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HYPERVITAMINOSIS-D, WITH REPORT OF A FATAL CASE IN A CHILD.

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IT is now generally accepted that the faulty bone formation so characteristic of infantile rickets is directly due to a deficiency of vitamin D in the body, and that this factor is normally supplied in two ways—as part of the diet, and by its formation in the tissues themselves under the influence of light. We have no knowledge of its exact nature, but know that it can be provided therapeutically by means of heliotherapy, irradiation of the body with the ultraviolet lamp, cod liver oil, and irradiated ergosterol in some form or another; there is little to choose between them, for they all promote satisfactory healing. It is, of course, essential that a sufficiency of reasonably balanced fresh food is also supplied, and the importance of good hygiene and of muscular exercise emphasised; for rickets is a general nutritional disorder, in which the skeletal changes are only a part.

Cod Liver Oil has held a unique place in the management of rickets for over a hundred years. It was looked upon as a valuable food, more easily assimilated than any other fat, and able to form soluble soaps with calcium salts, thus bettering the absorption of lime. About twenty years ago, when the fat-soluble vitamins were recognised, their presence was found to be of primary importance; more recently, the specific properties of the D factor have caused it to be named the antirachitic or calcifying vitamin, so striking is its influence on calcium and phosphorus metabolism, including mineralisation of bone. The part played in osteogenesis by the other fat-soluble vitamin, the growth-promoting A factor, is not yet known, but

is possibly an important one.[1] Ol. Morrhuæ is by far the most potent natural source of these vitamins; oils of guaranteed activity are now available, and should always be prescribed.

It is known that experimental animals can be poisoned by excessive doses of this oil.[2] Agduhr[3] has shown that myocardial degeneration is the essential lesion brought about; he and Stenström[4] found that the toxic effects were just as severe after at least four-fifths of the fat-soluble vitamins had been removed; Norris and Church[5] conclude that the harmful agents are not these vitamins at all. Malmberg[6] recently published the cases of two malformed infants who were given enormous doses—up to two teaspoonfuls of the pure oil daily—soon after birth; when death ensued in a few weeks, changes identical with those described in animals were present. This was purely experimental work, for it is not accepted practice to give cod liver oil so early in life, and in such massive doses to babies; rarely, there may be passing intolerance to the few drops given three or four times daily after feeds, but this is usually combated without difficulty, and need not necessitate withholding the oil for long. We know of no contra-indication to its use, in therapeutic doses.

Ultraviolet Irradiation of the infant itself was strongly advocated by Huldschinsky in 1919. It has been shown that these rays are even more potent in antirachitic properties than those of the effective band of solar rays, which comprise waves from 290 to 313 millimicrons.[7] The efficacy of this therapy is undoubted, but infants may react with anorexia, loss of weight, undue drowsiness, and perhaps slight fever; these symptoms have nothing to do with excessive erythema, and clear up quickly when irradiation is stopped. I think that babies under a year old are better treated by other means. A point not always realised is that no immunity to rickets is brought about, and prophylactic exposures should be given regularly throughout the sunless months, if this therapy is being solely relied upon.

Irradiated Ergosterol.—It was discovered, in 1924,[8,9] that many substances could be endowed with antirachitic properties simply by exposing them to the rays of an ultraviolet lamp. Two years later, it was found[10] that the substance activated in this remarkable way was the ergosterol contained therein, and that its presence is essential. The vitamin D thus formed is indistinguishable from the factor as it exists in nature—notably in cod liver oil, in the milk of pasture-fed cows, and in green

leaves during summer. It matters not where the ergosterol may be, *e.g.* recently it was extracted from the brain of an Egyptian mummy[11] (500 A.D.), and found to be antirachitic after irradiation; green leaves in winter, when they contain little or no vitamin D, are strongly activated in the same way.

Ergosterol thus irradiated differs from all known natural sources of vitamin D in that its potency is extraordinary; a manufacturers' leaflet before me states that one-sixth of an ounce of their preparation, prior to dilution for the market, equals one ton of good cod liver oil in antirachitic power.

Medicinal dilutions of irradiated ergosterol have been on the open market of this country for years, with no uniformity of strength or of dosage. It has only recently become available in America, after its properties had been thoroughly investigated; manufacturers there have agreed to concentrate on one standardised "Pharmaceutical Viosterol" with a uniform strength of 100 D at first, but now increased to 250 D—250 times more potent than cod liver oil. The absence of any common standard of strength is most confusing, but the Medical Research Council has recently adopted *a unit of vitamin D* similar to that used by the British Pharmaceutical Society for some time; it is based on a standard solution of irradiated ergosterol maintained in the National Institute for Medical Research, the unit being defined as the antirachitic potency of a quantity of this preparation corresponding to 0·0001 mgrm. of the ergosterol used in its production.

In terms of this unit, the following approximate figures are given:—

		Units per gram.	
Fresh cows' milk contains		0·1 to 0·2	and often much less in winter.
Cod liver oil	„	60 to 150	usually about 100.
Ostelin	„	4000	
Vigantol	„	10,000	
Radiostol Solution	„	12,500	
Viosterol (250 D)	„	15,000	

With regard to the laboratory products, the recommended dosage does not vary with their reputed strengths; it is satisfactory to know that an official preparation of irradiated ergosterol may be included in the next edition of the *British Pharmacopœia*, for uniformity in the strength and dosage of this potent drug is most desirable. Until the discovery that vitamin D could be manufactured, it had been generally

accepted that all the known vitamins exerted their optimum physiological effects when presented in minute amounts, with some sort of balance between them; there is no evidence that this opinion should now be modified; fresh summer milk contains all the vitamins a baby needs; in winter, and at all seasons if the milk is sterilised, it is judicious to add a little cod liver oil and fresh fruit juice to the diet. It has been shown that rats only need a ration of dried summer milk to protect them against rickets in winter,[36] even although there is but common glass in the windows of the cage.

Irradiated ergosterol had not been long in use before experimental[12, 13] and clinical[14, 15] reports on its toxicity began to appear; the present position may be summed up from the work of Harris[16, 17, 18, 19] and his associates, Bills and Wireck,[20] and Herlitz,[21] Jundell, and Wahlgren. In rats, about 100 times the minimum antirachitic dose produces no recognisable effect on general appearance, growth, reproduction, and resistance to respiratory disease; 1000 times overdosage is definitely harmful when given over long periods, and 10,000 times is strongly toxic. Although it would appear that there is a considerable margin of safety, it is known that certain dietetic conditions exaggerate the ill effects; that young and non-rachitic animals have a lesser tolerance than mature and rachitic ones,[14, 24] and that there is a marked difference in the susceptibility of different species, as well as the possibility of individual idiocyncrasy.

The symptoms and signs of hypervitaminosis-D in animals are anorexia with marked inanition and loss of weight, diarrhœa, and a slow pulse; there is hypercalcæmia, an increase in the blood inorganic phosphate, and a gross increase in calcium output with the urine. Post mortem, a remarkable deposition of insoluble calcium salts is found in the tissues, especially kidneys and urinary tract—where there may be calculi—myocardium and walls of the great arteries; the thymus and spleen are atrophied, and the bones may show hypercalcification. It has been shown that, if the experiment lasts long enough, this may be followed by gradual demineralisation of the bones,[22] the weight of their ash being materially lessened. It is not unreasonable that calcium should be mobilised in this way, if the intake is low and excessive stimulation applied to the calcium - phosphorus metabolism, for the skeleton normally acts as a mineral reserve for the body with constant exchange taking place in it, even after growth is complete.[23] We do not

yet know how vitamin D influences this metabolism in such a profound way,[35] but it has been suggested that the parathyroids play an intermediate part,[25] as they do, directly, in generalised osteitis fibrosa.

It is noteworthy that there appear to be considerable powers of recovery, if the drug is stopped; animals will maintain a high excretion of calcium for long after all symptoms have disappeared, suggesting that the deposits are being taken into solution and got rid of.

Case of Hypervitaminosis-D.—Boy, aged 18 months, admitted 4.10.30, with the complaint of general weakness, anorexia, and refusal to take solid food. An only child, he was healthy at birth, but there was constant difficulty with feeding; after weaning at about five months he failed to gain weight, and digestive disturbance was persistent. At nine months old he was still getting diluted cows' milk in insufficient amount, and this underfeeding had to be continued.

Five months before admission, in May, he had a mild attack of diarrhœa; irradiated ergosterol was started during convalescence, and has been continued ever since. He has been having only ½ to ¾ pint of raw cows' milk daily, together with a little thin farinaceous food, orange juice, and Valentine's meat extract. He has never been ill, has been bright mentally although loth to move about, and will not walk unsupported; his appetite has been exceedingly poor for several weeks.

On admission, body length was 29 in., and circumference of head 18½ in., both about normal; but his weight was only 15½ lb.; he was said to have weighed 8½ lb. at birth, and 13½ lb. when six months old. He looked pale, puny and thin; the bones were slight, and muscles small and soft. The anterior fontanelle was open about half-an-inch, and the edge a little soft; there were no signs of rickets or the sequelæ thereof. Routine examination revealed nothing else, except a moderate albuminuria.

He had a temperature of 99·6 at night, but seemed quite comfortable: next day he was dull and apathetic, developing marked hyperpnœa with acid bodies in the urine but no sugar; this responded well to glucose and insulin. With increasing pyrexia he vomited several times. Blood urea was 90 (about three times normal); systolic blood-pressure 78. Urine was acid and contained albumin; there was a moderate number of pus cells and R.B.C. in the uncentrifuged specimen, and an occasional granular cast; culture gave a mixed growth of *Staph. alb.*, streptococci, and *B. pyocyaneus*, so that contamination was suspected.

A diagnosis of pyelonephritis was made, but as the case presented

many unusual features, the possibility of an underlying congenital abnormality of the kidney or urinary tract was considered. He became steadily worse, and died twelve days after admission.

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Kidneys.—Both kidneys were slightly enlarged, firm, and of a pale yellowish colour. Deposits of calcium were visible to the unaided eye as tiny greyish gritty particles in the medulla, especially at the bases of the pyramids. The cortex contained no visible deposits. The pelves of the ureters appeared healthy and contained no calculi. Ureters and bladder were healthy.

Microscopically, deposits of calcium were found throughout the medulla, most plentiful near the boundary zone, the cortex being unaffected. The calcareous masses were stained deep blue with hæmatoxylin, brown with silver nitrate, and strongly red by the alizarin method, which is considered to be almost a specific stain for calcium. Most of the deposits obviously lay within the lumen of collecting tubules; none could be shown to have formed in the interstitial tissue. Around many, the epithelium of the tubule was present, intact and uncalcified. In some of the smaller and more recently formed, the outlines of calcified cells were recognisable. The appearances suggested that the deposits were formed in the lumen as casts, and not by calcification of cells in position on the walls of the tubules. The latter is unlikely in the absence of necrosis of the cells. The calcified cells in the deposits were presumably desquamated at a higher level and entered into the composition of casts in the collecting tubules. Some of the deposits, especially the larger, were surrounded by increased fibrous tissue of a cellular character. In some instances the calcareous masses had evidently caused some obstruction to certain tubules, which were considerably dilated. Some of the dilated tubules contained pus, indicating the presence of a mild pyogenic infection.

The epithelium of the convoluted tubules of the cortex was of a low cubical form, differing from the normal pyramidal type. Fatty degeneration was present in these cells and in those lining Henle's tubules, and some desquamated cells lay in the lumina, but there was no severe catarrh and no necrosis. No increase of fibrous tissue was present, apart from that in direct relation to calcium deposits. The blood vessels were healthy.

Other Organs.—No calcium deposits were found apart from those in the kidneys. The myocardium was healthy to the naked eye and

on microscopic examination. The aorta and other arteries showed no macroscopic abnormality but were not microscopically examined. The spleen was of average size and healthy appearance. The thymus gland was smaller than the average in health, but no more reduced than is usual in under-nourished infants. The liver showed extensive fatty degeneration. The bones were well calcified. The enlargement at the costochondral junctions was somewhat less than that usually found in healthy infants. There was no evidence of rickets, present or past.

Comment.—The changes in the kidneys in this case closely resemble those described in experimental hypervitaminosis-D, and in Putschar's case in a baby, in which excess of vitamin D was ascribed as the cause. The fact that in this case the deposits were limited to the medulla of the kidneys and that the changes in the spleen had not occurred, suggest that we are here dealing with a relatively mild degree of the condition. The deposits were evidently formed within the lumen of the tubules, and it seems probable that the first site of deposition would be in the collecting tubules, where the concentration of calcium in the secretion is highest. With increasing severity of the condition, deposition would occur in the renal cortex, as in Putschar's case, and elsewhere, as in the experimental animals.

Nevertheless, the proliferation of fibrous tissue around some of the deposits in this case indicates that the condition had been in existence for some time, during which permanent structural damage was being done to the kidneys. The pyogenic infection, of which evidence was afforded by the presence of pus in certain dilated tubules, was slight and must be regarded as a late development. It explains the pyuria observed during life.

In view of these findings, for which no other explanation can be given, a diagnosis of hypervitaminosis-D must be made. This possibility was not considered during life; in retrospect, the following points might have guided us aright.

1. Four teaspoonfuls of an irradiated ergosterol emulsion, equal to about twice the recommended *curative* dose, were given daily throughout the summer months from May to September. The child was living under good conditions in a non-industrial seaside town, and was out of doors a great deal. The danger of overdosage is recognised to be greater when the drug is administered over a long period of time, and also during the sunny months when, under reasonable hygienic conditions, the body will not be short of vitamin D.

2. There was no sign of present or past rickets, and no history suggestive of it. Non-rachitic babies are known to be more

susceptible to the drug than are those with florid rickets.[14, 15] Putschar's case,[26] already quoted, was that of a baby six months old: there was no rickets, but six drops of vigantol were given daily for ninety-six days (the season is not stated); seventy days after it was started albumin and leucocytes were present in the urine. After death, pathognomonic changes in the kidneys were found. Rapidly growing babies are notoriously prone to develop rickets during the winter; conversely, stasis of growth and development may have rendered him more susceptible to the concentrated antirachitic regime to which he was subject throughout the summer months, when rickets hardly occurs; he had only gained about 2 lb. in his last year.

3. The anterior fontanelle was of about normal size, but elsewhere the bones seemed well calcified, and the enlargement at the costochondral junctions was somewhat less than that usually found in healthy infants. It is conceivable that, under the excessive vitamin D medication, calcium salts were being mobilised from the bones. This demineralisation, the occurrence of which has been confirmed both experimentally and clinically,[27, 28] may be encouraged by a deficient diet, as was the case here. It has been suggested that an excess of blood inorganic phosphate may be an essential cause; normally, this stands higher in summer than it does in winter,[29] and it has been shown that an increase up to about twice the normal figure is apt to occur in babies a few weeks after irradiated ergosterol has been started:[28] the reason why the bone changes of renal rickets[30] are made worse by ultra-violet irradiation is thought to be faulty excretion of phosphates, and a much increased level in the blood: experimentally,[17] overdosage to rabbits may lead to a 50 per cent. increase in the blood inorganic phosphate without any hypocalcæmia, and yet deposits of calcium will appear in their tissues. The influence of irradiated milk—with a vitamin D content about equal to that of fresh summer milk—on a series of rachitic cases is of interest;[31] they had resisted intensive treatment for long periods, correction of the abnormal bone formation being quite unsatisfactory; yet healing proceeded apace with this weak vitamin D preparation, diluted with unaltered fresh milk. An attractive explanation is that calcium-phosphorus metabolism had been unduly stimulated by the stronger concentration of the vitamin given for so long, and that calcium was being lost, instead of utilised.

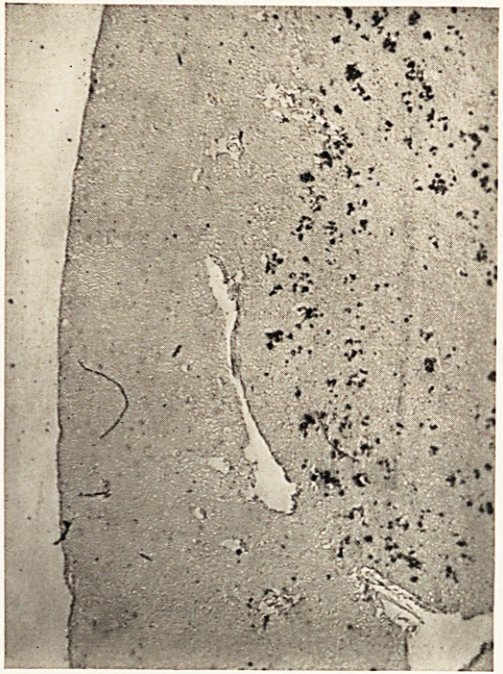

FIG 1.—Section of kidney stained with silver nitrate; low magnification; showing calcium deposits in medulla, and cortex free.

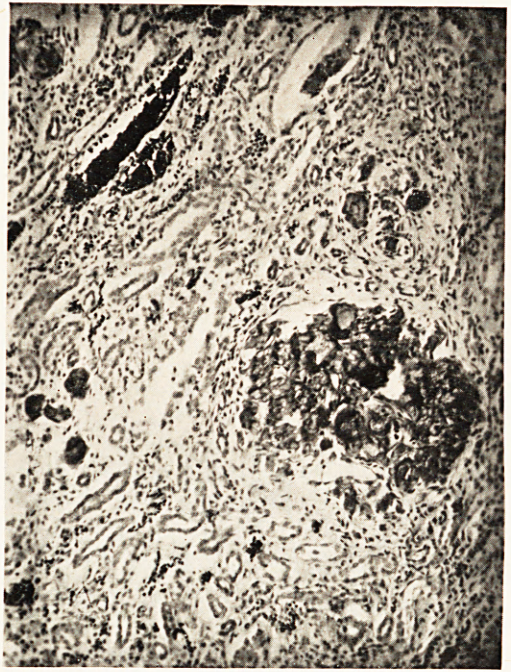

FIG. 2.—Section of kidney stained with hæmatoxylin and eosin, showing one of the larger deposits with proliferation of fibrous tissue around it. At the top of the picture a calcified cast is shown in a collecting tubule.

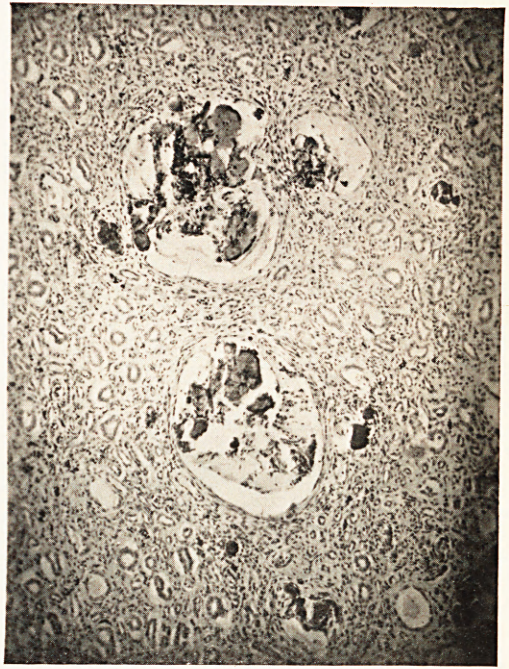

FIG. 3.—Section of kidney stained with hæmatoxylin and eosin, showing calcium deposits and pus cells in dilated collecting tubules.

Hypervitaminosis-D

The case of a rapidly growing premature infant was recently reported,[28] who showed progressive "rickets" in spite of the fact that large doses of viosterol were being given, and it has been noted [14] that such infants do not respond satisfactorily to irradiated ergosterol medication. These cases could be explained in a similar way, and bear out clinical experience that intensive treatment for the cure of rickets should be of short duration. The treatment of acute florid rickets by irradiated milk has been adversely criticised.[32]

4. The anorexia, general weakness, and marked underweight were ascribed to digestive disturbance of long standing and negativism, with consequent underfeeding; they might have been interpreted differently, if hypervitaminosis-D had been suspected. Symptoms suggestive of intolerance to irradiated ergosterol are loss of appetite, diarrhœa, slight fever, and a peculiar mental condition with drowsiness and stupor;[33] these bear a striking resemblance to the indications that ultra-violet irradiation is not agreeing, and clear up as quickly when treatment is stopped. Progressive loss of weight and cachexia, with pallor that may have a yellowish tinge,[34] are seen, and there may be albuminuria, with pyuria. Hypercalcæmia is a constant feature at first, and hyperphosphatæmia may also be found; X-rays may show excessive calcification of bone; it is as yet, not possible to say what effect this excessive calcification may have on future skeletal growth, but precipitate healing should surely be deprecated, for the correction of bony deformities constitutes an essential part in the treatment of rickets. There is no reason why recovery should not take place, as it does in animals when the drug is withheld, and such cases have been reported.[15]

Summary.—Irradiated ergosterol may be toxic to infants when given in excessive doses or over too long a period of time.

The possibility of idiosyncrasy constitutes a real danger.

The symptoms of intolerance to it are well defined, and should be borne in mind whenever the drug is being used. Non-rachitic babies are more susceptible than are those with florid rickets.

It should be used with special caution in summer, and should not be given to feeble babies, or to those who are premature.

There is no evidence that it is a better remedy than good cod liver oil either for prophylaxis or for the routine management of rickets. The influence of the growth-promoting vitamin A therein on growth, development, and susceptibility to infection should be looked upon as a valuable adjunct to the specific action of the vitamin D on calcium-phosphorus metabolism, and calcification of bone.

REFERENCES.

1 Harris, H. A., "Report of the Medical Research Council, 1928-29."

2 Hopkins, F. G., *Brit. Med. Journ.*, 1923, vol. ii., p. 691.

3 Agduhr, E., *Acta Pæd.*, 1926, vol. v., p. 319.

4 Agduhr, E., and Stenström, N., *Acta Pæd.*, 1928-29, vol. viii., p. 493.

5 Norris, E. R., and Church, A. E., *Journ. Biol. Chem.*, 1930, vol. lxxxix., p. 437.

6 Malmberg, N., *Acta Pæd.*, 1928-29, vol. viii., p. 364.

7 Hess, A. F., *Rickets, Osteomalacia and Tetany*, Kimpton, London, 1930, p. 115.

8 Hess, A. F., *Amer. Journ. Dis. Child.*, 1924, vol. xxviii., p. 517.

9 Steenbock, H., and Nelson, M. T., *Journ. Biol. Chem.*, 1924-25, vol. lxii., p. 209.

10 Rosenheim, O., and Webster, T. A., *Journ. Soc. Chem. Indust.*, 1926, vol. xlv., p. 932.

11 King, H., Rosenheim, O., and Webster, T. A., *Biochem. Journ.*, 1929, vol. xxiii., p. 166.

12 Pfannenstiel, W., *Klin. Wchnschr.*, 1927, vol. vi., p. 2310.

13 Kreitmair, H., and Moll, T., *München. Med. Wchnschr.*, 1928, vol. lxxv., p. 637.

14 Hottinger, A., *Zeitschr. f. Kinderheilk.*, 1927, vol. xliv., p. 61.

15 Hess, A. F., and Lewis, J. M., *Journ. Am. Med. Ass.*, 1928, vol. xci., p. 783.

16 Harris, L. J., and Moore, T., *Biochem. Journ.*, 1928, vol. xxii., p. 1461, and 1929, vol. xxiii., p. 261.

17 Harris, L. J., and Stewart, C. P., *Biochem. Journ.*, 1929, vol. xxiii., p. 206.

18 Harris, L. J., *Lancet*, 1930, vol. i., p. 236.

19 Watchorn, E., *Biochem. Journ.*, 1930, vol. xxiv., p. 631.

20 Bills, C. E., and Wireck, A. M., *Journ. Biol. Chem.*, 1930, vol. lxxxvi., p. 117.

21 Herlitz, C. W., Jundell, I., and Wahlgren, F., *Acta Pæd.*, 1929, vol. viii., p. 443.

22 Kreitmair, H., and Hintzelmann, U., *Arch. f. Exper. Path. u. Pharm.*, 1928, vol. cxxxvii., p. 203.

23 Hunter, D., "Goulstonian Lectures," *Lancet*, 1930, vol. i., pp. 897, 947, 999.

24 Light, R. F., Miller, G., and Frey, C. N., *Journ. Biol. Chem.*, 1929, vol. lxxxiv., p. 487.

[25] Morgan, A. F., and Garrison, E. A., *Journ. Biol. Chem.*, 1930, vol. lxxxv., p. 687.
[26] Putschar, W., *Zeitschr. f. Kinderheilk.*, 1929, vol. xlvii., p. 269.
[27] Hottinger, A., *Zeitschr. f. Kinderheilk.*, 1929, vol. xlvii., p. 341.
[28] Hess, A. F., Lewis, J. M., and Rivkin, H., *Journ. Am. Med. Ass.*, 1929, vol. xciii., p. 661.
[29] Hess, A. F., and Weinstock, M. A., *Journ. Am. Med. Ass.*, 1923, vol. lxxx., p. 687.
[30] Parsons, L. G., *Archiv. of Dis. in Childhood*, 1927, vol. ii., p. 1.
[31] Watson, D. C., Finlay, T. Y., and King, J. B., *Lancet*, 1929, vol. ii., p. 704.
[32] Hentschel, H., and Roszkowski, A., *Münch. Med. Woch.*, 1929, vol. lxxvi., p. 1423.
[33] Hess, J. H., Poncher, H. G., Dale, M. L., and Klein, R. I., *Journ. Am. Med. Ass.*, 1930, vol. xcv., p. 316.
[34] Rodecurt, M., *Münch. Med. Wchnschr.*, 1929, vol. lxxvi., p. 1420.
[35] Brown, H. B., and Shohl, A. T., *Journ. Biol. Chem.*, 1930, vol. lxxxvi., p. 245.
[36] Editorial, *Journ. Am. Med. Ass.*, 1929, vol. xciii., p. 1386.