Case X

Persistent microbes: *Staph. aureus*, *Str. pyogenes*, diphtheroid Type I.

20/1/41.—At 7.45 p.m. patient, a man aged 61, was knocked down by a bus. Admitted to W.M.O.H. at 8.5 p.m. Found to have compound fracture of upper third left tibia and fibula, with extensive violence to the skin, and a large wound in the popliteal space. No loss of skin on posterior aspect. Medial dislocation of left ankle. General condition satisfactory. 9.50 p.m., operation: Skin cleansed with soap and water; antiseptic applied to margins of wound; the extensive wound of the back of the leg was excised and the skin sutured; the fracture and dislocation of the ankle were reduced by manipulation; dependent drainage was effected by means of rubber tubes through the stab wound. Plaster was applied.

26/1/41.—Patient has had no pain in the leg. Rise in temperature and respiration rate and some sputum. Has been on sulphapyridine for the past five days. General and local condition now satisfactory.

5/2/41.—Plaster changed because of profuse discharge. On removal it was found that the posterior wound was satisfactory, but that a large area of damaged skin on the upper anterior surface of the leg had separated and was lying as a free slough. This was removed. Wound dressed and fresh plaster applied.

21/2/41.—Patient has been running slight evening rise of temperature, but has made no complaint with regard to the leg. Considerable discharge from plaster. Plaster removed. Posterior wound well healed, anterior wound shows large clear area of granulations, about 6 in. long by 4 in. wide. No surrounding infection. Following change of plaster patient had no rise of temperature. General and local condition satisfactory.

Discussion

The cases investigated were selected from a much larger series as being suitable for complete bacteriological examination from the earliest stages to the final healing. One of us is in process of analysing the clinical aspects of the larger series as a whole. Neither the general composition of the wound flora under closed plasters nor the changes of its composition in the early or later stages have given any clear explanation of the virtue of the closed-plaster method of treatment. We have found no striking difference in flora between our wounds and the open wounds described (Miles and others, 1940) during the present war. We have not seen, as we thought we might see, a disappearance or diminution of pathogenic bacteria under the influence of saprophytic anaerobes or of relatively harmless Gram-negative aerobic rods such as *Proteus* or *Ps. pyocyanea*.

Although it is impossible to assert that *Str. pyogenes* (Group A) is completely innocuous in properly immobilized and protected wounds, it is clear enough that this microbe may be present from first to last in wounds which, under these conditions, heal without obvious complications or gross delay; and the same is true of *Staph. aureus*. But these phenomena, it seems, may also be seen sometimes in open wounds.

The method of treatment, we feel, owes its efficacy rather to its physical and physiological effects than to any specific influence on the bacterial flora (Trueta and Barnes, 1940).

The window-sampling method has proved satisfactory when true access to the tissues is provided, and has enabled us to observe changes in the flora at all periods of treatment and to form provisional views about the reasons for the appearance and disappearance of species, and about the protection afforded by the plaster against gross infection.

Summary

A satisfactory method has been devised for securing bacteriological samples from wounds encased in plaster without interfering with the treatment.

The flora of wounds treated in closed plaster does not appear to differ from that of open wounds, and neither its character nor its fluctuations explain the efficacy of the closed-plaster method. Infection of such wounds during the period of hospital treatment occurs fairly often during changes of plaster, but no cross-infection has been detected at any other time.

It is suggested that the multiplication of bacteria is delayed for some days in wounds which are excised and cleansed within a few hours of the accident. Some organisms appear to be permanently removed by this procedure.

No evidence has been found that *Ps. pyocyanea* or any other organism inhibits the growth of haemolytic streptococci or of *Staph. aureus* in wounds.

The Medical Research Council has provided a part-time grant for one of us (J. O.-E.) and a whole-time salary for a laboratory assistant (W. Fincham), as well as money for expenses. Prof. Gardner owes his leisure for research partly to the University of Oxford and partly to the Nuffield Trust. Prof. H. J. Seddon and Prof. H. W. Florey played a large part in launching the research, and Mr. Elliot Smith collaborated on the surgical side during the early stages. Dr. F. Griffith, whose death we lament, kindly typed our streptococci, and Prof. A. A. Miles struggled nobly and successfully with our anaerobes.

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DIABETIC COMA IN A SERIES
OF YOUNG DIABETICS*

BY

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This clinical study of diabetic coma is based on a series of 24 young diabetics who have attended Addenbrooke's Hospital during the last twelve years. Some of these cases have already been referred to (Cole, 1934). In 23 the disease came on before the age of 15, and in one patient, aged 18, coma was the first symptom. After standardization as in-patients they have attended as out-patients at intervals of from one to three months until the time (1939) when this study was completed (or in fatal cases until death). With the exception of Case 24 they are unselected and comprise all the diabetics attending my department between 1927 and 1939 who were under 15 at their first attendance. Four live in Cambridge and the remainder in towns and small villages within a radius of fifty miles, often at considerable distances from their doctors, and when complications such as infections or coma develop there is often some delay before they can be treated or be admitted to hospital. A series of young diabetics has been chosen for this study because in youth the results are less likely to be complicated by chronic intercurrent disease.

Incidence of Coma

Table I shows that in 24 diabetics coma occurred 13 times: 7 patients had one attack and 3 had two. In 6 coma was the first recognized symptom of diabetes, and in 7 it occurred during the course of treatment. The whole series covers a period of 165 diabetic years, giving an average of approximately one attack every thirteen years for all cases, including patients who had had no treatment before coma. In cases under treatment with insulin the average was one attack every twenty-three years. These figures are quoted to show the incidence in a small group of patients living under somewhat similar conditions and treated on similar lines.

Table II indicates the possible causes of coma. In 6 out of 13 instances the attack occurred in patients in whom diabetes had not been previously diagnosed, and in 4 of these its onset coincided with an infection. In the remain-

*A communication given to the Ulster Medical Society at Belfast in November, 1940.

TABLE I.—Incidence of Coma in 24 Young Diabetics

Case No.	Sex	Year of Onset	Age at Onset	Age in 1939	Insulin Dose 1 in 1939	Carbo-hydrate in 1939	No. of Times in Coma
1	F.	1925	7	21	90	gm.	0
2	M.	1925	12	26	60	200	0
3	M.	1926	7	20	50	250	0
4	F.	1931	14	22	50	120	2
5	F.	1929	12	23	50	125	1
6	M.	1933	10	16	70	150	1
7	M.	1929	6	16	32	250	2
8	F.	1929	7	17	50	150	0
9	F.	1926	11	24	40	120	0
10	M.	1927	9	16 D ²	16 ³	200	0
11	F.	1929	3	13	46	90 ³	0
12	F.	1926	13	26	55	200	0
13	M.	1931	13	21	75	140	0
14	M.	1932	12	19	110	130	1
15	M.	1933	9	15	75	230	0
16	F.	1935	12	16	65	200	0
17	F.	1931	4	5 D	40 ³	230	1
18	M.	1931	13	13 D	—	110 ³	2
19	M.	1932	13	16 D	48 ³	—	1
20	F.	1938	13	14	90	120 ³	0
21	F.	1938	14	15	56	200	1
22	F.	1938	12	13	30	200	0
23	M.	1934	14	19	36	180	0
24	F.	1939	18	18 D	—	160	0

D = died.

1 Total units per day. Soluble or P.-Z.-I. Usually in two injections.

2 Also congenital heart disease.

3 Before death. (5 died. Cause: Coma 3, congenital heart I, unknown I.)

TABLE II.—Details of Coma

Case No.	Time after Onset of Diabetes	Insulin Dose before Coma	Cause of Coma	Blood Sugar at Onset*	Units of Insulin in Coma	Result
3	(1) 4 yrs.	25	Vomiting; insulin stopped	—	70 in 6 hrs.	Recovered
4	(2) 4½ ..	40	Maxillary antritis	—	60 in 6 hrs.	"
5	6 ..	70	Acute enteritis	—	200 in 12 hrs.	"
5	3 ..	?	Bronchitis; insulin stopped	0.38	160 in 6 hrs.	"
6	(1) At onset	None	Scalded foot	0.41	85 in 12 hrs.	"
6	(2) 5 yrs.	50	"Cold in head"; insulin stopped	1.13	800 in 24 hrs.	"
13	6 ..	35	No cause	—	460 in 12 hrs.	"
16	At onset	None	Very septic mouth and throat	0.73	210 in 24 hrs.	"
17	(1) ..	36	Feverish cold	0.5	50 in 6 hrs.	"
17	(2) 1 yr.	36	Bronchitis; insulin stopped	1.37	Died 1 hr. after admission	Died
18	At onset	None	Mumps 5 weeks before? cause	1.4	190 in 12 hrs.	"
20	" ..	"	No cause	0.7	270 in 24 hrs.	Recovered
24	" ..	"	Bronchopneumonia; septicaemia	0.8	1,370 in 28 hrs.	Died

* Hagedorn-Jensen.

ing 7 instances, when it developed during insulin treatment, an infection was also present in 5. In 4 of the latter the normal dose of insulin had been discontinued on account of either vomiting or failure to take food.

These cases, few as they are, indicate the great importance of infection in precipitating diabetic coma. Occasionally it may develop suddenly in a hitherto unrecognized diabetic (Cases 18 and 20), and rarely in a patient on insulin, without any accompanying signs of infection (Case 13), but in the greater number an acute or chronic infection is a prelude. The most certain way of inducing coma when an infection develops is to stop or reduce the regular dose of insulin.

Usually coma does not occur without some warning history or symptoms to suggest diabetes. Joslin (1935) records 12 cases in a series of 55 in which the diagnosis had not been made before the onset of coma. In children and young adults symptoms may not be present for more than a few days before and may be slight enough for an intelligent parent to ignore. In those who had reported to their doctors, failure to examine the urine in the face of slight but suggestive symptoms was the cause of disaster. The fact that some of these patients were children made the diagnosis more difficult when the essential urine tests were ignored.

Diagnosis of Coma

Some factors which suggest a diagnosis of coma are: previous attacks of coma, untreated or badly controlled diabetes, recent chronic or acute infection, and reduction or stoppage of the regular dose of insulin. The more important warning signs and symptoms are: vomiting, abdominal pain, signs of dehydration, alteration of breathing, sugar in the urine, a positive Gerhardt test, and a raised blood sugar. The incidence of these symptoms in the 13 cases of coma in this series is shown in Table III.

TABLE III.—Signs and Symptoms in 13 Cases of Coma

Inability to take regular diet at onset	10
Vomiting at onset	7
Abdominal pain at onset	5
Dehydration	13
Altered breathing (sighing 7; hyperpnoea 6)	13
Sugar in urine (heavy reduction)	13
Rothera's test (strong; 1 weak for 6 hours)	13
Gerhardt's test (absent for first 6 hours in 1)	13
Blood sugar at onset	0.38 to 1.4%

This table shows the importance of vomiting and abdominal pain as early symptoms of coma. If these were more widely recognized as such, insulin would be less often stopped or reduced at the onset. Inability to eat the usual food may be a symptom of coma, and is not an indication to reduce insulin.

The urinary findings were almost constant. Rothera's and Gerhardt's tests were strongly positive in all but Case 6, which is unusual enough to quote.

Case 6.—The patient developed diabetes in 1933 at the age of 10, when he was admitted in early coma after scalding his foot. Diabetes had not been previously diagnosed. He recovered, but for the next five years he was always difficult to control, and mild infections were very apt to upset him. He was tried on various diets and did best on: C. 180, F. 56, and P. 105, with 70 units of insulin daily. He was a sensible boy, with anxious but not very intelligent parents.

His second attack of coma occurred in 1938. Five days before admission he developed a cold in his head. The day before admission nausea and later vomiting came on, and because of this no insulin was given on the morning of admission. He was admitted at midday almost unconscious, with all the classical clinical signs of coma (see Table III). His blood sugar was 1.13%.

The urinary and blood-sugar findings were as follows:

	Rothera	Gerhardt	Blood Sugar
Midday	Faint positive	Negative	1.13%
3 p.m.	Positive	"	"
6 p.m.	"	Faint positive	"
7 p.m.	"	Positive	0.98%

At 4 p.m., two hours after 100 units of insulin, the CO₂-combining power was 15 volumes %, the blood urea 39 mg. per 100 c.cm., and the blood chlorides 500 mg. per 100 c.cm. Throughout the whole coma there was no marked diminution of urine.

After 800 units in twenty-four hours (700 in the first ten hours) and a continuous intravenous-drip saline, 3,000 c.cm. in twelve hours (the last 1,500 c.cm. contained only 5% glucose), the blood sugar was normal, Gerhardt's test was negative, and the patient had recovered.

This patient, although a very severe case of diabetic coma, showed only a faintly positive Rothera and a negative Gerhardt test on admission, and the latter did not become strongly positive until he had been in coma for at least six hours.

Joslin (1935) states that in coma the urine almost invariably contains a large quantity of diacetic acid, as shown by a positive Gerhardt test, and that only in cases with an associated renal block does one see a negative test for acetone bodies. Richardson (1932) describes a case with a CO₂ of 7 volumes % which had no diacetic acid or acetone in the urine. Payne and Poulton (1925), Oliver (1926),

and Graham *et al.* (1929) also describe cases. In this patient there did not appear to be renal block, and the explanation of the slow appearance of diacetic acid in the urine is not clear. In diagnosis it is important to remember that although a positive Gerhardt test is present in nearly all cases of coma there are occasional exceptions to this.

Blood-sugar readings of over 1% occurred in three patients: one (Case 6) recovered, the other two (Cases 17 and 18) had both been unconscious for many hours before admission and died. The blood-sugar readings were 1.13, 1.37, and 1.4% respectively. In Case 24 (broncho-pneumonia and septicaemia in a hitherto undiagnosed diabetic) the blood sugar was 0.8% on admission. 1,370 units of insulin in twenty-eight hours reduced it to normal, but death occurred a day later. Joslin states that in a series of 293 the blood sugar was over 1% in 11, and of these 4 died. Curtis and Dixon (1928) describe a patient with a blood sugar of 1.68% who recovered, and Haines and Davis (1932) 3 others of over 1%, with recovery.

Treatment of Coma

Diabetic coma is one of the most acute emergencies in medicine, and an hour lost may mean death. The indications are: insulin and glucose to make possible the complete oxidation of fats, fluid for dehydration, sodium chloride for salt deficiency, and warmth and ephedrine for circulatory failure and shock. Symptomatic treatment, which includes gastric lavage for severe vomiting and enemas for constipation, is also important.

Insulin cannot work without glucose, but in the early stages the blood sugar is usually above 0.4% and there is no likelihood of glucose deficiency. When the blood sugar is known to be high it would seem unnecessary to give additional glucose. In the later stages of treatment, when the blood sugar is falling, and particularly when it cannot be watched by frequent readings, it is important to give extra glucose. This also ensures that there is no overshoot into hypoglycaemia. In practice the decision whether to give glucose or not in the early stages depends on the experience of the doctor and the biochemical facilities available. If no blood-sugar reading can be obtained, or if the doctor is inexperienced, glucose should be given from the start.

The dose of insulin is difficult to judge, as there is great variation in the requirements of different patients. Dosage depends on the depth and duration of the coma, the severity of any infection present, the previous dose of insulin and whether this had been discontinued, and what is known of the patient's response to insulin in the past. A patient who goes into coma while balanced on a certain dose of insulin (usually because of an infection) tends not to need such a large dose. Insulin should be given as soon as possible in a dose of from 20 to 100 units, but usually not less than 50, repeated every one or two hours according to the clinical and biochemical progress. In these patients the average dose needed in the 10 who recovered was 236 units in from twelve to twenty-four hours. This average was raised by 1 patient who needed 800 units. Of the 3 fatal cases, 1 died at once, 1 had insufficient insulin, and 1 had 1,370 units in twenty-eight hours.

The early administration of fluid and sodium chloride in the form of normal saline is as important as insulin. This may be given by the mouth to patients who are still able to swallow, and also rectally, subcutaneously, or by intravenous drip. The last method is the one of choice in all patients with severe dehydration. 5% glucose should be added when it is considered necessary. In this way 6 pints or more may be given in twelve hours. Root and Riseman (1938) emphasize the importance of very large amounts of fluid intravenously in severe cases, particu-

larly after a history of prolonged acidosis, unconsciousness for more than six hours, repeated vomiting, excessive dehydration, and suppression or diminution of urine, and quote cases in which 8,000 c.cm. and 6,800 c.cm. were given intravenously in eight and thirty hours respectively, in addition to large amounts of subcutaneous saline. In our series continuous intravenous drip was given to severe cases in which the patients were unable to swallow fluids. When the initial blood sugar was very high glucose was not added until it had fallen. In milder cases, when fluid was given orally, rectally, or subcutaneously only, glucose was added from the start.

Prevention of Coma

In diabetes, even under the best conditions, some attacks of coma are inevitable. The series quoted here, although it cannot be regarded as a random sample of the diabetic population, does indicate how far in one area the management and treatment in the home fall short of the best that could now be obtained. There are two causes for this: (1) failure to diagnose diabetes before the onset of coma (6 cases, 2 fatal); (2) failure to treat diabetes properly during an infection, or when for any reason the usual diet cannot be taken (6 cases, 1 fatal).

Thus in this series of known diabetics under treatment coma occurred only once without an obvious cause. In the remainder proper treatment of infections or failure to take food, by rest, warmth, fluids, glucose, and continuation or increase of the regular dose of insulin, would almost certainly have prevented coma.

The remedy lies, first, in more thorough teaching of the medical student at hospital on the routine management of diabetes. In many teaching hospitals diabetes tends to be treated in separate clinics, and if, as is often the case, a student clerks for a physician who is not interested in the subject, he may fail to receive any practical instruction. Secondly, there must be more thorough teaching of the patients or, in young children, of their relatives. Failure here is often due to insufficient trained staff at the diabetic clinic. Thirdly, co-operation between the patient, the family doctor, and the specialist at the clinic must be closer. It is unfortunate that many diabetics who attend clinics regularly tend to lose touch with their home doctors. This is unsatisfactory, because when an emergency arises at home their doctors are not in possession of the necessary facts.

Diabetes is still, twenty years after the discovery of insulin, one of those conditions in which there is a great lag between knowledge and its application.

Summary

The incidence, causes, symptoms, and treatment of diabetic coma in a series of 24 young diabetics are analysed.

13 attacks occurred in these patients. In 6 of these diabetes had not previously been diagnosed. In 7 which came on during treatment insulin had been discontinued in 4 on account of vomiting or failure to take food. An acute infection preceded the onset of coma in 9.

Most attacks could have been prevented either by earlier diagnosis of diabetes or by proper management of infection during its course.

I should like to thank Dr. J. F. Gaskell, under whom 3 of the cases were admitted, and Dr. R. J. Twort for his help with several severe cases of coma.

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