mittee of the Royal Cancer Hospital (Free) for permission to publish details of those cases under their charge, and to Imperial Chemical Industries Ltd. (Dyestuffs Division) for supplies of triphenylchlor-ethylene and triphenylmethylethylene.

REFERENCES

- Allen, E. (1942). *Endocrinology*, **30**, 942.
 Badger, G. M., Elson, L. A., Haddow, A., Hewett, C. L., and Robinson, A. M. (1942). *Proc. roy. Soc., B*, **130**, 255.
 Bonser, G. M., and Robson, J. M. (1940). *J. Path. Bact.*, **51**, 9.
 Emmens, C. W. (1941). *J. Endocrinol.*, **2**, 444.
 Gardner, W. U. (1937). *Anat. Rec.*, **68**, 339.
 — (1939). *Arch. Pathol.*, **27**, 138.
 Haddow, A. (1935). *Nature*, **136**, 868.
 Hooker, C. W., Gardner, W. U., and Pfeiffer, C. A. (1940). *J. Amer. med. Ass.*, **115**, 443.
 Lacassagne, A. (1938). *C. r. Soc. Biol., Paris*, **129**, 641.
 Robson, J. M., and Bonser, G. M. (1938). *Nature*, **142**, 836.
 — Schönberg, A., and Fahim, H. A. (1938). *Ibid.*, **142**, 292.
 Shimkin, M. B., and Grady, H. G. (1940). *J. nat. Cancer Inst.*, **1**, 119.
 Watkinson, J. M., Delory, G. E., King, E. J., and Haddow, A. (1944). (In press.)

ADDENDUM.—CYTOLOGY OF SERIAL BIOPSIES FROM A CASE OF CARCINOMA OF THE BREAST TREATED WITH STILBOESTROL

BY

P. C. KOLLER, D.Sc., Ph.D.

The following is a summary of the cytology of serial biopsies from Case 11 (carcinoma of the breast, Table II, above) taken during a period of markedly favourable response (tumour regression) after treatment with stilboestrol.

Biopsy I. Before Treatment: Feb. 7, 1944

In respect of nuclear morphology two main cell types could be distinguished in the resting stage. One is characterized by a nucleus which contains several Feulgen-positive chromocentres (the potentially dividing cell). The other has a nucleus with one large or several small nucleoli (the differentiated cell). The proportion of potentially dividing cells in different regions of the biopsy material was found to vary between 12.5 and 27.3%. The division rate was determined in four cell populations (600 cells in each) taken from different regions of the specimen: in these the division rate was found to be 2.3, 5.2, 5.6, and 7.5%. Synchronous division of three or four tumour cells was frequently observed. Chromosome behaviour and spindle formation were normal. The highest incidence of degenerated cells was 2.5%.

Biopsy II. March 10, 1944 (Treatment started Feb. 9, 1944)

Nuclear and cytoplasmic changes were observed. Cells were found with one or more vacuoles in the nucleus, which latter gave a weakly positive Feulgen reaction. The frequency of such cells varied between 4 and 7.5% in different regions. Other abnormal cells were seen with deeply staining cytoplasm. The division rate was apparently lower in this biopsy specimen as compared with Biopsy I: the highest division rate found was 4.6%. In some dividing cells chromosomes were seen lying off the equatorial plate, and these were shorter and thicker than usual. While there appeared to be a decrease in division rate, a significant increase was observed in the proportion of degenerated cells. In one region it was found to be 12.5%. The morphology of the degenerating cells differs from that of cells degenerating as the result of x- or gamma-radiation.

Biopsy III. During Treatment: April 25, 1944

The number of cells showing nuclear and cytoplasmic alterations has further increased. Division rate was estimated to vary between 4.2 and 5.6%. Apart from chromosome lagging at anaphase in a few dividing cells, no other mitotic abnormalities were seen. The frequency of degenerating cells was about the same as in Biopsy II.

Biopsy IV. During Treatment: May 29, 1944

The biopsy material shows marked alterations. The division rate has increased and regions were encountered with 14.3% of cells in division. Synchronous division of several adjacent cells was very frequent. The chromosomes of cells in mitosis were thick and short, they failed to form an equatorial plate at metaphase, and were scattered in the cells. Cells with multipolar spindles were also encountered. The proportion of degenerating cells was found to vary between 7.3 and 16.3%. While the cellular abnormalities and the various stages of cell necrosis observed in the second and third biopsies indicated that cell degeneration is brought about by nuclear vacuolization, evidence was obtained from this fourth specimen that cell degeneration may also be due to a breakdown of the mitotic mechanism. The cytological evidence thus suggests that the primary effect of stilboestrol in this case may be localized to the nucleus of the tumour cell.

REACTIVE HYPERINSULINISM

CASE REPORT, WITH A DISCUSSION OF THE DIFFERENTIATION FROM ISLET TUMOUR

BY

F. T. G. PRUNTY, M.D., M.R.C.P.

(From the Department of Pathology, St. Thomas's Hospital Medical School)

The condition known in this country as "hypoglycaemia" (Cambridge, 1924) is described under the term of "hyperinsulinism" or "dysinsulinism" in America, according to the manifestations encountered—dysinsulinism implying an erratic under- and over-secretion of insulin (Harris, 1934). According to this terminology, hyperinsulinism would not include hypoglycaemia due to hepatic damage. The conditions here to be discussed are those in which the pancreatic activity is mainly at fault, and therefore exclude those due to other glandular dyscrasias and hepatic disease. It is the object of this communication to draw attention to a condition which may be termed "reactive hyperinsulinism," as opposed to hyperinsulinism due to overactivity of the pancreas as a result of tumour of the islets, malignant or benign. The term "reactive hyperinsulinism" is to be preferred to that of "functional hyperinsulinism" of Conn (1940), since the word "functional" has other less well defined associations.

Case Report

A professional man aged 56 complained of attacks consisting of a sinking feeling during the preceding five years and

of continuous tiredness for four years. He had had three attacks of arthritis, mainly affecting the larger joints, in the course of ten years. The family history was noteworthy (see genealogical chart). The patient's mother had died of diabetes mellitus, but the father was a healthy man, and lived to the age of 84. The eldest brother had renal glycosuria, and his eldest son has been found to have glycosuria. A second brother has also had glycosuria for many years, recently having had an operation for cataract. There are also a healthy brother and two sisters.

The patient stated that for the last four years he had had a continual feeling of tiredness accompanied by considerable difficulty in concentrating. During this period his work had greatly increased and his hours had been long, with short intervals for meals. For five years he had had acute attacks consisting of a sinking feeling in the epigastrium and intense weakness, followed by a cold sweat. He was forced to sit down during the attacks, but never fainted. After the attack had passed off his appetite was ravenous. The attacks always occurred in the afternoon or early evening, about three hours after the last meal. It appeared that his wife had been in the habit of "fortifying" him daily with a large tea consisting mainly of carbohydrate, including a great amount of honey or jam. Furthermore, the greater the quantity of such food consumed the greater the severity of the subsequent attack. The attacks passed off spontaneously with rest for about ten minutes or on taking carbohydrate. Their frequency was variable, six weeks sometimes elapsing between them, at other times two occurring in a week. In general their frequency and severity had increased with the passage of time. Occasionally exercise—e.g., gardening—brought on an attack, but only at the time of day already mentioned. Usually he could take considerable exercise and little food without getting symptoms. He had had no polydipsia or polyuria and no headache. He had lost one stone in weight in three years.

On examination the patient was not obese. There were no physical signs and no evidence suggestive of glandular or hepatic disease. Circumstances did not permit of special investigations of liver function, but the blood-sugar curve does not conform to the type seen in hepatic disease. There was no glycosuria.

Investigations of Blood Sugar

A month before he was seen reports on his blood sugar were: 8 p.m. (during an attack), 48 mg. per 100 ml.; 14 days later, at 8 a.m. (before breakfast), 71 mg. per 100 ml. At 8.30 a.m. a carbohydrate breakfast was taken; at 10 a.m. the blood sugar was 80 mg. and at 11 a.m. 65 mg. per 100 ml., the value at 12 noon being the same.

While in hospital the blood sugar was found to be 85 mg. per 100 ml. on two occasions before breakfast. Immediately after lunch the value was 87 mg. per 100 ml. The patient then took a rapid two-hour walk in hilly country, producing a moderate degree of fatigue, and at the end of this time the blood sugar was 97 mg. per 100 ml. The accompanying Graph shows the results obtained with

Continuous line represents glucose-tolerance test: 50 g. glucose orally after 12 hours' fast. Dotted line represents insulin tolerance: 6 units of insulin intravenously, fasting.

glucose-tolerance and insulin-sensitivity tests, the patient at the time receiving a full ward diet. There was no glycosuria during the glucose-tolerance test. Typical symptoms of one of the patient's hypoglycaemic attacks occurred when the blood sugar had fallen to 48 mg. per 100 ml., and persisted for one hour. The symptoms consisted of blurring of vision, the distant appearance of near objects, difficulty of finding words in speech or writing, inability to concentrate, coldness and clamminess, and a sinking feeling in the epigastrium. The insulin-tolerance test showed a slight increase of sensitivity to insulin. During this test there was another typical hypoglycaemic reaction when the blood sugar had fallen to 40 mg. per 100 ml. The symptoms disappeared without intervention, and there was no question of the patient's approaching a comatose state.

A diagnosis was made of reactive hyperinsulinism due to excessive insulin response resulting from the stimulus of administered carbohydrate. The patient was advised to cut down the consumption of carbohydrate at tea and replace this with protein or fat—e.g., in the form of an egg—if necessary. Having reduced the consumption of potato for lunch and dinner, together with the omission of jam or honey and curtailment of bread-and-butter and cake at tea, the patient has experienced no further attacks over a period of twelve months. This is in spite of the fact that his work has continued as before.

Discussion

The chief differential diagnosis in this case is from organic hyperinsulinism due to tumour of the pancreatic islets, which if present might be malignant. A search of the literature reveals that there is a lack of criteria for establishing this diagnosis (see especially Harris, 1936-7). However, there are apparently certain points that may be of diagnostic value. For instance, Conn (1940) considers that the presence of a low value for the fasting blood sugar before breakfast, the diet being normal, is a point strongly in favour of organic disease. It is well known that there is no relation between the blood-sugar level and the severity of a hypoglycaemic attack, although many of the cases do in fact have such attacks at this time. The second point for special examination is the shape of the glucose-tolerance curve. Conn and Conn (1941) consider that in "functional hyperinsulinism" the blood-sugar level shows a precipitate fall after a large amount of carbohydrate. Examination of the case reports of Finney and Finney (1928), Feinier *et al.*

(1935-6), and Fraser *et al.* (1938) show, for example, sugar-tolerance tests of the "plateau type." Whipple *et al.* (1941) in an analysis of 17 cases due to tumour found that the curve had a decided trend towards the diabetic type, this presumably being a manifestation of dysinsulinism. Their average figures showed a resting value below normal, with a subsequent persistent blood-sugar level of about 150 mg. per 100 ml. for a period of two to three hours. However, in their report two cases diverged from this type and gave low flat curves—a finding also observed by Conn and Conn (1941).

There are fewer reports available on the value of the insulin tolerance. Hartmann and Jaudon (1937) found an unusual sensitivity to insulin in newborn hypoglycaemic children whose mothers were diabetic, the hypoglycaemia being due to prolonged foetal islet stimulation. Furthermore, the findings of Fraser *et al.* (1938) in a case of islet tumour are so striking, and in such contrast to those in the present case, that they merit further study. Those authors found that, although the sensitivity to insulin was approximately normal, there was no tendency for the spontaneous recovery of the blood sugar within two hours. The injection of insulin in the fasting state was a reliable means of producing a severe hypoglycaemic reaction which only terminated on the administration of adrenaline or glucose. The finding of the adrenaline sensitivity is opposed to the views of Wilder *et al.* (1927)—who were supported by Allen (1941)—that resistance to adrenaline is a diagnostic point in favour of tumour. Cammidge and Poulton (1933), commenting on the case reported by Griffiths and de Wesselow (1933), pointed out that this test may be difficult to interpret.

A final point that may be of value in the differential diagnosis is the severity and irregularity of the symptoms. In general it appears that the more severe they are, without any tendency to spontaneous alleviation if glucose is not given, and the more irregular their onset, the more likely is organic disease. Conn (1940) and Harris (1936-7) both gave criteria indicating the necessity for laparotomy, the latter author suggesting that the inability to control the attacks by diet within a few weeks should be taken into account. Allen (1941) considered that the ability to control symptoms by means of a high-protein diet is indicative of but a mild degree of insulin excess. However, in view of the malignancy of carcinoma of the pancreatic islets and the inoperability consequent upon the occurrence of metastases, it is clearly essential to establish criteria for laparotomy requiring as short a period of observation as possible.

The following summarizes the features of the present case for contrast with the foregoing points:

1. Absence of low fasting blood sugar before breakfast and after exercise.
2. The marked post-prandial fall in blood sugar during the glucose-tolerance test, accompanied by the onset of symptoms of hypoglycaemia, together with an instability of the blood-sugar-regulating mechanism for a period of two hours. This finding is in close agreement with the history obtained of the most severe attacks occurring after the largest amounts of carbohydrate had been taken for tea.
3. A slight increase in the sensitivity to insulin, the occurrence of a typical hypoglycaemic attack after intravenous administration of insulin, and the spontaneous return of the blood-sugar level to normal limits with disappearance of symptoms.
4. The mildness and ease of control of the symptoms by means of reduction in carbohydrate intake.
5. The family history of diabetes and renal glycosuria.

In connexion with the last of the above points the case of MacPherson (1941) may help to throw some light on the aetiology of these attacks. His case showed a sugar-tolerance curve resembling that in the present case. In addition to this his patient had renal glycosuria—a condition recognized as occurring with, and possibly playing a part in the production of, "functional hyperinsulinism" (Conn, 1940). MacPherson suggested that two of the precipitating factors in his case were irregularity in meals and hard work. In the present case it appears from the history that there was some definite relation of the onset of symptoms to increasing severity of work and to increase of worry. Although humoral mechanisms are involved in the control of blood-sugar levels, Wauchope (1933) and Conn (1940) indicated that imbalance of the autonomic

nervous system may have a bearing on the production of "functional hyperinsulinism." Cori (1931) in an extensive review concluded that vagal impulses play a part in the finer regulation of the insulin production, and Cannon *et al.* (1924) have shown that nervous control of the adrenal medulla via the splanchnic nerves ensures a rapid adrenaline response.

It can well be appreciated how the continuance of abnormal stress in a susceptible individual may give rise to abnormality or instability in the control of these opposing impulses by the hypothalamic region. The terminal stages of the glucose-tolerance test is illustrative of this.

Summary

A case of "reactive hyperinsulinism," manifest by an excessive post-prandial fall of the blood-sugar level, is described. Points in the differential diagnosis from hyperinsulinism due to tumour of the pancreatic islets are discussed.

My thanks are due to Dr. H. Gardiner-Hill for his interest and permission to publish this case, and to Dr. C. Ede for assistance, especially with the history.

REFERENCES

- Allen, F. M. (1941). *J. clin. Endocrin.*, **1**, 595.
 Cammidge, P. J. (1924). *Lancet*, **2**, 1277.
 — and Poulton, E. P. (1933). *Ibid.*, **1**, 520.
 Cannon, W. B., McIver, M. A., and Bliss, S. W. (1924). *Amer. J. Physiol.*, **69**, 46.
 Conn, J. W. (1940). *J. Amer. med. Ass.*, **115**, 1669.
 — and Conn, E. S. (1941). *Arch. intern. Med.*, **68**, 876.
 Cori, C. F. (1931). *Physiol. Rev.*, **11**, 143.
 Feinier, L., Soltz, S. E., and Haun, P. (1935-6). *Bull. neurol. Inst. N.Y.*, **4**, 310.
 Finney, J. M. T., and Finney, J. M. T. jun. (1928). *Ann. Surg.*, **88**, 584.
 Fraser, R., MacLay, W. S., and Mann, S. A. (1938). *Quart. J. Med.*, n.s., **7**, 115.
 Griffiths, W. J., and de Wesselow, O. L. V. (1933). *Lancet*, **1**, 519.
 Harris, S. (1934). *Ann. intern. Med.*, **7**, 1084.
 — (1936-7). *Ibid.*, **10**, 514.
 Hartmann, A. F., and Jaudon, J. C. (1937). *J. Pediatr.*, **11**, 1.
 MacPherson, I. (1941). *Lancet*, **2**, 338.
 Wauchope, C. M. (1933). *Quart. J. Med.*, n.s., **2**, 117.
 Whipple, A. O., Bauman, L., and Hamlin, M. (1941). *Amer. J. med. Sci.*, **201**, 629.
 Wilder, R. M., Allan, F. N., Power, M. H., and Robertson, H. E. (1927). *J. Amer. med. Ass.*, **89**, 348.

the wall, particularly in the region of the base of the heart. On the posterior wall of the first part of the aorta there were three tears in the vessel—one just above the valve cusps, a second at the beginning of the arch, and a third midway between the first two. The upper tear was half an inch and the others each a quarter of an inch in length. All the tears were oblique to the transverse axis of the vessel, but were not parallel to one another. The aorta was not dilated, and the only abnormality was some early atheroma, which appeared as small patches hardly elevated from the general level of the intima and free from calcification and ulceration. The heart weighed 28 oz. (793.5 g.), but the hypertrophy was evenly distributed throughout all the chambers; there was no dilatation; all the valves were competent and their cusps healthy. The heart muscle was of excellent tone and free from all sign of disease, both on gross examination and microscopically, but the individual fibres were hypertrophied. The coronary vessels were capacious, and on the left one there were a few small patches of early atheroma, but quite insufficient to interfere with the blood supply. The right coronary artery was healthy.

In the peritoneal cavity there was a little slightly blood-stained serum. On the posterior abdominal wall some haemorrhage could be seen shining through the peritoneum in the region of the pancreas. The left half of the body and tail of that organ were haemorrhagic, but no fat necrosis was anywhere observed. The other structures in this cavity were uninjured. The only abdominal disease found was an early hydronephrosis of the left kidney, and, though the entire urinary tract was dissected, no satisfactory explanation was discovered for this abnormality. There was no sign of chronic nephritis or any significant abnormality in other structures.

Comment

Contusion and rupture of the pancreas are relatively rare injuries. Vance (1928) quotes Gall to the effect that they occur in 4.4% of all visceral injuries, and most other authors agree with this figure. The pancreas lies in such a position that it could only be injured, in the absence of an open wound, by some hard object coming forcibly in contact with the epigastrium and crushing the gland against the body of the second lumbar vertebra. It is possible, however, that the view of Boesch (1921) is correct—namely, that the gland may frequently be injured without the condition being recognized during life. This case tends to support that view, as the patient made no complaint referable to the abdomen and was neither rigid nor tender in that region. Furthermore, the fact that fat necrosis was not present indicates that the pancreas was contused and not ruptured, and it seems likely that the condition might have resolved and remained unrecognized had the patient not sustained other more serious injuries which proved fatal.

It is clear, then, that the handle of the plough struck him a deep, powerful blow in the epigastrium. There were no injuries of any kind to the thoracic wall in the shape either of subcutaneous or muscular bruises or of fractures of the ribs or sternum, and it is almost inconceivable that a relatively sharp object like a plough handle could strike that region with enough force to produce the internal injuries described without leaving some mark on the soft tissues or the thoracic cage. It follows, therefore, that the damage to the aorta must have been produced indirectly by transmission of the force through the diaphragm. This thesis is supported by the fact that the anterior mediastinal tissues were contused in the absence of more superficial damage, the bleeding being no doubt due to the rupture of small vessels consequent upon the sudden dislocation of the pericardial sac. The heart is suspended in the pericardium by the aorta and superior vena cava, but is given basal fixation by the inferior vena cava and the structures of the lung roots. Its potential mobility is strictly limited in all directions, and it seems unlikely that rupture of the aorta alone could occur, due purely to displacement of the heart and traction on the vessels, by a force applied to the diaphragmatic surface of the heart from the abdomen.

Ruptures of the aorta are relatively frequent, but when they occur it is nearly always as a result of crush injuries, in which the osseous structures of the thoracic wall may or may not be fractured, depending largely on their elasticity. The tear is usually transverse, and is located just above the aortic valve cusps. It is due to a force thrusting the heart downwards and tearing it from its points of suspension. In these cases, as a rule, the tear is complete and the outcome immediately fatal. Partial ruptures—which become complete later—are more uncommon, and may arise in the absence of trauma if the

TRAUMATIC RUPTURE OF THE AORTA

BY

GILBERT FORBES, B.Sc., M.D., F.R.F.P.S., F.R.C.S.Ed.

*Lecturer in Forensic Medicine at the University of Sheffield;
Police Surgeon to the City of Sheffield*

The following case of rupture of the aorta due to a blow on the epigastrium presents clinical and pathological features interesting enough to be placed on record.

Clinical History

The patient was a farmer, aged 37, who was described by his relatives as being in robust health. He had no relevant medical history, but his family doctor had observed that he had a very high threshold for pain. On Jan. 20, 1944, he went ploughing at 1 p.m., and at 3 p.m. left the field to call at a neighbouring farmhouse for a drink of water. He there complained that shortly before that time his plough had struck a stone, and the plough handle, rearing up, had hit him somewhere in the region of the praecordium. The blow had shaken him badly, and from statements he made to various people it appears that immediately after the accident he felt very ill, owing presumably to shock; but he soon recovered, continued to plough till about 4 p.m., and made no further reference to the accident. He returned home at 5 p.m., when he complained of pain in the left side of the chest radiating through to his back. It was observed that he was cold, clammy, and pale, and he had to go to bed. He was examined later the same evening by his doctor, who found that his temperature was 100° F. and that friction could be heard in the cardiac area. The patient made no reference to the accident, and his doctor was in complete ignorance of the incident till after the man died. He passed a restless night because of chest pain, and vomited three times. Next morning the pyrexia had disappeared, and though he still complained of pain he did not seem to be particularly ill. His condition remained much the same till late afternoon, when he died suddenly within a few minutes of sitting up in bed to drink a cup of tea.

Post-mortem Findings

The deceased was well built and there was no external evidence of injury. No bones were broken. There was an area of bruising in the areolar tissue of the anterior mediastinum, and the bruising extended up the right side of the neck as far as the level of the larynx in the line of the great vessels and sterno-mastoid muscle. The pericardial sac was distended with blood, which had infiltrated