Commentary

Several points of interest arise from consideration of this case:

1. *Source of Haemorrhage.*—The source of bleeding seems to have been a capillary ooze from the mucoperiosteum of the alveolus. Although external haemorrhage was controlled by stitches, blood must still have been escaping into the submucosa of the floor of the mouth. Extraction had been simple and trauma slight.

2. *Control of Haemorrhage in Haemophilia.*—It is doubtful if in the present state of knowledge it is possible to take adequate pre-operative measures to control haemorrhage in haemophilia. The time-honoured premedications with calcium and other agents are recognized to be of little value, the only promising one of these, according to Mead (1940), being intensive feeding with citrus fruit. Tainter, Thronsdon, and Richardson (1939) after an investigation of various agents concluded that "the results of this study leave no doubt that the agents commonly advocated for oral administration as haemostatics in dentistry are not effective when so used. The dental practitioner is advised to direct his efforts at controlling haemorrhage to local application of demonstrably effective agents rather than to try to speed up the coagulation processes by systemic medication." Perhaps the safest method of dealing with the problem is by slow exfoliation of the tooth, using a rubber band as recommended by Birch and Snider (1939).

3. *Path of Extravasation of Blood.*—A further point that arises is in connexion with the path of the blood down into the neck. It is quite clear that in this case blood extravasated from the floor of the mouth downwards through the base of the tongue in the plane above and behind the mylohyoid muscles and the hyoid, thus reaching the submucous tissues

of the aryepiglottic region and thence the submucosa of the larynx. It provides an admirable illustration of the path of spread of infection in Ludwig's angina.

A most important anatomical feature in the neck influencing the spread of inflammatory fluids is the musculo-membranous layer represented by the mylohyoid muscles, the hyoid bone, and the thyrohyoid membrane (Fig. 2). Infections of the floor of the mouth and submaxillary region can be considered clinically in two groups according to their anatomical relation to this layer, this being the most important factor in prognosis and treatment, especially with reference to involvement of the larynx. Cellulitis primarily

FIG. 2.—Diagram showing the relation between the musculo-membranous layer and the path taken by extravasated blood.

situated below the mylohyoid, as from a lymphadenitis of the submaxillary glands, if it extends downwards in the neck, will be superficial to the thyrohyoid membrane, and therefore does not endanger the larynx. Infections which are primarily in the submucosa of the floor of the mouth above the mylohyoid may easily track downwards, and will then be deep to the thyrohyoid membrane, thus involving the submucous layer of the larynx, this path of spread being well illustrated by the extravasation of blood in the case described above (Fig. 2).

Oedema of the larynx is therefore a complication essentially to be expected in infections above the mylohyoid—i.e., of the floor of the mouth or tongue. It is true that oedema of the larynx may complicate a superficial infection of the neck by spread along the stylopharyngeus to the laryngeal submucosa, as pointed out by Hamilton Bailey (1931), but this must be extremely rare. Oedema of the larynx is nearly always a complication of infection above the mylohyoid—that is to say, it is to be feared in true Ludwig's angina, and not in the

superficial infections of the neck below and anterior to the mylohyoid-thyrohyoid layer which are often incorrectly called Ludwig's angina.

It is fortunate, therefore, that most dental infections spreading out from the lower alveolus reach the periosteum on the labial border of the gum owing to the thinner layer of bone on this aspect of the alveolus (Hamilton Bailey). If infection spreads downwards it will then be superficial in the neck. In the region of the third molar the alveolar bone is thinner on the lingual side, and dental infections may thus reach the submucosa of the floor of the mouth; spread downwards will then be above the mylohyoid, in the base of the tongue—a true Ludwig's angina.

Summary

A case of asphyxia following dental extraction in a haemophiliac is described. Obstruction of the airway was due to massive haemorrhagic infiltration of the floor of the mouth.

Control of haemorrhage in haemophilia is briefly discussed.

The path of extravasation of blood and inflammatory fluids into the neck is discussed, the importance of the mylohyoid muscle layer being stressed. Oedema of the larynx is essentially a complication of infections above the mylohyoid, and very rarely occurs in infections superficial to this layer.

We are indebted to the Registrars at St. Bartholomew's Hospital and Guy's Hospital for access to old notes.

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INSULIN HYPOGLYCAEMIC COMA WITH A REPORT OF TWO FATAL CASES

BY

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Before the introduction of protamine-insulin, deaths from insulin hypoglycaemic coma were very rare, and were confined to cases of gross overdosage with insulin or cases in which the sudden onset of coma caused the patient to fall into water or sustain serious injury. The ordinary hypoglycaemic attack was as a rule of short duration, and coma, if promptly treated, was practically never fatal. The records of the Auckland Public Hospital (800 beds) from the introduction of insulin to May 31, 1941, do not include a single fatal case. The possible effect of protamine-insulin, however, upon the character and outcome of hypoglycaemic coma has not yet been fully studied; consequently, the occurrence within a period of six weeks of two fatal cases in which the usual treatment was of no avail may be considered worthy of record.

Case I

This patient, a man aged 50, was drawing a military pension for achlorhydria. He had undergone an operation for ischio-rectal abscess in August, 1937, but urine tests do not seem to have been made. He was admitted to the Auckland Public Hospital on May 5, 1941, with 6 months' history of polyuria, thirst, and loss of weight and strength. His blood sugar was 374 mg. per 100 c.cm. This and all subsequent blood-sugar estimations were made by the ordinary method of Folin and Wu. He was quickly stabilized on a diet of carbohydrate 200 g., protein 80 g., and fat 90 g., with a morning injection of zinc-protamine-insulin 20 units and ordinary insulin 16 units. On this dosage he had for 11 days consistently shown a small amount of sugar in specimens taken at 9 and 11 a.m. and frequently also at 4 p.m., but those taken before breakfast and at night were for the most part sugar-free. To prevent this small daily loss of sugar the ordinary insulin was increased from 16 to 20 units on May 30, and the next day he was transferred to a Returned Soldiers' Hospital for further observation.

On June 3 he left the Soldiers' Hospital at 10 a.m. apparently quite well, and at 12.20 p.m. was readmitted to the Public

Hospital in deep coma. The pupils were small and fixed, but all other reflexes were brisk. The cranial nerves, so far as they could be examined, were intact. The pulse was full and bounding at 60 a minute, and the temperature was 95°. Radiant heat was applied and the blood sugar was estimated immediately and found to be 41 mg. per 100 c.cm. At 1 p.m., therefore, he was given 100 c.cm. of 25% glucose intravenously by syringe and 250 c.cm. of 5% glucose by rectal drip, and a catheter was tied in so that the excretion of sugar could be closely watched. At 2 p.m. a further 100 c.cm. of 25% glucose was given by syringe, making a total of 50 g. of glucose intravenously, in addition to that which might have been absorbed per rectum. In spite of this, at 3 p.m. the blood sugar had fallen to the extremely low level of 16 mg. per 100 c.cm. The total non-protein nitrogen was 22 mg. per 100 c.cm. Two pints of 5% glucose-saline was then added to the rectal drip, and at 4 p.m. 500 c.cm. of 10% glucose was given by rapid intravenous drip. At 5 p.m. the blood sugar had risen to 80 mg., but the patient remained in deep coma. The temperature had risen to 100.6°, and thereafter remained moderately elevated and somewhat erratic. At 9 p.m. he received a further 250 c.cm. of 10% glucose-saline, and at 10 p.m. the blood sugar had risen to 190 mg., Benedict's urine test then giving a brick-red deposit (8 drops of urine to 5 c.cm. reagent—boiling-water bath for 5 minutes).

Thereafter for the next 7 days hourly specimens were tested and the greatest care was taken to maintain an adequate blood-sugar level, in the forlorn hope that the cerebral depression might lift. Throughout this period small amounts of sugar—green to yellow—were present in nearly every specimen of urine, but the Rothera test remained for the most part negative. By continuous intravenous drip an average of nearly 6 pints of 5% glucose-saline was administered daily, and small doses of insulin were given when indicated. Details of this treatment together with the temperature are recorded on the Chart. By

Chart of Case I

11 p.m. on June 7 he had recovered consciousness sufficiently to make some attempt at speech and to take 6 oz. of fluid containing 25 g. of glucose by mouth. Next day he took 18 oz. of fluid by mouth, and, though still stuporous, had a few moderately lucid intervals. On the seventh day he took 24 oz. of fluid by mouth, but remained stuporous. At 8 a.m. on June 10 he became suddenly weaker, lapsed into deep coma, and died 2 hours later. During the last 2 days approximately 0.5% sugar had been present in every specimen and the Rothera test had remained consistently negative.

The necropsy revealed a pancreas of normal appearance, as were all other organs except the lungs, which showed early patchy bronchopneumonia at both bases, and the brain, which showed congestion of the surface vessels and, microscopically, perivascular softening in the thalamus and caudate and lenticular nuclei.

Case II

This patient, a man aged 55, was admitted to the Auckland Public Hospital on July 3, 1941, with 3 years' history of loss of weight, lassitude, frequency, and thirst. His urine gave a brick-red Benedict and a negative Rothera reaction, and the blood sugar 3 hours after breakfast was 328 mg. per 100 c.cm. He responded rapidly to treatment and was quickly stabilized on a morning dose of 24 units of zinc-protamine-insulin.

On July 11 he was discharged from the ward and referred for further supervision to the diabetic clinic, where, however, he did not report. On July 21 he drove into town with his wife. The morning was so fully occupied with calls that he missed his 12 o'clock lunch. On the way home he drove recklessly, and occasionally swerved without reason across the centre of the road. At 12.30 p.m. he collided with another vehicle, wrecking his own car. He was shaken, but escaped bodily injury and had no difficulty in walking 100 yards and giving detailed instructions as to his car. Arriving home at 1.30 p.m., he sat down heavily and announced that he felt very hungry. His wife hastened to prepare lunch, but he had scarcely begun to eat when he rolled off his chair and could not be roused. A doctor who was called diagnosed diabetic coma and, finding in his room a syringe and bottle of insulin (protamine-zinc), gave him an injection of 12 units. At 3.45 p.m. he was admitted to hospital in deep coma. The pupils were small and fixed. His throat was so thickly coated with mucus as to impede respiration and cause cyanosis: 4 oz. of mucus was aspirated. The blood sugar on admission was at the very low level of 15 mg. per 100 c.cm. The temperature was 98.4°, pulse 96, and respirations 16. Radiant heat was applied, and 50 g. of glucose in normal saline was given at once intravenously. There was a definite response, deep coma giving place to restlessness and the pupils dilating to a diameter of 1/8 inch and reacting sluggishly to light. At 4 p.m. 50 g. was given intravenously and at 6 p.m. 25 g., but without further recovery of consciousness. At 8 p.m. a specimen was taken for blood-sugar estimation, but before the completion of this test the patient's condition suddenly deteriorated, the respiration rate fell to 8 a minute, further mucus collected, and cyanosis developed. Aspiration and stimulants met with no response, and death ensued at 9.15 p.m. The blood sugar at 8 p.m. proved to be only 20 mg. per 100 c.cm.

The post-mortem examination revealed a poorly nourished body with no marks of injury. The pancreas was rather small but otherwise normal, and all the other organs except the lungs and brain appeared to be normal. The lungs showed in the right upper lobe a primary caseous tuberculous lesion about half an inch in diameter, with involvement of the corresponding root gland. The brain was very oedematous, with marked excess of cerebrospinal fluid upon its surface. There was general softening, especially in the cerebellum.

Discussion

A. Causes of Coma

Both cases had been under observation in hospital until 3 days (Case I) and 10 days (Case II) before the onset of coma. During that period they behaved as ordinary diabetic patients of average intelligence and their response to insulin and diet was normal. They had been carefully instructed as to their diets and were fully competent to give their own injections of insulin. Further, the subsequent necropsy failed to reveal any organic cause of hypoglycaemia such as tumour of the pancreas or pituitary or any disease of the suprarenal or thyroid glands or liver or pons. Our study of these cases suggests that coma was at least partly due to the following:

1. In Case II the full cumulative effect of zinc-protamine-insulin may not have developed at the time of discharge from hospital. When this effect was obtained, perhaps on the day after discharge, it may have been too great.
2. The shock of the motor accident in Case II may have disturbed the endocrine balance in such a way as to increase sugar utilization.
3. Escape from Public Hospital discipline may have resulted in considerable increase in bodily exercise with consequent improvement in sugar utilization. This effect would be enhanced in Case I by the small increase of insulin (from 36 to 40 units) which was ordered, inadvisedly, on the day before discharge.
4. The ever-present risk of an error in the measurement of insulin and the natural tendency of a man feeling vaguely unwell to prescribe for himself an extra dose of anything that has previously done him good.

B. The Fatal Outcome

Necropsy revealed organic changes in the brain consisting of perivascular softening in the thalamus and lenticular and caudate nuclei in Case I, and of an abnormal amount of cerebrospinal fluid and general oedema of the brain with softening, particularly in the cerebellum, in Case II. These changes, or their physico-chemical precursors, were undoubtedly the cause of death and must have been responsible for the continuance of coma in Case I when, 4½ hours from

the onset, the blood sugar returned to normal. Other possible causes such as encephalitis and head injury must be excluded. In Case I the history is unlike that of encephalitis, and the pyrexia can be accounted for by the bronchopneumonia. There was no evidence of head injury in Case II.

There remains only hypoglycaemia to account for the cerebral damage. Pathological changes, including chromatolysis, vacuolation of protoplasm, fragmentation of cell processes, pyknosis of nuclei, petechial haemorrhages, and oedema widely and irregularly disseminated through the nervous system, have been described by Terplan (1932), Baker and Lufkin (1937), and many others, in fatal cases of pancreatic tumour and insulin hypoglycaemic coma in man and animals. Baker and Lufkin, however, being unable to find similar changes in hypoglycaemic rabbits upon which necropsy was performed immediately after death, considered that most if not all the changes observed in their 3 human cases occurred post mortem. They believed, further, that similar changes could be found in normal brains at the same period after death and doubted whether hypoglycaemia had played any part in their causation. Baker (1939), however, later found incontrovertible evidence of hypoglycaemic cerebral damage. Among his 26 rabbits 7 were examined after a single induction of hypoglycaemia with convulsions. A great many petechial haemorrhages and widespread severe demyelination and encephalomalacia were demonstrated. In these experiments the hypoglycaemia, though doubtless severe, was limited to an hour's duration, and only one rabbit actually died in coma. Accornero (1939) and Ferraro and Jervis (1939) present corroborative evidence.

Tyler (1941) confirmed the presence of hypoglycaemic brain damage in cats even when convulsions were prevented by sodium pentobarbital (nembutal). He made the important observation that a fall of body temperature and the administration of drugs such as nembutal, which depressed cerebral metabolism, gave an appreciable measure of protection against brain damage. He attributed the damage to inadequate cerebral respiration, in which glucose plays a vital part. We cannot escape the conclusion that severe hypoglycaemia as a cause of cerebral damage and death is now well established. But hypoglycaemia pushed to the stage of convulsions is a common and comparatively safe method of treatment for schizophrenia. An interesting study of therapeutic hypoglycaemia in 25 cases of schizophrenia has been made by Day, Niver, and Greenberg (1938). After shock-doses of ordinary insulin, estimations of glucose in the blood and cerebrospinal fluid were made by Benedict's method. The Folin-Wu method, which I used, is sensitive to many non-glucose-reducing substances equivalent to 20 to 27 mg. of glucose per 100 c.cm. of blood; the Benedict method is insensitive to all but a few, equivalent to 4 to 8 mg. per 100 c.cm. of blood. It follows, therefore, that when comparing the results obtained by these different methods a correction of 15 to 20 mg. per 100 c.cm. of blood must first be applied. Out of 28 inductions of hypoglycaemia by Day and his colleagues, in one case the blood sugar remained for 2½ hours between 5 and 20 mg. per 100 c.cm. (Benedict). In every case consciousness was promptly restored on the administration of 15 g. of glucose intravenously, and no after-effects were observed.

The lowest blood sugar recorded in my two cases was lower than that present in any of the schizophrenic cases, allowing for the effect of the non-glucose-reducing substances. In fact, with the correction for the Folin-Wu method there was apparently a complete absence of glucose from the blood. This aglycaemia may have lasted from 1 p.m. till 3 to 4 p.m. (2 to 3 hours). In Case II the duration of aglycaemia was about 4 hours, and this implies that at some time during that period there was free insulin in the blood with no glucose upon which to act. In Case I also the same condition was almost certainly present. The effect of such a glucose vacuum may well be more destructive to the nervous tissues than any degree of mere hypoglycaemia in which the blood retains a reserve of glucose, however small. In view of Tyler's work previously mentioned it is probable that the destructive effect of aglycaemia was increased in both our cases by the application of radiant heat. It is possible that the tissues of diabetics, inured to a raised blood sugar, would be more susceptible than those of normal persons to damage from sudden extreme hypoglycaemia.

Conclusions

Too much must not be deduced from evidence based upon limited clinical material, but we venture to draw the following tentative conclusions:

1. Zinc-protamine-insulin, while constituting an advance in the treatment of diabetes and while diminishing the frequency and in most cases the severity of hypoglycaemic symptoms, adds seriously to the gravity of hypoglycaemic coma when established.

2. Patients who are exposed to shock and strain while under treatment with zinc-protamine-insulin may develop profound hypoglycaemia of rapid onset and fatal outcome.

3. Patients who develop hypoglycaemic coma while under treatment with zinc-protamine-insulin should be treated much more vigorously than is necessary for similar cases under ordinary insulin. We suggest the following measures in such cases:

(a) An immediate intravenous injection of 100 g. of glucose (400 c.cm. of 25% solution) by syringe or cannula—the same dose to be repeated within half an hour if necessary. In the absence of immediate intravenous facilities a still larger dose should be administered by stomach-tube.

(b) An immediate subcutaneous injection of adrenaline 15 minims and pituitrin 1 c.cm.

(c) Except perhaps in cases of extreme fall in body temperature no warmth should be applied and no cerebral stimulants given.

Summary

An account is given of two cases of insulin hypoglycaemic coma which failed to respond to prompt and moderately vigorous treatment. In each case there was a period of aglycaemia with probably excess of free insulin in the blood. The damaging effect of aglycaemia upon the brain and the relative safety of insulin-shock treatment for schizophrenia are discussed. Attention is drawn to the gravity of hypoglycaemic coma in diabetic patients under treatment with zinc-protamine-insulin, and measures which should prove effective are suggested.

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A CASE OF HUMAN ISO-AGGLUTININ ANTI-M

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Antibodies for diagnosing the M-N blood-group factors have to be made by injecting appropriate red blood cells into an animal—nearly always a rabbit—and later absorbing suitably the rabbit serum to remove unwanted species antibodies. Because anti-M and anti-N do not occur naturally in man serum, and because M and N do not seem to be antigenic for man, the M-N groups can be neglected almost entirely in considering compatibility in blood transfusion. Wiener (1941) wrote: "Only 3 individuals have been observed to date with natural isoagglutinins anti-M, none with anti-N, among several hundreds of thousands

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