tion of the decrease in blood sugar was that hepatectomy either removed the control of the blood sugar supply or interfered with sugar utilization by depleting the carbohydrate store or a substance concerned in carbohydrate utilization. Further, Mann and Magath⁵ later showed that hepatectomized hypoglycaemic dogs, showing the above symptoms, could be immediately restored to a seemingly normal condition by the intravenous injection of 0.5 gram glucose per kilogram of body weight. Immediately after the glucose injection the blood sugar reached a high level, and then gradually fell. By repeated intravenous injections of glucose the animals could be kept alive and without the characteristic symptoms (which were apparently almost entirely due to hypoglycaemia) for about twenty-four hours, but then, notwithstanding a normal blood sugar level still being maintained, the animals suddenly became comatose and died quietly. The hypoglycaemic symptoms were thus different from the final picture, which was probably "dependent on some change in metabolism other than carbohydrate."

It is tempting to suggest that the case now reported is almost the clinical equivalent of the physiological experiments of Mann and Magath, that hypoglycaemia due to liver cell destruction from disease largely coloured the clinical picture, and that death was due to hepatic failure. It is interesting, also, in this connexion to note that signs of marked listlessness and slowing of mentality, with some flaccidity of muscles, began to reappear soon after the intravenous glucose injection, and that coma reappeared when the blood sugar was 104 mg. per 100 c.cm., four hours after the intravenous injection.

INTERPRETATION

As we were not permitted to perform a complete post-mortem examination, the exact aetiology of the condition is necessarily somewhat doubtful. However, taking into account the possible pathogeny, we suggest that, although a remotely possible cause was functional hyperinsulinism, the most probable one was disease of the liver interfering with its glycogenic function. Certainly no tumour of the islands was discovered in the pancreas, and if there was an excessive secretion by the cells of the islands of Langerhans, it must have been purely "functional." On the other hand, a definite alteration of the liver structure was found, and although this was an unusual condition, it is interpreted as being a subacute parenchymatous hepatitis. Although no determination was made of the liver glycogen content (it is doubtful whether this would yield information of great importance nine hours after death), it is quite probable that this structural change in the liver was consistent with an alteration of its function in carbohydrate metabolism. Consequently, we are inclined to the view that the cause of the hypoglycaemia in this case was parenchymatous hepatic degeneration; whether the latter condition has any relation to so-called acute yellow atrophy of the liver, and whether it had any connexion with pregnancy, we cannot say; from the information at our disposal its aetiology is obscure.

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ULTIMATE HISTORY OF A PREVIOUSLY REPORTED CASE OF ACUTE SPONTANEOUS HYPOGLYCAEMIA

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This case was fully described in the *British Medical Journal*¹ in 1931. The patient, a woman aged 27 years, was admitted to the Mater Misericordiae Hospital in May, 1930, in hypoglycaemic coma, the blood sugar being 35 mg. per 100 c.cm.; her limbs were rigid and the Babinski sign was bilaterally positive. She promptly recovered consciousness on the intravenous injection of 10 grams of glucose, the rigidity passed off, the Babinski sign became negative, the blood sugar rose to 111, and the coma never recurred during fourteen months of observation. The acute hypoglycaemia was associated with amyloseous dyspepsia, which was successfully treated; but, although acute hypoglycaemia did not reappear, there remained a mild continuous chronic hypoglycaemia (62 to 78 mg. sugar per 100 c.cm. of blood), upon which the acute hypoglycaemia causing coma was apparently superadded.

On November 19th, 1933, the patient was again admitted to the hospital in an unconscious condition; the clinical picture was, however, different from that seen on the first admission: there was no rigidity of the limbs; on the contrary, the muscles were flaccid; the tendon reflexes and Babinski's sign were negative; there was some resistance to forcing the eyelids apart, the conjunctival reflex was present, and the pupils reacted to light; loud bubbling rales were heard all over the chest, so that the heart sounds could scarcely be distinguished. No pulse could be felt at the wrists, but the right superficial temporal artery pulse rate was 84, and the blood pressure could not be determined over the brachial artery. There was no cough or sputum, and the clinical picture suggested post-influenzal pneumonia. The axillary temperature was 100° F. and the respirations were 44 per minute. The blood sugar, a couple of hours after admission, was 66 and the blood urea 84 mg. per 100 c.cm. The urine was normal. Twenty-five grams of glucose were given intravenously, after which the blood sugar rose to 217 mg. per 100 c.cm. Glucose was given by stomach tube and per rectum, but was not retained, and the patient died about twelve hours after her admission to hospital.

Inquiry from her husband revealed that she had felt quite well on the morning of admission and arose after breakfast. Feeling cold about 11 a.m., she went to bed again. She refused her dinner at 2.30 p.m., and vomited a little whisky taken about 5 p.m. At 6 p.m. she became unconscious, and at 8 p.m. was seen by Dr. L. Masterson, who noted the rales in the chest and referred her to one of us as he knew we were interested in the case. She had become comatose, without convulsions, about nine months previously for about two hours, but recovered without treatment. During the past two years she occasionally complained of staggering or giddiness, and

blurring of vision when reading; apart from constipation and frequent listlessness we could learn nothing further of significance.

POST-MORTEM EXAMINATION

Fortunately we were able to obtain, about two hours after death, a complete necropsy, of which the following is a relevant summary:

The body was well nourished, the pubic and axillary hair was scanty and short, the hair of the head was fine and rather sparse at the vertex. All the organs were carefully examined by the naked eye and microscopically, unless otherwise stated.

Abdomen.—The spleen weighed 180 grams; its substance was dark red and firm, and on microscopical examination there was venous engorgement. The kidneys were normal, except for venous congestion and slight fibrosis of the interstitial tissue. The suprarenals were normal macroscopically and microscopically. The pancreas was normal. It was carefully sectioned in a search for adenomata of the island tissue, but none were found; the cells of the island tissue appeared normal, and the islands did not seem to be increased in number or size. Sections from various parts of the pancreas showed a slight general fibrosis. The liver weighed 1,300 grams; its surface was smooth and pale; on incision it showed a slightly "marbled" appearance. Microscopical examination showed a general venous congestion, with some slight round-celled infiltration about the smaller bile ducts; there was slight fatty change, which was in the nature of an infiltration confined to a small zone about the intralobular veins; slices were fixed in alcohol, but no glycogen could be demonstrated. The stomach and intestines were normal on naked-eye and microscopical examination, and the gall-bladder, urinary bladder, and uterus and its adnexae were normal on naked-eye examination.

Heart and Lungs.—The pericardium contained about 110 c.cm. of pale fluid; the heart, which weighed 240 grams, was macroscopically normal, except for slight thickening of the mitral valve cusps and some flaccidity of the right ventricle. Both lungs showed bronchopneumonia. There were petechial haemorrhages under the visceral pleura. The substance of the lung felt "shotty," and incision showed numerous scattered, plum-coloured, consolidated patches of various sizes. A large consolidated area about the size of a tangerine orange was present in the central part of the upper lobe of the left lung. Pus exuded from the smaller bronchi in the consolidated areas. Microscopical examination showed bronchopneumonia, and Gram-Weigert stain showed pneumococci to be present.

Other Organs.—The thyroid was small, and weighed only 8 grams. Stained sections showed normal structure and no lack of colloid substance; there was slight flattening of the cells lining the alveoli, and there was no fibrosis. The brain and brain stem were normal on naked-eye section, but the brain surface was slightly congested and oedematous.

The pituitary gland was normal on naked-eye and microscopical examination. The thymus was absent.

BIOCHEMICAL INVESTIGATION OF LIVER

As it seemed important to learn, if possible, something about the carbohydrate and glycogen content of the liver, Professor E. J. Conway kindly undertook to investigate this question, and his report is as follows:

Considering that two hours had elapsed from the death of the subject to the time of excision of the liver, it was decided to estimate the total carbohydrate, and so obtain at least a maximum value for the ante-mortem glycogen content. It is well known, since the classical experiments of Claude Bernard, that a marked breakdown of glycogen into glucose takes place in the liver after death, and that in two to three hours the greater part of the pre-formed glycogen may have disappeared. The estimate of the total carbohydrate under such conditions, with subsequent calculation of the glycogen, supposes that none of the formed glucose disappears by glycolysis. That no appreciable glycolysis takes

place is shown by the early experiments of F. Rohmann, described in his *Lehrbuch der Biochemie* (Berlin, 1908), in which no marked diminution of the total carbohydrate had occurred in one and a half to two hours after death. The estimate of the total carbohydrate, according to the same worker, using acid hydrolysis, gives figures always in excess of that reckoned from the original glycogen and glucose content. The present results will state, therefore, only a maximum possible value for the original glycogen content of the sample provided, and are almost certainly higher than the true figure.

In the method used 10 grams of liver, cut into sections, were boiled in 50 c.cm. of distilled water for twenty minutes. From the stoppered flask—after remaining overnight—the liver substance was removed and carefully ground to a paste with the finest Merck's quartz sand, continued extractions with water being taken, and finally the whole made up to 100 c.cm. with water. The mixture was shaken for some time and filtered; 5 c.cm. portions of the filtrate were taken and, equal quantities of N/1 acid having been added, the mixtures were boiled for ten to thirty minutes. These were subsequently neutralized and made up to 100 c.cm. with water. The glucose content was then examined by the Hagedorn-Jansen method, using the precipitation stage of this method as well—it being necessary, however, to take upwards of 4 c.cm. of the fluid for analysis.

The results were certified by several repeats, controls, and blanks, and may be summarized as follows:

- (1) Glucose in liver sample examined, 0.9 per cent.
- (2) Total carbohydrate in liver sample examined (as glucose), 1.01 per cent.
- (3) Maximum value of glycogen in liver examined, 0.12 per cent.
- (4) Maximum value of glycogen in ante-mortem liver, 0.94 per cent.

In the calculation of the third and fourth items it is reckoned that 1 gram of glycogen gives 1.07 grams of glucose. The values given by Hammersten for the glycogen content of the liver in the normal animal are from 1.2 to 4 per cent. Figures of 18 and even 20 per cent. have been obtained in experimental animals. The values given by Rohmann for upwards of twenty experimental animals receiving dietaries with normal food constituents (these being varied in different ways) show 1.69 as the lowest for a dog fed on meat alone. For two dogs fed on sugar and biscuits he obtained the surprising figures of 19.5 and 19.3 per cent. glycogen. The figures of Rohmann show that post-mortem glycolysis in the liver is practically negligible for two hours after death, although glycogenolysis is marked. Therefore one may conclude that the figures obtained suggest that the liver before death was poor in glycogen.

DISCUSSION

The interpretation of the case from the history and post-mortem findings is by no means clear. Apparently the acute hypoglycaemic coma was in some degree related to amylaceous dyspepsia occurring in conjunction with chronic hypoglycaemia, but the cause of the latter condition is still obscure. Possibly, in view of the small size of the thyroid gland, a mild degree of hypothyroidism might be held responsible, but, on the other hand, the thyroid, though small, did not, on microscopical examination, show any great departure from the normal, and there was no gross clinical sign of hypothyroidism. It is unfortunate in this connexion that the patient on her first admission refused to allow her basal metabolic rate to be estimated. However, it is difficult to believe that whatever degree of hypothyroidism the patient may have had would be great enough to keep the blood sugar down to the levels existing after the cure of the amylaceous dyspepsia. Again, liver disease could hardly be held definitely responsible for the chronic hypoglycaemia, because the pathological changes in the liver were too slight—the hepatic venous congestion must have been terminal. As regards the liver glycogenic function, the maximum possible ante-mortem

glycogen value for this liver was below what one might expect as normal, but normal control figures for the human do not seem to be readily available. All that can be said is that apparently this liver was poor in glycogen. But in the absence of further evidence, and remembering that the patient took or retained little food for twenty-four hours (apart from the intravenous glucose given about eleven hours before death), it would be rash on this score to attribute the chronic hypoglycaemia to a hepatic cause. To account for the chronic hypoglycaemia one is apparently driven, in the present state of knowledge of this complicated subject, for want of a better explanation, to consider absolute hyperinsulinism; but here again there is very little evidence to go upon. Finally, it is interesting to speculate as to whether the fulminant

course of the bronchopneumonia may have been determined to some degree by the chronic hypoglycaemia.

NOTE.—Since the above was written we have come across a case of apparently true hyperinsulinism, or what certain authors might call dysinsulinism. This was a man, aged 28 years, who complained of slight mental confusion, slight dimness of vision, and weakness about three hours after the heavier meals. The fasting blood sugar was only 80 mg. per 100 c.cm. After ingesting 50 grams of glucose the blood sugar in half an hour was 90, in one hour 135, in two hours 97, in three hours 64, in four hours 66, and in five hours 78 mg. per 100 c.cm. His physical examination was normal in all respects, and we could find no evidence to implicate either the ductless glands or the liver.

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A CASE OF OVARIAN PREGNANCY*

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(With Special Plate)

The following case of ovarian pregnancy appears worthy of record in view, first, of the great rarity of the condition, and, secondly, of the circumstances leading up to it.

Mrs. C., aged 38, a European, formerly a maternity nurse, consulted me privately on April 26th, 1933, for sterility.

Although married for only twenty months, in view of her age and the fact that her menstruation was becoming scanty she was anxious to become pregnant as soon as possible.

Menstruation.—Every twenty-six days, duration five days; latterly duration three and two days. Last menstrual period April 20th to 22nd.

Physical Examination.—Perfectly healthy type. Pelvic organs normal.

Advised a Rubin inflation of the Fallopian tubes about ten days after first day of each period for three or four months, and to take agomensin for a week before each period.

Treatment.—A Rubin inflation of the Fallopian tubes was carried out on May 1st; pressure 120, both tubes patent. The patient had sexual connexion two or three times in the following few days as advised, but it was later ascertained that she had also had connexion three days before the test was performed.

The patient took agomensin (two tablets three times a day) from May 11th, and was seized with severe lower abdominal pain on the 14th. The pain was so severe that she was admitted to a nursing home. I was out of Bombay, and so am unable to particularize further about this attack. She was given hyoscine. The pain subsided, and she left the home in two days.

She herself attributes the pain to the agomensin. The period expected at the middle of May did not appear. She came to see me again on May 31st. She then had a slight uterine haemorrhage, like a mild menstruation, but no pain. She stated that, since the pain of May 14th, she could not lie comfortably on her left side.

She was not examined, in view of the probability of the missed period indicating pregnancy and the slight haemorrhage a threatened abortion, but she was ordered rest and sedatives, and told to return again in a few days and to keep in touch with me meanwhile.

* This case was reported at a meeting of the Bombay Branch, held in the Grant Medical College, Bombay.

She returned on June 14th and reported that she had "miscarried" on June 8th. From her description of what she passed, and her experience as a nurse, I at first considered that this was probable, but on examining her I found the uterus anteverted, normal in size, and a lump, situated behind and to the left of it, slightly tender, about the size of a plum, and firm in consistency. There was pulsation between this lump and the left side of the uterus. She had a slight blood-stained discharge, brownish red in colour, and slight pain in the lower abdomen. She was told that the condition indicated a possibility of extrauterine gestation, was cautioned to keep very quiet, to remain in communication with me, and to report any developments. In the event of any pain or feeling of illness she was instructed to go to the nursing home immediately and to ring up her doctor.

In the absence of such developments she returned on June 19th, when the following condition was found.

Slight uterine bleeding as before. Slight pain in the hypogastrium. Per vaginam, the lump was found to be nearly double the size noted on the 14th. She was ordered immediately into the nursing home as a case of extrauterine gestation, and I operated on the same day, assisted by Captain H. S. Waters, I.M.S.

On opening the abdomen, there was extremely little free blood in the peritoneum, but, on raising the sigmoid flexure of the colon, the left ovary was found enlarged to the size of a peach, deep red in colour, and with loose adhesions formed by blood clot to the lateral wall of Douglas's pouch, which was subdivided into two halves by oedematous appendices epiploicae. The right half of Douglas's pouch was quite normal. The left half, besides this enlarged ovary, contained a small amount of blood-stained serum. The ovary presented exactly the appearance of a twisted ovary, or ovarian haematoma, clearly limited to the ovary, except for a shell of blood clot on the outer side.

The left Fallopian tube was entirely normal throughout its length, its abdominal ostium being patent and entirely free from any swelling or blood. On freeing the ovary a small amount of this blood clot detached itself from the outer wall of Douglas's pouch, but the ovary remained adherent to the back of the left broad ligament by the ovarian ligament. In fact, the ovary maintained its normal relation to the unaltered mesosalpinx and corresponding tube.

The ovary was resected and the ovarian ligament tied off. The right tube and ovary were both normal. The patient had specially requested the operator to leave both tubes if possible (!), and, the operation being done under spinal anaesthesia, she kept inquiring as to the condition found; for these reasons the left tube, being entirely normal, was allowed to remain. The patient made a good recovery from the operation.