V Antic, S Mitic Zlatkovic, M Vlahovic, P Diabetes-Metab-Res-Revolume 1999 Nov-December; 15(6): 400-4 1520-7552

- **Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes.**
  Author(s): Baylor College of Medicine and The Methodist Hospital, Houston, Texas 77030, USA. agarber@bcm.tmc.edu
  Source: Garber, A J Larsen, J Schneider, S H Piper, B A Henry, D Diabetes-Obes-Metab. 2002 May; 4(3): 201-8 1462-8902

- **Sulfonylurea-metformin-combination versus sulfonylurea-insulin-combination in secondary failures of sulfonylurea monotherapy. Results of a prospective randomized study in 50 patients.**
  Author(s): Department of Internal Medicine, Hospital of Berlin-Spandau, Germany.
  Source: Klein, W Diabete-Metab. 1991 May; 17(1 Pt 2): 235-40 0338-1684

- **The influence of Guar gum on absorption of metformin from the gut in healthy volunteers.**
  Author(s): Clinique Medicale et des maladies infectieuses, Hopital Pellegrin, Bordeaux, France.

Source: Gin, H Orgerie, M B Aubertin, J Horm-Metab-Res. 1989 February; 21(2): 81-3 0018-5043

- **Three-month treatment with metformin or dexfenfluramine does not modify the effects of diet on anthropometric and endocrine-metabolic parameters in abdominal obesity.**
  Author(s): Dipartimento di Medicina Interna, Universita di Torino, Italy.
  Source: Oleandri, S E Maccario, M Rossetto, R Procopio, M Grottoli, S Avogadri, E Gauna, C Ganzaroli, C Ghigo, E J-Endocrinol-Invest. 1999 February; 22(2): 134-40 0391-4097
- **Treatment of NIDDM patients with secondary failure to glyburide: comparison of the addition of either metformin or bed-time NPH insulin to glyburide.**
  Author(s): Cattedra di Endocrinologia dell'Universita di Catania, Italy.
  Source: Vigneri, R Trischitta, V Italia, S Mazzarino, S Rabuazzo, M A Squatrito, S Diabete-Metab. 1991 May; 17(1 Pt 2): 232-4 0338-1684
- **Treatment of type 2 diabetes: a review of metformin in clinical practice.**
  Author(s): Physician Assistant Program, Medical University of South Carolina, Charleston 29425, USA.
  Source: Hadley, R D Whaley, J W Askins, D G J-S-C-Med-Assoc. 1998 January; 94(1): 12-5 0038-3139
- **Treatment strategies for secondary sulfonylurea failure. Should we start insulin or add metformin? Is there a place for intermittent insulin therapy?**
  Author(s): Fourth Department of Medicine, Helsinki University Hospital, Finland.
  Source: Groop, L Widen, E Diabete-Metab. 1991 May; 17(1 Pt 2): 218-23 0338-1684
- **Utility of metformin as an adjunct to hydroxycitrate/carnitine for reducing body fat in diabetics.**
  Author(s): Nutrition 21, San Diego, CA 92109, USA.
  Source: McCarty, M F Med-Hypotheses. 1998 November; 51(5): 399-403 0306-9877

Federal Resources on Nutrition

In addition to the IBIDS, the United States Department of Health and Human Services (HHS) and the United States Department of Agriculture (USDA) provide many sources of information on general nutrition and health. Recommended resources include:

- healthfinder®, HHS's gateway to health information, including diet and nutrition: **http://www.healthfinder.gov/scripts/SearchContext.asp?topic=238&page=0**
- The United States Department of Agriculture's Web site dedicated to nutrition information: **www.nutrition.gov**
- The Food and Drug Administration's Web site for federal food safety information: **www.foodsafety.gov**
- The National Action Plan on Overweight and Obesity sponsored by the United States Surgeon General: **http://www.surgeongeneral.gov/topics/obesity/**
- The Center for Food Safety and Applied Nutrition has an Internet site sponsored by the Food and Drug Administration and the Department of Health and Human Services: **http://vm.cfsan.fda.gov/**

- Center for Nutrition Policy and Promotion sponsored by the United States Department of Agriculture: **http://www.usda.gov/cnpp/**
- Food and Nutrition Information Center, National Agricultural Library sponsored by the United States Department of Agriculture: **http://www.nal.usda.gov/fnic/**
- Food and Nutrition Service sponsored by the United States Department of Agriculture: **http://www.fns.usda.gov/fns/**

Additional Web Resources

A number of additional Web sites offer encyclopedic information covering food and nutrition. The following is a representative sample:

- AOL: **http://search.aol.com/cat.adp?id=174&layer=&from=subcats**
- Family Village: **http://www.familyvillage.wisc.edu/med_nutrition.html**
- Google: **http://directory.google.com/Top/Health/Nutrition/**
- Healthnotes: **http://www.healthnotes.com/**
- Open Directory Project: **http://dmoz.org/Health/Nutrition/**
- Yahoo.com: **http://dir.yahoo.com/Health/Nutrition/**
- WebMD®Health: **http://my.webmd.com/nutrition**
- WholeHealthMD.com: **http://www.wholehealthmd.com/reflib/0,1529,00.html**

The following is a specific Web list relating to metformin; please note that any particular subject below may indicate either a therapeutic use, or a contraindication (potential danger), and does not reflect an official recommendation:

- **Vitamins**

  Folic Acid
  Source: Healthnotes, Inc.; www.healthnotes.com

  Niacin
  Alternative names: Vitamin B3 (Niacin)
  Source: Integrative Medicine Communications; www.drkoop.com

  Vitamin B12
  Source: Healthnotes, Inc.; www.healthnotes.com

  Vitamin B12
  Source: Prima Communications, Inc.www.personalhealthzone.com

  Vitamin B12 (cobalamin)
  Alternative names: Cobalamin
  Source: Integrative Medicine Communications; www.drkoop.com

Vitamin B3 (niacin)
Alternative names: Niacin
Source: Integrative Medicine Communications; www.drkoop.com

- **Minerals**

  Calcium
  Source: Healthnotes, Inc.; www.healthnotes.com

  Chromium
  Source: Integrative Medicine Communications; www.drkoop.com

  Magnesium
  Source: Healthnotes, Inc.; www.healthnotes.com

CHAPTER 3. ALTERNATIVE MEDICINE AND METFORMIN

Overview

In this chapter, we will begin by introducing you to official information sources on complementary and alternative medicine (CAM) relating to metformin. At the conclusion of this chapter, we will provide additional sources.

National Center for Complementary and Alternative Medicine

The National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (**http://nccam.nih.gov/**) has created a link to the National Library of Medicine's databases to facilitate research for articles that specifically relate to metformin and complementary medicine. To search the database, go to the following Web site: **http://www.nlm.nih.gov/nccam/camonpubmed.html**. Select "CAM on PubMed." Enter "metformin" (or synonyms) into the search box. Click "Go." The following references provide information on particular aspects of complementary and alternative medicine that are related to metformin:

- **A preliminary evaluation of the efficacy and safety of Cogent db (an ayurvedic drug) in the glycemic control of patients with type 2-diabetes.**
  Author(s): Shekhar KC, Achike FI, Kaur G, Kumar P, Hashim R.
  Source: Journal of Alternative and Complementary Medicine (New York, N.Y.). 2002 August; 8(4): 445-57.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12230905&dopt=Abstract

- **Anti-diabetic property of ethanolic extract of Andrographis paniculata in streptozotocin-diabetic rats.**
  Author(s): Zhang XF, Tan BK.
  Source: Acta Pharmacologica Sinica. 2000 December; 21(12): 1157-64.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11603293&dopt=Abstract

- **Antihyperglycaemic and anti-oxidant properties of Andrographis paniculata in normal and diabetic rats.**
  Author(s): Zhang XF, Tan BK.
  Source: Clinical and Experimental Pharmacology & Physiology. 2000 May-June; 27(5-6): 358-63.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10831236&dopt=Abstract

- **Antihyperglycemic activity of phenolics from Pterocarpus marsupium.**
  Author(s): Manickam M, Ramanathan M, Jahromi MA, Chansouria JP, Ray AB.
  Source: Journal of Natural Products. 1997 June; 60(6): 609-10.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9214733&dopt=Abstract

- **Argyria associated with colloidal silver supplementation.**
  Author(s): McKenna JK, Hull CM, Zone JJ.
  Source: International Journal of Dermatology. 2003 July; 42(7): 549.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12839605&dopt=Abstract

- **Caloric restriction in primates and relevance to humans.**
  Author(s): Roth GS, Ingram DK, Lane MA.
  Source: Annals of the New York Academy of Sciences. 2001 April; 928: 305-15. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11795522&dopt=Abstract

- **Chronic diseases management in the Jamaican setting: HOPE worldwide Jamaica's experience.**
  Author(s): Swaby P, Wilson E, Swaby S, Sue-Ho R, Pierre R.
  Source: P N G Med J. 2001 September-December; 44(3-4): 171-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12422988&dopt=Abstract

- **Cryptolepis sanguinolenta: an ethnobotanical approach to drug discovery and the isolation of a potentially useful new antihyperglycaemic agent.**
  Author(s): Luo J, Fort DM, Carlson TJ, Noamesi BK, nii-Amon-Kotei D, King SR, Tsai J, Quan J, Hobensack C, Lapresca P, Waldeck N, Mendez CD, Jolad SD, Bierer DE, Reaven GM.
  Source: Diabetic Medicine : a Journal of the British Diabetic Association. 1998 May; 15(5): 367-74.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9609357&dopt=Abstract

- **Demonstration of the hypoglycemic action of Momordica charantia in a validated animal model of diabetes.**
  Author(s): Sarkar S, Pranava M, Marita R.

Source: Pharmacological Research : the Official Journal of the Italian Pharmacological Society. 1996 January; 33(1): 1-4.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8817639&dopt=Abstract

- **Determination of metformin in plasma by high-performance liquid chromatography after ultrafiltration.**
  Author(s): Vesterqvist O, Nabbie F, Swanson B.
  Source: J Chromatogr B Biomed Sci Appl. 1998 September 25; 716(1-2): 299-304.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9824244&dopt=Abstract

- **Dietary and medical treatments of obesity: an evaluative review.**
  Author(s): Chlouverakis C.
  Source: Addictive Behaviors. 1975 July; 1(1): 3-21.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1234706&dopt=Abstract

- **Differential effects of rosiglitazone and metformin on adipose tissue distribution and glucose uptake in type 2 diabetic subjects.**
  Author(s): Virtanen KA, Hallsten K, Parkkola R, Janatuinen T, Lonnqvist F, Viljanen T, Ronnemaa T, Knuuti J, Huupponen R, Lonnroth P, Nuutila P.
  Source: Diabetes. 2003 February; 52(2): 283-90.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12540598&dopt=Abstract

- **Drugs controlling triglyceride metabolism.**
  Author(s): Franceschini G, Paoletti R.
  Source: Medicinal Research Reviews. 1993 March; 13(2): 125-38. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8445954&dopt=Abstract

- **Effect of Luffa aegyptiaca (seeds) and Carissa edulis (leaves) extracts on blood glucose level of normal and streptozotocin diabetic rats.**
  Author(s): El-Fiky FK, Abou-Karam MA, Afify EA.
  Source: Journal of Ethnopharmacology. 1996 January; 50(1): 43-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8778506&dopt=Abstract

- **Effect of masoprocol on carbohydrate and lipid metabolism in a rat model of Type II diabetes.**
  Author(s): Reed MJ, Meszaros K, Entes LJ, Claypool MD, Pinkett JG, Brignetti D, Luo J, Khandwala A, Reaven GM.
  Source: Diabetologia. 1999 January; 42(1): 102-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10027587&dopt=Abstract

- **Effects of an ethanolic extract of Gynura procumbens on serum glucose, cholesterol and triglyceride levels in normal and streptozotocin-induced diabetic rats.**
  Author(s): Zhang XF, Tan BK.

Source: Singapore Med J. 2000 January; 41(1): 9-13.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10783673&dopt=Abstract

- **Effects of Averrhoa bilimbi leaf extract on blood glucose and lipids in streptozotocin-diabetic rats.**
  Author(s): Pushparaj P, Tan CH, Tan BK.
  Source: Journal of Ethnopharmacology. 2000 September; 72(1-2): 69-76.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10967456&dopt=Abstract

- **Effects of konjac extract on insulin sensitivity in high fat diet rats.**
  Author(s): Mao CP, Xie ML, Gu ZL.
  Source: Acta Pharmacologica Sinica. 2002 September; 23(9): 855-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12230958&dopt=Abstract

- **Evidence of a threshold value of glycated hemoglobin to improve the course of renal function in type 2 diabetes with typical diabetic glomerulopathy.**
  Author(s): Brocco E, Velussi M, Cernigoi AM, Abaterusso C, Bruseghin M, Carraro A, Sambataro M, Piarulli F, Sfriso A, Nosadini R.
  Source: Journal of Nephrology. 2001 November-December; 14(6): 461-71.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11783602&dopt=Abstract

- **General practice care of non-insulin-dependent diabetes with fasting blood glucose measurements.**
  Author(s): Muir A, Howe-Davies SA, Turner RC.
  Source: The American Journal of Medicine. 1982 November; 73(5): 637-40.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7137201&dopt=Abstract

- **Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group.**
  Author(s): Turner RC, Cull CA, Frighi V, Holman RR.
  Source: Jama : the Journal of the American Medical Association. 1999 June 2; 281(21): 2005-12.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10359389&dopt=Abstract

- **Hepatothermic therapy of obesity: rationale and an inventory of resources.**
  Author(s): McCarty MF.
  Source: Medical Hypotheses. 2001 September; 57(3): 324-36.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11516225&dopt=Abstract

- **Hypoglycemic effect of guava juice in mice and human subjects.**
  Author(s): Cheng JT, Yang RS.

Source: The American Journal of Chinese Medicine. 1983; 11(1-4): 74-6.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=6660217&dopt=Abstract

- **Hypoglycemic effects of Potentilla fulgens L in normal and alloxan-induced diabetic mice.**
  Author(s): Syiem D, Syngai G, Khup PZ, Khongwir BS, Kharbuli B, Kayang H.
  Source: Journal of Ethnopharmacology. 2002 November; 83(1-2): 55-61.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12413707&dopt=Abstract

- **Impaired beta-cell responses improve when fasting blood glucose concentration is reduced in non-insulin-dependent diabetes.**
  Author(s): Ferner RE, Rawlins MD, Alberti KG.
  Source: The Quarterly Journal of Medicine. 1988 February; 66(250): 137-46.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3051084&dopt=Abstract

- **In vivo metformin treatment ameliorates insulin resistance: evidence for potentiation of insulin-induced translocation and increased functional activity of glucose transporters in obese (fa/fa) Zucker rat adipocytes.**
  Author(s): Matthaei S, Reibold JP, Hamann A, Benecke H, Haring HU, Greten H, Klein HH.
  Source: Endocrinology. 1993 July; 133(1): 304-11.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8391425&dopt=Abstract

- **Increase of insulin sensitivity in diabetic rats received die-huang-wan, a herbal mixture used in Chinese traditional medicine.**
  Author(s): Wu YC, Hsu JH, Liu IM, Liou SS, Su HC, Cheng JT.
  Source: Acta Pharmacologica Sinica. 2002 December; 23(12): 1181-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12466058&dopt=Abstract

- **Management of non-insulin-dependent diabetes mellitus.**
  Author(s): Lefebvre PJ, Scheen AJ.
  Source: Drugs. 1992; 44 Suppl 3: 29-38. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1280575&dopt=Abstract

- **Metformin but not glyburide prevents high glucose-induced abnormalities in relaxation and intracellular Ca2+ transients in adult rat ventricular myocytes.**
  Author(s): Ren J, Dominguez LJ, Sowers JR, Davidoff AJ.
  Source: Diabetes. 1999 October; 48(10): 2059-65.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10512374&dopt=Abstract

- **Metformin reduces platelet hypersensitivity in hypercholesterolemic rabbits.**
  Author(s): Tremoli E, Ghiselli G, Maderna P, Colli S, Sirtori CR.

Source: Atherosclerosis. 1982 January; 41(1): 53-60.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7073794&dopt=Abstract

- **Metformin-like effects of Quei Fu Di Huang Wan, a Chinese herbal mixture, on streptozotocin-induced diabetic rat.**
  Author(s): Cheng JT, Liu IM, Chi TC, Su HC, Chang CG.
  Source: Hormone and Metabolic Research. Hormon- Und Stoffwechselforschung. Hormones Et Metabolisme. 2001 December; 33(12): 727-32.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11753758&dopt=Abstract

- **One-year acarbose treatment raises fasting serum acetate in diabetic patients.**
  Author(s): Wolever TM, Radmard R, Chiasson JL, Hunt JA, Josse RG, Palmason C, Rodger NW, Ross SA, Ryan EA, Tan MH.
  Source: Diabetic Medicine : a Journal of the British Diabetic Association. 1995 February; 12(2): 164-72.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7743764&dopt=Abstract

- **Pancreatic beta cell response in insulin treated NIDDM patients limitations of a random C-peptide measurement.**
  Author(s): Snehalatha C, Ramachandran A, Mohan V, Viswanathan M.
  Source: Diabete Metab. 1987 February; 13(1): 27-30.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3552773&dopt=Abstract

- **Pharmacological control of hypertriglyceridemia.**
  Author(s): Franceschini G, Paoletti R.
  Source: Cardiovascular Drugs and Therapy / Sponsored by the International Society of Cardiovascular Pharmacotherapy. 1993 June; 7(3): 297-302. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8364001&dopt=Abstract

- **Pharmacotherapy of type 2 diabetes mellitus.**
  Author(s): Rendell MS, Kirchain WR.
  Source: The Annals of Pharmacotherapy. 2000 July-August; 34(7-8): 878-95. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10928401&dopt=Abstract

- **Reversal of diabetes-induced rat graft transplant coronary artery disease by metformin.**
  Author(s): Cantin B, Zhu D, Wen P, Panchal SN, Dai X, Gwathmey JK, Reaven GM, Valantine HA.
  Source: The Journal of Heart and Lung Transplantation : the Official Publication of the International Society for Heart Transplantation. 2002 June; 21(6): 637-43.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12057696&dopt=Abstract

- **Rosiglitazone but not metformin enhances insulin- and exercise-stimulated skeletal muscle glucose uptake in patients with newly diagnosed type 2 diabetes.**
  Author(s): Hallsten K, Virtanen KA, Lonnqvist F, Sipila H, Oksanen A, Viljanen T, Ronnemaa T, Viikari J, Knuuti J, Nuutila P.
  Source: Diabetes. 2002 December; 51(12): 3479-85.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12453903&dopt=Abstract

- **The blooming of the French lilac.**
  Author(s): Witters LA.
  Source: The Journal of Clinical Investigation. 2001 October; 108(8): 1105-7. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11602616&dopt=Abstract

- **The mechanism of hypoglycemic action of the semi-purified fractions of Averrhoa bilimbi in streptozotocin-diabetic rats.**
  Author(s): Pushparaj PN, Tan BK, Tan CH.
  Source: Life Sciences. 2001 December 21; 70(5): 535-47.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11811898&dopt=Abstract

- **The role of the family in managing therapy in minority children with type 2 diabetes mellitus.**
  Author(s): Bradshaw B.
  Source: J Pediatr Endocrinol Metab. 2002 April; 15 Suppl 1: 547-51.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12017230&dopt=Abstract

- **Toward practical prevention of type 2 diabetes.**
  Author(s): McCarty MF.
  Source: Medical Hypotheses. 2000 May; 54(5): 786-93.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10859688&dopt=Abstract

- **Trivalent chromium and the diabetes prevention program.**
  Author(s): Linday LA.
  Source: Medical Hypotheses. 1997 July; 49(1): 47-9. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9247907&dopt=Abstract

Additional Web Resources

A number of additional Web sites offer encyclopedic information covering CAM and related topics. The following is a representative sample:

- Alternative Medicine Foundation, Inc.: **http://www.herbmed.org/**
- AOL: **http://search.aol.com/cat.adp?id=169&layer=&from=subcats**
- Chinese Medicine: **http://www.newcenturynutrition.com/**

- drkoop.com®: **http://www.drkoop.com/InteractiveMedicine/IndexC.html**
- Family Village: **http://www.familyvillage.wisc.edu/med_altn.htm**
- Google: **http://directory.google.com/Top/Health/Alternative/**
- Healthnotes: **http://www.healthnotes.com/**
- MedWebPlus: **http://medwebplus.com/subject/Alternative_and_Complementary_Medicine**
- Open Directory Project: **http://dmoz.org/Health/Alternative/**
- HealthGate: **http://www.tnp.com/**
- WebMD®Health: **http://my.webmd.com/drugs_and_herbs**
- WholeHealthMD.com: **http://www.wholehealthmd.com/reflib/0,1529,00.html**
- Yahoo.com: **http://dir.yahoo.com/Health/Alternative_Medicine/**

The following is a specific Web list relating to metformin; please note that any particular subject below may indicate either a therapeutic use, or a contraindication (potential danger), and does not reflect an official recommendation:

- **General Overview**

  Diabetes Mellitus
  Source: Integrative Medicine Communications; www.drkoop.com

  Hirsuitism
  Source: Integrative Medicine Communications; www.drkoop.com

- **Herbs and Supplements**

  Biguanides
  Source: Integrative Medicine Communications; www.drkoop.com

  Cobalamin
  Alternative names: Vitamin B12 (Cobalamin)
  Source: Integrative Medicine Communications; www.drkoop.com

  Dehydroepiandrosterone
  Source: Healthnotes, Inc.; www.healthnotes.com

  Fiber
  Source: Integrative Medicine Communications; www.drkoop.com

  Garcinia Cambogia
  Alternative names: Citrin, Gambooge
  Source: Alternative Medicine Foundation, Inc.; www.amfoundation.org

  Gymnema Sylvestre
  Source: WholeHealthMD.com, LLC.; www.wholehealthmd.com

Hyperlink:
http://www.wholehealthmd.com/refshelf/substances_view/0,1525,10034,00.html

Luffa
Alternative names: Luffa sp.
Source: Alternative Medicine Foundation, Inc.; www.amfoundation.org

Metformin
Source: Healthnotes, Inc.; www.healthnotes.com

Oral Hypoglycemics
Source: Prima Communications, Inc.www.personalhealthzone.com

General References

A good place to find general background information on CAM is the National Library of Medicine. It has prepared within the MEDLINEplus system an information topic page dedicated to complementary and alternative medicine. To access this page, go to the MEDLINEplus site at **http://www.nlm.nih.gov/medlineplus/alternativemedicine.html**. This Web site provides a general overview of various topics and can lead to a number of general sources.

CHAPTER 4. DISSERTATIONS ON METFORMIN

Overview

In this chapter, we will give you a bibliography on recent dissertations relating to metformin. We will also provide you with information on how to use the Internet to stay current on dissertations. **IMPORTANT NOTE:** When following the search strategy described below, you may discover non-medical dissertations that use the generic term "metformin" (or a synonym) in their titles. To accurately reflect the results that you might find while conducting research on metformin, we have not necessarily excluded non-medical dissertations in this bibliography.

Dissertations on Metformin

ProQuest Digital Dissertations, the largest archive of academic dissertations available, is located at the following Web address: **http://wwwlib.umi.com/dissertations**. From this archive, we have compiled the following list covering dissertations devoted to metformin. You will see that the information provided includes the dissertation's title, its author, and the institution with which the author is associated. The following covers recent dissertations found when using this search procedure:

- **Metformin As an Adjunct to Insulin Therapy in Adolescents with Type 1 Diabetes: a Pilot Study** by Hamilton, Jill Krysti; MSC from University of Toronto (Canada), 2002, 90 pages
  http://wwwlib.umi.com/dissertations/fullcit/MQ68793

Keeping Current

Ask the medical librarian at your library if it has full and unlimited access to the *ProQuest Digital Dissertations* database. From the library, you should be able to do more complete searches via **http://wwwlib.umi.com/dissertations**.

CHAPTER 5. CLINICAL TRIALS AND METFORMIN

Overview

In this chapter, we will show you how to keep informed of the latest clinical trials concerning metformin.

Recent Trials on Metformin

The following is a list of recent trials dedicated to metformin.[8] Further information on a trial is available at the Web site indicated.

- **Evaluation of the Effect on Glucose Control and Safety of AC2993 in Patients With Type 2 Diabetes Treated With Metformin, Sulfonylurea, or Metformin and Sulfonylurea Combination**

  Condition(s): Diabetes Mellitus, Non-Insulin-Dependent

  Study Status: This study is currently recruiting patients.

  Sponsor(s): Amylin Pharmaceuticals

  Purpose - Excerpt: This multi-center, open-label study is designed to examine the effects on long-term glucose control and safety of AC2993 in patients with type 2 diabetes treated with metformin, sulfonylurea, or metformin and sulfonylurea combination.

  Phase(s): Phase III

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00044668

- **Improving Compliance with Metformin**

  Condition(s): Diabetes

  Study Status: This study is currently recruiting patients.

  Sponsor(s): Department of Veterans Affairs Medical Research Service

[8] These are listed at **www.ClinicalTrials.gov**.

Purpose - Excerpt: This is a randomized controlled trial of adherence. The study involves monitoring and managing focused intervention in patients prescribed metformin.

Phase(s): Phase II

Study Type: Interventional

Contact(s): see Web site below

Web Site: http://clinicaltrials.gov/ct/show/NCT00018616

- **Metformin and Rosiglitazone, Alone or in Combination, in HIV-Infected Patients with Insulin and Fat Abnormalities**

  Condition(s): HIV Infections; Lipodystrophy; Hyperinsulinemia

  Study Status: This study is currently recruiting patients.

  Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID)

  Purpose - Excerpt: The purpose of this study is to see whether metformin alone, rosiglitazone alone, or metformin and rosiglitazone together will lower insulin levels in the blood and decrease fat in the abdomen or other parts of the body. Studies have shown that certain anti-HIV medications can cause a number of side effects, including high blood sugar (resulting from the body's failure to use insulin), high insulin, and excess fat build-up in the abdominal area. These side effects are known to increase the risk of heart disease. Metformin and rosiglitazone are 2 drugs that have been shown to lower insulin resistance and lessen abdominal fat in patients who are not HIV-infected. This study will investigate the use of these drugs in HIV-infected patients.

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00015691

- **Metformin to Treat Obesity in Children with Insulin Resistance**

  Condition(s): Hyperinsulinemia; Obesity

  Study Status: This study is currently recruiting patients.

  Sponsor(s): National Institute of Child Health and Human Development (NICHD)

  Purpose - Excerpt: This study will examine the safety and effectiveness of the medicine metformin to help overweight children control their food intake, weight, insulin, cholesterol, and triglyceride (blood fat) levels. Obesity and high insulin levels can lead to high blood pressure, diabetes, high cholesterol and triglyceride levels and heart disease. Metformin-approved by the Food and Drug Administration to treat adults with type 2 diabetes mellitus-helps lower insulin levels and may control weight gain in adults. Overweight children 6 to 11 years old who are in general good health may be eligible for this study. Children will be studied at the National Institutes of Health in Bethesda, Maryland, and at the Phoenix Indian Medical Center and the Gila River Reservation in the Phoenix, Arizona area. Candidates will have a medical history and physical examination and fasting blood test, and will provide a 7-day record of their food intake as part of the screening process. Those enrolled will be randomly assigned to receive either metformin or placebo (a look-alike tablet with no active medicine) twice a day for a six month period. After the 6 month study period, all children will be offered the opportunity to take metformin for another 6 months. Participants will be hospitalized for 2-3 days for the following procedures: history and physical

examination; fasting blood test; several urine collections; X-ray studies to determine bone age and amount of body fat and muscle; magnetic resonance imaging (MRI) scan to measure body fat; "hyperglycemic clamp study" to evaluate insulin resistance; food intake testing; nutrition consultation; resting metabolic rate; and a "doubly labeled water" test. For the hyperglycemic clamp study, a catheter (thin flexible tube) is inserted into a vein in each arm. A sugar solution is given through one tube and blood samples are drawn every 5 minutes through the other to measure insulin. For the food intake testing, the child is asked about his or her hunger level, then given various foods he or she may choose to eat, then questioned again at various intervals both during and after finishing eating about his or her hunger level. The doubly labeled water study involves drinking "heavy water" (water which is enriched to have special kinds of hydrogen and oxygen). Urine specimens are collected 2, 3 and 4 hours after drinking the water. The child also drinks a special milk shake called a Scandishake and repeats the calorie intake and hunger study. (Two food intake studies are done on separate days.) One week after the heavy water test, additional urine samples are collected one week later. After completing the tests, the child will begin treatment with metformin or placebo, plus a daily vitamin tablet. Participants will be followed once a month with a brief history and physical examination, including a blood test. After 6 months, all of the tests described above will be repeated. All children who complete the second round of tests-both those who took metformin and those who took placebo-will be offered metformin for an additional 6 months and will be seen once a month for follow-up evaluations. Parents will not be told which children received metformin and which received placebo until all children in the study complete the first 6 months of the trial.

Phase(s): Phase II

Study Type: Interventional

Contact(s): see Web site below

Web Site: http://clinicaltrials.gov/ct/show/NCT00005669

- **Treating Nonalcoholic Steatohepatitis (NASH) with Metformin**

  Condition(s): Hepatitis

  Study Status: This study is currently recruiting patients.

  Sponsor(s): National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

  Purpose - Excerpt: Nonalcoholic Steatohepatitis (NASH) is associated with progressive liver disease, fibrosis, and cirrhosis. Although the cause of NASH is unknown, it is often associated with obesity, type 2 diabetes, and insulin resistance. At present, there are no approved treatments for NASH patients, but an experimental approach has focused on improving their insulin sensitivity. Metformin is one of the most commonly used medications for the treatment of diabetes. The purpose of this study is to determine whether the medical problems of NASH patients, specifically liver damage, improves when their insulin sensitivity is enhanced with metformin. The study will last 3 to 5 years and will enroll up to 30 patients. Participants will undergo a complete medical examination, a series of lab tests, and a liver biopsy. They will then start taking a single 500-mg tablet of metformin once a day for 2 weeks, then the same dosage twice a day for 2 more weeks, if they tolerate the first dosage. The dosage will increase to 1,000 mg twice a day for the remaining 44 weeks of the study. After 1 year, participants will undergo a repeat medical examination and liver biopsy.

  Phase(s): Phase II

  Study Type: Interventional

Contact(s): see Web site below

Web Site: http://clinicaltrials.gov/ct/show/NCT00063232

Keeping Current on Clinical Trials

The U.S. National Institutes of Health, through the National Library of Medicine, has developed ClinicalTrials.gov to provide current information about clinical research across the broadest number of diseases and conditions.

The site was launched in February 2000 and currently contains approximately 5,700 clinical studies in over 59,000 locations worldwide, with most studies being conducted in the United States. ClinicalTrials.gov receives about 2 million hits per month and hosts approximately 5,400 visitors daily. To access this database, simply go to the Web site at **http://www.clinicaltrials.gov/** and search by "metformin" (or synonyms).

While ClinicalTrials.gov is the most comprehensive listing of NIH-supported clinical trials available, not all trials are in the database. The database is updated regularly, so clinical trials are continually being added. The following is a list of specialty databases affiliated with the National Institutes of Health that offer additional information on trials:

- For clinical studies at the Warren Grant Magnuson Clinical Center located in Bethesda, Maryland, visit their Web site: **http://clinicalstudies.info.nih.gov/**
- For clinical studies conducted at the Bayview Campus in Baltimore, Maryland, visit their Web site: **http://www.jhbmc.jhu.edu/studies/index.html**
- For cancer trials, visit the National Cancer Institute: **http://cancertrials.nci.nih.gov/**
- For eye-related trials, visit and search the Web page of the National Eye Institute: **http://www.nei.nih.gov/neitrials/index.htm**
- For heart, lung and blood trials, visit the Web page of the National Heart, Lung and Blood Institute: **http://www.nhlbi.nih.gov/studies/index.htm**
- For trials on aging, visit and search the Web site of the National Institute on Aging: **http://www.grc.nia.nih.gov/studies/index.htm**
- For rare diseases, visit and search the Web site sponsored by the Office of Rare Diseases: **http://ord.aspensys.com/asp/resources/rsch_trials.asp**
- For alcoholism, visit the National Institute on Alcohol Abuse and Alcoholism: **http://www.niaaa.nih.gov/intramural/Web_dicbr_hp/particip.htm**
- For trials on infectious, immune, and allergic diseases, visit the site of the National Institute of Allergy and Infectious Diseases: **http://www.niaid.nih.gov/clintrials/**
- For trials on arthritis, musculoskeletal and skin diseases, visit newly revised site of the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health: **http://www.niams.nih.gov/hi/studies/index.htm**
- For hearing-related trials, visit the National Institute on Deafness and Other Communication Disorders: **http://www.nidcd.nih.gov/health/clinical/index.htm**
- For trials on diseases of the digestive system and kidneys, and diabetes, visit the National Institute of Diabetes and Digestive and Kidney Diseases: **http://www.niddk.nih.gov/patient/patient.htm**

- For drug abuse trials, visit and search the Web site sponsored by the National Institute on Drug Abuse: **http://www.nida.nih.gov/CTN/Index.htm**
- For trials on mental disorders, visit and search the Web site of the National Institute of Mental Health: **http://www.nimh.nih.gov/studies/index.cfm**
- For trials on neurological disorders and stroke, visit and search the Web site sponsored by the National Institute of Neurological Disorders and Stroke of the NIH: **http://www.ninds.nih.gov/funding/funding_opportunities.htm#Clinical_Trials**

CHAPTER 6. PATENTS ON METFORMIN

Overview

Patents can be physical innovations (e.g. chemicals, pharmaceuticals, medical equipment) or processes (e.g. treatments or diagnostic procedures). The United States Patent and Trademark Office defines a patent as a grant of a property right to the inventor, issued by the Patent and Trademark Office.[9] Patents, therefore, are intellectual property. For the United States, the term of a new patent is 20 years from the date when the patent application was filed. If the inventor wishes to receive economic benefits, it is likely that the invention will become commercially available within 20 years of the initial filing. It is important to understand, therefore, that an inventor's patent does not indicate that a product or service is or will be commercially available. The patent implies only that the inventor has "the right to exclude others from making, using, offering for sale, or selling" the invention in the United States. While this relates to U.S. patents, similar rules govern foreign patents.

In this chapter, we show you how to locate information on patents and their inventors. If you find a patent that is particularly interesting to you, contact the inventor or the assignee for further information. **IMPORTANT NOTE:** When following the search strategy described below, you may discover non-medical patents that use the generic term "metformin" (or a synonym) in their titles. To accurately reflect the results that you might find while conducting research on metformin, we have not necessarily excluded non-medical patents in this bibliography.

Patents on Metformin

By performing a patent search focusing on metformin, you can obtain information such as the title of the invention, the names of the inventor(s), the assignee(s) or the company that owns or controls the patent, a short abstract that summarizes the patent, and a few excerpts from the description of the patent. The abstract of a patent tends to be more technical in nature, while the description is often written for the public. Full patent descriptions contain much more information than is presented here (e.g. claims, references, figures, diagrams, etc.). We will tell you how to obtain this information later in the chapter. The following is an

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[9]Adapted from the United States Patent and Trademark Office: **http://www.uspto.gov/web/offices/pac/doc/general/whatis.htm**.

example of the type of information that you can expect to obtain from a patent search on metformin:

- **Biphasic controlled release delivery system for high solubility pharmaceuticals and method**

  Inventor(s): Dennis; Andrew B. (Barnston, GB), Timmins; Peter (Irby, GB), Vyas; Kiren A. (Canterbury, GB)

  Assignee(s): Bristol-Myers Squibb Co. (Princeton, NJ)

  Patent Number: 6,475,521

  Date filed: September 16, 1999

  Abstract: A biphasic controlled release delivery system for pharmaceuticals which have high water solubility, such as the antidiabetic **metformin** HCl salt, is provided which provides a dosage form that has prolonged gastric residence so that a dosing regimen of at least one gram **metformin,** once daily, may be achieved while providing effective control of plasma glucose. The delivery system includes (1) an inner solid particulate phase formed of substantially uniform granules containing a pharmaceutical having a high water solubility, and one or more hydrophilic polymers, one or more hydrophobic polymers and/or one or more hydrophobic materials such as one or more waxes, fatty alcohols and/or fatty acid esters, and (2) an outer solid continuous phase in which the above granules of inner solid particulate phase are embedded and dispersed throughout, the outer solid continuous phase including one or more hydrophilic polymers, one or more hydrophobic polymers and/or one or more hydrophobic materials such as one or more waxes, fatty alcohols and/or fatty acid esters, which may be compressed into tablets or filled into capsules. Methods for forming the so-described biphasic controlled release delivery system and using such biphasic controlled release delivery system for treating diabetes are also provided.

  Excerpt(s): The present invention relates to a new dosage form for highly water soluble medicaments, such as the antidiabetic **metformin,** which provides for extended release of the drug and also for prolonged gastric residence, so that a dosing regimen of at least one gram **metformin** once daily, may be achieved while providing effective control of plasma glucose, and to a method for treating diabetes employing such dosage form. Metformin is an antihyperglycemic agent of the biguanide class used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). It is usually marketed in the form of its hydrochloride salt as **Glucophage.**RTM. (TM-BMS). Metformin hydrochloride has intrinsically poor permeability in the lower portion of the gastrointestinal tract leading to absorption almost exclusively in the upper part of the gastrointestinal tract. Its oral bioavailability is in the range of 40 to 60% decreasing with increasing dosage which suggests some kind of saturable absorption process, or permeability/transit time limited absorption. It also has a very high water solubility (>300 mg/ml at 25.degree. C.). This can lead to difficulty in providing a slow release rate from a formulation and problems in controlling the initial burst of drug from such a formulation. These two difficulties are further compounded by the high unit dose, 500 mg per tablet, usually required for **metformin** hydrochloride (1997-PDR).

  Web site: http://www.delphion.com/details?pn=US06475521__

- **Composition containing ascorbic acid**

  Inventor(s): Ichihara; Junji (Takatsuki, JP), Itakura; Yasushi (Nara, JP), Noguchi; Hiroshi (Kawanishi, JP), Taiji; Mutsuo (Takatsuki, JP), Yamaga; Hiroshi (Suita, JP)

  Assignee(s): Sumitomo Pharmaceuticals Co., Ltd. (Osaka, JP)

  Patent Number: 6,399,658

  Date filed: June 9, 1999

  Abstract: L-ascorbic acid, L-ascorbic acid derivatives and salts thereof can reduce lactic acid levels in blood, and are useful for treating lactic acidosis and the like caused by administration of amoxapine, theophylline, **metformin,** phenformin, buformin, nalidixic acid, hopantenic acid, azidothymidine, dideoxycytidine, high caloric transfusion, propylene glycol, ethylene glycol, xylitol, lactose, sorbitol or the like.

  Excerpt(s): The present invention relates to a composition containing L-ascorbic acid, an L-ascorbic acid derivative or a salt thereof as an active ingredient. The composition of the present invention has the effect of reducing lactic acid levels in blood, and is useful, for example, for reducing side effect caused by a drug which has lactic acidosis as a side effect. Lactic acidosis is a state in which the lactic acid level in blood is 45 mg/dL or more, and pH of arterial blood is 7.25 or less. As to clinical symptoms, though lactic acidosis usually does not result in any symptoms in the early stage, later there appear, for example, low blood pressure, unconsciousness, nausea, vomiting, stomach ache, diarrhea, muscular ache, the state of hyperventilation and circulatory disorder etc. These symptoms often occur especially severely in elderly persons and patients with cardiac or renal disease etc. Certain kind of drugs and medical supplements are known to cause lactic acid levels to increase in blood as a side effect and to induce lactic acidosis. After lactic acidosis occurs, usage of the drugs and the medical supplements may be restricted, because of the possibility that they might worsen renal failure etc.

  Web site: http://www.delphion.com/details?pn=US06399658__

- **Core formulation comprised of troglitazone and a biguanide**

  Inventor(s): Adjei; Akwete L. (Bridgewater, NJ), Cutie; Anthony J. (Bridgewater, NJ), Zhu; Yaping (Highland Park, NJ)

  Assignee(s): Aeropharm Technology Incorporated ()

  Patent Number: 6,451,342

  Date filed: February 15, 2001

  Abstract: This invention relates to a controlled release combination drug product comprising troglitazone, e.g. its hydrochloride, and a biguamide, e.g. **metformin.** In particular, the product comprises a core of **metformin,** at least a portion thereof has a layer or coat thereon of troglitazone.

  Excerpt(s): This invention relates to a core formulation, and, more particularly, to a core formulation comprising a first layer comprising troglitazone, which covers at least a portion of a core comprising a biguanide, such as for example **metformin** (i.e., glucophage), with a modulating release polymer comprising a silicate. Metformin and troglitazone, and their salts such as the hydrochlorides, maleates, tartrates, etc., are two active ingredients of anti-diabetic drugs that are used to treat diabetic patients, e.g. human beings. These two active agents are administered orally to patients in need thereof in protocols calling for the single administration of either ingredient. Heretofore,

there has not been revealed or hinted at combining both ingredients and certainly not a physically combined core formulation comprising both ingredients. The advantage of such a core formulation is advantageous to patients and prescribers because both medicaments are synergistic to each other in the body when used in the management of blood glucose control, i.e., diabetes. Furthermore, the use of a modulating agent, like silica gel, in the preparation, controls the rate of drug release over a clinically meaningful period to enable better control of the effect of the medicinal agents in such preparation. This invention relates to a core formulation, and, more particularly, to a core formulation comprising a first layer comprising troglitazone or a derivative thereof, e.g. troglitazone hydrochloride, which covers at least a portion of a core comprising a biguanide, one or both of which are intimately dispersed in a silicate based modulating agent.

Web site: http://www.delphion.com/details?pn=US06451342__

- **Direct compression metformin hydrochloride tablets**

  Inventor(s): Kumar; Vijai (Morris Plains, NJ)

  Assignee(s): Pharmalogix, Inc. (Denville, NJ)

  Patent Number: 6,117,451

  Date filed: August 25, 1998

  Abstract: Metformin Hydrochloride (herein referred to as **metformin** HCl) that may be 98.5%-100% pure is a high dose drug capable of being directly compressed with specific excipients into tablets having desired, hardness, disintegrating ability, and acceptable dissolution characteristics. **Metformin** HCl is not inherently compressible and thus presents formulation problems. Excipients used in the formulation enhance the flow and compaction properties of the drug and tableting mix. Optimal flow contributes to uniform die fill and weight control. The binder used ensures sufficient cohesive properties that allow **metformin** HCl to be compressed using the direct compression method. The tablets produced provide an acceptable in-vitro dissolution profile.

  Excerpt(s): This invention relates to new direct compression **metformin** hydrochloride tablets, a process for the preparation thereof, and to new **metformin** hydrochloride formulations in the form of a tableting powder, capable of being directly compressed into the **metformin** hydrochloride tablets. The invention relates further to a process for preparing the direct compression **metformin** hydrochloride tablets by blending **metformin** and specific excipients into the new **metformin** hydrochloride formulations and then directly compressing the formulations into the direct compression tablets. Metformin HCl is hygroscopic, presents stability problems, and is not inherently compressible. Consequently, there is a need to provide a free-flowing and cohesive **metformin** HCl composition capable of being directly compressed into strong tablets with an acceptable in vitro dissolution profile. Tablets may be defined as solid dosage pharmaceutical forms containing drug substances with or without suitable fillers. They are produced by compression or compaction of a formulation containing the drug and certain excipients selected to aid in the processing and to improve the properties of the product. Tablets may be coated or uncoated and are made from powdered, crystalline materials. They may include various diluents, binders, disintegrants, lubricants, glidants and in many cases, colorants. Excipients used are classified according to the function they perform. For example, a glidant may be used to improve the flow of powder blend in the hopper and into the tablet die.

Web site: http://www.delphion.com/details?pn=US06117451__

- **Directly compressible extended-release matrix formulation for metformin hydrochloride**

  Inventor(s): Kumar; Vijai (67 Whitewood Dr., Morris Plains, NJ 07950), McGuffy; Kevin Scott (11 River Rd., Stanhope, NJ 07874)

  Assignee(s): none reported

  Patent Number: 6,524,618

  Date filed: June 12, 2001

  Abstract: An extended-release matrx formulation capable of being directly compressed into tablets comprising **metformin** hydrochloride blended with specific excipients. The excipients used in the formulation enhance the flow and compaction properties of the drug and insure that the formulation is directly compressible into a tablet containing about 100 mg to about 800 mg, preferably about 250 mg to about 750 mg, of **metformin** hydrochloride in unit dosage form. Each tablet produced by direct compression of the formulaton has the desired hardness and dissolution characteristics such that the drug is released in the body of the subject over an extended period of time.

  Excerpt(s): The invention relates to a directly compressible extended-release matrix formulaton containing N,N-dethyl-imidodicaboimdic diarnide hydrochloride (hereinafter referred to as "metformin hydrochlorido" or "metformin HCl"). The formulaton is prepared in the form of a tableting powder which is capable of being directly compressed into **metformin** HCl tablets. The invention also relate to a process for preparing extended-release **metformin** HCl tablets by blending the drug with specific excipients and therefore directly compressing the blend into tablets. Metformin is an antihyperglycemic agent of the bigande elms used in the treatment of non-insulin dependent diabetes mellitus ("NIDDM"). It is usually marketed in the form of its hydrochloride salt as **Glucophage.**RTM. **Metformin** hydrochloride is hygroscopic and somewhat unstable. Moreover, **metformin** hydrochloride is not inherently compressible and thus presents formulation problems. Metformin hydrochloride has intinsically poor permeability in the lower portion of the gastrointestinal tract leading to absorption almost exclusively in the upper part of the gastrointestinal tract. Its oral bioavailability is in the range of 40 to 60% decreasing with increasing dosage, which suggests some kind of saturable absorption process, or permeability/transit time limited absorption. It also has a very high water solubility (>300 mg/ml at 250.degree. C.). This can lead to difficulty in providing an extended, i.e., slow, release rate from a formulation and problems in controlling the initial burst of drug from such a formulaton. These two difficulties are further compounded by the high unit dose, about 500 mg to about 750 mg per tablet, usually required for **metformin** hydrochloride to provide optimal dosing.

  Web site: http://www.delphion.com/details?pn=US06524618__

- **Glibenclamide-metformin combination for the treatment of diabetes mellitus of type II**

  Inventor(s): Barelli; Giulio (Pisa, IT), De Regis; Massimo (Pisa, IT)

  Assignee(s): Abiogen Pharma s.r.l. (IT)

  Patent Number: 5,922,769

  Date filed: May 13, 1998

  Abstract: Non-insulin dependent diabetes mellitus in cases of secondary failure is treated with a combination of glibenclamide and **metformin.**

  Excerpt(s): The present invention relates to the use of a combination consisting of glibenclamide and **metformin** in one specific ratio as medicament for the treatment of diabetes mellitus of type II. Non-insulin dependent diabetes of type II (NID) is known to be a frequent metabolic disease and the main cause of hyperglycemia. In recent years, diabetes mellitus of type II has been proved to be a heterogeneous disease, with complex, unclarified metabolic aspects, which disease is characterized by three main metabolic abnormalities contributing to hyperglycemia: the partial or complete decrease in insulin secretion, the resistance of the peripheral tissues to insulin and the increased hepatic production of glucose in fasting conditions. Diet and physical exertion are unanimously recognized to be the foundation of the therapy of diabetes of type II: both of them lead to a reduction in insulin-resistance and, in the long run, to an improvement in the pancreas secretive deficit.

  Web site: http://www.delphion.com/details?pn=US05922769__

- **Inhibition of emetic effect of metformin with 5-HT3 receptor antagonists**

  Inventor(s): Cowles; Verne E. (Dublin, CA)

  Assignee(s): DepoMed, Inc. (Menlo Park, CA)

  Patent Number: 6,451,808

  Date filed: October 17, 2000

  Abstract: Metformin is formulated as a pharmaceutical composition that also includes a 5-hydroxytryptamine-3 receptor antagonist to suppress the gastrointestinal side effects that are associated with **metformin** administration in many patients.

  Excerpt(s): This invention addresses the drug **metformin** and its possible side effects. An unfortunate side effect associated with **metformin** is the occurrence of gastrointestinal reactions such as diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia. These reactions occur with approximately 30% greater frequency when compared to placebo-treated subjects, particularly at the initiation stages of **metformin** administration. The reactions are dose-related, and methods of controlling these reactions include reducing the dose, escalating the dose gradually, or taking the drug with meals. In severe cases, however, dehydration and prerenal azotemia can occur, and many subjects undergoing **metformin** therapy are forced to discontinue their use of the drug. It has now been discovered that emesis and other gastrointestinal side effects of **metformin** can be reduced or eliminated by administering a 5-hydroxytryptamine-3 (5-HT.sub.3) receptor antagonist in combination with the **metformin.** With this co-administration, **metformin** can be administered at higher dosages for many patients without the need to take the drug with meals. The patient can thus apply greater flexibility in the manner and timing by which the drug is taken

without concern about the side effects that are unpleasant to both the patient and to those in the presence of the patient. The use of 5-HT.sub.3 antagonists in accordance with this invention is particularly useful when administered during the first week or first month of **metformin** therapy, since nausea is most prevalent during this initial period. The administration of 5-HT.sub.3 antagonists improves the ease by which the patient can be "titrated" to an effective level of **metformin** for controlling blood glucose.

Web site: http://www.delphion.com/details?pn=US06451808__

- **Metforimin-containing compositions for the treatment of diabetes**

  Inventor(s): Fine; Stuart A. (Northbrook, IL), Kinsella; Kevin J. (La Jolla, CA)

  Assignee(s): Akesis Pharmaceuticals, Inc. (La Jolla, CA)

  Patent Number: 6,376,549

  Date filed: September 17, 1998

  Abstract: Compositions and methods using same for the treatment of diabetes its sequelae and pre-diabetic conditions are provided. Invention compositions include the anti-diabetic agent **metformin,** and bioavailable sources of one or more of chromium, vanadium and magnesium. Also provided are pharmaceutical agents containing invention compositions and methods for administering such agents.

  Excerpt(s): This invention relates to pharmaceutical compounds formulated in conjugation with dietary supplements; and to methods of using the resulting compositions for the treatment of a number of conditions. Particularly, this invention relates to metformin-containing pharmaceutical compositions and to methods of using the same for the treatment of diabetes and a number of symptoms which precede and/or accompany diabetes. Diabetes mellitus is a mammalian condition in which the amount of glucose in the blood plasma is abnormally high. Elevated glucose levels in some instances can lead to higher than normal amounts of a particular hemoglobin, HbA1c. This condition can be life-threatening and high glucose levels in the blood plasma (hyperglycemia) can lead to a number of chronic diabetes syndromes, for example, atherosclerosis, microangiopathy, kidney disorders or failure, cardiac disease, diabetic retinopathy and other ocular disorders, including blindness. Diabetes mellitus is known to affect at least 10 million Americans, and millions more may unknowingly have the disease. There are two forms of the disease. In the form of this disease known as Type II, non-insulin dependent diabetes (NIDDM) or adult-onset (as opposed to juvenile diabetes or Type I), the pancreas often continues to secrete normal amounts of insulin. However, this insulin is ineffective in preventing the symptoms of diabetes which include cardiovascular risk factors such as hyperglycemia, impaired carbohydrate (particularly glucose) metabolism, glycosuria, decreased insulin sensitivity, centralized obesity hypertriglyceridemia, low HDL levels, elevated blood pressure and various cardiovascular effects attending these risk factors. Many of these cardiovascular risk factors are known to precede the onset of diabetes by as much as a decade. These symptoms, if left untreated, often lead to severe complications, including premature atherosclerosis, retinopathy, nephropathy, and neuropathy. Insulin resistance is believed to be a precursor to overt NIDDM and strategies directed toward ameliorating insulin resistance may provide unique benefits to patients with NIDDM.

  Web site: http://www.delphion.com/details?pn=US06376549__

- **Metformin 2-(p-chlorophenoxy)-2-methylpropionate**

  Inventor(s): Bohuon; Claude (Paris, FR)

  Assignee(s): Societe d'Etudes et d'Exploitation de Marques et Brevets S.E.M.S. (FR)

  Patent Number: 4,080,472

  Date filed: December 17, 1976

  Abstract: A new salt, **metformin** clofibrate, is disclosed. This salt has useful therutic properties and can be used in the control of glycaemia and cholesterolaemia and in the treatment of atheromatous conditions.

  Excerpt(s): The present invention relates to the **metformin** salt of clofibric acid. (Clofibric acid is also known as 2-p-chlorophenoxy-2-methyl-propionic acid, and **metformin** is the biguanide, 1,1-dimethylbiguanide.) It also relates to a process for the preparation of this salt and its application in therapy. This salt can be prepared from **metformin** and clofibric acid by a method which is in itself known. Since the free base of **metformin** is not commercially available, it is preferred, according to the process of this invention, to use **metformin** hydrochloride as starting material. According to this preferred process, **metformin** hydrochloride, dissolved in a lower alcohol, especially methanol containing 2% by volume of water, is contacted with an anionic resin in order to obtain **metformin** base. **Metformin** base is then contacted with clofibric acid in acetone to produce the salt of this invention.

  Web site: http://www.delphion.com/details?pn=US04080472__

- **Metformin formulations and method for treating intermittent claudication employing same**

  Inventor(s): Rogosky; Karen M. (Robbinsville, NJ)

  Assignee(s): Bristol-Myers Squibb Company (Princeton, NJ)

  Patent Number: 6,100,300

  Date filed: April 28, 1998

  Abstract: Novel **metformin** formulations are provided which include **metformin** or **metformin** salts preferably the hydrochloride salt in doses below that employed for treating diabetes such as **metformin** in daily amounts of 400 mg or below. A method for treating peripheral vascular disease including intermittent claudication employing such **metformin** formulations is also provided.

  Excerpt(s): The present invention relates to novel **metformin** formulations which include **metformin** and salts thereof, preferably the hydrochloride salt, preferably in amounts below the threshold levels for treating diabetes, and to a method for treating peripheral vascular disease including intermittent claudication employing such **metformin** formulations. The biguanide antihyperglycemic agent **metformin** is concurrently marketed in the U.S. in the form of its hydrochloride salt (Glucophage.TM., Bristol-Myers Squibb Company). U.S. Pat. No. 4,028,402 discloses the dichloroacetic acid salt of **metformin.**

  Web site: http://www.delphion.com/details?pn=US06100300__

- **Pharmaceutical composition comprising a combination of metformin and fibrate, and its use for the preparation of medicines intended to reduce hyperglycaemia**

  Inventor(s): Bonhomme; Yves (Charbonnieres les Bains, FR), Briet; Philippe (Lyons, FR)

  Assignee(s): Merck Patent Gesellschaft mit beschrankter Haftung (Darnstadt, DE)

  Patent Number: 6,372,790

  Date filed: November 30, 2000

  Abstract: A pharmaceutical composition comprising: (i) **metformin,** optionally in the form one of its pharmaceutically acceptable salts; (ii) a fibrate selected from fenofibrate and bezafibrate; and optionally one or more pharmaceutically acceptable excipients, is suitable for use in the treatment of non-insulin-dependent diabetes.

  Excerpt(s): The invention relates to a pharmaceutical composition containing a combination of **metformin** and of a fibrate chosen from fenofibrate and bezafibrate, as active principles. The invention also relates to the use of **metformin** and of a fibrate chosen from fenofibrate and bezafibrate for the preparation of a medicinal combination intended to reduce the hyperglycaemia of non-insulin-dependent diabetes. Metformin is mainly known for its anti-hyperglycaemic activity and is widely used in the treatment of non-insulin-dependent diabetes. In the case of insulin-dependent diabetes, **metformin** is also administered to the patient in combination with insulin. Bezafibrate and fenofibrate belong to the family of fibrates whose anti-hyperlipidic properties are well known. More specifically, the fibrates act on hypercholesterolaemia and hypertriglyceridaemia by inducing a reduction in the total cholesterol level as well as the cholesterol linked to low density lipoproteins (LDL-cholesterol) and an even greater reduction in the levels of triglycerides and in particular of triglycerides linked to very low density lipoproteins (VLDL-triglycerides).

  Web site: http://www.delphion.com/details?pn=US06372790__

- **Pharmaceutical preparation containing metformin and a process for producing it**

  Inventor(s): Gabel; Rolf-Dieter (Kurpfalzring 96, D-68723 Schwetzingen, DE), Moeckel; Jorn (Am Baechenbuckel 24/1, D-69118 Heidelberg, DE), Woog; Heinrich (Lindenstrasse 6, D-69514 Laudenbach, DE)

  Assignee(s): none reported

  Patent Number: 5,955,106

  Date filed: March 14, 1997

  Abstract: The present invention concerns pharmaceutical compositions containing **metformin** as an active substance and a hydrocolloid-forming agent as a retardant and optionally standard pharmaceutical auxiliary substances, the residual moisture content in the pharmaceutical composition being 0.5-3% by weight. The invention also concerns a process for producing pharmaceutical compositions containing **metformin** as an active substance and a hydrocolloid-forming agent as a retardant and optionally standard pharmaceutical auxiliary substances characterized in that the active substance and retarding agent or a portion thereof are granulated with an aqueous solvent which can optionally contain a binder and where appropriate the other portion of the retardant or other standard pharmaceutical auxiliaries are admixed with the granulate which is then dried until the residual moisture content is reduced to 0.5-3% by weight.

Excerpt(s): The invention concerns pharmaceutical preparations containing **metformin** hydrochloride (also called **metformin** in the following) as an active substance and a hydrocolloid-forming agent as a retardant and a process for their production. It is known that **metformin** hydrochloride is a biguanide derivative (1,1-dimethylbiguanide monohydrochloride) which has an oral antidiabetic action. **Metformin** delayed release tablets containing 850 mg **metformin** hydrochloride per film tablet (Glucophage.RTM. retard) are on the market. Since **metformin** in contrast to other active substances cannot be pressed in its pure form (the mass disintegrates in an unchanged form after the compression) framework-forming auxiliary substances such as polyvinylacetate were used in these high-dose delayed release tablets as a retarding agent (Lipha, technical information **Glucophage.**RTM. August 1991, "Bundesverband der Pharmazeutischen Industrie e.V.", publ. Rote Liste 1993, Edition Cantor, Aulendorf 1993). The mechanism of action of such framework tablets is based on the fact that the readily water-soluble **metformin** diffuses out of the tablet independently of pH in the gastrointestinal tract whereas the tablet framework with the coating is excreted largely unchanged. The disadvantage of using such framework-forming auxiliary substances such as polyvinylacetate is, however, that they have to be processed with organic solvents in particular during the granulation process, the organic solvent having to be removed again as completely as possible before the granulate is processed further to compressed pharmaceutical forms of administration and for example pressed into tablets.

Web site: http://www.delphion.com/details?pn=US05955106__

- **Salts of metformin and method**

  Inventor(s): Bretnall; Alison E. (Chester, GB), Powers; Gerald L. (North Brunswick, NJ), Srivastava; Sushil K. (Dayton, NJ), Timmins; Peter (Merseyside, GB), Wei; Chenkou (Princeton Junction, NJ), Winter; William J. (Lebanon, NJ)

  Assignee(s): Bristol-Myers Squibb Company (Princeton, NJ)

  Patent Number: 6,031,004

  Date filed: March 4, 1999

  Abstract: Novel salts of the antidiabetic agent **metformin** acre provided which are **metformin** salts of dibasic acids (2:1 molar ratio), preferably **metformin** (2:1) fumarate and **metformin** (2:1) succinate, which may be employed alone or in combination with another antihyperglycemic agent such as glyburide, for treating diabetes. A method for treating diabetes employing the novel **metformin** salt by itself or in combination with another antidiabetic agent is also provided.

  Excerpt(s): The present invention relates to salts of the anti-diabetic agent **metformin,** and more particularly to **metformin** salts of dibasic acids, preferably dibasic organic carboxylic acids, optionally in combination with other anti-diabetic agent and to a method employing such salts or combinations for treating diabetes. The biguanide antihyperglycemic agent **metformin** is concurrently marketed in the U.S. in the form of its hydrochloride salt (Glucophage.TM., Bristol-Myers Squibb Company). Metformin hydrochloride is a cohesive white powder which is highly soluble in water (>300 mg/ml at ambient temperature), has a hygroscopicity measured at 95% relative humidity /25.degree. C. of greater than 20% moisture uptake at 6 hours, and a high compaction susceptibility. Accordingly, handling of **metformin** hydrochloride in a pharmaceutical manufacturing facility could present problems especially in high humidity environments. Furthermore, formulation of the **metformin** hydrochloride in a controlled

release system is exceedingly difficult due, at least in part, to its extremely high water solubility.

Web site: http://www.delphion.com/details?pn=US06031004__

- **Solid oral dosage form comprising a combination of metformin and glibenclamide**

  Inventor(s): Bonhomme; Yves (Charbonnieres les Bains, FR), Cave; Gillian (Ellesmere Port, GB), Nicholson; Geoffrey (Aylesbury, GB), Nicholson; Sarah J. (Helsby, GB)

  Assignee(s): LIPHA (Lyons, FR)

  Patent Number: 6,303,146

  Date filed: July 14, 1999

  Abstract: The present invention relates to a solid oral dosage form comprising a combination of **metformin** and glibenclamide in which the size of glibenclamide is such that the glibenclamide bioavailability is comparable to the glibenclamide bioavailability obtained with a separate administration of **metformin** and glibenclamide.

  Excerpt(s): The present invention relates to solid oral dosage forms for the treatment of non-insulin dependent diabetes. Non-insulin dependent diabetes is a metabolic disorder characterized by hyperglycaemia, which occurs due to insulin deficiency, insulin resistance and reduced glucose tolerance. There are two main groups of oral antidiabetic drugs available: these are the sulphonylureas and the biguanidines. Sulphonylureas act by stimulating insulin release and are thus only effective with some residual pancreatic beta-cell activity, examples of sulphonylureas available are glibenclamide, gliclazide, tolbutamide, glipizide, tolazamide, gliquidone and chlorpropamide. The biguanidines, such as **metformin,** act by decreasing gluconeogenesis and by increasing peripheral utilisation of glucose, and as they require endogenous insulin they are only effective with some residual pancreatic islet cell activity.

  Web site: http://www.delphion.com/details?pn=US06303146__

- **Use of metformin to counteract weight gain associated with valproate and other psychotropic medications**

  Inventor(s): Cottingham; Elizabeth Marie (300 Warren Ave., Cincinnati, OH 45219), Morrison; John Ainslie (3740 Clifton Ave., Cincinnati, OH 45220)

  Assignee(s): none reported

  Patent Number: 6,194,466

  Date filed: October 12, 1999

  Abstract: A method for minimizing the weight gain side effect associated with Valproate treatment is disclosed. In this method, **Metformin,** a biguanide compound, is concurrently administered to a patient taking the Valproate therapy. A pharmaceutical composition containing the combination of Valproate and **Metformin** is also disclosed.

  Excerpt(s): The present invention relates to improvements in the treatment of patients for seizure, bipolar disorders and psychoses. Clinical experience and published studies indicate the effectiveness of Valproate (depakote) in the treatment of seizure disorders and bipolar disorders. See, for example, Mattson, et al., Department of Veterans Affairs Epilepsy Cooperative Study No. 264: A Comparison of Valproate with Carbazapine for

the Treatment of Complex Partial Seizures and Secondarily Generalized Tonic-Chronic Seizures In Adults. N. Eng. J. Med., 327: 765-771 (1992); Freeman, et al., Mood Stabilizer Combinations: A Review of Safety and Efficacy. Am. J. Psychiatry, 155: 12-21 (1998); and Verity, et al., A Multi-Center Comparative Trial Of Sodium Valproate And Carbamazepine In Pediatric Epilepsy. Developmental Medicine And Child Neurology, 37: 97-108 (1993). Use of Valproate, however, is also associated with side effects in as many as 50% of the patients taking it; these side effects include marked weight gain. Isojarvi et al., Polycystic Ovaries And Hyperandrogenism In Women Taking Valproate For Epilepsy, N. Eng. J. Med., 329: 1383-1388 (1993). Although not all patients experience this weight gain side effect, in those that do, the weight gain can be considerable, as much as 40-50 pounds. This side effect presents a number of patient issues, both medical and psychological, for the treating physician to consider. Such a marked weight gain can place a significant burden on the heart and circulatory system of the patient. In addition, particularly in-patients suffering from depression, such weight gain can hurt self-image and adversely impact the depressed state. Finally, and perhaps most importantly, such side effects can reduce patient compliance with the therapy regimen, thereby resulting in ineffective treatment for the primary disorder. Identification of a means to counteract these side effects partially or completely is, therefore, important. There is at present no way to prevent or treat obesity associated with the use of Valproate, except through behavioral changes such as increased physical activity or decreased caloric intake. Metformin is a biguanide drug which is known to improve insulin action at the cellular level, but not affect insulin secretion. **Metformin** is used to treat patients with non-insulin dependent diabetes and has recently been used to treat women with polycystic ovary syndrome, a syndrome characterized by hirsutism, hyperandrogenism, and polycystic ovaries. It has not, however, been suggested for use in controlling the weight gain caused by Valproate or other psychotropic actives. See, for example, Valazquez, et al, **Metformin** Therapy Is Associated With A Decrease In Plasma Plasminogen Activator Inhibitor-1, Lipoprotein (a) and Immunoreactive Insulin Levels In-Patients With Polycystic Ovary Syndrome. Metabolism, 46: 454-457 (1997); Valazquez, et al, **Metformin** Therapy In Polycystic Ovary Syndrome Reduces Hyperinsulinemia, Insulin Resistance, Hyperandrogenism, And Systolic Blood Pressure, While Facilitating Normal Menses And Pregnancy. Metabolism, 43: 647-654 (1994); Jackson, et al., Mechanism of **Metformin** Action In Non-Insulin Dependent Diabetes. Diabetes; 36: 632-640 (1987); Landin, et al., Treating Insulin Resistance in Hypertension With **Metformin** Reduces Both Blood Pressure And Metabolic Risk Factors. J. Intern. Med.; 229: 181-187 (1991); and Nestler, et al., Effects of **Metformin** on Spontaneous and Clomiphene-Induced Ovulation in the Polycystic Ovary Syndrome. N. Engl. J. Med. 338: 1876-1880 (1998).

Web site: http://www.delphion.com/details?pn=US06194466__

Patent Applications on Metformin

As of December 2000, U.S. patent applications are open to public viewing.[10] Applications are patent requests which have yet to be granted. (The process to achieve a patent can take several years.) The following patent applications have been filed since December 2000 relating to metformin:

[10] This has been a common practice outside the United States prior to December 2000.

- **Antidiabetic formulation and method**

  Inventor(s): Desai, Divyakant S.; (West Windsor, NJ), Li, Danping; (East Brunswick, NJ), Phusanti, Lawan; (Princeton, NJ)

  Correspondence: Stephen B. Davis; Bristol-myers Squibb Company; Patent Department; P O Box 4000; Princeton; NJ; 08543-4000; US

  Patent Application Number: 20030139461

  Date filed: December 17, 2001

  Abstract: An antidiabetic pharmaceutical formulation is provided, especially adapted for treating Type II diabetes, which includes a combination of **metformin** and glipizide in a manner to control moisture in the formulation so that the glipizide does not hydrolyze, yet the **metformin** is compressible, if necessary. A method for treating diabetes is also provided employing the above formulation.

  Excerpt(s): The present invention relates to a pharmaceutical formulation and method for treating type 2 diabetes. The formulation includes **metformin** and glipizide (a sulfonyl urea) in a manner to control moisture in the formulation so that the glipizide does not hydrolyze, yet the **metformin** is compressible, if necessary. The biguanide antihyperglycemic agent **metformin** disclosed in U.S. Pat. No. 3,174,901 is currently marketed in the U.S. in the form of its hydrochloride salt (Glucophage.RTM.), by the Bristol-Myers Squibb Company. The diagnosis and management of type 2 diabetes mellitus is rapidly undergoing progressive changes. It is now widely accepted that glycemic control makes a difference. The goal of diabetes therapy today is to achieve and maintain as near normal glycemia as possible to prevent the long-term microvascular and macrovascular complications of an elevated blood glucose. The diagnosis of diabetes has undergone significant changes as evidenced by the new ADA diagnostic and classification guidelines. Oral therapeutic options for the treatment of type 2 diabetes mellitus, until recently, have been severely limited. Prior to 1995, sulfonyl ureas had been the mainstay of oral diabetes agents in the United States. Sulfonyl ureas target one mechanism of hyperglycemia by augmenting insulin secretion from the beta cell. Since 1995, three new classes of agents have been added to the anti-diabetes armamentarium for the management of hyperglycemia. **Metformin,** a biguanide, targets additional mechanisms of hyperglycemia by inhibiting hepatic glucose production and enhancing peripheral glucose uptake and thereby reducing insulin resistance; thiazolidinediones such as troglitazone, rosiglitazone and pioglitazone decrease peripheral insulin resistance; and alpha-glucosidase inhibitors such as acarbose and miglitol help control postprandial glucose excursion by delaying absorption of dietary carbohydrate. These agents are all indicated as monotherapy and some are indicated for use in combination therapy, generally after monotherapy has been found to be inadequate.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Biguanide and sulfonylurea formulations for the prevention and treatment of insulin resistance and type 2 diabetes mellitus**

  Inventor(s): Pearson, Don C.; (Lakewood, WA), Richardson, Kenneth T.; (Anchorage, AK)

  Correspondence: Townsend And Townsend And Crew, Llp; Two Embarcadero Center; Eighth Floor; San Francisco; CA; 94111-3834; US

  Patent Application Number: 20030078269

  Date filed: March 7, 2002

  Abstract: The invention describes formulations that include either **metformin,** sulfonylurea or a biguanide-sulfonylurea combination as one active ingredient in addition to specific, other active ingredients. The compositions and dosage forms of the invention are clinically useful as methods for increasing the effectiveness, efficiency and safety of the included biguanide (metformin) and/or sulfonylurea in the prevention and treatment of insulin resistance and diabetes mellitus. The carefully chosen additional active ingredients of the invention are designed in a modular fashion to prevent and rectify adverse events associated with insulin resistance syndrome and diabetes mellitus, and those adverse incidences associated with the concurrent use of **metformin** and/or the sulfonylureas. When clinically administered, the invention will provide therapeutic levels of **metformin** and of a sulfonylurea, alone or in combination, and broaden their usefulness. The invention will retard the progression of insulin resistance to type 2 diabetes, and reduce the serious microvascular and macrovascular complications commonly associated with insulin resistance syndrome and diabetes mellitus.

  Excerpt(s): This application is related to U.S. provisional patent applications nos. 60/278,296, filed Mar. 22, 2001, 60/278,270, also filed Mar. 22, 2001, and 60/278,271, also filed Mar. 22, 2001, all three of which are incorporated herein by reference in their entirety. The present application claims benefits from all three such provisional patent applications for all purposes legally capable of being served thereby. This invention is in the field of pharmacology, and relates to multi-component formulations, which contain **metformin,** a sulfonylurea or a combination of both, in concert with one or more other active ingredients, for use in the pharmacological treatment of insulin resistance and type 2 diabetes mellitus. Insulin resistance and non-insulin-dependent diabetes are prevalent in up to 35% of the population depending upon the age and nature of the subset. In the United States alone, 16 million people have type 2 diabetes and 13 million have impaired glucose tolerance. In fact type 2 diabetes has reached epidemic proportions worldwide. By 2025, an estimated 300 million people will have diabetes, most of who will inhabit China, India, and the United States. Because of an aging and increasingly sedentary, obese population with changing, unhealthy diets, insulin resistance is also increasing alarmingly (it is already two to three times more prevalent than type 2 diabetes). This apparent increase in the prevalence of insulin resistance and type 2 diabetes occurs in all ethnic populations, but especially in those that have migrated from their native lands to more urbanized and westernized regions of the world.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Combination therapy for type II diabetes or Syndrome X**

  Inventor(s): Gwynne, John Thomas; (Doylestown, PA), Randazzo, Bruce Paul; (Rydal, PA), Vitou, Philippe John Robert; (Paris, FR)

  Correspondence: Arnold S. Milowsky; 5 Giralda Farms; Madison; NJ; 07940; US

  Patent Application Number: 20030018028

  Date filed: June 6, 2002

  Abstract: This invention provides methods of using a pharmacological combination of a biguanide agents, such as **metformin,** and one or more PTPase inhibiting agents and, optionally, one or more sulfonlylurea agents, including glyburide, glyburide, glipizide, glimepiride, chlorpropamide, tolbutamide, or tolazamide, for treatment in a mammal of Syndrome X, type II diabetes or metabolic disorders mediated by insulin resistance or hyperglycemia. Further included in this invention is a method of modulating blood glucose levels in a mammal utilizing the combination of one or more PTPase inhibiting agents and one or more sulfonlylurea agents.

  Excerpt(s): This application claims priority from copending provisional application Ser. No. 60/296,502, filed Jun. 7, 2001, the entire disclosure of which is hereby incorporated by reference. This invention relates to pharmaceutical combinations of PTPase inhibiting compounds, a biguanide agent and, optionally, a sulfonylurea agent. Particularly, this invention concerns methods of treating or inhibiting type II diabetes or Syndrome X and related conditions in a mammal in need of such treatment utilizing combinations of these classes of pharmacological agents. The prevalence of insulin resistance in glucose intolerant subjects has long been recognized. Reaven et al (American Journal of Medicine 1976, 60, 80) used a continuous infusion of glucose and insulin (insulin/glucose clamp technique) and oral glucose tolerance tests to demonstrate that insulin resistance existed in a diverse group of nonobese, nonketotic subjects. These subjects ranged from borderline glucose tolerant to overt, fasting hyperglycemia. The diabetic groups in these studies included both insulin dependent (IDDM) and noninsulin dependent (NIDDM) subjects.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Controlled release metformin formulations**

  Inventor(s): Chen, Chih-Ming; (Davie, FL), Cheng, Xiu Xiu; (Davie, FL), Chou, Joseph; (Manassas, VA), Jan, Steve; (Coral Springs, FL)

  Correspondence: Davidson, Davidson & Kappel, Llc; 485 Seventh Avenue, 14th Floor; New York; NY; 10018; US

  Patent Application Number: 20010024659

  Date filed: November 29, 2000

  Abstract: Sustained release pharmaceutical formulations comprising an antihyperglycemic drug or a pharmaceutically acceptable salt thereof are disclosed. The formulations provide therapeutic plasma levels of the antihyperglycemic drug to a human patient over a 24 hour period after administration.

  Excerpt(s): The present application is a continuation of U.S. Ser. No. 09/594,637 filed Jun. 15, 00 which is a continuation of U.S. Ser. No. 09/045,330 filed Mar. 20, 1998, now issued as U.S. Pat. No. 6,099,859, the enclosures of which are hereby incorporated by reference. The present invention relates to controlled release unit dose formulations

containing an antihyperglycemic drug. More specifically, the present invention relates to an oral dosage form comprising a biguanide such as **metformin** or buformin or a pharmaceutically acceptable salt thereof such as **metformin** hydrochloride or the **metformin** salts described in U.S. Pat. Nos. 3,957,853 and 4,080,472 which are incorporated herein by reference. In the prior art, many techniques have been used to provide controlled and extended-release pharmaceutical dosage forms in order to maintain therapeutic serum levels of medicaments and to minimize the effects of missed doses of drugs caused by a lack of patient compliance.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Controlled release tablets of metformin**

  Inventor(s): Chawla, Manish; (Rohini, IN), Raghuvanshi, Rajeev S.; (New Delhi, IN), Rampal, Ashok; (Amritsar, IN)

  Correspondence: Ranbaxy Pharmaceuticals INC.; Suite 2100; 600 College Road East; Princeton; NJ; 08540; US

  Patent Application Number: 20030104059

  Date filed: November 6, 2002

  Abstract: Controlled-release **metformin** and processes for their preparation, using a combination of non-ionic and anionic hydrophilic polymers, wherein the total hydrophilic polymer concentration is at least about 16% by weight of the composition.

  Excerpt(s): The present invention relates to controlled release tablets of **metformin,** and processes for their preparation. Controlled drug delivery applications include both sustained/extended delivery and targeted delivery on a one-time or sustained basis. Controlled release formulations can be used to reduce the amount of drug necessary to cause the same therapeutic effect in patients. The convenience of fewer and more effective doses also increases patient compliance. in which A is the anion of the non-toxic salt are the preferred medicaments. It is estimated that 60 percent of patients with type 2 diabetes who receive oral therapy are currently required to take doses of multiple pills several times a day in order to manage this condition. Controlled release formulation would help these patients to better control their blood sugar by making it easier to comply with their daily treatment regimen.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Core formulation**

  Inventor(s): Adjei, Akwete L.; (Bridgewater, NJ), Cutie, Anthony J.; (Bridgewater, NJ), Zhu, Yaping; (Highland Park, NJ)

  Correspondence: Jerome Rosenstock, Esq; C/o Frommer Lawrence & Haug Llp; 745 Fifth Avenue; New York; NY; 10151; US

  Patent Application Number: 20010034374

  Date filed: February 15, 2001

  Abstract: This invention relates to a controlled release combination drug product comprising troglitazone, e.g. its hydrochloride, and a biguamide, e.g. **metformin.** In particular, the product comprises a core of **metformin,** at least a portion thereof has a layer or coat thereon of troglitazone.

Excerpt(s): This application claims priority from U.S. provisional application Ser. No. 60/201,233, filed May 1, 2000, which is incorporated herein by reference. This invention relates to a core formulation, and, more particularly, to a core formulation comprising a first layer comprising troglitazone, which covers at least a portion of a core comprising a biguanide, such as for example **metformin** (i.e., glucophage), with a modulating release polymer comprising a silicate. 2. Description of the Related Art **Metformin** and troglitazone, and their salts such as the hydrochlorides, maleates, tartrates, etc., are two active ingredients of anti-diabetic drugs that are used to treat diabetic patients, e.g. human beings. These two active agents are administered orally to patients in need thereof in protocols calling for the single administration of either ingredient. Heretofore, there has not been revealed or hinted at combining both ingredients and certainly not a physically combined core formulation comprising both ingredients. The advantage of such a core formulation is advantageous to patients and prescribers because both medicaments are synergistic to each other in the body when used in the management of blood glucose control, i.e., diabetes. Furthermore, the use of a modulating agent, like silica gel, in the preparation, controls the rate of drug release over a clinically meaningful period to enable better control of the effect of the medicinal agents in such preparation.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Core formulation**

  Inventor(s): Adjei, Akwete L.; (Bridgewater, NY), Cutie, Anthony J.; (Bridgewater, NJ), Zhu, Yaping; (Highland Park, NJ)

  Correspondence: Jerome Rosenstock; Frommer Lawrence & Haug Llp; 745 Fifth Avenue; New York; NY; 10151; US

  Patent Application Number: 20010046515

  Date filed: February 15, 2001

  Abstract: This invention relates to a modulating formulation comprising pioglitazone hydrochloride and a biguamide, e.g. **metformin.** In particular, the product comprises a core of the biguamide, e.g. **metformin,** at least a portion thereof has a layer or coat thereon of pioglitazone. PATENT

  Excerpt(s): This application claims priority from U.S. provisional application Ser. No. 60/201,057, filed May 1, 2000, which is incorporated herein by reference. This invention relates to a core formulation, and, more particularly, to a core formulation comprising a first layer comprising pioglitazone, which covers at least a portion of a core comprising a biguanide, **metformin** (i.e., glucophage), with a modulating release polymer comprising a silicate. Metformin and pioglitazone, or their salts such as the hydrochlorides, maleates, tartrates, etc., are two active ingredients of anti-diabetic drugs that are used to treat diabetic patients, e.g. human beings. These two active agents are administered orally to patients in need thereof in protocols calling for the single administration of either ingredient. Heretofore, there has not been revealed or hinted at combining both ingredients and certainly not a physically combined core formulation comprising both ingredients. The use of such a core formulation is advantageous to patients and prescribers because both medicaments are synergistic to each other in the body when used in the management of blood glucose control, i.e., diabetes. Furthermore, the use of a modulating agent, like silica gel, in the preparation, controls the rate of drug release over a clinically meaningful period to enable better control of the effect of the medicinal agents in such preparation.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Cyclopropyl-fused pyrrolidine-based inhibitors of dipeptidyl peptidase IV and method**

  Inventor(s): Augeri, David J.; (Princeton, NJ), Betebenner, David A.; (Lawrenceville, NJ), Hamann, Lawrence G.; (Cherry Hill, NJ), Magnin, David R.; (Hamilton, NJ), Robl, Jeffrey A.; (Newtown, PA), Sulsky, Richard B.; (West Trenton, NJ)

  Correspondence: Marla J Mathias; Bristol-myers Squibb Company; Patent Department; P O Box 4000; Princeton; NJ; 08543-4000; US

  Patent Application Number: 20020019411

  Date filed: February 16, 2001

  Abstract: Dipeptidyl peptidase IV (DP 4) inhibiting compounds are provided having the formula 1where x is 0 or 1 and y is 0 or 1 (provided that x=1 when y=0 and x=0 when y=1);n is 0 or 1; X is H or CN;and wherein R.sup.1, R.sup.2, R.sup.3 and R.sup.4 are as described herein.A method is also provided for treating diabetes and related diseases, especially Type II diabetes, and other diseases as set out herein, employing such DP 4 inhibitor or a combination of such DP 4 inhibitor and one or more of another antidiabetic agent such as **metformin,** glyburide, troglitazone, pioglitazone, rosiglitazone and/or insulin and/or one or more of a hypolipidemic agent and/or anti-obesity agent and/or other therapeutic agent.

  Excerpt(s): This application takes priority from U.S. provisional application No. 60/188,555, filed Mar. 10, 2000. The present invention relates to cyclopropyl-fused pyrrolidine-based inhibitors of dipeptidyl peptidase IV (DP-4), and to a method for treating diabetes, especially Type II diabetes, as well as hyperglycemia, Syndrome X, diabetic complications, hyperinsulinemia, obesity, atherosclerosis and related diseases, as well as various immunomodulatory diseases and chronic inflammatory bowel disease, employing such cyclopropyl-fused pyrrolidines alone or in combination with another type antidiabetic agent and/or other type therapeutic agent. Depeptidyl peptidase IV (DP-4) is a membrane bound non-classical serine aminodipeptidase which is located in a variety of tissues (intestine, liver, lung, kidney) as well as on circulating T-lymphocytes (where the enzyme is known as CD-26). It is responsible for the metabolic cleavage of certain endogenous peptides (GLP-1(7-36), glucagon) in vivo and has demonstrated proteolytic activity against a variety of other peptides (GHRH, NPY, GLP-2, VIP) in vitro.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Dual inhibitors of adipocyte fatty acid binding protein and keratinocyte fatty acid binding protein**

  Inventor(s): Caulfield, Thomas J.; (Paris, FR), Magnin, David R.; (Hamilton, NJ), Parker, Rex A.; (Titusville, NJ), Robl, Jeffrey A.; (Newtown, PA), Sulsky, Richard B.; (West Trenton, NJ)

  Correspondence: Stephen B. Davis; Bristol-myers Squibb Company; Patent Department; P O Box 4000; Princeton; NJ; 08543-4000; US

  Patent Application Number: 20030225091

  Date filed: November 15, 2002

Abstract: Compounds that are dual aP2/k-FABP inhibitors are provided having the formula 1wherein A, B, X, Y, R.sup.1, R.sup.2 and R.sup.3 are as described herein.A method is also provided for treating diabetes and related diseases, especially Type II diabetes, employing dual aP2/k-FABP inhibitors alone or in combination with at least one other antidiabetic agent such as **metformin,** glyburide, troglitazone and/or insulin.

Excerpt(s): This application claims priority to U.S. Provisional Application Serial No. 60/333,194 filed Nov. 16, 2001, the entirety of which is incorporated herein by reference. The present invention relates to inhibitors of the adipocyte fatty acid binding protein (aP2), and to dual inhibitors of aP2 and keratinocyte fatty acid binding protein (k-FABP), especially aryl carboxylic acids and tetrazoles of Formula I. The present invention further relates to a method for treating diabetes, especially Type II diabetes, as well as hyperglycemia, hyperinsulinemia, obesity, Syndrome X, diabetic complications, atherosclerosis and related diseases, and other chronic inflammatory and autoimmune/inflammatory diseases, employing the compounds of the present invention alone or in combination with one or more types of therapuetic agents. Fatty acid binding proteins (FABPs) are small cytoplasmic proteins that bind to fatty acids such as oleic acids which are important metabolic fuels and cellular regulators. Dysregulation of fatty acid metabolism in adipose tissue is a prominent feature of insulin resistance and the transition from obesity to non-insulin dependent diabetes mellitus (NIDDM or Type II diabetes).

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Extended release tablet of metformin**

  Inventor(s): Seth, Pawan; (Irvine, CA)

  Correspondence: Harness, Dickey & Pierce, P.L.C.; P.O. Box 828; Bloomfield Hills; MI; 48303; US

  Patent Application Number: 20030118647

  Date filed: December 4, 2001

  Abstract: The invention provides an extended release tablet, comprising: (i) a core comprising **metformin;** and (ii) a coating consisting essentially of a water-insoluble, water-permeable film-forming polymer, a plasticizer and a water-soluble polymer.

  Excerpt(s): There is a need to obtain new release dosage form of **Metformin,** especially sustained or extended. (ii) a coating consisting essentially of a water-insoluble, water-permeable film-forming polymer, a plasticizer and a water-soluble polymer. The invention thus provides a new **metformin** extended release composition under the form of a tablet, the core of which comprising mainly **metformin.** Also, the extended release is obtained thanks to a semi-permeable release coating, free of (monomeric) pore-forming agent. The tablets of the invention exhibit specific dissolution profiles.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Liquid formulation of metformin**

  Inventor(s): Chandran, Ravi; (Bolton Landing, NY), Gogia, Ashish; (New Delhi, IN)

  Correspondence: Ranbaxy Pharmaceuticals INC.; Suite 2100; 600 College Road East; Princeton; NJ; 08540; US

  Patent Application Number: 20020040063

  Date filed: August 7, 2001

  Abstract: The present invention is directed to a liquid formulation of **metformin** or its pharmaceutically acceptable salts thereof. The liquid pharmaceutical composition comprises a therapeutically effective amount of **metformin** or its pharmaceutically acceptable salt, in a liquid carrier, which may also include a sweetener that does not increase the blood glucose level of a subject after ingestion thereof. In one embodiment, it may also include alkyl hydroxyethylcellulose, and/or a polyhydroxy alcohol. In another embodiment, the carrier may contain a sweetener, mineral acid, and bicarbonate salt maintained at a pH of 4.0 to 9.0. It is useful for treating hyperglycemia and diabetes.

  Excerpt(s): This application is claiming benefit of U.S. Provisional Application Ser. No. 60/223,391, filed on Aug. 7, 2000. The present invention relates to a liquid formulation of **metformin** and salts thereof and to the use thereof in treating hyperglycemia and/or diabetes. Diabetes Mellitus is the most common of the serious metabolic diseases affecting humans. It has been estimated that there are over 200 million people that have diabetes in the world.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Metformin Hydrochloride tablets**

  Inventor(s): Sherman, Bernard Charles; (Willowdale, CA)

  Correspondence: Nixon & Vanderhye P.C.; 8th Floor; 1100 North Glebe Road; Arlington; VA; 22201-4714; US

  Patent Application Number: 20030104049

  Date filed: December 5, 2001

  Abstract: Tablets for oral administration comprising **metformin** hydrochloride and methylcellulose.

  Excerpt(s): Metformin hydrochloride is an orally-administered antihyperglycemic agent, used in the management of non-insulin-dependent diabetes mellitus. The function of the magnesium stearate in the core tablet is to act as a lubricant to prevent sticking to the tooling (punches and dies) in the tabletting process. The function of the povidone is to act as a binder to cause the **metformin** hydrochloride to bind into a sufficiently hard tablet under compression in the tabletting process. In general, pharmaceutical tablets are made either by a "dry-mix" process or a "wet-granulation" process.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Metformin salts of lipophilic acids**

  Inventor(s): Kessler, Dean; (Edmonds, WA), Lal, Manjari; (Bellevue, WA), Palepu, Nagesh; (Mill Creek, WA)

  Correspondence: Christensen, O'connor, Johnson, Kindness, Pllc; 1420 Fifth Avenue; Suite 2800; Seattle; WA; 98101-2347; US

  Patent Application Number: 20030220301

  Date filed: February 14, 2003

  Abstract: Metformin salts of lipophilic acids, their pharmaceutical formulations, and methods of administrating the **metformin** salts for the treatment of hyperglycemia.

  Excerpt(s): The present application claims the benefit of U.S. Provisional Patent Application No. 60/357,196, filed Feb. 14, 2002, which is incorporated herein by reference in its entirety. The present invention relates to **metformin** salts of lipophilic acids, formulations including **metformin** salts of lipophilic acids, and methods for administering **metformin** salts of lipophilic acids. Metformin is a biguanide, anti-hyperglycemic agent currently marketed in the United States in the form of its hydrochloride salt (GLUCOPHAGE, Bristol-Myers Squibb Company). The oral medication is designed to help control elevated blood sugar levels in NIDDM (non-insulin-dependent diabetes mellitus) or Type II diabetes. Current **metformin** therapy has proven less than optimal as it is associated with a high incidence of gastrointestinal side effects. Further, the drug is commonly administered at high doses (as oral tablets) 2 or 3 times per day to achieve effective glucose-lowering treatment. Anonymous, "Glucophage Prescription Information," Bristol-Myers Squibb Company, Princeton, N.J., 1999.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Method of treating metabolic disorders, especially diabetes, or a disease or condition associated with diabetes**

  Inventor(s): Allison, Malcolm; (Basel, CH), Ball, Michele Ann; (Morris Plains, NJ), Gatlin, Marjorie Regan; (Hoboken, NJ), Guitard, Christiane; (Hagenheim, FR), Karnachi, Anees Abdulquadar; (Hillsborough, NJ), Mannion, Richard Owen; (Mount Arlington, NJ)

  Correspondence: Thomas Hoxie; Novartis, Corporate Intellectual Property; One Health Plaza 430/2; East Hanover; NJ; 07936-1080; US

  Patent Application Number: 20030162816

  Date filed: January 16, 2003

  Abstract: The invention relates to a combination, such as a combined preparation or pharmaceutical composition, respectively, which comprises nateglinide (I) 1or repaglinide and at least one other antidiabetic compound selected from the group consisting of thiazolidinedione derivatives (glitazones), sulfonyl urea derivatives and **metformin** for simultaneous, separate or sequential use in the prevention, delay of progression or treatment of diseases, especially metabolic disorders and in particular type 2 diabetes and diseases and conditions associated with diabetes; to a composition, respectively, which comprises nateglinide and a pharmaceutically acceptable carrier and to a process of making such composition; the use of such combination or composition for the preparation of a medicament for the prevention, delay of progression or treatment of metabolic disorders; a method of prevention, delay of progression or

treatment of diseases in warm-blooded animals; the use of such combination or composition for the cosmetic treatment of a mammal in order to effect a cosmetically beneficial loss of body weight; and to a method of improving the bodily appearance of a warm-blooded animal.

Excerpt(s): The invention relates to a combination, such as a combined preparation or pharmaceutical composition, respectively, which comprises nateglinide or repaglinide and at least one other antidiabetic compound selected from the group consisting of thiazolidinedione derivatives (glitazones), sulfonyl urea derivatives and **metformin** for simultaneous, separate or sequential use in the prevention, delay of progression or treatment of diseases, especially metabolic disorders and in particular type 2 diabetes and diseases and conditions associated with diabetes; the use of such combination for the preparation of a medicament for the prevention, delay of progression or treatment of metabolic disorders; the use of such combination for the cosmetic treatment of a mammal in order to effect a cosmetically beneficial loss of body weight; a method of prevention, delay of progression or treatment of diseases in warm-blooded animals; a method of improving the bodily appearance of a warm-blooded animal; to a pharmaceutical composition which comprises nateglinide as the sole active agent in the composition and a pharmaceutically acceptable carrier and to a process of making such pharmaceutical composition. The generally accepted aims in the treatment of diabetes are to provide relief from symptoms, improvement of the quality of life and prevention of both acute (hyperosmolar coma and ketoacidosis) and chronic complications (e.g. diabetic neuropathy, diabetic nephropathy and premature atherosclerosis). Type 2 diabetes is characterized by both increased peripheral insulin resistance and abnormal insulin secretion. At least two abnormalities of insulin secretion are recognized: in the first phase insulin is both delayed and inadequate in the face of elevated circulating glucose levels and in the second phase insulin secretion is lost. Several metabolic, hormonal, and pharmacological entities are known to stimulate insulin secretion including glucose, amino-acids and gastrointestinal peptides. The Diabetes Control and Complications Trial (DCCT) performed in Type I IDDM subjects has established that lowering of blood glucose is associated with decreases in the onset and progression of diabetic microvascular complications (Diabetes Control and Complications Trial Research Group; N. Engl. J. Med. 1993, 329, 977-986). Therefore, one therapeutic focus is on optimizing and potentially normalizing glycemic control in subjects with type 2 diabetes. Presently available oral agents fail to meet this therapeutic challenge in some patient subgroups, result sometimes in side-effects or are fraught with other problems. in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use, particularly in the prevention, delay of progression or treatment of diseases, especially metabolic disorders and in particular type 2 diabetes mellitus and diseases and conditions associated with diabetes mellitus. Such a combination is preferably a combined preparation or a pharmaceutical composition.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Novel breakers of advanced glycation endproducts**

  Inventor(s): Rahbar, Samuel; (Encino, CA)

  Correspondence: Rothwell, Figg, Ernst & Manbeck, P.C.; 555 13th Street, N.W.; Suite 701, East Tower; Washington; DC; 20004; US

  Patent Application Number: 20020002203

  Date filed: April 5, 2001

  Abstract: Advanced glycation endproducts (AGEs) have been implicated in the pathogenesis of a variety of debilitating diseases such as diabetes, atherosclerosis, Alzheimer's and rheumatoid arthritis, as well as in the normal aging process. Seven compounds are here reported to be active in breaking AGE-protein cross-links. These compounds are 1,4-benzene-bis[4-methyleneaminophenoxyisobutyric acid] (LR102); 4-[(3,5-dichlorophenylureidophenoxyisobutyryl]-4-aminobenzoic acid (LR99); L-bis-[4-(4-chlorobenzamidophenoxyisobutyryl)cystine] (LR20); 4-(3,5-dichlorophenylureido)phenoxyisobutyryl-1-amidocyclohexane-1-carbox- ylic acid (LR23); methylene bis [4,4'-(2-chlorophenylureidophenoxyisobutyr- ic acid)] (LR90); 5-aminosalicylic acid (5-ASA); and **metformin.** These compounds may be used to reverse the debilitating effects of those diseases in which AGEs are formed.

  Excerpt(s): The present invention is a continuation-in-part of application Ser. No. 09/800,976, filed Mar. 8, 2001, which is a continuation-in-part of application Ser. No. 09/543,703, filed Apr. 5, 2000, which is related to provisional application Serial No. 60/127,835, filed Apr. 5, 1999, and the present application is a continuation-in-part of application Ser. No. 09/626,859, filed Jul. 27, 2000, which is a continuation-in-part of application Ser. No. 09/543,703 filed Apr. 5, 2000 which is related to application Ser. No. 60/127,835 filed Apr. 5, 1999, and the present application is a continuation-in-part of application Ser. No. 09/559,913 filed Apr. 28, 2000 which is related to application Ser. No. 60/131,675 filed Apr. 29, 1999, all of which are incorporated herein by reference and all of which are claimed as priority documents. Glucose and other reducing sugars react and bind covalently to proteins, lipoproteins and DNA by a process known as non-enzymatic glycation. Glucose latches onto tissue proteins by coupling its carbonyl group to a side-chain amino group such as that found on lysine. Over time, these adducts form structures called advanced glycation endproducts (AGEs) (protein-aging). These cross-linked proteins stiffen connective tissue and lead to tissue damage in the kidney, retina, vascular wall and nerves. The formation of AGEs on long-lived connective tissue accounts for the increase in collagen cross-linking that accompanies normal aging which occurs at an accelerated rate in diabetes. The publications and other materials used herein to illuminate the background of the invention or provide additional details respecting the practice, are incorporated by reference, and for convenience are respectively grouped in the appended List of References.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Pentoxifylline, pioglitazone and metformin are inhibitors of formation of advanced glycation endproducts (AGE' s)**

  Inventor(s): Nadler, Jerry L.; (Charlottesville, VA), Rahbar, Samuel; (Encino, CA)

  Correspondence: Rothwell, Figg, Ernst & Manbeck, P.C.; 1425 K Street, N.W.; Suite 800; Washington; DC; 20005; US

  Patent Application Number: 20020123501

  Date filed: March 14, 2002

  Abstract: Pentoxifylline, pioglitazone and **metformin** have been found to inhibit the nonenzymatic glycation of proteins which often results in formation of advanced glycation endproducts and crosslinks. The nonenzymatic glycation and crosslinking of proteins is a part of the aging process with the glycation endproducts and crosslinking of long-lived proteins increasing with age. This process is increased at elevated concentrations of reducing sugars in the blood and in the intracellular environment such as occurs with diabetes. The structural and functional integrity of the affected molecules become perturbed by these modifications and can result in severe consequences. The compounds of the present invention can be used to inhibit this process of nonenzymatic glycation and therefore to inhibit some of the ill effects caused by diabetes or by aging. The compounds are also useful for preventing premature aging, rheumatoid arthritis, Alzheimer's disease, uremia, neurotoxicity, atherosclerosis and spoilage of proteins in food and can prevent discoloration of teeth.

  Excerpt(s): This application is a continuation of Ser. No. 09/559,913 which is related to Ser. No. 60/131,675 which was filed Apr. 29, 1999 and which is incorporated herein by reference. The present invention relates generally to the modification and aging of proteins through reaction with glucose and other reducing sugars, such as fructose or ribose and more particularly to the inhibition of nonenzymatic glycation of proteins which often results in formation of advanced glycation endproducts and crosslinks. An elevated concentration of reducing sugars in the blood and in the intracellular environment results in the nonenzymatic formation of glycation and dehydration condensation complexes known as advanced glycation end-products (AGE's). These complex products form on free amino groups on proteins, on lipids and on DNA (Bucala and Cerami, 1992; Bucala et al., 1993; Bucala et al., 1984). This phenomenon is called "browning" or "Maillard" reaction and was discovered early in this century by the food industry (Maillard, 1916). The significance of a similar process in biology became evident only after the discovery of the glycosylated hemoglobins and their increased presence in diabetic patients (Rahbar, 1968; Rahbar et al., 1969). In human diabetic patients and in animal models of diabetes, these nonenzymatic reactions are accelerated and cause increased AGE formation and increased glycation of long-lived proteins such as collagen, fibronectin, tubulin, lens crystallin, myelin, laminin and actin, in addition to hemoglobin and albumin, and also of LDL associated lipids and apoprotein. Moreover, brown pigments with spectral and fluorescent properties similar to those of late-stage Maillard products have also been found in vivo in association with several long-lived proteins such as lens crystallin proteins and collagen from aged individuals. An age-related linear increase in pigments was observed in human dura collagen between the ages of 20 to 90 years. AGE modified proteins increase slowly with aging and are thought to contripbute to normal tissue remodeling. Their level increases markedly in diabetic patients as a result of sustained high blood sugar levels and lead to tissue damage through a variety of mechanisms including alteration of tissue protein structure and function, stimulation of cellular responses through AGE specific receptors or the generation of reactive oxygen species (ROS) (for a recent review see Boel et al., 1995).

The structural and functional integrity of the affected molecules, which often have major roles in cellular functions, become perturbed by these modifications, with severe consequences on affected organs such as kidney, eye, nerve, and micro-vascular functions (Silbiger et al., 1993; Brownlee et al., 1985).

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Pharmaceutical composition**

  Inventor(s): Matharu, Amol Singh; (Cranbury, NJ), Patel, Mahendra R.; (East Brunswick, NJ)

  Correspondence: Thomas Hoxie; Novartis Corporation; Patent And Trademark Dept; 564 Morris Avenue; Summit; NJ; 079011027

  Patent Application Number: 20030021841

  Date filed: June 27, 2002

  Abstract: The present invention relates to a process for preparing tablet dosage forms of poorly-compressible pharmaceutical agents and to tablet dosage forms prepared according to the inventive process. The inventive process is especially useful for preparing tablets of the poorly-compressible drug **metformin** HCl.

  Excerpt(s): The present invention relates to a process for preparing a pharmaceutical tablet formulation of a poorly-compressible pharmaceutical agent, for example, the drug **metformin** HCl formulated as a monolithic or single phase homogenous system. Some pharmaceutical agents are difficult to formulate into a tablet dosage form due to agent's poor compressibility. Conventional tablet formulations of such poorly-compressible pharmaceutical agents lack adequate hardness and are often friable. Thus, special formulation techniques are required to formulate poorly-compressible pharmaceutical agents into a commercially viable tablet dosage form. One way to overcome the poor compressibility of pharmaceutical agents is to utilize wet granulation techniques to prepare the tablet formulation. This involves additional unit operations of wet milling, drying and milling of dried granulation. However, tablets prepared by wet methods often show incremental hardness as a function of time and storage temperature. Therefore, tablets prepared by wet methods are more likely to show variable product performance.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Therapeutic methods employing disulfide derivatives of dithiocarbamates and compositions useful therefor**

  Inventor(s): Lai, Ching-San; (Carlsbad, CA), Vassilev, Vassil P.; (San Diego, CA)

  Correspondence: Foley & Lardner; P.O. Box 80278; San Diego; CA; 92138-0278; US

  Patent Application Number: 20030181495

  Date filed: March 21, 2003

  Abstract: The present invention provides novel combinations of dithiocarbamate disulfide dimers with other active agents. In one method, the disulfide derivative of a dithiocarbamate is coadministered with a thiazolidinedione for the treatment of diabetes. In another embodiment, In another embodiment, invention combinations further comprise additional active agents such as, for example, **metformin,** insulin,

sulfonylureas, and the like. In another embodiment, the present invention relates to compositions and formulations useful in such therapeutic methods.

Excerpt(s): This application is a continuation-in-part of application Ser. No. 10/044,096, filed Jan. 11, 2002, now pending, which is in turn, a divisional of application Ser. No. 09/565,665, filed May 5, 2000, now issued as U.S. Pat. No. 6,316,502, which is in turn, a divisional of application Ser. No. 09/103,639, filed Jun. 23, 1998, now issued as U.S. Pat. No. 6,093,743, each of which is hereby incorporated by reference herein in its entirety. The present invention relates to therapeutic methods employing dithiocarbamates to reduce the level of species associated with disease states in mammals. In one aspect, the invention relates to compositions containing disulfide derivatives of dithiocarbamates and to therapeutic methods employing such compositions. In 1987, nitric oxide (.NO), a gaseous free-radical, was discovered in humans (see, for example, Ignarro et al., in Proc. Natl. Acad. Sci., USA 84:9265-69 (1987) and Palmer et al., in Nature 327:524-26 (1987)). As an indication of the significance of this discovery for the understanding of human physiology and pathophysiology, Science magazine selected nitric oxide as the molecule of the year in 1992.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Treatment for complications of type 2 diabetes**

  Inventor(s): Beisswenger, Paul J.; (Hanover, NH), Szwergold, Benjamin S.; (Hanover, NH)

  Correspondence: Licata & Tyrrell P.C.; 66 E. Main Street; Marlton; NJ; 08053; US

  Patent Application Number: 20010031790

  Date filed: December 13, 2000

  Abstract: A method of lowering plasma levels of.alpha.-dicarbonyl precursors of advanced alycation end products such as methylglyoxal in a patient having type 2 diabetes by administrating **metformin** in a dosage at least twenty five percent in excess of its antidiabetic therapeutic regimen for the patient is provided. The high dosage of **metformin** acts to reduce plasma levels of.alpha.-dicarbonyl compounds by a mechanism distinct from that whereby it exerts its antidiabetic activity.

  Excerpt(s): This invention relates to the use of **metformin** in increased dosages to treat or prevent long-term complications that often characterize type 2 diabetes. This application claims benefit of priority of U.S. Provisional Patent Application No. 60/171,378 filed Dec. 22, 1999. Metformin, i.e. N,N-dimethylimidocarbonimide diamide, is a known compound approved by the U.S. Food & Drug Administration for the therapeutic treatment of diabetes. The compound and its preparation are disclosed, for example, in U.S. Pat. No. 3,174,901, issued May 23, 1965. It is known that **metformin** is effective in the treatment of type 2 diabetes, otherwise known as non-insulin-dependent diabetes mellitus (NIDDM). **Metformin** was the first oral antidiabetic agent introduced that is chemically and pharmacologically unrelated to the oral sulfonylurea diabetic agents, such as tolbutamide. A statement used to describe **metformin** in the Informed Drug Guide is that proof that it has an advantageous effect on the prognosis of diabetes (complications, mortality) does not exist. In accordance with the present invention, it has unexpectedly been found that **metformin** does exert an effect against long term complications that are frequently associated with type 2 diabetes. This effect, not previously known, is quite possibly due to a mechanism of activity separate and distinct from its hypoglycemic activity.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Treatment of diabetes with thiazolidinedione and metformin**

  Inventor(s): Smith, Stephen Alistair; (Bramfield, GB)

  Correspondence: Glaxosmithkline; Corporate Intellectual Property - Uw2220; P.O. Box 1539; King OF Prussia; PA; 19406-0939; US

  Patent Application Number: 20020004515

  Date filed: August 9, 2001

  Abstract: A method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a mammal which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser and a biguanidine antihyperglycaemic agent, to a mammal in need thereof and a pharmaceutical composition comprising an insulin sensitiser and a biguanide antihyperglycaemic agent.

  Excerpt(s): This invention relates to a method of treatment, in particular to a method for the treatment of diabetes mellitus, especially non-insulin dependent diabetes (NIDDM) or Type II diabetes and conditions associated with diabetes mellitus. Biguanide antihyperglycaemic agents are commonly used in the treatment of NIDDM (or Type II diabetes). 1,1-Dimethylbiguanidine (or Metformin) is an example of a biguanides antihyperglycaemic agent. European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-methyl-N-(2-pyrid- yl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter `Compound (I)`). WO94/05659 discloses certain salts of Compound (I) including the maleate salt at example 1 thereof.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Unit-dose combination composition for the simultaneous delivery of a short-acting and a long-acting oral hypoglycemic agent**

  Inventor(s): Bhagwatwar, Harshal P.; (Aurangabad, IN), DeSouza, Noel J.; (Mumbai, IN), Rao, Vinay; (Aurangabad, IN), Saoji, Dilip G.; (Aurangabad, IN), Shukla, Milind C.; (Aurangabad, IN)

  Correspondence: Kenyon & Kenyon; One Broadway; New York; NY; 10004; US

  Patent Application Number: 20030224046

  Date filed: December 31, 2002

  Abstract: A stable unit-dose combination composition for the simultaneous delivery of a short-acting oral hypoglycemic biologically active agent (such as, for example, repaglinide or nateglinide), and a long-acting oral hypoglycemic biologically active agent (such as, for example, metformin). Such a composition can be used for the treatment of non-insulin dependent diabetes mellitus (NIDDM) and the improvement of glycemic control.

  Excerpt(s): This application claims the benefit of U.S. Provisional Application No. 60/385,786, filed on Jun. 3, 2002. The present invention relates to a stable unit-dose combination composition for the simultaneous delivery of a short-acting oral

hypoglycemic biologically active agent, and a long-acting oral hypoglycemic biologically active agent. Such a composition can be used for the treatment of non-insulin dependent diabetes mellitus (NIDDM) and the improvement of glycemic control. The present invention also relates to processes for the preparation of such combination unit-dose compositions and the use of such combination compositions in the treatment of NIDDM. Diabetes mellitus is a progressive metabolic disorder in human beings characterized by hyperglycemia and insulin resistance, and is often associated with other disorders such as obesity, hypertension, hyperlipidemia, as well as complications such as cardiovascular disease, retinopathy, and nephropathy. These underlying defects lead to a classification of diabetes into two major classes: (1) Insulin dependent diabetes mellitus (IDDM or Type I diabetes)--where the patients lack.beta.-cells in the pancreas, and such patients are treated with insulin; and (2) Non-insulin dependent diabetes mellitus (NIDDM or Type II diabetes)--where the patients possess.beta.-cells with impaired insulin secretion function.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

Keeping Current

In order to stay informed about patents and patent applications dealing with metformin, you can access the U.S. Patent Office archive via the Internet at the following Web address: **http://www.uspto.gov/patft/index.html**. You will see two broad options: (1) Issued Patent, and (2) Published Applications. To see a list of issued patents, perform the following steps: Under "Issued Patents," click "Quick Search." Then, type "metformin" (or synonyms) into the "Term 1" box. After clicking on the search button, scroll down to see the various patents which have been granted to date on metformin.

You can also use this procedure to view pending patent applications concerning metformin. Simply go back to **http://www.uspto.gov/patft/index.html**. Select "Quick Search" under "Published Applications." Then proceed with the steps listed above.

CHAPTER 7. BOOKS ON METFORMIN

Overview

This chapter provides bibliographic book references relating to metformin. In addition to online booksellers such as **www.amazon.com** and **www.bn.com**, excellent sources for book titles on metformin include the Combined Health Information Database and the National Library of Medicine. Your local medical library also may have these titles available for loan.

Book Summaries: Federal Agencies

The Combined Health Information Database collects various book abstracts from a variety of healthcare institutions and federal agencies. To access these summaries, go directly to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. You will need to use the "Detailed Search" option. To find book summaries, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer. For the format option, select "Monograph/Book." Now type "metformin" (or synonyms) into the "For these words:" box. You should check back periodically with this database which is updated every three months. The following is a typical result when searching for books on metformin:

- **Advances of Diabetes Mellitus in East Asia**

  Source: Amsterdam, Netherlands: Elsevier Science. 1997. 288 p.

  Contact: Available from Elsevier Science. P.O. Box 945, New York, NY 10159-0945. (888) 437-4636 or (212) 633-3730. Fax (212) 633-3680. E-mail: usinfo-f@elsevier.com. PRICE: $184.50. ISBN: 0444826645.

  Summary: This book summarizes recent experimental and clinical developments and results which were reported during the proceedings of the 5th China-Japan Symposium on Diabetes Mellitus. The papers are presented in nine categories: plenary lectures; invited lecture; epidemiology; etiology and metabolism; insulin secretion; glycation; obesity and hyperlipidemia; complications; and treatment and education. Specific topics addressed include the prevalence of diabetes and its risk factors in China; incidence of IDDM in Beijing; treatment trends in Japan; malnutrition-related diabetes; current

clinical research; intensive insulin therapy; **Metformin;** Chinese herbal drugs; patient education; and quality of life. An index of authors concludes the book. (AA-M).

- **Diabetes Mellitus: Diagnosis and Treatment. 4th ed**

  Source: Philadelphia, PA: W.B. Saunders Company. 1998. 461 p.

  Contact: Available from W.B. Saunders Company. Order Fulfillment, 6277 Sea Harbor Drive, Orlando, FL 32887. (800) 545-2522. Fax (800) 874-6418 or (407) 352-3445. PRICE: $68.00. ISBN: 0721664032.

  Summary: This book, which has been updated to reflect the changes that have occurred in diabetes care since the last edition was published, presents the latest information on all basic aspects of diabetes. Chapter one describes the new classification and diagnostic criteria recently adopted by the American Diabetes Association and the World Health Organization. Chapter two differentiates the clinical and pathogenetic features of type 1 and type 2 diabetes and provides evidence to demonstrate the relationship between diabetes control and complications. Chapter three explains how to apply the recent American Diabetes Association changes in nutritional therapy involving sucrose, other carbohydrates, and fat content in the diet. Chapter four presents general considerations for using insulin, offers guidelines on initiating insulin therapy in hospitalized and nonhospitalized patients, describes various regimens, and discusses the side effects of insulin therapy. Chapter five examines the use of oral antidiabetes agents, focusing on sulfonylurea agents, **metformin,** and acarbose. Information includes mechanism of action, pharmacology, clinical use, and side effects. Chapter six provides information on the pathophysiology, etiology, symptoms, diagnosis, and treatment of diabetic ketoacidosis and hyperosmolar nonketotic syndrome. Chapter seven presents new evidence based guidelines on diabetes care, discusses the monitoring of diabetic control, and provides information on various aspects of self care. Chapter eight examines the features and treatment of complications, focusing on macrovascular, microvascular, and neuropathic complications. Chapter nine explores the impact of pregestational and gestational diabetes on pregnancy. The final chapter provides an overview of the material that a diabetes educator can use to teach and treat people who have diabetes. 2 appendixes. Numerous figures. Numerous tables. Numerous references.

- **Therapy for Diabetes Mellitus and Related Disorders. 3rd ed**

  Source: Alexandria, VA: American Diabetes Association. 1998. 487 p.

  Contact: Available from American Diabetes Association (ADA). Order Fulfillment Department, P.O. Box 930850, Atlanta, GA 31193-0850. (800) 232-6733. Fax (770) 442-9742. Website: www.diabetes.org. PRICE: $39.95 plus shipping and handling. ISBN: 0945448945.

  Summary: This handbook focuses on the treatment of problems that are of importance in the management of people with diabetes mellitus. The book attempts to help health professionals apply major advances in health care to their patients. Topics include the diagnosis and classification of diabetes mellitus, genetic counseling for type 1 diabetes, gestational diabetes mellitus, the management of pregnant women who have diabetes, antepartum and intrapartum obstetric care, neonatal problems and their management, type 1 diabetes and diabetic ketoacidosis in children, psychosocial adjustment in children who have type 1 diabetes, psychosocial aspects in adults, diabetic ketoacidosis and hyperosmolar hyperglycemic nonketotic syndrome in adults, and lactic acidosis. Other topics include the role of diabetes education in patient management; self monitoring of blood glucose; the rationale for management of hyperglycemia; medical

nutrition therapy; pharmacological treatment of obesity; exercise; oral hypoglycemic agents such as sulfonylureas, repaglinide, **metformin,** alpha glucosidase inhibitors, and thiazolidinediones; insulin treatment; insulin pump therapy; combination therapy for hyperglycemia; and diabetes complications. In addition, the book discusses surgery and anesthesia in people with diabetes, geriatric patient care, hypoglycemia in patients who have type 1 diabetes, insulin allergy and insulin resistance, drugs and hormones that increase blood glucose levels, diabetic dyslipidemia, antihypertensive therapy, cutaneous disorders associated with diabetes mellitus, infections, visual loss, ocular complications, drug induced renal dysfunction, diabetic nephropathy, chronic kidney disease, painful or insensitive lower extremity, mononeuropathy and amyoradiculopathy, gastrointestinal disturbances, and bladder dysfunction. Final topics include erectile dysfunction, female sexual disorders, postural hypotension, sudomotor dysfunction and dark vision, cardiac denervation syndrome, noninvasive cardiac testing, angina and congestive heart failure, myocardial infarction, peripheral vascular disease, and foot ulcers and infections. The book includes an index. Numerous figures. Numerous tables. Numerous references.

- **Annual Review of Diabetes 2002**

  Source: Alexandria, VA: American Diabetes Association. 2002. 284 p.

  Contact: Available from American Diabetes Association. 1701 North Beauregard Street, Alexandria, VA 22311. (800) 232-3472. E-mail: AskADA@diabetes.org. Fax: (770) 442-9742. Website: www.diabetes.org. PRICE: $49.95 plus shipping and handling.

  Summary: This issue of the Annual Review of Diabetes includes twenty-one research articles in three categories: epidemiology and pathogenesis, treatment, and complications. Specific topics include neurovascular dysfunction in type 2 diabetes; fatty acid metabolism in the etiology (cause) of type 2 diabetes; diabetes, impaired fasting glucose, and elevated HbA1c levels in adolescents; projection of diabetes burden through 2050; autoimmune diabetes; high familial risk and genetic susceptibility in early onset childhood diabetes; fasting versus postload glucose levels; influence of intensive diabetes treatment on body weight and composition of adults with type 1 diabetes; interventions to improve the management of diabetes in primary care, outpatient, and community settings; evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications; select vitamins and minerals in the management of diabetes; biological complementary therapies (botanical products in diabetes); effect of **metformin** in pediatric patients with type 2 diabetes; pump therapy for children; gene and cell-replacement therapy in type 1 diabetes; the prevalence of comorbid depression in adults with diabetes; preventing cardiovascular complications of type 2 diabetes by lipid management; diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome; the barrier of hypoglycemia; and the treatment of hypertension in adult patients with diabetes. Each article concludes with a list of references.

- **Diabetes Mellitus in the Elderly**

  Source: Binghamton, NY: Pharmaceutical Products Press. 1999. 84 p.

  Contact: Available from Pharmaceutical Products Press. 10 Alice Stret, Binghamton, NY 13904-1580. (800)429-6784. E-mail: getinfo@haworthpressinc.com. Website: www.haworthpressinc.com. PRICE: $49.95 plus shipping and handling. ISBN: 0789006820.

Summary: This volume is devoted to the diagnosis and treatment of diabetes mellitus in the elderly. The first chapter in the monograph addresses the frustration and futility health care providers and ministers sometimes experience in attempting to help patients with diabetes care for themselves. The monograph then includes four articles: the pathophysiology of diabetes in aging; the management of type 2 diabetes in the elderly patient; the use of acarbose in Europe; and insulin use in the elderly. The first article stresses that the recently revised American Diabetes Association (ADA) guidelines that include impaired glucose tolerance (IGT) and a lower level of fasting plasma glucose for the diagnosis of diabetes underscore the need for earlier detection of diabetes in the older adult and the relationship of diabetes with obesity. The articles on drug therapy offer practical insight to using the four new oral agents (acarbose, **metformin,** repaglinide and troglitazone) for type 2 diabetes, particularly in light of the ADA revised guidelines that suggest the trial of all oral agents before resorting to insulin. The last article discusses the comorbidities (other illnesses present at the same time as the diabetes), nutritional issues, pharmacodynamics, and physiologic effects of various insulin preparations and regimens. Each chapter concludes with a list of references and a subject index concludes the volume. This monograph has been copublished simultaneously as Journal of Geriatric Drug Therapy, Volume 12, Number 2, 1999.

The National Library of Medicine Book Index

The National Library of Medicine at the National Institutes of Health has a massive database of books published on healthcare and biomedicine. Go to the following Internet site, **http://locatorplus.gov/**, and then select "Search LOCATORplus." Once you are in the search area, simply type "metformin" (or synonyms) into the search box, and select "books only." From there, results can be sorted by publication date, author, or relevance. The following was recently catalogued by the National Library of Medicine:[11]

- **Diabetes and metformin: a research and clinical update** Author: Krans, Hendrik Michiel Jan.; Year: 2001; London: Royal Society of Medicine; Oxford: Distributed by Oxford University Press, 1985; ISBN: 0199220182
- **Glucophage.** Author: Biguanid Symposium (1972: Copenhagen); Year: 1973
- **Metformintherapie 1980**; Year: 1995; Stuttgart; New York: Schattauer, 1980; ISBN: 3794507657

Chapters on Metformin

In order to find chapters that specifically relate to metformin, an excellent source of abstracts is the Combined Health Information Database. You will need to limit your search to book chapters and metformin using the "Detailed Search" option. Go to the following hyperlink:

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[11] In addition to LOCATORPlus, in collaboration with authors and publishers, the National Center for Biotechnology Information (NCBI) is currently adapting biomedical books for the Web. The books may be accessed in two ways: (1) by searching directly using any search term or phrase (in the same way as the bibliographic database PubMed), or (2) by following the links to PubMed abstracts. Each PubMed abstract has a "Books" button that displays a facsimile of the abstract in which some phrases are hypertext links. These phrases are also found in the books available at NCBI. Click on hyperlinked results in the list of books in which the phrase is found. Currently, the majority of the links are between the books and PubMed. In the future, more links will be created between the books and other types of information, such as gene and protein sequences and macromolecular structures. See **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Books**.

http://chid.nih.gov/detail/detail.html. To find book chapters, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Book Chapter." Type "metformin" (or synonyms) into the "For these words:" box. The following is a typical result when searching for book chapters on metformin:

- **New Therapies for Non-Insulin-Dependent Diabetes Mellitus: Thiazolidinediones**

  Source: in LeRoith, D.; Taylor, S.I.; Olefsky, J.M., eds. Diabetes Mellitus: A Fundamental and Clinical Text. Philadelphia, PA: Lippincott-Raven Publishers. 1996. p. 661-668.

  Contact: Available from Lippincott-Raven Publishers. 12107 Insurance Way, Hagerstown, MD 21740-5184. (800) 777-2295. Fax (301) 824-7390. PRICE: $199.00. ISBN: 0397514565.

  Summary: The treatment of noninsulin-dependent diabetes mellitus (NIDDM) has involved the use of insulin or insulin secretagogues such as sulfonylureas or biguanides such as **metformin.** Although these agents have been effective to a degree, they do not deal directly with the underlying pathology of insulin resistance. This chapter, from a medical textbook on diabetes, describes the use of the thiazolidinediones, a class of drugs that may directly decrease insulin resistance by enhancing insulin action in skeletal muscle, liver, and adipose (fat) tissue. One of these compounds, troglitazone, has progressed to late-stage clinical development. The authors cover how thiazolidinediones improve insulin sensitivity in animal models of diabetes, how these drugs may improve the insulin resistance syndrome, the use of troglitazone in NIDDM, the use of troglitazone in impaired glucose tolerance (IGT), and the potential use of troglitazone in polycystic ovarian syndrome. The authors conclude that persons with other insulin-resistant states such as steroid-induced glucose intolerance and severe insulin resistance, as well as women with a history of gestational diabetes, are also populations in whom insulin-sensitizing agents would be valuable, both in treating and potentially preventing hyperglycemic states. 6 figures. 49 references.

- **Why Is Managing Your Blood Glucose So Important?**

  Source: in Hirsch, I.B. 12 Things You Must Know About Diabetes Care Right Now!. Alexandria, VA: American Diabetes Association. 2000. p. 21-32.

  Contact: Available from American Diabetes Association (ADA). Order Fulfillment Department, P.O. Box 930850, Atlanta, GA 31193-0850. (800) 232-6733. Fax (770) 442-9742. Website: www.diabetes.org. PRICE: $14.95 plus shipping and handling. ISBN: 1580400612.

  Summary: This chapter focuses on the importance of self management of blood glucose and the implications of the Diabetes Control and Complications Trial (DCCT) for diabetes self care. The DCCT found that intensive treatment for people who had type 1 diabetes resulted in fewer cases of eye and kidney disease. The major drawback of intensive therapy was severe hypoglycemia. The United Kingdom Prospective Diabetes Study examined the effects of diabetes control in people with type 2 diabetes. This study found that people who were less than 120 percent of their ideal body weight slowed the progression of retinopathy by 21 percent and the progression of microalbuminuria by 34 percent. They also reduced their risk of having a heart attack by 16 percent. For overweight participants, **metformin** was used with one of the treatment groups. The use of this drug improved outcomes. Although these studies underscore the benefits of intensive diabetes management, intensive blood glucose control will not work for everyone, including people who do not know when they are hypoglycemic; people who

have advanced complications, another serious disease, advanced heart disease, and history of stroke; and children under 13. The chapter presents guidelines so that readers can determine whether intensive therapy may be beneficial for them. The chapter includes a list of questions a patient may ask a doctor and questions a doctor may ask a patient. 1 table.

- **Antidiabetic Agents and Glucagon**

  Source: in Moreau, D., ed. Nursing96 Drug Handbook. Springhouse, PA: Nursing96 Books. Springhouse Corporation. 1996. p. 748-763.

  Contact: Available from Springhouse Publishing. 1111 Bethlehem Pike, P.O. Box 908, Springhouse, PA 19477. (800) 331-3170 or (215) 646-4670 or (215) 646-4671. Fax (215) 646-8716. PRICE: $29.95. ISBN: 087434817X. ISSN: 0273320X.

  Summary: This chapter on antidiabetic agents and glucagon is from a nursing handbook on pharmaceuticals. The handbook is designed to provide the nursing profession with drug information that focuses on what nurses need to know by emphasizing the clinical aspects of drug therapy. The chapter begins with an alphabetically-arranged list of the generic names of drugs described in the chapter; this is immediately followed by an alphabetized list of its brand names. This is then followed by a list of selected combination products in which these drugs are found. Information on each drug is arranged under the following headings: How Supplied, Action, Onset, Peak, Duration, Indications and Dosage, Adverse Reactions, Interactions, Contraindications, and Nursing Considerations. Drugs include acetohexamide; chlorpropamide; glipizide; glucagon; glyburide; insulins; **metformin** hydrochloride; tolazamide; tolbutamide.

- **Oral Agents**

  Source: in Edelman, S.V. and Henry, R.R. Diagnosis and Management of Type 2 Diabetes. Caddo, OK: Professional Communications, Inc. 2002. p. 69-120.

  Contact: Available from Professional Communications, Inc., Fulfillment Center, PO Box 10, Caddo, OK 74729-0010. (800)337-9838. Fax (580)367-9989. E-mail: profcomm@netcommander.com. ISBN: 1884735754. PRICE: $21.95, plus shipping and handling.

  Summary: This chapter on the use of oral hypoglycemic agents is from a handbook for primary care providers that offers a concise overview of the diagnosis and management of type 2 diabetes. The majority of patients with type 2 diabetes have less than ideal metabolic control despite the medical community's understanding of the underlying pathophysiologic mechanisms of hyperglycemia (high blood glucose) and the availability of a wide variety of new treatment options. The authors contend that failure to achieve glycemic (blood glucose) goals is related in part to a misconception by patients and caregivers that type 2 diabetes is a mild disease, and not as serious as type 1 diabetes. Drug therapy with oral antidiabetes agents is required when dietary modification and exercise therapy do not result in normalization or near normalization of metabolic abnormalities. Topics include the pathophysiologic basis of pharmacologic therapy, the importance of controlling postprandial (after a meal) hyperglycemia, intensive therapy in type 2 diabetes, diabetes prevention study results, oral antidiabetes agents, thiazolidinediones (including rosiglitazone, pioglitazone), **metformin** (Glucophage), alpha-glucosidase inhibitors, sulfonylureas, meglitinides, monotherapy with oral antidiabetes agents, combination therapy with oral antidiabetes agents, taking patients with type 2 diabetes off insulin, and drugs under development. 5 figures. 4 tables. 31 references.

- **Therapy for Diabetes**

  Source: in Harris, M.I., et al., eds., for the National Diabetes Data Group (NDDG). Diabetes in America. 2nd ed. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. 1995. p. 519-540.

  Contact: Available from National Diabetes Information Clearinghouse (NDIC). 1 Information Way, Bethesda, MD 20892-3560. (800) 860-8747 or (301) 654-3327. Fax (301) 634-0716. E-mail: ndic@info.niddk.nih.gov. Also available at http://www.niddk.nih.gov/. PRICE: Full-text book and chapter available online at no charge; book may be purchased for $20.00. Order number: DM-96 (book).

  Summary: This chapter on therapy for diabetes is from a compilation and assessment of data on diabetes and its complications in the United States. The authors note that the most recent information about use of diet, oral agents, and insulin by people with diabetes in the United States is from the 1989 National Health Interview Survey (NHIS). For all diabetes patients older than 18 years, 43 percent were treated with insulin, 49 percent were treated with oral agents, and 64 percent reported they were following a diet for their diabetes. Two or more insulin injections daily were taken by 61 percent of insulin-dependent diabetes (IDDM) patients and 48 percent of insulin-treated NIDDM patients; use of an insulin pump was rare. Nutritional therapy is a challenging but crucial element in the management of diabetes. For children with IDDM, a goal is to match diet to insulin requirements to ensure normal growth and development. By contrast, in obese NIDDM patients, it is important to achieve and maintain a reasonable or realistic body weight. The authors outline recommendations for dietary intake for patients with diabetes. When optimal diet with weight reduction and exercise fail to restore adequate glycemic control in NIDDM patients, pharmacologic treatment should be considered. The sulfonylureas are the major group of oral hypoglycemic agents currently used, with the biguanide drug **metformin** recently approved for use. The Diabetes Control and Complications Trial (DCCT) evaluated the effect of intensive insulin therapy in IDDM and found a 40 to 70 percent risk reduction in retinopathy, nephropathy, and neuropathy, compared with conventionally treated subjects. The authors report that favorable effects of patient education, notably increased self management skills, such as self glucose monitoring (SMBG), compliance with overall management, improved glycemia for insulin-treated diabetes, and reduction in complications. The authors conclude with a brief discussion of pancreatic transplantation. Pancreatic transplant is the only treatment for IDDM capable of establishing an insulin-independent state with euglycemia and normal glycosylated hemoglobin. 2 appendices. 10 figures. 14 tables. 152 references. (AA-M).

- **Diabetes Agents**

  Source: in Pirsch, J.; Simmons, W.; Sollinger, H. Transplantation Drug Manual. 3rd ed. Georgetown, TX: Landes Bioscience. 1999. p. 91-102.

  Contact: Available from Landes Bioscience. 810 South Church Street, Georgetown, TX 78626. (512) 863-7762. Fax (512) 863-0081. Website: www.landesbioscience.com. PRICE: $45.00. ISBN: 1570595933.

  Summary: This chapter presents an overview of various agents, including insulin, glyburide, glipizide, troglitazone, and **metformin,** and begins with information on their initial and maintenance dosage. This is followed by a discussion of each agent in terms of its brand name, manufacturer, mechanism of action, indication, contraindications, adverse reactions, and drug interactions. For each brand of insulin, the ingredient, concentration, and product form are provided, and for each class of insulin, the onset,

peak, duration, and compatibility with other forms are discussed. In addition, special precautions and dosage information are provided for glyburide, glipizide, troglitazone, and **metformin.**

- **Mastering Diabetes Medications**

  Source: in McCool, M.H. and Woodruff, S. My Doctor Says I Have a Little Diabetes. Garden City Park, NY: Avery Publishing Group. 1997. p. 69-89.

  Contact: Available from Avery Publishing Group. 120 Old Broadway, Garden City Park, NY 11040. (800) 548-5757 or (516) 741-2155. Fax (516) 742-1892. E-mail: info@averypublishing.com. Website: www.averypublishing.com. PRICE: $9.95 plus shipping and handling. ISBN: 0895298600.

  Summary: This chapter uses a question and answer format to discuss different diabetes medications, medication interactions and precautions, and the effects that many prescription and over the counter medications have on diabetes. Oral diabetes medications and insulin are the two types of medications prescribed for people who have diabetes. Categories of oral diabetes medications include sulfonylureas, the biguanide **metformin,** alpha-glucosidase inhibitors, the thiazolidinedione troglitazone, and the meglitinide repaglinide. The chapter explains how each drug works and presents important considerations for using the drug. The chapter then discusses the use of insulin in terms of sources of insulin, types of insulin, the side effects of insulin, and the prescribed dosage of insulin. In addition, the chapter provides guidelines for drawing up a single type of insulin, mixing different types of insulin, drawing up a mixed dose of insulin, choosing an injection site, and injecting insulin. The chapter concludes with lists of drugs that tend to lower blood glucose levels or raise blood glucose levels. 1 figure. 3 tables.

- **Plasminogen Activator Inhibitor-1 and Vascular Disease in Diabetes Mellitus**

  Source: in Johnstone, M.T. and Veves, A. Diabetes and Cardiovascular Disease. Totowa, NJ: The Humana Press, Inc. 2001. p. 237-243.

  Contact: Humana Press, Inc. 999 Riverview Dr., Suite 208 Totowa, NJ 07512. (973) 256-1699. Fax (973) 256-8341. E-mail: humana@humanapr.com PRICE: $125.00, plus shipping and handling. ISBN: 089603755X.

  Summary: With over ten million diagnosed patients and another five million undiagnosed, diabetes mellitus and its complications is a major public health problem that will assume epidemic proportions as the population grows older. This chapter on plasminogen activator inhibitor 1 and vascular (blood vessel) disease is from a textbook that offers physicians practical knowledge about cardiovascular disease and diabetes. This chapter is in Part I, which focuses on pathophysiology, including the mechanisms and risk factors for diabetic cardiovascular disease. The author notes that atherosclerosis (hardening and narrowing of the arteries) is a major cause of morbidity (illness) and mortality (death) in patients with both type 1 and type 2 diabetes mellitus. A number of different factors are involved in the development of atherosclerosis in patients with diabetes. Hyperglycemia (high levels of blood glucose) has direct toxic effects on vascular tissue and appears to facilitate free radical formation and oxidative damage to the vascular wall. Recent studies have identified elevated levels of the fibrinolytic inhibitor plasminogen activator inhibitor 1 (PAI-1) in patients with type 2 diabetes. The author describes the fibrinolytic system, the physiology of PAI-1, the clinical consequences of increased PAI-1, practical guidelines for the measurement of PAI-1, and therapeutic implications. Drugs that reduce plasma insulin levels or that attenuate

insulin resistance may have secondary benefits in reducing PAI-1 levels. **Metformin** and troglitazone are mentioned as possible therapeutic agents in this arena. The author also notes that improved glycemic control and the use of ACE inhibitors may contribute to reduced plasma PAI-1 levels. 1 figure. 48 references.

CHAPTER 8. MULTIMEDIA ON METFORMIN

Overview

In this chapter, we show you how to keep current on multimedia sources of information on metformin. We start with sources that have been summarized by federal agencies, and then show you how to find bibliographic information catalogued by the National Library of Medicine.

Video Recordings

An excellent source of multimedia information on metformin is the Combined Health Information Database. You will need to limit your search to "Videorecording" and "metformin" using the "Detailed Search" option. Go directly to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. To find video productions, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Videorecording (videotape, videocassette, etc.)." Type "metformin" (or synonyms) into the "For these words:" box. The following is a typical result when searching for video recordings on metformin:

- **Meeting the Diabetes Challenge in Long Term Care**

  Source: Cypress, CA: Medcom, Inc. 1995. (videocassette).

  Contact: Available from Medical Audio Visual Communications, Inc. P.O. Box 84548, 2336 Bloor Street West, Toronto, Ontario M6S 1TO Canada. (800) 757-4868 or (905) 602-1160. Fax (905) 602-8720. E-mail: dwc@mavc.com. PRICE: $235.00 plus shipping and handling. Order number MED307.

  Summary: This video describes the effects of diabetes on long-term care residents and presents the treatment methods used to manage this disease. Diabetes is widespread among the elderly, and it is easily overlooked because many of its symptoms are the same as those of other diseases. Treating long-term care residents who have diabetes involves balancing nutrition therapy, exercise, and medication. The video identifies the goals of nutrition therapy, discusses meal planning, and highlights the challenges posed by nutrition therapy. Other topics include diabetes pathology, exercise therapy, and medication and insulin. The video provides information on the side effects of oral

hypoglycemic agents such as sulfonylureas and **metformin** and identifies the steps involved in monitoring residents who have diabetes. The video also describes the symptoms of acute and long-term complications of diabetes. Acute complications include hyperglycemia, hypoglycemia, ketoacidosis, and hyperosmolar syndrome. Long-term complications include microvascular and macrovascular problems and peripheral neuropathy. The video also offers guidelines on proper leg and foot care.

Audio Recordings

The Combined Health Information Database contains abstracts on audio productions. To search CHID, go directly to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. To find audio productions, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Sound Recordings." Type "metformin" (or synonyms) into the "For these words:" box. The following is a typical result when searching for sound recordings on metformin:

- **Bernstein Plan: Type II**

  Source: Van Nuys, CA: Prana Publications. 1995. (audiocassettes).

  Contact: Available from Prana Publications. 5623 Matilija Avenue, Van Nuys, CA 91401. (800) 735-7726 or (818) 780-1308. Fax (818) 786-7359. E-Mail prana@earthspirit.org. PRICE: $22.95 plus $3.25 shipping and handling (as of 1995). Order Number A05.

  Summary: These audiocassette tapes familiarize listeners with Dr. R.K. Bernstein's method of diabetes control for noninsulin-dependent diabetes. Dr. Bernstein, who has had insulin-dependent diabetes for 49 years, believes high blood sugar causes diabetes complications and that complications can be prevented and at times reversed by normalizing blood sugar. Topics on the tapes include the low carbohydrate diet; muscle building; blood glucose tests; the use of **metformin** and/or insulin; and how to break the obesity cycle by cutting carbohydrates to reduce hunger, blood sugar, and weight. (AA-M).

- **Effective Drug Therapy for Diabetes Mellitus**

  Source: Alexandria, VA: American Diabetes Association. 1998. (audiocassette).

  Contact: Available from American Diabetes Association (ADA). Order Fulfillment Department, P.O. Box 930850, Atlanta, GA 31193-0850. (800) 232-6733. Fax (770) 442-9742. Website: www.diabetes.org. PRICE: $17.95 for members; $22.95 for nonmembers; plus shipping and handling. ISBN: 1580400213.

  Summary: These audiocassettes provide information on effective drug therapy for diabetes mellitus. They feature articles first published in 'Clinical Diabetes.' An article on the use of **metformin** to treat diabetes provides an overview of this agent. Another article describes the use of acarbose to inhibit alpha-glucosidase. This agent decreases postprandial hyperglycemia by delaying carbohydrate digestion and absorption. A third article focuses on the use of lispro insulin, a rapid acting synthetic analog, to treat diabetes. Topics include the molecular structure of lispro insulin, immunologic concerns, and clinical applications and concerns. Another article deals with the use of troglitazone, a thiazolidinedione that improves insulin resistance without stimulating insulin secretion, to treat diabetes and the insulin resistance syndrome. Topics include the pathophysiology of impaired glucose tolerance and type 2 diabetes, the

pathophysiological basis of pharmacological therapy, clinical studies, the effects of troglitazone on body weight and lipids, and the safety and adverse effects of the agent. An article on the use of combination oral agent and insulin therapy in patients who have type 2 diabetes includes discussions of the rationale for the use of combination therapy and the mechanism of action, efficacy, and side effects of various oral agents combined with insulin. The final article focuses on converting patients who have type 2 diabetes from insulin-requiring to noninsulin-requiring. Topics include the disadvantages of insulin utilization in people who have type 2 diabetes, once daily insulin and combination oral therapy, improved glycemic control on oral therapy, weight loss on combination oral therapy, oral monotherapy, and other potential drug combinations.

CHAPTER 9. PERIODICALS AND NEWS ON METFORMIN

Overview

In this chapter, we suggest a number of news sources and present various periodicals that cover metformin.

News Services and Press Releases

One of the simplest ways of tracking press releases on metformin is to search the news wires. In the following sample of sources, we will briefly describe how to access each service. These services only post recent news intended for public viewing.

PR Newswire

To access the PR Newswire archive, simply go to **http://www.prnewswire.com/**. Select your country. Type "metformin" (or synonyms) into the search box. You will automatically receive information on relevant news releases posted within the last 30 days. The search results are shown by order of relevance.

Reuters Health

The Reuters' Medical News and Health eLine databases can be very useful in exploring news archives relating to metformin. While some of the listed articles are free to view, others are available for purchase for a nominal fee. To access this archive, go to **http://www.reutershealth.com/en/index.html** and search by "metformin" (or synonyms). The following was recently listed in this archive for metformin:

- **Combined data fail to show link between metformin and lactic acidosis**
  Source: Reuters Industry Breifing
  Date: November 26, 2003
- **Repaglinide plus metformin is safe, effective for type 2 diabetes**
  Source: Reuters Industry Breifing
  Date: July 23, 2003

- **Inappropriate metformin prescribing in hospitalized patients continues**
  Source: Reuters Industry Breifing
  Date: June 17, 2003
- **Andrx submits EU market application for branded generic version of Glucophage XR**
  Source: Reuters Industry Breifing
  Date: May 28, 2003
- **Metformin's diabetes preventive effects persist after drug withdrawal**
  Source: Reuters Industry Breifing
  Date: May 01, 2003
- **Pioglitazone, metformin provide comparable glycemic control in diabetics**
  Source: Reuters Industry Breifing
  Date: April 29, 2003
- **Acarbose effective for type 2 diabetes inadequately controlled by metformin**
  Source: Reuters Industry Breifing
  Date: February 19, 2003
- **Metformin linked to reduced risk of mortality in a population-based study**
  Source: Reuters Industry Breifing
  Date: January 10, 2003
- **More data still needed on efficacy, safety of metformin for PCOS**
  Source: Reuters Industry Breifing
  Date: December 10, 2002
- **Metformin benefits in patients with HIV lipodystrophy sustained for months**
  Source: Reuters Industry Breifing
  Date: November 08, 2002
- **Orlistat a useful adjunct to metformin in overweight diabetics**
  Source: Reuters Industry Breifing
  Date: July 16, 2002
- **Biovail buys DepoMed's once-daily metformin, takes equity stake**
  Source: Reuters Industry Breifing
  Date: May 29, 2002
- **Metformin increases fertility in PCOS patients**
  Source: Reuters Industry Breifing
  Date: May 14, 2002
- **Metformin restores glucose tolerance in teens with polycystic ovary syndrome**
  Source: Reuters Industry Breifing
  Date: May 08, 2002
- **Andrx wins tentative approval for generic Glucophage XR**
  Source: Reuters Industry Breifing
  Date: April 25, 2002
- **DepoMed says Bristol-Myers' Glucophage XR infringes patent**
  Source: Reuters Industry Breifing
  Date: March 26, 2002
- **Metformin prescribing guidelines often ignored**
  Source: Reuters Industry Breifing
  Date: February 25, 2002

- **Type 2 diabetes onset in at-risk patients reduced with lifestyle changes, metformin**
  Source: Reuters Industry Breifing
  Date: February 06, 2002
- **Troglitazone better than metformin at increasing glucose disposal**
  Source: Reuters Industry Breifing
  Date: January 30, 2002
- **Caraco gets US approval for generic Glucophage**
  Source: Reuters Industry Breifing
  Date: January 30, 2002
- **Pharmaceutical Resources gets FDA approval for Glucophage generic**
  Source: Reuters Industry Breifing
  Date: January 28, 2002
- **FDA grants final approval to generic versions of Glucophage**
  Source: Reuters Industry Breifing
  Date: January 25, 2002
- **Metformin is safe, effective for treatment of type 2 diabetes in pediatric patients**
  Source: Reuters Industry Breifing
  Date: January 16, 2002
- **Caraco's stock rises on tentative FDA approval for generic metformin**
  Source: Reuters Industry Breifing
  Date: January 02, 2002
- **Ivax gets conditional approval for generic Glucophage**
  Source: Reuters Industry Breifing
  Date: November 23, 2001
- **Metformin and carbohydrate-modified diet effective for obesity treatment**
  Source: Reuters Industry Breifing
  Date: November 02, 2001
- **Generic firms ask lawmakers to block Bristol-Myers' Glucophage strategy**
  Source: Reuters Industry Breifing
  Date: October 10, 2001
- **Metformin combined with insulin does not affect awareness of hypoglycemia**
  Source: Reuters Industry Breifing
  Date: October 03, 2001
- **DepoMed initiates phase III trial of Metformin GR for type II diabetes**
  Source: Reuters Industry Breifing
  Date: June 21, 2001
- **DepoMed's once-a-day Glucophage rival moves into phase III**
  Source: Reuters Industry Breifing
  Date: April 26, 2001
- **Metformin may lower obesity-related diabetes risk in adolescents**
  Source: Reuters Industry Breifing
  Date: April 16, 2001
- **Metformin may lower adolescents' diabetes risk**
  Source: Reuters Health eLine
  Date: April 13, 2001

- **Metformin prevents pancreatic adenocarcinoma in hamsters**
  Source: Reuters Industry Breifing
  Date: April 10, 2001
- **Metformin improves endothelial function in patients with type 2 diabetes**
  Source: Reuters Industry Breifing
  Date: April 03, 2001
- **Metformin may reduce CVD risk in lipodystrophic HIV-infected patients**
  Source: Reuters Industry Breifing
  Date: February 27, 2001
- **Metformin plus clomiphene induces ovulation despite polycystic ovary syndrome**
  Source: Reuters Industry Breifing
  Date: February 15, 2001
- **FDA approves new formulation of Bristol-Myers' antidiabetic Glucophage**
  Source: Reuters Industry Breifing
  Date: October 16, 2000
- **Addition of nateglinide to metformin helps control glucose in type 2 diabetes**
  Source: Reuters Industry Breifing
  Date: September 25, 2000
- **Metformin reverses fatty liver disease in mouse model**
  Source: Reuters Industry Breifing
  Date: August 31, 2000
- **DepoMed announces promising phase I results for once-daily metformin**
  Source: Reuters Industry Breifing
  Date: July 20, 2000
- **Metformin useful in treating adolescents with PCOS**
  Source: Reuters Industry Breifing
  Date: June 26, 2000
- **Glucovance superior to glucophage in trial**
  Source: Reuters Health eLine
  Date: June 12, 2000

The NIH

Within MEDLINEplus, the NIH has made an agreement with the New York Times Syndicate, the AP News Service, and Reuters to deliver news that can be browsed by the public. Search news releases at **http://www.nlm.nih.gov/medlineplus/alphanews_a.html**. MEDLINEplus allows you to browse across an alphabetical index. Or you can search by date at the following Web page: **http://www.nlm.nih.gov/medlineplus/newsbydate.html**. Often, news items are indexed by MEDLINEplus within its search engine.

Business Wire

Business Wire is similar to PR Newswire. To access this archive, simply go to **http://www.businesswire.com/**. You can scan the news by industry category or company name.

Market Wire

Market Wire is more focused on technology than the other wires. To browse the latest press releases by topic, such as alternative medicine, biotechnology, fitness, healthcare, legal, nutrition, and pharmaceuticals, access Market Wire's Medical/Health channel at **http://www.marketwire.com/mw/release_index?channel=MedicalHealth**. Or simply go to Market Wire's home page at **http://www.marketwire.com/mw/home**, type "metformin" (or synonyms) into the search box, and click on "Search News." As this service is technology oriented, you may wish to use it when searching for press releases covering diagnostic procedures or tests.

Search Engines

Medical news is also available in the news sections of commercial Internet search engines. See the health news page at Yahoo (**http://dir.yahoo.com/Health/News_and_Media/**), or you can use this Web site's general news search page at **http://news.yahoo.com/**. Type in "metformin" (or synonyms). If you know the name of a company that is relevant to metformin, you can go to any stock trading Web site (such as **http://www.etrade.com/**) and search for the company name there. News items across various news sources are reported on indicated hyperlinks. Google offers a similar service at **http://news.google.com/**.

BBC

Covering news from a more European perspective, the British Broadcasting Corporation (BBC) allows the public free access to their news archive located at **http://www.bbc.co.uk/**. Search by "metformin" (or synonyms).

Newsletter Articles

Use the Combined Health Information Database, and limit your search criteria to "newsletter articles." Again, you will need to use the "Detailed Search" option. Go directly to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. Go to the bottom of the search page where "You may refine your search by." Select the dates and language that you prefer. For the format option, select "Newsletter Article." Type "metformin" (or synonyms) into the "For these words:" box. You should check back periodically with this database as it is updated every three months. The following is a typical result when searching for newsletter articles on metformin:

- **Great News About Avoiding Diabetes**

  Source: University of California, Berkeley, Wellness Letter. 18(2): 1-2. November 2001.

  Contact: Health Letter Associates. P.O. Box 412, Prince Street Station, New York, NY 10012-0007-.

  Summary: In August 2001, a study from the National Institutes of Health (NIH) showed that relatively simple measures can dramatically lower diabetes risk. The 3-year study included 3,234 overweight Americans who had impaired glucose tolerance. One group of study participants followed a low-fat diet to lose about 7 percent of their body weight. They exercised half an hour a day, usually by walking. The participants also

received counseling about making these changes, as well as a follow-up. A second group took the drug **metformin,** currently used to treat diabetes. A third group took placebo pills. The latter two groups received general advice about healthy habits but no follow- up. In the lifestyle change group, 14 percent developed diabetes, compared to almost 30 percent in the placebo group and 22 percent in the **metformin** group. Study results indicate that **metformin** may have some use in the prevention of diabetes but is not as effective as diet, exercise, and weight loss. Study participants increased their intake of fruits and vegetables, decreased fat, and cut down, but did not entirely eliminate, their sweets. A promising finding to emerge from the study is that the behavior changes necessary to prevent or postpone diabetes worked in all racial, ethnic, and age groups.

Academic Periodicals covering Metformin

Numerous periodicals are currently indexed within the National Library of Medicine's PubMed database that are known to publish articles relating to metformin. In addition to these sources, you can search for articles covering metformin that have been published by any of the periodicals listed in previous chapters. To find the latest studies published, go to **http://www.ncbi.nlm.nih.gov/pubmed**, type the name of the periodical into the search box, and click "Go."

If you want complete details about the historical contents of a journal, you can also visit the following Web site: **http://www.ncbi.nlm.nih.gov/entrez/jrbrowser.cgi**. Here, type in the name of the journal or its abbreviation, and you will receive an index of published articles. At **http://locatorplus.gov/**, you can retrieve more indexing information on medical periodicals (e.g. the name of the publisher). Select the button "Search LOCATORplus." Then type in the name of the journal and select the advanced search option "Journal Title Search."

CHAPTER 10. RESEARCHING MEDICATIONS

Overview

While a number of hard copy or CD-ROM resources are available for researching medications, a more flexible method is to use Internet-based databases. Broadly speaking, there are two sources of information on approved medications: public sources and private sources. We will emphasize free-to-use public sources.

U.S. Pharmacopeia

Because of historical investments by various organizations and the emergence of the Internet, it has become rather simple to learn about the medications recommended for metformin. One such source is the United States Pharmacopeia. In 1820, eleven physicians met in Washington, D.C. to establish the first compendium of standard drugs for the United States. They called this compendium the U.S. Pharmacopeia (USP). Today, the USP is a non-profit organization consisting of 800 volunteer scientists, eleven elected officials, and 400 representatives of state associations and colleges of medicine and pharmacy. The USP is located in Rockville, Maryland, and its home page is located at **http://www.usp.org/**. The USP currently provides standards for over 3,700 medications. The resulting USP DI® Advice for the Patient® can be accessed through the National Library of Medicine of the National Institutes of Health. The database is partially derived from lists of federally approved medications in the Food and Drug Administration's (FDA) Drug Approvals database, located at **http://www.fda.gov/cder/da/da.htm**.

While the FDA database is rather large and difficult to navigate, the Phamacopeia is both user-friendly and free to use. It covers more than 9,000 prescription and over-the-counter medications. To access this database, simply type the following hyperlink into your Web browser: **http://www.nlm.nih.gov/medlineplus/druginformation.html**. To view examples of a given medication (brand names, category, description, preparation, proper use, precautions, side effects, etc.), simply follow the hyperlinks indicated within the United States Pharmacopeia (USP).

Below, we have compiled a list of medications associated with metformin. If you would like more information on a particular medication, the provided hyperlinks will direct you to ample documentation (e.g. typical dosage, side effects, drug-interaction risks, etc.). The

following drugs have been mentioned in the Pharmacopeia and other sources as being potentially applicable to metformin:

Antidiabetic Agents, Sulfonylurea

- **Systemic - U.S. Brands:** Amaryl; DiaBeta; Diabinese; Dymelor; Glucotrol; Glucotrol XL; Glynase PresTab; Micronase; Orinase; Tolinase
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202742.html

Glyburide and Metformin

- **Systemic - U.S. Brands:** Glucovance
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/500237.html

Metformin

- **Systemic - U.S. Brands:** Glucophage
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202756.html

Nateglinide

- **Systemic - U.S. Brands:** Starlix
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/500277.html

Pioglitazone

- **Systemic - U.S. Brands:** Actos
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/500036.html

Repaglinide

- **Systemic - U.S. Brands:** Prandin
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/203463.html

Rosiglitazone

- **Systemic - U.S. Brands:** Avandia
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/500022.html

Commercial Databases

In addition to the medications listed in the USP above, a number of commercial sites are available by subscription to physicians and their institutions. Or, you may be able to access these sources from your local medical library.

Mosby's Drug Consult™

Mosby's Drug Consult™ database (also available on CD-ROM and book format) covers 45,000 drug products including generics and international brands. It provides prescribing information, drug interactions, and patient information. Subscription information is available at the following hyperlink: **http://www.mosbysdrugconsult.com/**.

PDR*health*

The PDR*health* database is a free-to-use, drug information search engine that has been written for the public in layman's terms. It contains FDA-approved drug information adapted from the Physicians' Desk Reference (PDR) database. PDR*health* can be searched by brand name, generic name, or indication. It features multiple drug interactions reports. Search PDR*health* at **http://www.pdrhealth.com/drug_info/index.html**.

Other Web Sites

Drugs.com (**www.drugs.com**) reproduces the information in the Pharmacopeia as well as commercial information. You may also want to consider the Web site of the Medical Letter, Inc. (**http://www.medletter.com/**) which allows users to download articles on various drugs and therapeutics for a nominal fee.

If you have any questions about a medical treatment, the FDA may have an office near you. Look for their number in the blue pages of the phone book. You can also contact the FDA through its toll-free number, 1-888-INFO-FDA (1-888-463-6332), or on the World Wide Web at **www.fda.gov**.

APPENDICES

APPENDIX A. PHYSICIAN RESOURCES

Overview

In this chapter, we focus on databases and Internet-based guidelines and information resources created or written for a professional audience.

NIH Guidelines

Commonly referred to as "clinical" or "professional" guidelines, the National Institutes of Health publish physician guidelines for the most common diseases. Publications are available at the following by relevant Institute[12]:

- Office of the Director (OD); guidelines consolidated across agencies available at **http://www.nih.gov/health/consumer/conkey.htm**
- National Institute of General Medical Sciences (NIGMS); fact sheets available at **http://www.nigms.nih.gov/news/facts/**
- National Library of Medicine (NLM); extensive encyclopedia (A.D.A.M., Inc.) with guidelines: **http://www.nlm.nih.gov/medlineplus/healthtopics.html**
- National Cancer Institute (NCI); guidelines available at **http://www.cancer.gov/cancerinfo/list.aspx?viewid=5f35036e-5497-4d86-8c2c-714a9f7c8d25**
- National Eye Institute (NEI); guidelines available at **http://www.nei.nih.gov/order/index.htm**
- National Heart, Lung, and Blood Institute (NHLBI); guidelines available at **http://www.nhlbi.nih.gov/guidelines/index.htm**
- National Human Genome Research Institute (NHGRI); research available at **http://www.genome.gov/page.cfm?pageID=10000375**
- National Institute on Aging (NIA); guidelines available at **http://www.nia.nih.gov/health/**

[12] These publications are typically written by one or more of the various NIH Institutes.

- National Institute on Alcohol Abuse and Alcoholism (NIAAA); guidelines available at **http://www.niaaa.nih.gov/publications/publications.htm**
- National Institute of Allergy and Infectious Diseases (NIAID); guidelines available at **http://www.niaid.nih.gov/publications/**
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); fact sheets and guidelines available at **http://www.niams.nih.gov/hi/index.htm**
- National Institute of Child Health and Human Development (NICHD); guidelines available at **http://www.nichd.nih.gov/publications/pubskey.cfm**
- National Institute on Deafness and Other Communication Disorders (NIDCD); fact sheets and guidelines at **http://www.nidcd.nih.gov/health/**
- National Institute of Dental and Craniofacial Research (NIDCR); guidelines available at **http://www.nidr.nih.gov/health/**
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); guidelines available at **http://www.niddk.nih.gov/health/health.htm**
- National Institute on Drug Abuse (NIDA); guidelines available at **http://www.nida.nih.gov/DrugAbuse.html**
- National Institute of Environmental Health Sciences (NIEHS); environmental health information available at **http://www.niehs.nih.gov/external/facts.htm**
- National Institute of Mental Health (NIMH); guidelines available at **http://www.nimh.nih.gov/practitioners/index.cfm**
- National Institute of Neurological Disorders and Stroke (NINDS); neurological disorder information pages available at **http://www.ninds.nih.gov/health_and_medical/disorder_index.htm**
- National Institute of Nursing Research (NINR); publications on selected illnesses at **http://www.nih.gov/ninr/news-info/publications.html**
- National Institute of Biomedical Imaging and Bioengineering; general information at **http://grants.nih.gov/grants/becon/becon_info.htm**
- Center for Information Technology (CIT); referrals to other agencies based on keyword searches available at **http://kb.nih.gov/www_query_main.asp**
- National Center for Complementary and Alternative Medicine (NCCAM); health information available at **http://nccam.nih.gov/health/**
- National Center for Research Resources (NCRR); various information directories available at **http://www.ncrr.nih.gov/publications.asp**
- Office of Rare Diseases; various fact sheets available at **http://rarediseases.info.nih.gov/html/resources/rep_pubs.html**
- Centers for Disease Control and Prevention; various fact sheets on infectious diseases available at **http://www.cdc.gov/publications.htm**

NIH Databases

In addition to the various Institutes of Health that publish professional guidelines, the NIH has designed a number of databases for professionals.[13] Physician-oriented resources provide a wide variety of information related to the biomedical and health sciences, both past and present. The format of these resources varies. Searchable databases, bibliographic citations, full-text articles (when available), archival collections, and images are all available. The following are referenced by the National Library of Medicine:[14]

- **Bioethics:** Access to published literature on the ethical, legal, and public policy issues surrounding healthcare and biomedical research. This information is provided in conjunction with the Kennedy Institute of Ethics located at Georgetown University, Washington, D.C.: **http://www.nlm.nih.gov/databases/databases_bioethics.html**
- **HIV/AIDS Resources:** Describes various links and databases dedicated to HIV/AIDS research: **http://www.nlm.nih.gov/pubs/factsheets/aidsinfs.html**
- **NLM Online Exhibitions:** Describes "Exhibitions in the History of Medicine": **http://www.nlm.nih.gov/exhibition/exhibition.html**. Additional resources for historical scholarship in medicine: **http://www.nlm.nih.gov/hmd/hmd.html**
- **Biotechnology Information:** Access to public databases. The National Center for Biotechnology Information conducts research in computational biology, develops software tools for analyzing genome data, and disseminates biomedical information for the better understanding of molecular processes affecting human health and disease: **http://www.ncbi.nlm.nih.gov/**
- **Population Information:** The National Library of Medicine provides access to worldwide coverage of population, family planning, and related health issues, including family planning technology and programs, fertility, and population law and policy: **http://www.nlm.nih.gov/databases/databases_population.html**
- **Cancer Information:** Access to cancer-oriented databases: **http://www.nlm.nih.gov/databases/databases_cancer.html**
- **Profiles in Science:** Offering the archival collections of prominent twentieth-century biomedical scientists to the public through modern digital technology: **http://www.profiles.nlm.nih.gov/**
- **Chemical Information:** Provides links to various chemical databases and references: **http://sis.nlm.nih.gov/Chem/ChemMain.html**
- **Clinical Alerts:** Reports the release of findings from the NIH-funded clinical trials where such release could significantly affect morbidity and mortality: **http://www.nlm.nih.gov/databases/alerts/clinical_alerts.html**
- **Space Life Sciences:** Provides links and information to space-based research (including NASA): **http://www.nlm.nih.gov/databases/databases_space.html**
- **MEDLINE:** Bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the healthcare system, and the pre-clinical sciences: **http://www.nlm.nih.gov/databases/databases_medline.html**

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[13] Remember, for the general public, the National Library of Medicine recommends the databases referenced in MEDLINE*plus* (**http://medlineplus.gov/** or **http://www.nlm.nih.gov/medlineplus/databases.html**).

[14] See **http://www.nlm.nih.gov/databases/databases.html**.

- **Toxicology and Environmental Health Information (TOXNET):** Databases covering toxicology and environmental health: **http://sis.nlm.nih.gov/Tox/ToxMain.html**
- **Visible Human Interface:** Anatomically detailed, three-dimensional representations of normal male and female human bodies: **http://www.nlm.nih.gov/research/visible/visible_human.html**

The NLM Gateway[15]

The NLM (National Library of Medicine) Gateway is a Web-based system that lets users search simultaneously in multiple retrieval systems at the U.S. National Library of Medicine (NLM). It allows users of NLM services to initiate searches from one Web interface, providing one-stop searching for many of NLM's information resources or databases.[16] To use the NLM Gateway, simply go to the search site at **http://gateway.nlm.nih.gov/gw/Cmd**. Type "metformin" (or synonyms) into the search box and click "Search." The results will be presented in a tabular form, indicating the number of references in each database category.

Results Summary

Category	Items Found
Journal Articles	2373
Books / Periodicals / Audio Visual	8
Consumer Health	910
Meeting Abstracts	10
Other Collections	0
Total	3301

HSTAT[17]

HSTAT is a free, Web-based resource that provides access to full-text documents used in healthcare decision-making.[18] These documents include clinical practice guidelines, quick-reference guides for clinicians, consumer health brochures, evidence reports and technology assessments from the Agency for Healthcare Research and Quality (AHRQ), as well as AHRQ's Put Prevention Into Practice.[19] Simply search by "metformin" (or synonyms) at the following Web site: **http://text.nlm.nih.gov**.

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[15] Adapted from NLM: **http://gateway.nlm.nih.gov/gw/Cmd?Overview.x**.

[16] The NLM Gateway is currently being developed by the Lister Hill National Center for Biomedical Communications (LHNCBC) at the National Library of Medicine (NLM) of the National Institutes of Health (NIH).

[17] Adapted from HSTAT: **http://www.nlm.nih.gov/pubs/factsheets/hstat.html**.

[18] The HSTAT URL is **http://hstat.nlm.nih.gov/**.

[19] Other important documents in HSTAT include: the National Institutes of Health (NIH) Consensus Conference Reports and Technology Assessment Reports; the HIV/AIDS Treatment Information Service (ATIS) resource documents; the Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Treatment (SAMHSA/CSAT) Treatment Improvement Protocols (TIP) and Center for Substance Abuse Prevention (SAMHSA/CSAP) Prevention Enhancement Protocols System (PEPS); the Public Health Service (PHS) Preventive Services Task Force's *Guide to Clinical Preventive Services*; the independent, nonfederal Task Force on Community Services' *Guide to Community Preventive Services*; and the Health Technology Advisory Committee (HTAC) of the Minnesota Health Care Commission (MHCC) health technology evaluations.

Coffee Break: Tutorials for Biologists[20]

Coffee Break is a general healthcare site that takes a scientific view of the news and covers recent breakthroughs in biology that may one day assist physicians in developing treatments. Here you will find a collection of short reports on recent biological discoveries. Each report incorporates interactive tutorials that demonstrate how bioinformatics tools are used as a part of the research process. Currently, all Coffee Breaks are written by NCBI staff.[21] Each report is about 400 words and is usually based on a discovery reported in one or more articles from recently published, peer-reviewed literature.[22] This site has new articles every few weeks, so it can be considered an online magazine of sorts. It is intended for general background information. You can access the Coffee Break Web site at the following hyperlink: **http://www.ncbi.nlm.nih.gov/Coffeebreak/**.

Other Commercial Databases

In addition to resources maintained by official agencies, other databases exist that are commercial ventures addressing medical professionals. Here are some examples that may interest you:

- **CliniWeb International:** Index and table of contents to selected clinical information on the Internet; see **http://www.ohsu.edu/cliniweb/**.
- **Medical World Search:** Searches full text from thousands of selected medical sites on the Internet; see **http://www.mwsearch.com/**.

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[20] Adapted from **http://www.ncbi.nlm.nih.gov/Coffeebreak/Archive/FAQ.html**.

[21] The figure that accompanies each article is frequently supplied by an expert external to NCBI, in which case the source of the figure is cited. The result is an interactive tutorial that tells a biological story.

[22] After a brief introduction that sets the work described into a broader context, the report focuses on how a molecular understanding can provide explanations of observed biology and lead to therapies for diseases. Each vignette is accompanied by a figure and hypertext links that lead to a series of pages that interactively show how NCBI tools and resources are used in the research process.

APPENDIX B. PATIENT RESOURCES

Overview

Official agencies, as well as federally funded institutions supported by national grants, frequently publish a variety of guidelines written with the patient in mind. These are typically called "Fact Sheets" or "Guidelines." They can take the form of a brochure, information kit, pamphlet, or flyer. Often they are only a few pages in length. Since new guidelines on metformin can appear at any moment and be published by a number of sources, the best approach to finding guidelines is to systematically scan the Internet-based services that post them.

Patient Guideline Sources

The remainder of this chapter directs you to sources which either publish or can help you find additional guidelines on topics related to metformin. Due to space limitations, these sources are listed in a concise manner. Do not hesitate to consult the following sources by either using the Internet hyperlink provided, or, in cases where the contact information is provided, contacting the publisher or author directly.

The National Institutes of Health

The NIH gateway to patients is located at **http://health.nih.gov/**. From this site, you can search across various sources and institutes, a number of which are summarized below.

Topic Pages: MEDLINEplus

The National Library of Medicine has created a vast and patient-oriented healthcare information portal called MEDLINEplus. Within this Internet-based system are "health topic pages" which list links to available materials relevant to metformin. To access this system, log on to **http://www.nlm.nih.gov/medlineplus/healthtopics.html**. From there you can either search using the alphabetical index or browse by broad topic areas. Recently, MEDLINEplus listed the following when searched for "metformin":

- Other guides

  Aneurysms
  http://www.nlm.nih.gov/medlineplus/aneurysms.html

  Diabetes
  http://www.nlm.nih.gov/medlineplus/diabetes.html

  Juvenile Diabetes
  http://www.nlm.nih.gov/medlineplus/juvenilediabetes.html

  Metabolic Syndrome X
  http://www.nlm.nih.gov/medlineplus/metabolicsyndromex.html

  Ovarian Cysts
  http://www.nlm.nih.gov/medlineplus/ovariancysts.html

  Pregnancy Loss
  http://www.nlm.nih.gov/medlineplus/pregnancyloss.html

  Vasculitis
  http://www.nlm.nih.gov/medlineplus/vasculitis.html

You may also choose to use the search utility provided by MEDLINEplus at the following Web address: **http://www.nlm.nih.gov/medlineplus/**. Simply type a keyword into the search box and click "Search." This utility is similar to the NIH search utility, with the exception that it only includes materials that are linked within the MEDLINEplus system (mostly patient-oriented information). It also has the disadvantage of generating unstructured results. We recommend, therefore, that you use this method only if you have a very targeted search.

The Combined Health Information Database (CHID)

CHID Online is a reference tool that maintains a database directory of thousands of journal articles and patient education guidelines on metformin. CHID offers summaries that describe the guidelines available, including contact information and pricing. CHID's general Web site is **http://chid.nih.gov/**. To search this database, go to **http://chid.nih.gov/detail/detail.html**. In particular, you can use the advanced search options to look up pamphlets, reports, brochures, and information kits. The following was recently posted in this archive:

- **Diabetes Pills**

  Source: Little Rock, AR: Arkansas Department of Health. 199x. [1 p.].

  Contact: Available from Arkansas Department of Health Diabetes Control Program. 4815 West Markham Street, Slot Number 3, Little Rock, AR 72205-3867. (501) 661-2627. Fax (501) 661-2009. PRICE: Single copy free.

  Summary: This master copy of a diabetes education sheet, which was developed by the Arkansas Diabetes Control Program in cooperation with the Education Subcommittee of the Diabetes Coalition, uses a question and answer format to provide information on diabetes medications. People who have diabetes must understand how their medicine works and know when and how to take their medication. Types of diabetes oral medications include sulfonylureas, troglitazone, acarbose, **metformin,** and repaglinide. This education sheet explains how these medications work to improve blood glucose

levels. In addition, the sheet presents facts people should know about diabetes pills, identifies causes of low blood glucose, and explains how to deal with a low blood glucose reaction.

- **New Treatments for Diabetes**

  Source: American Family Physician. 59(10): 2849-2850. May 15, 1999.

  Contact: Available from American Academy of Family Physicians. 11400 Tomahawk Creek Parkway, Leawood, KS 66211-2672. (800) 274-2237. Website: www.aafp.org.

  Summary: This patient information sheet uses a question and answer format to provide information on new treatments for type 2 diabetes. This form of diabetes occurs when the body cannot make enough insulin or cannot use the insulin it makes in the right way. Initial treatment involves eating a healthy diet and exercising to keep blood sugar levels as close to normal as possible. If diet and exercise alone do not keep blood sugar levels normal, oral medications or insulin may be needed. Oral medications may be combined to help keep blood sugar as normal as possible. The five kinds of diabetes medication available in pill form are sulfonylureas, **metformin,** troglitazone, alpha-glucosidase inhibitors, and repaglinide. The information sheet describes each medication and highlights its side effects.

The NIH Search Utility

The NIH search utility allows you to search for documents on over 100 selected Web sites that comprise the NIH-WEB-SPACE. Each of these servers is "crawled" and indexed on an ongoing basis. Your search will produce a list of various documents, all of which will relate in some way to metformin. The drawbacks of this approach are that the information is not organized by theme and that the references are often a mix of information for professionals and patients. Nevertheless, a large number of the listed Web sites provide useful background information. We can only recommend this route, therefore, for relatively rare or specific disorders, or when using highly targeted searches. To use the NIH search utility, visit the following Web page: **http://search.nih.gov/index.html**.

Additional Web Sources

A number of Web sites are available to the public that often link to government sites. These can also point you in the direction of essential information. The following is a representative sample:

- AOL: **http://search.aol.com/cat.adp?id=168&layer=&from=subcats**
- Family Village: **http://www.familyvillage.wisc.edu/specific.htm**
- Google: **http://directory.google.com/Top/Health/Conditions_and_Diseases/**
- Med Help International: **http://www.medhelp.org/HealthTopics/A.html**
- Open Directory Project: **http://dmoz.org/Health/Conditions_and_Diseases/**
- Yahoo.com: **http://dir.yahoo.com/Health/Diseases_and_Conditions/**
- WebMD®Health: **http://my.webmd.com/health_topics**

Finding Associations

There are several Internet directories that provide lists of medical associations with information on or resources relating to metformin. By consulting all of associations listed in this chapter, you will have nearly exhausted all sources for patient associations concerned with metformin.

The National Health Information Center (NHIC)

The National Health Information Center (NHIC) offers a free referral service to help people find organizations that provide information about metformin. For more information, see the NHIC's Web site at **http://www.health.gov/NHIC/** or contact an information specialist by calling 1-800-336-4797.

Directory of Health Organizations

The Directory of Health Organizations, provided by the National Library of Medicine Specialized Information Services, is a comprehensive source of information on associations. The Directory of Health Organizations database can be accessed via the Internet at **http://www.sis.nlm.nih.gov/Dir/DirMain.html**. It is composed of two parts: DIRLINE and Health Hotlines.

The DIRLINE database comprises some 10,000 records of organizations, research centers, and government institutes and associations that primarily focus on health and biomedicine. To access DIRLINE directly, go to the following Web site: **http://dirline.nlm.nih.gov/**. Simply type in "metformin" (or a synonym), and you will receive information on all relevant organizations listed in the database.

Health Hotlines directs you to toll-free numbers to over 300 organizations. You can access this database directly at **http://www.sis.nlm.nih.gov/hotlines/**. On this page, you are given the option to search by keyword or by browsing the subject list. When you have received your search results, click on the name of the organization for its description and contact information.

The Combined Health Information Database

Another comprehensive source of information on healthcare associations is the Combined Health Information Database. Using the "Detailed Search" option, you will need to limit your search to "Organizations" and "metformin". Type the following hyperlink into your Web browser: **http://chid.nih.gov/detail/detail.html**. To find associations, use the drop boxes at the bottom of the search page where "You may refine your search by." For publication date, select "All Years." Then, select your preferred language and the format option "Organization Resource Sheet." Type "metformin" (or synonyms) into the "For these words:" box. You should check back periodically with this database since it is updated every three months.

The National Organization for Rare Disorders, Inc.

The National Organization for Rare Disorders, Inc. has prepared a Web site that provides, at no charge, lists of associations organized by health topic. You can access this database at the following Web site: **http://www.rarediseases.org/search/orgsearch.html**. Type "metformin" (or a synonym) into the search box, and click "Submit Query."

APPENDIX C. FINDING MEDICAL LIBRARIES

Overview

In this Appendix, we show you how to quickly find a medical library in your area.

Preparation

Your local public library and medical libraries have interlibrary loan programs with the National Library of Medicine (NLM), one of the largest medical collections in the world. According to the NLM, most of the literature in the general and historical collections of the National Library of Medicine is available on interlibrary loan to any library. If you would like to access NLM medical literature, then visit a library in your area that can request the publications for you.[23]

Finding a Local Medical Library

The quickest method to locate medical libraries is to use the Internet-based directory published by the National Network of Libraries of Medicine (NN/LM). This network includes 4626 members and affiliates that provide many services to librarians, health professionals, and the public. To find a library in your area, simply visit **http://nnlm.gov/members/adv.html** or call 1-800-338-7657.

Medical Libraries in the U.S. and Canada

In addition to the NN/LM, the National Library of Medicine (NLM) lists a number of libraries with reference facilities that are open to the public. The following is the NLM's list and includes hyperlinks to each library's Web site. These Web pages can provide information on hours of operation and other restrictions. The list below is a small sample of

[23] Adapted from the NLM: **http://www.nlm.nih.gov/psd/cas/interlibrary.html**.

libraries recommended by the National Library of Medicine (sorted alphabetically by name of the U.S. state or Canadian province where the library is located)[24]:

- **Alabama:** Health InfoNet of Jefferson County (Jefferson County Library Cooperative, Lister Hill Library of the Health Sciences), **http://www.uab.edu/infonet/**
- **Alabama:** Richard M. Scrushy Library (American Sports Medicine Institute)
- **Arizona:** Samaritan Regional Medical Center: The Learning Center (Samaritan Health System, Phoenix, Arizona), **http://www.samaritan.edu/library/bannerlibs.htm**
- **California:** Kris Kelly Health Information Center (St. Joseph Health System, Humboldt), **http://www.humboldt1.com/~kkhic/index.html**
- **California:** Community Health Library of Los Gatos, **http://www.healthlib.org/orgresources.html**
- **California:** Consumer Health Program and Services (CHIPS) (County of Los Angeles Public Library, Los Angeles County Harbor-UCLA Medical Center Library) - Carson, CA, **http://www.colapublib.org/services/chips.html**
- **California:** Gateway Health Library (Sutter Gould Medical Foundation)
- **California:** Health Library (Stanford University Medical Center), **http://www-med.stanford.edu/healthlibrary/**
- **California:** Patient Education Resource Center - Health Information and Resources (University of California, San Francisco), **http://sfghdean.ucsf.edu/barnett/PERC/default.asp**
- **California:** Redwood Health Library (Petaluma Health Care District), **http://www.phcd.org/rdwdlib.html**
- **California:** Los Gatos PlaneTree Health Library, **http://planetreesanjose.org/**
- **California:** Sutter Resource Library (Sutter Hospitals Foundation, Sacramento), **http://suttermedicalcenter.org/library/**
- **California:** Health Sciences Libraries (University of California, Davis), **http://www.lib.ucdavis.edu/healthsci/**
- **California:** ValleyCare Health Library & Ryan Comer Cancer Resource Center (ValleyCare Health System, Pleasanton), **http://gaelnet.stmarys-ca.edu/other.libs/gbal/east/vchl.html**
- **California:** Washington Community Health Resource Library (Fremont), **http://www.healthlibrary.org/**
- **Colorado:** William V. Gervasini Memorial Library (Exempla Healthcare), **http://www.saintjosephdenver.org/yourhealth/libraries/**
- **Connecticut:** Hartford Hospital Health Science Libraries (Hartford Hospital), **http://www.harthosp.org/library/**
- **Connecticut:** Healthnet: Connecticut Consumer Health Information Center (University of Connecticut Health Center, Lyman Maynard Stowe Library), **http://library.uchc.edu/departm/hnet/**

[24] Abstracted from **http://www.nlm.nih.gov/medlineplus/libraries.html**.

- **Connecticut:** Waterbury Hospital Health Center Library (Waterbury Hospital, Waterbury), **http://www.waterburyhospital.com/library/consumer.shtml**
- **Delaware:** Consumer Health Library (Christiana Care Health System, Eugene du Pont Preventive Medicine & Rehabilitation Institute, Wilmington), **http://www.christianacare.org/health_guide/health_guide_pmri_health_info.cfm**
- **Delaware:** Lewis B. Flinn Library (Delaware Academy of Medicine, Wilmington), **http://www.delamed.org/chls.html**
- **Georgia:** Family Resource Library (Medical College of Georgia, Augusta), **http://cmc.mcg.edu/kids_families/fam_resources/fam_res_lib/frl.htm**
- **Georgia:** Health Resource Center (Medical Center of Central Georgia, Macon), **http://www.mccg.org/hrc/hrchome.asp**
- **Hawaii:** Hawaii Medical Library: Consumer Health Information Service (Hawaii Medical Library, Honolulu), **http://hml.org/CHIS/**
- **Idaho:** DeArmond Consumer Health Library (Kootenai Medical Center, Coeur d'Alene), **http://www.nicon.org/DeArmond/index.htm**
- **Illinois:** Health Learning Center of Northwestern Memorial Hospital (Chicago), **http://www.nmh.org/health_info/hlc.html**
- **Illinois:** Medical Library (OSF Saint Francis Medical Center, Peoria), **http://www.osfsaintfrancis.org/general/library/**
- **Kentucky:** Medical Library - Services for Patients, Families, Students & the Public (Central Baptist Hospital, Lexington), **http://www.centralbap.com/education/community/library.cfm**
- **Kentucky:** University of Kentucky - Health Information Library (Chandler Medical Center, Lexington), **http://www.mc.uky.edu/PatientEd/**
- **Louisiana:** Alton Ochsner Medical Foundation Library (Alton Ochsner Medical Foundation, New Orleans), **http://www.ochsner.org/library/**
- **Louisiana:** Louisiana State University Health Sciences Center Medical Library-Shreveport, **http://lib-sh.lsuhsc.edu/**
- **Maine:** Franklin Memorial Hospital Medical Library (Franklin Memorial Hospital, Farmington), **http://www.fchn.org/fmh/lib.htm**
- **Maine:** Gerrish-True Health Sciences Library (Central Maine Medical Center, Lewiston), **http://www.cmmc.org/library/library.html**
- **Maine:** Hadley Parrot Health Science Library (Eastern Maine Healthcare, Bangor), **http://www.emh.org/hll/hpl/guide.htm**
- **Maine:** Maine Medical Center Library (Maine Medical Center, Portland), **http://www.mmc.org/library/**
- **Maine:** Parkview Hospital (Brunswick), **http://www.parkviewhospital.org/**
- **Maine:** Southern Maine Medical Center Health Sciences Library (Southern Maine Medical Center, Biddeford), **http://www.smmc.org/services/service.php3?choice=10**
- **Maine:** Stephens Memorial Hospital's Health Information Library (Western Maine Health, Norway), **http://www.wmhcc.org/Library/**

- **Manitoba, Canada:** Consumer & Patient Health Information Service (University of Manitoba Libraries), **http://www.umanitoba.ca/libraries/units/health/reference/chis.html**
- **Manitoba, Canada:** J.W. Crane Memorial Library (Deer Lodge Centre, Winnipeg), **http://www.deerlodge.mb.ca/crane_library/about.asp**
- **Maryland:** Health Information Center at the Wheaton Regional Library (Montgomery County, Dept. of Public Libraries, Wheaton Regional Library), **http://www.mont.lib.md.us/healthinfo/hic.asp**
- **Massachusetts:** Baystate Medical Center Library (Baystate Health System), **http://www.baystatehealth.com/1024/**
- **Massachusetts:** Boston University Medical Center Alumni Medical Library (Boston University Medical Center), **http://med-libwww.bu.edu/library/lib.html**
- **Massachusetts:** Lowell General Hospital Health Sciences Library (Lowell General Hospital, Lowell), **http://www.lowellgeneral.org/library/HomePageLinks/WWW.htm**
- **Massachusetts:** Paul E. Woodard Health Sciences Library (New England Baptist Hospital, Boston), **http://www.nebh.org/health_lib.asp**
- **Massachusetts:** St. Luke's Hospital Health Sciences Library (St. Luke's Hospital, Southcoast Health System, New Bedford), **http://www.southcoast.org/library/**
- **Massachusetts:** Treadwell Library Consumer Health Reference Center (Massachusetts General Hospital), **http://www.mgh.harvard.edu/library/chrcindex.html**
- **Massachusetts:** UMass HealthNet (University of Massachusetts Medical School, Worchester), **http://healthnet.umassmed.edu/**
- **Michigan:** Botsford General Hospital Library - Consumer Health (Botsford General Hospital, Library & Internet Services), **http://www.botsfordlibrary.org/consumer.htm**
- **Michigan:** Helen DeRoy Medical Library (Providence Hospital and Medical Centers), **http://www.providence-hospital.org/library/**
- **Michigan:** Marquette General Hospital - Consumer Health Library (Marquette General Hospital, Health Information Center), **http://www.mgh.org/center.html**
- **Michigan:** Patient Education Resouce Center - University of Michigan Cancer Center (University of Michigan Comprehensive Cancer Center, Ann Arbor), **http://www.cancer.med.umich.edu/learn/leares.htm**
- **Michigan:** Sladen Library & Center for Health Information Resources - Consumer Health Information (Detroit), **http://www.henryford.com/body.cfm?id=39330**
- **Montana:** Center for Health Information (St. Patrick Hospital and Health Sciences Center, Missoula)
- **National:** Consumer Health Library Directory (Medical Library Association, Consumer and Patient Health Information Section), **http://caphis.mlanet.org/directory/index.html**
- **National:** National Network of Libraries of Medicine (National Library of Medicine) - provides library services for health professionals in the United States who do not have access to a medical library, **http://nnlm.gov/**
- **National:** NN/LM List of Libraries Serving the Public (National Network of Libraries of Medicine), **http://nnlm.gov/members/**

- **Nevada:** Health Science Library, West Charleston Library (Las Vegas-Clark County Library District, Las Vegas), **http://www.lvccld.org/special_collections/medical/index.htm**
- **New Hampshire:** Dartmouth Biomedical Libraries (Dartmouth College Library, Hanover), **http://www.dartmouth.edu/~biomed/resources.htmld/conshealth.htmld/**
- **New Jersey:** Consumer Health Library (Rahway Hospital, Rahway), **http://www.rahwayhospital.com/library.htm**
- **New Jersey:** Dr. Walter Phillips Health Sciences Library (Englewood Hospital and Medical Center, Englewood), **http://www.englewoodhospital.com/links/index.htm**
- **New Jersey:** Meland Foundation (Englewood Hospital and Medical Center, Englewood), **http://www.geocities.com/ResearchTriangle/9360/**
- **New York:** Choices in Health Information (New York Public Library) - NLM Consumer Pilot Project participant, **http://www.nypl.org/branch/health/links.html**
- **New York:** Health Information Center (Upstate Medical University, State University of New York, Syracuse), **http://www.upstate.edu/library/hic/**
- **New York:** Health Sciences Library (Long Island Jewish Medical Center, New Hyde Park), **http://www.lij.edu/library/library.html**
- **New York:** ViaHealth Medical Library (Rochester General Hospital), **http://www.nyam.org/library/**
- **Ohio:** Consumer Health Library (Akron General Medical Center, Medical & Consumer Health Library), **http://www.akrongeneral.org/hwlibrary.htm**
- **Oklahoma:** The Health Information Center at Saint Francis Hospital (Saint Francis Health System, Tulsa), **http://www.sfh-tulsa.com/services/healthinfo.asp**
- **Oregon:** Planetree Health Resource Center (Mid-Columbia Medical Center, The Dalles), **http://www.mcmc.net/phrc/**
- **Pennsylvania:** Community Health Information Library (Milton S. Hershey Medical Center, Hershey), **http://www.hmc.psu.edu/commhealth/**
- **Pennsylvania:** Community Health Resource Library (Geisinger Medical Center, Danville), **http://www.geisinger.edu/education/commlib.shtml**
- **Pennsylvania:** HealthInfo Library (Moses Taylor Hospital, Scranton), **http://www.mth.org/healthwellness.html**
- **Pennsylvania:** Hopwood Library (University of Pittsburgh, Health Sciences Library System, Pittsburgh), **http://www.hsls.pitt.edu/guides/chi/hopwood/index_html**
- **Pennsylvania:** Koop Community Health Information Center (College of Physicians of Philadelphia), **http://www.collphyphil.org/kooppg1.shtml**
- **Pennsylvania:** Learning Resources Center - Medical Library (Susquehanna Health System, Williamsport), **http://www.shscares.org/services/lrc/index.asp**
- **Pennsylvania:** Medical Library (UPMC Health System, Pittsburgh), **http://www.upmc.edu/passavant/library.htm**
- **Quebec, Canada:** Medical Library (Montreal General Hospital), **http://www.mghlib.mcgill.ca/**

- **South Dakota:** Rapid City Regional Hospital Medical Library (Rapid City Regional Hospital), **http://www.rcrh.org/Services/Library/Default.asp**
- **Texas:** Houston HealthWays (Houston Academy of Medicine-Texas Medical Center Library), **http://hhw.library.tmc.edu/**
- **Washington:** Community Health Library (Kittitas Valley Community Hospital), **http://www.kvch.com/**
- **Washington:** Southwest Washington Medical Center Library (Southwest Washington Medical Center, Vancouver), **http://www.swmedicalcenter.com/body.cfm?id=72**

ONLINE GLOSSARIES

The Internet provides access to a number of free-to-use medical dictionaries. The National Library of Medicine has compiled the following list of online dictionaries:

- ADAM Medical Encyclopedia (A.D.A.M., Inc.), comprehensive medical reference: **http://www.nlm.nih.gov/medlineplus/encyclopedia.html**
- MedicineNet.com Medical Dictionary (MedicineNet, Inc.): **http://www.medterms.com/Script/Main/hp.asp**
- Merriam-Webster Medical Dictionary (Inteli-Health, Inc.): **http://www.intelihealth.com/IH/**
- Multilingual Glossary of Technical and Popular Medical Terms in Eight European Languages (European Commission) - Danish, Dutch, English, French, German, Italian, Portuguese, and Spanish: **http://allserv.rug.ac.be/~rvdstich/eugloss/welcome.html**
- On-line Medical Dictionary (CancerWEB): **http://cancerweb.ncl.ac.uk/omd/**
- Rare Diseases Terms (Office of Rare Diseases): **http://ord.aspensys.com/asp/diseases/diseases.asp**
- Technology Glossary (National Library of Medicine) - Health Care Technology: **http://www.nlm.nih.gov/nichsr/ta101/ta10108.htm**

Beyond these, MEDLINEplus contains a very patient-friendly encyclopedia covering every aspect of medicine (licensed from A.D.A.M., Inc.). The ADAM Medical Encyclopedia can be accessed at **http://www.nlm.nih.gov/medlineplus/encyclopedia.html**. ADAM is also available on commercial Web sites such as drkoop.com (**http://www.drkoop.com/**) and Web MD (**http://my.webmd.com/adam/asset/adam_disease_articles/a_to_z/a**).

Online Dictionary Directories

The following are additional online directories compiled by the National Library of Medicine, including a number of specialized medical dictionaries:

- Medical Dictionaries: Medical & Biological (World Health Organization): **http://www.who.int/hlt/virtuallibrary/English/diction.htm#Medical**
- MEL-Michigan Electronic Library List of Online Health and Medical Dictionaries (Michigan Electronic Library): **http://mel.lib.mi.us/health/health-dictionaries.html**
- Patient Education: Glossaries (DMOZ Open Directory Project): **http://dmoz.org/Health/Education/Patient_Education/Glossaries/**
- Web of Online Dictionaries (Bucknell University): **http://www.yourdictionary.com/diction5.html#medicine**

METFORMIN DICTIONARY

The definitions below are derived from official public sources, including the National Institutes of Health [NIH] and the European Union [EU].

1-Methyl-4-phenylpyridinium: 1-Methyl-4-phenylpyridinium (MPP+). An active neurotoxic metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The compound reduces dopamine levels, inhibits the biosynthesis of catecholamines, depletes cardiac norepinephrine and inactivates tyrosine hydroxylase. These and other toxic effects lead to cessation of oxidative phosphorylation, ATP depletion, and cell death. The compound, which is related to paraquat, has also been used as an herbicide. [NIH]

Abdomen: That portion of the body that lies between the thorax and the pelvis. [NIH]

Abdominal: Having to do with the abdomen, which is the part of the body between the chest and the hips that contains the pancreas, stomach, intestines, liver, gallbladder, and other organs. [NIH]

Abdominal fat: Fat (adipose tissue) that is centrally distributed between the thorax and pelvis and that induces greater health risk. [NIH]

Abdominal Pain: Sensation of discomfort, distress, or agony in the abdominal region. [NIH]

Aberrant: Wandering or deviating from the usual or normal course. [EU]

Acceptor: A substance which, while normally not oxidized by oxygen or reduced by hydrogen, can be oxidized or reduced in presence of a substance which is itself undergoing oxidation or reduction. [NIH]

Acetaldehyde: A colorless, flammable liquid used in the manufacture of acetic acid, perfumes, and flavors. It is also an intermediate in the metabolism of alcohol. It has a general narcotic action and also causes irritation of mucous membranes. Large doses may cause death from respiratory paralysis. [NIH]

Acetohexamide: A sulfonylurea hypoglycemic agent that is metabolized in the liver to 1-hydrohexamide. [NIH]

Acetone: A colorless liquid used as a solvent and an antiseptic. It is one of the ketone bodies produced during ketoacidosis. [NIH]

Acetylcholine: A neurotransmitter. Acetylcholine in vertebrates is the major transmitter at neuromuscular junctions, autonomic ganglia, parasympathetic effector junctions, a subset of sympathetic effector junctions, and at many sites in the central nervous system. It is generally not used as an administered drug because it is broken down very rapidly by cholinesterases, but it is useful in some ophthalmological applications. [NIH]

Acidemia: Increased acidity of blood. [NIH]

Acidosis: A pathologic condition resulting from accumulation of acid or depletion of the alkaline reserve (bicarbonate content) in the blood and body tissues, and characterized by an increase in hydrogen ion concentration. [EU]

Acne: A disorder of the skin marked by inflammation of oil glands and hair glands. [NIH]

Actin: Essential component of the cell skeleton. [NIH]

Adenine: A purine base and a fundamental unit of adenine nucleotides. [NIH]

Adenocarcinoma: A malignant epithelial tumor with a glandular organization. [NIH]

Adenosine: A nucleoside that is composed of adenine and d-ribose. Adenosine or adenosine

derivatives play many important biological roles in addition to being components of DNA and RNA. Adenosine itself is a neurotransmitter. [NIH]

Adenosine Triphosphate: Adenosine 5'-(tetrahydrogen triphosphate). An adenine nucleotide containing three phosphate groups esterified to the sugar moiety. In addition to its crucial roles in metabolism adenosine triphosphate is a neurotransmitter. [NIH]

Adenovirus: A group of viruses that cause respiratory tract and eye infections. Adenoviruses used in gene therapy are altered to carry a specific tumor-fighting gene. [NIH]

Adipocytes: Fat-storing cells found mostly in the abdominal cavity and subcutaneous tissue. Fat is usually stored in the form of tryglycerides. [NIH]

Adipose Tissue: Connective tissue composed of fat cells lodged in the meshes of areolar tissue. [NIH]

Adjustment: The dynamic process wherein the thoughts, feelings, behavior, and biophysiological mechanisms of the individual continually change to adjust to the environment. [NIH]

Adjuvant: A substance which aids another, such as an auxiliary remedy; in immunology, nonspecific stimulator (e.g., BCG vaccine) of the immune response. [EU]

Adjuvant Therapy: Treatment given after the primary treatment to increase the chances of a cure. Adjuvant therapy may include chemotherapy, radiation therapy, or hormone therapy. [NIH]

Adolescence: The period of life beginning with the appearance of secondary sex characteristics and terminating with the cessation of somatic growth. The years usually referred to as adolescence lie between 13 and 18 years of age. [NIH]

Adrenal Cortex: The outer layer of the adrenal gland. It secretes mineralocorticoids, androgens, and glucocorticoids. [NIH]

Adrenergic: Activated by, characteristic of, or secreting epinephrine or substances with similar activity; the term is applied to those nerve fibres that liberate norepinephrine at a synapse when a nerve impulse passes, i.e., the sympathetic fibres. [EU]

Adult-Onset Diabetes: Former term for noninsulin-dependent or type II diabetes. [NIH]

Adverse Effect: An unwanted side effect of treatment. [NIH]

Aerobic: In biochemistry, reactions that need oxygen to happen or happen when oxygen is present. [NIH]

Aerobic Exercise: A type of physical activity that includes walking, jogging, running, and dancing. Aerobic training improves the efficiency of the aerobic energy-producing systems that can improve cardiorespiratory endurance. [NIH]

Afferent: Concerned with the transmission of neural impulse toward the central part of the nervous system. [NIH]

Affinity: 1. Inherent likeness or relationship. 2. A special attraction for a specific element, organ, or structure. 3. Chemical affinity; the force that binds atoms in molecules; the tendency of substances to combine by chemical reaction. 4. The strength of noncovalent chemical binding between two substances as measured by the dissociation constant of the complex. 5. In immunology, a thermodynamic expression of the strength of interaction between a single antigen-binding site and a single antigenic determinant (and thus of the stereochemical compatibility between them), most accurately applied to interactions among simple, uniform antigenic determinants such as haptens. Expressed as the association constant (K litres mole -1), which, owing to the heterogeneity of affinities in a population of antibody molecules of a given specificity, actually represents an average value (mean intrinsic association constant). 6. The reciprocal of the dissociation constant. [EU]

Age Groups: Persons classified by age from birth (infant, newborn) to octogenarians and older (aged, 80 and over). [NIH]

Age of Onset: The age or period of life at which a disease or the initial symptoms or manifestations of a disease appear in an individual. [NIH]

Aged, 80 and Over: A person 80 years of age and older. [NIH]

Agonist: In anatomy, a prime mover. In pharmacology, a drug that has affinity for and stimulates physiologic activity at cell receptors normally stimulated by naturally occurring substances. [EU]

Albumin: 1. Any protein that is soluble in water and moderately concentrated salt solutions and is coagulable by heat. 2. Serum albumin; the major plasma protein (approximately 60 per cent of the total), which is responsible for much of the plasma colloidal osmotic pressure and serves as a transport protein carrying large organic anions, such as fatty acids, bilirubin, and many drugs, and also carrying certain hormones, such as cortisol and thyroxine, when their specific binding globulins are saturated. Albumin is synthesized in the liver. Low serum levels occur in protein malnutrition, active inflammation and serious hepatic and renal disease. [EU]

Algorithms: A procedure consisting of a sequence of algebraic formulas and/or logical steps to calculate or determine a given task. [NIH]

Alkaline: Having the reactions of an alkali. [EU]

Alternative medicine: Practices not generally recognized by the medical community as standard or conventional medical approaches and used instead of standard treatments. Alternative medicine includes the taking of dietary supplements, megadose vitamins, and herbal preparations; the drinking of special teas; and practices such as massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

Ameliorating: A changeable condition which prevents the consequence of a failure or accident from becoming as bad as it otherwise would. [NIH]

Amenorrhea: Absence of menstruation. [NIH]

Amino Acid Sequence: The order of amino acids as they occur in a polypeptide chain. This is referred to as the primary structure of proteins. It is of fundamental importance in determining protein conformation. [NIH]

Amino Acids: Organic compounds that generally contain an amino (-NH2) and a carboxyl (-COOH) group. Twenty alpha-amino acids are the subunits which are polymerized to form proteins. [NIH]

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Ammonia: A colorless alkaline gas. It is formed in the body during decomposition of organic materials during a large number of metabolically important reactions. [NIH]

Amoxapine: The N-demethylated derivative of the antipsychotic agent loxapine that works by blocking the reuptake of norepinephrine, serotonin, or both. It also blocks dopamine receptors. [NIH]

Anaemia: A reduction below normal in the number of erythrocytes per cu. mm., in the quantity of haemoglobin, or in the volume of packed red cells per 100 ml. of blood which occurs when the equilibrium between blood loss (through bleeding or destruction) and blood production is disturbed. [EU]

Anaesthesia: Loss of feeling or sensation. Although the term is used for loss of tactile

sensibility, or of any of the other senses, it is applied especially to loss of the sensation of pain, as it is induced to permit performance of surgery or other painful procedures. [EU]

Anal: Having to do with the anus, which is the posterior opening of the large bowel. [NIH]

Analog: In chemistry, a substance that is similar, but not identical, to another. [NIH]

Analogous: Resembling or similar in some respects, as in function or appearance, but not in origin or development;. [EU]

Anatomical: Pertaining to anatomy, or to the structure of the organism. [EU]

Androgenic: Producing masculine characteristics. [EU]

Androgens: A class of sex hormones associated with the development and maintenance of the secondary male sex characteristics, sperm induction, and sexual differentiation. In addition to increasing virility and libido, they also increase nitrogen and water retention and stimulate skeletal growth. [NIH]

Androstenedione: A steroid with androgenic properties that is produced in the testis, ovary, and adrenal cortex. It is a precursor to testosterone and other androgenic hormones. [NIH]

Anemia: A reduction in the number of circulating erythrocytes or in the quantity of hemoglobin. [NIH]

Anesthesia: A state characterized by loss of feeling or sensation. This depression of nerve function is usually the result of pharmacologic action and is induced to allow performance of surgery or other painful procedures. [NIH]

Angina: Chest pain that originates in the heart. [NIH]

Angiography: Radiography of blood vessels after injection of a contrast medium. [NIH]

Animal model: An animal with a disease either the same as or like a disease in humans. Animal models are used to study the development and progression of diseases and to test new treatments before they are given to humans. Animals with transplanted human cancers or other tissues are called xenograft models. [NIH]

Anionic: Pertaining to or containing an anion. [EU]

Anions: Negatively charged atoms, radicals or groups of atoms which travel to the anode or positive pole during electrolysis. [NIH]

Anorexia: Lack or loss of appetite for food. Appetite is psychologic, dependent on memory and associations. Anorexia can be brought about by unattractive food, surroundings, or company. [NIH]

Anovulation: Suspension or cessation of ovulation in animals and humans. [NIH]

Antagonism: Interference with, or inhibition of, the growth of a living organism by another living organism, due either to creation of unfavorable conditions (e. g. exhaustion of food supplies) or to production of a specific antibiotic substance (e. g. penicillin). [NIH]

Anthropometric measurements: Measurements of human body height, weight, and size of component parts, including skinfold measurement. Used to study and compare the relative proportions under normal and abnormal conditions. [NIH]

Antibacterial: A substance that destroys bacteria or suppresses their growth or reproduction. [EU]

Antibiotic: A drug used to treat infections caused by bacteria and other microorganisms. [NIH]

Antibodies: Immunoglobulin molecules having a specific amino acid sequence by virtue of which they interact only with the antigen that induced their synthesis in cells of the lymphoid series (especially plasma cells), or with an antigen closely related to it. [NIH]

Antibody: A type of protein made by certain white blood cells in response to a foreign substance (antigen). Each antibody can bind to only a specific antigen. The purpose of this binding is to help destroy the antigen. Antibodies can work in several ways, depending on the nature of the antigen. Some antibodies destroy antigens directly. Others make it easier for white blood cells to destroy the antigen. [NIH]

Anticoagulant: A drug that helps prevent blood clots from forming. Also called a blood thinner. [NIH]

Antidiabetic: An agent that prevents or alleviates diabetes. [EU]

Antidiabetic Agent: A substance that helps a person with diabetes control the level of glucose (sugar) in the blood so that the body works as it should. [NIH]

Antigen: Any substance which is capable, under appropriate conditions, of inducing a specific immune response and of reacting with the products of that response, that is, with specific antibody or specifically sensitized T-lymphocytes, or both. Antigens may be soluble substances, such as toxins and foreign proteins, or particulate, such as bacteria and tissue cells; however, only the portion of the protein or polysaccharide molecule known as the antigenic determinant (q.v.) combines with antibody or a specific receptor on a lymphocyte. Abbreviated Ag. [EU]

Antihypertensive: An agent that reduces high blood pressure. [EU]

Anti-infective: An agent that so acts. [EU]

Anti-inflammatory: Having to do with reducing inflammation. [NIH]

Antimetabolite: A chemical that is very similar to one required in a normal biochemical reaction in cells. Antimetabolites can stop or slow down the reaction. [NIH]

Antimicrobial: Killing microorganisms, or suppressing their multiplication or growth. [EU]

Antioxidant: A substance that prevents damage caused by free radicals. Free radicals are highly reactive chemicals that often contain oxygen. They are produced when molecules are split to give products that have unpaired electrons. This process is called oxidation. [NIH]

Antipsychotic: Effective in the treatment of psychosis. Antipsychotic drugs (called also neuroleptic drugs and major tranquilizers) are a chemically diverse (including phenothiazines, thioxanthenes, butyrophenones, dibenzoxazepines, dibenzodiazepines, and diphenylbutylpiperidines) but pharmacologically similar class of drugs used to treat schizophrenic, paranoid, schizoaffective, and other psychotic disorders; acute delirium and dementia, and manic episodes (during induction of lithium therapy); to control the movement disorders associated with Huntington's chorea, Gilles de la Tourette's syndrome, and ballismus; and to treat intractable hiccups and severe nausea and vomiting. Antipsychotic agents bind to dopamine, histamine, muscarinic cholinergic, a-adrenergic, and serotonin receptors. Blockade of dopaminergic transmission in various areas is thought to be responsible for their major effects : antipsychotic action by blockade in the mesolimbic and mesocortical areas; extrapyramidal side effects (dystonia, akathisia, parkinsonism, and tardive dyskinesia) by blockade in the basal ganglia; and antiemetic effects by blockade in the chemoreceptor trigger zone of the medulla. Sedation and autonomic side effects (orthostatic hypotension, blurred vision, dry mouth, nasal congestion and constipation) are caused by blockade of histamine, cholinergic, and adrenergic receptors. [EU]

Antiseptic: A substance that inhibits the growth and development of microorganisms without necessarily killing them. [EU]

Antiviral: Destroying viruses or suppressing their replication. [EU]

Anus: The opening of the rectum to the outside of the body. [NIH]

Apolipoproteins: The protein components of lipoproteins which remain after the lipids to

which the proteins are bound have been removed. They play an important role in lipid transport and metabolism. [NIH]

Apoptosis: One of the two mechanisms by which cell death occurs (the other being the pathological process of necrosis). Apoptosis is the mechanism responsible for the physiological deletion of cells and appears to be intrinsically programmed. It is characterized by distinctive morphologic changes in the nucleus and cytoplasm, chromatin cleavage at regularly spaced sites, and the endonucleolytic cleavage of genomic DNA (DNA fragmentation) at internucleosomal sites. This mode of cell death serves as a balance to mitosis in regulating the size of animal tissues and in mediating pathologic processes associated with tumor growth. [NIH]

Aqueous: Having to do with water. [NIH]

Arginine: An essential amino acid that is physiologically active in the L-form. [NIH]

Aromatic: Having a spicy odour. [EU]

Arterial: Pertaining to an artery or to the arteries. [EU]

Arteries: The vessels carrying blood away from the heart. [NIH]

Arterioles: The smallest divisions of the arteries located between the muscular arteries and the capillaries. [NIH]

Arteriosclerosis: Thickening and loss of elasticity of arterial walls. Atherosclerosis is the most common form of arteriosclerosis and involves lipid deposition and thickening of the intimal cell layers within arteries. Additional forms of arteriosclerosis involve calcification of the media of muscular arteries (Monkeberg medial calcific sclerosis) and thickening of the walls of small arteries or arterioles due to cell proliferation or hyaline deposition (arteriolosclerosis). [NIH]

Ascites: Accumulation or retention of free fluid within the peritoneal cavity. [NIH]

Ascorbic Acid: A six carbon compound related to glucose. It is found naturally in citrus fruits and many vegetables. Ascorbic acid is an essential nutrient in human diets, and necessary to maintain connective tissue and bone. Its biologically active form, vitamin C, functions as a reducing agent and coenzyme in several metabolic pathways. Vitamin C is considered an antioxidant. [NIH]

Assay: Determination of the amount of a particular constituent of a mixture, or of the biological or pharmacological potency of a drug. [EU]

Atrial: Pertaining to an atrium. [EU]

Atrial Fibrillation: Disorder of cardiac rhythm characterized by rapid, irregular atrial impulses and ineffective atrial contractions. [NIH]

Atrophy: Decrease in the size of a cell, tissue, organ, or multiple organs, associated with a variety of pathological conditions such as abnormal cellular changes, ischemia, malnutrition, or hormonal changes. [NIH]

Azotemia: An excess of urea or other nitrogenous compounds in the blood. [EU]

Bacteria: Unicellular prokaryotic microorganisms which generally possess rigid cell walls, multiply by cell division, and exhibit three principal forms: round or coccal, rodlike or bacillary, and spiral or spirochetal. [NIH]

Bactericidal: Substance lethal to bacteria; substance capable of killing bacteria. [NIH]

Bacterium: Microscopic organism which may have a spherical, rod-like, or spiral unicellular or non-cellular body. Bacteria usually reproduce through asexual processes. [NIH]

Baroreflex: A negative feedback system which buffers short-term changes in blood pressure. Increased pressure stretches blood vessels which activates pressoreceptors (baroreceptors) in

the vessel walls. The net response of the central nervous system is a reduction of central sympathetic outflow. This reduces blood pressure both by decreasing peripheral vascular resistance and by lowering cardiac output. Because the baroreceptors are tonically active, the baroreflex can compensate rapidly for both increases and decreases in blood pressure. [NIH]

Base: In chemistry, the nonacid part of a salt; a substance that combines with acids to form salts; a substance that dissociates to give hydroxide ions in aqueous solutions; a substance whose molecule or ion can combine with a proton (hydrogen ion); a substance capable of donating a pair of electrons (to an acid) for the formation of a coordinate covalent bond. [EU]

Basement Membrane: Ubiquitous supportive tissue adjacent to epithelium and around smooth and striated muscle cells. This tissue contains intrinsic macromolecular components such as collagen, laminin, and sulfated proteoglycans. As seen by light microscopy one of its subdivisions is the basal (basement) lamina. [NIH]

Benign: Not cancerous; does not invade nearby tissue or spread to other parts of the body. [NIH]

Benzene: Toxic, volatile, flammable liquid hydrocarbon biproduct of coal distillation. It is used as an industrial solvent in paints, varnishes, lacquer thinners, gasoline, etc. Benzene causes central nervous system damage acutely and bone marrow damage chronically and is carcinogenic. It was formerly used as parasiticide. [NIH]

Bezafibrate: Antilipemic agent that lowers cholesterol and triglycerides. It decreases low density lipoproteins and increases high density lipoproteins. [NIH]

Bilateral: Affecting both the right and left side of body. [NIH]

Bile: An emulsifying agent produced in the liver and secreted into the duodenum. Its composition includes bile acids and salts, cholesterol, and electrolytes. It aids digestion of fats in the duodenum. [NIH]

Bile Acids: Acids made by the liver that work with bile to break down fats. [NIH]

Bile Acids and Salts: Steroid acids and salts. The primary bile acids are derived from cholesterol in the liver and usually conjugated with glycine or taurine. The secondary bile acids are further modified by bacteria in the intestine. They play an important role in the digestion and absorption of fat. They have also been used pharmacologically, especially in the treatment of gallstones. [NIH]

Bile Pigments: Pigments that give a characteristic color to bile including: bilirubin, biliverdine, and bilicyanin. [NIH]

Bilirubin: A bile pigment that is a degradation product of heme. [NIH]

Binding agent: A substance that makes a loose mixture stick together. For example, binding agents can be used to make solid pills from loose powders. [NIH]

Bioavailability: The degree to which a drug or other substance becomes available to the target tissue after administration. [EU]

Bioavailable: The ability of a drug or other substance to be absorbed and used by the body. Orally bioavailable means that a drug or other substance that is taken by mouth can be absorbed and used by the body. [NIH]

Biochemical: Relating to biochemistry; characterized by, produced by, or involving chemical reactions in living organisms. [EU]

Biological therapy: Treatment to stimulate or restore the ability of the immune system to fight infection and disease. Also used to lessen side effects that may be caused by some cancer treatments. Also known as immunotherapy, biotherapy, or biological response modifier (BRM) therapy. [NIH]

Biopsy: Removal and pathologic examination of specimens in the form of small pieces of tissue from the living body. [NIH]

Biosynthesis: The building up of a chemical compound in the physiologic processes of a living organism. [EU]

Biotechnology: Body of knowledge related to the use of organisms, cells or cell-derived constituents for the purpose of developing products which are technically, scientifically and clinically useful. Alteration of biologic function at the molecular level (i.e., genetic engineering) is a central focus; laboratory methods used include transfection and cloning technologies, sequence and structure analysis algorithms, computer databases, and gene and protein structure function analysis and prediction. [NIH]

Biotransformation: The chemical alteration of an exogenous substance by or in a biological system. The alteration may inactivate the compound or it may result in the production of an active metabolite of an inactive parent compound. The alteration may be either non-synthetic (oxidation-reduction, hydrolysis) or synthetic (glucuronide formation, sulfate conjugation, acetylation, methylation). This also includes metabolic detoxication and clearance. [NIH]

Biphasic: Having two phases; having both a sporophytic and a gametophytic phase in the life cycle. [EU]

Bipolar Disorder: A major affective disorder marked by severe mood swings (manic or major depressive episodes) and a tendency to remission and recurrence. [NIH]

Bladder: The organ that stores urine. [NIH]

Bloating: Fullness or swelling in the abdomen that often occurs after meals. [NIH]

Blood Coagulation: The process of the interaction of blood coagulation factors that results in an insoluble fibrin clot. [NIH]

Blood Glucose: Glucose in blood. [NIH]

Blood pressure: The pressure of blood against the walls of a blood vessel or heart chamber. Unless there is reference to another location, such as the pulmonary artery or one of the heart chambers, it refers to the pressure in the systemic arteries, as measured, for example, in the forearm. [NIH]

Blood vessel: A tube in the body through which blood circulates. Blood vessels include a network of arteries, arterioles, capillaries, venules, and veins. [NIH]

Blood Volume: Volume of circulating blood. It is the sum of the plasma volume and erythrocyte volume. [NIH]

Blot: To transfer DNA, RNA, or proteins to an immobilizing matrix such as nitrocellulose. [NIH]

Blotting, Western: Identification of proteins or peptides that have been electrophoretically separated by blotting and transferred to strips of nitrocellulose paper. The blots are then detected by radiolabeled antibody probes. [NIH]

Body Composition: The relative amounts of various components in the body, such as percent body fat. [NIH]

Body Mass Index: One of the anthropometric measures of body mass; it has the highest correlation with skinfold thickness or body density. [NIH]

Body Weight Changes: A clinical manifestation consisting of alterations in an individual's weight from his or her norm. [NIH]

Bone Density: The amount of mineral per square centimeter of bone. This is the definition used in clinical practice. Actual bone density would be expressed in grams per milliliter. It is

most frequently measured by photon absorptiometry or x-ray computed tomography. [NIH]

Bone Marrow: The soft tissue filling the cavities of bones. Bone marrow exists in two types, yellow and red. Yellow marrow is found in the large cavities of large bones and consists mostly of fat cells and a few primitive blood cells. Red marrow is a hematopoietic tissue and is the site of production of erythrocytes and granular leukocytes. Bone marrow is made up of a framework of connective tissue containing branching fibers with the frame being filled with marrow cells. [NIH]

Bowel: The long tube-shaped organ in the abdomen that completes the process of digestion. There is both a small and a large bowel. Also called the intestine. [NIH]

Bowel Movement: Body wastes passed through the rectum and anus. [NIH]

Bradykinin: A nonapeptide messenger that is enzymatically produced from kallidin in the blood where it is a potent but short-lived agent of arteriolar dilation and increased capillary permeability. Bradykinin is also released from mast cells during asthma attacks, from gut walls as a gastrointestinal vasodilator, from damaged tissues as a pain signal, and may be a neurotransmitter. [NIH]

Branch: Most commonly used for branches of nerves, but applied also to other structures. [NIH]

Breakdown: A physical, metal, or nervous collapse. [NIH]

Broad-spectrum: Effective against a wide range of microorganisms; said of an antibiotic. [EU]

Bronchi: The larger air passages of the lungs arising from the terminal bifurcation of the trachea. [NIH]

Bronchial: Pertaining to one or more bronchi. [EU]

Buffers: A chemical system that functions to control the levels of specific ions in solution. When the level of hydrogen ion in solution is controlled the system is called a pH buffer. [NIH]

Buformin: An oral hypoglycemic agent that inhibits gluconeogenesis, increases glycolysis, and decreases glucose oxidation. [NIH]

Calcium: A basic element found in nearly all organized tissues. It is a member of the alkaline earth family of metals with the atomic symbol Ca, atomic number 20, and atomic weight 40. Calcium is the most abundant mineral in the body and combines with phosphorus to form calcium phosphate in the bones and teeth. It is essential for the normal functioning of nerves and muscles and plays a role in blood coagulation (as factor IV) and in many enzymatic processes. [NIH]

Caloric intake: Refers to the number of calories (energy content) consumed. [NIH]

Capillary: Any one of the minute vessels that connect the arterioles and venules, forming a network in nearly all parts of the body. Their walls act as semipermeable membranes for the interchange of various substances, including fluids, between the blood and tissue fluid; called also vas capillare. [EU]

Capsules: Hard or soft soluble containers used for the oral administration of medicine. [NIH]

Carbohydrate: An aldehyde or ketone derivative of a polyhydric alcohol, particularly of the pentahydric and hexahydric alcohols. They are so named because the hydrogen and oxygen are usually in the proportion to form water, (CH2O)n. The most important carbohydrates are the starches, sugars, celluloses, and gums. They are classified into mono-, di-, tri-, poly- and heterosaccharides. [EU]

Carbon Dioxide: A colorless, odorless gas that can be formed by the body and is necessary for the respiration cycle of plants and animals. [NIH]

Carboxy: Cannabinoid. [NIH]

Carboxylic Acids: Organic compounds containing the carboxy group (-COOH). This group of compounds includes amino acids and fatty acids. Carboxylic acids can be saturated, unsaturated, or aromatic. [NIH]

Carcinogen: Any substance that causes cancer. [NIH]

Carcinogenic: Producing carcinoma. [EU]

Carcinoma: Cancer that begins in the skin or in tissues that line or cover internal organs. [NIH]

Cardiac: Having to do with the heart. [NIH]

Cardiac Output: The volume of blood passing through the heart per unit of time. It is usually expressed as liters (volume) per minute so as not to be confused with stroke volume (volume per beat). [NIH]

Cardiorespiratory: Relating to the heart and lungs and their function. [EU]

Cardiovascular: Having to do with the heart and blood vessels. [NIH]

Cardiovascular disease: Any abnormal condition characterized by dysfunction of the heart and blood vessels. CVD includes atherosclerosis (especially coronary heart disease, which can lead to heart attacks), cerebrovascular disease (e.g., stroke), and hypertension (high blood pressure). [NIH]

Carnitine: Constituent of striated muscle and liver. It is used therapeutically to stimulate gastric and pancreatic secretions and in the treatment of hyperlipoproteinemias. [NIH]

Case report: A detailed report of the diagnosis, treatment, and follow-up of an individual patient. Case reports also contain some demographic information about the patient (for example, age, gender, ethnic origin). [NIH]

Case series: A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment. [NIH]

Catecholamine: A group of chemical substances manufactured by the adrenal medulla and secreted during physiological stress. [NIH]

Cathode: An electrode, usually an incandescent filament of tungsten, which emits electrons in an X-ray tube. [NIH]

Cations: Postively charged atoms, radicals or groups of atoms which travel to the cathode or negative pole during electrolysis. [NIH]

Cause of Death: Factors which produce cessation of all vital bodily functions. They can be analyzed from an epidemiologic viewpoint. [NIH]

Cell: The individual unit that makes up all of the tissues of the body. All living things are made up of one or more cells. [NIH]

Cell Adhesion: Adherence of cells to surfaces or to other cells. [NIH]

Cell Death: The termination of the cell's ability to carry out vital functions such as metabolism, growth, reproduction, responsiveness, and adaptability. [NIH]

Cell Division: The fission of a cell. [NIH]

Cell Physiology: Characteristics and physiological processes of cells from cell division to cell death. [NIH]

Cell proliferation: An increase in the number of cells as a result of cell growth and cell

division. [NIH]

Cell Survival: The span of viability of a cell characterized by the capacity to perform certain functions such as metabolism, growth, reproduction, some form of responsiveness, and adaptability. [NIH]

Cellulose: A polysaccharide with glucose units linked as in cellobiose. It is the chief constituent of plant fibers, cotton being the purest natural form of the substance. As a raw material, it forms the basis for many derivatives used in chromatography, ion exchange materials, explosives manufacturing, and pharmaceutical preparations. [NIH]

Central fat distribution: The waist circumference is an index of body fat distribution. Increasing waist circumference is accompanied by increasing frequencies of overt type 2 diabetes, dyslipidemia, hypertension, coronary heart disease, stroke, and early mortality. In the body fat patterns called android type (apple shaped) fat is deposited around the waist and upper abdominal area and appears most often in men. Abdominal body fat is thought to be associated with a rapid mobilization of fatty acids rather than resulting from other fat depots, although it remains a point of contention. If abdominal fat is indeed more active than other fat depots, it would then provide a mechanism by which we could explain (in part) the increase in blood lipid and glucose levels. The latter have been clearly associated with an increased risk for cardiovascular disease, hypertension, and type 2 diabetes. The gynoid type (pear-shaped) of body fat is usually seen in women. The fat is deposited around the hips, thighs, and buttocks, and presumably is used as energy reserve during pregnancy and lactation. [NIH]

Central Nervous System: The main information-processing organs of the nervous system, consisting of the brain, spinal cord, and meninges. [NIH]

Cephalexin: A semisynthetic cephalosporin antibiotic with antimicrobial activity similar to that of cephaloridine or cephalothin, but somewhat less potent. It is effective against both gram-positive and gram-negative organisms. [NIH]

Cephaloridine: A cephalosporin antibiotic. [NIH]

Cephalothin: A cephalosporin antibiotic. [NIH]

Ceramide: A type of fat produced in the body. It may cause some types of cells to die, and is being studied in cancer treatment. [NIH]

Cerebral: Of or pertaining of the cerebrum or the brain. [EU]

Cerebral Aqueduct: Narrow channel in the mesencephalon that connects the third and fourth ventricles. [NIH]

Cerebrovascular: Pertaining to the blood vessels of the cerebrum, or brain. [EU]

Cervix: The lower, narrow end of the uterus that forms a canal between the uterus and vagina. [NIH]

Chemotherapy: Treatment with anticancer drugs. [NIH]

Cholesterol: The principal sterol of all higher animals, distributed in body tissues, especially the brain and spinal cord, and in animal fats and oils. [NIH]

Cholesterol Esters: Fatty acid esters of cholesterol which constitute about two-thirds of the cholesterol in the plasma. The accumulation of cholesterol esters in the arterial intima is a characteristic feature of atherosclerosis. [NIH]

Choroid: The thin, highly vascular membrane covering most of the posterior of the eye between the retina and sclera. [NIH]

Chromatin: The material of chromosomes. It is a complex of DNA, histones, and nonhistone proteins (chromosomal proteins, non-histone) found within the nucleus of a cell. [NIH]

Chromium: A trace element that plays a role in glucose metabolism. It has the atomic symbol Cr, atomic number 24, and atomic weight 52. According to the Fourth Annual Report on Carcinogens (NTP85-002,1985), chromium and some of its compounds have been listed as known carcinogens. [NIH]

Chromosomal: Pertaining to chromosomes. [EU]

Chromosome: Part of a cell that contains genetic information. Except for sperm and eggs, all human cells contain 46 chromosomes. [NIH]

Chronic: A disease or condition that persists or progresses over a long period of time. [NIH]

Chronic Disease: Disease or ailment of long duration. [NIH]

Chronic renal: Slow and progressive loss of kidney function over several years, often resulting in end-stage renal disease. People with end-stage renal disease need dialysis or transplantation to replace the work of the kidneys. [NIH]

Chylomicrons: A class of lipoproteins that carry dietary cholesterol and triglycerides from the small intestines to the tissues. [NIH]

Circulatory system: The system that contains the heart and the blood vessels and moves blood throughout the body. This system helps tissues get enough oxygen and nutrients, and it helps them get rid of waste products. The lymph system, which connects with the blood system, is often considered part of the circulatory system. [NIH]

CIS: Cancer Information Service. The CIS is the National Cancer Institute's link to the public, interpreting and explaining research findings in a clear and understandable manner, and providing personalized responses to specific questions about cancer. Access the CIS by calling 1-800-4-CANCER, or by using the Web site at http://cis.nci.nih.gov. [NIH]

Citrus: Any tree or shrub of the Rue family or the fruit of these plants. [NIH]

Clamp: A u-shaped steel rod used with a pin or wire for skeletal traction in the treatment of certain fractures. [NIH]

Claudication: Limping or lameness. [EU]

Clear cell carcinoma: A rare type of tumor of the female genital tract in which the inside of the cells looks clear when viewed under a microscope. [NIH]

Clinical Medicine: The study and practice of medicine by direct examination of the patient. [NIH]

Clinical Protocols: Precise and detailed plans for the study of a medical or biomedical problem and/or plans for a regimen of therapy. [NIH]

Clinical study: A research study in which patients receive treatment in a clinic or other medical facility. Reports of clinical studies can contain results for single patients (case reports) or many patients (case series or clinical trials). [NIH]

Clinical trial: A research study that tests how well new medical treatments or other interventions work in people. Each study is designed to test new methods of screening, prevention, diagnosis, or treatment of a disease. [NIH]

Clofibric Acid: An antilipemic agent and the biologically active metabolite of clofibrate. [NIH]

Clomiphene: A stilbene derivative that functions both as a partial estrogen agonist and complete estrogen antagonist depending on the target tissue. It antagonizes the estrogen receptor thereby initiating or augmenting ovulation in anovulatory women. [NIH]

Cloning: The production of a number of genetically identical individuals; in genetic engineering, a process for the efficient replication of a great number of identical DNA molecules. [NIH]

Clot Retraction: Retraction of a clot resulting from contraction of platelet pseudopods attached to fibrin strands that is dependent on the contractile protein thrombosthenin. Used as a measure of platelet function. [NIH]

Coagulation: 1. The process of clot formation. 2. In colloid chemistry, the solidification of a sol into a gelatinous mass; an alteration of a disperse phase or of a dissolved solid which causes the separation of the system into a liquid phase and an insoluble mass called the clot or curd. Coagulation is usually irreversible. 3. In surgery, the disruption of tissue by physical means to form an amorphous residuum, as in electrocoagulation and photocoagulation. [EU]

Coal: A natural fuel formed by partial decomposition of vegetable matter under certain environmental conditions. [NIH]

Cod Liver Oil: Oil obtained from fresh livers of the cod family, Gadidae. It is a source of vitamins A and D. [NIH]

Coenzyme: An organic nonprotein molecule, frequently a phosphorylated derivative of a water-soluble vitamin, that binds with the protein molecule (apoenzyme) to form the active enzyme (holoenzyme). [EU]

Cofactor: A substance, microorganism or environmental factor that activates or enhances the action of another entity such as a disease-causing agent. [NIH]

Colchicine: A major alkaloid from Colchicum autumnale L. and found also in other Colchicum species. Its primary therapeutic use is in the treatment of gout, but it has been used also in the therapy of familial Mediterranean fever (periodic disease). [NIH]

Colitis: Inflammation of the colon. [NIH]

Collagen: A polypeptide substance comprising about one third of the total protein in mammalian organisms. It is the main constituent of skin, connective tissue, and the organic substance of bones and teeth. Different forms of collagen are produced in the body but all consist of three alpha-polypeptide chains arranged in a triple helix. Collagen is differentiated from other fibrous proteins, such as elastin, by the content of proline, hydroxyproline, and hydroxylysine; by the absence of tryptophan; and particularly by the high content of polar groups which are responsible for its swelling properties. [NIH]

Colloidal: Of the nature of a colloid. [EU]

Combination Therapy: Association of 3 drugs to treat AIDS (AZT + DDC or DDI + protease inhibitor). [NIH]

Complement: A term originally used to refer to the heat-labile factor in serum that causes immune cytolysis, the lysis of antibody-coated cells, and now referring to the entire functionally related system comprising at least 20 distinct serum proteins that is the effector not only of immune cytolysis but also of other biologic functions. Complement activation occurs by two different sequences, the classic and alternative pathways. The proteins of the classic pathway are termed 'components of complement' and are designated by the symbols C1 through C9. C1 is a calcium-dependent complex of three distinct proteins C1q, C1r and C1s. The proteins of the alternative pathway (collectively referred to as the properdin system) and complement regulatory proteins are known by semisystematic or trivial names. Fragments resulting from proteolytic cleavage of complement proteins are designated with lower-case letter suffixes, e.g., C3a. Inactivated fragments may be designated with the suffix 'i', e.g. C3bi. Activated components or complexes with biological activity are designated by a bar over the symbol e.g. C1 or C4b,2a. The classic pathway is activated by the binding of C1 to classic pathway activators, primarily antigen-antibody complexes containing IgM, IgG1, IgG3; C1q binds to a single IgM molecule or two adjacent IgG molecules. The alternative pathway can be activated by IgA immune complexes and also by nonimmunologic materials

including bacterial endotoxins, microbial polysaccharides, and cell walls. Activation of the classic pathway triggers an enzymatic cascade involving C1, C4, C2 and C3; activation of the alternative pathway triggers a cascade involving C3 and factors B, D and P. Both result in the cleavage of C5 and the formation of the membrane attack complex. Complement activation also results in the formation of many biologically active complement fragments that act as anaphylatoxins, opsonins, or chemotactic factors. [EU]

Complementary and alternative medicine: CAM. Forms of treatment that are used in addition to (complementary) or instead of (alternative) standard treatments. These practices are not considered standard medical approaches. CAM includes dietary supplements, megadose vitamins, herbal preparations, special teas, massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

Complementary medicine: Practices not generally recognized by the medical community as standard or conventional medical approaches and used to enhance or complement the standard treatments. Complementary medicine includes the taking of dietary supplements, megadose vitamins, and herbal preparations; the drinking of special teas; and practices such as massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

Computational Biology: A field of biology concerned with the development of techniques for the collection and manipulation of biological data, and the use of such data to make biological discoveries or predictions. This field encompasses all computational methods and theories applicable to molecular biology and areas of computer-based techniques for solving biological problems including manipulation of models and datasets. [NIH]

Conception: The onset of pregnancy, marked by implantation of the blastocyst; the formation of a viable zygote. [EU]

Concomitant: Accompanying; accessory; joined with another. [EU]

Confusion: A mental state characterized by bewilderment, emotional disturbance, lack of clear thinking, and perceptual disorientation. [NIH]

Congestive heart failure: Weakness of the heart muscle that leads to a buildup of fluid in body tissues. [NIH]

Conjugated: Acting or operating as if joined; simultaneous. [EU]

Conjugation: 1. The act of joining together or the state of being conjugated. 2. A sexual process seen in bacteria, ciliate protozoa, and certain fungi in which nuclear material is exchanged during the temporary fusion of two cells (conjugants). In bacterial genetics a form of sexual reproduction in which a donor bacterium (male) contributes some, or all, of its DNA (in the form of a replicated set) to a recipient (female) which then incorporates differing genetic information into its own chromosome by recombination and passes the recombined set on to its progeny by replication. In ciliate protozoa, two conjugants of separate mating types exchange micronuclear material and then separate, each now being a fertilized cell. In certain fungi, the process involves fusion of two gametes, resulting in union of their nuclei and formation of a zygote. 3. In chemistry, the joining together of two compounds to produce another compound, such as the combination of a toxic product with some substance in the body to form a detoxified product, which is then eliminated. [EU]

Connective Tissue: Tissue that supports and binds other tissues. It consists of connective tissue cells embedded in a large amount of extracellular matrix. [NIH]

Connective Tissue: Tissue that supports and binds other tissues. It consists of connective tissue cells embedded in a large amount of extracellular matrix. [NIH]

Connective Tissue Cells: A group of cells that includes fibroblasts, cartilage cells, adipocytes, smooth muscle cells, and bone cells. [NIH]

Constipation: Infrequent or difficult evacuation of feces. [NIH]

Constriction: The act of constricting. [NIH]

Constriction, Pathologic: The condition of an anatomical structure's being constricted beyond normal dimensions. [NIH]

Consultation: A deliberation between two or more physicians concerning the diagnosis and the proper method of treatment in a case. [NIH]

Consumption: Pulmonary tuberculosis. [NIH]

Continuous infusion: The administration of a fluid into a blood vessel, usually over a prolonged period of time. [NIH]

Contraception: Use of agents, devices, methods, or procedures which diminish the likelihood of or prevent conception. [NIH]

Contraceptive: An agent that diminishes the likelihood of or prevents conception. [EU]

Contraindications: Any factor or sign that it is unwise to pursue a certain kind of action or treatment, e. g. giving a general anesthetic to a person with pneumonia. [NIH]

Contrast Media: Substances used in radiography that allow visualization of certain tissues. [NIH]

Control group: In a clinical trial, the group that does not receive the new treatment being studied. This group is compared to the group that receives the new treatment, to see if the new treatment works. [NIH]

Controlled clinical trial: A clinical study that includes a comparison (control) group. The comparison group receives a placebo, another treatment, or no treatment at all. [NIH]

Controlled study: An experiment or clinical trial that includes a comparison (control) group. [NIH]

Coronary: Encircling in the manner of a crown; a term applied to vessels; nerves, ligaments, etc. The term usually denotes the arteries that supply the heart muscle and, by extension, a pathologic involvement of them. [EU]

Coronary Disease: Disorder of cardiac function due to an imbalance between myocardial function and the capacity of the coronary vessels to supply sufficient flow for normal function. It is a form of myocardial ischemia (insufficient blood supply to the heart muscle) caused by a decreased capacity of the coronary vessels. [NIH]

Coronary heart disease: A type of heart disease caused by narrowing of the coronary arteries that feed the heart, which needs a constant supply of oxygen and nutrients carried by the blood in the coronary arteries. When the coronary arteries become narrowed or clogged by fat and cholesterol deposits and cannot supply enough blood to the heart, CHD results. [NIH]

Coronary Thrombosis: Presence of a thrombus in a coronary artery, often causing a myocardial infarction. [NIH]

Coronary Vessels: The veins and arteries of the heart. [NIH]

Corpus: The body of the uterus. [NIH]

Corpus Callosum: Broad plate of dense myelinated fibers that reciprocally interconnect regions of the cortex in all lobes with corresponding regions of the opposite hemisphere. The corpus callosum is located deep in the longitudinal fissure. [NIH]

Corpus Luteum: The yellow glandular mass formed in the ovary by an ovarian follicle that has ruptured and discharged its ovum. [NIH]

Corpuscle: A small mass or body; a sensory nerve end bulb; a cell, especially that of the

blood or the lymph. [NIH]

Cortisol: A steroid hormone secreted by the adrenal cortex as part of the body's response to stress. [NIH]

Cost-benefit: A quantitative technique of economic analysis which, when applied to radiation practice, compares the health detriment from the radiation doses concerned with the cost of radiation dose reduction in that practice. [NIH]

Creatinine: A compound that is excreted from the body in urine. Creatinine levels are measured to monitor kidney function. [NIH]

Creatinine clearance: A test that measures how efficiently the kidneys remove creatinine and other wastes from the blood. Low creatinine clearance indicates impaired kidney function. [NIH]

Curative: Tending to overcome disease and promote recovery. [EU]

Cutaneous: Having to do with the skin. [NIH]

Cyclic: Pertaining to or occurring in a cycle or cycles; the term is applied to chemical compounds that contain a ring of atoms in the nucleus. [EU]

Cyproterone: An anti-androgen that, in the form of its acetate, also has progestational properties. It is used in the treatment of hypersexuality in males, as a palliative in prostatic carcinoma, and, in combination with estrogen, for the therapy of severe acne and hirsutism in females. [NIH]

Cyproterone Acetate: An agent with anti-androgen and progestational properties. It shows competitive binding with dihydrotestosterone at androgen receptor sites. [NIH]

Cyst: A sac or capsule filled with fluid. [NIH]

Cysteine: A thiol-containing non-essential amino acid that is oxidized to form cystine. [NIH]

Cystine: A covalently linked dimeric nonessential amino acid formed by the oxidation of cysteine. Two molecules of cysteine are joined together by a disulfide bridge to form cystine. [NIH]

Cytokine: Small but highly potent protein that modulates the activity of many cell types, including T and B cells. [NIH]

Cytoplasm: The protoplasm of a cell exclusive of that of the nucleus; it consists of a continuous aqueous solution (cytosol) and the organelles and inclusions suspended in it (phaneroplasm), and is the site of most of the chemical activities of the cell. [EU]

Cytoskeleton: The network of filaments, tubules, and interconnecting filamentous bridges which give shape, structure, and organization to the cytoplasm. [NIH]

Dairy Products: Raw and processed or manufactured milk and milk-derived products. These are usually from cows (bovine) but are also from goats, sheep, reindeer, and water buffalo. [NIH]

Databases, Bibliographic: Extensive collections, reputedly complete, of references and citations to books, articles, publications, etc., generally on a single subject or specialized subject area. Databases can operate through automated files, libraries, or computer disks. The concept should be differentiated from factual databases which is used for collections of data and facts apart from bibliographic references to them. [NIH]

De novo: In cancer, the first occurrence of cancer in the body. [NIH]

Deamination: The removal of an amino group (NH2) from a chemical compound. [NIH]

Defense Mechanisms: Unconscious process used by an individual or a group of individuals in order to cope with impulses, feelings or ideas which are not acceptable at their conscious

level; various types include reaction formation, projection and self reversal. [NIH]

Degenerative: Undergoing degeneration : tending to degenerate; having the character of or involving degeneration; causing or tending to cause degeneration. [EU]

Dehydration: The condition that results from excessive loss of body water. [NIH]

Deletion: A genetic rearrangement through loss of segments of DNA (chromosomes), bringing sequences, which are normally separated, into close proximity. [NIH]

Delivery of Health Care: The concept concerned with all aspects of providing and distributing health services to a patient population. [NIH]

Density: The logarithm to the base 10 of the opacity of an exposed and processed film. [NIH]

Deoxyglucose: 2-Deoxy-D-arabino-hexose. An antimetabolite of glucose with antiviral activity. [NIH]

DES: Diethylstilbestrol. A synthetic hormone that was prescribed from the early 1940s until 1971 to help women with complications of pregnancy. DES has been linked to an increased risk of clear cell carcinoma of the vagina in daughters of women who used DES. DES may also increase the risk of breast cancer in women who used DES. [NIH]

Detoxification: Treatment designed to free an addict from his drug habit. [EU]

Deuterium: Deuterium. The stable isotope of hydrogen. It has one neutron and one proton in the nucleus. [NIH]

Dexfenfluramine: The S-isomer of fenfluramine. It is a serotonin agonist and is used as an anorectic. Unlike fenfluramine, it does not possess any catecholamine agonist activity. [NIH]

Diabetes Mellitus: A heterogeneous group of disorders that share glucose intolerance in common. [NIH]

Diabetes, Gestational: Either symptomatic diabetes or impaired glucose tolerance induced by pregnancy but resolved at the end of pregnancy. It does not include previously diagnosed diabetics who become pregnant (pregnancy in diabetics). [NIH]

Diabetic Ketoacidosis: Complication of diabetes resulting from severe insulin deficiency coupled with an absolute or relative increase in glucagon concentration. The metabolic acidosis is caused by the breakdown of adipose stores and resulting increased levels of free fatty acids. Glucagon accelerates the oxidation of the free fatty acids producing excess ketone bodies (ketosis). [NIH]

Diabetic Retinopathy: Retinopathy associated with diabetes mellitus, which may be of the background type, progressively characterized by microaneurysms, interretinal punctuate macular edema, or of the proliferative type, characterized by neovascularization of the retina and optic disk, which may project into the vitreous, proliferation of fibrous tissue, vitreous hemorrhage, and retinal detachment. [NIH]

Diagnostic procedure: A method used to identify a disease. [NIH]

Dialysate: A cleansing liquid used in the two major forms of dialysis--hemodialysis and peritoneal dialysis. [NIH]

Diamide: A sulfhydryl reagent which oxidizes sulfhydryl groups to the disulfide form. It is a radiation-sensitizing agent of anoxic bacterial and mammalian cells. [NIH]

Diarrhea: Passage of excessively liquid or excessively frequent stools. [NIH]

Diastole: Period of relaxation of the heart, especially the ventricles. [NIH]

Diastolic: Of or pertaining to the diastole. [EU]

Diastolic blood pressure: The minimum pressure that remains within the artery when the heart is at rest. [NIH]

Diathermy: The induction of local hyperthermia by either short radio waves or high-frequency sound waves. [NIH]

Diencephalon: The paired caudal parts of the prosencephalon from which the thalamus, hypothalamus, epithalamus, and subthalamus are derived. [NIH]

Dietary Fats: Fats present in food, especially in animal products such as meat, meat products, butter, ghee. They are present in lower amounts in nuts, seeds, and avocados. [NIH]

Diffusion: The tendency of a gas or solute to pass from a point of higher pressure or concentration to a point of lower pressure or concentration and to distribute itself throughout the available space; a major mechanism of biological transport. [NIH]

Digestion: The process of breakdown of food for metabolism and use by the body. [NIH]

Digestive system: The organs that take in food and turn it into products that the body can use to stay healthy. Waste products the body cannot use leave the body through bowel movements. The digestive system includes the salivary glands, mouth, esophagus, stomach, liver, pancreas, gallbladder, small and large intestines, and rectum. [NIH]

Digestive tract: The organs through which food passes when food is eaten. These organs are the mouth, esophagus, stomach, small and large intestines, and rectum. [NIH]

Dihydrotestosterone: Anabolic agent. [NIH]

Dihydroxy: AMPA/Kainate antagonist. [NIH]

Dilatation: The act of dilating. [NIH]

Direct: 1. Straight; in a straight line. 2. Performed immediately and without the intervention of subsidiary means. [EU]

Disinfectant: An agent that disinfects; applied particularly to agents used on inanimate objects. [EU]

Dissection: Cutting up of an organism for study. [NIH]

Dissociation: 1. The act of separating or state of being separated. 2. The separation of a molecule into two or more fragments (atoms, molecules, ions, or free radicals) produced by the absorption of light or thermal energy or by solvation. 3. In psychology, a defense mechanism in which a group of mental processes are segregated from the rest of a person's mental activity in order to avoid emotional distress, as in the dissociative disorders (q.v.), or in which an idea or object is segregated from its emotional significance; in the first sense it is roughly equivalent to splitting, in the second, to isolation. 4. A defect of mental integration in which one or more groups of mental processes become separated off from normal consciousness and, thus separated, function as a unitary whole. [EU]

Distal: Remote; farther from any point of reference; opposed to proximal. In dentistry, used to designate a position on the dental arch farther from the median line of the jaw. [EU]

Diuresis: Increased excretion of urine. [EU]

Diuretic: A drug that increases the production of urine. [NIH]

Diverticulum: A pathological condition manifested as a pouch or sac opening from a tubular or sacular organ. [NIH]

Dopamine: An endogenous catecholamine and prominent neurotransmitter in several systems of the brain. In the synthesis of catecholamines from tyrosine, it is the immediate precursor to norepinephrine and epinephrine. Dopamine is a major transmitter in the extrapyramidal system of the brain, and important in regulating movement. A family of dopaminergic receptor subtypes mediate its action. Dopamine is used pharmacologically for its direct (beta adrenergic agonist) and indirect (adrenergic releasing) sympathomimetic

effects including its actions as an inotropic agent and as a renal vasodilator. [NIH]

Dosage Forms: Completed forms of the pharmaceutical preparation in which prescribed doses of medication are included. They are designed to resist action by gastric fluids, prevent vomiting and nausea, reduce or alleviate the undesirable taste and smells associated with oral administration, achieve a high concentration of drug at target site, or produce a delayed or long-acting drug effect. They include capsules, liniments, ointments, pharmaceutical solutions, powders, tablets, etc. [NIH]

Dose-dependent: Refers to the effects of treatment with a drug. If the effects change when the dose of the drug is changed, the effects are said to be dose dependent. [NIH]

Double-blinded: A clinical trial in which neither the medical staff nor the person knows which of several possible therapies the person is receiving. [NIH]

Drive: A state of internal activity of an organism that is a necessary condition before a given stimulus will elicit a class of responses; e.g., a certain level of hunger (drive) must be present before food will elicit an eating response. [NIH]

Drug Interactions: The action of a drug that may affect the activity, metabolism, or toxicity of another drug. [NIH]

Drug Monitoring: The process of observing, recording, or detecting the effects of a chemical substance administered to an individual therapeutically or diagnostically. [NIH]

Drug Tolerance: Progressive diminution of the susceptibility of a human or animal to the effects of a drug, resulting from its continued administration. It should be differentiated from drug resistance wherein an organism, disease, or tissue fails to respond to the intended effectiveness of a chemical or drug. It should also be differentiated from maximum tolerated dose and no-observed-adverse-effect level. [NIH]

Duodenum: The first part of the small intestine. [NIH]

Dyslipidemia: Disorders in the lipoprotein metabolism; classified as hypercholesterolemia, hypertriglyceridemia, combined hyperlipidemia, and low levels of high-density lipoprotein (HDL) cholesterol. All of the dyslipidemias can be primary or secondary. Both elevated levels of low-density lipoprotein (LDL) cholesterol and low levels of HDL cholesterol predispose to premature atherosclerosis. [NIH]

Echocardiography: Ultrasonic recording of the size, motion, and composition of the heart and surrounding tissues. The standard approach is transthoracic. [NIH]

Edema: Excessive amount of watery fluid accumulated in the intercellular spaces, most commonly present in subcutaneous tissue. [NIH]

Efficacy: The extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions. Ideally, the determination of efficacy is based on the results of a randomized control trial. [NIH]

Elastin: The protein that gives flexibility to tissues. [NIH]

Electrode: Component of the pacing system which is at the distal end of the lead. It is the interface with living cardiac tissue across which the stimulus is transmitted. [NIH]

Electrolysis: Destruction by passage of a galvanic electric current, as in disintegration of a chemical compound in solution. [NIH]

Electrolyte: A substance that dissociates into ions when fused or in solution, and thus becomes capable of conducting electricity; an ionic solute. [EU]

Electrons: Stable elementary particles having the smallest known negative charge, present in all elements; also called negatrons. Positively charged electrons are called positrons. The numbers, energies and arrangement of electrons around atomic nuclei determine the

chemical identities of elements. Beams of electrons are called cathode rays or beta rays, the latter being a high-energy biproduct of nuclear decay. [NIH]

Electrophoresis: An electrochemical process in which macromolecules or colloidal particles with a net electric charge migrate in a solution under the influence of an electric current. [NIH]

Emboli: Bit of foreign matter which enters the blood stream at one point and is carried until it is lodged or impacted in an artery and obstructs it. It may be a blood clot, an air bubble, fat or other tissue, or clumps of bacteria. [NIH]

Embolism: Blocking of a blood vessel by a blood clot or foreign matter that has been transported from a distant site by the blood stream. [NIH]

Embolization: The blocking of an artery by a clot or foreign material. Embolization can be done as treatment to block the flow of blood to a tumor. [NIH]

Embryo: The prenatal stage of mammalian development characterized by rapid morphological changes and the differentiation of basic structures. [NIH]

Emesis: Vomiting; an act of vomiting. Also used as a word termination, as in haematemesis. [EU]

Emetic: An agent that causes vomiting. [EU]

Emollient: Softening or soothing; called also malactic. [EU]

Emulsion: A preparation of one liquid distributed in small globules throughout the body of a second liquid. The dispersed liquid is the discontinuous phase, and the dispersion medium is the continuous phase. When oil is the dispersed liquid and an aqueous solution is the continuous phase, it is known as an oil-in-water emulsion, whereas when water or aqueous solution is the dispersed phase and oil or oleaginous substance is the continuous phase, it is known as a water-in-oil emulsion. Pharmaceutical emulsions for which official standards have been promulgated include cod liver oil emulsion, cod liver oil emulsion with malt, liquid petrolatum emulsion, and phenolphthalein in liquid petrolatum emulsion. [EU]

Enalapril: An angiotensin-converting enzyme inhibitor that is used to treat hypertension. [NIH]

Endocrine System: The system of glands that release their secretions (hormones) directly into the circulatory system. In addition to the endocrine glands, included are the chromaffin system and the neurosecretory systems. [NIH]

Endocrinologist: A doctor that specializes in diagnosing and treating hormone disorders. [NIH]

Endocrinology: A subspecialty of internal medicine concerned with the metabolism, physiology, and disorders of the endocrine system. [NIH]

Endometrial: Having to do with the endometrium (the layer of tissue that lines the uterus). [NIH]

Endometrium: The layer of tissue that lines the uterus. [NIH]

Endopeptidases: A subclass of peptide hydrolases. They are classified primarily by their catalytic mechanism. Specificity is used only for identification of individual enzymes. They comprise the serine endopeptidases, EC 3.4.21; cysteine endopeptidases, EC 3.4.22; aspartic endopeptidases, EC 3.4.23, metalloendopeptidases, EC 3.4.24; and a group of enzymes yet to be assigned to any of the above sub-classes, EC 3.4.99. EC 3.4.-. [NIH]

Endothelial cell: The main type of cell found in the inside lining of blood vessels, lymph vessels, and the heart. [NIH]

Endothelium: A layer of epithelium that lines the heart, blood vessels (endothelium, vascular), lymph vessels (endothelium, lymphatic), and the serous cavities of the body. [NIH]

Endothelium, Lymphatic: Unbroken cellular lining (intima) of the lymph vessels (e.g., the high endothelial lymphatic venules). It is more permeable than vascular endothelium, lacking selective absorption and functioning mainly to remove plasma proteins that have filtered through the capillaries into the tissue spaces. [NIH]

Endothelium, Vascular: Single pavement layer of cells which line the luminal surface of the entire vascular system and regulate the transport of macromolecules and blood components from interstitium to lumen; this function has been most intensively studied in the blood capillaries. [NIH]

Endothelium-derived: Small molecule that diffuses to the adjacent muscle layer and relaxes it. [NIH]

Endotoxin: Toxin from cell walls of bacteria. [NIH]

End-stage renal: Total chronic kidney failure. When the kidneys fail, the body retains fluid and harmful wastes build up. A person with ESRD needs treatment to replace the work of the failed kidneys. [NIH]

Energy balance: Energy is the capacity of a body or a physical system for doing work. Energy balance is the state in which the total energy intake equals total energy needs. [NIH]

Environmental Health: The science of controlling or modifying those conditions, influences, or forces surrounding man which relate to promoting, establishing, and maintaining health. [NIH]

Enzymatic: Phase where enzyme cuts the precursor protein. [NIH]

Enzyme: A protein that speeds up chemical reactions in the body. [NIH]

Ependyma: A thin membrane that lines the ventricles of the brain and the central canal of the spinal cord. [NIH]

Epidemic: Occurring suddenly in numbers clearly in excess of normal expectancy; said especially of infectious diseases but applied also to any disease, injury, or other health-related event occurring in such outbreaks. [EU]

Epidemiological: Relating to, or involving epidemiology. [EU]

Epigastric: Having to do with the upper middle area of the abdomen. [NIH]

Epinephrine: The active sympathomimetic hormone from the adrenal medulla in most species. It stimulates both the alpha- and beta- adrenergic systems, causes systemic vasoconstriction and gastrointestinal relaxation, stimulates the heart, and dilates bronchi and cerebral vessels. It is used in asthma and cardiac failure and to delay absorption of local anesthetics. [NIH]

Epithelial: Refers to the cells that line the internal and external surfaces of the body. [NIH]

Epithelial Cells: Cells that line the inner and outer surfaces of the body. [NIH]

Epithelium: One or more layers of epithelial cells, supported by the basal lamina, which covers the inner or outer surfaces of the body. [NIH]

Erectile: The inability to get or maintain an erection for satisfactory sexual intercourse. Also called impotence. [NIH]

Erection: The condition of being made rigid and elevated; as erectile tissue when filled with blood. [EU]

Erythrocyte Membrane: The semipermeable outer portion of the red corpuscle. It is known as a 'ghost' after hemolysis. [NIH]

Erythrocytes: Red blood cells. Mature erythrocytes are non-nucleated, biconcave disks containing hemoglobin whose function is to transport oxygen. [NIH]

Esophagus: The muscular tube through which food passes from the throat to the stomach. [NIH]

Estrogen: One of the two female sex hormones. [NIH]

Estrogen receptor: ER. Protein found on some cancer cells to which estrogen will attach. [NIH]

Ethanol: A clear, colorless liquid rapidly absorbed from the gastrointestinal tract and distributed throughout the body. It has bactericidal activity and is used often as a topical disinfectant. It is widely used as a solvent and preservative in pharmaceutical preparations as well as serving as the primary ingredient in alcoholic beverages. [NIH]

Ethinyl Estradiol: A semisynthetic estrogen with high oral estrogenic potency. It is often used as the estrogenic component in oral contraceptives. [NIH]

Ethnic Groups: A group of people with a common cultural heritage that sets them apart from others in a variety of social relationships. [NIH]

Ethylene Glycol: A colorless, odorless, viscous dihydroxy alcohol. It has a sweet taste, but is poisonous if ingested. Ethylene glycol is the most important glycol commercially available and is manufactured on a large scale in the United States. It is used as an antifreeze and coolant, in hydraulic fluids, and in the manufacture of low-freezing dynamites and resins. [NIH]

Eukaryotic Cells: Cells of the higher organisms, containing a true nucleus bounded by a nuclear membrane. [NIH]

Excipients: Usually inert substances added to a prescription in order to provide suitable consistency to the dosage form; a binder, matrix, base or diluent in pills, tablets, creams, salves, etc. [NIH]

Exercise Therapy: Motion of the body or its parts to relieve symptoms or to improve function, leading to physical fitness, but not physical education and training. [NIH]

Exocrine: Secreting outwardly, via a duct. [EU]

Exogenous: Developed or originating outside the organism, as exogenous disease. [EU]

Expander: Any of several colloidal substances of high molecular weight. used as a blood or plasma substitute in transfusion for increasing the volume of the circulating blood. called also extender. [NIH]

Extensor: A muscle whose contraction tends to straighten a limb; the antagonist of a flexor. [NIH]

Extracellular: Outside a cell or cells. [EU]

Extracellular Matrix: A meshwork-like substance found within the extracellular space and in association with the basement membrane of the cell surface. It promotes cellular proliferation and provides a supporting structure to which cells or cell lysates in culture dishes adhere. [NIH]

Extrapyramidal: Outside of the pyramidal tracts. [EU]

Extremity: A limb; an arm or leg (membrum); sometimes applied specifically to a hand or foot. [EU]

Eye Infections: Infection, moderate to severe, caused by bacteria, fungi, or viruses, which occurs either on the external surface of the eye or intraocularly with probable inflammation, visual impairment, or blindness. [NIH]

Fallopian Tubes: Two long muscular tubes that transport ova from the ovaries to the uterus. They extend from the horn of the uterus to the ovaries and consist of an ampulla, an infundibulum, an isthmus, two ostia, and a pars uterina. The walls of the tubes are

composed of three layers: mucosal, muscular, and serosal. [NIH]

Family Planning: Programs or services designed to assist the family in controlling reproduction by either improving or diminishing fertility. [NIH]

Fat: Total lipids including phospholipids. [NIH]

Fatigue: The state of weariness following a period of exertion, mental or physical, characterized by a decreased capacity for work and reduced efficiency to respond to stimuli. [NIH]

Fatty acids: A major component of fats that are used by the body for energy and tissue development. [NIH]

Fatty Liver: The buildup of fat in liver cells. The most common cause is alcoholism. Other causes include obesity, diabetes, and pregnancy. Also called steatosis. [NIH]

Fenfluramine: A centrally active drug that apparently both blocks serotonin uptake and provokes transport-mediated serotonin release. [NIH]

Fetus: The developing offspring from 7 to 8 weeks after conception until birth. [NIH]

Fibrin: A protein derived from fibrinogen in the presence of thrombin, which forms part of the blood clot. [NIH]

Fibrinogen: Plasma glycoprotein clotted by thrombin, composed of a dimer of three non-identical pairs of polypeptide chains (alpha, beta, gamma) held together by disulfide bonds. Fibrinogen clotting is a sol-gel change involving complex molecular arrangements: whereas fibrinogen is cleaved by thrombin to form polypeptides A and B, the proteolytic action of other enzymes yields different fibrinogen degradation products. [NIH]

Fibrinolysis: The natural enzymatic dissolution of fibrin. [NIH]

Fibrinolytic: Pertaining to, characterized by, or causing the dissolution of fibrin by enzymatic action [EU]

Fibronectin: An adhesive glycoprotein. One form circulates in plasma, acting as an opsonin; another is a cell-surface protein which mediates cellular adhesive interactions. [NIH]

Fibrosis: Any pathological condition where fibrous connective tissue invades any organ, usually as a consequence of inflammation or other injury. [NIH]

Fistula: Abnormal communication most commonly seen between two internal organs, or between an internal organ and the surface of the body. [NIH]

Flatulence: Production or presence of gas in the gastrointestinal tract which may be expelled through the anus. [NIH]

Flexor: Muscles which flex a joint. [NIH]

Flutamide: An antiandrogen with about the same potency as cyproterone in rodent and canine species. [NIH]

Folate: A B-complex vitamin that is being studied as a cancer prevention agent. Also called folic acid. [NIH]

Fold: A plication or doubling of various parts of the body. [NIH]

Folic Acid: N-(4-(((2-Amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl)amino)benzoyl)-L-glutamic acid. A member of the vitamin B family that stimulates the hematopoietic system. It is present in the liver and kidney and is found in mushrooms, spinach, yeast, green leaves, and grasses. Folic acid is used in the treatment and prevention of folate deficiencies and megaloblastic anemia. [NIH]

Follicles: Shafts through which hair grows. [NIH]

Foot Care: Taking special steps to avoid foot problems such as sores, cuts, bunions, and

calluses. Good care includes daily examination of the feet, toes, and toenails and choosing shoes and socks or stockings that fit well. People with diabetes have to take special care of their feet because nerve damage and reduced blood flow sometimes mean they will have less feeling in their feet than normal. They may not notice cuts and other problems as soon as they should. [NIH]

Foot Ulcer: Lesion on the surface of the skin of the foot, usually accompanied by inflammation. The lesion may become infected or necrotic and is frequently associated with diabetes or leprosy. [NIH]

Forearm: The part between the elbow and the wrist. [NIH]

Formulary: A book containing a list of pharmaceutical products with their formulas and means of preparation. [NIH]

Fourth Ventricle: An irregularly shaped cavity in the rhombencephalon, between the medulla oblongata, the pons, and the isthmus in front, and the cerebellum behind. It is continuous with the central canal of the cord below and with the cerebral aqueduct above, and through its lateral and median apertures it communicates with the subarachnoid space. [NIH]

Fructosamine: An amino sugar formed when glucose non-enzymatically reacts with the N-terminal amino group of proteins. The fructose moiety is dervied from glucose by the "classical" Amadori rearrangement. [NIH]

Fructose: A type of sugar found in many fruits and vegetables and in honey. Fructose is used to sweeten some diet foods. It is considered a nutritive sweetener because it has calories. [NIH]

Fungi: A kingdom of eukaryotic, heterotrophic organisms that live as saprobes or parasites, including mushrooms, yeasts, smuts, molds, etc. They reproduce either sexually or asexually, and have life cycles that range from simple to complex. Filamentous fungi refer to those that grow as multicelluar colonies (mushrooms and molds). [NIH]

Gallbladder: The pear-shaped organ that sits below the liver. Bile is concentrated and stored in the gallbladder. [NIH]

Gas: Air that comes from normal breakdown of food. The gases are passed out of the body through the rectum (flatus) or the mouth (burp). [NIH]

Gasoline: Volative flammable fuel (liquid hydrocarbons) derived from crude petroleum by processes such as distillation reforming, polymerization, etc. [NIH]

Gastric: Having to do with the stomach. [NIH]

Gastrin: A hormone released after eating. Gastrin causes the stomach to produce more acid. [NIH]

Gastrointestinal: Refers to the stomach and intestines. [NIH]

Gastrointestinal tract: The stomach and intestines. [NIH]

Gelatin: A product formed from skin, white connective tissue, or bone collagen. It is used as a protein food adjuvant, plasma substitute, hemostatic, suspending agent in pharmaceutical preparations, and in the manufacturing of capsules and suppositories. [NIH]

Gene: The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein. [NIH]

Gene Expression: The phenotypic manifestation of a gene or genes by the processes of gene action. [NIH]

Generator: Any system incorporating a fixed parent radionuclide from which is produced a

daughter radionuclide which is to be removed by elution or by any other method and used in a radiopharmaceutical. [NIH]

Genetic Counseling: Advising families of the risks involved pertaining to birth defects, in order that they may make an informed decision on current or future pregnancies. [NIH]

Genetic Markers: A phenotypically recognizable genetic trait which can be used to identify a genetic locus, a linkage group, or a recombination event. [NIH]

Genetics: The biological science that deals with the phenomena and mechanisms of heredity. [NIH]

Genotype: The genetic constitution of the individual; the characterization of the genes. [NIH]

Geriatric: Pertaining to the treatment of the aged. [EU]

Germ Cells: The reproductive cells in multicellular organisms. [NIH]

Gestation: The period of development of the young in viviparous animals, from the time of fertilization of the ovum until birth. [EU]

Gestational: Psychosis attributable to or occurring during pregnancy. [NIH]

Gland: An organ that produces and releases one or more substances for use in the body. Some glands produce fluids that affect tissues or organs. Others produce hormones or participate in blood production. [NIH]

Gliclazide: An oral sulfonylurea hypoglycemic agent which stimulates insulin secretion. [NIH]

Glipizide: An oral hypoglycemic agent which is rapidly absorbed and completely metabolized. [NIH]

Glomerular: Pertaining to or of the nature of a glomerulus, especially a renal glomerulus. [EU]

Glucokinase: A group of enzymes that catalyzes the conversion of ATP and D-glucose to ADP and D-glucose 6-phosphate. They are found in invertebrates and microorganisms and are highly specific for glucose. (Enzyme Nomenclature, 1992) EC 2.7.1.2. [NIH]

Gluconeogenesis: The process by which glucose is formed from a non-carbohydrate source. [NIH]

Glucose: D-Glucose. A primary source of energy for living organisms. It is naturally occurring and is found in fruits and other parts of plants in its free state. It is used therapeutically in fluid and nutrient replacement. [NIH]

Glucose Clamp Technique: Maintenance of a constant blood glucose level by perfusion or infusion with glucose or insulin. It is used for the study of metabolic rates (e.g., in glucose, lipid, amino acid metabolism) at constant glucose concentration. [NIH]

Glucose Intolerance: A pathological state in which the fasting plasma glucose level is less than 140 mg per deciliter and the 30-, 60-, or 90-minute plasma glucose concentration following a glucose tolerance test exceeds 200 mg per deciliter. This condition is seen frequently in diabetes mellitus but also occurs with other diseases. [NIH]

Glucose tolerance: The power of the normal liver to absorb and store large quantities of glucose and the effectiveness of intestinal absorption of glucose. The glucose tolerance test is a metabolic test of carbohydrate tolerance that measures active insulin, a hepatic function based on the ability of the liver to absorb glucose. The test consists of ingesting 100 grams of glucose into a fasting stomach; blood sugar should return to normal in 2 to 21 hours after ingestion. [NIH]

Glucose Tolerance Test: Determination of whole blood or plasma sugar in a fasting state before and at prescribed intervals (usually 1/2 hr, 1 hr, 3 hr, 4 hr) after taking a specified

amount (usually 100 gm orally) of glucose. [NIH]

Glucuronic Acid: Derivatives of uronic acid found throughout the plant and animal kingdoms. They detoxify drugs and toxins by conjugating with them to form glucuronides in the liver which are more water-soluble metabolites that can be easily eliminated from the body. [NIH]

Glutamic Acid: A non-essential amino acid naturally occurring in the L-form. Glutamic acid (glutamate) is the most common excitatory neurotransmitter in the central nervous system. [NIH]

Glutamine: A non-essential amino acid present abundantly throught the body and is involved in many metabolic processes. It is synthesized from glutamic acid and ammonia. It is the principal carrier of nitrogen in the body and is an important energy source for many cells. [NIH]

Glyburide: An antidiabetic sulfonylurea derivative with actions similar to those of chlorpropamide. [NIH]

Glycerol: A trihydroxy sugar alcohol that is an intermediate in carbohydrate and lipid metabolism. It is used as a solvent, emollient, pharmaceutical agent, and sweetening agent. [NIH]

Glycine: A non-essential amino acid. It is found primarily in gelatin and silk fibroin and used therapeutically as a nutrient. It is also a fast inhibitory neurotransmitter. [NIH]

Glycogen: A sugar stored in the liver and muscles. It releases glucose into the blood when cells need it for energy. Glycogen is the chief source of stored fuel in the body. [NIH]

Glycogen Synthase: An enzyme that catalyzes the transfer of D-glucose from UDPglucose into 1,4-alpha-D-glucosyl chains. EC 2.4.1.11. [NIH]

Glycolysis: The pathway by which glucose is catabolized into two molecules of pyruvic acid with the generation of ATP. [NIH]

Glycoprotein: A protein that has sugar molecules attached to it. [NIH]

Glycosuria: The presence of glucose in the urine; especially the excretion of an abnormally large amount of sugar (glucose) in the urine, i.e., more than 1 gm. in 24 hours. [EU]

Gonad: A sex organ, such as an ovary or a testicle, which produces the gametes in most multicellular animals. [NIH]

Gonadal: Pertaining to a gonad. [EU]

Gonadorelin: A decapeptide hormone released by the hypothalamus. It stimulates the synthesis and secretion of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland. [NIH]

Gonadotropin: The water-soluble follicle stimulating substance, by some believed to originate in chorionic tissue, obtained from the serum of pregnant mares. It is used to supplement the action of estrogens. [NIH]

Governing Board: The group in which legal authority is vested for the control of health-related institutions and organizations. [NIH]

Gp120: 120-kD HIV envelope glycoprotein which is involved in the binding of the virus to its membrane receptor, the CD4 molecule, found on the surface of certain cells in the body. [NIH]

Graft: Healthy skin, bone, or other tissue taken from one part of the body and used to replace diseased or injured tissue removed from another part of the body. [NIH]

Graft Rejection: An immune response with both cellular and humoral components, directed against an allogeneic transplant, whose tissue antigens are not compatible with those of the

recipient. [NIH]

Gram-negative: Losing the stain or decolorized by alcohol in Gram's method of staining, a primary characteristic of bacteria having a cell wall composed of a thin layer of peptidoglycan covered by an outer membrane of lipoprotein and lipopolysaccharide. [EU]

Gram-Negative Bacteria: Bacteria which lose crystal violet stain but are stained pink when treated by Gram's method. [NIH]

Gram-positive: Retaining the stain or resisting decolorization by alcohol in Gram's method of staining, a primary characteristic of bacteria whose cell wall is composed of a thick layer of peptidologlycan with attached teichoic acids. [EU]

Growth: The progressive development of a living being or part of an organism from its earliest stage to maturity. [NIH]

Growth factors: Substances made by the body that function to regulate cell division and cell survival. Some growth factors are also produced in the laboratory and used in biological therapy. [NIH]

Guanylate Cyclase: An enzyme that catalyzes the conversion of GTP to 3',5'-cyclic GMP and pyrophosphate. It also acts on ITP and dGTP. (From Enzyme Nomenclature, 1992) EC 4.6.1.2. [NIH]

Haematemesis: The vomiting of blood. [EU]

Haemodialysis: The removal of certain elements from the blood by virtue of the difference in the rates of their diffusion through a semipermeable membrane, e.g., by means of a haemodialyzer. [EU]

Haemostasis: The arrest of bleeding, either by the physiological properties of vasoconstriction and coagulation or by surgical means. [EU]

Haplotypes: The genetic constitution of individuals with respect to one member of a pair of allelic genes, or sets of genes that are closely linked and tend to be inherited together such as those of the major histocompatibility complex. [NIH]

Haptens: Small antigenic determinants capable of eliciting an immune response only when coupled to a carrier. Haptens bind to antibodies but by themselves cannot elicit an antibody response. [NIH]

Headache: Pain in the cranial region that may occur as an isolated and benign symptom or as a manifestation of a wide variety of conditions including subarachnoid hemorrhage; craniocerebral trauma; central nervous system infections; intracranial hypertension; and other disorders. In general, recurrent headaches that are not associated with a primary disease process are referred to as headache disorders (e.g., migraine). [NIH]

Health Care Costs: The actual costs of providing services related to the delivery of health care, including the costs of procedures, therapies, and medications. It is differentiated from health expenditures, which refers to the amount of money paid for the services, and from fees, which refers to the amount charged, regardless of cost. [NIH]

Health Expenditures: The amounts spent by individuals, groups, nations, or private or public organizations for total health care and/or its various components. These amounts may or may not be equivalent to the actual costs (health care costs) and may or may not be shared among the patient, insurers, and/or employers. [NIH]

Heart attack: A seizure of weak or abnormal functioning of the heart. [NIH]

Heart failure: Loss of pumping ability by the heart, often accompanied by fatigue, breathlessness, and excess fluid accumulation in body tissues. [NIH]

Hemodiafiltration: The combination of hemodialysis and hemofiltration either

simultaneously or sequentially. Convective transport (hemofiltration) may be better for removal of larger molecular weight substances and diffusive transport (hemodialysis) for smaller molecular weight solutes. [NIH]

Hemodialysis: The use of a machine to clean wastes from the blood after the kidneys have failed. The blood travels through tubes to a dialyzer, which removes wastes and extra fluid. The cleaned blood then flows through another set of tubes back into the body. [NIH]

Hemofiltration: Extracorporeal ultrafiltration technique without hemodialysis for treatment of fluid overload and electrolyte disturbances affecting renal, cardiac, or pulmonary function. [NIH]

Hemoglobin: One of the fractions of glycosylated hemoglobin A1c. Glycosylated hemoglobin is formed when linkages of glucose and related monosaccharides bind to hemoglobin A and its concentration represents the average blood glucose level over the previous several weeks. HbA1c levels are used as a measure of long-term control of plasma glucose (normal, 4 to 6 percent). In controlled diabetes mellitus, the concentration of glycosylated hemoglobin A is within the normal range, but in uncontrolled cases the level may be 3 to 4 times the normal conentration. Generally, complications are substantially lower among patients with Hb levels of 7 percent or less than in patients with HbA1c levels of 9 percent or more. [NIH]

Hemoglobin A: Normal adult human hemoglobin. The globin moiety consists of two alpha and two beta chains. [NIH]

Hemoglobin C: A commonly occurring abnormal hemoglobin in which lysine replaces a glutamic acid residue at the sixth position of the beta chains. It results in reduced plasticity of erythrocytes. [NIH]

Hemolysis: The destruction of erythrocytes by many different causal agents such as antibodies, bacteria, chemicals, temperature, and changes in tonicity. [NIH]

Hemolytic: A disease that affects the blood and blood vessels. It destroys red blood cells, cells that cause the blood to clot, and the lining of blood vessels. HUS is often caused by the Escherichia coli bacterium in contaminated food. People with HUS may develop acute renal failure. [NIH]

Hemorrhage: Bleeding or escape of blood from a vessel. [NIH]

Hemostasis: The process which spontaneously arrests the flow of blood from vessels carrying blood under pressure. It is accomplished by contraction of the vessels, adhesion and aggregation of formed blood elements, and the process of blood or plasma coagulation. [NIH]

Heparin: Heparinic acid. A highly acidic mucopolysaccharide formed of equal parts of sulfated D-glucosamine and D-glucuronic acid with sulfaminic bridges. The molecular weight ranges from six to twenty thousand. Heparin occurs in and is obtained from liver, lung, mast cells, etc., of vertebrates. Its function is unknown, but it is used to prevent blood clotting in vivo and vitro, in the form of many different salts. [NIH]

Hepatic: Refers to the liver. [NIH]

Hepatocellular: Pertaining to or affecting liver cells. [EU]

Hepatocyte: A liver cell. [NIH]

Hepatoma: A liver tumor. [NIH]

Herbicide: A chemical that kills plants. [NIH]

Heredity: 1. The genetic transmission of a particular quality or trait from parent to offspring. 2. The genetic constitution of an individual. [EU]

Heterodimer: Zippered pair of nonidentical proteins. [NIH]

Heterogeneity: The property of one or more samples or populations which implies that they are not identical in respect of some or all of their parameters, e. g. heterogeneity of variance. [NIH]

Heterogenic: Derived from a different source or species. Also called heterogenous. [NIH]

Heterogenous: Derived from a different source or species. Also called heterogenic. [NIH]

Hirsutism: Excess hair in females and children with an adult male pattern of distribution. The concept does not include hypertrichosis, which is localized or generalized excess hair. [NIH]

Histology: The study of tissues and cells under a microscope. [NIH]

Homeostasis: The processes whereby the internal environment of an organism tends to remain balanced and stable. [NIH]

Hormonal: Pertaining to or of the nature of a hormone. [EU]

Hormone: A substance in the body that regulates certain organs. Hormones such as gastrin help in breaking down food. Some hormones come from cells in the stomach and small intestine. [NIH]

Hormone therapy: Treatment of cancer by removing, blocking, or adding hormones. Also called endocrine therapy. [NIH]

Host: Any animal that receives a transplanted graft. [NIH]

Humoral: Of, relating to, proceeding from, or involving a bodily humour - now often used of endocrine factors as opposed to neural or somatic. [EU]

Humour: 1. A normal functioning fluid or semifluid of the body (as the blood, lymph or bile) especially of vertebrates. 2. A secretion that is itself an excitant of activity (as certain hormones). [EU]

Hydrogen: The first chemical element in the periodic table. It has the atomic symbol H, atomic number 1, and atomic weight 1. It exists, under normal conditions, as a colorless, odorless, tasteless, diatomic gas. Hydrogen ions are protons. Besides the common H1 isotope, hydrogen exists as the stable isotope deuterium and the unstable, radioactive isotope tritium. [NIH]

Hydrogen Peroxide: A strong oxidizing agent used in aqueous solution as a ripening agent, bleach, and topical anti-infective. It is relatively unstable and solutions deteriorate over time unless stabilized by the addition of acetanilide or similar organic materials. [NIH]

Hydrolysis: The process of cleaving a chemical compound by the addition of a molecule of water. [NIH]

Hydrophilic: Readily absorbing moisture; hygroscopic; having strongly polar groups that readily interact with water. [EU]

Hydrophobic: Not readily absorbing water, or being adversely affected by water, as a hydrophobic colloid. [EU]

Hydroxylysine: A hydroxylated derivative of the amino acid lysine that is present in certain collagens. [NIH]

Hydroxyproline: A hydroxylated form of the imino acid proline. A deficiency in ascorbic acid can result in impaired hydroxyproline formation. [NIH]

Hyperandrogenism: A state characterized or caused by an excessive secretion of androgens by the adrenal cortex, ovaries, or testes. The clinical significance in males is negligible, so the term is used most commonly with reference to the female. The common manifestations in women are hirsutism and virilism. It is often caused by ovarian disease (particularly the

polycystic ovary syndrome) and by adrenal diseases (particularly adrenal gland hyperfunction). [NIH]

Hyperbilirubinemia: Pathologic process consisting of an abnormal increase in the amount of bilirubin in the circulating blood, which may result in jaundice. [NIH]

Hypercholesterolemia: Abnormally high levels of cholesterol in the blood. [NIH]

Hyperglycaemia: Abnormally increased content of sugar in the blood. [EU]

Hyperglycemia: Abnormally high blood sugar. [NIH]

Hyperlipidemia: An excess of lipids in the blood. [NIH]

Hyperlipoproteinemia: Metabolic disease characterized by elevated plasma cholesterol and/or triglyceride levels. The inherited form is attributed to a single gene mechanism. [NIH]

Hypersecretion: Excessive secretion. [EU]

Hypersensitivity: Altered reactivity to an antigen, which can result in pathologic reactions upon subsequent exposure to that particular antigen. [NIH]

Hypertension: Persistently high arterial blood pressure. Currently accepted threshold levels are 140 mm Hg systolic and 90 mm Hg diastolic pressure. [NIH]

Hyperthermia: A type of treatment in which body tissue is exposed to high temperatures to damage and kill cancer cells or to make cancer cells more sensitive to the effects of radiation and certain anticancer drugs. [NIH]

Hypertrichosis: Localized or generalized excess hair. The concept does not include hirsutism, which is excess hair in females and children with an adult male pattern of distribution. [NIH]

Hypertriglyceridemia: Condition of elevated triglyceride concentration in the blood; an inherited form occurs in familial hyperlipoproteinemia IIb and hyperlipoproteinemia type IV. It has been linked to higher risk of heart disease and arteriosclerosis. [NIH]

Hyperventilation: A pulmonary ventilation rate faster than is metabolically necessary for the exchange of gases. It is the result of an increased frequency of breathing, an increased tidal volume, or a combination of both. It causes an excess intake of oxygen and the blowing off of carbon dioxide. [NIH]

Hypoglycemia: Abnormally low blood sugar [NIH]

Hypoglycemic: An orally active drug that produces a fall in blood glucose concentration. [NIH]

Hypoglycemic Agents: Agents which lower the blood glucose level. [NIH]

Hypolipidemic: A drug that lowers abnormally high plasma concentrations of cholesterol or triglycerides or both. [NIH]

Hypotension: Abnormally low blood pressure. [NIH]

Hypothalamic: Of or involving the hypothalamus. [EU]

Hypothalamus: Ventral part of the diencephalon extending from the region of the optic chiasm to the caudal border of the mammillary bodies and forming the inferior and lateral walls of the third ventricle. [NIH]

Hypoxia: Reduction of oxygen supply to tissue below physiological levels despite adequate perfusion of the tissue by blood. [EU]

Id: The part of the personality structure which harbors the unconscious instinctive desires and strivings of the individual. [NIH]

Immune response: The activity of the immune system against foreign substances (antigens). [NIH]

Immune system: The organs, cells, and molecules responsible for the recognition and disposal of foreign ("non-self") material which enters the body. [NIH]

Immunization: Deliberate stimulation of the host's immune response. Active immunization involves administration of antigens or immunologic adjuvants. Passive immunization involves administration of immune sera or lymphocytes or their extracts (e.g., transfer factor, immune RNA) or transplantation of immunocompetent cell producing tissue (thymus or bone marrow). [NIH]

Immunoblotting: Immunologic methods for isolating and quantitatively measuring immunoreactive substances. When used with immune reagents such as monoclonal antibodies, the process is known generically as western blot analysis (blotting, western). [NIH]

Immunodeficiency: The decreased ability of the body to fight infection and disease. [NIH]

Immunohistochemistry: Histochemical localization of immunoreactive substances using labeled antibodies as reagents. [NIH]

Immunologic: The ability of the antibody-forming system to recall a previous experience with an antigen and to respond to a second exposure with the prompt production of large amounts of antibody. [NIH]

Immunology: The study of the body's immune system. [NIH]

Immunosuppressive: Describes the ability to lower immune system responses. [NIH]

Immunosuppressive therapy: Therapy used to decrease the body's immune response, such as drugs given to prevent transplant rejection. [NIH]

Immunotherapy: Manipulation of the host's immune system in treatment of disease. It includes both active and passive immunization as well as immunosuppressive therapy to prevent graft rejection. [NIH]

Impairment: In the context of health experience, an impairment is any loss or abnormality of psychological, physiological, or anatomical structure or function. [NIH]

Impotence: The inability to perform sexual intercourse. [NIH]

In situ: In the natural or normal place; confined to the site of origin without invasion of neighbouring tissues. [EU]

In Situ Hybridization: A technique that localizes specific nucleic acid sequences within intact chromosomes, eukaryotic cells, or bacterial cells through the use of specific nucleic acid-labeled probes. [NIH]

In vitro: In the laboratory (outside the body). The opposite of in vivo (in the body). [NIH]

In vivo: In the body. The opposite of in vitro (outside the body or in the laboratory). [NIH]

Incision: A cut made in the body during surgery. [NIH]

Incontinence: Inability to control the flow of urine from the bladder (urinary incontinence) or the escape of stool from the rectum (fecal incontinence). [NIH]

Incubated: Grown in the laboratory under controlled conditions. (For instance, white blood cells can be grown in special conditions so that they attack specific cancer cells when returned to the body.) [NIH]

Incubation: The development of an infectious disease from the entrance of the pathogen to the appearance of clinical symptoms. [EU]

Indicative: That indicates; that points out more or less exactly; that reveals fairly clearly. [EU]

Induction: The act or process of inducing or causing to occur, especially the production of a specific morphogenetic effect in the developing embryo through the influence of evocators

or organizers, or the production of anaesthesia or unconsciousness by use of appropriate agents. [EU]

Infant, Newborn: An infant during the first month after birth. [NIH]

Infantile: Pertaining to an infant or to infancy. [EU]

Infarction: A pathological process consisting of a sudden insufficient blood supply to an area, which results in necrosis of that area. It is usually caused by a thrombus, an embolus, or a vascular torsion. [NIH]

Infection: 1. Invasion and multiplication of microorganisms in body tissues, which may be clinically unapparent or result in local cellular injury due to competitive metabolism, toxins, intracellular replication, or antigen-antibody response. The infection may remain localized, subclinical, and temporary if the body's defensive mechanisms are effective. A local infection may persist and spread by extension to become an acute, subacute, or chronic clinical infection or disease state. A local infection may also become systemic when the microorganisms gain access to the lymphatic or vascular system. 2. An infectious disease. [EU]

Infertility: The diminished or absent ability to conceive or produce an offspring while sterility is the complete inability to conceive or produce an offspring. [NIH]

Inflammation: A pathological process characterized by injury or destruction of tissues caused by a variety of cytologic and chemical reactions. It is usually manifested by typical signs of pain, heat, redness, swelling, and loss of function. [NIH]

Inflammatory bowel disease: A general term that refers to the inflammation of the colon and rectum. Inflammatory bowel disease includes ulcerative colitis and Crohn's disease. [NIH]

Infusion: A method of putting fluids, including drugs, into the bloodstream. Also called intravenous infusion. [NIH]

Ingestion: Taking into the body by mouth [NIH]

Initiation: Mutation induced by a chemical reactive substance causing cell changes; being a step in a carcinogenic process. [NIH]

Inlay: In dentistry, a filling first made to correspond with the form of a dental cavity and then cemented into the cavity. [NIH]

Inositol: An isomer of glucose that has traditionally been considered to be a B vitamin although it has an uncertain status as a vitamin and a deficiency syndrome has not been identified in man. (From Martindale, The Extra Pharmacopoeia, 30th ed, p1379) Inositol phospholipids are important in signal transduction. [NIH]

Inotropic: Affecting the force or energy of muscular contractions. [EU]

Insecticides: Pesticides designed to control insects that are harmful to man. The insects may be directly harmful, as those acting as disease vectors, or indirectly harmful, as destroyers of crops, food products, or textile fabrics. [NIH]

Insight: The capacity to understand one's own motives, to be aware of one's own psychodynamics, to appreciate the meaning of symbolic behavior. [NIH]

Insomnia: Difficulty in going to sleep or getting enough sleep. [NIH]

Insulin: A protein hormone secreted by beta cells of the pancreas. Insulin plays a major role in the regulation of glucose metabolism, generally promoting the cellular utilization of glucose. It is also an important regulator of protein and lipid metabolism. Insulin is used as a drug to control insulin-dependent diabetes mellitus. [NIH]

Insulin-dependent diabetes mellitus: A disease characterized by high levels of blood

glucose resulting from defects in insulin secretion, insulin action, or both. Autoimmune, genetic, and environmental factors are involved in the development of type I diabetes. [NIH]

Insulin-like: Muscular growth factor. [NIH]

Integrins: A family of transmembrane glycoproteins consisting of noncovalent heterodimers. They interact with a wide variety of ligands including extracellular matrix glycoproteins, complement, and other cells, while their intracellular domains interact with the cytoskeleton. The integrins consist of at least three identified families: the cytoadhesin receptors, the leukocyte adhesion receptors, and the very-late-antigen receptors. Each family contains a common beta-subunit combined with one or more distinct alpha-subunits. These receptors participate in cell-matrix and cell-cell adhesion in many physiologically important processes, including embryological development, hemostasis, thrombosis, wound healing, immune and nonimmune defense mechanisms, and oncogenic transformation. [NIH]

Intermittent: Occurring at separated intervals; having periods of cessation of activity. [EU]

Internal Medicine: A medical specialty concerned with the diagnosis and treatment of diseases of the internal organ systems of adults. [NIH]

Interstitial: Pertaining to or situated between parts or in the interspaces of a tissue. [EU]

Intestinal: Having to do with the intestines. [NIH]

Intestine: A long, tube-shaped organ in the abdomen that completes the process of digestion. There is both a large intestine and a small intestine. Also called the bowel. [NIH]

Intoxication: Poisoning, the state of being poisoned. [EU]

Intracellular: Inside a cell. [NIH]

Intravascular: Within a vessel or vessels. [EU]

Intravenous: IV. Into a vein. [NIH]

Intrinsic: Situated entirely within or pertaining exclusively to a part. [EU]

Invasive: 1. Having the quality of invasiveness. 2. Involving puncture or incision of the skin or insertion of an instrument or foreign material into the body; said of diagnostic techniques. [EU]

Invertebrates: Animals that have no spinal column. [NIH]

Involuntary: Reaction occurring without intention or volition. [NIH]

Iodine: A nonmetallic element of the halogen group that is represented by the atomic symbol I, atomic number 53, and atomic weight of 126.90. It is a nutritionally essential element, especially important in thyroid hormone synthesis. In solution, it has anti-infective properties and is used topically. [NIH]

Ions: An atom or group of atoms that have a positive or negative electric charge due to a gain (negative charge) or loss (positive charge) of one or more electrons. Atoms with a positive charge are known as cations; those with a negative charge are anions. [NIH]

Irritable Bowel Syndrome: A disorder that comes and goes. Nerves that control the muscles in the GI tract are too active. The GI tract becomes sensitive to food, stool, gas, and stress. Causes abdominal pain, bloating, and constipation or diarrhea. Also called spastic colon or mucous colitis. [NIH]

Islet: Cell producing insulin in pancreas. [NIH]

Isozymes: The multiple forms of a single enzyme. [NIH]

Jaundice: A clinical manifestation of hyperbilirubinemia, consisting of deposition of bile pigments in the skin, resulting in a yellowish staining of the skin and mucous membranes. [NIH]

Kb: A measure of the length of DNA fragments, 1 Kb = 1000 base pairs. The largest DNA fragments are up to 50 kilobases long. [NIH]

Ketone Bodies: Chemicals that the body makes when there is not enough insulin in the blood and it must break down fat for its energy. Ketone bodies can poison and even kill body cells. When the body does not have the help of insulin, the ketones build up in the blood and then "spill" over into the urine so that the body can get rid of them. The body can also rid itself of one type of ketone, called acetone, through the lungs. This gives the breath a fruity odor. Ketones that build up in the body for a long time lead to serious illness and coma. [NIH]

Ketosis: A condition of having ketone bodies build up in body tissues and fluids. The signs of ketosis are nausea, vomiting, and stomach pain. Ketosis can lead to ketoacidosis. [NIH]

Kidney Disease: Any one of several chronic conditions that are caused by damage to the cells of the kidney. People who have had diabetes for a long time may have kidney damage. Also called nephropathy. [NIH]

Kinetic: Pertaining to or producing motion. [EU]

Lactation: The period of the secretion of milk. [EU]

Laminin: Large, noncollagenous glycoprotein with antigenic properties. It is localized in the basement membrane lamina lucida and functions to bind epithelial cells to the basement membrane. Evidence suggests that the protein plays a role in tumor invasion. [NIH]

Large Intestine: The part of the intestine that goes from the cecum to the rectum. The large intestine absorbs water from stool and changes it from a liquid to a solid form. The large intestine is 5 feet long and includes the appendix, cecum, colon, and rectum. Also called colon. [NIH]

Latent: Phoria which occurs at one distance or another and which usually has no troublesome effect. [NIH]

Lateral Ventricles: Cavity in each of the cerebral hemispheres derived from the cavity of the embryonic neural tube. They are separated from each other by the septum pellucidum, and each communicates with the third ventricle by the foramen of Monro, through which also the choroid plexuses of the lateral ventricles become continuous with that of the third ventricle. [NIH]

Laxative: An agent that acts to promote evacuation of the bowel; a cathartic or purgative. [EU]

Lens: The transparent, double convex (outward curve on both sides) structure suspended between the aqueous and vitreous; helps to focus light on the retina. [NIH]

Leprosy: A chronic granulomatous infection caused by Mycobacterium leprae. The granulomatous lesions are manifested in the skin, the mucous membranes, and the peripheral nerves. Two polar or principal types are lepromatous and tuberculoid. [NIH]

Leptin: A 16-kD peptide hormone secreted from white adipocytes and implicated in the regulation of food intake and energy balance. Leptin provides the key afferent signal from fat cells in the feedback system that controls body fat stores. [NIH]

Lesion: An area of abnormal tissue change. [NIH]

Leukocytes: White blood cells. These include granular leukocytes (basophils, eosinophils, and neutrophils) as well as non-granular leukocytes (lymphocytes and monocytes). [NIH]

Leuprolide: A potent and long acting analog of naturally occurring gonadotropin-releasing hormone (gonadorelin). Its action is similar to gonadorelin, which regulates the synthesis and release of pituitary gonadotropins. [NIH]

Libido: The psychic drive or energy associated with sexual instinct in the broad sense (pleasure and love-object seeking). It may also connote the psychic energy associated with instincts in general that motivate behavior. [NIH]

Library Services: Services offered to the library user. They include reference and circulation. [NIH]

Life cycle: The successive stages through which an organism passes from fertilized ovum or spore to the fertilized ovum or spore of the next generation. [NIH]

Ligaments: Shiny, flexible bands of fibrous tissue connecting together articular extremities of bones. They are pliant, tough, and inextensile. [NIH]

Ligands: A RNA simulation method developed by the MIT. [NIH]

Linkage: The tendency of two or more genes in the same chromosome to remain together from one generation to the next more frequently than expected according to the law of independent assortment. [NIH]

Lipase: An enzyme of the hydrolase class that catalyzes the reaction of triacylglycerol and water to yield diacylglycerol and a fatty acid anion. It is produced by glands on the tongue and by the pancreas and initiates the digestion of dietary fats. (From Dorland, 27th ed) EC 3.1.1.3. [NIH]

Lipid: Fat. [NIH]

Lipid A: Lipid A is the biologically active component of lipopolysaccharides. It shows strong endotoxic activity and exhibits immunogenic properties. [NIH]

Lipid Peroxidation: Peroxidase catalyzed oxidation of lipids using hydrogen peroxide as an electron acceptor. [NIH]

Lipodystrophy: A collection of rare conditions resulting from defective fat metabolism and characterized by atrophy of the subcutaneous fat. They include total, congenital or acquired, partial, abdominal infantile, and localized lipodystrophy. [NIH]

Lipolysis: The hydrolysis of lipids. [NIH]

Lipophilic: Having an affinity for fat; pertaining to or characterized by lipophilia. [EU]

Lipoprotein: Any of the lipid-protein complexes in which lipids are transported in the blood; lipoprotein particles consist of a spherical hydrophobic core of triglycerides or cholesterol esters surrounded by an amphipathic monolayer of phospholipids, cholesterol, and apolipoproteins; the four principal classes are high-density, low-density, and very-low-density lipoproteins and chylomicrons. [EU]

Lipoprotein Lipase: An enzyme of the hydrolase class that catalyzes the reaction of triacylglycerol and water to yield diacylglycerol and a fatty acid anion. The enzyme hydrolyzes triacylglycerols in chylomicrons, very-low-density lipoproteins, low-density lipoproteins, and diacylglycerols. It occurs on capillary endothelial surfaces, especially in mammary, muscle, and adipose tissue. Genetic deficiency of the enzyme causes familial hyperlipoproteinemia Type I. (Dorland, 27th ed) EC 3.1.1.34. [NIH]

Liver: A large, glandular organ located in the upper abdomen. The liver cleanses the blood and aids in digestion by secreting bile. [NIH]

Localization: The process of determining or marking the location or site of a lesion or disease. May also refer to the process of keeping a lesion or disease in a specific location or site. [NIH]

Localized: Cancer which has not metastasized yet. [NIH]

Long-Term Care: Care over an extended period, usually for a chronic condition or disability, requiring periodic, intermittent, or continuous care. [NIH]

Loop: A wire usually of platinum bent at one end into a small loop (usually 4 mm inside diameter) and used in transferring microorganisms. [NIH]

Lovastatin: A fungal metabolite isolated from cultures of Aspergillus terreus. The compound is a potent anticholesteremic agent. It inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase (hydroxymethylglutaryl CoA reductases), which is the rate-limiting enzyme in cholesterol biosynthesis. It also stimulates the production of low-density lipoprotein receptors in the liver. [NIH]

Low-density lipoprotein: Lipoprotein that contains most of the cholesterol in the blood. LDL carries cholesterol to the tissues of the body, including the arteries. A high level of LDL increases the risk of heart disease. LDL typically contains 60 to 70 percent of the total serum cholesterol and both are directly correlated with CHD risk. [NIH]

Loxapine: An antipsychotic agent used in schizophrenia. [NIH]

Lubricants: Oily or slippery substances. [NIH]

Lucida: An instrument, invented by Wollaton, consisting essentially of a prism or a mirror through which an object can be viewed so as to appear on a plane surface seen in direct view and on which the outline of the object may be traced. [NIH]

Luteal Phase: The period of the menstrual cycle that begins with ovulation and ends with menstruation. [NIH]

Lymph: The almost colorless fluid that travels through the lymphatic system and carries cells that help fight infection and disease. [NIH]

Lymphatic: The tissues and organs, including the bone marrow, spleen, thymus, and lymph nodes, that produce and store cells that fight infection and disease. [NIH]

Lymphocyte: A white blood cell. Lymphocytes have a number of roles in the immune system, including the production of antibodies and other substances that fight infection and diseases. [NIH]

Lymphoid: Referring to lymphocytes, a type of white blood cell. Also refers to tissue in which lymphocytes develop. [NIH]

Lysine: An essential amino acid. It is often added to animal feed. [NIH]

Magnetic Resonance Imaging: Non-invasive method of demonstrating internal anatomy based on the principle that atomic nuclei in a strong magnetic field absorb pulses of radiofrequency energy and emit them as radiowaves which can be reconstructed into computerized images. The concept includes proton spin tomographic techniques. [NIH]

Major Histocompatibility Complex: The genetic region which contains the loci of genes which determine the structure of the serologically defined (SD) and lymphocyte-defined (LD) transplantation antigens, genes which control the structure of the immune response-associated (Ia) antigens, the immune response (Ir) genes which control the ability of an animal to respond immunologically to antigenic stimuli, and genes which determine the structure and/or level of the first four components of complement. [NIH]

Malabsorption: Impaired intestinal absorption of nutrients. [EU]

Malignant: Cancerous; a growth with a tendency to invade and destroy nearby tissue and spread to other parts of the body. [NIH]

Malnutrition: A condition caused by not eating enough food or not eating a balanced diet. [NIH]

Mammary: Pertaining to the mamma, or breast. [EU]

Manic: Affected with mania. [EU]

Meat: The edible portions of any animal used for food including domestic mammals (the

major ones being cattle, swine, and sheep) along with poultry, fish, shellfish, and game. [NIH]

Medial: Lying near the midsaggital plane of the body; opposed to lateral. [NIH]

Mediate: Indirect; accomplished by the aid of an intervening medium. [EU]

Mediator: An object or substance by which something is mediated, such as (1) a structure of the nervous system that transmits impulses eliciting a specific response; (2) a chemical substance (transmitter substance) that induces activity in an excitable tissue, such as nerve or muscle; or (3) a substance released from cells as the result of the interaction of antigen with antibody or by the action of antigen with a sensitized lymphocyte. [EU]

Medical Records: Recording of pertinent information concerning patient's illness or illnesses. [NIH]

Medical Staff: Professional medical personnel who provide care to patients in an organized facility, institution or agency. [NIH]

Medicament: A medicinal substance or agent. [EU]

MEDLINE: An online database of MEDLARS, the computerized bibliographic Medical Literature Analysis and Retrieval System of the National Library of Medicine. [NIH]

Melanin: The substance that gives the skin its color. [NIH]

Membrane: A very thin layer of tissue that covers a surface. [NIH]

Memory: Complex mental function having four distinct phases: (1) memorizing or learning, (2) retention, (3) recall, and (4) recognition. Clinically, it is usually subdivided into immediate, recent, and remote memory. [NIH]

Menstrual Cycle: The period of the regularly recurring physiologic changes in the endometrium occurring during the reproductive period in human females and some primates and culminating in partial sloughing of the endometrium (menstruation). [NIH]

Menstruation: The normal physiologic discharge through the vagina of blood and mucosal tissues from the nonpregnant uterus. [NIH]

Mental Disorders: Psychiatric illness or diseases manifested by breakdowns in the adaptational process expressed primarily as abnormalities of thought, feeling, and behavior producing either distress or impairment of function. [NIH]

Mental Health: The state wherein the person is well adjusted. [NIH]

Mesenteric: Pertaining to the mesentery : a membranous fold attaching various organs to the body wall. [EU]

Meta-Analysis: A quantitative method of combining the results of independent studies (usually drawn from the published literature) and synthesizing summaries and conclusions which may be used to evaluate therapeutic effectiveness, plan new studies, etc., with application chiefly in the areas of research and medicine. [NIH]

Metabolic Clearance Rate: Volume of biological fluid completely cleared of drug metabolites as measured in unit time. Elimination occurs as a result of metabolic processes in the kidney, liver, saliva, sweat, intestine, heart, brain, or other site. [NIH]

Metabolic disorder: A condition in which normal metabolic processes are disrupted, usually because of a missing enzyme. [NIH]

Metabolite: Any substance produced by metabolism or by a metabolic process. [EU]

Methanol: A colorless, flammable liquid used in the manufacture of formaldehyde and acetic acid, in chemical synthesis, antifreeze, and as a solvent. Ingestion of methanol is toxic and may cause blindness. [NIH]

Methylcellulose: Methylester of cellulose. Methylcellulose is used as an emulsifying and suspending agent in cosmetics, pharmaceutics and the chemical industry. It is used therapeutically as a bulk laxative. [NIH]

MI: Myocardial infarction. Gross necrosis of the myocardium as a result of interruption of the blood supply to the area; it is almost always caused by atherosclerosis of the coronary arteries, upon which coronary thrombosis is usually superimposed. [NIH]

Microbe: An organism which cannot be observed with the naked eye; e. g. unicellular animals, lower algae, lower fungi, bacteria. [NIH]

Microorganism: An organism that can be seen only through a microscope. Microorganisms include bacteria, protozoa, algae, and fungi. Although viruses are not considered living organisms, they are sometimes classified as microorganisms. [NIH]

Micro-organism: An organism which cannot be observed with the naked eye; e. g. unicellular animals, lower algae, lower fungi, bacteria. [NIH]

Microscopy: The application of microscope magnification to the study of materials that cannot be properly seen by the unaided eye. [NIH]

Milliliter: A measure of volume for a liquid. A milliliter is approximately 950-times smaller than a quart and 30-times smaller than a fluid ounce. A milliliter of liquid and a cubic centimeter (cc) of liquid are the same. [NIH]

Minority Groups: A subgroup having special characteristics within a larger group, often bound together by special ties which distinguish it from the larger group. [NIH]

Mitochondrial Swelling: Increase in volume of mitochondria due to an influx of fluid; it occurs in hypotonic solutions due to osmotic pressure and in isotonic solutions as a result of altered permeability of the membranes of respiring mitochondria. [NIH]

Mitosis: A method of indirect cell division by means of which the two daughter nuclei normally receive identical complements of the number of chromosomes of the somatic cells of the species. [NIH]

Mobility: Capability of movement, of being moved, or of flowing freely. [EU]

Mobilization: The process of making a fixed part or stored substance mobile, as by separating a part from surrounding structures to make it accessible for an operative procedure or by causing release into the circulation for body use of a substance stored in the body. [EU]

Modeling: A treatment procedure whereby the therapist presents the target behavior which the learner is to imitate and make part of his repertoire. [NIH]

Modification: A change in an organism, or in a process in an organism, that is acquired from its own activity or environment. [NIH]

Molecular: Of, pertaining to, or composed of molecules : a very small mass of matter. [EU]

Molecular Structure: The location of the atoms, groups or ions relative to one another in a molecule, as well as the number, type and location of covalent bonds. [NIH]

Molecule: A chemical made up of two or more atoms. The atoms in a molecule can be the same (an oxygen molecule has two oxygen atoms) or different (a water molecule has two hydrogen atoms and one oxygen atom). Biological molecules, such as proteins and DNA, can be made up of many thousands of atoms. [NIH]

Monitor: An apparatus which automatically records such physiological signs as respiration, pulse, and blood pressure in an anesthetized patient or one undergoing surgical or other procedures. [NIH]

Monoclonal: An antibody produced by culturing a single type of cell. It therefore consists of

a single species of immunoglobulin molecules. [NIH]

Monoclonal antibodies: Laboratory-produced substances that can locate and bind to cancer cells wherever they are in the body. Many monoclonal antibodies are used in cancer detection or therapy; each one recognizes a different protein on certain cancer cells. Monoclonal antibodies can be used alone, or they can be used to deliver drugs, toxins, or radioactive material directly to a tumor. [NIH]

Mononuclear: A cell with one nucleus. [NIH]

Monotherapy: A therapy which uses only one drug. [EU]

Monounsaturated fat: An unsaturated fat that is found primarily in plant foods, including olive and canola oils. [NIH]

Morphology: The science of the form and structure of organisms (plants, animals, and other forms of life). [NIH]

Motion Sickness: Sickness caused by motion, as sea sickness, train sickness, car sickness, and air sickness. [NIH]

Multicenter study: A clinical trial that is carried out at more than one medical institution. [NIH]

Myelin: The fatty substance that covers and protects nerves. [NIH]

Myocardial infarction: Gross necrosis of the myocardium as a result of interruption of the blood supply to the area; it is almost always caused by atherosclerosis of the coronary arteries, upon which coronary thrombosis is usually superimposed. [NIH]

Myocardial Ischemia: A disorder of cardiac function caused by insufficient blood flow to the muscle tissue of the heart. The decreased blood flow may be due to narrowing of the coronary arteries (coronary arteriosclerosis), to obstruction by a thrombus (coronary thrombosis), or less commonly, to diffuse narrowing of arterioles and other small vessels within the heart. Severe interruption of the blood supply to the myocardial tissue may result in necrosis of cardiac muscle (myocardial infarction). [NIH]

Myocardium: The muscle tissue of the heart composed of striated, involuntary muscle known as cardiac muscle. [NIH]

Myogenic Regulatory Factors: A family of muscle-specific transcription factors which bind to DNA in control regions and thus regulate myogenesis. All members of this family contain a conserved helix-loop-helix motif which is homologous to the myc family proteins. These factors are only found in skeletal muscle. Members include the myoD protein, myogenin, myf-5, and myf-6 (also called MRF4 or herculin). [NIH]

Myogenin: A myogenic regulatory factor that controls myogenesis. Myogenin is induced during differentiation of every skeletal muscle cell line that has been investigated, in contrast to the other myogenic regulatory factors that only appear in certain cell types. [NIH]

Nalidixic Acid: Synthetic antimicrobial agent used in urinary tract infections. It is active against gram-negative bacteria but has little activity against gram-positive organisms or Pseudomonas. [NIH]

Narcotic: 1. Pertaining to or producing narcosis. 2. An agent that produces insensibility or stupor, applied especially to the opioids, i.e. to any natural or synthetic drug that has morphine-like actions. [EU]

Nausea: An unpleasant sensation in the stomach usually accompanied by the urge to vomit. Common causes are early pregnancy, sea and motion sickness, emotional stress, intense pain, food poisoning, and various enteroviruses. [NIH]

NCI: National Cancer Institute. NCI, part of the National Institutes of Health of the United

States Department of Health and Human Services, is the federal government's principal agency for cancer research. NCI conducts, coordinates, and funds cancer research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer. Access the NCI Web site at http://cancer.gov. [NIH]

Necrosis: A pathological process caused by the progressive degradative action of enzymes that is generally associated with severe cellular trauma. It is characterized by mitochondrial swelling, nuclear flocculation, uncontrolled cell lysis, and ultimately cell death. [NIH]

Need: A state of tension or dissatisfaction felt by an individual that impels him to action toward a goal he believes will satisfy the impulse. [NIH]

Neonatal: Pertaining to the first four weeks after birth. [EU]

Neoplasm: A new growth of benign or malignant tissue. [NIH]

Nephron: A tiny part of the kidneys. Each kidney is made up of about 1 million nephrons, which are the working units of the kidneys, removing wastes and extra fluids from the blood. [NIH]

Nephropathy: Disease of the kidneys. [EU]

Nerve: A cordlike structure of nervous tissue that connects parts of the nervous system with other tissues of the body and conveys nervous impulses to, or away from, these tissues. [NIH]

Nervous System: The entire nerve apparatus composed of the brain, spinal cord, nerves and ganglia. [NIH]

Neural: 1. Pertaining to a nerve or to the nerves. 2. Situated in the region of the spinal axis, as the neutral arch. [EU]

Neuroendocrine: Having to do with the interactions between the nervous system and the endocrine system. Describes certain cells that release hormones into the blood in response to stimulation of the nervous system. [NIH]

Neurologic: Having to do with nerves or the nervous system. [NIH]

Neuropathy: A problem in any part of the nervous system except the brain and spinal cord. Neuropathies can be caused by infection, toxic substances, or disease. [NIH]

Neurotoxic: Poisonous or destructive to nerve tissue. [EU]

Neurotoxicity: The tendency of some treatments to cause damage to the nervous system. [NIH]

Neurotransmitters: Endogenous signaling molecules that alter the behavior of neurons or effector cells. Neurotransmitter is used here in its most general sense, including not only messengers that act directly to regulate ion channels, but also those that act through second messenger systems, and those that act at a distance from their site of release. Included are neuromodulators, neuroregulators, neuromediators, and neurohumors, whether or not acting at synapses. [NIH]

Niacin: Water-soluble vitamin of the B complex occurring in various animal and plant tissues. Required by the body for the formation of coenzymes NAD and NADP. Has pellagra-curative, vasodilating, and antilipemic properties. [NIH]

Nitric Oxide: A free radical gas produced endogenously by a variety of mammalian cells. It is synthesized from arginine by a complex reaction, catalyzed by nitric oxide synthase. Nitric oxide is endothelium-derived relaxing factor. It is released by the vascular endothelium and mediates the relaxation induced by some vasodilators such as acetylcholine and bradykinin. It also inhibits platelet aggregation, induces disaggregation of aggregated platelets, and inhibits platelet adhesion to the vascular endothelium. Nitric oxide activates cytosolic guanylate cyclase and thus elevates intracellular levels of cyclic GMP. [NIH]

Nitrogen: An element with the atomic symbol N, atomic number 7, and atomic weight 14. Nitrogen exists as a diatomic gas and makes up about 78% of the earth's atmosphere by volume. It is a constituent of proteins and nucleic acids and found in all living cells. [NIH]

Norepinephrine: Precursor of epinephrine that is secreted by the adrenal medulla and is a widespread central and autonomic neurotransmitter. Norepinephrine is the principal transmitter of most postganglionic sympathetic fibers and of the diffuse projection system in the brain arising from the locus ceruleus. It is also found in plants and is used pharmacologically as a sympathomimetic. [NIH]

Normotensive: 1. Characterized by normal tone, tension, or pressure, as by normal blood pressure. 2. A person with normal blood pressure. [EU]

Nuclear: A test of the structure, blood flow, and function of the kidneys. The doctor injects a mildly radioactive solution into an arm vein and uses x-rays to monitor its progress through the kidneys. [NIH]

Nuclei: A body of specialized protoplasm found in nearly all cells and containing the chromosomes. [NIH]

Nucleic acid: Either of two types of macromolecule (DNA or RNA) formed by polymerization of nucleotides. Nucleic acids are found in all living cells and contain the information (genetic code) for the transfer of genetic information from one generation to the next. [NIH]

Nucleus: A body of specialized protoplasm found in nearly all cells and containing the chromosomes. [NIH]

Observational study: An epidemiologic study that does not involve any intervention, experimental or otherwise. Such a study may be one in which nature is allowed to take its course, with changes in one characteristic being studied in relation to changes in other characteristics. Analytical epidemiologic methods, such as case-control and cohort study designs, are properly called observational epidemiology because the investigator is observing without intervention other than to record, classify, count, and statistically analyze results. [NIH]

Octreotide: A potent, long-acting somatostatin octapeptide analog which has a wide range of physiological actions. It inhibits growth hormone secretion, is effective in the treatment of hormone-secreting tumors from various organs, and has beneficial effects in the management of many pathological states including diabetes mellitus, orthostatic hypertension, hyperinsulinism, hypergastrinemia, and small bowel fistula. [NIH]

Ocular: 1. Of, pertaining to, or affecting the eye. 2. Eyepiece. [EU]

Odour: A volatile emanation that is perceived by the sense of smell. [EU]

Ointments: Semisolid preparations used topically for protective emollient effects or as a vehicle for local administration of medications. Ointment bases are various mixtures of fats, waxes, animal and plant oils and solid and liquid hydrocarbons. [NIH]

Oleic Acids: A group of fatty acids that contain 16 carbon atoms and a double bond at the omega 9 carbon. [NIH]

Oligomenorrhea: Abnormally infrequent menstruation. [NIH]

Oncogenic: Chemical, viral, radioactive or other agent that causes cancer; carcinogenic. [NIH]

Oocytes: Female germ cells in stages between the prophase of the first maturation division and the completion of the second maturation division. [NIH]

Opacity: Degree of density (area most dense taken for reading). [NIH]

Optic Disk: The portion of the optic nerve seen in the fundus with the ophthalmoscope. It is

formed by the meeting of all the retinal ganglion cell axons as they enter the optic nerve. [NIH]

Optic Nerve: The 2nd cranial nerve. The optic nerve conveys visual information from the retina to the brain. The nerve carries the axons of the retinal ganglion cells which sort at the optic chiasm and continue via the optic tracts to the brain. The largest projection is to the lateral geniculate nuclei; other important targets include the superior colliculi and the suprachiasmatic nuclei. Though known as the second cranial nerve, it is considered part of the central nervous system. [NIH]

Orlistat: A lipase inhibitor used for weight loss. Lipase is an enzyme found in the bowel that assists in lipid absorption by the body. Orlistat blocks this enzyme, reducing the amount of fat the body absorbs by about 30 percent. It is known colloquially as a "fat blocker." Because more oily fat is left in the bowel to be excreted, Orlistat can cause an oily anal leakage and fecal incontinence. Orlistat may not be suitable for people with bowel conditions such as irritable bowel syndrome or Crohn's disease. [NIH]

Orthostatic: Pertaining to or caused by standing erect. [EU]

Osmotic: Pertaining to or of the nature of osmosis (= the passage of pure solvent from a solution of lesser to one of greater solute concentration when the two solutions are separated by a membrane which selectively prevents the passage of solute molecules, but is permeable to the solvent). [EU]

Outpatient: A patient who is not an inmate of a hospital but receives diagnosis or treatment in a clinic or dispensary connected with the hospital. [NIH]

Ovarian Follicle: Spheroidal cell aggregation in the ovary containing an ovum. It consists of an external fibro-vascular coat, an internal coat of nucleated cells, and a transparent, albuminous fluid in which the ovum is suspended. [NIH]

Ovarian Hyperstimulation Syndrome: Syndrome composed of a combination of ovarian enlargement and an acute fluid shift out of the intravascular space. The enlargement is caused by ovarian cyst formation and the fluid shift may result in ascites, hydrothorax, or generalized edema. The syndrome is most usually seen as a complication of ovulation induction, a treatment for infertility. [NIH]

Ovaries: The pair of female reproductive glands in which the ova, or eggs, are formed. The ovaries are located in the pelvis, one on each side of the uterus. [NIH]

Ovary: Either of the paired glands in the female that produce the female germ cells and secrete some of the female sex hormones. [NIH]

Overdose: An accidental or deliberate dose of a medication or street drug that is in excess of what is normally used. [NIH]

Overweight: An excess of body weight but not necessarily body fat; a body mass index of 25 to 29.9 kg/m2. [NIH]

Ovulation: The discharge of a secondary oocyte from a ruptured graafian follicle. [NIH]

Ovulation Induction: Techniques for the artifical induction of ovulation. [NIH]

Ovum: A female germ cell extruded from the ovary at ovulation. [NIH]

Oxidation: The act of oxidizing or state of being oxidized. Chemically it consists in the increase of positive charges on an atom or the loss of negative charges. Most biological oxidations are accomplished by the removal of a pair of hydrogen atoms (dehydrogenation) from a molecule. Such oxidations must be accompanied by reduction of an acceptor molecule. Univalent o. indicates loss of one electron; divalent o., the loss of two electrons. [EU]

Oxidative Stress: A disturbance in the prooxidant-antioxidant balance in favor of the

former, leading to potential damage. Indicators of oxidative stress include damaged DNA bases, protein oxidation products, and lipid peroxidation products (Sies, Oxidative Stress, 1991, pxv-xvi). [NIH]

Palliative: 1. Affording relief, but not cure. 2. An alleviating medicine. [EU]

Pancreas: A mixed exocrine and endocrine gland situated transversely across the posterior abdominal wall in the epigastric and hypochondriac regions. The endocrine portion is comprised of the Islets of Langerhans, while the exocrine portion is a compound acinar gland that secretes digestive enzymes. [NIH]

Pancreatic: Having to do with the pancreas. [NIH]

Pathogen: Any disease-producing microorganism. [EU]

Pathogenesis: The cellular events and reactions that occur in the development of disease. [NIH]

Pathologic: 1. Indicative of or caused by a morbid condition. 2. Pertaining to pathology (= branch of medicine that treats the essential nature of the disease, especially the structural and functional changes in tissues and organs of the body caused by the disease). [EU]

Pathologic Processes: The abnormal mechanisms and forms involved in the dysfunctions of tissues and organs. [NIH]

Pathophysiology: Altered functions in an individual or an organ due to disease. [NIH]

Patient Compliance: Voluntary cooperation of the patient in following a prescribed regimen. [NIH]

Patient Education: The teaching or training of patients concerning their own health needs. [NIH]

Patient Selection: Criteria and standards used for the determination of the appropriateness of the inclusion of patients with specific conditions in proposed treatment plans and the criteria used for the inclusion of subjects in various clinical trials and other research protocols. [NIH]

Penis: The external reproductive organ of males. It is composed of a mass of erectile tissue enclosed in three cylindrical fibrous compartments. Two of the three compartments, the corpus cavernosa, are placed side-by-side along the upper part of the organ. The third compartment below, the corpus spongiosum, houses the urethra. [NIH]

Pentosephosphate Pathway: A pathway of hexose oxidation in which glucose-6-phosphate undergoes two successive oxidations by NADP, the final one being an oxidative decarboxylation to form a pentose phosphate. [NIH]

Peptide: Any compound consisting of two or more amino acids, the building blocks of proteins. Peptides are combined to make proteins. [NIH]

Peptide T: N-(N-(N(2)-(N-(N-(N-(N-D-Alanyl L-seryl)-L-threonyl)-L-threonyl) L-threonyl)-L-asparaginyl)-L-tyrosyl) L-threonine. Octapeptide sharing sequence homology with HIV envelope protein gp120. It is potentially useful as antiviral agent in AIDS therapy. The core pentapeptide sequence, TTNYT, consisting of amino acids 4-8 in peptide T, is the HIV envelope sequence required for attachment to the CD4 receptor. [NIH]

Perfusion: Bathing an organ or tissue with a fluid. In regional perfusion, a specific area of the body (usually an arm or a leg) receives high doses of anticancer drugs through a blood vessel. Such a procedure is performed to treat cancer that has not spread. [NIH]

Perioperative: Around the time of surgery; usually lasts from the time of going into the hospital or doctor's office for surgery until the time the patient goes home. [NIH]

Peripheral Nervous System: The nervous system outside of the brain and spinal cord. The

peripheral nervous system has autonomic and somatic divisions. The autonomic nervous system includes the enteric, parasympathetic, and sympathetic subdivisions. The somatic nervous system includes the cranial and spinal nerves and their ganglia and the peripheral sensory receptors. [NIH]

Peripheral Neuropathy: Nerve damage, usually affecting the feet and legs; causing pain, numbness, or a tingling feeling. Also called "somatic neuropathy" or "distal sensory polyneuropathy." [NIH]

Peripheral Vascular Disease: Disease in the large blood vessels of the arms, legs, and feet. People who have had diabetes for a long time may get this because major blood vessels in their arms, legs, and feet are blocked and these limbs do not receive enough blood. The signs of PVD are aching pains in the arms, legs, and feet (especially when walking) and foot sores that heal slowly. Although people with diabetes cannot always avoid PVD, doctors say they have a better chance of avoiding it if they take good care of their feet, do not smoke, and keep both their blood pressure and diabetes under good control. [NIH]

Peritoneal: Having to do with the peritoneum (the tissue that lines the abdominal wall and covers most of the organs in the abdomen). [NIH]

Peritoneal Cavity: The space enclosed by the peritoneum. It is divided into two portions, the greater sac and the lesser sac or omental bursa, which lies behind the stomach. The two sacs are connected by the foramen of Winslow, or epiploic foramen. [NIH]

Peritoneal Dialysis: Dialysis fluid being introduced into and removed from the peritoneal cavity as either a continuous or an intermittent procedure. [NIH]

Peritoneum: Endothelial lining of the abdominal cavity, the parietal peritoneum covering the inside of the abdominal wall and the visceral peritoneum covering the bowel, the mesentery, and certain of the organs. The portion that covers the bowel becomes the serosal layer of the bowel wall. [NIH]

Petrolatum: A colloidal system of semisolid hydrocarbons obtained from petroleum. It is used as an ointment base, topical protectant, and lubricant. [NIH]

PH: The symbol relating the hydrogen ion (H+) concentration or activity of a solution to that of a given standard solution. Numerically the pH is approximately equal to the negative logarithm of H+ concentration expressed in molarity. pH 7 is neutral; above it alkalinity increases and below it acidity increases. [EU]

Pharmaceutical Preparations: Drugs intended for human or veterinary use, presented in their finished dosage form. Included here are materials used in the preparation and/or formulation of the finished dosage form. [NIH]

Pharmaceutical Solutions: Homogeneous liquid preparations that contain one or more chemical substances dissolved, i.e., molecularly dispersed, in a suitable solvent or mixture of mutually miscible solvents. For reasons of their ingredients, method of preparation, or use, they do not fall into another group of products. [NIH]

Pharmacodynamics: The study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of actions and effects of drugs with their chemical structure; also, such effects on the actions of a particular drug or drugs. [EU]

Pharmacokinetic: The mathematical analysis of the time courses of absorption, distribution, and elimination of drugs. [NIH]

Pharmacologic: Pertaining to pharmacology or to the properties and reactions of drugs. [EU]

Pharmacology, Clinical: The branch of pharmacology that deals directly with the effectiveness and safety of drugs in humans. [NIH]

Phenolphthalein: An acid-base indicator which is colorless in acid solution, but turns pink

to red as the solution becomes alkaline. It is used medicinally as a cathartic. [NIH]

Phenotype: The outward appearance of the individual. It is the product of interactions between genes and between the genotype and the environment. This includes the killer phenotype, characteristic of yeasts. [NIH]

Phenylalanine: An aromatic amino acid that is essential in the animal diet. It is a precursor of melanin, dopamine, noradrenalin, and thyroxine. [NIH]

Phospholipids: Lipids containing one or more phosphate groups, particularly those derived from either glycerol (phosphoglycerides; glycerophospholipids) or sphingosine (sphingolipids). They are polar lipids that are of great importance for the structure and function of cell membranes and are the most abundant of membrane lipids, although not stored in large amounts in the system. [NIH]

Phosphorus: A non-metallic element that is found in the blood, muscles, nevers, bones, and teeth, and is a component of adenosine triphosphate (ATP; the primary energy source for the body's cells.) [NIH]

Phosphorylation: The introduction of a phosphoryl group into a compound through the formation of an ester bond between the compound and a phosphorus moiety. [NIH]

Physical Examination: Systematic and thorough inspection of the patient for physical signs of disease or abnormality. [NIH]

Physical Fitness: A state of well-being in which performance is optimal, often as a result of physical conditioning which may be prescribed for disease therapy. [NIH]

Physiologic: Having to do with the functions of the body. When used in the phrase "physiologic age," it refers to an age assigned by general health, as opposed to calendar age. [NIH]

Physiology: The science that deals with the life processes and functions of organismus, their cells, tissues, and organs. [NIH]

Pigments: Any normal or abnormal coloring matter in plants, animals, or micro-organisms. [NIH]

Pilot study: The initial study examining a new method or treatment. [NIH]

Placenta: A highly vascular fetal organ through which the fetus absorbs oxygen and other nutrients and excretes carbon dioxide and other wastes. It begins to form about the eighth day of gestation when the blastocyst adheres to the decidua. [NIH]

Plants: Multicellular, eukaryotic life forms of the kingdom Plantae. They are characterized by a mainly photosynthetic mode of nutrition; essentially unlimited growth at localized regions of cell divisions (meristems); cellulose within cells providing rigidity; the absence of organs of locomotion; absense of nervous and sensory systems; and an alteration of haploid and diploid generations. [NIH]

Plasma: The clear, yellowish, fluid part of the blood that carries the blood cells. The proteins that form blood clots are in plasma. [NIH]

Plasma cells: A type of white blood cell that produces antibodies. [NIH]

Plasma protein: One of the hundreds of different proteins present in blood plasma, including carrier proteins (such albumin, transferrin, and haptoglobin), fibrinogen and other coagulation factors, complement components, immunoglobulins, enzyme inhibitors, precursors of substances such as angiotension and bradykinin, and many other types of proteins. [EU]

Plasmid: An autonomously replicating, extra-chromosomal DNA molecule found in many bacteria. Plasmids are widely used as carriers of cloned genes. [NIH]

Plasmin: A product of the lysis of plasminogen (profibrinolysin) by plasminogen activators. It is composed of two polypeptide chains, light (B) and heavy (A), with a molecular weight of 75,000. It is the major proteolytic enzyme involved in blood clot retraction or the lysis of fibrin and quickly inactivated by antiplasmins. EC 3.4.21.7. [NIH]

Plasminogen: Precursor of fibrinolysin (plasmin). It is a single-chain beta-globulin of molecular weight 80-90,000 found mostly in association with fibrinogen in plasma; plasminogen activators change it to fibrinolysin. It is used in wound debriding and has been investigated as a thrombolytic agent. [NIH]

Plasminogen Activator Inhibitor 1: A member of the serpin family of proteins. It inhibits both the tissue-type and urokinase-type plasminogen activators. [NIH]

Plasminogen Activators: A heterogeneous group of proteolytic enzymes that convert plasminogen to plasmin. They are concentrated in the lysosomes of most cells and in the vascular endothelium, particularly in the vessels of the microcirculation. EC 3.4.21.-. [NIH]

Plasticity: In an individual or a population, the capacity for adaptation: a) through gene changes (genetic plasticity) or b) through internal physiological modifications in response to changes of environment (physiological plasticity). [NIH]

Platelet Aggregation: The attachment of platelets to one another. This clumping together can be induced by a number of agents (e.g., thrombin, collagen) and is part of the mechanism leading to the formation of a thrombus. [NIH]

Platelets: A type of blood cell that helps prevent bleeding by causing blood clots to form. Also called thrombocytes. [NIH]

Platinum: Platinum. A heavy, soft, whitish metal, resembling tin, atomic number 78, atomic weight 195.09, symbol Pt. (From Dorland, 28th ed) It is used in manufacturing equipment for laboratory and industrial use. It occurs as a black powder (platinum black) and as a spongy substance (spongy platinum) and may have been known in Pliny's time as "alutiae". [NIH]

Poisoning: A condition or physical state produced by the ingestion, injection or inhalation of, or exposure to a deleterious agent. [NIH]

Polycystic: An inherited disorder characterized by many grape-like clusters of fluid-filled cysts that make both kidneys larger over time. These cysts take over and destroy working kidney tissue. PKD may cause chronic renal failure and end-stage renal disease. [NIH]

Polycystic Ovary Syndrome: Clinical symptom complex characterized by oligomenorrhea or amenorrhea, anovulation, and regularly associated with bilateral polycystic ovaries. [NIH]

Polymers: Compounds formed by the joining of smaller, usually repeating, units linked by covalent bonds. These compounds often form large macromolecules (e.g., polypeptides, proteins, plastics). [NIH]

Polypeptide: A peptide which on hydrolysis yields more than two amino acids; called tripeptides, tetrapeptides, etc. according to the number of amino acids contained. [EU]

Portal Vein: A short thick vein formed by union of the superior mesenteric vein and the splenic vein. [NIH]

Posterior: Situated in back of, or in the back part of, or affecting the back or dorsal surface of the body. In lower animals, it refers to the caudal end of the body. [EU]

Postprandial: Occurring after dinner, or after a meal; postcibal. [EU]

Postural: Pertaining to posture or position. [EU]

Potassium: An element that is in the alkali group of metals. It has an atomic symbol K, atomic number 19, and atomic weight 39.10. It is the chief cation in the intracellular fluid of

muscle and other cells. Potassium ion is a strong electrolyte and it plays a significant role in the regulation of fluid volume and maintenance of the water-electrolyte balance. [NIH]

Potentiate: A degree of synergism which causes the exposure of the organism to a harmful substance to worsen a disease already contracted. [NIH]

Potentiating: A degree of synergism which causes the exposure of the organism to a harmful substance to worsen a disease already contracted. [NIH]

Potentiation: An overall effect of two drugs taken together which is greater than the sum of the effects of each drug taken alone. [NIH]

Povidone: A polyvinyl polymer of variable molecular weight; used as suspending and dispersing agent and vehicle for pharmaceuticals; also used as blood volume expander. [NIH]

Practice Guidelines: Directions or principles presenting current or future rules of policy for the health care practitioner to assist him in patient care decisions regarding diagnosis, therapy, or related clinical circumstances. The guidelines may be developed by government agencies at any level, institutions, professional societies, governing boards, or by the convening of expert panels. The guidelines form a basis for the evaluation of all aspects of health care and delivery. [NIH]

Precursor: Something that precedes. In biological processes, a substance from which another, usually more active or mature substance is formed. In clinical medicine, a sign or symptom that heralds another. [EU]

Predisposition: A latent susceptibility to disease which may be activated under certain conditions, as by stress. [EU]

Pregnancy in Diabetics: Previously diagnosed diabetics that become pregnant. This does not include either symptomatic diabetes or impaired glucose tolerance induced by pregnancy but resolved at the end of pregnancy (diabetes, gestational). [NIH]

Pressoreceptors: Receptors in the vascular system, particularly the aorta and carotid sinus, which are sensitive to stretch of the vessel walls. [NIH]

Prevalence: The total number of cases of a given disease in a specified population at a designated time. It is differentiated from incidence, which refers to the number of new cases in the population at a given time. [NIH]

Primary endpoint: The main result that is measured at the end of a study to see if a given treatment worked (e.g., the number of deaths or the difference in survival between the treatment group and the control group). What the primary endpoint will be is decided before the study begins. [NIH]

Primary Prevention: Prevention of disease or mental disorders in susceptible individuals or populations through promotion of health, including mental health, and specific protection, as in immunization, as distinguished from the prevention of complications or after-effects of existing disease. [NIH]

Probe: An instrument used in exploring cavities, or in the detection and dilatation of strictures, or in demonstrating the potency of channels; an elongated instrument for exploring or sounding body cavities. [NIH]

Progeny: The offspring produced in any generation. [NIH]

Progesterone: Pregn-4-ene-3,20-dione. The principal progestational hormone of the body, secreted by the corpus luteum, adrenal cortex, and placenta. Its chief function is to prepare the uterus for the reception and development of the fertilized ovum. It acts as an antiovulatory agent when administered on days 5-25 of the menstrual cycle. [NIH]

Progression: Increase in the size of a tumor or spread of cancer in the body. [NIH]

Progressive: Advancing; going forward; going from bad to worse; increasing in scope or severity. [EU]

Projection: A defense mechanism, operating unconsciously, whereby that which is emotionally unacceptable in the self is rejected and attributed (projected) to others. [NIH]

Proline: A non-essential amino acid that is synthesized from glutamic acid. It is an essential component of collagen and is important for proper functioning of joints and tendons. [NIH]

Promoter: A chemical substance that increases the activity of a carcinogenic process. [NIH]

Prophase: The first phase of cell division, in which the chromosomes become visible, the nucleus starts to lose its identity, the spindle appears, and the centrioles migrate toward opposite poles. [NIH]

Prophylaxis: An attempt to prevent disease. [NIH]

Proportional: Being in proportion : corresponding in size, degree, or intensity, having the same or a constant ratio; of, relating to, or used in determining proportions. [EU]

Propylene Glycol: A clear, colorless, viscous organic solvent and diluent used in pharmaceutical preparations. [NIH]

Prostate: A gland in males that surrounds the neck of the bladder and the urethra. It secretes a substance that liquifies coagulated semen. It is situated in the pelvic cavity behind the lower part of the pubic symphysis, above the deep layer of the triangular ligament, and rests upon the rectum. [NIH]

Protease: Proteinase (= any enzyme that catalyses the splitting of interior peptide bonds in a protein). [EU]

Protease Inhibitors: Compounds which inhibit or antagonize biosynthesis or actions of proteases (endopeptidases). [NIH]

Protein C: A vitamin-K dependent zymogen present in the blood, which, upon activation by thrombin and thrombomodulin exerts anticoagulant properties by inactivating factors Va and VIIIa at the rate-limiting steps of thrombin formation. [NIH]

Protein S: The vitamin K-dependent cofactor of activated protein C. Together with protein C, it inhibits the action of factors VIIIa and Va. A deficiency in protein S can lead to recurrent venous and arterial thrombosis. [NIH]

Proteins: Polymers of amino acids linked by peptide bonds. The specific sequence of amino acids determines the shape and function of the protein. [NIH]

Proteinuria: The presence of protein in the urine, indicating that the kidneys are not working properly. [NIH]

Proteolytic: 1. Pertaining to, characterized by, or promoting proteolysis. 2. An enzyme that promotes proteolysis (= the splitting of proteins by hydrolysis of the peptide bonds with formation of smaller polypeptides). [EU]

Protocol: The detailed plan for a clinical trial that states the trial's rationale, purpose, drug or vaccine dosages, length of study, routes of administration, who may participate, and other aspects of trial design. [NIH]

Protons: Stable elementary particles having the smallest known positive charge, found in the nuclei of all elements. The proton mass is less than that of a neutron. A proton is the nucleus of the light hydrogen atom, i.e., the hydrogen ion. [NIH]

Protozoa: A subkingdom consisting of unicellular organisms that are the simplest in the animal kingdom. Most are free living. They range in size from submicroscopic to macroscopic. Protozoa are divided into seven phyla: Sarcomastigophora, Labyrinthomorpha, Apicomplexa, Microspora, Ascetospora, Myxozoa, and Ciliophora. [NIH]

Proximal: Nearest; closer to any point of reference; opposed to distal. [EU]

Psychotropic: Exerting an effect upon the mind; capable of modifying mental activity; usually applied to drugs that effect the mental state. [EU]

Puberty: The period during which the secondary sex characteristics begin to develop and the capability of sexual reproduction is attained. [EU]

Public Health: Branch of medicine concerned with the prevention and control of disease and disability, and the promotion of physical and mental health of the population on the international, national, state, or municipal level. [NIH]

Public Policy: A course or method of action selected, usually by a government, from among alternatives to guide and determine present and future decisions. [NIH]

Publishing: "The business or profession of the commercial production and issuance of literature" (Webster's 3d). It includes the publisher, publication processes, editing and editors. Production may be by conventional printing methods or by electronic publishing. [NIH]

Pulmonary: Relating to the lungs. [NIH]

Pulmonary Artery: The short wide vessel arising from the conus arteriosus of the right ventricle and conveying unaerated blood to the lungs. [NIH]

Pulmonary Embolism: Embolism in the pulmonary artery or one of its branches. [NIH]

Pulmonary Ventilation: The total volume of gas per minute inspired or expired measured in liters per minute. [NIH]

Pulse: The rhythmical expansion and contraction of an artery produced by waves of pressure caused by the ejection of blood from the left ventricle of the heart as it contracts. [NIH]

Purines: A series of heterocyclic compounds that are variously substituted in nature and are known also as purine bases. They include adenine and guanine, constituents of nucleic acids, as well as many alkaloids such as caffeine and theophylline. Uric acid is the metabolic end product of purine metabolism. [NIH]

Pyruvate Kinase: ATP:pyruvate 2-O-phosphotransferase. A phosphotransferase that catalyzes reversibly the phosphorylation of pyruvate to phosphoenolpyruvate in the presence of ATP. It has four isozymes (L, R, M1, and M2). Deficiency of the enzyme results in hemolytic anemia. EC 2.7.1.40. [NIH]

Quality of Life: A generic concept reflecting concern with the modification and enhancement of life attributes, e.g., physical, political, moral and social environment. [NIH]

Race: A population within a species which exhibits general similarities within itself, but is both discontinuous and distinct from other populations of that species, though not sufficiently so as to achieve the status of a taxon. [NIH]

Radiation: Emission or propagation of electromagnetic energy (waves/rays), or the waves/rays themselves; a stream of electromagnetic particles (electrons, neutrons, protons, alpha particles) or a mixture of these. The most common source is the sun. [NIH]

Radiation therapy: The use of high-energy radiation from x-rays, gamma rays, neutrons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body in the area near cancer cells (internal radiation therapy, implant radiation, or brachytherapy). Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that circulates throughout the body. Also called radiotherapy. [NIH]

Radio Waves: That portion of the electromagnetic spectrum beyond the microwaves, with

wavelengths as high as 30 KM. They are used in communications, including television. Short Wave or HF (high frequency), UHF (ultrahigh frequency) and VHF (very high frequency) waves are used in citizen's band communication. [NIH]

Radioactive: Giving off radiation. [NIH]

Radiography: Examination of any part of the body for diagnostic purposes by means of roentgen rays, recording the image on a sensitized surface (such as photographic film). [NIH]

Radiopharmaceutical: Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose. [NIH]

Random Allocation: A process involving chance used in therapeutic trials or other research endeavor for allocating experimental subjects, human or animal, between treatment and control groups, or among treatment groups. It may also apply to experiments on inanimate objects. [NIH]

Randomization: Also called random allocation. Is allocation of individuals to groups, e.g., for experimental and control regimens, by chance. Within the limits of chance variation, random allocation should make the control and experimental groups similar at the start of an investigation and ensure that personal judgment and prejudices of the investigator do not influence allocation. [NIH]

Randomized: Describes an experiment or clinical trial in which animal or human subjects are assigned by chance to separate groups that compare different treatments. [NIH]

Randomized clinical trial: A study in which the participants are assigned by chance to separate groups that compare different treatments; neither the researchers nor the participants can choose which group. Using chance to assign people to groups means that the groups will be similar and that the treatments they receive can be compared objectively. At the time of the trial, it is not known which treatment is best. It is the patient's choice to be in a randomized trial. [NIH]

Reactive Oxygen Species: Reactive intermediate oxygen species including both radicals and non-radicals. These substances are constantly formed in the human body and have been shown to kill bacteria and inactivate proteins, and have been implicated in a number of diseases. Scientific data exist that link the reactive oxygen species produced by inflammatory phagocytes to cancer development. [NIH]

Reagent: A substance employed to produce a chemical reaction so as to detect, measure, produce, etc., other substances. [EU]

Receptor: A molecule inside or on the surface of a cell that binds to a specific substance and causes a specific physiologic effect in the cell. [NIH]

Recombinant: A cell or an individual with a new combination of genes not found together in either parent; usually applied to linked genes. [EU]

Recombination: The formation of new combinations of genes as a result of segregation in crosses between genetically different parents; also the rearrangement of linked genes due to crossing-over. [NIH]

Rectum: The last 8 to 10 inches of the large intestine. [NIH]

Recurrence: The return of a sign, symptom, or disease after a remission. [NIH]

Reductase: Enzyme converting testosterone to dihydrotestosterone. [NIH]

Refer: To send or direct for treatment, aid, information, de decision. [NIH]

Reflex: An involuntary movement or exercise of function in a part, excited in response to a stimulus applied to the periphery and transmitted to the brain or spinal cord. [NIH]

Refraction: A test to determine the best eyeglasses or contact lenses to correct a refractive

error (myopia, hyperopia, or astigmatism). [NIH]

Regimen: A treatment plan that specifies the dosage, the schedule, and the duration of treatment. [NIH]

Remission: A decrease in or disappearance of signs and symptoms of cancer. In partial remission, some, but not all, signs and symptoms of cancer have disappeared. In complete remission, all signs and symptoms of cancer have disappeared, although there still may be cancer in the body. [NIH]

Renal failure: Progressive renal insufficiency and uremia, due to irreversible and progressive renal glomerular tubular or interstitial disease. [NIH]

Reproductive system: In women, this system includes the ovaries, the fallopian tubes, the uterus (womb), the cervix, and the vagina (birth canal). The reproductive system in men includes the prostate, the testes, and the penis. [NIH]

Research Support: Financial support of research activities. [NIH]

Respiration: The act of breathing with the lungs, consisting of inspiration, or the taking into the lungs of the ambient air, and of expiration, or the expelling of the modified air which contains more carbon dioxide than the air taken in (Blakiston's Gould Medical Dictionary, 4th ed.). This does not include tissue respiration (= oxygen consumption) or cell respiration (= cell respiration). [NIH]

Respiratory Paralysis: Complete or severe weakness of the muscles of respiration. This condition may be associated with motor neuron diseases; peripheral nerve disorders; neuromuscular junction diseases; spinal cord diseases; injury to the phrenic nerve; and other disorders. [NIH]

Resting metabolic rate: RMR accounts for 65 to 75 percent of daily energy expenditure and represents the minimum energy needed to maintain all physiological cell functions in the resting state. The principal determinant of RMR is lean body mass (LBM). Obese subjects have a higher RMR in absolute terms than lean individuals, an equivalent RMR when corrected for LBM and per unit surface area, and a lower RMR when expressed per kilogram of body weight. Obese persons require more energy for any given activity because of a larger mass, but they tend to be more sedentary than lean subjects. [NIH]

Restoration: Broad term applied to any inlay, crown, bridge or complete denture which restores or replaces loss of teeth or oral tissues. [NIH]

Retina: The ten-layered nervous tissue membrane of the eye. It is continuous with the optic nerve and receives images of external objects and transmits visual impulses to the brain. Its outer surface is in contact with the choroid and the inner surface with the vitreous body. The outer-most layer is pigmented, whereas the inner nine layers are transparent. [NIH]

Retinal: 1. Pertaining to the retina. 2. The aldehyde of retinol, derived by the oxidative enzymatic splitting of absorbed dietary carotene, and having vitamin A activity. In the retina, retinal combines with opsins to form visual pigments. One isomer, 11-cis retinal combines with opsin in the rods (scotopsin) to form rhodopsin, or visual purple. Another, all-trans retinal (trans-r.); visual yellow; xanthopsin) results from the bleaching of rhodopsin by light, in which the 11-cis form is converted to the all-trans form. Retinal also combines with opsins in the cones (photopsins) to form the three pigments responsible for colour vision. Called also retinal, and retinene1. [EU]

Retinopathy: 1. Retinitis (= inflammation of the retina). 2. Retinosis (= degenerative, noninflammatory condition of the retina). [EU]

Retrospective: Looking back at events that have already taken place. [NIH]

Retrospective study: A study that looks backward in time, usually using medical records

and interviews with patients who already have or had a disease. [NIH]

Rheumatism: A group of disorders marked by inflammation or pain in the connective tissue structures of the body. These structures include bone, cartilage, and fat. [NIH]

Rheumatoid: Resembling rheumatism. [EU]

Rheumatoid arthritis: A form of arthritis, the cause of which is unknown, although infection, hypersensitivity, hormone imbalance and psychologic stress have been suggested as possible causes. [NIH]

Ribose: A pentose active in biological systems usually in its D-form. [NIH]

Risk factor: A habit, trait, condition, or genetic alteration that increases a person's chance of developing a disease. [NIH]

Risk patient: Patient who is at risk, because of his/her behaviour or because of the type of person he/she is. [EU]

Rod: A reception for vision, located in the retina. [NIH]

Rosiglitazone: A drug taken to help reduce the amount of sugar in the blood. Rosiglitazone helps make insulin more effective and improves regulation of blood sugar. It belongs to the family of drugs called thiazolidinediones. [NIH]

Saliva: The clear, viscous fluid secreted by the salivary glands and mucous glands of the mouth. It contains mucins, water, organic salts, and ptylin. [NIH]

Salivary: The duct that convey saliva to the mouth. [NIH]

Salivary glands: Glands in the mouth that produce saliva. [NIH]

Saponins: Sapogenin glycosides. A type of glycoside widely distributed in plants. Each consists of a sapogenin as the aglycon moiety, and a sugar. The sapogenin may be a steroid or a triterpene and the sugar may be glucose, galactose, a pentose, or a methylpentose. Sapogenins are poisonous towards the lower forms of life and are powerful hemolytics when injected into the blood stream able to dissolve red blood cells at even extreme dilutions. [NIH]

Saturated fat: A type of fat found in greatest amounts in foods from animals, such as fatty cuts of meat, poultry with the skin, whole-milk dairy products, lard, and in some vegetable oils, including coconut, palm kernel, and palm oils. Saturated fat raises blood cholesterol more than anything else eaten. On a Step I Diet, no more than 8 to 10 percent of total calories should come from saturated fat, and in the Step II Diet, less than 7 percent of the day's total calories should come from saturated fat. [NIH]

Schizoid: Having qualities resembling those found in greater degree in schizophrenics; a person of schizoid personality. [NIH]

Schizophrenia: A mental disorder characterized by a special type of disintegration of the personality. [NIH]

Schizotypal Personality Disorder: A personality disorder in which there are oddities of thought (magical thinking, paranoid ideation, suspiciousness), perception (illusions, depersonalization), speech (digressive, vague, overelaborate), and behavior (inappropriate affect in social interactions, frequently social isolation) that are not severe enough to characterize schizophrenia. [NIH]

Screening: Checking for disease when there are no symptoms. [NIH]

Secretion: 1. The process of elaborating a specific product as a result of the activity of a gland; this activity may range from separating a specific substance of the blood to the elaboration of a new chemical substance. 2. Any substance produced by secretion. [EU]

Secretory: Secreting; relating to or influencing secretion or the secretions. [NIH]

Sedentary: 1. Sitting habitually; of inactive habits. 2. Pertaining to a sitting posture. [EU]

Self Care: Performance of activities or tasks traditionally performed by professional health care providers. The concept includes care of oneself or one's family and friends. [NIH]

Semisynthetic: Produced by chemical manipulation of naturally occurring substances. [EU]

Sensor: A device designed to respond to physical stimuli such as temperature, light, magnetism or movement and transmit resulting impulses for interpretation, recording, movement, or operating control. [NIH]

Sepsis: The presence of bacteria in the bloodstream. [NIH]

Sequence Homology: The degree of similarity between sequences. Studies of amino acid and nucleotide sequences provide useful information about the genetic relatedness of certain species. [NIH]

Serine: A non-essential amino acid occurring in natural form as the L-isomer. It is synthesized from glycine or threonine. It is involved in the biosynthesis of purines, pyrimidines, and other amino acids. [NIH]

Serotonin: A biochemical messenger and regulator, synthesized from the essential amino acid L-tryptophan. In humans it is found primarily in the central nervous system, gastrointestinal tract, and blood platelets. Serotonin mediates several important physiological functions including neurotransmission, gastrointestinal motility, hemostasis, and cardiovascular integrity. Multiple receptor families (receptors, serotonin) explain the broad physiological actions and distribution of this biochemical mediator. [NIH]

Serous: Having to do with serum, the clear liquid part of blood. [NIH]

Serum: The clear liquid part of the blood that remains after blood cells and clotting proteins have been removed. [NIH]

Sex Characteristics: Those characteristics that distinguish one sex from the other. The primary sex characteristics are the ovaries and testes and their related hormones. Secondary sex characteristics are those which are masculine or feminine but not directly related to reproduction. [NIH]

Shock: The general bodily disturbance following a severe injury; an emotional or moral upset occasioned by some disturbing or unexpected experience; disruption of the circulation, which can upset all body functions: sometimes referred to as circulatory shock. [NIH]

Sibutramine: A drug used for the management of obesity that helps reduce food intake and is indicated for weight loss and maintenance of weight loss when used in conjunction with a reduced-calorie diet. It works to suppress the appetite primarily by inhibiting the reuptake of the neurotransmitters norepinephrine and serotonin. Side effects include dry mouth, headache, constipation, insomnia, and a slight increase in average blood pressure. In some patients it causes a higher blood pressure increase. [NIH]

Side effect: A consequence other than the one(s) for which an agent or measure is used, as the adverse effects produced by a drug, especially on a tissue or organ system other than the one sought to be benefited by its administration. [EU]

Signal Transduction: The intercellular or intracellular transfer of information (biological activation/inhibition) through a signal pathway. In each signal transduction system, an activation/inhibition signal from a biologically active molecule (hormone, neurotransmitter) is mediated via the coupling of a receptor/enzyme to a second messenger system or to an ion channel. Signal transduction plays an important role in activating cellular functions, cell differentiation, and cell proliferation. Examples of signal transduction systems are the GABA-postsynaptic receptor-calcium ion channel system, the receptor-mediated T-cell

activation pathway, and the receptor-mediated activation of phospholipases. Those coupled to membrane depolarization or intracellular release of calcium include the receptor-mediated activation of cytotoxic functions in granulocytes and the synaptic potentiation of protein kinase activation. Some signal transduction pathways may be part of larger signal transduction pathways; for example, protein kinase activation is part of the platelet activation signal pathway. [NIH]

Simvastatin: A derivative of lovastatin and potent competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase (hydroxymethylglutaryl CoA reductases), which is the rate-limiting enzyme in cholesterol biosynthesis. It may also interfere with steroid hormone production. Due to the induction of hepatic LDL receptors, it increases breakdown of LDL-cholesterol (lipoproteins, LDL cholesterol). [NIH]

Skeletal: Having to do with the skeleton (boney part of the body). [NIH]

Skeleton: The framework that supports the soft tissues of vertebrate animals and protects many of their internal organs. The skeletons of vertebrates are made of bone and/or cartilage. [NIH]

Small intestine: The part of the digestive tract that is located between the stomach and the large intestine. [NIH]

Smooth muscle: Muscle that performs automatic tasks, such as constricting blood vessels. [NIH]

Social Environment: The aggregate of social and cultural institutions, forms, patterns, and processes that influence the life of an individual or community. [NIH]

Soft tissue: Refers to muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of the body. [NIH]

Solvent: 1. Dissolving; effecting a solution. 2. A liquid that dissolves or that is capable of dissolving; the component of a solution that is present in greater amount. [EU]

Somatic: 1. Pertaining to or characteristic of the soma or body. 2. Pertaining to the body wall in contrast to the viscera. [EU]

Somatostatin: A polypeptide hormone produced in the hypothalamus, and other tissues and organs. It inhibits the release of human growth hormone, and also modulates important physiological functions of the kidney, pancreas, and gastrointestinal tract. Somatostatin receptors are widely expressed throughout the body. Somatostatin also acts as a neurotransmitter in the central and peripheral nervous systems. [NIH]

Sorbitol: A polyhydric alcohol with about half the sweetness of sucrose. Sorbitol occurs naturally and is also produced synthetically from glucose. It was formerly used as a diuretic and may still be used as a laxative and in irrigating solutions for some surgical procedures. It is also used in many manufacturing processes, as a pharmaceutical aid, and in several research applications. [NIH]

Sound wave: An alteration of properties of an elastic medium, such as pressure, particle displacement, or density, that propagates through the medium, or a superposition of such alterations. [NIH]

Specialist: In medicine, one who concentrates on 1 special branch of medical science. [NIH]

Species: A taxonomic category subordinate to a genus (or subgenus) and superior to a subspecies or variety, composed of individuals possessing common characters distinguishing them from other categories of individuals of the same taxonomic level. In taxonomic nomenclature, species are designated by the genus name followed by a Latin or Latinized adjective or noun. [EU]

Specificity: Degree of selectivity shown by an antibody with respect to the number and

types of antigens with which the antibody combines, as well as with respect to the rates and the extents of these reactions. [NIH]

Spectrum: A charted band of wavelengths of electromagnetic vibrations obtained by refraction and diffraction. By extension, a measurable range of activity, such as the range of bacteria affected by an antibiotic (antibacterial s.) or the complete range of manifestations of a disease. [EU]

Sperm: The fecundating fluid of the male. [NIH]

Spinal cord: The main trunk or bundle of nerves running down the spine through holes in the spinal bone (the vertebrae) from the brain to the level of the lower back. [NIH]

Splenic Vein: Vein formed by the union (at the hilus of the spleen) of several small veins from the stomach, pancreas, spleen and mesentery. [NIH]

Spontaneous Abortion: The non-induced birth of an embryo or of fetus prior to the stage of viability at about 20 weeks of gestation. [NIH]

Statistically significant: Describes a mathematical measure of difference between groups. The difference is said to be statistically significant if it is greater than what might be expected to happen by chance alone. [NIH]

Steatosis: Fatty degeneration. [EU]

Steel: A tough, malleable, iron-based alloy containing up to, but no more than, two percent carbon and often other metals. It is used in medicine and dentistry in implants and instrumentation. [NIH]

Sterility: 1. The inability to produce offspring, i.e., the inability to conceive (female s.) or to induce conception (male s.). 2. The state of being aseptic, or free from microorganisms. [EU]

Steroid: A group name for lipids that contain a hydrogenated cyclopentanoperhydrophenanthrene ring system. Some of the substances included in this group are progesterone, adrenocortical hormones, the gonadal hormones, cardiac aglycones, bile acids, sterols (such as cholesterol), toad poisons, saponins, and some of the carcinogenic hydrocarbons. [EU]

Stimulus: That which can elicit or evoke action (response) in a muscle, nerve, gland or other excitable issue, or cause an augmenting action upon any function or metabolic process. [NIH]

Stomach: An organ of digestion situated in the left upper quadrant of the abdomen between the termination of the esophagus and the beginning of the duodenum. [NIH]

Stress: Forcibly exerted influence; pressure. Any condition or situation that causes strain or tension. Stress may be either physical or psychologic, or both. [NIH]

Stroke: Sudden loss of function of part of the brain because of loss of blood flow. Stroke may be caused by a clot (thrombosis) or rupture (hemorrhage) of a blood vessel to the brain. [NIH]

Stromal: Large, veil-like cell in the bone marrow. [NIH]

Subacute: Somewhat acute; between acute and chronic. [EU]

Subclinical: Without clinical manifestations; said of the early stage(s) of an infection or other disease or abnormality before symptoms and signs become apparent or detectable by clinical examination or laboratory tests, or of a very mild form of an infection or other disease or abnormality. [EU]

Subcutaneous: Beneath the skin. [NIH]

Subspecies: A category intermediate in rank between species and variety, based on a smaller number of correlated characters than are used to differentiate species and generally conditioned by geographical and/or ecological occurrence. [NIH]

Substance P: An eleven-amino acid neurotransmitter that appears in both the central and peripheral nervous systems. It is involved in transmission of pain, causes rapid contractions of the gastrointestinal smooth muscle, and modulates inflammatory and immune responses. [NIH]

Substrate: A substance upon which an enzyme acts. [EU]

Superoxide: Derivative of molecular oxygen that can damage cells. [NIH]

Supplementation: Adding nutrients to the diet. [NIH]

Suppositories: A small cone-shaped medicament having cocoa butter or gelatin at its basis and usually intended for the treatment of local conditions in the rectum. [NIH]

Suppression: A conscious exclusion of disapproved desire contrary with repression, in which the process of exclusion is not conscious. [NIH]

Sweat: The fluid excreted by the sweat glands. It consists of water containing sodium chloride, phosphate, urea, ammonia, and other waste products. [NIH]

Sympathomimetic: 1. Mimicking the effects of impulses conveyed by adrenergic postganglionic fibres of the sympathetic nervous system. 2. An agent that produces effects similar to those of impulses conveyed by adrenergic postganglionic fibres of the sympathetic nervous system. Called also adrenergic. [EU]

Symptomatic: Having to do with symptoms, which are signs of a condition or disease. [NIH]

Synergistic: Acting together; enhancing the effect of another force or agent. [EU]

Systemic: Affecting the entire body. [NIH]

Systolic: Indicating the maximum arterial pressure during contraction of the left ventricle of the heart. [EU]

Systolic blood pressure: The maximum pressure in the artery produced as the heart contracts and blood begins to flow. [NIH]

Terminalis: A groove on the lateral surface of the right atrium. [NIH]

Testis: Either of the paired male reproductive glands that produce the male germ cells and the male hormones. [NIH]

Testosterone: A hormone that promotes the development and maintenance of male sex characteristics. [NIH]

Theca Cells: The connective tissue cells of the ovarian follicle. [NIH]

Theophylline: Alkaloid obtained from Thea sinensis (tea) and others. It stimulates the heart and central nervous system, dilates bronchi and blood vessels, and causes diuresis. The drug is used mainly in bronchial asthma and for myocardial stimulation. Among its more prominent cellular effects are inhibition of cyclic nucleotide phosphodiesterases and antagonism of adenosine receptors. [NIH]

Therapeutics: The branch of medicine which is concerned with the treatment of diseases, palliative or curative. [NIH]

Thiamine: 3-((4-Amino-2-methyl-5-pyrimidinyl)methyl)-5-(2-hydroxyethyl)-4-methylthiazolium chloride. [NIH]

Third Ventricle: A narrow cleft inferior to the corpus callosum, within the diencephalon, between the paired thalami. Its floor is formed by the hypothalamus, its anterior wall by the lamina terminalis, and its roof by ependyma. It communicates with the fourth ventricle by the cerebral aqueduct, and with the lateral ventricles by the interventricular foramina. [NIH]

Thorax: A part of the trunk between the neck and the abdomen; the chest. [NIH]

Threonine: An essential amino acid occurring naturally in the L-form, which is the active

form. It is found in eggs, milk, gelatin, and other proteins. [NIH]

Threshold: For a specified sensory modality (e. g. light, sound, vibration), the lowest level (absolute threshold) or smallest difference (difference threshold, difference limen) or intensity of the stimulus discernible in prescribed conditions of stimulation. [NIH]

Thrombin: An enzyme formed from prothrombin that converts fibrinogen to fibrin. (Dorland, 27th ed) EC 3.4.21.5. [NIH]

Thrombolytic: 1. Dissolving or splitting up a thrombus. 2. A thrombolytic agent. [EU]

Thrombomodulin: A cell surface glycoprotein of endothelial cells that binds thrombin and serves as a cofactor in the activation of protein C and its regulation of blood coagulation. [NIH]

Thrombosis: The formation or presence of a blood clot inside a blood vessel. [NIH]

Thyroid: A gland located near the windpipe (trachea) that produces thyroid hormone, which helps regulate growth and metabolism. [NIH]

Thyroxine: An amino acid of the thyroid gland which exerts a stimulating effect on thyroid metabolism. [NIH]

Tidal Volume: The volume of air inspired or expired during each normal, quiet respiratory cycle. Common abbreviations are TV or V with subscript T. [NIH]

Tin: A trace element that is required in bone formation. It has the atomic symbol Sn, atomic number 50, and atomic weight 118.71. [NIH]

Tissue: A group or layer of cells that are alike in type and work together to perform a specific function. [NIH]

Tolazamide: A sulphonylurea hypoglycemic agent with actions and uses similar to those of chlorpropamide. [NIH]

Tolerance: 1. The ability to endure unusually large doses of a drug or toxin. 2. Acquired drug tolerance; a decreasing response to repeated constant doses of a drug or the need for increasing doses to maintain a constant response. [EU]

Tomography: Imaging methods that result in sharp images of objects located on a chosen plane and blurred images located above or below the plane. [NIH]

Topical: On the surface of the body. [NIH]

Toxic: Having to do with poison or something harmful to the body. Toxic substances usually cause unwanted side effects. [NIH]

Toxicity: The quality of being poisonous, especially the degree of virulence of a toxic microbe or of a poison. [EU]

Toxicokinetics: Study of the absorption, distribution, metabolism, and excretion of test substances. [NIH]

Toxicology: The science concerned with the detection, chemical composition, and pharmacologic action of toxic substances or poisons and the treatment and prevention of toxic manifestations. [NIH]

Toxins: Specific, characterizable, poisonous chemicals, often proteins, with specific biological properties, including immunogenicity, produced by microbes, higher plants, or animals. [NIH]

Trace element: Substance or element essential to plant or animal life, but present in extremely small amounts. [NIH]

Traction: The act of pulling. [NIH]

Transaldolase: An enzyme of the transferase class that catalyzes the reaction sedoheptulose

7-phosphate and D-glyceraldehyde 3-phosphate to yield D-erythrose 4-phosphate and D-fructose phosphate in the pentosephosphate pathway. (Dorland, 27th ed) EC 2.2.1.2. [NIH]

Transcription Factors: Endogenous substances, usually proteins, which are effective in the initiation, stimulation, or termination of the genetic transcription process. [NIH]

Transfection: The uptake of naked or purified DNA into cells, usually eukaryotic. It is analogous to bacterial transformation. [NIH]

Transfusion: The infusion of components of blood or whole blood into the bloodstream. The blood may be donated from another person, or it may have been taken from the person earlier and stored until needed. [NIH]

Translational: The cleavage of signal sequence that directs the passage of the protein through a cell or organelle membrane. [NIH]

Translocation: The movement of material in solution inside the body of the plant. [NIH]

Transmitter: A chemical substance which effects the passage of nerve impulses from one cell to the other at the synapse. [NIH]

Transplantation: Transference of a tissue or organ, alive or dead, within an individual, between individuals of the same species, or between individuals of different species. [NIH]

Trauma: Any injury, wound, or shock, must frequently physical or structural shock, producing a disturbance. [NIH]

Triad: Trivalent. [NIH]

Triglyceride: A lipid carried through the blood stream to tissues. Most of the body's fat tissue is in the form of triglycerides, stored for use as energy. Triglycerides are obtained primarily from fat in foods. [NIH]

Troglitazone: A drug used in diabetes treatment that is being studied for its effect on reducing the risk of cancer cell growth in fat tissue. [NIH]

Truncal: The bilateral dissection of the abdominal branches of the vagus nerve. [NIH]

Tryptophan: An essential amino acid that is necessary for normal growth in infants and for nitrogen balance in adults. It is a precursor serotonin and niacin. [NIH]

Tuberculosis: Any of the infectious diseases of man and other animals caused by species of Mycobacterium. [NIH]

Tubulin: A microtubule subunit protein found in large quantities in mammalian brain. It has also been isolated from sperm flagella, cilia, and other sources. Structurally, the protein is a dimer with a molecular weight of approximately 120,000 and a sedimentation coefficient of 5.8S. It binds to colchicine, vincristine, and vinblastine. [NIH]

Tumor Necrosis Factor: Serum glycoprotein produced by activated macrophages and other mammalian mononuclear leukocytes which has necrotizing activity against tumor cell lines and increases ability to reject tumor transplants. It mimics the action of endotoxin but differs from it. It has a molecular weight of less than 70,000 kDa. [NIH]

Tumour: 1. Swelling, one of the cardinal signs of inflammations; morbid enlargement. 2. A new growth of tissue in which the multiplication of cells is uncontrolled and progressive; called also neoplasm. [EU]

Type 2 diabetes: Usually characterized by a gradual onset with minimal or no symptoms of metabolic disturbance and no requirement for exogenous insulin. The peak age of onset is 50 to 60 years. Obesity and possibly a genetic factor are usually present. [NIH]

Tyrosine: A non-essential amino acid. In animals it is synthesized from phenylalanine. It is also the precursor of epinephrine, thyroid hormones, and melanin. [NIH]

Ultrafiltration: The separation of particles from a suspension by passage through a filter with very fine pores. In ultrafiltration the separation is accomplished by convective transport; in dialysis separation relies instead upon differential diffusion. Ultrafiltration occurs naturally and is a laboratory procedure. Artificial ultrafiltration of the blood is referred to as hemofiltration or hemodiafiltration (if combined with hemodialysis). [NIH]

Unconscious: Experience which was once conscious, but was subsequently rejected, as the "personal unconscious". [NIH]

Urea: A compound (CO(NH2)2), formed in the liver from ammonia produced by the deamination of amino acids. It is the principal end product of protein catabolism and constitutes about one half of the total urinary solids. [NIH]

Uremia: The illness associated with the buildup of urea in the blood because the kidneys are not working effectively. Symptoms include nausea, vomiting, loss of appetite, weakness, and mental confusion. [NIH]

Urethra: The tube through which urine leaves the body. It empties urine from the bladder. [NIH]

Urinary: Having to do with urine or the organs of the body that produce and get rid of urine. [NIH]

Urinary tract: The organs of the body that produce and discharge urine. These include the kidneys, ureters, bladder, and urethra. [NIH]

Urinary tract infection: An illness caused by harmful bacteria growing in the urinary tract. [NIH]

Urine: Fluid containing water and waste products. Urine is made by the kidneys, stored in the bladder, and leaves the body through the urethra. [NIH]

Urokinase: A drug that dissolves blood clots or prevents them from forming. [NIH]

Uterus: The small, hollow, pear-shaped organ in a woman's pelvis. This is the organ in which a fetus develops. Also called the womb. [NIH]

Vaccine: A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms, such as bacteria or viruses. [NIH]

Vagina: The muscular canal extending from the uterus to the exterior of the body. Also called the birth canal. [NIH]

Vagus Nerve: The 10th cranial nerve. The vagus is a mixed nerve which contains somatic afferents (from skin in back of the ear and the external auditory meatus), visceral afferents (from the pharynx, larynx, thorax, and abdomen), parasympathetic efferents (to the thorax and abdomen), and efferents to striated muscle (of the larynx and pharynx). [NIH]

Vanadium: Vanadium. A metallic element with the atomic symbol V, atomic number 23, and atomic weight 50.94. It is used in the manufacture of vanadium steel. Prolonged exposure can lead to chronic intoxication caused by absorption usually via the lungs. [NIH]

Vascular: Pertaining to blood vessels or indicative of a copious blood supply. [EU]

Vascular Resistance: An expression of the resistance offered by the systemic arterioles, and to a lesser extent by the capillaries, to the flow of blood. [NIH]

Vasculitis: Inflammation of a blood vessel. [NIH]

Vasoactive: Exerting an effect upon the calibre of blood vessels. [EU]

Vasoconstriction: Narrowing of the blood vessels without anatomic change, for which constriction, pathologic is used. [NIH]

Vasodilator: An agent that widens blood vessels. [NIH]

Vasomotor: 1. Affecting the calibre of a vessel, especially of a blood vessel. 2. Any element or agent that effects the calibre of a blood vessel. [EU]

Vein: Vessel-carrying blood from various parts of the body to the heart. [NIH]

Venous: Of or pertaining to the veins. [EU]

Venous Thrombosis: The formation or presence of a thrombus within a vein. [NIH]

Ventricle: One of the two pumping chambers of the heart. The right ventricle receives oxygen-poor blood from the right atrium and pumps it to the lungs through the pulmonary artery. The left ventricle receives oxygen-rich blood from the left atrium and pumps it to the body through the aorta. [NIH]

Ventricular: Pertaining to a ventricle. [EU]

Venules: The minute vessels that collect blood from the capillary plexuses and join together to form veins. [NIH]

Veterinary Medicine: The medical science concerned with the prevention, diagnosis, and treatment of diseases in animals. [NIH]

Vinblastine: An anticancer drug that belongs to the family of plant drugs called vinca alkaloids. It is a mitotic inhibitor. [NIH]

Vincristine: An anticancer drug that belongs to the family of plant drugs called vinca alkaloids. [NIH]

Virilism: Development of masculine traits in the female. [NIH]

Virulence: The degree of pathogenicity within a group or species of microorganisms or viruses as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host. [NIH]

Virus: Submicroscopic organism that causes infectious disease. In cancer therapy, some viruses may be made into vaccines that help the body build an immune response to, and kill, tumor cells. [NIH]

Visceral: , from viscus a viscus) pertaining to a viscus. [EU]

Visceral fat: One of the three compartments of abdominal fat. Retroperitoneal and subcutaneous are the other two compartments. [NIH]

Vitamin A: A substance used in cancer prevention; it belongs to the family of drugs called retinoids. [NIH]

Vitreous Body: The transparent, semigelatinous substance that fills the cavity behind the crystalline lens of the eye and in front of the retina. It is contained in a thin hyoid membrane and forms about four fifths of the optic globe. [NIH]

Vitreous Hemorrhage: Hemorrhage into the vitreous body. [NIH]

Vitro: Descriptive of an event or enzyme reaction under experimental investigation occurring outside a living organism. Parts of an organism or microorganism are used together with artificial substrates and/or conditions. [NIH]

Vivo: Outside of or removed from the body of a living organism. [NIH]

Waist circumference: To define the level at which the waist circumference is measured, a bony landmark is first located and marked. The subject stands, and the technician, positioned to the right of the subject, palpates the upper hip bone to locate the right ileum. Just above the uppermost lateral border of the right ileum, a horizontal mark is drawn and then crossed with a vertical mark on the midaxillary line. The measuring tape is then placed around the trunk, at the level of the mark on the right side, making sure that it is on a level horizontal plane on all sides. The tape is then tightened slightly without compressing the

skin and underlying subcutaneous tissues. The measure is recorded in centimeters to the nearest millimeter. [NIH]

Warfarin: An anticoagulant that acts by inhibiting the synthesis of vitamin K-dependent coagulation factors. Warfarin is indicated for the prophylaxis and/or treatment of venous thrombosis and its extension, pulmonary embolism, and atrial fibrillation with embolization. It is also used as an adjunct in the prophylaxis of systemic embolism after myocardial infarction. Warfarin is also used as a rodenticide. [NIH]

Weight Gain: Increase in body weight over existing weight. [NIH]

White blood cell: A type of cell in the immune system that helps the body fight infection and disease. White blood cells include lymphocytes, granulocytes, macrophages, and others. [NIH]

Withdrawal: 1. A pathological retreat from interpersonal contact and social involvement, as may occur in schizophrenia, depression, or schizoid avoidant and schizotypal personality disorders. 2. (DSM III-R) A substance-specific organic brain syndrome that follows the cessation of use or reduction in intake of a psychoactive substance that had been regularly used to induce a state of intoxication. [EU]

Womb: A hollow, thick-walled, muscular organ in which the impregnated ovum is developed into a child. [NIH]

Wound Healing: Restoration of integrity to traumatized tissue. [NIH]

Xenobiotics: Chemical substances that are foreign to the biological system. They include naturally occurring compounds, drugs, environmental agents, carcinogens, insecticides, etc. [NIH]

Xenograft: The cells of one species transplanted to another species. [NIH]

X-ray: High-energy radiation used in low doses to diagnose diseases and in high doses to treat cancer. [NIH]

Yeasts: A general term for single-celled rounded fungi that reproduce by budding. Brewers' and bakers' yeasts are Saccharomyces cerevisiae; therapeutic dried yeast is dried yeast. [NIH]

Zygote: The fertilized ovum. [NIH]

Zymogen: Inactive form of an enzyme which can then be converted to the active form, usually by excision of a polypeptide, e. g. trypsinogen is the zymogen of trypsin. [NIH]

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