capacity, but his oxygen intake and carbon dioxide production, measured as a percentage of ventilation, changed from markedly abnormal to normal figures.

The results may be improved after a longer follow-up period than three to four months, but it is thought that as preliminary observations they are encouraging enough to warrant further application of the procedure to patients who for various reasons are unsuitable for the types of surgery already devised.

Our thanks are due to Miss M. Young, of the Sherrington School of Physiology, and to Dr. Evan Jones and Dr. M. B. Matthews, of the cardiac department, St. Thomas's Hospital. We would also like to state that Dr. James W. Brown has seen these patients and encouraged us to further trials.

REFERENCES

Baldwin, E. de F., Cournand, A., and Richards, D. W. (1948). *Medicine*, **27**, 243.
Bing, R. J., Vandam, L. D., and Gray, F. D. (1947). *Bull. Johns Hopk. Hosp.*, **80**, 107, 121, 323; and **81**, 192.
Blalock, A. (1947). *Lancet*, **2**, 478.
Brock, R. C. (1948). *British Medical Journal*, **1**, 1121.
Potts, W. J., and Gibson, S. (1948). *J. Amer. med. Ass.*, **137**, 343.
Sellors, T. H. (1948). *Lancet*, **1**, 988.

THE ASSOCIATION OF MATERNAL OBESITY, LARGE BABIES, AND DIABETES

BY

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The obstetric histories of the majority of diabetic women are characterized by an abnormally high foetal loss rate before the onset of clinical diabetes (Miller, Hurwitz, and Kuder, 1944; Miller, 1945; Henley, 1947; Gilbert and Dunlop, 1949). The foetal loss rate shows a progressive increase during this period, reaching a maximum in the immediately pre-diabetic phase, and is higher among women developing diabetes before the age of 45 than among those in whom the disease has its onset after this age.

Allen (1939), in reviewing the obstetric histories of diabetic women, noted that a high percentage of large babies were born many years before the onset of clinical diabetes. Further, Miller, Hurwitz, and Kuder (1944) report the incidence of babies with birth weights in excess of 11 lb. (5 kg.) to be as follows; non-diabetic women, 0.07%; pre-diabetic women, 3.9%; and diabetic women, 6.4%. Miller (1945, 1946) surveyed the birth weights of 22 babies born to 16 mothers who eventually developed diabetes after the age of 40. All deliveries were carried out in the hospital at which these women later sought treatment for their diabetes. Of the 22 babies three weighed 5 kg. (11 lb.) or more, six weighed 4.5 kg. (9.9 lb.) or more, and 15 weighed 4 kg. (8.8 lb.) or more. The number of babies in each weight group was 200, 27, and 7 times the expected incidence respectively, which led him to conclude that women developing diabetes after the child-bearing age are recruited almost wholly from the 5–7% of mothers giving birth to babies weighing more than 4 kg. (8.8 lb.). The recent publication of Kriss and Futcher (1948) confirms these observations. These workers report that 58% of their diabetic women had at some time prior to the onset of clinical diabetes given birth to at least one baby of 10 lb. (4.53 kg.) or more in weight. The average "latent period" between the birth of the first of such babies and the development of diabetes was 24.2 years.

Large babies were formerly attributed to maternal hyperglycaemia, resulting in the transfer of an excess of glucose to the foetus. Bill and Posey (1944), Bigby and Jones (1945), and Henley (1947), however, report the delivery of large babies in spite of well-controlled diabetes, and this has also been my experience.

White and Hunt (1943) and White (1946) conclude from observations of diabetic pregnancies that the unusually large babies are accounted for by an excess of chorionic gonadotropin.

Allen (1939) observed a relationship between excessive maternal gain in weight during pregnancy and the birth of large babies. Watts (1935) and others, who injected into pregnant rats what was at that time assumed to be anterior pituitary growth hormone, observed an unusual gain in maternal weight and in foetal size; such findings may in some measure explain Allen's observations. The report of Miller (1946) again suggests the importance of the growth hormone in the production of large babies: he drew attention to the similarity of the splanchnomegaly observed in the babies of diabetic mothers to that found in acromegalic patients.

Young has often stressed the relationship between the growth-promoting and the diabetogenic effects of anterior pituitary extracts. Thus in 1941 he reported that puppies treated for long periods with daily injections of diabetogenic pituitary extract failed to exhibit glycosuria as did adult dogs, but rapidly increased in weight. Diabetes did eventually develop, however, in some of the animals after many months' treatment. Further injections of the anterior pituitary extract produced only a diabetogenic effect, the growth-promoting influence having been lost. Lukens (1946) suggests that diabetes does not result from an excess of any one anterior pituitary hormone but from the combined oversecretion of both the growth and the adrenotropic hormones.

It is thus apparent that maternal obesity, an abnormally high foetal loss rate, and an unusually high incidence of large babies may occur many years before the onset of clinical diabetes, and that the investigation of women with such obstetric histories may show that a considerable proportion of them become diabetic in the course of time. Such a group of women form the basis of the present investigation.

Selection of Patients

Pre-diabetic foetal loss reaches a maximum during the two-year period immediately before the diagnosis of diabetes (Gilbert and Dunlop, 1949). It follows that some of the women who in 1941–3 had abnormal obstetric histories but showed no signs of diabetes might in 1948 have developed this disease.

The obstetric histories of 5,000 women confined in the Simpson Memorial Maternity Pavilion, Edinburgh, between August, 1941, and April, 1943, were therefore examined, and 150 of these were found to have unexplained histories of repeated abortions, miscarriages, intrauterine deaths, neonatal deaths, and babies weighing 10 lb. or more. Mimeographed forms asking for the results of all pregnancies since 1941–3 were sent to these women, but owing to the evanescent nature of Edinburgh's wartime population only 75 replies were received. Thirty-five of these gave histories of one or more normal pregnancies since 1941–3 and were therefore discarded from the investigation. The remaining 40 had either not been pregnant since 1941–3 or had had abnormal pregnancies. Of these it has been possible to examine 21 in hospital, the remaining 19 having declined admission owing to pressing domestic obligations.

The usual glucose-tolerance test was performed on all 21 patients, six of whom showed curves which were typically diabetic—i.e., they had fasting blood-sugar levels of more than 120 mg. per 100 ml. and levels which rose to more than 200 mg., remaining above 120 mg. at the end of two hours.

Table Comparing Patients with Diabetic Blood-sugar Curves and those with Normal Curves

	Diabetic G. T. T.	Non-diabetic G. T. T.
No. of patients	6	15
Age	39–46 years; aver. 44·2 years	28–45 years; aver. 39·3 years
Obese	6	8
No. of live births	25	40
No. of babies more than 10 lb.	11	5
No. of patients with babies of 10 lb. or more	5	3

G. T. T. = Glucose-tolerance test.

From the accompanying table it will be seen that the average age of those patients with diabetic blood-sugar curves was five years above that of those with normal curves. It seems probable, therefore, that some women of the latter group may yet develop a diabetic tendency.

The very high incidence of obesity is remarkable, 14 of the 21 patients being more than 14 lb. (6.35 kg.) in excess of the normal mean weight for their age and height, while all six patients with diabetic blood-sugar curves were 30 lb. (13.6 kg.) or more above their "correct" weight. All patients dated the onset of obesity from their first or second pregnancy, and with each successive pregnancy there had occurred a further gain in weight. Obesity was a less pronounced feature among the women with normal blood-sugar curves than among those who had become diabetic.

Women with unsatisfactory first pregnancies are usually admitted to the Simpson Memorial Maternity Pavilion for second and subsequent confinements. Consequently, accurate birth weights of the majority of viable infants in this group were available. The difference in the incidence of babies weighing 10 lb. or more among the diabetic and non-diabetic groups of women is striking—11 out of 25 compared with 5 out of 40. Thus there seems to be an association between the production of large babies and ensuing maternal diabetes.

Obese Non-diabetic Women

The high incidence of obesity among women with unsatisfactory obstetric histories suggests that maternal obesity may be related to a high foetal loss rate. The second step in the present investigation therefore consisted in a survey of the obstetric histories of 84 obese non-diabetic women attending the dietetic out-patient department of the Royal Infirmary, Edinburgh. All patients were interviewed personally. The group was unselected, and represented 84 consecutive attendances of obese non-diabetic women at the department.

As in the previous group of patients, the vast majority of these women associated the onset of obesity with an early pregnancy. The ages of these patients varied between 35 and 72 years, with an average of 46.8. Among the 341 pregnancies involved there was a foetal loss rate of 13.4%. This rate is similar to the pre-diabetic foetal loss rate of 12.5% observed by Gilbert and Dunlop in women developing diabetes after the age of 45, the majority of whom were over weight, and contrasts with the control foetal loss rate of 8%.

The majority of confinements among the obese non-diabetic women and among the women developing diabetes after the age of 45 were carried out either at home or in institutions from which birth-weight records were not available. Consequently it was impossible to ascertain the precise incidence of large babies. However, many patients spontaneously volunteered the information that they had had large babies, quoting birth weights of up to 14 lb.

Discussion

The present investigation reveals that six out of 21 women who had had obstetric histories of a high foetal loss rate and who had given birth to babies weighing 10 lb. or more eventually developed diabetes and that the diabetes was associated with obesity. Thus the incidence of diabetes in those women far exceeds the expected incidence of diabetes in a similar age group of women which is given by Joslin (1946) as 0.864%. The association between the production of large babies and the development of maternal diabetes which was noted by Miller (1945) and Kriss and Futcher (1948) is therefore confirmed by the present study.

The abnormally high foetal loss rate in the obese non-diabetic women of the present survey is similar to that occurring in the obstetric histories of women developing diabetes after the age of 45, most of whom were also obese (Gilbert and Dunlop, 1949). The unusually high incidence of the birth of large babies was a further similarity in the obstetric histories of these two groups of patients. The present observations therefore suggest that close correlation exists between increasing maternal obesity, the production of large babies, and ensuing maternal diabetes.

Both clinical and experimental studies suggest that the anterior pituitary lobe plays an important part in the production of obesity, large babies, and diabetes. The frequent onset of obesity and diabetes at the time of the menopause has been attributed to anterior pituitary overactivity secondary to the loss of the inhibiting effect of oestrogens on the pituitary. Further, the onset of obesity and a diminished carbohydrate tolerance following spontaneously occurring or artificially produced amenorrhoea, as was reported by Ogilvie (1935), supports this hypothesis. The reported results, however, of oestrogen therapy in menopausal diabetes are conflicting.

Young (1941, 1945), from his experimental observations, concludes that excess diabetogenic activity of the anterior pituitary lobe may be balanced by hyperfunction of the pancreatic islets induced through an overproduction of the anterior pituitary pancreatropic hormone. The effect of such a balance is the production of growth by a reduction in carbohydrate oxidation and an associated conservation of nitrogen (Young, 1941, 1945; Ogilvie, 1944). The resulting growth manifests itself, according to the age of the patient, either in the abnormal height of the pre-diabetic juvenile or in the obesity of the middle-aged subject. This growth is maintained only so long as the pancreatic islets respond to the excessive secretion of pancreatropic hormone, but ultimately islet exhaustion may supervene, manifesting itself in cessation of growth and clinical diabetes. Other observations are in accord with this hypothesis. Thus, Ogilvie (1933, 1935) has reported pancreatic islet hypertrophy in a high proportion of obese non-diabetic subjects and a latent period of many years between the onset of obesity and the occurrence of diabetes. Further, Joslin (1946) notes that a rapid loss of weight by obese subjects may precede the onset of diabetes.

Applied to the present study these findings suggest that the anterior pituitary growth factor may be in part responsible for the maternal obesity and diabetes, and that this factor passes across the placenta, causing the foetus to be both abnormally long and abnormally fat. The foetus

thus appears to combine the type of growth displayed by both the pre-diabetic juvenile and the obese middle-aged diabetic.

The clinical and experimental observations discussed suggest that an excessive secretion of the anterior pituitary growth factor during pregnancy may account for the production of progressive maternal obesity, large babies, and ultimate maternal diabetes.

Summary

Twenty-one women with obstetric histories of unexplained abortions, miscarriages, intrauterine deaths, stillbirths, and neonatal deaths, and the birth of babies weighing 10 lb. or more, were admitted to hospital for investigation. Six of these patients were found to be diabetic. All six were grossly obese and five had had babies weighing 10 lb. or more.

Evidence is brought forward to show a correlation between progressive maternal obesity, the birth of unusually large babies, and ensuing maternal diabetes. It is suggested that an excessive secretion of the growth factor during pregnancy may account for the associated phenomena.

I wish to thank Professor D. M. Dunlop and Dr. R. F. Ogilvie for their helpful advice and criticism, and Professor R. J. Kellar for so kindly putting the case records of the Simpson Memorial Maternity Pavilion at my disposal.

REFERENCES

Allen, E. (1939). *Amer. J. Obstet. Gynec.*, **38**, 982.
Bigby, M. A. M., and Jones, F. Avery (1945). *British Medical Journal*, **1**, 360.
Bill, A. H., and Posey, F. M. (1944). *Amer. J. Obstet. Gynec.*, **48**, 405.
Gilbert, J. A. L., and Dunlop, D. M. (1949). *British Medical Journal*, **1**, 48.
Henley, W. E. (1947). *N.Z. med. J.*, **46**, 386.
Joslin, E. P. (1946). *The Treatment of Diabetes Mellitus*, 8th ed. Kimpton, London.
Kriss, J. P., and Futcher, P. H. (1948). *J. clin. Endocrinol.*, **8**, 380.
Lukens, F. D. W. (1946). *Amer. J. med. Sci.*, **212**, 229.
Miller, H. C. (1945). *New Engl. J. Med.*, **233**, 376.
—— (1946). *J. Pediat.*, **29**, 455.
—— Hurwitz, D., and Kuder, K. (1944). *J. Amer. med. Ass.*, **124**, 271.
Ogilvie, R. F. (1933). *J. Path. Bact.*, **37**, 473.
—— (1935). *Quart. J. Med.*, n.s. **4**, 345.
—— (1944). *Edinb. med. J.*, **51**, 460.
Watts, R. M. (1935). *Amer. J. Obstet. Gynec.*, **30**, 174.
White, P. (1946). In Joslin's *Treatment of Diabetes Mellitus*, 8th ed. London.
—— and Hunt, H. (1943). *J. clin. Endocrinol.*, **3**, 500.
Young, F. G. (1941). *British Medical Journal*, **2**, 897.
—— (1945). *Biochem. J.*, **39**, 515.

GLOSSITIS IN ADDISONIAN PERNICIOUS ANAEMIA

EFFECT OF SYNTHETIC VITAMINS OF THE B COMPLEX

BY

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Glossitis has been recognized as a common feature of Addisonian pernicious anaemia since the work of Hunter (1909). Some evidence of involvement of the tongue is obtained in about 70% of cases (Brown, 1946). Adequate treatment of the anaemia with potent liver extract usually results in the disappearance of oral symptoms.

Glossitis is also a common feature of the sprue syndrome and of many deficiency states such as pellagra. Its occurrence has been attributed to deficiency of specific vitamins such as nicotinic acid and riboflavin. The fact that the sore tongue of the pernicious anaemia syndrome is indistinguishable from that occurring in well-recognized nutritional deficiencies suggests that in pernicious anaemia it may again be due to a vitamin deficiency, and that it may be corrected by appropriate treatment with one or more of the members of the vitamin B complex.

The present report describes the occurrence of glossitis and a syndrome suggestive of ariboflavinosis in patients with Addisonian pernicious anaemia and the effect of treatment with certain synthetic vitamins of the B complex.

Clinical Observations

Seven patients with pernicious anaemia are described in whom there was a well-marked disturbance suggestive of deficiency of one or more members of the vitamin B complex. The diagnosis of pernicious anaemia was made on the following grounds. In all cases the clinical picture was compatible with the diagnosis; all had a macrocytic anaemia with a megaloblastic bone-marrow reaction which showed a satisfactory response after treatment with highly purified liver extract; all had a histamine-fast achlorhydria; and in none was there evidence of steatorrhoea or dietary defect.

Of the seven patients, six had severe painful glossitis. Five of the six had been receiving parenteral liver therapy for periods ranging from four months to two years; they were receiving it regularly every two to four weeks during the period of this present study. As indicated in the case reports, the glossitis had either existed since the original illness or developed during its treatment with parenteral liver. The development of a sore tongue was not always controlled by liver therapy, and on occasion bore no relation to the immediate or subsequent haematological status of the patient. In the seventh case (treated for five years) glossitis was associated with angular stomatitis and vascularization of the cornea.

Case 1

A man aged 58 developed pernicious anaemia, for which liver therapy was started in February, 1946. His tongue was red, glazed, and smooth, but did not cause pain until June, 1946, when its appearance deteriorated and it became extremely sensitive and painful. Blood levels at this time and during the subsequent six months were maintained above 4,500,000 red cells per c.mm. by regular administration of anahaemin. From June 15, 200 mg. of nicotinic acid daily for seven days left the condition of the tongue, if anything, worse. On June 22 100 mg. of calcium pantothenate was given intramuscularly and then 100 mg. daily by mouth.

By the third day discomfort had disappeared; by the seventh day only slight redness at the tip remained, and by July 6 the organ was merely clean and atrophic. Calcium pantothenate was stopped on July 6, and from this date only routine liver therapy was given. Lingual discomfort returned within 14 days. By July 27 the organ was diffusely red and raw-looking, painful, and extremely sensitive, with numerous deep fissures. From July 27, 100 mg. of calcium pantothenate was given daily by mouth. By the fourth day undue discomfort could not be provoked even by hot foods or by deliberate friction against the teeth. By the seventh day objective evidence had almost entirely disappeared. By Aug. 17 the tongue looked more nearly normal than at any time since the patient had first been seen. Atrophy was less marked and central furring had developed. Fissuring was no longer present. Treatment with pantothenate was discontinued, and by March, 1947, there had been no recurrence of the glossitis.

Case 2

A married women aged 40 had received liver therapy for two years, when the tongue, previously pale and atrophic, became red and very uncomfortable. When seen with this complaint in February, 1946, blood values had been maintained for two years at normal levels (between 4,800,000 and 5,570,000 red cells per c.mm.). From Feb. 23, in addition to the continued regular administration of highly refined liver extract (anahaemin), 300 mg. of nicotinic acid was given daily by