and deep follicles present. (Fig. 6). This work requires confirmation, but if this is forthcoming it is certainly suggestive as a possible reason for the decline in the protective mechanism of the organism against infection and also for the loss of immunity against bacterial infection in vitamin A deficiency.

Professor McCoy lectured recently upon "Immunity in Helminth Infections," and he stated that an immunity is developed in some way at present unknown while the worms are in the alimentary canal. He demonstrated that the development of this immunity could not be brought about after animals had been for two weeks on a vitamin A deficient diet and before there was time for the development of epithelial changes. May it not well be due to the effect of a lack of vitamin A upon the lymphoid tissue of the alimentary tract?

Commentary

You may ask why a surgeon should venture into the sacred domain of bacteriology and dietetics; the answer is that I believe that just as you have a recognized department of medicine known as "preventive medicine," so there ought to be an endeavour to establish "preventive surgery." I visualize the time when the physician will try to prevent and even treat his typhoid cases, which after all are probably simply attacks on the lymphoid tissue of the Peyer's patches by *B. typhosus*, and the surgeon will try to prevent an attack of appendicitis, which is probably an attack of septic organisms on the lymphoid tissue of the vermiform appendix—possibly in both cases by a well-balanced diet or by vitamin therapy.

Anyhow, every advance in the science of medicine brings nearer the time when medical and surgical advice will be sought more for the prevention than for the cure of disease; for, as recently pointed out by Sir Robert McCarrison, Medicine is not simply concerned with the cure but still more with the prevention of disease, and we surgeons are quite willing and anxious to do our share in the discovery of means whereby we can beat our scalpels and forceps into forks, spoons, and chopsticks for the administration of a well-balanced diet.

I want to thank Drs. H. C. Hou, F. F. Tang, and Yu-ho for much helpful advice, Mr. Henderson for his painstaking efforts in assisting me in this piece of work, and Mr. R. V. Dent for the photomicrography.

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H. v. Heuss (*Med. Welt*, November 6, 1937) describes the effects of the "yellow-cross" poison gas, dichloroethyl sulphide. It is lipid-soluble and it impregnates the superficial layers of the skin, reaches the subpapillary blood vessels and their nervous plexuses, and since these plexuses are rich in lipoids it tends to accumulate there. The general clinical picture is somewhat similar to that of Addison's disease. The affected individuals are apathetic and adynamic; they suffer from vomiting and diarrhoea and they lose weight, and some cases may show pigmentation of the skin. The author, therefore, recommends for these cases extracts of suprarenal cortex in combination with glucose administered intravenously or intramuscularly.

THE MODERN TREATMENT OF DIABETES MELLITUS AND THE USE OF ZINC PROTAMINE INSULIN*

BY

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Until about fifteen years ago the treatment of diabetes mellitus in the young and middle-aged was generally unsatisfactory to the doctor, and often almost cruelty to the patient: carbohydrates, fats, and proteins were progressively restricted as the disease advanced, so that the unfortunate patient eventually existed in a state of semi-starvation, until coma and death released him from his sufferings, usually within two or three years from the time the diagnosis was first made. About the year 1922, however, with the introduction of insulin, the renaissance of the treatment of diabetes took place. Even then the policy was still to limit the patient's diet so that only a minimum dose of insulin was required; for it was then uncertain what the exact effect of insulin would be if given over a long period.

Modern Methods of Dieting

It has been only during the last few years that, as a result of the increasing knowledge of the effect of insulin, gradually more liberal carbohydrate diets have been allowed, and lately, unless the patient be overweight, 150 to 200 grammes or more of carbohydrate per day have been given, with a somewhat restricted amount of fat. It has not been found that the insulin has to be increased to any great extent on this account. I have a patient, a young woman, suffering from a severe toxic goitre with much wasting, together with true diabetes mellitus. On a diet of 300 grammes of carbohydrate with as much fat and protein as she likes, and with sufficient zinc protamine insulin to keep her free from glycosuria, she is improving; so much so that a subtotal thyroidectomy will be possible in the near future.

The advantages of an increased carbohydrate diet are:

1. Patients feel much fitter, both physically and psychologically, as the diet approximates to that of an ordinary healthy individual and is more correctly balanced.
2. Life is made easier for them. The modern diabetic can stay at an hotel, and with care is able to choose his food from the ordinary menu; the child can have his meals at the family table, provided he keeps within his fixed ration of carbohydrates, which is now a satisfying one.
3. The chances of hypoglycaemia occurring, which the diabetic dreads, are much lessened.
4. The occurrence of ketosis is much decreased.

5. It has been claimed that an increased carbohydrate diet with a relative decrease of fat lessens the incidence of arteriosclerosis, which is such a common complication of diabetes in later life. This, however, is too large a subject to be referred to any further here.

The simplest method of arranging the diet for a diabetic is, I find, the Lawrence line ration scheme. The number of black lines to be taken, each containing ten grammes of carbohydrate, is settled for each patient. At first this food is weighed, but later on the patient can guess the amount with sufficient accuracy. The number of the red lines containing fixed amounts of fat and

* The substance of the Presidential Address delivered before the Derbyshire Branch of the British Medical Association, June 23, 1937.

protein can be neglected unless the patient is obese, the amount taken being left to him, according to his appetite. Thus there are no difficulties in calculating elaborate diets which many patients in the past never understood.

Action of Soluble Insulin

Insulin has a profound effect in lowering the concentration of the sugar in the blood. How this is done is, however, not quite understood. The time relations of its action and of its duration are fairly constant and do not depend on the size of the dose, though the extent of the fall of the sugar in the blood does. The blood sugar begins to fall within fifteen to thirty minutes after injection; the insulin then acts with its maximum force for three to six hours, and its effect has worn off by the end of eight to ten hours. Practically all young patients with diabetes mellitus, and about three-quarters of the middle-aged patients, need insulin.

Diabetes in young and middle-aged people can generally be controlled during the day with one, two, or even three injections of insulin, but in severe cases the glycosuria usually returns during the night, and ketosis may even occur; and if attempts are made to check the nocturnal glycosuria by increasing the amount of insulin there is a great danger of hypoglycaemia occurring when the patient is asleep.

The New Insulins

It has for some time been realized that for these cases of diabetes in which the glycosuria cannot be controlled for twenty-four hours an insulin whose action will last longer is needed. Although much research had previously been done, it was not until 1934 that Hagedorn in Copenhagen found that if insulin is mixed with a protamine, a special type of protein derived from trout sperm, a precipitate is formed which if injected into the subcutaneous tissues has the same effect as ordinary insulin, but is absorbed more slowly, comes into action later, and is more lasting in its effect. This suspension of protamine and insulin is known as "insulin retard." It is absorbed so slowly that it has no appreciable action on the blood sugar for one and a half to three hours after injection. It exerts its maximum action in from six to ten hours, and this ceases after twelve to eighteen hours.

The most recent advance has been that by Scott of Toronto in 1936. He found that if a trace of zinc is added to the "insulin retard" a yet more stable and less soluble insulin is formed, which if injected subcutaneously after shaking is more slowly absorbed; consequently its effect lasts still longer. It is called zinc protamine insulin. It has no appreciable action on the concentration of the sugar in the blood for three to six hours following the injection, after which it slowly begins to work, exerting its maximum effect in from eight to twelve hours. In moderate doses its action lasts from fourteen to twenty-four hours, and in larger doses it has worn off in thirty hours. In practice, however, the insoluble insulins do not act always quite so exactly: there may be a little variation; they may either come into action a little earlier or their effect may be delayed.

Advantages and Disadvantages of the New Insulins

There are certain advantages, but also disadvantages, in using zinc protamine insulin instead of soluble insulin. The following are the chief advantages:

1. Zinc protamine insulin lowers the blood sugar, and owing to its slow action should control it not only during part of the

day but in most cases during the night also; consequently no glycosuria and ketosis should occur during the night, as so often happens in patients treated with soluble insulin. In many cases only one injection in twenty-four hours is necessary.

2. The high carbohydrate diet can be spread more evenly over all the meals instead of confining the bulk of it to those following the injections of soluble insulin.

3. Owing to the slowness of the absorption of zinc protamine insulin no sudden reduction of blood sugar will take place, so that the not infrequent hypoglycaemic attacks in diabetics treated with soluble insulin occur with much less frequency. This is a great advantage, especially in diabetics in whom exercise is followed by attacks of hypoglycaemia.

4. Patients who have been treated with both soluble insulin and zinc protamine insulin say they have a greater sense of well-being with the latter. Possibly this is because of the better control of the glycosuria, the absence of hypoglycaemic attacks, and the need for only one injection a day.

There are, however, certain disadvantages in the use of the newer insulin:

- (a) Since the less soluble insulin is absorbed more slowly it will take longer to come into action—at least from three to six hours. Thus if it is given before breakfast, as is generally the case, the effect of the zinc protamine insulin taken the previous day will very likely have worn off; if not, then the patient has been given too much, for any post-breakfast glycosuria should not be controlled by the zinc protamine insulin which was given the day before. Consequently, as for three to six hours there will not be enough insulin in the blood stream to deal with the sugar absorbed from breakfast, the concentration of sugar in the blood will rise and glycosuria will occur. In such cases the most satisfactory way of dealing with the difficulty is to give along with the zinc protamine insulin, in the same syringe, a requisite dose of soluble insulin. This will act within fifteen to thirty minutes of the injection, and its effect should last until the zinc protamine insulin starts to act.

- (b) As the newer insulins are less soluble the rate of absorption, being dependent on the state of vascularity of the tissues into which they are injected, may vary a little from day to day, and consequently so may the concentration of the blood sugar.

- (c) It is true that hypoglycaemic attacks are not nearly so common in the cases treated with the less soluble insulins, but when they do occur they are much more severe and dangerous, coming on without warning and taking the form of convulsions or sudden unconsciousness, without any of the premonitory symptoms such as sweating, dizziness, etc. Further, these attacks of hypoglycaemia come on later than do those which are due to an excess of soluble insulin, because zinc protamine insulin takes longer to exert its maximum effect. Thus if an injection is given before breakfast, the attack, if it does occur, will take place some time during the following night when the patient is asleep.

Treatment of Hypoglycaemic Attacks

The important thing is, of course, to prevent these attacks from occurring. The stabilization of a patient with zinc protamine insulin should, with our present knowledge, be undertaken only in an institution where the patient can be under proper supervision and where adequate urinary and blood examinations can be carried out. Any increase in zinc protamine insulin must be made with caution and at not less than three-day intervals. A high carbohydrate diet should also always be given and a carbohydrate meal be taken at bedtime.

To prevent the danger of nocturnal hypoglycaemia it has been suggested that the insoluble insulin be given at night alone, with a carbohydrate meal. The disadvantage of

this is that the blood sugar cannot then be controlled during the night. I have not used this method.

The best treatment when a severe hypoglycaemic attack does occur consists of intravenous injections of dextrose, as the patient will be unable to swallow. Improvement will follow, but relapses are apt to occur, and several injections may be necessary before the patient is fully restored.

Conclusions Drawn from the Use of Zinc Protamine Insulin and High Carbohydrate Diets

As it is now some time since the appearance of the original papers describing the action of the less soluble insulins the publication of further information which may or may not support the claims made for them may be considered opportune.

My own experience with zinc protamine insulin is confined to twenty-five patients, all of whom, with the exception of the obese, are taking a high carbohydrate diet and have been carefully stabilized either in hospital or in a nursing home. They are attending the "follow-up department."

I have found it possible to keep all the mild cases of diabetes needing insulin well controlled, in good health, and free from symptoms on one dose of zinc protamine insulin, given once a day before breakfast. In the more severe cases the blood sugar was kept within normal limits during the later part of the day, and also during the night, with one dose each day. But its slow action was noted, and glycosuria invariably occurred after breakfast; this was abolished, however, with a dose of ordinary insulin given at the same time as the less soluble insulin. One case of glycosuria after dinner occurred in spite of a large dose of zinc protamine insulin. However, on adding "insulin retard" to the original dose this disappeared. Two of the patients suffered from hypoglycaemic reactions after exercise, and on this account their blood sugars had to be kept a little raised. They were given enough zinc protamine insulin to keep their blood sugars within normal bounds, and some soluble insulin was also given at the same time. No reactions have occurred since.

Only one patient in this series, a labourer, has suffered from a severe hypoglycaemic attack. He had been stabilized with 50 units of zinc protamine insulin and 12 units of soluble insulin. Some weeks after leaving hospital he was working on a morning shift, and was given a heavier job to do than usual. Soon afterwards he became unconscious and was admitted to hospital. He responded well to intravenous glucose, but relapsed a little later. However, after the third dose of dextrose he completely recovered.

All these patients appreciate the fact that they need only the one injection each day.

Method of Use of the Newer Insulins

When stabilizing a patient suffering from diabetes, and one who has never before received insulin, it is quite safe to begin with a daily dose of zinc protamine insulin of 20 to 30 units, or 30 to 40 in a more severe case. The injection is generally given shortly before breakfast, and this may suffice to control the disease in mild cases.

It is usually necessary, however, to increase the amount of insoluble insulin, and the simplest check at first is the state of the urine, providing the patient has a normal renal threshold for sugar; (an abnormal renal threshold is, I find, quite common in diabetes, even in the young).

The urine is tested every three hours, the patient being told to empty the bladder half an hour beforehand, this specimen being neglected. When the urine is sugar-free the blood sugar may have fallen too low; therefore some periodical blood-sugar estimations are necessary at this stage, the specimens being taken about three hours after the injection of soluble insulin and breakfast; about twelve hours after injecting zinc protamine insulin, when it should be working at its maximum force; and before breakfast next morning, when the effect of the insoluble insulin should nearly have worn off. A blood-sugar estimation is of little use unless its time relation to food and the dose of insulin is known.

One's aim in treating young and middle-aged diabetics is to keep them in good health, with a urine free from sugar and a blood sugar within normal limits. But there are some cases of diabetes—generally severe, especially in young people—in which it is impossible to keep the blood sugar within normal bounds without risk of hypoglycaemia: with these patients the blood sugar is very labile, and they may even alternate between hyperglycaemia and hypoglycaemia on the same dose of insulin. One must be content to let them continue with a somewhat raised blood sugar.

When it is thought desirable to change a patient over to zinc protamine insulin from soluble insulin it is safe to start with the same dose and number of units of the former as the patient was taking of the soluble insulin, but given in one injection. This can be increased if necessary, and a dose of soluble insulin added if there is any glycosuria after breakfast. But one certainly hesitates at present to change over to insoluble insulin the large number of diabetics who are well controlled and in good health with soluble insulin and who do not mind having two injections a day.

In cases of very severe diabetes where there is much ketosis, and also in cases of coma, it has been recommended that the patient should have a large dose of soluble insulin in order to get a quick response, and at the same time an injection of zinc protamine insulin, so that the insulin effect can be prolonged. I find, however, that the best plan is to treat these severe diabetics in the ordinary way with large and repeated doses of soluble insulin alone until the condition has improved, when they can be switched over to insoluble insulin if necessary.

Follow-up of Patients

On leaving hospital, where he has been thoroughly trained to manage his diet and to give himself insulin, the patient must be instructed to see his doctor at regular intervals, or to attend a follow-up department, which should be established at every hospital where diabetes is treated. It is well known that the severity of the disease fluctuates from time to time for better or worse: the sugar tolerance may improve; but after some infection or adverse circumstances, and quite often for no apparent reason, the disease may progress. Therefore the amount of insulin may need adjusting periodically. This is a little more difficult to manage with insoluble insulin than with the soluble. With the latter the patient can conveniently attend the follow-up clinic about three hours after his morning dose of insulin, and the blood sugar can be estimated. This gives an idea as to whether or not the dose is suitable. But the optimum time for estimating the blood sugar with zinc protamine insulin taken once a day is before the morning dose. Patients living near the clinic therefore come up periodically before breakfast and the morning dose of insoluble

insulin, and their blood sugars are estimated. Every patient tests his own urine before breakfast about three times a week, and enters the result in a notebook, which is produced each time he attends the follow-up clinic. I find little difficulty in persuading patients to attend the clinic regularly. It is only by careful clinical and chemical after-care that the diabetic can be kept in good health and the disease held in check.

Treatment of Elderly Diabetics

The treatment of diabetes in elderly people is rather different from that which is adopted in the case of the young or middle-aged, since arteriosclerosis is so often associated with the disease, and may appear to be the primary condition. In such cases symptoms of diabetes may be absent, so that the condition may not be discovered until a routine examination is made for some other complaint, often one due to the cardiovascular, ocular, or central nervous system. If, however, the diabetes is allowed to continue unchecked symptoms will very likely occur, and ketosis and even coma may follow, though not so commonly as in younger people; but I have during the past year seen one patient with diabetic coma and two on the verge of it who were over 65 years of age.

In elderly people diabetes unaccompanied by ketosis should not be treated too energetically by great restriction of carbohydrates, or by large doses of insulin with the idea of lowering the blood sugar to the so-called normal values and rendering the urine free from sugar for the whole of the twenty-four hours, because they will certainly not feel so well, and their general condition, including quite possibly their heart muscle, will deteriorate. On the other hand treatment must not be neglected: judicious limitation of diet of all kinds, especially if the patient is obese, together with increased exercise and possibly thyroid, and insulin in selected cases, will help. Zinc protamine insulin with its slow action is very useful for elderly patients who need insulin.

The criterion of improvement in patients suffering from diabetes associated with arteriosclerosis is certainly not determined in the laboratory by finding a urine free from sugar and a blood sugar of normal value, because the normal level of the blood sugar may not be the ideal. Rather it is the general clinical improvement, with absence of symptoms, at which one must aim in treatment.

Conclusion

With regard to the value of the newer and less soluble insulins, whilst they have passed the purely experimental stage and are ready for clinical use, nobody yet has sufficient experience to lay down hard-and-fast rules. At present one can only indicate how they are used, try them out on suitable cases under proper control, and note the results. The time is hardly ripe to decide whether or not they are a success. The newer insulins are powerful weapons with certain dangers, and therefore should not be used except with proper precautions, and their effects suitably controlled so that serious hypoglycaemic attacks may be avoided.

Although one must not generalize from this small series of cases which have been investigated personally and treated with high carbohydrate diets and zinc protamine insulin, yet my experience is that in suitable cases, with the proper use of the newer less soluble insulins, a step forward has been made in the treatment of diabetes mellitus.

PERSISTENT OVERMOULDING OF THE SKULL BONES CAUSING FITS IN AN INFANT

BY

G. C. GORDON, M.B., Ch.B.

(WITH SPECIAL PLATE)

A female infant 14 days old was admitted to hospital with a history of one fit, occurring approximately an hour before admission.

Case Report

When first seen the child was very pale and rather drowsy, and lay perfectly still with closed eyes. Its temperature was 97.8°F., the pulse rate 138, and respirations 26. The mother said that the pregnancy had been normal and full-time. On March 29, 1937, the membranes ruptured; labour pains began at 11 p.m., and the child was born at 11.55 p.m. the same day. It weighed 7 lb. 8 oz. No instruments were used. The child cried after birth, but the mother stated that on being washed it made a "curious noise" for the rest of the night. Afterwards it became abnormally quiet, and was continually drowsy without remission. The infant had to be "wakened" for every feed, and did not suck satisfactorily. Although fed every three hours its weight dropped to 6 lb. 1 oz. The stools had been normal since birth.

This was the second child, the first being a healthy, normal boy, now 3½ years old. There was no history of illness or fits, and there had been no miscarriages. Investigation of the family history of both father and mother revealed no specific disease, epilepsy, or other illness which might have a bearing on the child's condition. The mother was Wassermann-negative.

Soon after admission another fit occurred. The child suddenly became deathly pale, the pulse and respiration were imperceptible, and the lips took on the light bluish coloration usually seen in death. The limbs were flaccid, and not the slightest muscular movement could be observed; the eyelids were peacefully closed and the child did not cry out—in other words it appeared to be dead. Very slight movement of the chest could be seen on close examination, and the heart sounds were slow and almost inaudible. Oxygen was administered, and after two minutes the colour improved and pulse and respirations returned to normal.

A complete examination failed to show any pathological change. The stools were offensive and relaxed. No abnormality of the heart was present, and between fits examination revealed no lesion of the central nervous system, the child having full use of its limbs with no apparent sensory loss. The temperature was found to be invariably subnormal during the fits, and at no time did pyrexia occur. The usual causes of convulsions and fits were ruled out one by one, and further cause had to be sought. The skull bones were seen to be persistently overmoulded, the frontal and occipital bones being inserted below the parietals, with complete obliteration of both anterior and posterior fontanelles. In view of this a provisional diagnosis of slight cerebral haemorrhage, causing irritation and pressure on the brain without paresis, was made. The frequency of the fits increased, however, and during the period from the fourth to the eighth day after admission they were almost continuous. Their length varied from fifteen seconds to two minutes roughly, with an interval between each of from five to fifteen minutes. All the fits were similar to the one previously described, and it was noticed that they were prone to occur immediately after feeds or when the child was handled.

Since admission almost all feeds had been vomited. Starving, rectal wash-outs, stomach wash-outs, and the usual methods of treatment were carried out, but they failed to allay this symptom. In consequence the child lost 1 lb. 4 oz. in seventeen days, dropping to 4 lb. 13 oz. By a combination of rectal salines with glucose and frequent feeding with a pipette enough nourishment was given to keep it alive.