in some patches the cells were still well preserved but had pyknotic nuclei; in some the cells were only just discernible; and in others the cells were lost, but the general architecture of the pituitary was still preserved (see Figs. 2, 3, and 4). It was thus obvious that the various patches of necrosis were not of the same age, though none was of more than a few days' duration. In the brain, sections from the pons showed various degrees of degeneration of ganglion cells. A few appeared normal. Most showed moderate or severe chromatolysis up to complete loss of nuclei. Shrinkage of ganglion cells was a feature, most being surrounded by a clear zone. There was no evidence that glial proliferation had begun. In the liver, glycogen was increased, as was to be expected. Otherwise the histological appearances were normal.

Comment

The notable feature of this case is the sudden development of a series of severe hypoglycaemic episodes in a diabetic patient who seems to have been under at least moderately satisfactory control for 19 years. The last of these episodes, which terminated in coma lasting four and a half days and death of the patient, began two hours after he had been treated successfully for an insulin reaction, and in spite of the fact that additional glucose, but no insulin, was given. In hospital, extremely large doses of glucose were required to raise the blood-sugar level, which, however, fell spontaneously to a severe hypoglycaemic level. Later, when small doses of insulin were given to combat ketosis, the blood sugar fell to unexpectedly low levels even while glucose was being administered by intravenous drip. This state of affairs suggests suddenly acquired extreme insulin sensitivity, and the explanation for this may lie in the pathological changes found in the pituitary.

Death in this case resulted from extended hypoglycaemia. Since the brain can utilize only glucose for its metabolism, if this is virtually absent from the blood for a considerable period irreversible changes may be expected in the brain cells. These changes have been studied by Baker and Lufkin (1937), Baker (1938), Sahs and Alexander (1939), and Lawrence, Meyer, and Nevin (1942). The duration of hypoglycaemia required for these changes is not known exactly, although Lawrence *et al.* state that hypoglycaemic coma of one to three hours is compatible with recovery. In the above case the patient had been in coma for 11 hours before admission, and remained in coma despite the rise of blood sugar. Cellular changes in the brain similar to those reported by these observers were, in fact, present.

Summary

Pituitary necrosis is occasionally encountered in routine necropsies. Its occurrence in diabetic subjects is noted.

The Houssay phenomenon is described, and cases are cited of this phenomenon occurring in man.

Irradiation of the hypophysis and hypophysectomy as a treatment of diabetes is mentioned.

Another case of pituitary insufficiency in a diabetic is reported.

Extended hypoglycaemia as the ultimate cause of death is discussed.

I wish to thank Dr. Ian Murray, of the Department of Metabolic Diseases, Victoria Infirmary, for his help and encouragement in the preparation of this article, and for his permission to publish this case; also the staff of the Department of Biochemistry, and Mr. Grey, of the Photographic Department, for their assistance.

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FRIEDREICH'S ATAXIA COMBINED WITH DIABETES MELLITUS IN SISTERS

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The combination of Friedreich's ataxia with diabetes mellitus in families has been mentioned mainly in Continental literature. Schlezinger and Goldstein (1940), in the only comprehensive survey in the English language, list 18 patients from the literature with two of their own. The comparative rarity of the association prompts us to record its occurrence in two sisters.

Case 1

A woman aged 28 was admitted to hospital on September 15, 1950. She had been a full-term normally delivered infant. During her childhood her family noticed that she tended to stumble, to walk on her toes, and to be unable to play or skip normally. The stumbling increased, until at the age of 14 she could just walk along a narrow passage by supporting herself with her hands on the walls, and at this time she could not sit upright in a chair. From the age of 22 she had been partly confined to bed, being able to get around only by holding on to objects in her room, and from 27 she had been wholly bedridden. In 1948 she had been investigated for joint pains and was found to have diabetes mellitus. She was put on a diet without insulin, to which she had since adhered. Menstruation had been scanty, only two to three days every three months, following menarche at 16.

Physical Examination.—The patient sat slumped in a chair and was unable to walk even with assistance. No abnormal signs were found in the heart, lungs, or abdomen. The blood pressure was 108/80. *Skeletal system:* Scoliosis and bilateral pes cavus were present. *Central nervous system:* The patient was fully co-operative. Well-marked head-nodding, particularly during questioning, slurred and slow speech, and coarse lateral and rotary nystagmus were noted. The pupils were equal and reacted briskly to light and on accommodation. The fundi were normal. Right eye 6/12, left 6/6. Colour vision was normal. Other cranial nerves were normal. The upper limbs showed gross hypotonia, ataxia, dysmetria, dysdiadochokinesia, intention tremor, and diminished power, particularly of grip. The biceps, triceps, and supinator jerks were present and equal, though diminished, and there was no wasting or sensory change apart from absent postural sensibility of the fingers. The legs showed hypotonia, incoordination, dysmetria, and

ataxia. Knee- and ankle-jerks were absent, plantar responses extensor. Postural and vibration sense were absent in lower limbs. *Endocrine system:* The pubic and axillary hair normal, no facial hirsuties. There was no abnormal pigmentation. Breast development was normal. The thyroid was of normal size. The reproductive organs were hypoplastic.

Investigations.—The urine contained sugar but no acetone or albumin. On a 140-g. carbohydrate diet and 38 units of soluble insulin morning and evening, blood sugars after a 40-g. breakfast were : 8 a.m., 163 mg. ; 10 a.m., 135 mg. ; 12 noon, 120 mg. per 100 ml. The fasting blood sugar (receiving insulin) was 140 mg. per 100 ml. A chest radiograph showed normal lung fields and heart shadow. A radiograph of the skull showed a normal sella. Electrocardiograph: Sinus rhythm, 100 a minute ; standard leads showed left axis deviation ; P–R interval 0.1 second, QRS 0.08 second, T2 flat, T3 inverted, ST3 0.5 mm. depression ; leads V4 and V6 showed low-voltage and notched T waves. The serum Wassermann reaction was negative ; serum sodium, 300 mg. per 100 ml. ; blood cholesterol, 85 mg. per 100 ml. The basal metabolic rate was within normal limits. Cerebrospinal fluid : Normal pressure, normal chemistry and cytology ; Wassermann reaction, negative. The 17-ketosteroids were normal, 13 mg. per 24 hours.

Case 2

A woman aged 26, a sister of Case 1, was admitted to the same hospital on February 6, 1951. Schooling had been normal until the age of 13. She had had scarlet fever at 7. After this she had begun to stumble like her sister, to be unable to skip, and to walk on her toes, so that her shoes became worn beneath them. At 19, after an influenzal illness, she was no longer able to walk without help. Her symptoms progressed without remission until the year before admission, from which time she had been confined to her bed, although able to walk with assistance. Two years previously she had been losing weight and her doctor had discovered sugar in her urine. She had been stabilized on insulin with diet. Her menstruation was normal, with menarche at 15.

Physical Examination.—Although confined to bed during the previous year, she was able to walk with aid or with a walking-machine. No abnormal signs were found in the heart, lungs, or abdomen. The blood pressure was 110/85. Lower limbs showed acrocyanosis. *Skeletal system:* Pes cavus on right was present. *Central nervous system:* She was less affected by ataxia than her sister and was brighter mentally. There were oscillating movements of the head and restless movements of the arms, and nystagmus with coarse component to the right. Pupils were equal and reacted briskly to light and on accommodation. Other cranial nerves were normal. The fundi were normal; right eye 6/18, left 6/6. Colour vision was normal. The upper limbs showed hypotonia, dysmetria, and dysdiadochokinesia. The right biceps-jerk was diminished. There were no wasting and no sensory changes. The lower limbs showed weakness without wasting, hypotonia, absent knee- and ankle-jerks, and bilateral extensor plantar responses. Weakness was more marked in the proximal segments ; the grip and ankle movements were fair, shoulder and hip movements weak. Vibration sense was absent at the ankles, but other forms of sensation were normal. *Endocrine system:* The pubic and axillary hair were normal ; no facial hirsuties. There was no abnormal pigmentation. Breast development was normal. The thyroid was of normal size. The reproductive organs, though hypoplastic, were more developed than her sister's.

Investigations.—The urine contained sugar but no acetone or albumin. On a 100-g. carbohydrate diet with 35 units of soluble insulin morning and evening, blood sugars after a 30-g. carbohydrate breakfast were : 8 a.m., 215 mg. ; 10 a.m., 150 mg. ; 12 noon, 140 mg. per 100 ml. Fasting blood sugar (receiving insulin) was 180 mg. per 100 ml. A radiograph of the chest showed normal lung fields and heart shadow. A radiograph of the spine showed no spina bifida. The serum Wassermann reaction was negative. Electrocardiograph: Sinus rhythm 100 a minute ; low voltage QRS complexes, P–R interval 0.12 second ; T waves—changes in all leads, particularly diphasic in T1 and T2, inverted aVL flat in V_6. A radiograph of the skull showed the sella, though small, to be within normal limits. The serum sodium was 315 mg. per 100 ml. ; blood cholesterol, 206 mg. per 100 ml. The basal metabolic rate was within normal limits. Cerebrospinal fluid : normal pressure, normal chemistry, and cytology ; Wassermann reaction negative. The 17-ketosteroids were normal, 10 mg. per 24 hours.

Family History

Among the patients' parents and their siblings there was no history of clumsiness of gait, foot deformity, twisted spine, or diabetes. III(4), III(6), and II(3) (see Fig. 1) were found to be free from neurological disorder, glycosuria, and

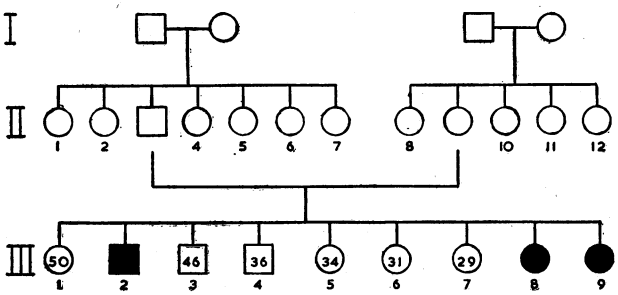

FIG. 1.—Family tree.

congenital deformities. The urines of III(1), III(5), and III(7) did not reduce Benedict's reagent. The eldest brother, III(2), is stated by the sisters to have had a nervous disease similar to their own and to have died from the effects of diabetes at the age of 31. Records of his death have not been available. There was no consanguinity between their parents. Information about the grandparents was scanty.

Recorded Cases of the Combination

Since Schlezinger and Goldstein's paper Segall (1948) has described diabetes in taste-blind identical twins, one of whom had a peculiar dragging walk ; both had pes cavus and gradually developing muscular incoordination. Although

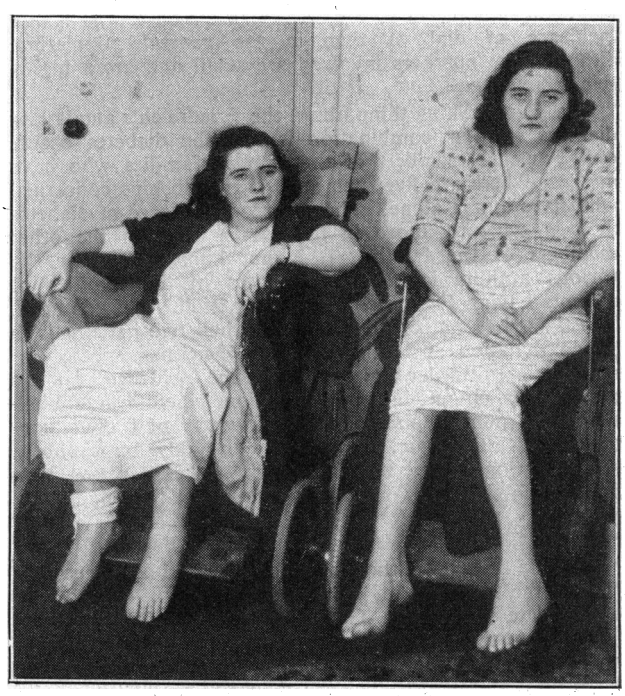

FIG. 2.—Photograph of the two sisters. Case 1 is on the right.

the diagnosis of Friedreich's ataxia was not made in these twins, it seems reasonable to suppose that this was in fact the diagnosis. Dassen, Soto Romay, and Fustinoni (1939), have described two cases, not included in Schlezinger and Goldstein's review. Further mention of the combination comes from Bell (1939), who records one patient and a sibling with Friedreich's ataxia, not previously recorded, and from Richards (1946), who described three patients with Friedreich's ataxia in one family, of whom two were diabetic, both males. The present pair brings the total to 29 patients, 20 being females, one pair of these being twins. They are members of the seventh family to be recorded.

Onset of Ataxia and Diabetes

The onset was usually in the first two decades of life, and the Friedreich's ataxia has always preceded the diabetes, which began acutely, requiring insulin for its control or leading to death. However, one of the patients described by Schloss (1932) had merely glycosuria after a high carbohydrate diet, while Mollaret's (1929) patient had only a single episode of severe diabetes mellitus, leading to coma, then subsiding, ultimately requiring no treatment.

Pathogenesis

Schlezinger and Goldstein discuss, apart from coincidence, theories of hereditary predisposition, chromosome linkage, diabetic myelopathy, and neurogenic diabetes.

Coincidence

That the association of Friedreich's ataxia with diabetes mellitus is more than a chance coincidence has been claimed by Curtius, Störring, and Schönberg (1935), and re-emphasized, though with little further evidence, by Schlezinger and Goldstein. A demonstration that the incidence of diabetes mellitus is greater in people with Friedreich's ataxia than in the general population would rule out coincidence. The former authors give the estimated incidence of Friedreich's ataxia in Switzerland as 1 in 90,000. If the incidence were the same in this country there would be about 400 to 500 cases. Taking the total number of diabetics as 150 to 200,000 (Lawrence, 1944)—an incidence of about 1 in 250—one might perhaps expect two of the cases of Friedreich's ataxia to have diabetes mellitus. There is no way of confirming these estimates, but Bell (1939) lists 846 cases of Friedreich's ataxia and hereditary spastic paraplegia (which may be due to a similar genetic fault), including five cases of the combination with diabetes. This is a somewhat higher incidence of diabetes than in the general population, although the numbers involved are small and are a highly selected group.

The most striking thing about the Friedreich's ataxia and diabetes mellitus combination is that the diabetes occurs only in those members of the affected families who have ataxia. There are five members of the sibships concerned who have ataxia alone. The recorded incidence of diabetes then is evidently more in the ataxics than in the other members of the family. It is not known how far the various authors looked for diabetes in the families of patients having Friedreich's ataxia by itself. Curtius *et al.* investigated 41 out of 51 relatives of their two patients with the combination, and found evidence of neither diabetes nor neurological disorder among them. The incidence of status dysraphicus, comprising such conditions as enuresis, funnel-shaped sternum, kyphoscoliosis, asymmetry of breasts, contracture of little finger, pes cavus, spina bifida, acrocyanosis, lumbarization of first sacral vertebra, and cleft palate, was, however, higher than in random samples of the population.

Chromosome Linkage and Genetic Factors

Juvenile diabetes is thought to be inherited as a recessive, though the frequency of manifestation is low in those with appropriate constitution (Gates, 1946). Bell and Carmichael (1939) state that approximately two-thirds of their cases of ataxia were inherited as recessives. If linkage occurs two types of sibships should result : (1) three normal siblings to one with both diseases, and (2) two normal siblings to one with ataxia and one with diabetes. The second type should be three times as common as the first. Most of the reported sibships containing diabetes and ataxia are of the first type, though some also contain one or more cases of ataxia alone, which could be explained on the basis of failure of manifestation of the diabetes. Sibships of the second type seem very uncommon. There are none in Bell and Carmichael's series, and it seems unlikely that diabetes has been missed in the family histories, as it is such a striking disease to the relatives. Moreover, in the pedigree of Curtius *et al.* the histories of 96 members were elicited, 41 out of 51 living members being examined and no diabetes being found.

The lack of sibships with individuals showing one condition or other, and not both, also tells against a hypothesis of looser linkage with cross-overs.

There are three other possibilities to be considered : (1) the ataxia gene may occasionally give rise to diabetes ; (2) there may be two separate genes, one giving rise to ataxia only, the other giving ataxia and diabetes ; and (3) the ataxia gene may express itself in different ways according to the genetic pattern of its environment.

The first possibility does not explain multiple cases of diabetes and ataxia in the same sibship. It would be supported if a high percentage of subclinical diabetes could be found in ataxic families without manifest diabetes. With regard to the second hypothesis, it is known that there are at least three different genetic types of ataxia—dominant, recessive, and sex-linked recessive (Bell and Carmichael). There is no definite proof that these three types are each due to a single gene. Ataxia combined with diabetes may well be a hereditary syndrome due to a gene different from that of recessive ataxia ; the combination of these two diseases may represent the fully developed syndrome, ataxia alone being a milder form with failure of manifestation of the diabetes. This would explain the occurrence of both diseases in one or more members of a sibship and ataxia alone in another. The third possibility is attractive because it would link diabetes with some of the other dysbiotrophies mentioned later and would also effectively explain the multiplicity of cases of diabetes and ataxia within the one sibship. Both diabetes and other dysbiotrophies could result from the effect of certain genetic environments on the ataxia gene. For instance, retinitis pigmentosa has been reported as occurring in the siblings affected by ataxia in two different families (Claus, Frenkel, and Dide, quoted by Alpers and Waggoner, 1929).

Neurogenic Diabetes

No neurogenic lesion causing permanent diabetes has been described. Claude Bernard (1855) produced transient hyperglycaemia by puncture of the fourth ventricle, stimulation of the posterior part of the hypothalamus having a similar transient effect. Stimulation of the ventro-medial nucleus also causes hyperglycaemia, while destruction of these nuclei protects the animals from diabetes normally produced by pancreatectomy (Le Gros Clark *et al.*, 1938). Clinically, such conditions as basal meningitis, cerebral haemorrhage, trauma, and neighbourhood tumours may all produce transient hyperglycaemia, but not permanent diabetes. Friedreich's ataxia does not produce irritative neurological phenomena, and it is difficult to see how a degenerative lesion of the above-mentioned hypothalamic nuclei could cause a diabetes presenting clinically as what Lawrence (1951) calls the " insulin-deficient type." Further evidence against the concept of neurogenic diabetes is afforded by the lack of correlation between the course of the diabetes, which develops acutely over a few weeks or months, and the slow course of the Friedreich's ataxia. In those patients who died in coma there is no report of any dramatic increase in signs of damage to the central nervous system. Moreover, other symptoms of hypothalamic disturbance, such as changes in sleep rhythm, polyphagia, hyperthermia, hyperhidrosis, diabetes insipidus, excessive emaciation, or obesity, have not been described in those cases which have diabetes. Of the 26 patients described in detail, two were physically

underdeveloped and had menstrual irregularity, and three (including our Case 1) showed an infantile uterus with amenorrhoea or oligomenorrhoea. These are the only symptoms which might conceivably be put down to hypothalamic damage. Records of histological examination of brain stem and hypothalamus are scanty. Rossi (1893), quoted by Schlezinger and Goldstein, described areas of degeneration subcortically, including the basal ganglia; and Wichtel (1943), cited by the same authors, reported degenerative change in the dorsal vagus and dentate nuclei, but normal basal ganglia and tuber cinereum. Köhne (1941) demonstrated normal supraoptic and paraventricular nuclei. The pituitary gland showed only an excess of eosinophil cells. There is thus little or no positive evidence in favour of the hypothesis of neurogenic diabetes.

Diabetic Myelopathy

As Friedreich's ataxia precedes the onset of diabetes mellitus, and is unlike any recognized neurological complication of it, theories of diabetic myelopathy need not receive serious consideration.

Dysbiotrophy

Endocrine disturbances in Friedreich's disease are almost always due to hypofunction of one or more glands of internal secretion—for example, myoedema, genital infantilism (Curtius *et al.*; Schlezinger and Goldstein). As diabetes can be a manifestation of islet-cell hypofunction, it can be regarded as analogous to these and other non-neurological dysbiotrophies that occur, such as spina bifida, supernumerary digits, etc. The occurrence of some of these conditions, particularly the endocrine disturbances, may be determined by the genetic *milieu* of the ataxia-bearing gene, thus providing cases analogous to those with diabetes mellitus and Friedreich's ataxia.

Summary

Cases of Friedreich's ataxia and diabetes occurring in siblings are described; the previous literature is reviewed and theories of causation are discussed. Of these, the hypothesis that the combination is either a hereditary syndrome or an effect determined by the genetic *milieu* of the ataxia-bearing gene seems most satisfactory.

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ADDENDUM.—Since this paper was submitted for publication Dr. H. A. Dewar has kindly drawn our attention to two further sisters. One, aged 16, has recently been under his care at the Royal Victoria Infirmary, Newcastle-upon-Tyne. She has mild ataxia, optic atrophy, and diabetes mellitus requiring insulin for its control. Her sister died in diabetic coma at the age of 19, and is said to have had ataxia and optic atrophy as well.

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TIME OF ERUPTION OF PERMANENT TEETH IN BRITISH CHILDREN IN 1947-8

BY

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The most recent study of the times of eruption of the permanent teeth in British children is the survey made by Ainsworth in 1925. The object of the present paper is to bring the subject up to date, both by the assembly of new data and by the use of modern methods of analysis. Graphical techniques have usually been employed for estimating the mean eruption times of human teeth—for summaries of the data see Schultz (1934), Dahlberg and Maunsbach (1948), and Gödény (1951). Dahlberg and Maunsbach, and Gödény, have based their own analyses upon the observation of Klein, Palmer, and Kramer (1937) that the frequencies of erupting teeth at successive ages follow the normal probability function. The precision of the statistical methods for analysing integral responses of this function has been greatly improved over the past twenty years by the development of probit analysis (see Finney, 1947), and it is now possible to specify the statistical error of the estimates.

This paper is based on the analysis of dental observtions made during the course of the Birmingham Anthropometric Survey on 1,427 boys and 1,365 girls attending elementary schools. The children, who ranged in age from 5 to 13 years, were unselected and were drawn from 87 infant, junior, and secondary modern schools representing all types of area in the City of Birmingham.

Survey

Dental Examination.—The children were examined by one observer throughout (E.D.-T.). Examination was made in a good light with a dental mirror and probe. The observations were dictated to a clerical assistant, who recorded the findings on a standard form. Unerupted and extracted teeth were recorded as not present. The number of teeth extracted during the period of eruption will be very small, and will not have affected the analysis materially. A tooth was classified as erupted as soon as the gum was pierced. Clinical observations on the teeth were also recorded, but these have not been analysed in this paper.

Social and Anthropometric Data.—The Birmingham Anthropometric Survey recorded the occupation of either the father or the family's chief wage-earner. This information was coded into the appropriate socio-economic classification of the Registrar-General by reference to the Classification of Occupations. Class I comprises the professional, Class II the intermediate, Class III the skilled, Class IV the semi-skilled, and Class V the unskilled occupations. The development of puberty was assessed and scored on a four-point scale, using a scheme based on the classification proposed by Greulich *et al.* (1942). The age in months was recorded from the school records to the month below—that is, the age reached. The mean eruption times which are presented have not been adjusted for this grouping. At the examination an index number was allocated to each child to identify both the child and its school.