remembered that prothrombin estimations are essential for their control. The possibility of an urgent operation being necessary in a patient on dicoumarol or allied drugs has always been a drawback to their use. This drawback is largely overcome by the use of vitamin K_1.

In considering the use of such a potent drug as vitamin K_1 it must be remembered that the prompt restoration of the prothrombin to a normal, or near normal, level in a patient requiring the use of anticoagulants will inevitably restore the dangers of thrombo-embolism. Vitamin K_1 must therefore be used with caution and only in cases where the danger of severe prothrombin deficiency overrides that of thrombo-embolism. This statement applies to the doses of vitamin K_1 used in this report. Further work is in progress with smaller doses of vitamin K_1, which it is hoped will overcome a dangerous prothrombin deficiency that may arise from anticoagulant therapy but will not restore the prothrombin to a level where thrombo-embolism is likely.

In using large doses of vitamin K_1 it must also be remembered that the patient may become refractory to anticoagulants and require much larger doses of the anticoagulant drug after the administration of the vitamin.

Summary

In 18 patients, vitamin K_1, in a single oral dose of 500 mg., was completely effective in restoring a safe prothrombin level after a severe and prolonged prothrombin deficiency due to such anticoagulant drugs as dicoumarol, tromexan, and phenylindandione.

This effect was evident within eight hours, and the action of the vitamin was apparent within four hours.

In three cases of frank haemorrhage due to anticoagulant drugs, an oral dose of vitamin K_1 was in itself sufficient to stop bleeding in a matter of hours.

I wish to thank Roche Products Ltd. for the generous supplies of the vitamin K_1 used in this work, and in particular Dr. F. Wrigley for his advice and help.

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Nation-wide hunts for donors of rare types of blood should no longer be necessary with the coming into use this week of a national panel of nearly 2,000 donors whose red blood cells have been classified down to the finest subdivisions of the blood groups. Several hundred distinguishable kinds of blood are included in the panel. The preliminary testing and selection of donors for the panel was done by the regional transfusion centres of the National Blood Transfusion Service, the Scottish National Blood Transfusion Association, and the Northern Ireland Blood Transfusion Service. The Blood Group Reference Laboratory, run on behalf of the Ministry of Health by the Medical Research Council, was responsible for the detailed testing and classification. The testing of the donors and the classifying and checking of the results have occupied several members of the laboratory staff for about a year. The register will be kept up to date by replacing any donor who resigns by a new donor. The regional transfusion centre in whose region the resigning donor lives will be responsible for replacing him, and the Blood Group Reference Laboratory will carry out the necessary detailed tests and issue periodical amendments to the register. No other country has a panel of donors in any way comparable with this one, which has only become possible through the unique organization of the National Blood Transfusion Services and the leading position which this country holds in blood-group research and technology.

STUDIES IN PRE-DIABETES

BY

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PART I

ITS INCIDENCE IN THE CAPE, ITS EARLY DETECTION, AND THE CONCEPT OF THE PRE-DIABETIC FATHER

Coming events cast their shadows before. The woman destined to develop diabetes divulges her future fate by producing infants which are dead,[1-7] or large,[1 3 7-11] by rapid obesity during pregnancy,[6 8 11 12] and perhaps by overlactation.[12] The only dissentient voice has been that of Herzstein and Dolger,[13] and their figures are of doubtful validity.[1]

Observations on Pre-diabetic Women

The high foetal loss rate and, particularly, the macro-infantia are applicable to pre-diabetic women in the Cape, both white and "coloured" (mixed race), and probably African also.

Method.—The method of personal questioning of unselected consecutive patients which was adopted is admittedly subject to great inaccuracy. For controls we took a series of cases of similar race and age distribution who were attending hospital for various reasons, none of them being known diabetics. As there is no reason to believe that diabetics are greater exaggerators of birth size than other hospital patients, conclusions drawn from a comparison of the two groups should be valid. Absolute figures, however, cannot be regarded as accurate. Babies are included in the survey only when the mothers knew their weight with reasonable and credible accuracy. "Large" was not considered good enough, nor "I'm sure he was over 10 lb.," unless the latter was confirmed by definite memory of the use of a scale and suitable remarks by doctor or midwife. Whenever a large baby was claimed every verbal effort was made to obtain confirmatory evidence before acceptance.

"Stillbirths" here include deaths within 48 hours of birth, and their recorded percentages are also subject to inaccuracies.

Large Babies

Table I shows that 62% of the women who develop overt diabetes after child-bearing claim to have had at least one baby over 10 lb. (4.5 kg.) in weight. This compares with

TABLE I.—*Pre-diabetic and Control Mothers*

	Total Mothers		Mothers with at Least 1 Child over 10 lb.		Mothers with No Child over 8·lb.		Mothers with at Least 1 Stillbirth	
	P.	C.	P.	C.	P.	C.	P.	C.
White ..	50	50	31	7	2	23	8	4
Coloured	50	50	31	5	6	30	22	9
Total	100	100*	62%	12%	8%	53%	30%†	13%†

P = Pre-diabetic. C. = Control.
* Total number of control mothers was actually 130—reduced to 100 for easy comparison.
† Difference between these two proportions is two and a half times its standard error.

Kriss and Futcher's[9] 58% and the figures of Miller[1] and Moss and Mulholland.[7] So commonly is there a story of several large babies, sometimes with stillbirths, that we have come to regard this as strongly confirmatory of diabetes in a doubtful new case, so that necessary treatment may be started without awaiting the results of chemical analyses.

TABLE II.—*Children of Pre-diabetic and Control Mothers*

	Total Children of		% Over 9 lb.		% Over 10 lb.		% Over 11 lb.		% Under 8 lb.		% Stillbirths	
	P.M.	C.M.	P.M.	C.M.	P.M.	C.M.	P.M.	C.M.	P.M.	C.M.	P.M.	C.M.
White ..	210	136	55%	17%	34%	7·4%	17·6%	2·2%	19%	72%	7·6%	3%
Coloured ..	218	303	40%	8·3%	28%	3·3%	11%	1%	25%	72%	21%	6·8%
Total ..	428	439	47%	11%	31%	4·6%	13%	1·4%	22%	72%	14%	5%

P.M. = Pre-diabetic mothers; C.M. = Control mothers.

Table II shows that 31% of babies of the pre-diabetic women (the women shown in Table I) were over 10 lb. (4.5 kg.), as against 4.6% of the control women's babies. This rate compares with that in several other series,[7 9 10] but is higher than most for reasons already considered. The high mean birth weight in the pre-diabetic period may be better appreciated from the fact that only 22% of the babies were under 8 lb. (3.6 kg.), as opposed to 72% in the control series.

The only pure negress who knew accurately her babies' birth weights had had two sets of twins in the 10-year period preceding the onset of clinical diabetes, both in hospital. The combined weights were 12 lb. (5.4 kg.) and 15 lb. (6.8 kg.). From this and other observations mentioned later it appears that the pre-diabetic state may apply to the African.

The actual birth weights of 1,000 children (500 white and 500 coloured) born in hospital were also recorded (Table III) to see how the proportion in the various groups differed

TABLE III.—*Birth Weights of Unselected Children in Hospital*

	Total	Under 8 lb.	8–9 lb.	9–10 lb.	Over 10 lb.
White	500	63%	25%	10%	2%
Coloured ..	500	86%	10%	4%	<1%
Total ..	1,000	75·5%	17·2%	6%	1·3%

from those calculated from questioning the mothers. In this way we hoped to get some idea of parents' "exaggerator rate." Actually the proportion in the comparable weight groups were very similar, except in the over 10 lb. group, with 4.6% of children by questioning and only 1.3% by records (the usual figure for 10-pounders[15–17]). This exaggeration of claimed 10-pounders demonstrates the necessity for our control series of mothers. Incidentally, Table III shows also the tendency for the coloured baby to be smaller on the whole than that of pure white stock (cf. Woodrow and Robertson[18]).

Stillbirths

Tables I and II also indicate that the stillbirth rate is higher in the pre-diabetic, the 14% of total babies comparing with several other reports,[2–5 7 10 14] whose figures vary from 10 to 25%, most of which are not, however, strictly comparable. Incidentally, the stillbirth rate in established diabetics in the Cape nears 50%.[19] It may be noted that both tables indicate a much higher stillbirth rate in coloured women than in white, both pre-diabetic and control, which may be related to environmental conditions.

Time Interval Before Development of Diabetes

It is often stated that the tendency to produce large babies and stillbirths is evident for 15 to 20 years before manifest diabetes develops. Table IV suggests that this tendency goes back indefinitely, so that there is still an excess of large babies and stillbirths more than 30 years before the onset of diabetes. Thus 26% of such babies were over 10 lb. (as against the 4.6% of the control series). The figures have not been subjected to statistical analysis from this angle because of their inherent inaccuracies, but they are certainly very suggestive, and compare with those of Kriss and Futcher[9] and of Moss and Mulholland.[7] One old but

TABLE IV.—*Length of Pre-diabetic Period*

	Total Babies	Babies over 10 lb.	Stillbirths
0–4 years before diabetes	35	54%	29%
5–9 ,, ,, ,,	55	44%	13%
10–14 ,, ,, ,,	61	23%	23%
15–19 ,, ,, ,,	92	28%	13%
20–29 ,, ,, ,,	102	35%	8%
30+ ,, ,, ,,	43	26%	9·3%
Control series	39%	33% (4·6%)	14% (5%)
Whole series			

intelligent woman claimed to have had an 11-lb. (5-kg.) baby 58 years before developing diabetes. As in other series,[1 7 11] the proportion of large babies and stillbirths rises as the onset of diabetes approaches.

Pre-diabetic Fathers

Discredited theories attributed large babies to maternal hyperglycaemia. Since then the work of Young[20] has established the identity of, or at least the close connexion between, the diabetogenic and growth factors of the anterior pituitary. An excessive anterior pituitary function, particularly with respect to this hormone, might therefore account both for the large babies and for the maternal diabetes,[1 3 11] and perhaps maternal obesity[3] and superlactation[12] as well. An extension of pituitary overactivity to the gonadotropic hormone might explain the high foetal death rate.[21] Wilder[22] objects that none of the usual manifestations of hypophysial overactivity are present in these cases. Moreover, the rather naive assumption that the mother is solely responsible for the child is tacitly understood. I am indebted to Professor G. C. Linder for suggesting that inquiry should be made to see whether *paternal* diabetes and pre-diabetes may not be associated with large babies and high foetal loss. In other words, why should there not be a genetic factor, linked with that for diabetes, which makes for these features? Why should they necessarily be conditioned solely by the *milieu intérieur* of the mother ("maternal environment")?

Method.—We have attempted, by the methods described above, to tackle this possibility by interviewing the men who attended our diabetic clinic. It was a prolonged task, since

TABLE V.—*Pre-diabetic Fathers and Control Fathers*

	Total	Fathers with at Least One Child over 9 lb	Fathers with at Least One Child Over 10 lb.	Fathers with at Least One Stillbirth
Pre-diabetic fathers ..	49	56%	35%	8%
Control fathers ..	50	14%	12%	8%
Difference	—	—	23	—
S.E. of difference ..	—	—	8·2	—
Difference/its S.E. ..	—	—	2·8	—

TABLE VI.—*Children of Pre-diabetic and Control Fathers*

	Total Children	Under 8 lb.	8–9 lb.	9–10 lb.	Over 10 lb.	Stillbirth Rate
Of pre-diabetic fathers ..	189	72 (38%)	69 (36·5%)	22 (11·7%)	*26 (14·1%)	3%
Of control fathers ..	147	88 (60%)	48 (32·6%)	3 (2·0%)	*8 (5·4%)	3%

$\chi^2 = 25·9$; d.f. = 3; $P << 0·01$.
* Difference between these two proportions is 2·7 times its standard error.

comparatively few knew their children's birth weights, and in addition we do not treat so many males at the clinic. Moreover, as this was a crucial experiment, we insisted on some sort of corroborative evidence. At the same time we obtained data from a comparable group of non-diabetic outpatient fathers as a control series in case it might be objected that to compare diabetic *males* with non-diabetic *females* was introducing a second variable. In fact, however, the data obtained in the male control series (Tables V and VI) were essentially the same as those in the female controls (Tables I and II), so that it would be legitimate to use both together as a control series.

Large Babies

When our figures were analysed we found to our surprise that there was in fact a high proportion of large birth weights among the children of diabetic men (Tables V and VI). Forty-nine fathers had 189 children, of whom 14% were said to be over 10 lb. (4.5 kg.) at birth, compared with 5% of the controls. Analysis of Table VI by two methods indicates that these birth-weight differences are highly significant. As in the stories of the women, some of these men gave an account of repeated large babies; one had all five over 10 lb., another had three out of four over 10 lb. It might be contended that such stories as these may have been due to pre-diabetic wives, but this is unlikely for various reasons. First, no similar histories were obtained in the control series; secondly, in two such fathers the youngest child was over 20 years old, yet the wife was still not diabetic; thirdly, one man had large babies by two wives; and, fourthly, the tolerance curve of one wife was quite normal.

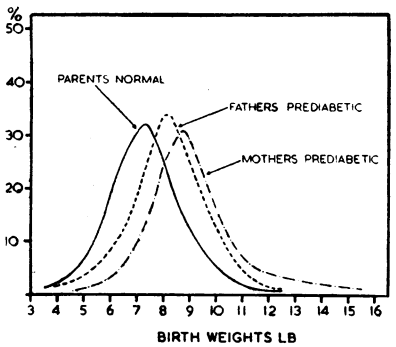

FIG. 1.—Frequency distribution curves of birth weights of babies born to normal parents, to pre-diabetic fathers, and to pre-diabetic mothers.

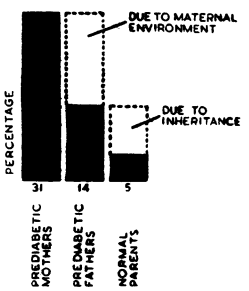

FIG. 2.—Comparison of proportion of infants over 10 lb. (4.5 kg.) born to pre-diabetic mothers, to pre-diabetic fathers, and to normal parents. Blocked differences show respectively the apparent importance of maternal internal environment and of inheritance in producing large babies.

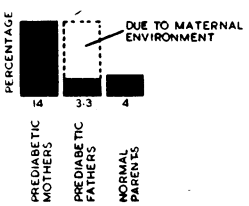

FIG. 3. — Comparison, similar to Fig. 2, of proportion of stillbirths born to pre-diabetic mothers, to pre-diabetic fathers, and to normal parents. The difference seems to be solely due to maternal environment.

Frequency distribution curves of birth weights (Fig. 1) demonstrate graphically the tendency of pre-diabetic mothers to produce large babies compared with the control series, while the curve for the babies of pre-diabetic fathers lies in between.

Interpretation

The stillbirth rate told quite another story—no difference between diabetic and control fathers. The evidence suggests, then, that the tendency to produce large babies is *partly* an inherited characteristic combined with a tendency to diabetes, passed on by the male as well as the female, and *partly* an effect of maternal environment as in the current hormonal hypothesis (Fig. 2). The excessive foetal loss, on the other hand, is entirely mediated by maternal factors (Fig. 3). Incidentally, the inherited factor must be autosomal, since about equal numbers of large girl and large boy babies are produced.

There is nothing inherently unlikely in this suggestion, no reason why large birth size should not be inherited, and some evidence that it is so inherited in *non-diabetic* families also.[9 12 23] Nevertheless, I do not claim that the present figures prove the existence of the pre-diabetic father syndrome, but it is hoped that further data from larger clinics may be able to substantiate or refute it.

EARLY DETECTION OF PRE-DIABETES AND "CHEMICAL DIABETES" IN MOTHERS

The recognition of the pre-diabetic state in retrospect by consideration of the obstetric history of a new diabetic patient may be of great theoretical importance, but can be of no value to the individuals directly concerned. We therefore decided to see whether, by means of a simple glucose-tolerance test on the sixth post-partum day, we could establish the presence of pre-diabetes or a mild diabetic state in women who gave birth to large babies in hospital. A curve at such a time is very largely reliable (see Part II).

Nearly 20 years ago Skipper[14] and White[6] suggested that mothers who have large babies should be examined for diabetes. This never appears to have been done on any scale, and at that time the significance of "pre-diabetes" was not realized, although Skipper seems to have been the first to notice that women may have large babies long before developing overt diabetes.

Kriss and Futcher[9] were able to predict that a mother of 23 having a first baby of over 10 lb. (4.5 kg.) had a 17.8% chance of becoming diabetic; but this did not help individual mothers, nor did it take account of *repeated* large babies or stillbirths.

Gilbert[11] approached the problem differently by examining the histories of 5,000 women confined some six years previously. Of these, he finally re-examined 21 who had had unexplained foetal losses or large babies, and found six to be diabetic, inasmuch as they had a raised tolerance curve.

Moss and Mulholland[7] found two patients without glycosuria who had given birth to several stillborn infants and who had diabetic tolerance curves.

Method.—All women confined in Groote Schuur Hospital (1949–50) whose babies weighed over 10 lb. were examined for glucose tolerance. Other mothers were sampled at random, so that their babies' weights fell into all groups. Most were tested on the sixth post-partum day, except that a few mothers of 10-pounders were sent to us from outside and were therefore rather later in the puerperium. None were known diabetics. Whenever possible all women who showed abnormal curves were re-examined six months later. No curve taken shortly after caesarean section is regarded as abnormal without repetition later. Altogether 165 parturient women have been tested, including 33 whose last baby weighed over 10 lb. and 14 whose babies were stillborn. A curve is called diabetic if either the two-hour level is over 140 mg. or the two-and-a-half-hour level over 130,

TABLE VII.—*Glucose-tolerance Curves in Parturient Mothers of Babies in Different Weight Groups*

	Last Baby Under 7 lb.	Last Baby 7–8½ lb.	Last Baby 8½–10 lb.	Last Baby Over 10 lb.	Total	Last Baby Stillborn
Mothers' diabetic curve	0	2	4	5	11	5
Mothers' pre-diabetic curve ..	1	1	2	4	8	3
Mothers' normal curve	41	43	38	24	146	6
Total ..	42	46	44	33	165	14

combined with a fasting level of over 120 mg. or a peak of over 200 mg.; it is considered pre-diabetic if the two-hour or the two-and-a-half-hour level is high but the curve otherwise normal (see Part II).

The main results are expressed baldly in Table VII. This shows only the bare fact that among our 165 mothers we found 11 unsuspected diabetics; in five cases the last baby weighed over 10 lb. and in five it was stillborn. The individual histories and tolerance curves of the 11 diabetics follow:

Results: Diabetic Mothers

Babies 7–8½ lb. (3.2–3.9 kg.)

Mother 1.—Aged 36, coloured, average size. Present infant 8 lb. (3.6 kg.), macerated foetus. Previous 11 pregnancies: "big babies," weights unknown.

Curve

36th week of pregnancy: 159 (fasting), 270, 367, 336, 251, 240.
Sixth post-partum day: 118 (fasting), 174, 174, 190, 221, 201. Sugar ++.

Mother 2.—Aged 38, coloured, average size. Previous five children, 11 lb. (5 kg.), 10 lb. (4.5 kg.), 13 lb. (5.9 kg.), 8 lb. (3.6 kg.), and 9 lb. (4.1 kg.).

Curve

Sixth post-partum day: 279 (fasting), 323, 340, 340, 232, 296. Sugar ++.

Babies 8½–10 lb. (3.9–4.5 kg.)

Mother 3.—Aged 34, coloured, small. Present baby stillborn. Previous children: 9 lb. (4.1 kg.), 8 lb. (3.6 kg.), 6 lb. (2.7 kg.), and 6½ lb. (2.9 kg.).

Curve

Sixth post-partum day: 176 (fasting), 260, 284, 301, 284, 268. Sugar +.

Mother 4.—Aged 45, white. Became obese during pregnancy. Only baby, 8½ lb. (3.9 kg.), premature stillborn. Mother and father both diabetic.

Curve

Sixth post-partum day: 120 (fasting), 206, 222, 181, 136. No sugar.
Six months later: 110 (fasting), 119, 141, 145, 145.
Year later: 106 (fasting), 188, 184, 180, 177, 141. Sugar +.

Mother 5.—Aged 36, coloured, small. Toxaemia in last two pregnancies. Lactation excessive. Nine previous babies of normal weight.

Curve

114 (fasting), 178, 230, 232, 149, 140. No sugar.

Mother 6.—Aged 33, negress, normal size. Eight previous pregnancies produced three stillbirths and four neonatal deaths, with weights of 10 lb. (4.5 kg.), 11 lb. (5 kg.), 12 lb. (5.4 kg.), and 14½ lb. (6.6 kg.) known.

Curve

150 (fasting), 227, 282, 202, 189. No sugar.

Babies over 10 lb. (4.5 kg.)

Mother 7.—Aged 33, coloured, small. Toxaemia with last two pregnancies. Ten previous pregnancies, one stillbirth, none above 9 lb. (4.1 kg.).

Curve

Sixth post-partum day: 130, 226, 243, 230, 178, 144. Sugar +.
Seven months later: 169, 223, 273, 269, 187, 169. Sugar +. Complaining of itching.

Mother 8.—Aged 43, white, obese since childhood. Last child died within 48 hours, weight 15 lb. (6.8 kg.). Previous children, 13 lb. (5.9 kg.) and 16 lb. (7.3 kg.) (neonatal deaths) and twins (live).

Curve

Sixth post-partum day: 247, 299, 346, 337, 287, 255. Sugar ++.

Mother 9.—Aged 46, coloured, slightly overweight. Toxaemia with last pregnancy, and baby weighed 11½ lb. (5.2 kg.), stillborn. Eight previous children, with stillbirth in 1930, none over 9 lb. (4.1 kg.).

Curve

Sixth post-partum day: 118 (fasting), 255 (1 hour), 152 (2½ hours). Sugar +.
Six months later: 229 (fasting), 239, 220 (1 hour), 171, 164 (2½ hours).

Mother 10.—Aged 42, coloured, obese. Ten babies 6–7 lb. (2.7–3.2 kg.), one 11 lb. (5 kg.), and present 10 lb. (4.5 kg.).

Curve

Sixth post-partum day: 219, 230, 268, 296, 262. Sugar +++.

Mother 11.—Aged 39, white, large, rather obese. Baby 11 lb. (5 kg.) stillborn. Aunt is a diabetic. Nine previous babies: last three 12 lb. (5.4 kg.), 10½ lb. (4.8 kg.), and 9½ lb. (4.3 kg.) stillborn.

Curve

171, 207, 199, 199, 171. No sugar.

Several things emerge from an inspection of these protocols. First, 10 out of the 11 women with a diabetic curve had one or more 10-lb. (4.5-kg.) babies and/or one or more stillbirths. Mother 5, with her 9-lb. (4.1-kg.) baby, had had toxaemia in her last two pregnancies and lactated excessively. In *every* case, therefore, there were "diabetic" hints in the obstetrical story. (The high incidence of toxaemia in the diabetic is well attested by Barns and Morgans,[3] White,[29] Mengert and Laughlin,[2] and Patterson and Burnstein.[4])

Secondly, there were no symptoms of diabetes in any parturient case, but Mother 7 complained of generalized itching seven months later.

Thirdly, the average age of the 11 was 37.9 years, as against 25.9 years for the 146 non-diabetic mothers. This striking difference compares with the finding of Gilbert[11] and suggests that several of the younger mothers of large babies may become diabetic later. Incidentally, the average age of all mothers of 10-lb. (4.5-kg.) babies, excluding diabetics, was 31.4 years, which suggests, further, that older women may be more likely to have larger babies. (This is at variance with White and Klein,[17] and is not claimed to be significant.)

Fourthly, maternal obesity was not a very outstanding feature in this series, only 4 of the 11 diabetic mothers being obese, despite their high mean age. This is very different from Gilbert's series in which "all six patients with diabetic blood-sugar curves were 30 lb. (13.6 kg.) or more above their 'correct' weight." It is noteworthy, however, that all three white women in our diabetic group were obese.

Fifthly, *glycosuria* during the tolerance test was absent or very slight in 4 of these 11 mothers, although one was recorded as having shown some sugar during pregnancy. It is plain that these four must have had a raised renal threshold, and it further follows that *an absence of glycosuria does not rule out lowered sugar tolerance in puerperal women.* The renal threshold, therefore, is certainly not always lowered in pregnancy—sometimes the reverse.

Incidentally, no woman in this series showed clinical evidence of hypophysial overactivity, such as the development of markedly acromegaloid features.

Results: Pre-diabetic Mothers

Mother 12.—Negress, aged 20. Only baby premature (said to be 7 months), 4 lb. (1.8 kg.).

Curve

94 (fasting), 140, 189, 165, **156**, 105.

Mother 13.—Negress, aged 33, normal size. Present child, 8 lb. (3.6 kg.), living. Glycosuria in pregnancy. Previous baby stillborn.

Curve

(1) 38 weeks antenatal: 90, 124, 153, 136, **153**, 90.
(2) 16 days post-natal: 85, 118, 121, 156, **149**, 75.
(3) 10 months later: 89, 109, 175, 167, **143**, 104.

Mother 14.—Coloured, aged 28, medium size. Present child, 9 lb. (4.1 kg.). Two previous children, 10 lb. (4.5 kg.) and 9½ lb. (4.3 kg.).

Curve

Sixth post-partum day: 94, 138, 149, 151, 133, 91.
Six months later: 95, 150, 130, 130, 130, **130**.
(Repeated-two-and-a-half hour figure alone: **152.**)

Mother 15.—Coloured, aged 29, not obese. All three children 8½–9 lb. (3.9–4.1 kg.). Lactated excessively.

Curve

Antenatal: 82, 114, 139, 143, 143, **142**.
Sixth day: 82, 150, 128, 175, **153**, 121.

Mother 16.—Coloured, aged 30, obese. Only infant 10½ lb. (4.8 kg.).

Curve

81, 126, 155, 184, **177**. No sugar.

Mother 17.—Negress, aged 38. Present baby, 10¼ lb. (4.6 kg.), stillborn. Seven previous children—the four latest over 11 lb. (5 kg.), last one 11½ lb. (5.2 kg.), stillborn.

Curve

93, 133, 188, 180, 156, **140**. No sugar.

Mother 18.—Coloured, aged 43, obese. Present infant 12½ lb. (5.7 kg.), stillborn. Thirteen children, weights unknown.

Curve

99, 128, 133, 156, **152**, 117.

Finally, there was one mother whose curve on the sixth day was "pre-diabetic" in character, but normal on repetition six months later.

Mother 19.—Negress, aged 34, obese. Present child, 10 lb. 2 oz. (4.6 kg.), stillborn. Previous infant, 9 lb. (4.1 kg.), stillborn.

Curve

103, 185, 170, 145, 145, **143**.
Six months later: 82, 153, 114, 105, 85.

Individually, these curves are not very convincing, but all are slightly abnormal in the same way, with high two- or two-and-a-half-hour figures. Then, again, it is highly suggestive that four should be those of women whose recent babies weighed over 10 lb. (4.5 kg.), while of the entire eight there was only one (Mother 12) who had neither large babies nor stillbirths in her history. Furthermore, three of the last babies of these eight mothers were stillborn, compared with six of the babies born to the 146 mothers whose curves were quite normal.

I suggest that this slight aberration in sugar tolerance may be the first indication of the dawning of diabetes, and that these people may later, perhaps only decades later, develop, first, diabetic curves and then overt diabetes. That such "pre-diabetic" curves may really be of significance is shown by John,[25] who was able to demonstrate the transition into true diabetes in several cases, and who makes the challenging statement, "Even the slightest elevation of blood sugar cannot be ignored, since it is likely in later years to progress into frank diabetes." Lambie[26] in 1926 and Skipper[14] in 1933 suggested that a diminished carbohydrate tolerance during pregnancy might progress to true diabetes in later years. Skipper showed further that "diabetes" during pregnancy does not really disappear after childbirth, even though the curve may become normal (Wiener[31]; Strouse and Daly[28]), for the diabetic state always reappears later. Consequently one would feel that Mother 4 is still, at least potentially, diabetic, despite the improvement in her sugar tolerance, and that this probably applies also to Mother 19, especially as her two babies were both large and stillborn.

The Meaning of "Diabetic"

It is evident from the foregoing and from the work of John[25] and the experience of many physicians that some people must be walking about for years blissfully ignorant of their lowered sugar tolerance. If this state is discovered, as in this investigation, I suggest that it should be called "chemical diabetes" in contradistinction to that overt or clinical diabetes which is manifested by characteristic symptoms. This chemical diabetes—and perhaps even the "pre-diabetes" in which only the two or two-and-a-half-hour tolerance figure is raised—may nevertheless make itself felt in the production of large babies, babies who are macerated or stillborn or who die soon after birth, maternal obesity, and, possibly, an increased liability to toxaemia of pregnancy and over-lactation. It follows, further, that many of our "new" female diabetic patients have really been chemically diabetic and pre-diabetic for many years, and that their previously unsuspected metabolic abnormality is correlated with an abnormal obstetrical history.

Importance of the Discovery of Chemical Diabetes

Lower carbohydrate tolerance could often be discovered by performance of tolerance curves on all women who had repeated large babies and/or stillbirths; but would this be of any value? I suggest it might be, in two ways: (1) a moderate carbohydrate (120–200 g.) and low-calorie diet might prevent the emergence of overt diabetes and even rectify the biochemical abnormality, especially if the patient is obese[25]; and (2) a living child might be obtained from a further pregnancy if the methods of White[21 30] were adopted to correct any hormone imbalance in later pregnancy (though her conclusions have not everywhere been confirmed). Certainly these chemical diabetics seem to have a foetal death rate (5 out of 11) as high as that of any full diabetic series.

The importance of the pre-diabetic curve is more doubtful, though a person possessing one, with a suggestive obstetrical history, should at least be carefully watched in the future, especially since the stillbirth rate in this series was three out of eight, as against six out of 146 in the normal group.

Maternal Obesity and Large Babies

It has already been seen that the present series does not show any remarkable association between maternal obesity and abnormal sugar tolerance. There seemed to be some relationship, however, between maternal obesity and large babies; thus there was only 1 obese mother out of 41 with babies under 7 lb. (3.2 kg.); 4 obese out of 43 with babies 7–8½ lb. (3.2–3.9 kg.); 5 obese out of 38 with babies 8½–10 lb. (3.9–4.5 kg.), and 9 obese out of 25 with babies over 10 lb. (4.5 kg.). These proportions are expressed graphically in Fig. 4, and are statistically significant ($\chi^2 = 18$, d.f. = 3, $P < 0.01$). This finding agrees with Odell and Mengert,[27] Gilbert,[11] and Sheldon,[12] although Klein[17] believes that there is no correlation between maternal and foetal size, and reviews the conflicting literature on the subject.

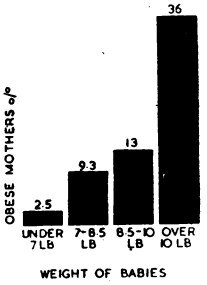

FIG. 4.—The frequency of obesity in mothers compared with the birth weights of their babies. There appears to be a positive correlation between maternal obesity and birth weight.

Summary

The existence of the maternal pre-diabetic state, during which there is a tendency to produce large babies or stillbirths, is shown to exist in the various races in the Cape. It is, moreover, found that this tendency is present for an indefinitely long period before manifest diabetes develops, even over 30 years.

Consideration of the children of diabetic *fathers* also indicates that their birth weights are above normal, while the stillbirth rate is not altered. It is realized that these results, though significant statistically, need corroboration from larger centres. They suggest that the onus of the production of large babies cannot be entirely borne by maternal hormones, but must in part be an inherited phenomenon, linked in some way to the diabetic genetic constitution of *either* parent.

An attempt has been made to discover early diabetics and those who are probably in the pre-diabetic phase by performing glucose-tolerance tests on mothers who were delivered in hospital of babies weighing over 10 lb. (4.5 kg.). In Part II we show that examination on the sixth post-partum day gives valid results. Mothers whose babies fell into lower weight groups were also tested for comparison.

Eleven unsuspected diabetics were disclosed out of 165 mothers. Of these, 10 had had babies over 10 lb. (4.5 kg.) and/or one or more stillbirths, while the eleventh had had toxaemia in her last two pregnancies. Their average age was high, only four were obese, and in four cases there was no glycosuria during the tolerance test.

A further eight mothers gave curves with high two-hour or two-and-a-half-hour levels, and are considered to be probably "pre-diabetic." It was very interesting to note that *all but one* had had large babies and/or stillbirths.

It is suggested that many "new" female diabetic patients have really been chemically diabetic or pre-diabetic for several years, and that this previously unsuspected minor metabolic abnormality is correlated with an abnormal obstetrical history. Consequently, examination by tolerance curve of all women who give birth to babies over 10 lb. (4.5 kg.) in weight or to unexplained stillbirths should reveal many potential diabetics. With this knowledge it might then be possible to prevent the development of overt diabetes or of further foetal loss.

Finally, our figures suggest a positive correlation between maternal obesity and infant birth weight.

Addendum to Part I

Bringing our figures up to date, we have now discovered 16 entirely unsuspected diabetic mothers by testing on the sixth post-partum day. Their last babies in nine cases weighed over 10 lb. (4.5 kg.) and eight were stillborn. Eleven other mothers gave a pre-diabetic curve, six of whose last babies were over 10 lb. (4.5 kg.) and five were stillborn.

In our obstetric department "pre-diabetes" has become a *clinical* diagnosis based on the previous obstetric history.

PART II

SUGAR TOLERANCE IN LATE PREGNANCY AND EARLY PUERPERIUM

It is common knowledge that the carbohydrate metabolism is altered during pregnancy. A lowered glucose tolerance was even mooted as a pregnancy test.[32 33] However, a search in the literature for authoritative information on glucose tolerance near term and in the puerperium was surprisingly unrevealing. Moss and Mulholland[7] cite seven references to tolerance curves during normal pregnancy. Four of these do not even mention such curves; one[34] states that tolerance is abnormal in 8% of pregnancies, but gives no further information; one[35] simply reports that no difference in the intravenous test was found between pregnant and non-pregnant women. Williams and Wills,[36] after 100 g. of glucose, found high two-hour to three-hour figures in a large proportion of pregnant and parturient women, the curve within ten days of delivery being invariably abnormal. Hurwitz and Jensen[37] used Folin's method on capillary blood, giving 1 g. of glucose per kg., and report in 25 healthy pregnant women fasting levels below 120 mg., and peaks below 200 mg., but very frequent two-hour values above 120 mg., especially in late pregnancy and the puerperium.

It was necessary for our investigations (see Part I) to know what sort of tolerance curves are usually obtained in the early puerperium by our methods. As the literature was insufficient for this purpose we have made our own observations, both in late pregnancy (36th week) and soon after childbirth (sixth day).

"Normal" Glucose Tolerance

Before proceeding it is necessary to define the range of normality of the tolerance curve. Unfortunately, authorities greatly differ in method of administration of glucose, in type of blood sample, in method of sugar estimation, and in interpretation. A consideration of the various points of view is beyond the scope of this article, and the reader is referred to discussions specifically concerned with this subject.[38–44] There emerges fairly general agreement:

(1) That the subject's recent diet must be unrestricted in regard to carbohydrates.

(2) That the "standard" one-dose (50 g.) glucose test is probably the best.

(3) That fasting and half-hourly readings up to two hours, and preferably two and a half or three hours, are necessary for full evaluation.

(4) That capillary blood gives the same fasting reading as venous, but is variably higher (up to 50 mg.) postprandially. It is impossible to say which gives "better" readings, but capillary blood is easier to obtain and does not miss the "lag" type of curve.

(5) That the Folin and the Hagedorn–Jensen types of sugar estimation give readings 10–20 mg. higher than the "true" blood sugar.

(6) That the fasting level is important, anything over 120 mg. (Hagedorn–Jensen) being highly suggestive of diabetes. On the other hand, a *lower level does not exclude reduced tolerance.*

(7) That the maximum reading is of little importance, although it should seldom exceed 200 mg. (capillary blood).

(8) That the two-hour level is of the greatest significance, figures above 140 mg. (capillary blood, Hagedorn–Jensen) definitely indicating lowered tolerance, while between 120 and 140 mg. is the doubtful range. Two-and-a-half to three-hour levels may be helpful where the two-hour reading is doubtful, and should certainly be not above 130 and 120 mg. respectively.

It is plain that there are all gradations of glucose tolerance, which does not even remain fixed from time to time in the same person, so that one cannot draw a sharp line to separate diabetes from normal. Our "normal" curve, therefore, lies below: fasting, 120 mg.; highest level, 200 mg.; two-hour level, ? 120 mg., certainly under 140 mg. (capillary blood, Hagedorn–Jensen).

Methods.—For this study we have taken at random 42 women attending the antenatal clinic at Groote Schuur Hospital and performed tolerance tests at the 36th week, and 140 mothers on their sixth post-partum day. Twenty-seven women were tested at both times. We have excluded known diabetics, all curves which were found to be diabetic or "pre-diabetic" (see Part I), and curves after caesarean section. All the women were either coloured (half-caste) or native (negresses). Their diet is on the whole high in carbohydrate, and childbirth only very briefly interfered with their intake.

We have used the 50-g. standard test, capillary blood, the Hagedorn–Jensen[45] estimation, and criteria of normality given above.

Results

Fasting Level.—On the whole the fasting levels were lower both at the 36th week and post partum than are found in general. The mean late pregnancy level was 83 mg., and the puerperal level 90 mg. (cf. Hurwitz and Jensen[37]). *No single fasting level was above 120 mg.* unless the curve was otherwise abnormal and definitely indicated lowered tolerance. On the other hand, four curves which were otherwise frankly diabetic had fasting levels below 120 mg.

Maximum Level.—Antenatally this averaged 128 mg. at one hour and 137 mg. post-natally. The significance of a high level, above 200 mg., was very similar to a high fasting sugar. *Not one curve which was otherwise normal showed a figure above 200 mg.* (excluding post-caesarean cases and two plainly technical errors). The only "lag" curve

discovered was after a caesarean section. Not all diabetic curves exceeded this level, nor did any of the "pre-diabetic" group (see below).

Two-hour Level.—Two out of 42 antenatal and 20 out of 140 post-natal curves exceeded 120 mg. at two hours; all were below 130 mg. at two and a half hours. Such curves are regarded as probably normal, although if accompanied by a suggestive obstetrical history (stillbirths and large babies) they should be repeated later. Figures *above 140 mg. at two hours* and 130 mg. at two and a half hours are very highly suspicious, and were found in eight cases (see Part I). *In all but one of these there was an obstetrical history suggestive of "pre-diabetes."*

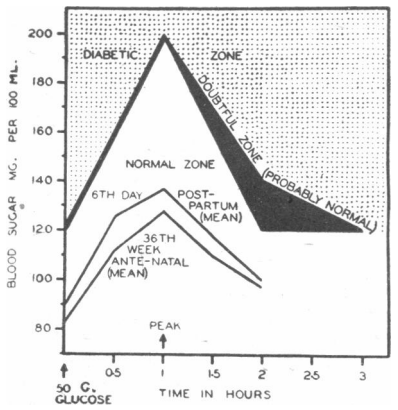

FIG. 5.—Glucose-tolerance curves. Upper thick curve shows the maximum normal. Lower curves are means of patients examined after sixth day post partum and at 36 weeks antenatal.

Curve as a Whole.—The mean post-natal curve runs at a higher level than that obtained from 36th-week examinations (Fig. 5). This tendency is confirmed by consideration of the 27 women tested at both times, 14 of whose post-natal curves were higher and only six lower, seven being virtually unchanged. Williams and Wills[36] also found a comparatively higher curve after delivery.

Conclusions Regarding Tolerance at 36th Week and Sixth Day Post Partum

It is plain that these figures, based on larger numbers of cases than elsewhere in the literature, do *not* confirm the usual contention that glucose tolerance is lowered in *normal* pregnancy and puerperium, at least not near to the time of delivery. At the very outside estimate, and applying the most stringent criteria (120 mg. fasting, 200 mg. peak, 120 mg. at two hours), only 30 curves out of 182 have a single figure outside normal, and we have reason to believe that several of these are truly "pre-diabetic."

This is very different from Williams and Wills's[36] finding of frequent markedly lowered post-partum tolerance, and Hurwitz and Jensen's[37] series in which half showed two-hour levels of over 120 mg. We conclude that *any lowering of carbohydrate tolerance in late pregnancy or the puerperium is probably abnormal.*

Melituria during the tolerance test was noted in about 20% of cases only. This is less than usually reported, but we regarded a result as positive only if a definite orange precipitate was formed with Benedict's reagent. It had no relation to the birth weight of the baby or to foetal loss. In some cases glucose was present with a low renal threshold, while in others the reducing substance was lactose. *Obesity* in this series had no relation to the tolerance curve.

Caesarean Section

Ten tests were made six days after caesarean section had been performed on the mothers. Five of these showed much reduced tolerance, but had all returned to normal when retested some months later. Operation itself is known to alter carbohydrate metabolism, and it is concluded that an abnormal tolerance curve is of no significance shortly after a caesarean section.

Conclusion and Summary

Using the 50-g. single-dose capillary blood and the Hagedorn–Jensen method for blood sugar, we have defined a normal glucose-tolerance curve at the 36th week and on the sixth post-partum day as below 120 mg. fasting, with a maximum level below 200 mg., a two-hour level below 140 mg., and a two-and-a-half-hour level below 130 mg.

Two-hour levels between 120 and 140 mg. are slightly suspicious but probably normal.

Two-hour and two-and-a-half-hour levels above these limits, with the rest of the curve normal, are often regarded as expected findings in pregnancy, but we believe they are a warning of "pre-diabetes" (cf. Lambie,[26] Skipper,[14] and John[25]).

Two-hour levels over 140 mg. with a high fasting level and a high maximum level, or diabetic symptoms, must be regarded as frankly diabetic.

Patients suspected of being diabetic may be expected to yield reliable information by testing on the sixth day after delivery.

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Home-grown prunes will soon be on the market. There was a glut of plums this year in many parts of England, and growers faced serious losses. To meet the situation the Agricultural Co-operative Association, with the support of the Ministry of Food, sponsored a scheme to convert the surplus plums to prunes. Some 170,000 lb. (77,000 kg.) of plums were dried, yielding 30,000 lb. (13,600 kg.) of prunes.