Before discussing the interpretation of these unexpected results, the effects of scarlet fever antitoxin treatment in our wards may be recorded. Out of 960 admissions 114 of the worst cases have been given doses of scarlet fever antitoxin in amounts of 10 to 40 c.cm., according to our estimate of the severity and duration of the disease. In 96 of these the results have been extremely favourable. In this group we have observed rapid decrease in the fever, cleaning of the throat, cessation of purulent nasal discharge, and a low incidence of septic complications, such as otorrhoea (7 per cent.), in view of the fact that all the cases are severe ones. We have found antitoxin effective even so late as the fifth day of disease in septic cases. Only 3 deaths occurred out of a total of 960 cases, compared with 15 in the immediately preceding cases of the same number, none of whom received serum.

One of the fatal cases was a patient with the malignant haemorrhagic type of infection, who died a few hours following admission, after thirty-six hours' illness; 2 died of septic pneumonia. In these 3 cases the serum had no appreciable effect. In 15 others the disease was not influenced by serum. One of these was a second-day case; 6 were third-day cases; 2 were fourth-day cases; and 6 fifth-day and after.

These failures are difficult to explain, since the patients appeared no worse than others with equal duration of disease who were strikingly benefited. For many years we have used galyl with good effect in cases of scarlet fever with phagedaenic ulceration of the throat; in some of these serum failures it was used with benefit. As this drug is no longer procurable in England we have recently tried sulpharsenobenzene (three different brands), but it does not appear to be nearly so effective.

One complication that appeared in 20 per cent. of the serum-treated cases was severe secondary cervical adenitis, although only one of these cases eventually suppurated.

Discussion.

In our results the most striking feature is the remarkably slight difference among the proportions of positives in the various groups: 31 per cent. in the scarlet fever convalescents, 34 per cent. in the staff group, and 41 per cent. in the diphtheria convalescents. The surprisingly high proportion of negatives in the acute stage of scarlet fever was also quite unexpected (51 per cent.). The fact that all the negative cases in the group remained negative and most of the positive cases positive on retesting strongly confirms our opinion that there was no error in observation.

Although some of the acute scarlet fever cases showed a reversal of reaction from positive to negative on retesting during convalescence more than half still remained positive. While our results on retesting in convalescence differ from those of many other observers who have retested scarlet fever cases repeatedly during convalescence, we think that others have not sufficiently recognized the powerful effect of a few repeated skin tests in producing immunity against the toxin in certain individuals.

Although four of the Dick-positive convalescents had second attacks of scarlet fever within a month clinical experience proves that the bulk of these persistently positive reactors are unlikely to contract scarlet fever again. It may be that the nose and pharynx acquire local immunity, although general antitoxic immunity is not developed.

We first thought the test material was at fault, but this cannot be the reason, because, if it had been too weak, while the number of positive reactions in convalescence would have diminished, the number of negative reactions in the acute stage would have increased. If strong enough to make all the acute cases positive it would presumably also have increased the number of positive reactions in convalescence.

Another curious fact in the etiology of scarlet fever is the rarity of attacks of scarlet fever in infancy; many observers have stated that this is indicated also by infants always being Dick (as Schick) negative. It has been too hastily assumed that this result is due to a passive immunity inherited from the mother. This view cannot be accepted in all cases, because we have frequently seen a nursing mother contract scarlet fever while her baby escaped. Two such instances occurred in our present series of cases. In one instance the 8-day-old infant of a woman with definite scarlet fever, contracted the day after parturition, was tested and found Dick-negative. She escaped infection, although in a scarlet fever ward, while her mother was actually suffering from the disease; it is obvious that an infant cannot inherit what her mother does not possess.

Recently Dr. Fletcher[1] has stated that in the Dutch East Indies, where scarlet fever does not occur, the bulk of young children give positive Dick reactions. With increasing age the number of negatives becomes equal to that found in countries where scarlet fever is endemic; thus an immunity is obtained in spite of the absence of scarlet fever.

We would suggest that immunity to scarlet fever is partly inborn or hereditary and partly a function of age, being high in infancy, rapidly decreasing in early childhood, rising again in later childhood, and becoming comparatively high in adult life. It would appear that in any age group outside infancy reactors to the Dick test might be placed in three groups: those who are persistently strongly negative; those who fluctuate between positive and negative; and those who are strongly positive and, though convertible into the negative by artificial means, tend soon to become positive again.

We do not think the doctrine of immunity increasing in age, due to subminimal doses of infection through life, will cover all the recognized facts, especially the immunity of infants.

If it were not for the strikingly beneficial results of streptococcal antitoxin in 90 per cent. of the cases we could feel doubtful of the etiological relationship of *Streptococcus scarlatinae* to scarlet fever; but even here there are some inexplicable complete failures. Moreover, although this serum reduces the fever within forty-eight hours by several degrees in most cases, in many it does not appear to extinguish it completely, as the temperature tends to hover between 99° and 100° F. for three or four further days.

Another interesting feature is that serum does not appear to prevent secondary cervical adenitis—that is, adenitis after the throat is apparently normal. This phenomenon does not commonly occur in other streptococcal throat infections, although in scarlet fever it is certainly common even after the mildest cases. These facts, coupled with our experience of the beneficial effect of galyl (one of the arsenicals) where serum has failed, suggest the possibility that there may be another symbiotic factor, at present unknown, which might explain much that is inexplicable in the recent discoveries concerning the etiology of scarlet fever.

Reference.

[1] *British Medical Journal*, March 17th, 1928, p. 448.

THE ANTIRACHITIC ACTION OF IRRADIATED ERGOSTEROL IN CHILDREN AND ADOLESCENTS.

BY

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It is now ten years since rickets was first proved by scientific experiment to be intimately related to the absence from the dietary of a specific food factor. This new conception of the etiology of the disease met with considerable opposition, but it has held its own against all previously recognized hypotheses, and to-day there are grounds for believing that the specific antirachitic food factor has actually been isolated as a pure chemical substance. The story of the experimental work that led from the original proof of the existence of the antirachitic factor to its isolation is a long but fascinating one, and the main steps in the chain of discovery may be condensed as follows.

To Mellanby[1] belongs the credit of establishing the existence of the antirachitic factor by means of his exhaustive investigations on puppies. He demonstrated that

rickets could be produced with certainty, and be prevented or cured with equal certainty, by the omission from, or addition to, the diet of certain foodstuffs, the most important of which were cod-liver oil, egg-yolk, cream, and butter. These foodstuffs, which he found were able to prevent the occurrence of rickets when given to growing animals, were known to be rich sources of the then comparatively recently discovered fat-soluble vitamin, or vitamin A. For some years it remained doubtful whether this growth-promoting vitamin A and the antirachitic vitamin were identical bodies, but in 1922 McCollum and his co-workers[2] proved that they were two distinct entities, one of which (vitamin A) was more easily destroyed by oxidation than the other.

Many attempts were made to isolate these factors, and though it was found possible to obtain highly concentrated active fractions from such substances as cod-liver oil which were rich in fat-soluble vitamins, efforts to separate the vitamins as pure chemical substances were never successful.

In the meantime Huldschinsky[3] had demonstrated that rickets could be cured in children by exposing them to ultra-violet light. Shortly afterwards it was found by Hume,[4] and by Goldblatt and Soames,[5] that rats kept without a supply of fat-soluble vitamin would grow better if they were exposed to ultra-violet light. Hume and Smith[6] later found that stimulation of growth and good bone calcification occurred in rats as the result of exposing the cages in which they were housed to ultra-violet light; it was subsequently found that this occurred only when sawdust was present in the cages during the irradiation, some of the sawdust being afterwards eaten by the animals. Steenbock and Black[7] were working at this time on the effects of ultra-violet irradiation, and they had already found that the irradiation of common foodstuffs previously devoid of any fat-soluble vitamins conferred on them the property of promoting growth and good bone calcification.

It seemed important to determine whether these findings were applicable to cases of human rickets, and in 1925 Cowell[8] showed that active rickets could be cured in children by giving them milk which had previously been irradiated. Hess shortly afterwards published similar results obtained with dried milk; the same worker later found that the irradiation of apparently pure cholesterol rendered it powerfully antirachitic both in animals and children. For a short time it was believed that irradiated cholesterol might prove to be the much sought after antirachitic vitamin. It was soon proved that perfectly pure cholesterol could not be made antirachitic by irradiation, and in 1927 Rosenheim and Webster,[9] and Windaus and Hess,[10] showed that the irradiation of the chemically related ergosterol converted it into an intensely potent antirachitic agent. It is now considered highly probable that this sterol is the true parent substance of the antirachitic vitamin, or "provitamin," and is converted into the actual antirachitic vitamin under the influence of ultra-violet light.

Irradiated ergosterol was shown to have a marked curative effect in clinical cases of rickets, and commercial preparations have been put on the market by reputable firms both in this country and in Germany. The German preparation is sold under the trade name of "vigantol"; numerous articles have been published in Continental medical journals during the past few months describing the successful results obtained by its use in cases of rickets and osteomalacia. Three widely advertised British preparations are sold by the British Drug Houses under the names of (1) radiostol, which contains the antirachitic vitamin alone; (2) radiostoleum, which contains vitamin A as well as the antirachitic vitamin; (3) radiomalt, which contains both vitamins, together with malt. Few reports as to the efficacy of these preparations in clinical cases have yet been published. Aidin[11] has recently recorded a series of five cases of rickets in young children treated successfully by radiostol. The dose given to his patients was at first 3 minims three times a day; this was found to be insufficient to bring about rapid healing, and the amount was increased to 10 minims three times a day.

The cases of rickets about to be described were treated with the commercial preparations of irradiated ergosterol under controlled conditions in hospital. The diagnosis of active rickets was confirmed in every case by means of radiograms, and progress was followed by a series of *x*-ray photographs taken at frequent intervals. The patients' diets were chosen in such a way as to exclude the possibility of any considerable amount of antirachitic vitamin being consumed—that is to say, they were given but a small daily allowance of milk, no eggs, and no butter; they were allowed green vegetables, which furnished a supply of vitamin A. The patients themselves were kept in such positions in the wards that direct sunlight could not fall on them. It has previously been shown that under these conditions no appreciable healing of active rickets takes place in the course of a few weeks.

Case 1.—A girl, aged 1¾ years, with marked deformities of the lower limbs, and bronchial and nasal catarrh. Treatment: For the first twenty days 3 minims of radiostol were given twice a day; subsequently 5 minims three times a day. Slight healing at the epiphyses was noted after three weeks, and rapid healing after four weeks; healing was virtually complete in six weeks. After ten days in hospital she developed acute bronchitis; her allowance of milk was at once increased to 1½ pints a day, and she became afebrile in three days. She gained 4 lb. in weight during the six weeks of treatment.

Case 2.—A boy, aged 5, with marked rickety deformities. Treatment: For the first twenty days 4 minims of radiostol twice a day, subsequently 5 minims three times a day. Pronounced healing was apparent in three weeks, very dense calcification at the ends of the diaphyses in six weeks, though the margins were still irregular. He gained 4½ lb. in the course of the treatment.

Case 3.—A girl, aged 2, with moderate deformities of the lower limbs; florid rickets radiographically. Treatment: 5 minims of radiostoleum three times a day. Pronounced healing was apparent in three weeks, and healing was complete by the sixth week. Her general condition was much improved, and she gained 1½ lb. during the six weeks.

Case 4.—A girl, aged 13, with late rickets; she had noticed pain in her knees and slight knock-knee deformity for about two months; active rickets was clearly shown in the *x*-ray photographs. Treatment: 5 minims of radiostol three times a day. Healing was just beginning after ten days, and was practically complete in five weeks.

Case 5.—A girl, aged 17, with late rickets. She was small and under-developed for her age; she began to menstruate at the age of 16. When she was 15 she first noticed that she was getting knock-kneed; for two or three months before admission she had had considerable pain in her knees. Treatment: 5 minims of radiostol three times a day. Healing was just beginning after ten days; it proceeded rapidly after three weeks, and was almost complete in five weeks.

These cases show that the commercial preparations of irradiated ergosterol employed will bring about the healing of active rickets in young children of various ages and in adolescents. The minimal effective dose for bringing about rapid healing was approximately determined in Case 1, where 6 minims of radiostol a day produced only very slight healing in three weeks, whereas the later cases healed very rapidly in this space of time with 15 minims a day. It would appear probable that 15 minims of either radiostol or radiostoleum is a sufficient daily dose for most cases of rickets. It is unlikely that any ill effects would follow the giving of even considerably larger doses, though Kreitmar and Moll[12] have recently shown that certain experimental animals can be poisoned in a few weeks by giving them daily doses of irradiated ergosterol of the order of 1,000 times the minimal effective antirachitic dose.

It may perhaps be emphasized that though irradiated ergosterol will bring about the healing of rickets it does not, like cod-liver oil, contain vitamin A, and evidence is now accumulating to show that an adequate supply of this vitamin is all-important to secure resistance to infections. When, therefore, any preparation of irradiated ergosterol is employed as an antirachitic agent, it is essential to see that a sufficient supply of vitamin A is given at the same time. This can be done by including egg-yolk, butter, milk, and green vegetables in the diet, or by using a preparation which contains this vitamin in a concentrated form. All the young children whose cases are reported here put on weight during their treatment. Curiously enough the one that gained least weight was the one that received the extra supply of vitamin A in the form of radiostoleum.

This work was assisted by a grant from the Medical Research Council, to whom my thanks are due. I wish to express my thanks to Professor Mellanby for permission to publish these cases, which were under his care at the Royal Infirmary, Sheffield.

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REPORT ON THE RESULTS OF EXAMINATION OF NINE CASES AFTER THE ORAL INGESTION OF 1,000 GRAMS OF GLUCOSE.

BY

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IT has been stated by different authorities that it is impossible to make a normal person pass sugar in the urine after the oral ingestion of glucose.

The leak point of the kidney for glucose is now generally recognized as being between 0.16 and 0.18 per cent. MacLean[1] states that the hyperglycaemia resulting from the ingestion of carbohydrates appears, in the normal individual, to be limited to about this level, the threshold level for glucose, and cannot easily, if at all, be forced above it. He also goes on to state that in this fact lies the explanation of the difficulty in provoking glycosuria in the normal individual by giving glucose, a difficulty referred to in several recent publications. Later on in the same book[2] he quotes Taylor, who, as the result of experimental work,[3] stated that "in the majority of healthy males there is no limit of assimilation of glucose; glycosuria does not occur following the largest possible ingestion of pure glucose." These observers in five instances gave doses of 500 grams of glucose, with the production of glycosuria in one case only.

Shapland,[4] commenting on this subject, states that—

> A striking phenomenon in the curve of the healthy subject is the intervention of the storage mechanism, directly the blood sugar concentration approaches the normal renal threshold for sugar. This storage mechanism is so efficient that even if sugar ingestion is pushed to the limit of digestive tolerance, it is rarely possible to produce a demonstrable glycosuria in a normal subject. It is indeed doubtful if alimentary glycosuria can occur in perfect health. Should it occur in a subject with a normal renal threshold for sugar, it indicates a defect in dealing with excess of carbohydrate, and, therefore, the patient should be regarded as a potential diabetic.

Up to the present all attempts at giving doses of more than 500 grams of glucose have failed, owing to the nausea and vomiting which were induced. It occurred to me that, as the native races of Natal are fond of sugar, it might be possible to induce them to take larger doses than those previously recorded. Acting on this assumption nine natives were examined. In each case an ordinary glucose tolerance curve was first done in order to eliminate any cases in which there might be any disturbance of the glycogen-storing power of the liver. For this the usual dose of 50 grams of glucose was employed.

MacLean's method of estimating the blood sugar was employed throughout the investigation, and the urine tests were made with Benedict's solution. It will be seen from examination of the charts that, with the exception of Cases 3 and 5, a normal glucose tolerance was found. Cases 3 and 5 each showed a maximum blood sugar concentration of 200 mg. per 100 c.cm. of blood. I think that it may be assumed that these two readings are within the limits of experimental error. Each patient was then given a dose of 1,000 grams of glucose, and in each case this huge dose was swallowed without any nausea or vomiting. Cases 1, 5, 6, 7, and 9 show a distinct rise in the blood sugar and a definite glycosuria. Examination of the charts will show that the glycosuria varied from a trace up to 2 per cent. The hyperglycaemia varied within rather wider limits.

This series of cases, though small, shows definitely that the ingestion of huge doses of glucose strains the glycogen-storing capacity of the liver to its fullest extent, and that there is then a certain degree of overflow.

During the course of this investigation I discussed these cases with Professor MacLean, who pointed out that in his opinion the interesting point was that some of the cases passed sugar in the urine with a blood sugar content which was lower than that which is ordinarily accepted as the normal excreting level. (See Cases 2, 3, 4, and 8.) It

In each of these charts the continuous curve shows blood sugar after 50 grams of glucose; the interrupted curve shows blood sugar after 1,000 grams of glucose.

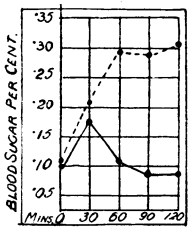

Chart 1.

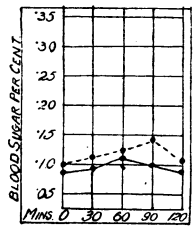

Chart 2.

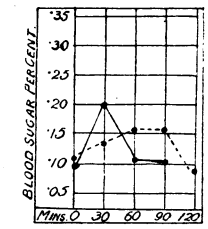

Chart 3.

CHART 1 (Case 1).—Urine after 50 grams of glucose: 1 hour, nil; 2 hours, nil. After 1,000 grams of glucose: 1 hour, trace; 2 hours, ½ per cent.

CHART 2 (Case 2).—Urine after 50 grams of glucose: 1 hour, nil; 2 hours, nil. After 1,000 grams of glucose: 1 hour, nil; 2 hours, 1 per cent.; 8 hours, 2 per cent.; 13 hours, 1 per cent.

CHART 3 (Case 3).—Urine after 50 grams of glucose: 1 hour, nil; 2 hours, nil. After 1,000 grams of glucose: 1 hour, nil; 2 hours, trace; 14 hours, trace; 20 hours, trace.

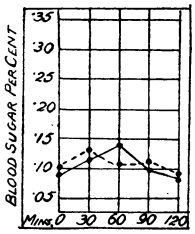

Chart 4.

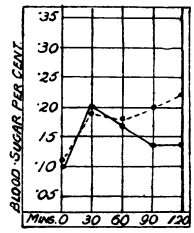

Chart 5.

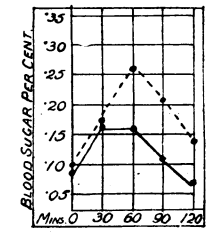

Chart 6.

CHART 4 (Case 4).—Urine after 50 grams of glucose: 1 hour, nil; 2 hours, nil. Urine after 1,000 grams of glucose: 1 hour, trace; 2 hours, 1 per cent.; 6 hours, ½ per cent.; 18 hours, 1 per cent.

CHART 5 (Case 5).—Urine after 50 grams of glucose: 1 hour, nil; 2 hours, nil; 3 hours, nil. After 1,000 grams of glucose: 1 hour, nil; 2 hours, 1 per cent.; 3 hours, 2 per cent.; 4 hours, 2 per cent.

CHART 6 (Case 6).—Urine after 50 grams of glucose: 1 hour, nil; 2 hours, nil. After 1,000 grams of glucose: 1 hour, trace; 2 hours, 1 per cent.; 6 hours, ½ per cent.; 18 hours, trace.

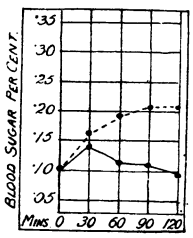

Chart 7.

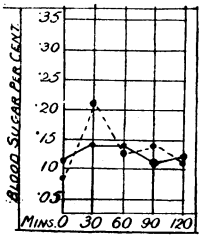

Chart 8.

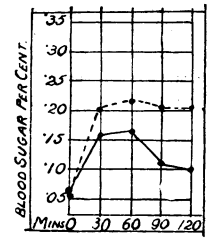

Chart 9.

CHART 7 (Case 7).—Urine after 50 grams of glucose: 1 hour, nil.; 2 hours, nil; 3 hours, nil. After 1,000 grams of glucose: 1 hour, nil; 2 hours, trace; 3 hours, 1 per cent.

CHART 8 (Case 8).—Urine after 50 grams of glucose: 0 hour, nil; 1 hour, nil; 2 hours, nil. After 1,000 grams of glucose: 3 hours, trace; 16 hours, 1 per cent.

CHART 9 (Case 9).—Urine after 50 grams of glucose: 1 hour, nil; 2 hours, nil; 3 hours, nil. After 1,000 grams of glucose: 1 hour, nil; 2 hours, 1 per cent.; 7 hours, trace.

was interesting also to note that in some cases the glycosuria persisted for periods up to eighteen hours after the ingestion of the glucose.

In view of the information derived from these experiments it is interesting to review again the current views on alimentary glycosuria and renal glycosuria. Cammidge[5] admits that if the glycogenetic powers of the liver are exceeded a portion of the carbohydrate derived from the food may enter the peripheral circulation, and so produce hyperglycaemia and glycosuria. In this way, he states, it