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The Carbohydrate Metabolism in Insulin Shock Therapy.

On the Significance of the Carbohydrate Content of the Diet to the Glucose Tolerance, Insulin Sensitivity and Minimal Coma-dose in Insulin Shock Treatment of Psychotics.

By

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The insulin shock treatment of psychotics has afforded an opportunity to study various, hitherto rather uncertain, aspects of the action of insulin in man. Indeed, from psychiatric clinics a great many physiological studies have been reported already on insulin effect and carbohydrate metabolism. In the work here presented we have aimed by examination of patients under insulin shock treatment to throw some light on certain aspects of the relation between the carbohydrate content of the diet and the insulin effect.

One question suggests itself at once, namely: Is it warrantable to look upon the examined patients as »normal» — that is, in this connection, is the carbohydrate metabolism of these patients normal?

In the literature several reports have appeared on the carbohydrate metabolism in psychoses, and the results of these studies have been divergent. Kooy (1919) and Mann (1925) most often obtained abnormally high curves in glucose tolerance tests on manic-depressive psychotics, but occasionally also in dementia paralytica, neurasthenia, schizophrenia, and especially catatonia.

Abnormal blood sugar curves in manic-depressive psychosis have been described by Barret & Serre (1924), Rafael, Ferguson & Searle (1928), Schou (1935), and Marshall (1939). On the other hand, several authors, including Lorenz (1922) and Barret & Serre found generally no abnormality of the carbohydrate metabolism in schizophrenics, but Lorenz thinks that high curves are common in catatonia.

All told, it seems rather probable that manic-depressive psychosis often is associated with abnormalities in the carbohydrate metabolism, whereas such deviations from the normal generally are not observed in other psychoses, especially schizophrenia. Most of these reports, however, are encumbered with the shortcoming that no attention has been paid to the diet of the examined patients — a very important point in estimating the outcome of various tests for the carbohydrate metabolism, as will be pointed out below. Besides, it can hardly escape notice that those states of psychosis in which an abnormal carbohydrate metabolism has been reported most often are the depressive phases of manic-depressive psychosis, and catatonic phases of schizophrenia, *i. e.*, conditions in which refusal of food is a common feature.

In the present studies we have taken for granted that the carbohydrate metabolism was normal in the patients here examined. The psychiatrical diagnoses have been either schizophrenia or schizophreniform psychosis. Only one of the patients presented some catatonic features, and he did not differ from the other patients with regard to the conditions investigated here. In each case, of course, we have made sure that the preliminary insulin, glucose and adrenalin tolerance tests prior to the treatment had revealed no abnormality. None of the patients has been suffering from diabetes mellitus or other demonstrated disorders of metabolism.

In the present studies we wanted in particular to elucidate these two questions: 1) the influence of the diet on the carbohydrate tolerance and on the insulin sensitivity under insulin shock treatment, and 2) its influence on the minimal coma-dose (see below). Before the introduction of the insulin shock therapy the influence of the diet on the carbohydrate tolerance and on the insulin sensitivity has been the subject of a fairly extensive literature, which it will be appropriate here to review briefly.

As early as 1913 Bang pointed out that there is a connection

between the diet and the glucose tolerance, and this observation was subsequently confirmed by many authors. In 1927 Sweeney carried out glucose tolerance tests on different diets. He found the tolerance to be greatest on a high-carbohydrate diet, and decreasing over protein and fat to the relatively very low tolerance after fasting completely for two days.

To explain this influence of the diet on the carbohydrate tolerance, most of the early authors — *e. g.*, Staub (1922), Abderhalden & Wertheimer (1924), and Macleod (1930) — assumed that with abundant carbohydrate supply the pancreas gets »accustomed» to secrete more profusely, and hence the glucose tolerance test on a high-carbohydrate diet brings about a more plentiful secretion of insulin than does the same tolerance test on a low-carbohydrate diet. Subsequent investigators — among others, Himsworth — have presented evidence suggesting that this theory presumably is not correct.

The influence of the diet on the sensitivity to administration of insulin was investigated in 1924 by Abderhalden & Wertheimer, in 1925 by Bainbridge, in 1925—26 by Tiitso, and in 1931 by Hynd & Rotter. All these authors have demonstrated that the sensitivity to administration of insulin, expressed by the point of time for the appearance of hypoglycæmic symptoms, or by the degree of the fall in blood sugar concentration after injection of a standard dose of insulin, is greatest on a high-carbohydrate diet. Even these results were enough to show that the difference in the carbohydrate tolerance on different diets could not at any rate be brought about merely by variations in the insulin production of the organism.

In recent years additional light has been thrown on these questions — above all by Himsworth who from 1931 has published a number of important papers dealing with the relation between the carbohydrate tolerance, the insulin sensitivity, and the composition of the diet. In 1933, working with glucose and insulin tolerance tests on human subjects getting different diets, he arrived at the result that an unknown factor must be taking a part in the regulation of the activity of the insulin, and that it was this unknown factor that was varied by variation in the composition of the diet. In 1935 he investigated these findings more thoroughly and found that the absolute carbohydrate content of the diet alone was of importance to the form of the glucose and insulin tolerance curves

obtained on different diets. He further demonstrated that alteration of the carbohydrate content of the diet gave a percentally equally great change in the glucose tolerance as in the insulin sensitivity, expressed by the »method of areas».

When it had been demontrated that administration of insulin has a stronger effect on the blood sugar concentration on a high-carbohydrate diet than on a low-carbohydrate, it was obvious that the improved carbohydrate tolerance on the high-carbohydrate diet could not in all instances be due to an increased insulin production alone. After the last-mentioned studies of Himsworth it seems more likely that a high-carbohydrate diet does not at all give an increase in the insulin secretion, and that the effect of this is attributable solely to an increased sensitivity — to injected insulin as well as to the insulin produced by the organism itself. As to the character of this unknown factor, Himsworth previously thought it might be some sort of an insulin-activator — an »insulin-kinase». Later, on the basis of his own experimental findings (1938) and studies reported by Marks (1936) on the role of the pituitary gland in the carbohydrate metabolism, he has gone on to look upon this factor as an insulin-inhibitor, probably identical with the diabetogenic hormone. According to this view, on a low-carbohydrate diet more diabetogenic hormone would be secreted from the pituitary, decreasing the insulin sensitivity and the glucose tolerance — and vice versa on a high-carbohydrate diet.

These studies of Himsworth have been acknowledged generally, even though they have met with some opposition too. On the basis of numerous animal experiments Soskin and collaborators (1934, 1937, 1938) have advanced the theory about the »homeostatic function» of the liver: when the blood sugar concentration rises above a certain »threshold value» the liver ceases giving off glucose to the blood; if the blood sugar falls below the threshold value, more glucose is given off by the liver to the blood. The threshold is the ordinary fasting blood sugar level of the subject, and the blood sugar level constitutes by itself the stimulus to a change in this function of the liver. The threshold is influenced by the hormonal balance, primarily by the internal secretion of the pancreas and the pituitary. When the insulin supply is lowered or when the secretion of pituitary hormone is increased, the threshold rises, the liver gives off more glucose, and the result is a state of diabetes. Conver-

sely, when the insulin supply is abundant, or when the pituitary function is inhibited, the threshold is lowered, the liver gives off less glucose to the blood — and hypoglycæmia develops.

In contrast to Himsworth, however, Soskin looks upon the high »pseudo-diabetic» tolerance curves obtained on fasting and on a low-carbohydrate diet as brought about entirely by the stronger gluconeogenesis on this diet, which gives a »delayed homeostatic reaction to exogenous sugar supply». Soskin has tried experimentally (1935) to demonstrate the central significance of the liver to the development of the abnormal tolerance curves on carbohydrate-starvation; in these experiments the fall in the blood sugar concentration after evisceration was observed on normal animals and on animals that had been starved for some length of time. The resulting blood sugar curves turned out quite alike. In similar studies, however, other authors (Bergmann & Drury, 1937) arrived at the opposite result: that after evisceration there is a distinct difference in the glucose consumption of normal and starved animals.

Finally it is to be mentioned that Best, Haist & Ridout (1939) have demonstrated a greater insulin content of the pancreas after a high-carbohydrate diet than after a low-carbohydrate diet — what seems to lend support to the old theory about changing of the insulin production.

Notwithstanding these difficulties, however, it appears justifiable for the time being to look upon that difference in the carbohydrate metabolism on high- and low-carbohydrate diets which can be demonstrated by tolerance tests as brought about chiefly by shifting in the antagonistic relation between the internal secretions of the pancreas and the anterior pituitary gland.

As to the other question — about the influence of the diet upon the minimal coma-dose in man — we have not been able to find any studies reported in the literature. Certain results of animal experiments that may be correlated with this phenomenon will be mentioned later.

The insulin shock therapy ad modum Sakel means a radical interference with the regulation of the carbohydrate metabolism. This is evident, for one thing, from the peculiar fact that the »coma resistance» is lowered considerably after the first coma, *i. e.*, that the patients now are »sensitized» — the prevailing expression for

this phenomenon — going into coma on a much lower dose than was required for production of the first coma. Thus it is a quite common finding that the dose may be halved without any change in the effect. In one case, in which the first coma was obtained with 300 units we were able even in 2 days to lower the dose to 104 units, and subsequently to 56 units. Something similar has been demonstrated in animal experiments by Corwin (1939, a). This author was not able under the progressing sensitization to demonstrate corresponding changes in the form of the blood sugar curve from day to day. On the other hand, such changes under the sensitization appear to be demonstrable in man — possibly as expression of the damage caused by the first severe hypoglycemic shock to the parts of the brain involved in the regulation of carbohydrate metabolism, the hypophysis and the hypothalamus. (At present this question is being investigated here in this department.)

In view of these and other changes in the carbohydrate metabolism during the course of the insulin shock treatment, we thought, for one thing that it might be of interest to investigate whether the above-mentioned effects from the composition of the diet (rich or poor in carbohydrates) on the blood sugar regulation might be found unchanged also under the insulin shock treatment. Further, it seemed obvious also to look into the relation between the carbohydrate content of the diet and the minimal coma-dose, *i. e*, the smallest insulin dose producing coma within about 3 hours, at the most 4 hours. (Coma is defined as the point of time when the patient no longer reacts with a coordinate adequate movement on an attempt to introduce a nasal tube.)

A priori and, in particular, after the appearance of Himsworth's studies it was to be expected that patients would go into coma more readily on a high-carbohydrate diet than on a diet poor in carbohydrates. It seemed reasonable to expect that by placing the patient on a high-carbohydrate diet, with its steep and deep insulin tolerance curve, it might be possible to lower the insulin dose required for production of coma. The converse might be expected by placing the patient on a low carbohydrate diet.

Procedure.

At our request, The University Institute of Hygiene, Copenhagen, obligingly composed two diets to be used in these studies:

one with a carbohydrate content of about 50 g daily, the other with a carbohydrate content of about 500 g daily, both fully sufficient with regard to their contents of calories, minerals and vitamins. [1]

These diets were given to a total of 20 patients (11 women, 9 men) under insulin shock treatment; at suitable intervals a change was made from one of these diets to the other. The keeping of the diet was watched closely. The carbohydrate content of each meal was known, and the carbohydrate content of the leavings was calculated after weighing. On each diet the intake of carbohydrate calculated in this way was found to vary from day to day but very little. The variations of the intake from one patient to another were found to slight too. On the high-carbohydrate diet, however, the women generally took in only about 400 g of carbohydrate daily. To the carbohydrate content of the food is further to be added 50—150 g of saccharose that was given daily for interruption of coma on the low-carbohydrate diet. On the high-carbohydrate diet the patients always received 200 g of saccharose for this purpose. Even though the low-carbohydrate diet thus on an average contained about 150 g of carbohydrate — at the most, 200 g — it is still to be regarded as poor in carbohydrates in proportion to a diet containing 600—700 g of carbohydrates.

One or several glucose and insulin tolerance tests were made on each patient on both diets.

The glucose tolerance tests were carried out by letting the patients take 70 g of glucose in the morning, while fasting. The blood sugar concentration was followed by taking double samples of blood from the lobe of the ear, in the first hour every 15 minutes, in the next two hours every 30 minutes. Here as throughout these studies the blood sugar determination was carried out after Hagedorn—Norman Jensen.

The insulin tolerance tests were at first carried out ad modum

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[1] The diets were composed of breakfast, dinner, and supper. The breakfast and supper were the same from day to day on the same diet. 10 dinners were composed, each consisting of two courses, and the meals on this bill of fare were given in rotation.

Both diets agreed with the patients and were easy to provide. Thus these diets may be recommended for physiological studies on persons on a fixed carbohydrate intake.

Schemas and directions may be obtained at request to »Statens praktisk-sundhedsmæssige Undersøgelse», Blegdamsvej 21, København Ø.

Himsworth, with intravenous injections of 4 units (here as elsewhere in this paper, »units» means international units). But this was soon found to be impracticable on psychotic patients. Even though we tried to avoid patients with marked motor restlessness, we were not able in all cases to obtain such a complete muscular rest and relaxation as are required if the insulin tolerance test with such a small dose is to give serviceable and uniform results. We therefore went on to give the dose most commonly employed in this country for tolerance tests, 16 units intravenously. With this dose it was found that slight restlessness did not influence the form of the blood sugar curve. After the injection, samples of blood were taken every 5 minutes for one hour.

On each diet we tried on every patient to »adjust» the minimal coma-dose (the smallest dose able to provoke coma within 3 hours, or 4 hours at the most) before a shift was made to another diet. On change of diet it often proved necessary to change this dose too.

Experimental Results.

Tolerance Tests.

Figs. 1—4 show average curves of all the glucose and insulin tolerance tests carried out on men and women on the two diets. The curves represent altogether 93 single glucose tolerance tests (45 on high-carbohydrate diet, 48 on low-carbohydrate diet) and 97 single insulin tolerance tests (55 on high-carbohydrate diet, 42 on low-carbohydrate diet), as in some cases several tests were made on the same diet. On all the figures, the average curves are corrected to the average fasting value for the high-carbohydrate diet.

(There was no statistically maintainable difference between the averages of *all* the fasting values on the two diets.)

Glucose Tolerance Tests.

As shown in Figs. 1 and 2, the tolerance curves are considerably higher on the low-carbohydrate diet than on the high-carbohydrate. Both curves are a little higher for women than for men. An analysis of the curves is presented in Figs. 5 and 6. Fig. 5 gives the maximal rise in mg% of the glucose tolerance curve obtained in the individual patient, the maximal rise on low-carbohydrate diet being plotted as ordinate, the maximal rise on high-carbohydrate diet as abscissa.

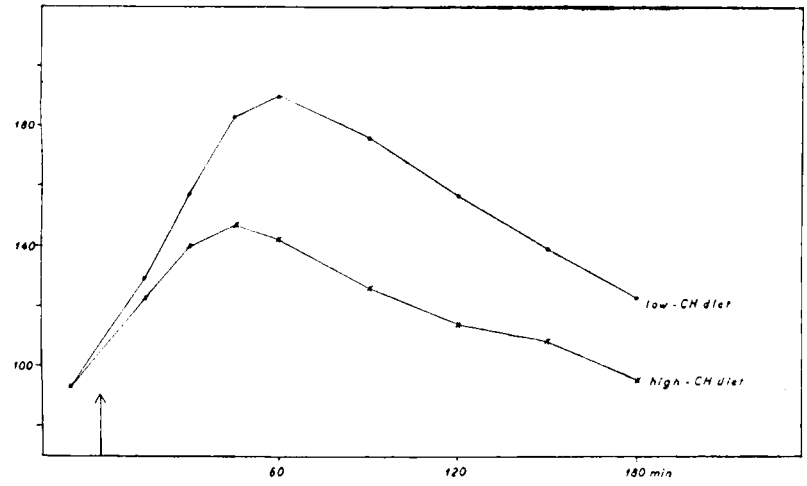

Fig. 1. Averages of curves obtained in glucose tolerance tests on males.

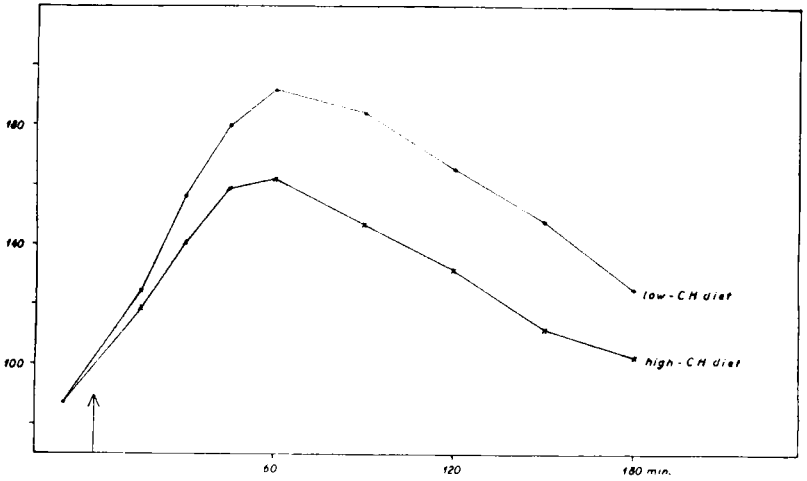

Fig. 2. Averages of curves obtained in glucose tolerance tests on females.

In most cases each individual point is plotted after the average of several values from different tolerance tests carried out on the same patient on the same diet. In a majority of the patients the maximal rise is greatest on the low-carbohydrate diet, as is plainly evident from the fact that nearly all the points fall above the 45° axis. Similarly Fig. 6 presents the distribution of the individual cases with regard to the blood sugar fall in the latter half of the tolerance

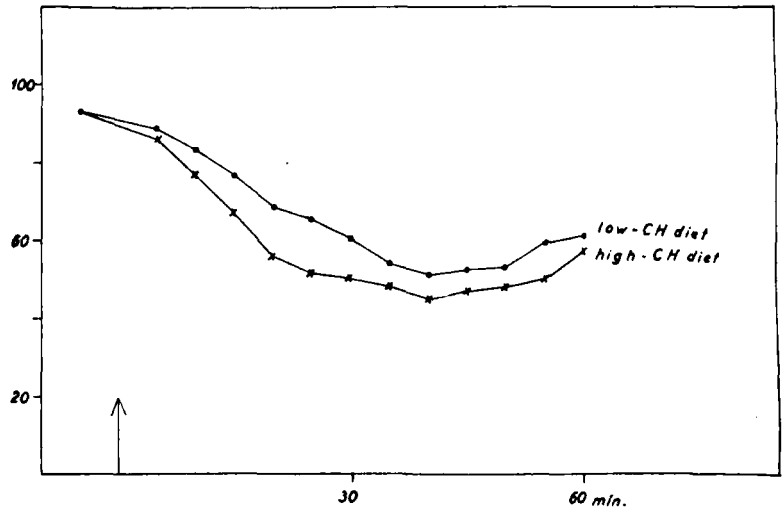

Fig. 3. Averages of curves obtained in Insulin tolerance tests on males.

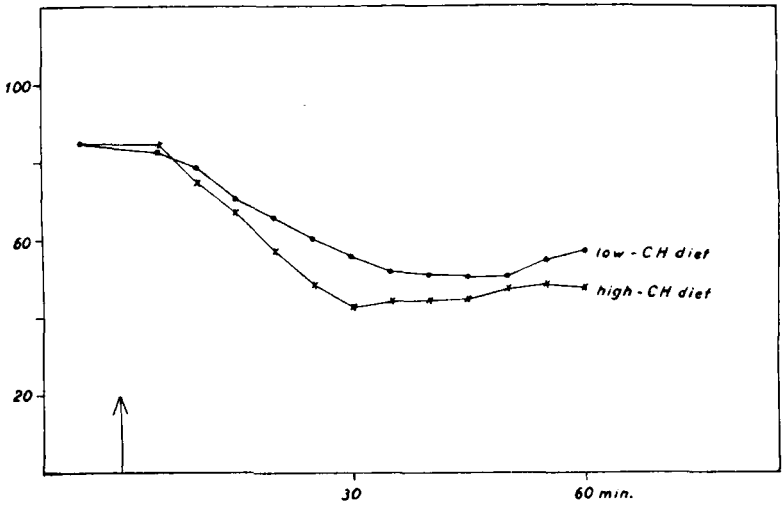

Fig. 4. Averages of curves obtained in Insulin tolerance tests on females.

curves. In nearly all the patients the fall is greater on the low-carbohydrate diet.

Insulin Tolerance Tests.

Figs. 3 and 4 show a small but characteristic difference in th e form of the curves on the high-carbohydrate and the low-carbo-

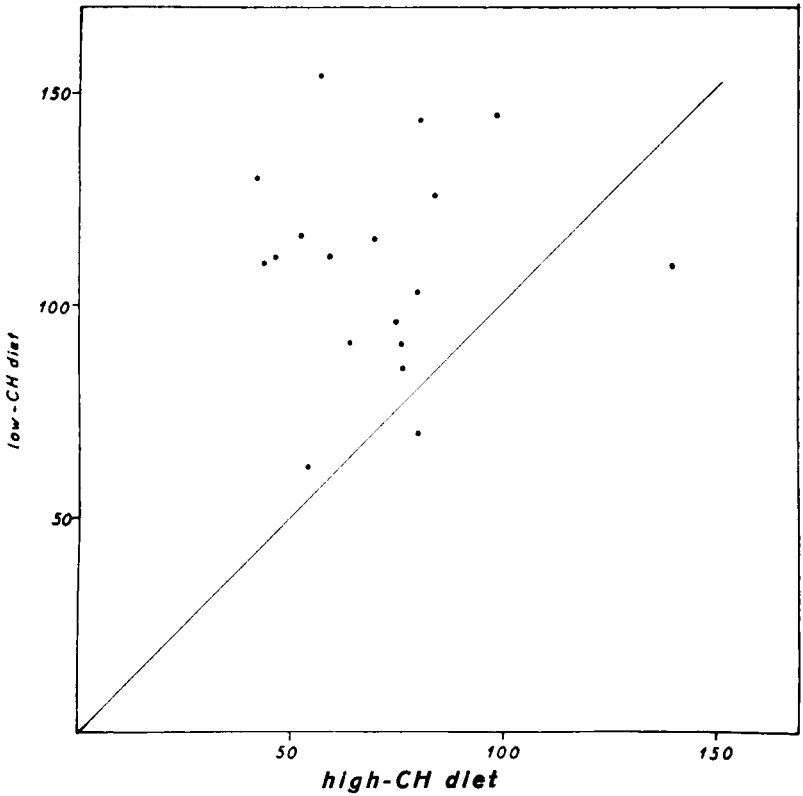

Fig. 5. Maximal increases in the blood sugar values in the glucose tolerance tests.

hydrate diets. On the high-carbohydrate diet the fall in blood sugar values is more abrupt and the curves are lower than on the low-carbohydrate diet. The distribution of the individual cases with regard to the steepness (expressed by the blood sugar fall in the first 20 minutes) and the maximal fall of the blood sugar curve is shown in Figs. 7 and 8, after the same principle as followed in Figs. 5 and 6. Fig 7 shows a pronounced inequality of the distribution, the abruptness being greater on the high-carbohydrate diet. As to the maximal blood sugar fall (Fig. 8) the outcome is not clearly defined. On calculation it is found, indeed, that the differences between the figures for the two diets average 7.2; but the mean error for this figure is 4.5. So evidently there is no demonstrable difference in the maximal fall of the blood sugar curves on the two

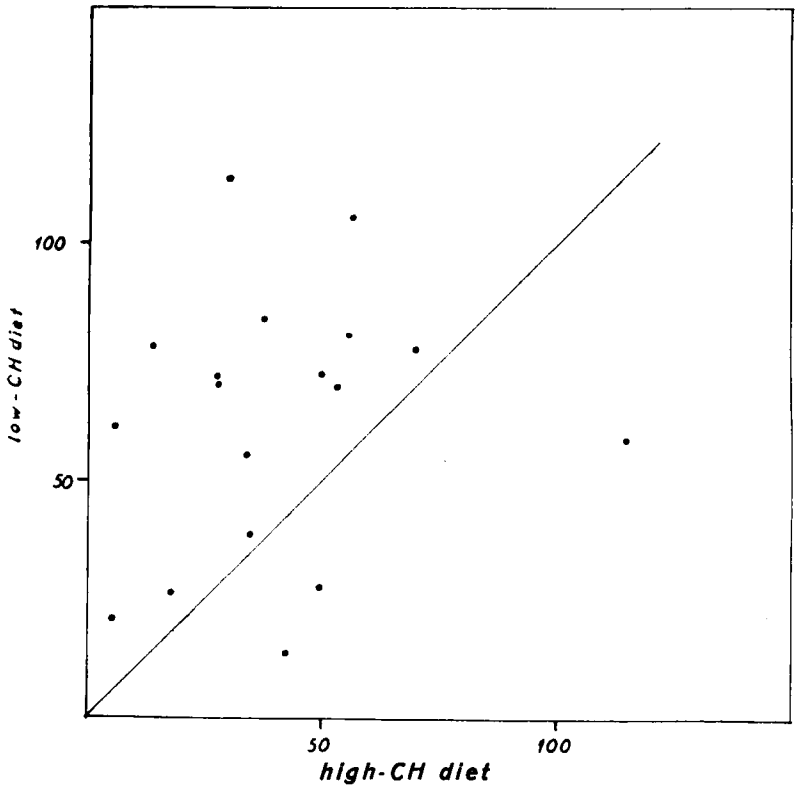

Fig. 6. Decrease in blood sugar values in the latter half of the glucose tolerance tests.

diets. (For comparison it may be mentioned that the average difference in abruptness is 11.8, and the mean error for this figure is only 2.5).

Minimal Coma-dose.

For each patient, after conclusion of the treatment, a diagram was drawn of the insulin doses given on the various days. Fig. 9 presents a typical example of these diagrams. The individual days of treatment are plotted along the axis of abscissa, while the logarithms of the doses are plotted as ordinates. The mark »,» means that the patient did not go into coma on this day.

On the first day the patient received 24 units, on the next day 40, and after this the dose was increased steadily with 16—24 units

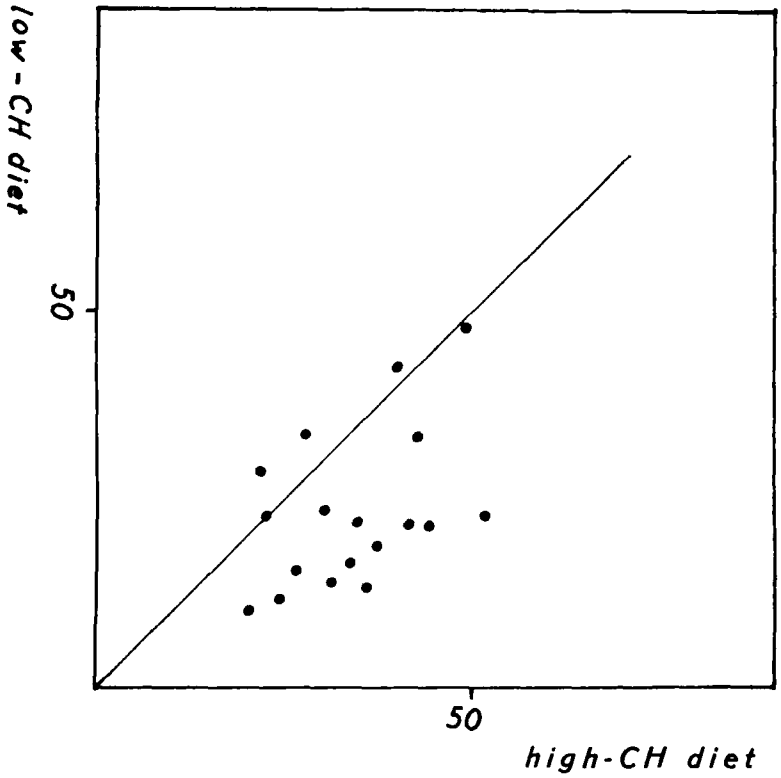

Fig. 7. Steepness of the Insulin tolerance curves.

till the 7th day, when 136 units produced a suitable coma. After this, the dose was decreased steadily — something that may be done in most cases, as formerly mentioned (»sensitization»). In 21 days the dose was lowered to 48 units. An attempt at a further decrease to 40 units did not give a satisfactory coma, and hence the dose was again increased to 48 units. After the 23rd day the diet of the patient was changed from high-carbohydrate to low-carbohydrate. On the following two days the patient got the same dose of insulin, and went into such an early and deep coma that the dose now was lowered to 32 units. On this dose, too, coma set in so early that, 2 days later, the dose could be lowered to 24 units. An attempt at a further decrease to 16 units gave no coma. After the 34th day the patient was again placed on the high-carbohydrate diet, and on

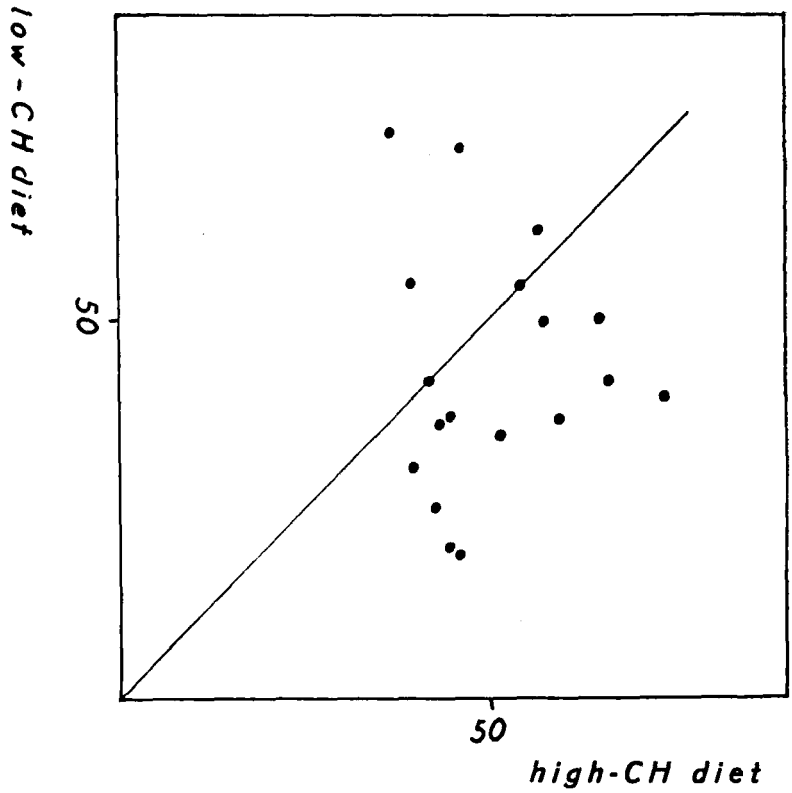

Fig. 8. Maximal decreases in the Insulin tolerance tests.

the following day she did not go into coma on the usual 24 units. The dose was now increased to 40 units, which one day proved sufficiently effective; but on the next day it gave no coma. An increase of the dose to 64 units resulted in a late coma; and the dose was further increased to 88 units. This gave an early and deep coma. The dose was then decreased again to 72 units, which now gave a suitable coma, so that this dose was maintained for some days. After this the dose could be decreased steadily until the last day of treatment, when coma was obtained with 20 units.

The course described in this patient was observed essentially, if not in details, in nearly all the other patients. We thought, therefore, that it would be more profitable to review a single case in detail rather than present all the curves.

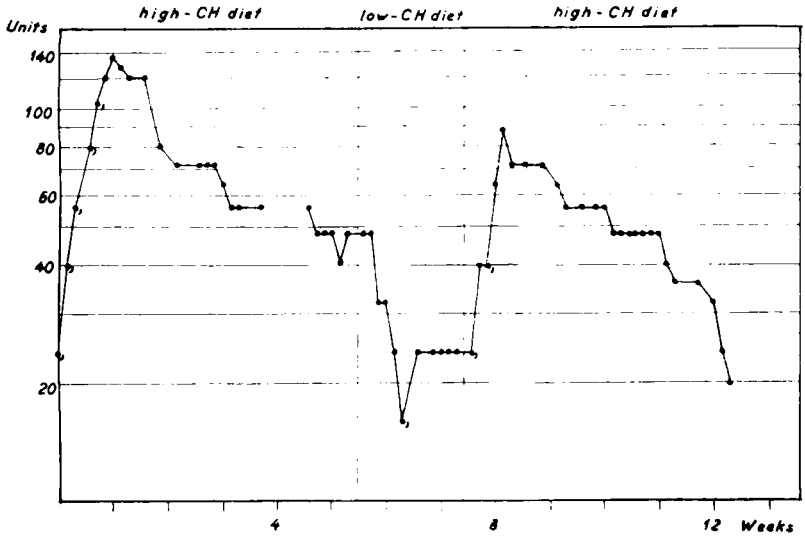

Fig. 9. Scheme of dosage for one of the patients.

The characteristic features of the curves are: 1) the sensitization, 2) protracted variations, and 3) changes following change in diet. The sensitization is observed in nearly every instance; and we have practically never changed the diet before we thought that the sensitization was at passed an end. In one case, however, the change from low-carbohydrate diet to high-carbohydrate was made just after the patient had passed the top of the sensitization curve. Even though at this point of time the patient no doubt was still undergoing sensitization, the dose had to be increased, exactly as in this kind of change after the conclusion of the sensitization in the other cases.

In the case cited above (Fig. 9) the protracted variations are represented by the gradual fall of the curve in the latter part of the treatment. On going through all the curves, it is found that most of them show such a fall or rise over long periods, corresponding to the general experience that during the treatment it often is necessary to alter the dose somewhat, raise or lower it to obtain a suitable coma. The significance of these protracted periodical variations is still an open question. At any rate, there is no demonstrable relation between the diet and these variations.

In a greater majority of the cases the changes in the minimal

Table 1.

Changes in Minimal Coma-dose on Change of Diet, from Low-carbohydrate to High-carbohydrate and vice versa.

Change of diet	Changes in dose (Number of cases)		
	Increased	Unchanged	Decreased
Low-carbohydrate→ high-carbohydrate	11	5	0
High-carbohydrate→ low-carbohydrate	1	2	9

coma-dose required on change of diet have been of the same character as shown in the cited case. On changing from high-carbohydrate to low-carbohydrate the dose can be lowered soon after, whereas it has to be increased on changing from low-carbohydrate diet to high-carbohydrate. Tabulation of all the changes of diet gave the result shown in Table 1: Only in one case was it necessary to increase the dose on changing to the low-carbohydrate diet, and in no case could the dose be lowered on changing to the high-carbohydrate diet. In 7 cases was there no indication for any change in dosage after the change of diet. In tabulating these changes of diet we have reckoned with the changes in dosage that were made in the first 2—4 days after the change of diet. Most often, however, the change in the minimal coma-dose has been merely transitory. As is evident from the last part of the example shown in Fig. 9, the minimal coma-dose rises briefly on the change to the high-carbohydrate diet, and then it again falls off to the same level as on the low-carbohydrate diet. Similar features are found in most of the other curves. On comparison of all the *complete* high-carbohydrate and low-carbohydrate periods there is no demonstrable difference in the level of the dosis.

Discussion.

It has been demonstrated here that the relation between the carbohydrate content of the diet, the glucose tolerance and the insulin sensitivity, which was recognized previously and has been studied in particular by Himsworth, is found to remain fundamentally unchanged under the insulin shock treatment.

In the glucose tolerance tests the difference in the maximal rise of the blood sugar concentration on the different diets is very dis-

tinct, and quite similar to that observed outside the insulin shock treatment. Also the maximal fall in the latter half of the glucose tolerance curves shows a clear-cut difference on the two diets: the higher the maximal value the more pronounced is the abruptness of the fall. The same feature is presented by the curves in Himsworth's works. As far as that goes, one might expect that the fall would be less abrupt on the low-carbohydrate diet with its decreased insulin sensitivity. But such a tendency is counteracted by the higher maximal value. Indeed the resultant of these two antagonistic factors show that the maximal value of the blood sugar curve is the decisive.

The insulin tolerance tests show the features usually observed in such tests outside the insulin shock treatment: the increased insulin sensitivity on the high-carbohydrate diet manifests itself by a more steep form of the tolerance curves. Himsworth characterizes the curves by the abruptness as well as by the maximal fall: but as he employs only the first 15-minute section of the curves, which never reaches the absolute minimum, these two characteristics become practically identical. Scott & Dotti (1932) and Chandler (1938) found, as also observed by us, that there is no demonstrable difference in the maximal fall proper of the insulin tolerance curves on different diets.

From this it is evident that under insulin shock treatment the glucose tolerance curves and the insulin tolerance curves are influenced as usually by changes in the carbohydrate content of the diet and by the thus resulting changes in the interaction between the internal secretion of the anterior pituitary and that of the pancreas. This feature appears not to be affected by the often very large amounts of insulin and the resulting violent acute and more protracted changes in the carbohydrate metabolism.

As to the minimal coma-dose, it was found that this question divided into two: 1) Is the minimal coma-dose altered by a change from high-carbohydrate diet to low-carbohydrate diet and vice versa? 2) Is there any difference in the level of the minimal coma-dose on high-carbohydrate and low-carbohydrate diets?

To the first question it may be said that the result of our studies has been just the opposite of what we had expected. From Himsworth's works, as mentioned already, it seemed obvious to think that the minimal coma-dose would turn out to be lower on the high-

carbohydrate diet than on the low-carbohydrate. On the contrary, it was found that in those cases where the insulin dose was altered by change of diet (21 out of 28 cases) a change to high-carbohydrate diet brought about that the dose had to be increased, whereas a change to low carbohydrate diet had the effect that the dose could be lowered — in all the cases but one.

In most of the cases (9 out of 12) the coma-provoking effect of a certain dose of insulin is increased by the change to low-carbohydrate diet. On the other hand, as a rule, the coma resistance (»the symptomatic resistance») is increased by the change to high-carbohydrate diet (11 out of 16 cases).

To the second question the answer has been that no characteristic form or level of the dosage curve could be demonstrated as corresponding to the two diets when the total dietary periods are considered. So it is not to be expected that the insulin shock treatment can be carried through with smaller doses of insulin by restricting the patients to a special diet like one of those here employed.

As a matter of fact, it is rather peculiar that a change of diet manifests itself as early as the following day, and that it is noticeable only in the very first days after the change. That changes in the carbohydrate metabolism *can* be demonstrated even very soon after a change of diet, is evident, for one thing, from the fact that the glucose tolerance curve may show the characteristic alteration already on the day after a change of diet (Adelsberger & Porges, 1926). When more protracted changes in the minimal coma-dose cannot be demonstrated, it is probably because the changes, so to speak, are superimposed on the protracted variations, so that an acute change in the required dose manifests itself merely as a slight undulation on the greater variations, whereas protracted changes are obliterated. On the other hand, it cannot be excluded with certainty that the alterations of the »symptomatic resistance» may really be of transitory nature, in contrast to the changes in glucose tolerance and insulin sensitivity demonstrated in tolerance tests; the latter changes turn up very soon after the change of diet, and they persist unchanged throughout the dietary period.

The studies here reported have shown a contrast between the effect of the carbohydrate content of the diet upon the form of the tolerance curves and upon the development of the hypoglycæmic symptoms, the »symptomatic resistance» in man. In animal expe-

riments these features have previously turned out differently. Abderhalden & Wertheimer (1924) did not find this antagonism in rats. In their experiments the low-carbohydrate diet increased the »symptomatic resistance» of the animals, the interval between the injection and the appearance of the hypoglycæmic symptoms was prolonged and at the same time the blood sugar curve was flattened. Bainbridge (1925) found the »symptomatic resistance» increased in mice and rats on a low-carbohydrate diet; but his blood sugar determinations are so few and accidental as to preclude any definite inference. Hynd & Rotter (1931) also found the »symptomatic resistance» increased in mice and rats on a low-carbohydrate diet. They claim that the blood sugar curve took a less abrupt form on this diet than on a high-carbohydrate, but from their tables it is obvious that there has been no distinct difference in this respect. In cats, on the other hand, they found the »symptomatic resistance» to be greater on the high-carbohydrate diet — that is, the same feature as demonstrated in man here in the present studies. Unfortunately, no blood sugar determinations were made on the cats. Tiitso (1925—26) and Himsworth (1934) have shown that the blood sugar curves in rabbits are more flat on a low-carbohydrate diet, but they make no mention of hypoglycæmic symptoms. So, with regard to the form of the blood sugar curve on different diets it appears as if man behaves like rodents. As to the development of hypoglycæmic symptoms on change of diet, according to Abderhalden & Wertheimer man would behave contrary to the rodents, and according to Hynd & Rotter man would react like the cat.

What it is that brings about the demonstrated changes in the minimal coma-dose cannot be stated with certainty. The question might first be raised whether these changes were directly dependent at all upon changes in the amount of carbohydrate supplied, or whether they possibly might be correlated with other metabolic changes secondary to the change of diet.

It is a well-known fact that the change to a high-carbohydrate diet or a sudden carbohydrate supply may give retention of water in the organism (Niemann, 1915, Meyer-Bisch & Wohlenberg, 1926, and Adolph, 1933). Such water retention might conceivably bring about a hyperhydration and lower the convulsion threshold of the subject as observed in diagnostic water balance tests on epileptics (Stubbe Teglbjerg, 1936). From the aforementioned work of

Corwin it is evident that when convulsions are produced in a dog by means of insulin, the same dose of insulin will on the next day elicit convulsions at an earlier juncture after the injection, and even more rapidly on the following days. This finding, which greatly reminds of the »sensitization» in our patients, — the lowered coma resistance after the first coma in patients under insulin shock treatment — makes it justifiable to compare the convulsion threshold with the coma resistance. As direct experiments aimed to show the significance of the water metabolism to the convulsion threshold after administration of insulin have given conflicting results (Hennequin, 1934, Corwin, 1939, b) it could not a priori be excluded that water retention from abundant carbohydrate intake might give changes in the coma resistance. In our studies, however, it was found that the change to a high-carbohydrate diet *increases* the coma resistance. So the water retention can play no role in this respect.

There appears then to be no other explanation on the findings here described than a direct effect on the coma resistance from changes in the carbohydrate content of the diet.

Primarily one will think of changes in the glycogen deposits brought about by change of diet. Changing to a high-carbohydrate diet will increase these deposits. After an insulin injection on a high-carbohydrate diet, then, one might imagine that it would take a longer time before the nutrition of the brain — which normally consists merely in the supply of glucose from the blood — would be jeopardized. From the insulin tolerance tests we know, however, that the blood sugar curve just falls more abruptly on a high-carbohydrate diet, so that the supply of glucose from the depots more rapidly will be lowered to a minimum. In the tests, it is true, the insulin was given intravenously, while in the insulin shock treatment proper the subcutaneous route vas used. This, no doubt, will diminish the difference in the steepness of the curves on the two diets, but it is not conceivable that it may reverse the relation of the curves, producing a steeper fall on the low-carbohydrate diet than on the high-carbohydrate. But, might it not be possible that the later course of the blood sugar curves from the individual days of treatment might indicate that more glucose would be at the disposal of the brain on a high-carbohydrate diet than on a low-carbohydrate?

Our attempts to follow the blood sugar curve throughout its course from the injection of insulin to the interruption of coma have not afforded any clear-cut answer to this question. As was to be expected, the last part of the blood sugar curve has proved to be so variable and obviously accidental from day to day, depending upon the degree of muscular restlessness and similar uncontrollable factors, that it did not seem practicable to obtain any accurate information about the glucose supply throughout the insulin period. So it cannot be excluded that the difference in the minimal coma-dose on high-carbohydrate and low-carbohydrate diets may be due to the difference in the total glycogen deposit of the organism.

Another conceivable explanation is that the difference may be due to changes in the small glycogen deposit of the brain itself. No doubt the brain glycogen is attacked every time the patient goes into coma (Himwich *et al.*, 1939), and it seems reasonable to think that the smaller this depot, the more rapidly will the cerebral symptoms set in. It is true that in animals this has been demonstrated by Kerr & Ghantus (1936) to be independent of the carbohydrate content of the food, but their experiments were carried out with direct quantitative determination of the glycogen content of the brain, and that is a difficult method, which implies considerable sources of error. Further, it is conceivable, we think, that small changes in the glycogen content might be sufficient to bring about the observed changes in the minimal coma-dose even though it might not be practicable by quantitative determination of the percental glycogen content to demonstrate any change.

It is rather likely, moreover, that the daily supply of large amounts of insulin gives rise to some particular conditions that are not directly comparable to the experimental conditions in the studies reported by Kerr & Ghantus. Large doses of insulin are known for sure to influence the glycogen content of the brain. Hence it is conceivable, we think, that the continual emptying and filling of the brain depots imply the possibility that changes of diet more readily may manifest themselves through changes in the glycogen content of the brain.

Summary.

The usual relation between insulin sensitivity, glucose tolerance and carbohydrate content of the diet is found unchanged in patients under insulin shock treatment. A high-carbohydrate diet increases the insulin sensitivity, and improves the glucose tolerance; a low-carbohydrate diet lowers the insulin sensitivity, and impairs the glucose tolerance. These findings may be taken to indicate that the daily administration of large, coma-provoking doses of Insulin produces no disturbance of the hormonal balance between the insulin secretion and secretion of the diabetogenic hormone that is regulated by the carbohydrate supply of the organism.

The minimal coma-dose decreases on the change to a low-carbohydrate diet, and increases on the change to a high-carbohydrate diet, *i. e.*, a high-carbohydrate diet lowers the coma-provoking effect of insulin, while a low-carbohydrate diet increases this effect. Under the given experimental conditions, these findings demonstrate that in man there is a contrast between the effect of the carbohydrate content of the diet upon the insulin sensitivity and glucose tolerance in tolerance tests and its effect on the »symptomatic resistance».

The changes in the minimal coma-dose is assumed to be connected with changes in the glycogen deposits of the organism — perhaps especially with the glycogen deposit of the brain.

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