ASSOCIATION OF DIABETES MELLITUS WITH CEREBRAL TUMOUR

BY

A. PATON, M.B., M.R.C.P.

Late Medical Registrar, St. Helier Hospital, Carshalton

AND

C. P. PETCH, M.D., M.R.C.P.

Consultant Physician, St. Helier Hospital, Carshalton

Ashby and Tweedy (1953) stated that "no neurogenic lesion causing permanent diabetes has been described," and they added that numerous cerebral lesions are known to cause transient hyperglycaemia, but not permanent diabetes. In view of this we are prompted to record the following case.

Case Report

A 51-year-old lorry driver was sent to the out-patients department on April 6, 1951, with symptoms of polydipsia and polyuria which he had had for three months; he had lost a good deal of weight in spite of an excellent appetite. There was no family history of diabetes.

Examination showed a well-built man, not obese, who was thought to be rather slow mentally, though co-operative. He had a thickly furred, dry tongue, and was moderately arterio-sclerotic, but all peripheral pulses were palpable. The blood pressure was normal. Fundi and media were clear and all reflexes were brisk and equal, with normal power and sensation in the limbs.

Chart showing results of oral glucose-tolerance test.

The urine was acid, specific gravity 1028, and orange to Benedict's reagent; there was no acetone or albumin. A glucose-tolerance test showed a diabetic curve (see Chart), and the patient was admitted a week later for stabilization. The above findings were confirmed, but in addition the ankle-jerks were now absent and the right knee-jerk was weak. There was some subjective difficulty in using the left leg, and both calves were tender.

He was placed on a 200-g. carbohydrate diet and was finally allowed out of hospital on April 30 on two injections of 48 and 24 units of soluble insulin daily. During his stay in hospital his diabetes was difficult to stabilize and the urine contained acetone on occasion. His weight remained steady and he felt better, though he was still rather slow in cerebration. He was seen in the clinic two weeks later, before going to a diabetics' convalescent home, when he seemed well, though complaining of some weakness in the right leg. On return from convalescence at the beginning of June, however, he was not at all well, appeared increasingly slow mentally, and had difficulty in getting about.

He was readmitted the next day, when he was found to have weakness of both quadriceps and foot extensors, with absent tendon reflexes. The plantar responses were flexor. His feet felt numb, but there was no objective sensory loss, except to light touch in the left palm, where the grip was poor. The fundi were normal. There were crepitations at the bases of the lungs, but no evidence of congestive failure. A diagnosis of peripheral neuritis was made, and he was treated with injections of vitamin B₁ and physiotherapy. A chest radiograph was normal. The Wasser-

mann reaction and Kahn test were negative. A lumbar puncture revealed normal fluid under a pressure of 220 mm., with a protein content of 20 mg. per 100 ml. His condition deteriorated rapidly and he became increasingly comatose. Eleven days after admission he was found to have regained his tendon reflexes in the legs and the left plantar response had become extensor. There was no papilloedema. A left hemiparesis developed, and he died in coma with hyperpyrexia 10 weeks after first attending hospital. His urine during the last period of admission still contained moderate amounts of sugar and acetone, but the blood sugar the day before death was normal.

At necropsy (Dr. T. Goodier) a large glioblastoma multiforme, containing mainly spongioblast-like cells, was found in the left temporal region, spreading down into the hypothalamus, but not involving the pituitary. The pancreas showed degenerative changes compatible with diabetes mellitus. There were no other gross findings.

Discussion

Since Claud Bernard (1849) produced glycosuria by puncture (piqûre) of the floor of the fourth ventricle in animals, repeated attempts to define a cerebral centre concerned with carbohydrate metabolism have yielded conflicting results. The centres for piqûre glycosuria are now thought to lie in the hypothalamic nuclei in the walls and floor of the third ventricle, but most authors agree that experimental damage to this region causes transient hyperglycaemia and glycosuria only, and that thereafter the blood sugar returns to normal or low normal figures (Long, 1940). Ranson *et al.* (1938) recorded the production of diabetes in only one of 50 monkeys and in none of 300 cats with hypothalamic lesions, and thought that the disturbance in carbohydrate metabolism in their one animal was related to obesity and overeating. No other worker has reported the production of permanent diabetes in the experimental animal.

Clinically, it is well known that cerebrovascular accidents, cerebral trauma, meningitis, and tumours may cause transient hyperglycaemia and glycosuria. Cushing (1930), however, stated that he had never seen even transient glycosuria after operations in the hypothalamic region. Joslin *et al.* (1952) also quite clearly subscribed to the view that there is no justification for assuming a cerebral role in the aetiology of diabetes mellitus, and that where the two are associated there is a coincident hereditary weakness of the pancreas. Nevertheless, van Bogaert (1928) mentioned two patients with tumours of the third ventricle, with hyperglycaemia and diabetic sugar-tolerance curves. The pancreas was normal in one case at necropsy. Byrom and Russell (1932) gave a detailed account of a woman with an insulin-resistant diabetes, who was found to have an ependymal cyst of the third ventricle. There was, however, a strong family history of diabetes, but they suggest that hypothalamic irritation may lead to hyperglycaemia through overactivity of the sympathetic nervous system, and eventually to diabetes. Penfield (1934) also mentioned a patient with insulin-resistant diabetes of five years' duration in whom a cyst of the mid-brain was found at necropsy.

In the present case the association of diabetes mellitus with the cerebral tumour seems inescapable. The short history, the absence of any hereditary predisposition, and the insulin resistance are points in favour of this. The retarded mental state was a striking feature, though there were no other hypothalamic symptoms. The mechanism of production of the diabetes, however, is difficult to explain.

There seems little doubt that the hypothalamus is concerned in the emergency regulation of the blood sugar through its control of sympathetic-parasympathetic pathways. If this control is upset hyperglycaemia might result from sympathetic overactivity; the hyperglycaemia would act as a stimulus to increased insulin production and might lead to eventual exhaustion of the β -cells of the pancreas. Permanent diabetes has been produced in animals by long-continued hyperglycaemia (Dohan and Lukens, 1947). Alternatively, parasympathetic overactivity might increase insulin production through vagal stimulation of the pan-

creas, which again might lead to islet atrophy and permanent diabetes. The evidence for vagal control of insulin secretion, however, is not very clear-cut (Long, 1940). With either hypothesis, the finding of changes in the pancreas at necropsy does not necessarily implicate that organ as being primarily responsible for the diabetes.

In conclusion, experimental and clinical evidence suggests that the production of diabetes mellitus by hypothalamic damage is exceptional. Nevertheless, the hypothalamus seems to play some part in the regulation of carbohydrate metabolism, and its role is worthy of further study.

Summary

A case is described in which diabetes mellitus of recent onset was associated at necropsy with a neoplasm in the region of the hypothalamus.

It is suggested that the cerebral lesion was responsible for the onset of diabetes.

Experimental and clinical evidence gives some support to the view that the hypothalamus is concerned in the regulation of carbohydrate metabolism.

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SYSTEMIC ANTIBIOTICS IN CERTAIN DERMATOSES

TRIAL CONDUCTED UNDER THE AUSPICES OF THE MEDICAL RESEARCH COUNCIL

Under the auspices of the Medical Research Council clinical trials were undertaken at St. John's Hospital for Diseases of the Skin* in order to evaluate the effect of the newer antibiotics when given systemically for certain chronic, recurrent, and resistant skin conditions. This trial was under the direction of Dr. J. O. Oliver (director of pathology) and was regarded as a "pilot" survey to indicate whether subsequent large-scale trials would be of value.

The trials were designed for use with out-patients, the antibiotics under scrutiny being aureomycin, chloramphenicol, and oxytetracycline ("terramycin"). For control purposes dummy capsules were prescribed to a second group of patients, and it was arranged that neither the doctor nor the patient knew which medication was being given. Dosage used for the antibiotic was 2 g. a day, taken in four divided doses, and the treatment was continued for three weeks unless the patient was forced to stop because of side-effects. A compound vitamin-B tablet was taken with each capsule. All cases which did not complete three weeks' treatment were regarded as failures. The observed results (see Table) were as follows.

1. *Herpes simplex recurrens* (31 cases, including 8 controls). No effect in preventing recurrence was observed as the result of the administration of aureomycin, chloramphenicol, or oxytetracycline. One case relapsed under active treatment.

2. *Plantar warts* (30 cases, including 9 controls). No indication of superiority of any of these antibiotics over the dummy capsules. In fact, in the control series six patients

Disease and Drug Used in Trial	Total	Cured	Improved	Unchanged	Failed to Complete Course	Observed Effect
<i>Herpes simplex recurrens</i>	31					
Chloramphenicol	12	0	0	12	4	} Nil
Aureomycin	6	0	0	4	2	
Oxytetracycline	5	0	0	3	2	
Controls	8	0	0	8	0	
<i>Plantar warts</i>	30					
Chloramphenicol	8	3	—	3	2	} Nil
Aureomycin	9	1	—	1	7	
Oxytetracycline	4	2	—	0	2	
Controls	9	6	—	3	0	
<i>Lichen planus</i>	19					
Chloramphenicol	7	0	1	4	2	} Nil
Aureomycin	5	0	1	2	2	
Oxytetracycline	3	0	1	2	0	
Controls	4	0	3	1	0	
<i>Pityriasis rosea</i>	25					
Chloramphenicol	8	0	0	8	—	} Nil
Aureomycin	8	0	0	3	—	
Oxytetracycline	3	0	0	3	—	
Controls	6	0	0	6	—	
<i>Dermatitis herpetiformis</i>	12					
Chloramphenicol	3	0	1	1	1	} Nil
Aureomycin	4	0	0	2	2	
Oxytetracycline	3	0	0	2	3	
Controls	2	0	0	2	0	
<i>Discoid eczema</i>	16					
Chloramphenicol	6	0	0	4	2	} Nil
Aureomycin	5	0	1	2	2	
Oxytetracycline	2	0	0	1	1	
Controls	3	0	1	2	0	
<i>Seborrhoeic infective eczema</i>						
Short duration	7					
Chloramphenicol	4	4	—	—	—	} Marked benefit
Aureomycin	2	2	—	—	—	
Oxytetracycline	1	1	—	—	—	
Controls	0	0	—	—	—	
Long-standing	7					
Chloramphenicol	3	0	—	3	—	} Possible benefit
Aureomycin	3	1	—	2	—	
Oxytetracycline	1	1	—	0	—	
Controls	0	0	—	0	—	

recovered out of the nine, substantiating the well-known observation that warts are unpredictable in their behaviour.

3. *Lichen planus* (19 cases, including 4 controls). No apparent effect was noticed.

4. *Pityriasis rosea* (25 cases, including 6 controls). There was no apparent reduction in the duration of the condition as a result of administration of any of the antibiotics.

5. *Dermatitis herpetiformis* (12 cases, including 2 controls). Although this series was small no indication was given that any of the antibiotics exerted a favourable effect.

6. *Discoid eczema* (16 cases, including 3 controls). No apparent effect was detected.

7. *Seborrhoeic infective eczema* (patients with red oozing scaps and faces with crusting, scaling, and fissuring of the ears). These were divided into two groups: (a) *Of short duration* (7 cases, with no controls). All seven patients made a rapid and uninterrupted recovery. (b) *Long-standing cases lasting for months or years* (7 cases, with no controls). Two apparently recovered but five were unaffected.

Summary

From the small number of patients treated it would appear that the use of aureomycin, chloramphenicol, and oxytetracycline, when given systemically, is not indicated for herpes simplex recurrens, plantar warts, lichen planus, pityriasis rosea, dermatitis herpetiformis, or discoid eczema. It would seem, however, that in infective seborrhoeic eczemas of recent origin, in which one must regard an infective process as being superimposed on a readily infectable soil, rapid results are often obtained by the use of these antibiotics. It also became apparent that the use of large doses of these antibiotics on ambulant patients may cause such unpleasant side-effects (nausea, vomiting, and gastro-intestinal upsets)—particularly so when aureomycin is being used—as to make such treatment impracticable.

Our thanks are due to Miss H. M. Tedham, pharmacist, for her assistance.

*The medical registrars responsible for this trial were Drs. R. H. Seville, C. D. Calnan, R. H. Meara, and J. H. S. Pettit. Dr. P. D. Samman undertook the lichen planus series.