A DEATH DURING INSULIN TREATMENT OF SCHIZOPHRENIA; WITH PATHOLOGICAL REPORT. *

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THE insulin treatment of schizophrenia has been practised at Hatton since June, 1937. The Vienna technique has been employed, with certain modifications described in a recent paper in this journal by Gillman and Parfitt (9).

Seventy-five cases have been completed, and there has been one death. This fatal case is reported below, with a pathological report.

CLINICAL HISTORY.

M. M. G. B—, aged 22, was admitted to Hatton on October 15, 1936. Her paternal grandparents were heavy drinkers, and her mother is said to have had a " nervous breakdown ".

The patient developed normally in infancy, and had only the ordinary illnesses of childhood. She was of average intelligence, but was rather shy and reserved. Menstruation commenced at 15½.

Mental changes developed insidiously from the age of 16. The first signs were lethargy and irritability, which gradually increased. She left school at 17 and was trained as a typist, but was unable to keep a job. Finally she began to neglect her appearance, and would wander out of the house at night.

When admitted to hospital she was in a state of agitated depression. She had delusions of reference, and at times was violent. She talked in a rambling way, but there was no disorientation or impairment of memory. A diagnosis of hebephrenic schizophrenia was made.

Her general build was asthenic in type. On examination no signs of physical disease were found. Her blood Wassermann reaction was negative and her blood-count normal.

Somnifaine narcosis had no effect on her mental condition. Her appetite

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remained poor, and for a long time she lost weight steadily. Prolonged rest in bed and occupational therapy were tried in turn without success. In March, 1937, she had slight pyuria. This responded promptly to the administration of potassium citrate, but there was no concomitant improvement in her mental condition.

Eventually, after eight months, she became rather more settled and cheerful, and lost her delusions of reference. On July 1, 1937, at the request of her relatives, she was allowed to go out on " prolonged trial ".

After two months, however, she began to relapse, and on October 13, 1937, she returned to Hatton, her mental condition being the same as when she was first admitted. Again no signs of physical disease were found. Insulin treatment was commenced on October 14.

Seventeen injections of insulin were given in twenty-one days, the dose varying from 10 to 208 units, as shown in the following table. No cardiazol was given. No fits occurred.

Day.	Injection No.	Dose of insulin in units.	Remarks.
1	1	10	No shock.
2	2	20	,,
3	3	20	,,
4	..	..	..
5	4	32	,,
6	5	48	,,
7	6	64	,,
8	7	80	,,
9	8	96	,,
10	8	120	,,
11	..	..	..
12	10	136	,,
13	11	160	" Light shock ".
14	12	176	Shock (1) at 11.0 a.m.
15	13	192	,, (2) at 10.20 a.m.
16	14	208	,, (3) at 10.10 a.m.
17	15	208	,, (4) at 9.50 a.m.
18	..	..	..
19	16	200	,, (5) at 10.55 a.m.
20	..	..	..
21	17	200	No primary shock ; secondary shock at 4.30 p.m.
22	..	..	..
23	..	..	..
24	..	..	Died.

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In general the patient reacted to the first fourteen injections in the usual way, which has been described in detail by Parfitt (21); but flushing of the face was more noticeable in her case than in others. On the occasion of the ninth injection she complained of nausea and diplopia at 10.30 a.m.

None of the first eleven injections produced a shock, though the dose of insulin was increased fairly rapidly. The events of the subsequent days may be summarized as follows:

14th day: 12th injection—176 units.
11.0 a.m. SHOCK.
11.35 a.m. Nasal glucose.

15th day: 192 units.
10.15 a.m. Grimacing.
10.20 a.m. SHOCK.
11.0 a.m. Severe clonic spasm of muscles.
11.15 a.m. Nasal glucose.

16th day: 208 units.
10.0 a.m. Facial congestion, with severe clonic spasm of muscles.
10.10 a.m. SHOCK.
11.15 a.m. Nasal glucose.
11.35 a.m. Intravenous glucose, because still unconscious.

17th day: 208 units.
8.45 a.m. Severe myoclonic twitching. Pupils dilated.
9 a.m. Facial congestion.
9.50 a.m. SHOCK.
10.15 a.m. Muscular rigidity, with arms extended. Face very congested.
10.50 a.m. Nasal glucose. Betaxin 1 c.c.
11.20 a.m. Cyanosis (relieved by O_2 and CO_2). Still unconscious. Salivation ++. (Atropine gr. $\frac{1}{60}$ subcutaneously.)
12 noon. Conscious, but very confused. Speech slurred.
1 p.m. Drowsy only.

18th day: No insulin.

19th day: 200 units.
10 a.m. Very restless. Facial congestion.
10.55 a.m. SHOCK. Muscular relaxation.
11.15 a.m. Face very congested.
11.20 a.m. Nasal feed.
11.45 a.m. Still comatose. Intravenous glucose. Corneal reflexes returned at once, but patient remained very confused and became wildly excited, throwing herself about.
12.45 p.m. Quieter, but still confused.
1.30 p.m. Drowsy only. Slurred speech. Temperature 100·6°.

20th day: No insulin.

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21st day : 200 units. No primary shock.

9 a.m. Myoclonic twitching.

9.15 a.m. Restless and noisy.

9.30 a.m. Muscular rigidity with unconsciousness.

10 a.m. Severe muscular spasm, with facial congestion.

10.20 a.m. Fully conscious and talking.

10.30 a.m. Unconscious again.

10.40 a.m. Conscious again.

11 a.m. Unconscious again. Nasal glucose (effective immediately). She got up after lunch, as usual.

3 p.m. Complained of feeling cold. Put to bed.

4.30 p.m. SECONDARY SHOCK. Corneal reflexes absent. Prompt response to intravenous and nasal glucose.

5.30 p.m. Suddenly collapsed, with extreme pallor, cold skin, sighing respiration, pulse impalpable, pupils dilated. Slow response to stimulants, etc.

6 p.m. Temperature 101°, pulse 120, respirations 42.

6.30 p.m. Persisting dyspnœa and rapid pulse. Restless. Said she could breathe better under the bedclothes. Complained of severe pain and tenderness in right iliac fossa.* Morphine gr. $\frac{1}{6}$ and atropine gr. $\frac{1}{100}$ subcutaneously.

10 a.m. Temperature 98°, pulse 120, respirations 36. Restful night. Oral fluids vomited. Rectal glucose salines retained.

22nd day :

6 a.m. Temperature 98·4°, pulse 114, respirations 34. Colour and general condition improved greatly. Fluids taken without vomiting.

6 p.m. Temperature 98°, pulse 100, respirations 36. Slept at intervals during the night.

23rd day :

6 a.m. Temperature 99·6°, pulse 112, respirations 36. General condition gradually deteriorated through the morning. She began to look grey, and vomited continually.

2.30 p.m. Cyanosed, restless and anxious. Intravenous and rectal glucose. Morphia gr. $\frac{1}{6}$ subcutaneously.

3.30 p.m. Extreme dyspnœa. Physical signs of pneumonia at the base of both lungs.

6 p.m. Temperature 102°, pulse 134, respirations 42. Restless during the night. Slept only two hours.

24th day :

5 a.m. Anxious and distressed.

* Subsequent post-mortem examination did not reveal any lesion of the appendix or any other part of the intestine. But attacks of abdominal colic simulating acute appendicitis have been reported by Gillman and Parfitt (9) to be a fairly frequent complication of insulin coma treatment.

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6 a.m. Temperature 97·2°, pulse 136, respirations 46. Much weaker. No response to oxygen, brandy, hourly coramine, etc.

9 a.m. Temperature 100·6°, respirations 46.

9.50 a.m. DIED.

POST-MORTEM FINDINGS.

The post-mortem examination was made on November 8, 1937, about fifty hours after death. Post-mortem rigidity was present. The body was well nourished, and there was no external evidence of disease.

Weights of organs.—Right lung, 31 oz.; left lung, 20 oz. Heart, 12½ oz. Liver, 47½ oz. Right kidney, 5½ oz.; left kidney, 5 oz. Spleen, 4 oz. Brain, 47½ oz. (Weight of whole body about 100 lb.)

Peritoneal cavity normal.

Stomach and intestines (including appendix).—No evidence of disease.

Pancreas.—No superficial evidence of disease.

Spleen.—No evidence of disease.

Gall-bladder normal. No gall-stones.

Liver.—Congested with blood.

Pericardial sac normal.

Heart slightly enlarged. Cavities dilated, with flattened columnæ carneæ. Ante-mortem clot present in left ventricle at apex. Valves healthy. Coronaries and aorta healthy.

Pleural sac healthy.

Lungs.—Right: Lower lobe, middle lobe, and part of upper lobe intensely congested with blood. They presented an appearance resembling "red hepatization" and sank in water. *Left:* Lower lobe and part of upper lobe, similar changes in a lesser degree.

Kidneys.—Both very congested with blood. They showed, when cut across, little whitish spots scattered diffusely in their substance.

Histological examination of various organs (lung, liver, and kidney) revealed very great congestion. In addition, the kidney showed widespread fibrinoid degeneration of the glomerular arterioles and capillaries. There were numerous areas of cortical necrosis, corresponding to the whitish patches already seen with the naked eye. These were probably secondary to the severe arteriolar degeneration.

The origin and significance of the kidney changes is doubtful, but pyelonephritis can be excluded. The changes are too recent to warrant ascribing to disorganized kidney function the histological changes in other organs.

EXAMINATION OF THE BRAIN.

The outward appearance was normal, except for a marked venous hyperæmia. On coronal section no abnormalities worth recording were found.

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Numerous regions of the cortex, basal ganglia, hypothalamus, brain-stem and cerebellum were examined histologically.

The cortical changes were slight. There were, particularly in the temporal region, a few circumscribed areas of paling situated predominantly in the deeper layers of the cortex (Fig. 1). In these foci all ganglion cells had either disappeared or were recognizable only as shadows. In the parastriatal region a whole convolution was with Nissl stain paler than its surroundings. The ganglion cells also were distinctly paler and somewhat shrunken, and in a few the nucleolus was broken up into chromatin granules. There was a slightly greater activity of the macroglia and vessel-wall cells (endothelial as well as adventitial) in this paler area. This change probably represents a very recent stage of ischæmic necrosis, but neither here nor elsewhere was typical ischæmic ganglion cell change seen. Throughout the brain the ganglion cell changes were neither marked nor of a characteristic pathological type.

In view of the recent experimental findings of Büchner and Luft (3), particular care was taken in the examination of the motor centres of the brain-stem and cerebellum, but no severe type of ganglion-cell change was detected. The Purkinjë cells throughout were somewhat paler than usual, but showed well the normal structures of cytoplasm and nucleus. There was no striking lipoid content of ganglion cells, glial cells and vessels throughout the brain. Only the cells of the olivary body contained some lipoid, and here and there were slightly ballooned; but this may be still within the normal range. The lipoid content of the globus pallidus was, however, excessive (increase of free globules and of lipoid in glial and adventitial cells).

The pyramidal cell layers of the cornu ammonis and gyrus dentatus were intact. There was only, in the white matter corresponding to the sector, a definite proliferation of the macroglia and blood-vessels. No pseudo-calcium or fat was seen.

The outstanding pathological feature of the case was the great mobilization and proliferation of the macroglia. It is best seen in the Holzer and Globus-Cajal preparations, whereas the Nissl picture gives only a slight indication. The regions affected are the subpial layer and, to a varying degree, the white cerebral and cerebellar matter and the globus pallidus. Fig. 2 depicts the astrocytosis in a Globus-Cajal preparation from the frontal white matter, while Fig. 3 shows the gliosis in the cerebellar white matter. The gliosis is in the stage of a proliferation and increase in number of the macroglia. In the cerebellar white matter and the globus pallidus there is, however, already a production of a fibrous glial felt. No indication of the process was seen in preparations stained for myelin, nor was there any damage of the axis cylinders.

Discussion.

In our present state of ignorance of the nature of the action of insulin on the brain, and the exact significance of the neurological phenomena during

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hypoglycæmia, it would be out of place to make any attempt to correlate in detail the post-mortem findings with the history of the patient's reactions to the insulin injections. It is, however, worthy of special note that, though she had no clear-cut epileptiform fits, she exhibited on each of her last five injection-days phenomena which might reasonably be regarded as "epileptoid"—tonic and clonic spasms during coma, and, on one occasion, wild excitement and restlessness.

Histologically, the case is characterized by the fact that there is only a slight manifestation of typical ischæmic necrosis, as instanced in Fig. 1, the predominant feature being fibrous glial proliferation in the subpial layer of the cortex, the globus pallidus, and the cerebral and cerebellar white matter. The glial proliferation was most marked within the cerebellar white matter and the globus pallidus.

Glial proliferation has not been lacking in previous cases, and this is not surprising, since it is a common feature of all processes of breakdown and repair. Its special significance in our case lies in the fact that the parenchyma was, except for a few circumscribed areas of necrosis, strikingly well preserved. We failed to find diffuse ganglion-cell changes of a significant degree and nature, nor was there any noticeable damage to myelin and axis cylinders. Fatty breakdown was absent, except for an increase of lipoid within the globus pallidus. More or less isolated proliferation of the glia has been previously reported by Schmid (24) and Lemke (15). The latter described it particularly within the white matter. There was, however, no full investigation of the fibrous glia. The changes of the nucleolus may be comparable to the nuclear changes described by Kobler (13), though in our case they are strictly limited to the ischæmic areas.

The question arises whether the difference in the histological appearances is due to an essential difference in pathogenesis. A satisfactory answer is difficult, since the effect of hyperinsulinism upon the central nervous system is still under discussion. Most histological workers have agreed upon the ischæmic character of most of the lesions (Stief and Tokay (29, 30), de Morsier and Mozer (20), Bodechtel (1), Weil and collaborators (32), and many more). In accordance with conceptions introduced by Ricker (23) and Spielmeyer (27), the idea has been prevalent that hyperinsulinism leads to vasomotor disturbances of the brain-vessels which produce the ischæmic lesions. Stief and Tokay (29, 30), particularly, insist upon angiospasm being the cause of the lesions. Whatever method of administration of insulin was used in their experiments—intravenous, intracisternal or intracerebral—lesions of an ischæmic nature were invariably produced, by angiospasm, as they thought. Since angiospasm is widely held to be responsible for ordinary epileptic convulsions, this hypothesis was not without attraction, the more so since Reitmann (22) and Köst (14) succeeded in suppressing or preventing the convulsions provoked by insulin and cardiazol respectively by application of vasodilator drugs,

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chiefly amyl nitrite. However, the fact that vasodilation suppresses epileptic fits does not necessarily imply that the latter are produced by angiospasm. Amyl nitrite and similar drugs have also other important pharmacological effects. Doubt has already been cast by Ricker on the theory that spasm of brain-vessels is capable of producing ischæmia, and this doubt has obtained very definite expression, on the strength of experimental evidence, in a recent paper by Forbes and Cobb (7). It is, therefore, safer to assume as the cause of the ischæmic and other vascular lesions, disturbances of the circulation in the widest sense, including even the power of the cell to activate oxygen for use. The importance of such a wider conception has been stressed by one of us (A. Meyer (19)), and it is also recognized for the pathogenesis of hypoglycæmic lesions by Weil and his collaborators (32). In this sense, and probably only in this, one might even admit the possibility of toxic changes, if " toxic " as used by histologists means a direct damage to the cell in contradistinction to that exerted via the vessels, though their effect—ischæmia of the tissue—might be essentially the same.

That lack of oxygen is an important factor is shown also by biochemical investigations (Holmes (12), Damashek, Myerson and Stephenson (4), Wortis (33), Gellhorn (8)). Gellhorn, particularly, is of the opinion that all the phenomena provoked by insulin are akin to, if not identical with, those produced by anoxia, and that there is a mutual sensitizing reaction between them. Parfitt (21) also stresses the importance of the anoxia produced by insulin. Thus histological, biochemical and clinical evidence, as far as it goes at present, points to an interference with the oxygen supply of the tissue.*

The production of histological lesions in hypoglycæmia seems largely to depend on the occurrence of epileptic fits and epileptoid phenomena. It is well known that the histological findings in essential epilepsy greatly resemble those found in fatal cases of hypoglycæmia. Stief (28) expressly states that, in his numerous experiments with Tokay, animals that had no fits did not reveal significant brain changes post mortem. His experiences tally with those of Tani (31) and Grayzell (10). This is a point of general importance, though it may be admitted that there is no strict parallel between the severity and frequency of the fits and the brain changes (Weil and collaborators (32)).

If we take the foregoing considerations as the basis for the discussion of the pathogenesis of our own case, it is highly probable that the findings, despite their difference in appearance, have the same origin as those described in previous cases. Sclerosis of the white matter as a possible result of vascular disturbances, or other types of anoxia, is nothing new. The white matter has been proved to be vulnerable in birth-injury (Schwartz (25)), congenital heart disease (Bodechtel (2)), carbon monoxide poisoning (Grinker (11), A. Meyer

* It is, of course, well to bear in mind that there are also other opinions on the effect of hypoglycæmia which it is difficult at present to reconcile with the anoxic principle (Drabkin and Ravdin (5)).

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(16)), cyanide of potassium poisoning (A. Meyer (17), Ferraro (6)), and other conditions. White matter sclerosis has been observed in various groups of mental deficiency (A. Meyer and L. C. Cook (18)), and here also there was some evidence for considering defective tissue oxygenation as a possible cause. The reason why it is sometimes the white matter, and sometimes other regions, that prove to be vulnerable in vascular disturbances is obscure. We should learn, however, from experimental work that the same nocuous agent, under conditions not yet known, varies, not only as regards the site of the lesion produced, but also in the detail of histological appearance. It has been seen that in white matter lesions following carbon monoxide poisoning, in some cases there is a mobile (Spielmeyer (26)) type of repair, in others no transformation of the glia into compound granular cells occurs. The scavenger cells may be derived in some cases predominantly from the glia, in others from adventitial histiocytes. It may well be that such variations are due to differences in intensity and tempo. The type of glial sclerosis without serious breakdown of the parenchyma has been compared recently (A. Meyer (19)) to the fibrosis of organs recognized as the result of chronic mild stasis. It is thus possible that in our case the effect of the disturbed circulation upon the brain was of a milder intensity that in other cases with more pronounced necrotic lesions. It may be of importance that in this case clear-cut epileptiform fits did not occur ; though it is difficult, of course, absolutely to differentiate from fits the various epileptoid phenomena exhibited by our patient during coma. If Stief and Tokay (29, 30) are right in stating that the production of severe lesions in the brain is conditional upon the occurrence of epileptiform convulsions, then the relatively mild manifestations of changes in the brain of our case may readily be explained. Indeed, the findings in our brain resemble the diffuse changes frequently seen in the brains of epileptics.

The brain lesions in our case are unlikely to have been the direct cause of death ; they are too slight to be considered as such. Nor would it be safe to regard them necessarily as the substrate of the typical and atypical clinical phenomena produced by the insulin treatment.* They are probably secondary to the functional breakdown ultimately produced by hyperinsulinism. It is interesting to find that this breakdown is more or less one of the circulation in its widest sense, but it would be a mistake to conclude from the histology of such complicated cases alone that the whole action of insulin is confined to the circulation. This could be established only by biochemical methods, since a less severe action of insulin on the tissue will probably not result in clear histological pictures. The biochemical evidence, as far as it goes at present, seems to support an anoxic pathogenesis of insulinism.

*It goes without saying that there is at present no justification for considering the lesions as a histological substrate of schizophrenia.

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Summary.

A death during hypoglycæmic treatment is described. The case is characterized pathologically by proliferation of the fibrous glia, chiefly within the white matter. Typical ischæmic necrosis is only slight. The pathogenesis of the lesions is discussed in the light of current histological and biochemical views.

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