Blood Sugar Findings During Pregnancy in Normals and Possible Prediabetics

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Numerous investigations indicate that women who acquired diabetes after the menopause have had a definitely increased tendency to bear big infants. A prediabetic syndrome in women has been postulated on this basis. Apart from the tendency to bear big infants (with an increased perinatal mortality) obesity appears to be an important sign in prediabetic women, as pointed out by Pirart.[1] The relationship between infant size and the risk of acquiring diabetes has been calculated by Kriss and Futcher.[2] These phenomena are well known and several reviews have been recorded.[3]

It would be reasonable to imagine that the glucose tolerance curves of women who are likely to bear big infants would be abnormal during pregnancy, even though they were normal in the nonpregnant state. Investigations by Basil Jones,[4] Gilbert,[5] John,[6] Kritzer,[7] Lund and Weese,[8] and Jackson[9] indicate that this is so. These investigations, however, were carried out before a possible diabetogenic effect of normal pregnancy had been well defined. Thus, what these authors observed may have been merely the ordinary shift in the glucose tolerance curve during pregnancy.

Glycosuria is the alteration in carbohydrate metabolism during normal pregnancy which has been known longest and is most easily detectable. Since 1856, when Blot[10] reported this observation, numerous investigations have been concerned with fasting blood sugar and glucose tolerance in normal pregnancy, but the results have been conflicting. The findings do not show a definite deviation in the blood sugar during normal pregnancy.

PROCEDURE

A. *Normals (Group A)*

In an effort to elucidate these matters, twenty-eight normal women were investigated. The observations included determination of blood sugar using the Hagedorn-Jensen method, tracing the glucose tolerance curve after oral administration of 1 gm. glucose per kilogram body weight at three, five, seven, and nine months of gestation and once after delivery. During glucose loading, qualitative tests for glycosuria were carried out. Eleven of the subjects also had intravenous glucose tolerance tests (50 ml. of 50 per cent glucose) at the time of the last investigation in pregnancy and postpartum. The women ranged in age from seventeen to twenty-seven years. On the basis of their past history, clinical findings and course of pregnancy they were classified as normal. In particular, the series did not include any patient known to be prediabetic. Details regarding the material and methods have been published.[3]

Table 1 and figure 1 show that during pregnancy the fasting blood sugar is lower, the peak is higher and occurs later, and the blood sugar values at two hours are higher than postpartum. The changes are most marked at seven months, when nine out of twenty-eight blood glucose values had not dropped below 120 mg. per 100 ml. at two and one-half hours. In the last investigation during pregnancy two of the curves were above this normal threshold.

These findings were subjected to statistical analysis by Mr. Arne Nielsen who arrived at the following result, using a "false x^2 test":

> The fasting blood sugar is lower at seven months than in the other pregnancy investigations, and the latter are lower than those following delivery. All values are significant at the 0.1 per cent limit. The maximum increase, i.e., the difference between the

TABLE 1

Group A. Oral glucose tolerance tests in twenty-eight normal women. Mean blood sugar values at four readings during gestation and postpartum (see also figure 1)

	Months of pregnancy				
Minutes	3	5	7	9	Postpartum
—60	89.1	88.1	83.4	88.3	100.1
—40	87.3	88.6	83.5	86.8	99.2
—20	86.5	89.5	83.8	88.0	100.3
0	88.4	89.5	83.1	89.6	99.5
+20	137.6	131.5	125.9	127.0	143.8
+40	149.3	146.7	151.6	145.9	154.8
+60	139.7	144.3	152.9	145.6	140.4
+80	127.6	133.7	144.1	136.2	126.7
+100	125.6	132.4	137.1	125.5	120.7
+120	119.1	116.0	125.6	112.0	111.4
+140	106.9	105.9	115.4	105.8	104.6
+160	90.3	93.8	103.3	96.2	94.8
+180	88.6	87.9	94.2	84.8	91.6

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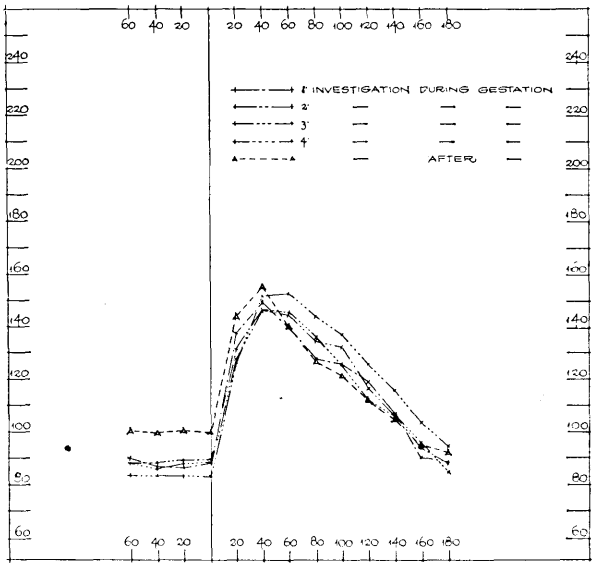

FIG. 1. Mean curves for twenty-eight normal subjects. Fasting blood sugar values and glucose tolerance curves from four investigations during pregnancy and one after. Blood sugar in milligrams per 100 milliliters is shown on the ordinate. Minutes before and after ingestion are shown on the abscissa.

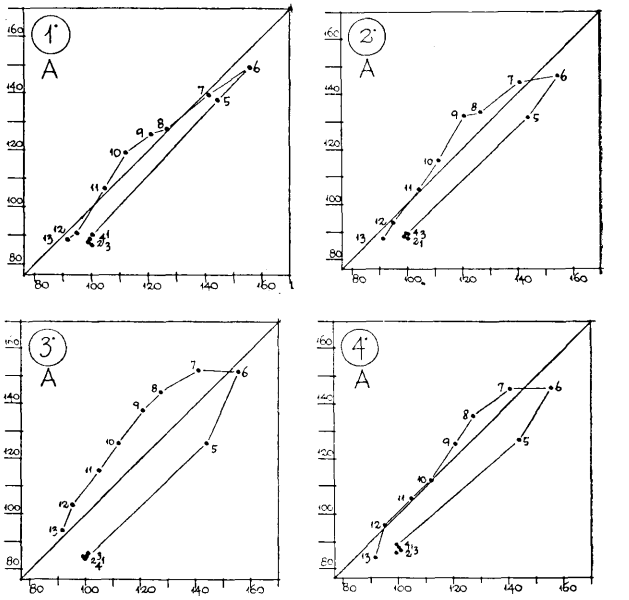

FIG. 2. Mean curves for twenty-eight normal subjects. Blood sugar values at the four investigations during pregnancy (ordinates) are plotted against the postpartum investigations (abscissas) in milligrams per 100 milliliters. 1. at three months 2. five months 3. seven months 4. nine months. See explanation in text.

fasting blood sugar value and the first peak (if this is followed by a decrease of more than 10 mg. per 100 ml. before the next value) is greatest at seven months. This is significant at the 1 per cent limit.

At seven months (1 per cent limit) and less so at nine months (5 per cent limit), the peak after administration of glucose occurs later than at five months.

Lastly, the blood sugar value two hours after glucose is highest at seven months (5 per cent limit) and lowest at postpartum (0.1 per cent limit).

In figure 2 the mean blood sugar values of the four tolerance tests during gestation have been plotted against corresponding values postpartum in such a way that the values of each investigation during pregnancy have been marked on the ordinate and those of the postpartum investigation on the abscissa. Thirteen blood sugar determinations were made during each glucose tolerance test, the first four fasting. The fasting values (1,2,3,4) during pregnancy are lower and fall below the identity line. (If they lay on this line it would indicate that the values were identical in pregnancy and postpartum.) The first two values after glucose ingestion (and the third at three months) are also below the identity line. The other values all are higher during pregnancy, except the last two (numbers 12, 13). Here again the seven-months' investigation is an exception as all values from No. 7 are higher than postpartum, i.e., above the identity line.

As shown in table 2 and figure 3, the initial value following intravenous injection of 50 ml. of glucose in 50 per cent solution is lower during than after pregnancy but recovery is slower during pregnancy and so the two curves cross.

The frequency of glycosuria following administration of glucose was as follows: 45 per cent in the third month, 57 per cent in the fifth month, 64 per cent in the seventh month, and 48 per cent in the ninth month. Glycosuria was found in 11 per cent postpartum.

TABLE 2

Intravenous glucose tolerance tests in eleven normal women. Mean blood sugar values during and after gestation (see also figure 3)

Minutes	During gestation	Postpartum
0	90.9	100.4
+2	289.5	330.9
+5	250.3	287.7
+10	209.4	244.2
+25	156.7	150.0
+40	124.2	108.7
+55	105.4	95.6
+70	94.5	92.0
+85	87.7	92.2
+100	84.4	94.9
+115	83.8	93.1

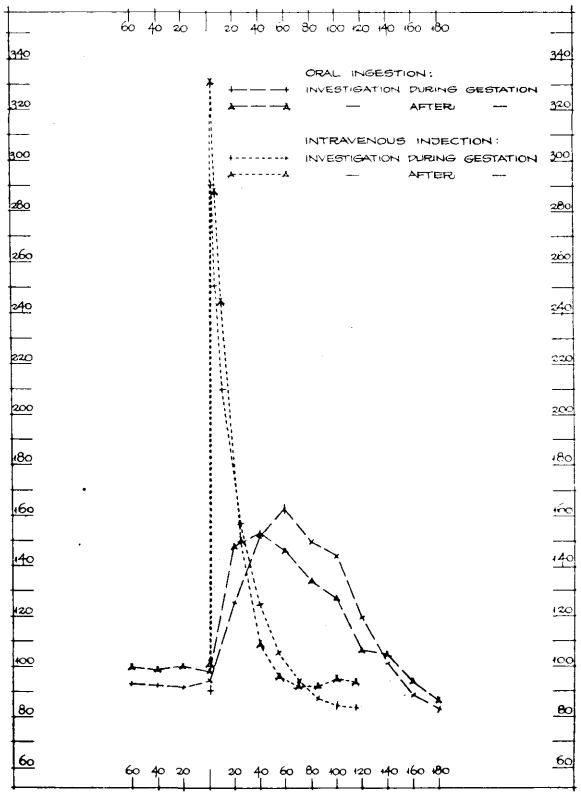

FIG. 3. Mean curves for eleven normal subjects. Intravenous and oral glucose tolerance curves during and after pregnancy. Blood sugar values in milligrams per 100 milliliters are shown on the ordinate; minutes before and after injection on the abscissa.

Fasting glycosuria was not found in any case. Glycosuria was thus most frequent in the seventh month.

Comment. The lower fasting blood sugar during pregnancy and the lower initial value following intravenous administration of glucose on the one hand and the higher increment and later peak in the oral curves (as well as the slower decrease in the oral and intravenous curves, on the other hand) might appear to represent opposite alterations of carbohydrate metabolism. The former might appear to represent intensification of blood sugar reduction and the latter a shift in the direction of a diabetic curve.

The intravenous curves give the impression that the lower initial value is simply a question of distribution, whereas the slower recovery is more suggestive of a true alteration in blood sugar regulation which would be present even though the initial value were not altered. In pregnant diabetics alterations in carbohydrate metabolism are represented by the increased tendency to insulin reactions in the second and third months and by the increased insulin requirement, especially in the seventh and eighth months.[11,12] In this connection it may be mentioned that, in patients with insulin-producing islet cell adenomas, spontaneous remission of the hypoglycemic attacks may occur during pregnancy.[13] Thus, the signs of augmented carbohydrate utilization must be considered secondary. It is concluded, therefore, that the effect of pregnancy upon the carbohydrate metabolism in normal subjects is a shift in the direction of diabetes, the shift being most pronounced at the beginning of the last trimester.

B. *Possible Prediabetics (Groups B 1 and B 2)*

Investigations similar to those described above were made in a group of forty-one women, each of whom had previously given birth to at least one child weighing more than 4,000 gm. Eleven such pregnant women were subjected to intravenous glucose tolerance tests.

Investigations on these forty-one subjects were conducted along the same lines as those on the twenty-eight normal pregnant subjects, but only thirteen mothers of large infants (group B 1) had four investigations during pregnancy, whereas the remainder (group B 2) were tested only once after the thirty-third week of pregnancy. All subjects were studied after delivery.

The women in group B 1 had previously given birth to a total of twenty-four infants with an average birth weight of 4,246 gm., and from the pregnancies under study all but one were delivered of live infants with an average birth weight of 3,846 gm. The sixty-four infants previously borne by the women in group B 2 had had an average weight of 4,097 gm., and the children they bore now weighed 3,852 gm. on the average. In seventeen of the forty-one cases labor was induced. The infant mortality in previous deliveries had been 13.6 per cent. The present pregnancy was terminated by the birth of living infants in forty. The mothers in group B ranged in age from twenty-one to thirty-four years and 29 per cent were more than 15 per cent overweight.

Tables 3 and 4 give the results of the tolerance tests in groups B 1 and 2, and figure 4 depicts the fasting blood sugar values and the glucose tolerance tests in group B 1. It is evident that the results correspond exactly to those in group A. This is confirmed by statistical analysis:

In group B 1 the fasting blood sugar value was lowest in the third pregnancy investigation (at seven months) and it was significant at the 5 per cent limit. Postpartum it was higher in both groups than during pregnancy (0.1 per cent limit). In group B 2 the maximum increase was greater during than after pregnancy (0.1 per cent limit), and the peak occurred later (1 per cent limit). Corresponding find-

TABLE 3

Group B 1. Oral glucose tolerance tests in thirteen mothers of big infants (see also figure 4)

Minutes	Months of pregnancy 3	5	7	9	Postpartum
—60	94.4	93.2	89.2	95.3	106.0
—40	92.4	93.2	87.5	94.7	104.8
—20	90.8	92.3	88.4	95.7	103.4
0	91.4	91.8	88.0	95.6	104.4
+20	140.3	138.3	127.2	125.6	143.8
+40	163.7	162.2	154.6	156.4	169.4
+60	157.2	157.3	160.7	154.3	159.8
+80	139.6	144.1	152.2	144.9	140.0
+100	133.3	133.9	142.6	135.9	132.0
+120	119.6	119.5	128.6	120.4	122.2
+140	104.5	106.8	118.3	111.8	110.8
+160	94.4	101.5	111.3	102.7	100.1
+180	90.0	95.1	108.6	94.9	94.9

TABLE 4

Group B 2. Oral glucose tolerance tests in twenty-eight mothers of big infants. Only one investigation during pregnancy and one postpartum (see text)

Minutes	During gestation	Postpartum
—60	93.5	102.5
—40	93.3	102.1
—20	93.1	100.8
0	93.2	100.8
+20	130.6	146.5
+40	159.7	165.1
+60	166.4	160.8
+80	153.6	137.9
+100	143.8	129.2
+120	122.1	115.3
+140	110.1	106.8
+160	98.4	97.6
+180	90.7	96.7

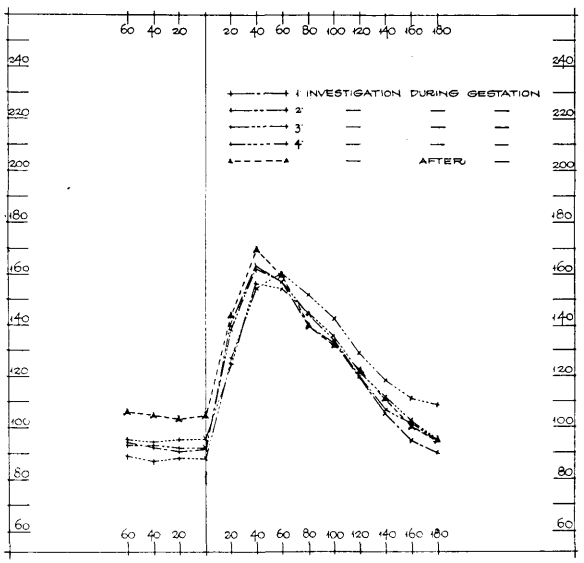

FIG. 4. Mean curves for thirteen pregnant women who had previously borne large infants. Blood sugar values in milligrams per 100 milliliters are shown on the ordinate; minutes before and after ingestion on the abscissa. Cf. figure 1.

ings were not definitely demonstrable in the B 1 group, but the trend was in the same direction. The blood sugar value two hours after administration of glucose was highest in the third pregnancy investigation in group B 1. In group B 2 this value was lower after than during pregnancy. This was also not definitely demonstrable in group B 1, but again the tendency was in the same direction as in group B 2.

Among mothers of large babies the blood sugar frequently exceeds 120 mg. per 100 ml. two and one-half hours after the administration of glucose. Thus, in the third (seven months) pregnancy investigation, seven out of thirteen in group B 1 exceeded that limit, and two in the fourth investigation. When investigated during pregnancy (corresponding approximately to the fourth investigation in groups A and B 1) the blood sugar of seven out of the twenty-eight patients in group B 2 exceeded 120 mg. per 100 ml. at two and one-half hours.

From table 5 it will be seen that the intravenous glucose tolerance curves were the same as in normal subjects, i.e., there was a less marked increase and a slower decrease in the level of blood sugar during pregnancy.

TABLE 5

Intravenous glucose tolerance tests in eleven mothers of big infants

Minutes	During gestation	Postpartum
0	92.7	104.8
+2	286.5	345.2
+5	246.3	313.3
+10	212.6	269.1
+25	162.3	158.2
+40	128.4	106.0
+55	109.0	92.4
+70	95.3	93.9
+85	87.0	97.5
+100	86.0	94.8
+115	88.4	98.0

The frequency of glycosuria varied approximately as in normal subjects. In the four stages of pregnancy it was 40 per cent, 38 per cent, 61 per cent, and 58 per cent. After delivery it was 17 per cent.

Comment. It is evident that the findings in women who had previously borne large infants are similar in many respects to the findings in normals. In order to evaluate the validity of calling the mothers of big infants possible prediabetics a detailed comparison of the findings must be made.

C. *Comparison of the findings in normals and in mothers of big infants*

Three findings stand out: (1) The tendency for the blood sugar to exceed limits of normal during pregnancy

is more outstanding among mothers of big infants, as mentioned above; (2) all values appear to be elevated in the mothers of large infants as compared with the normal subjects. The validity of this impression can be partially substantiated by the statistical findings:

Analysis showed that the fasting blood sugar values were higher in groups B than in group A and that this is significant in the ninth month. At other times the tendency is in the same direction. Furthermore, the maximum increase is greater in group B 2 than in group A, while no significance was found in this respect for group B 1, which, however, shows the same tendency. Finally, the time of the peak is later in group B 2 than in group A during pregnancy. Again, the tendency is the same for the entire B group, although significance could be shown only in one instance. As regards the blood sugar value at the end of two hours, results were not conclusive.

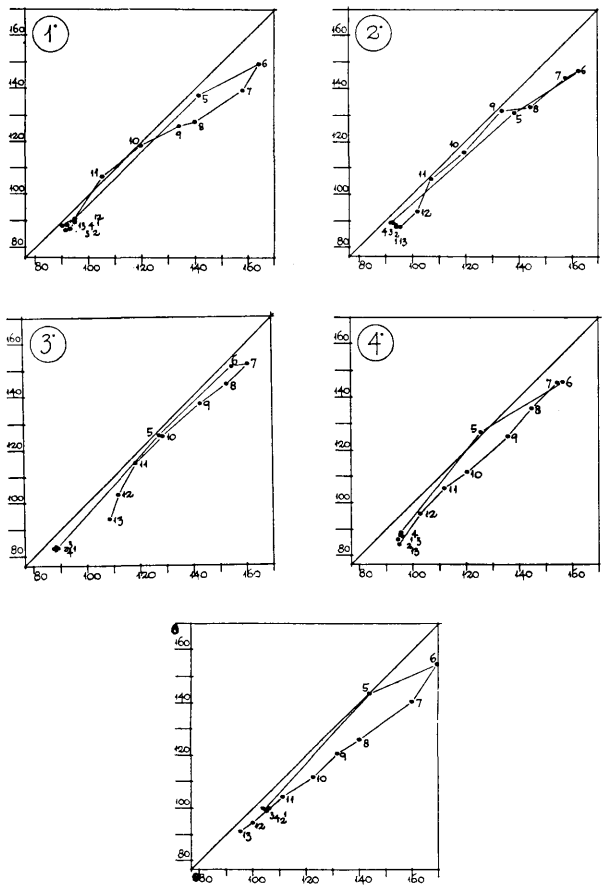

FIG. 5. Mean curves. Blood sugar values in milligrams per 100 milliliters at four investigations during pregnancy and one after delivery of twenty-eight normal women plotted against corresponding values of thirteen women who had previously given birth to large infants. Cf. text and figure 2. Note that practically all values are located below the identity line, i.e., the blood sugar values of mothers of big infants are higher than those of normal women. 1. at three months 2. five months 3. seven months 4. nine months 5. postpartum.

These findings are charted in figure 5 (cf. figure 2) in which the blood sugar values for normal subjects are plotted against the corresponding values for the mothers of large infants of group B 1. Clearly, the latter are located on their own side of the identity line, i.e., show higher values in practically all the investigations.

(3) The third conspicuous finding concerns the intravenous glucose tolerance tests. In the nonpregnant state the early increase in blood sugar is greater in groups B 1 and B 2 than in group A, but during pregnancy there is no difference. Since the dose of glucose was the same, the overweight mothers of large infants might be expected to show a less marked increase. The findings suggest that the blood sugar depressing factor of pregnancy is more active in mothers of large infants.

Comment. It must be concluded that the mothers of big infants exhibit higher blood sugar values than mothers of normal infants and also that the big babies during pregnancy receive a more copious flow of glucose via the maternal blood.

D. *An attempt to sort out the prediabetic patients*

The B groups were too small to permit subdivision into groups possessing different properties. Any attempt at subdivision meets with the difficulty which would also be encountered with a considerably larger series, viz. overlapping of important variables such as age, hereditary predisposition to diabetes, number of previous pregnancies, overweight in the pregnant and nonpregnant state, little weight loss after delivery, and the size of the infants, both in the previous and present pregnancy.

Some impression of the importance of the individual factors may be gained, however, and this impression proved a basis for further analysis. First, there seemed to be a tendency for a higher maximum and a slower decrease of the glucose tolerance curve with increasing age. This tendency is not very pronounced, and it is far from sufficient to explain the difference in the levels. Second, the glucose tolerance curves were different in pregnant women who were overweight postpartum and in those who had again given birth to large babies. The fasting blood sugar was relatively high, whence the curve rose abruptly to a maximum at the upper limit of normal and fell abruptly from the peak to values below the fasting level, after which it returned slowly to the initial value. These curves appear to correspond to the so-called "lag" or "oxyhyperglycemic"* curves.[14] (*See footnote page 443.*) They are not uncom-

mon in obese subjects and have been found previously in pregnancy.[15] They are interpreted as prediabetic curves by many authors.

There were nine women with oxyhyperglycemic curves, obesity and big infants in the observed pregnancies. These women possessed other common properties. First, there was a fairly high fertility rate with a total of twenty-five pregnancies. Two of these had ended in abortion (a low frequency) and four in stillbirths (a high frequency). The birth weights of the infants previously borne was high (4,347 gm.). Five infants had weighed more than 5,000 gm. Eight in the present series were delivered of living infants with an average birth weight of 3,861 gm., but the delivery was induced before term in five. The average body weight of the mothers was 96 kg., with a maximum of 128 kg.

Comment. It is probably justifiable to regard women with high fertility, particularly large infants with high perinatal mortality, and with marked obesity and "oxyhyperglycemic" glucose tolerance curves as potential diabetics.

SUMMARY

Determinations are presented of fasting blood sugar, oral and intravenous glucose tolerance tests, and glycosuria in pregnant women. The results are compared with similar investigations on the same persons in a nonpregnant condition. It was found that in pregnancy the fasting blood sugar was decreased, the oral glucose tolerance test was shifted in a diabetic direction, and the frequency of glycosuria was higher during pregnancy. These changes were most marked at seven months, at which stage the glucose tolerance curve was often in the abnormal range. Moreover, the blood sugar following intravenous injection of glucose did not rise as high during as after pregnancy, while the intravenous glucose tolerance curve was more prolonged during pregnancy. It is concluded that the most important alteration in carbohydrate metabolism in normal pregnancy is a shift in a diabetic direction, and thus, that normal pregnancy exerts a diabetogenic effect.

The same type of gestational blood sugar changes were found in normal pregnant women and in women who showed a tendency to bear big infants. However, the latter more often had abnormal glucose tolerance curves during pregnancy, and their blood sugar values on the whole were shifted toward a higher level. It seems possible to sort out among them a category with marked obesity, a history of high fertility and delivery of particularly big infants with a high perinatal mortality. Their oral glucose tolerance curves showed an "oxyhyperglycemic" course. They are considered potential diabetics.

*Such curves are characterized by the abrupt rise and fall and the high peak. This course of the curve may be looked upon as an exhaustion reaction of the blood sugar regulation.

SUMMARIO IN INTERLINGUA

Valores de Sucro Sanguinee Durante le Pregnantia in Gravidas Normal e Possibilemente Prediabetic

Es presentate le resultatos de determinationes del sucro sanguinee in stato jejun, de tests de tolerantia pro glucosa oral e intravenose, e de evalutationes del glycosuria in feminas pregnante. Iste resultatos es comparate con simile investigationes in le mesme subjectos in condition non-pregnante. Esseva trovate que in le pregnantia le nivellos del sucro sanguinee in stato jejun esseva reducite, le resultato del test de tolerantia pro glucosa oral esseva displaciate in le direction de diabete, e le incidentia de glycosuria esseva augmentate. Iste alterationes esseva le plus marcate post septe menses de graviditate. A iste tempore le curva de tolerantia pro glucosa esseva quasi in le region anormal. In plus, le nivello del sucro sanguinee post injectiones intravenose de glucosa non montava al mesme altor durante le pregnantia como post illo, e le curva de tolerantia pro glucosa intravenose esseva plus prolongate durante le pregnantia. Es concludite que le plus importante alteration del metabolismo de hydrato de carbon in pregnantia normal es un displaciamento in le direction de diabete e assi que pregnantias normal exerce un effecto diabetogenic.

Identic typos de alteration gestational del sucro sanguinee esseva trovate in gravidas normal e in gravidas tendente a parturir large infantes. Tamen, iste ultimas habeva plus frequentemente anormal curvas de tolerantia pro glucosa durante le pregnantia, e in illas—a generalmente parlar—le valores del sucro sanguinee se displaciava verso plus alte nivellos que in le gravidas normal. Il pare possibile differentiar inter illas un subcategoria con marcate grados de obesitate, un historia de alte fertilitate, e le tendentia de parturir exceptionalmente large infantes con alte mortalitate perinatal. Lor curva de tolerantia pro glucosa oral sequeva un curso "oxyhyperglycemic." Illas es considerate como diabeticas potential.

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On Teaching Diabetes

How Can the Practice of Medicine in the Treatment of Diabetes Be Improved?

The largest group of physicians who need training in improving diabetic care is practicing physicians. It was the consensus that a multiple and varied approach can be effective in the postgraduate education of practicing physicians. The first approach might be the same as that mentioned in regard to small hospitals. Through contact with an interested and informed internist who is available for consultation and for organization of subsidiary diabetic care and teaching, the practitioner can learn more about diabetes. In addition, postgraduate courses in diabetes such as those organized by the American Diabetes Association, are very helpful; but this particular program, valuable as it is, is limited to a relatively small number of physicians. Postgraduate courses in diabetes could be expanded to a great extent by medical schools and by local medical organizations at the state or regional level. In addition, teams from nearby medical centers might go out to local and regional meetings to stimulate interest in diabetes. This is being arranged in several states. Programs on diabetes could be incorporated in monthly staff meetings of community hospitals at which attendance is compulsory. Many practitioners could be reached through the Academy of General Practice. It is hoped that the least that could be accomplished through these approaches is to instill the attitude toward diabetes which we would like to see in physicians. Finally, it was suggested by some that teaching by mail with the help of visual aids be considered. Such concerted teaching programs by mail might be financed by interested agencies such as the American Diabetes Association, the United States Public Health Service, and possibly might be supported also by private organizations.

The second part of our discussion was concerned with possible improvements in the training and education of the patients. Two main questions can be asked: (1) How is the training best accomplished? and (2) What should the patient be taught? In regard to ways of teaching, it was the consensus that individual instruction by the physician as well as by the dietitian and nurse is still of great importance. In addition to individual attention, much can be gained by the patient's attending classes held by diabetes clinics in hospitals. The organization of classes for group therapy is one of the most important services which can be rendered for diabetic patients. Such classes may be conducted by physicians, dietitians and nurses.

In addition to these forms of therapy, there are several supplementary aids. Diabetic lay organizations can help in keeping up the patient's interest in self-education and should be supported by physicians, dietitians and nurses. Visiting public health nutritionists and nurses are available in many states to visit patients in outlying districts who cannot come to group meetings. Attempts should be made to stimulate and to encourage dietitians to go into the practice of diet therapy. There are many married dietitians who might be willing to work in such a capacity on a part-time basis and to whom physicians could send their patients for diet instruction. For diabetic children the availability of diabetes camps might be expanded.

By Stefan S. Fajans, M.D., in
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