SPONTANEOUS HYPOGLYCAEMIA.

By

IAN M. ANDERSON,

M.B., Ch.B. (Glasgow), M.R.C.P. (London),
Major R.A.M.C.

University Typewriting Office,
Lloyds Bank Chambers,
Carfax, Oxford.

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

INTRODUCTION.

Cowley in 1788 was the first person to associate the pancreas with sugar metabolism when he described a case of diabetes in which pancreatic calculi were found. The belief then gradually arose that the pancreas might be concerned in the causation of diabetes. The pathology of the pancreas was first described by Langerhans who mentioned the islands now named after him. Further details of the intimate knowledge of the islands were added by Languesse (1893) who described the finding of granules in the islet cells and also the capillary network. In view of his findings he suggested the possibility of an internal secretion.

In 1894 Hansemann found pancreatic fibrosis and atrophy in 40 cases of diabetes. Diamare (1899) confirmed the findings of Languesse. Lane was the first to demonstrate that there were two different types of cells in the islands and Bensley improved the staining technique and described a third kind of cell which was non-granular. Bloom (1931) described three kinds of granular cells in man.

From the physiological point of view the first important paper following that of Cowley was that of Claude Bernard in 1849. In this he discusses hyperglycaemia and glycosuria.

Arnozan and Vaillard (1884) showed that no diabetes ensued after ligation of the pancreatic duct. The proof of Cowley's theory was furnished in 1890 by von Mering and Minkowski who showed that ablation of the pancreas in dogs, rabbits and pigeons produced diabetes. Shäfer (1895) pointed out that ablation of the pancreas caused death of the animal, while a total pancreatic fistula did not. Ssobolew and Schulz (1900) ligated the pancreatic ducts and found that in those animals that survived there was atrophy of the organ as a whole but the islands remained preserved and the animals were not diabetic. Homans and Allan (1913-1915) in experimental diabetes showed changes in the pancreas confined to the beta cells.

In 1922 Banting and Best found an antidiabetic principle in degenerated pancreatic tissue in which the islet tissue was predominant. The discovery of this substance which was named insulin and their observations together with those of Macleod and Noble and Campbell and Fletcher that overdoses of hypodermic insulin produced hypoglycaemia with an associated symptomatology gave rise to further investigations on hypoglycaemia.

Claude Bernard in 1849 demonstrated hypoglycaemia in experimental animals. Von Mering (1884) and Minkowski (1892) produced hypoglycaemia in experimental animals by the use of phlorizin. Bierry and Malloizel (1908) found that the removal of the

suprarenal glands of dogs produced hypoglycaemia. Porges (1910) was the first to observe hypoglycaemia in man, reporting three cases of Addison's disease with low blood sugars. Frank and Isaac (1911) found that damage to the liver by phosphorus produced hypoglycaemia. Cushing (1912) published a case of pituitary tumour with a low blood sugar. Fischler (1916) first described hypoglycaemic shock under the title of glycoprivative intoxication. This appeared in dogs with Eck fistula rendered diabetic by phlorizin. Joslin (1922) published three cases of diabetes where hypoglycaemia had occurred on low diets.

One year after the discovery of insulin Seale Harris suggested that there might be a clinical entity of hyperinsulinism as opposed to hypoinsulinism. In 1924 he reported three cases.

PHYSIOLOGY.

When food is ingested the carbohydrate portion is converted into the monosaccharides galactose, glucose and fructose. They are rapidly absorbed from the small intestine. Galactose and fructose are converted in the liver into glucose. Some of the absorbed glucose is stored in the liver as liver glycogen, some is oxidised, and some is converted into muscle glycogen.

In order to maintain a stable blood sugar level various endrocrine glands come into play. In the event of there being a hypoglycaemic state in the blood there is sympathetic stimulation and there is a discharge of adrenalin from the suprarenal gland which breaks down glycogen in the liver into glucose, converts muscle glycogen into lactic acid, and retards absorption of sugar by the peripheral tissues. The pituitary is said to raise the blood sugar by stimulating the formation of glucose in the liver (Houssay). It is also said to have an anti-insulin factor (Young).

If, on the other hand, there is hyperglycaemia insulin is mobilised and acts by depositing the portal blood sugar in the liver as liver glycogen by increasing carbohydrate combustion, and by deposition of muscle glycogen. If insulin is injected into normal animals there is frequently a decrease in liver glycogen due to the excess insulin having a greater effect on the peripheral tissues which oxidise and store glycogen faster and thus tend to decrease tissue glucose concentration. Diffusion inwards is faster, blood sugar falls and, if hypoglycaemia occurs, adrenalin is mobilised. Only liver glycogen can directly support blood sugar concentration.

As far as the thyroid is concerned thyroxin has no immediate effect on blood sugar but if large doses are given for some time liver glycogen is easily mobilised leading to some hyperglycaemia

and glycosuria, but if the thyroxin is continued further there is a loss of liver and muscle glycogen and hypoglycaemia may be produced.

The causes of hypoglycaemia may then be classified as follows:-

(1) Excess of insulin

a. Therapeutic injections
b. Pancreatic islet tumours, hyperplasia or hyperfunction
c. Functional hyperinsulinism.

(2) Diminution in insulin-resistant factors

a. Adrenal disease (Addison's disease)
b. Pituitary disease (Simmonds disease; pituitary tumours.)
c. Thyroid disease (myxoedema).

(3) Diminution of glycogen reserves

a. Starvation
b. Liver disease
c. Renal diabetes
d. Lactation
e. Muscle wasting or excessive muscular exercise.

(4) Disturbance of C.N.S. control of blood sugar.

ISLET CELL TUMOURS.

The first case of adenoma of the pancreas described was by Nicholls in 1903. The tumour was found at autopsy. Thereafter tumours were described by Herxheimer (1905), Morse (1908), Cecil (1911), and Warren (1926), who reviewed the literature and found twenty cases.

The first operation for islet cell tumour was described by Wilder, Allan, Power and Robertson in 1927. This was a carcinoma of the islet cells with metastases in the liver and the patient died soon after the operation. The case was however of great interest as the metastases in the liver contained insulin. The first successful removal of an adenoma of the pancreas was performed by Roscoe Graham in 1929. This case was followed up and a ten year interval without symptoms reported in 1939.

There have now been over 100 cases of proven adenomata of islet cells published in the literature, but of these only 4 have been from this country (Barnard, Cairns and Tanner, Fraser, Maclay and Mann, Rudd and Walton) and in only 2 has there been an operation with successful result. The following two cases appear to have been cured by operation, though, of course, the follow up is very short.

Case 1. M.H. 19 years. Tin Worker.

Admitted to hospital on 26.2.41 complaining of fainting attacks.

Prior to August 1940 she was perfectly well, except for the fact that she had never menstruated. Her mental condition was quite normal, and she used to like reading and going to the pictures. Her mother says that she was a lively and jolly girl, and

that she enjoyed a joke. Last August, however, while standing at the street door one evening about 8 p.m., she suddenly became unconscious, although she did not fall down. She was not giddy and had no blurring of vision. She was helped indoors and sat on a chair for about 15 minutes. She was not incontinent and did not bite her tongue. For a few minutes afterwards she felt a bit light-headed, but was able to carry on as though nothing had happened.

After that she had no further attacks for about two months. She then began to be frequently affected, the attacks usually occurring as she was having her meal at home in the evening about 6 p.m. She was always able to finish her sentence, although she could not carry on eating. Her aunt, with whom she was living, would take her knife and fork from her hand and sit her back in her chair, or assist her to an arm chair where she would sit until she recovered. She would be unconscious for one, three, or even five hours. When she came round she was able to carry on at once. The attacks became more frequent and she had as many as five in a week.

Six weeks before admission she began to be affected while at work, and was usually attacked between 12.30 and 1 p.m. She would just stop working and would be assisted to the air raid shelter; after a few minutes she was able to go back to her work.

During this time her mental condition underwent a change. She became dull and unemotional, and in the words of her mother, "she didn't seem to care about anything any more".

During this time her diet was as follows:-

7.30 a.m. cup of tea with 1½ teaspoonfuls of sugar.

9.00 a.m. slice of bread and butter.

1.00 p.m. lunch e.g. sandwiches, egg and chips, etc.

5.30 p.m. supper, the principal meal of the day.

On February 2nd she went to a hospital out patient department; was diagnosed as a case of petit mal and from there admitted to Chase Farm Hospital.

On admission examination showed her to be rather plump with a greasy skin. Her c.v.s., chest and c.n.s. revealed nothing abnormal. Her external genitalia were normal but she had a small infantile antiflexed uterus.

In hospital she had no attacks until 4.3.41. At 12 noon on that day she was noted to be rather drowsy; she then lay on her side with her arms crossed and her legs drawn up. The thumbs periodically twitched. Her eyes were closed, and she did not resist having them opened, and her pupils were well dilated. The tone of her legs was increased, and they periodically moved across the bed. After about ten minutes, she resisted all attempts to open her eyes, and became rather violent if there was

any attempt made to move her, saying that she would tell her mother. The plantar responses were still flexor. She was not incontinent and did not bite her tongue or foam at the mouth. At 12.45 p.m. she recovered, remembering nothing about the attack. A blood sugar estimation showed a reading of 43 mg%. (At this time she was on a normal hospital diet with breakfast (sausage, egg, bacon, etc.) at 8 a.m., lunch (meat, potato, vegetable, pudding) at 12 noon, tea and bread and butter at 3 o'clock and some milk and biscuits at about 7 p.m.).

During all this time apart from the attack she was apathetic and profoundly unemotional, seeming to take little interest in her surroundings. It was noticed that she was more drowsy about mid-day and her blood sugar taken at mid-day on the 10th March was 0.040%.

On 12.3.41 blood sugars were done throughout the day, the patient being on an ordinary diet.

8 a.m.	0.054%
10 a.m.	0.067%
12 noon	0.038%
2 p.m.	0.100%
4 p.m.	0.110%
6 p.m.	0.061%
8 p.m.	0.056%
10 p.m.	0.039%
12 midnight	0.048%
2 a.m.	0.053%
4 a.m.	0.041%
6 a.m.	0.050%
8 a.m.	0.045%

At this time she was free from major attacks, but on March 17th at 2.30 a.m. she started wailing, at first softly and then louder. It was impossible to rouse her. She lay with her muscles completely relaxed, very hot, and perspiring profusely; the wailing continued until 3.50 a.m., when it gradually died away, and at 4 a.m. she asked for a bedpan in a very blurred voice. She used this and in 10 minutes was sleeping normally. The next day she appeared rather strange, sitting in bed staring in front of her without apparently taking any interest in her surroundings. At 12.15 p.m. she tried to get her food from her plate, but failed, her right hand shaking and her fork going round and round her plate. After about 15 minutes she was able to feed herself and appeared quite normal for the rest of the day. On 20.3.41 fasting blood sugars were done

10 a.m.	0.050%
12 noon	0.020%
2 p.m.	0.050%
4 p.m.	0.050%
6 p.m.	0.067%
8 p.m.	0.066%
10 p.m.	0.062%
12 midnight	0.071%
2 a.m.	0.066%
4 a.m.	0.062%
6 a.m.	0.083%
8 a.m.	0.091%
10 a.m.	0.066%

She had no further major attacks.

On March 23rd the following estimation was performed

10 a.m. Blood sugar 0.071%
11 a.m. Blood sugar 0.071%
11.30 a.m. 1/100 adrenalin given
12 noon Blood sugar 0.066%

On March 29th the blood sugar on an ordinary diet was estimated at 12 noon and was 0.062%.

The fasting blood sugar curve was repeated on April 4th.

8 a.m.	.. .. ..	0.089%
10 a.m.	.. .. ..	0.037%
12 noon	.. .. ..	0.050%
2 p.m.	.. .. ..	0.068%
4 p.m.	.. .. ..	0.091%
6 p.m.	.. .. ..	0.091%
8 p.m.	.. .. ..	0.102%
10 p.m.	.. .. ..	0.068%
3 a.m.	.. .. ..	0.086%
8 a.m.	.. .. ..	0.086%
10 a.m.	.. .. ..	0.082% *

* At this point she showed marked hypoglycaemic symptoms.

She continued to show the same daily variation in mood, being most affected about noon and 6 p.m., but had no further major attacks throughout her stay in hospital.

On the 15th April a glucose tolerance test was performed

10 a.m.	Fasting level	0.074%
	100 grams glucose given	
10.30 a.m.	.. ..	0.133%
11 a.m.	.. ..	0.154%
11.30 a.m.	.. ..	0.154%
12 noon	.. ..	0.133%
12.30 p.m.	.. ..	0.133%
1.00 p.m.	.. ..	0.111%
1.30 p.m.	.. ..	0.111%
2.00 p.m.	.. ..	0.087%

She was then put on a 2100 calorie diet and kept on this for one week and daily blood sugars were done.

8 a.m.		0.087%	0.059%	-	0.069%	0.053%	0.080%
10 a.m.	0.057%	0.058%	0.040%	0.067%	0.056%	0.037%	0.053%
12 noon	0.035%	0.030%	0.027%	*0.053%	0.037%	0.031%	
2 p.m.	0.083%	0.067%	0.100%	0.080%	0.095%	0.071%	
4 p.m.	0.077%	0.071%	0.064%	0.077%	0.105%	0.059%	
6 p.m.	0.083%	0.040%	0.071%	0.091%	0.077%	0.077%	
12 mid-night	0.083%	0.062%			0.083%	0.090%	

*At this point she was very drowsy and was unable to keep awake. Afterwards she did not remember having the specimen taken or having had her lunch, having a vague idea that she had been at home with her aunt.

The 12 mid-day blood sugar was repeated on several occasions, on May 6th, 7th, 8th and 10th respectively, 0.052%, 0.043%, 0.042%, 0.045%.

On May 15th a further glucose tolerance test was performed. The dose of glucose was 1.75 grams per kilo body weight (107 grams).

8 a.m.	Fasting level	0.095% - glucose given
9 a.m.	Blood Sugar	0.182% (Chart 1)
10 a.m.	" "	0.182%
11 a.m.	" "	0.143%
12 noon	" "	0.125%
1 p.m.	" "	0.071%
2 p.m.	" "	0.050%

It was now decided to perform a laparotomy and on 20.5.41 she was operated upon by Mr. Galloway.

A 4" incision was made from the mid-line to the umbilicus. Infantile subcutaneous fat 1½" thick was cut through before the

peritoneum was opened. Manual exploration revealed a hypoplastic uterus about the size of the index figure. The kidneys and liver were normal, the caecum large with a healthy appendix. There was no enlargement of the glands in the porta hepatis.

The spleen was normal, but a hard nob was felt just in front of the hilum. Further exploration showed this to be a tumour lying in the tail of the pancreas. Another similar mass was felt an inch nearer to the head of the pancreas, and a small cyst, the size of a small pea, was removed from the mid point of the lower border of the pancreas by finger dissection.

The tumour, ½" in diameter was removed, together with the last inch of the tail and the second lump, which turned out to be a haematoma 1 × 1½". The oozing area was packed by 3" gauze bandage, the end of which was brought out through a half inch incision just lateral to the stria semilunaris and 2" above the umbilicus. The peritoneum was closed with continuous cat gut suture, the rectus sheath (linea alba) similarly sutured, and the skin edges approximated with interrupted s.w.g. and Michel clips.

The pathology of the tumour was reported upon by Dr. J.G. Greenfield as follows:-

"A small cystic tumour was present near the tail of the pancreas and two firmer rounded masses, fairly smooth on the cut surface were present in the body, both coming to the surface but not protuding above it. These measured about 12.5 × 10 mms. and

12 x 7 mms. in cross section. Histologically the cystic tumour contains masses of small cubical or spheroidal epithelial cells inside a firm capsule of collagen. The cells are massed irregularly together in trabeculae which have clear cut almost straight outer margins and which are richly penetrated by fine thin walled blood vessels. The epithelial cells are to some extent arranged on the walls of these blood vessels as on a basement membrane, but the arrangement is very irregular. They have small, almost circular, nuclei with abundant dots of chromatin and a fairly large, finely granular, neutrophil cell body. Very occasional mitoses are seen in this tumour which contains practically no collagen except the wall of the blood vessels.

In the other tumours the cells are similar, but rather larger. They are arranged in fairly thin trabeculae, rarely more than three or four cells thick, between thick septa of vascularised collagen. In many places these give the tumour a papilliform structure. Several isolated binucleated cells of considerably larger size are seen among the trabeculae. These tend to stain rather more with haematoxylin and with aniline blue than the majority of the cells."

[Plate 1.]

The blood sugar was done on May 20th at 5.30 p.m. and found to be 0.236%. On May 21st at 10.30 a.m. the blood sugar was 0.220%.

On June 24th a fasting blood sugar estimation was made.

10 a.m.	0.077%
11 a.m.	0.083%
12 noon	0.087%
1 p.m.	0.090%
2 p.m.	0.087%
3 p.m.	0.077%
4 p.m.	0.067%
5 p.m.	0.089%
6 p.m.	0.100%

On June 28th a glucose tolerance test was done.

11.55 a.m. fasting	0.100%
107 grams glucose	
12.40 p.m.	0.154%
1.55 p.m.	0.087%
2.55 p.m.	0.087%
3.55 p.m.	0.100%

When she left the hospital she felt very well and since then she has lost weight and her figure has become less plump generally. She is much brighter. As yet, however, she has not menstruated.

A sugar tolerance was done on the 23rd November 1941. (Dose 107 grams.)

Fasting	0.097%
1 hour	0.143%
2 hours	0.143%
3 hours	0.105%
4 hours	0.095%
5 hours	0.105%
6 hours	0.100%

She has been seen periodically since then and her blood sugars have always been normal and she feels very well. She was last seen on 8th May, 1942.

Case 2. E.S., aged 54. Park Attendant.

Admitted on 30.4.41 in a comatose condition.

History (compiled from story subsequently elicited from patient and from the statement of his wife).

Quite well until January 1940 when he came home from work one afternoon at 4.30 p.m., and had an evening meal at 5.30 p.m. (2 eggs, bread and butter and tea. This was an unusually light meal for him in the evening as normally he had a hot dinner, but that night his wife was out and he had to get his own supper). After his meal he sat down by the fire and felt perfectly well the whole evening although the room seemed rather hot. At about 9.30 p.m. he remembers putting his feet up on the couch but then he remembers no more. When his wife came home at about 10.30 p.m. she tried without success to wake him up, and having failed called in his doctor. He was put to bed and stayed in his bed at home for two days, still unconscious before he was transferred to a cottage hospital. About two days after admission he regained consciousness wondering why he had arrived there. He felt all right when he recovered but within about one day his left shoulder and upper arm became stiff and painful and he was unable to raise it above a right angle.

He was discharged home after two days (owing to a shortage of beds) still with the painful shoulder but otherwise feeling fairly well. The doctor at the hospital told him he was short

of sugar in his body and because of this after returning home he tried to get extra sugar from the food office, but without success. His family, however, endeavoured to give him as much of their rations as possible. While in the hospital the following estimations were made:- Blood sugar 0.042%. Blood urea 0.066%. He was diagnosed as status epilepticus.

After discharge he was in bed at home for about one week and then gradually got about again although his legs were rather weak for some time. When he felt strong enough he was sent back to work again. He kept well until April 12th, 1941.

On that day he had his usual light breakfast at 5.30 a.m. and at 9.30 a.m. (just before his usual lunch time at 10 a.m.) while he was standing talking he suddenly became unconscious and fell down. He was unconscious for about two minutes after which a friend helped him up, and gave him tea and two aspirins and he then felt perfectly well.

On 28.4.41 he went to a new job starting as early in the morning but with the lunch hour from 1 p.m. to 2 p.m. instead of 12 noon to 1 p.m. as he had previously been used to.

On 30.4.41 at some time between 1 and 2 o'clock before he had had his lunch he suddenly became unconscious. He does not remember the events leading up to this. The work that morning had been quite light - mowing grass - and he had had bread and

jam at 10 o'clock as he always did.

His employer fetched a taxi and brought him to Chase Farm Hospital at 3.30 p.m. In the receiving room he was in a semi-comatose condition, being able to answer questions persistently asked, but only in a few words. The coma gradually deepened and when he was seen in the ward later on he could make no answer to questions nor obey instructions.

On examination at this time he was flushed in the face with some slight froth on his lips, his eyes closed, legs curled up and hands covering his face. When touched or moved he resisted and tended to curl up. Pulse was full, slow and regular - 64. T. 98. Resp. 22 and laboured. B.P. 150/95. C.N.S. Corneal reflexes absent. Pupils reacted to light and on accommodation and were equal and regular. Fundi normal.

Eye movements: The eyes wandered about when lids finally separated but movements seemed full and conjugate. There was considerable neck rigidity and a strongly positive bilateral Kernig sign. Abdominal reflexes were absent. Knee jerks present and equal. Ankle jerks present and equal. Plantars both flexor. Other systems were not examined at that time and as he was incontinent the urine was not tested that night. Lumbar puncture was performed and 4 ccs. of crystal clear fluid at pressure of 110 mm. was removed. Examination of fluid

reported as follows:- 4 ccs. clear colourless fluid. Cells 1 per cmm. Culture no growth. Total protein 0.06%. Glucose 0.022%. Pandy very weakly positive (these two facts received later with subsequent report). After admission he was vomiting and could not be made to take any fluids, so an attempt was made to feed him by tube, but he still vomited back his feeds of milk.

1.5.41. His condition remained unchanged through the night and the following day; further attempts were made to feed him and he managed to keep a little fluid down. A further lumbar puncture was done and clear fluid at 90 mm. pressure reported on as follows: 4 ccs. of clear colourless fluid. Cells 6 per cmm. Total protein 0.05%. Pandy negative. Glucose 0.013%.

White cell count was normal and W.R. was negative.

A blood sugar estimation was made and found to be 0.035% when the report was returned at about 6.30 p.m. 25 grams of glucose in normal saline (25% glucose) were given intravenously with an immediate return to complete consciousness and feeling of normal health. The blood sugar at 7 p.m. was 0.154%. He was given 7 ounces of milk at 7 p.m. and at 9 p.m. and spent a quiet night.

2.5.41. Shortly before 10 a.m. he was getting drowsy and unresponsive to questions and by 9.50 a.m. was unconscious. Blood sugar at this time was 0.035% and at 10 a.m. 25 grams of

glucose in 50 ccs. normal saline was given intravenously with immediate recovery of patient. His diet was fixed at 2100 calories.

3.5.41. At 2.20 a.m. he was seen as he was then violent and noisy. A blood sugar was done and found to be 0.037%. 30 grams of glucose given by mouth produced immediate improvement in his condition. During the day he was difficult, being argumentative about his food, and refusing to have anything to do with his wife - apparently blaming her for his presence in hospital. She said he was very unlike his normal self - being morose whereas usually he was very good natured.

4.5.41. After a good night he was quite well and taking his food without argument.

4.5.41 and 6.5.41 he was still quite well with no untoward symptoms.

7.5.41. A straight x-ray of the gall bladder was taken today - nothing abnormal was detected. He was complaining of a quite severe headache whenever he sat up or coughed. As he was going to have a cholecystogram on the following day he was given his usual supper at 7 p.m. and nothing afterwards; in addition the fats were excluded from his supper and only replaced by a small amount of green food. Ipecol was given at 8 p.m. At 8.45 p.m. he seemed unnaturally drowsy and uncommunicative and could only be roused with difficulty. Blood sugar at 8.45 p.m.

was 0.035%. He was given 20 grams of glucose in 40 ccs. of normal saline intravenously and recovered immediately and after a while went to sleep normally.

8.5.41. Cholecystogram done - gall bladder did not visualise; to be repeated. Blood sugar at 12.30 p.m. after fasting all morning for x-ray 0.041%.

9.5.41. Cholecystogram repeated at 14 and 16 hours. Report 'negative shadow in gall bladder. No x-ray evidence of gall stones. X-rays suggest pathological gall bladder. Cholecystitis'.

10.5.41. Patient felt very well although still had frontal headache when he sat up.

12.5.41. Dextrose tolerance test performed (dosage of dextrose 1.75 grams per kilo).

9 a.m.	Fasting blood sugar	0.071%	(125 grams glucose
10 a.m.	Blood sugar	0.154%	given)
11 a.m.	" "	0.181%	
12 noon	" "	0.166%	Chart I.
1 p.m.	" "	0.143%	
2 p.m.	" "	0.074%	
3 p.m.	" "	0.061%	
4 p.m.	" "	0.040%	
5 p.m.	" "	0.050%	

After this he was given a meal and progressed without incident through the night and following days.

14.5.41. Patient quite well and subjected to several blood tests.

Bromsulphalein test. 5 minutes -50%
30 minutes -0%
60 minutes -0%

Van den Bergh Reaction. Direct and indirect negative.

1. 138 ccs. Hippuric Acid = 4.046 grams for 4 hrs.
2. 204 ccs. Benzoic Acid = 2.72 grams for 4 hrs.
3. 186 ccs. Percentage of
4. 44 ccs. normal = 90.7%

Blood count. R.B.C. 5,5000,000
Hb. 108%
W.B.C. 7,600 Differential normal.

15.5.41.

Galactose Test

Time	Blood sugar		Urine	
8 a.m.	0.067%	40 grams galactose	No	reduction
9 a.m.	0.056%	given	"	"
10 a.m.	0.047%		"	"
11 a.m.	0.035%		"	"
12 noon	0.050%		"	"
1 p.m.	0.066%		"	"
2 p.m.	0.050%		"	"

10 a.m. and 11 a.m. specimens combined = 184 ccs.
Total galactose 0.36 grams.

16.5.41. Urine - no excess of urobilinogen. Diastatic index 10. Laparotomy at 2.15 p.m. by Mr. Galloway.

Right paramedian incision. Gall bladder greatly enlarged. Adherent to duodenum (adhesions freed) no gall stones. A fleshy tumour was palpated in the head of the pancreas about

1 cm. in diameter and lying just anterior to the superior mesenteric and splenic veins and to the left of the duodenum. This tumour was dissected out and removed. Cholceystostomy was performed and bile drained by tube passed out of stab wound to the right of main incision. Main incision closed without drainage.

Blood sugar one hour after operation 0.154%

Apart from post-operative collapse of the lung which responded well to treatment post-operative progress satisfactory. Patient had no further hypoglycaemic attacks. He has been very well and all blood sugars done since the operation have been within normal limits. He was last seen on 8.5.42.

Dr. J.G. Greenfield reported on the tumour as follows:- 'Sections show the tumour to consist of an irregularly arranged mass of medium sized cells with small rounded darkly staining nuclei. These cells are everywhere interspersed by fine blood vessels. There are a few rather fine strands of collagen running through the tumour from the larger vessels. The cells have a neutrophil finely granular cytoplasm, and closely resemble the cells of the islets of Langerhans.'

[Plate 2.]

SYMPTOMATOLOGY.

The best description of the symptomatology of hypoglycaemia is that of J. Wilder, quoted by G. Wauchope from whose paper the following description is taken.

"The vegetative nervous system gives rise to symptoms such as sweating or cold, flushes, pallor, dimness of vision, flickering before the eyes, increase of pulse rate and blood pressure; sometimes an increased flow of saliva; occasional strangury; rarely paraesthesia. The central nervous system is widely affected, and symptoms may be produced by disturbance at various levels.

General symptoms are headache and fatigue. The bulbopontine system gives rise to disorders of speech such as stammering, difficulty in forming words and slow articulation; ocular disturbance such as double vision, nystagmus, inequality of pupils; rarely deafness. The cortico-spinal group comprises paralyses, Babinski's sign, aphasia, agraphia, perseveration, apraxia, motor irritability, inco-ordination, trismus, twitchings and convulsions which may be tonic or clonic, localised or general, and may resemble an attack of epilepsy; occasionally disturbances of smell and taste or paraesthesia of the tongue; rarely incontinence of urine or faeces. To the strio-thalamic system belong

tremor, choreiform movements, fibrillary twitchings, grimacing, gesticulation, torsion, loud speech, rigor of muscles atonia and katatonia.

Psychic disturbances are frequent and may be slight, like anxiety, depression, negativism, irritability, querulousness; or bizarre, for instance excitability, desire to sing, shout or dance, maniacal behaviour; or they may result in dullness and confusion of the understanding and lead to disorientation, slowness of thought, inclination to loiter and dawdle, to give random answers, compulsions, impulsive actions, wandering, fughes, homicide, suicide, amnesia, drowsiness, stupor, coma."

Symptoms in cases of adenoma.

In reviewing 70 proven cases of pancreatic adenoma the commoner symptoms in order of frequency were:- mental confusion, unconsciousness, convulsive seizures, sweating, twitching of legs or arms or both, weakness, dizziness, fatigue, headache, diplopia, faintness, stupor, narcolepsy, ataxia, irritability, hemiplegia, trembling, cyanosis, blurring of vision, abdominal pain, drowsiness, intolerance for exercise, staring expression, pupillary dilatation, vomiting, hunger, pallor, coldness, aphasia, collapse, emotionalism, bladder trouble, aura, scotomata, movements of head, yawning, parkinsonism, nausea, joint pains, breathlessness.

In a large number of cases (55%) there was a definite relationship to food, that is to say the symptoms were either brought on through lack of food or were relieved by the administration of food or glucose.

It is noteworthy that in a large number of cases (72%) mental symptoms predominated. Such symptoms (Kepler and Moersch) as apathy, irritability, restlessness, fatigue, anxiety, incorrigibility, negativism, automatic behaviour, somnambulism, confusion, excitement, disorientation, 'drunken behaviour', fugue states, unconsciousness, delirium, mania, stupor, or coma.

Speech may be distorted; there may be garrulity, dysarthria or even aphasia. Emotional instability ranges from all forms of anxiousness to querulousness and violence. The character of the thinking becomes confused and sluggish. The patient may be delirious. There is loss of memory for events and the patient does not remember the attack. The mental symptoms may be associated with neurological disorders of varying types, as motor retardation, or convulsive attacks of tonic or clonic type.

In reviewing the symptomatology of the condition it is interesting to note that the average time between the onset of symptoms and the first blood sugar is three years. The condition is remarkable in that the patient may be very well between the attacks and this feature is well shown in the second of the two cases presented.

The age incidence varies from 11 years to 62 years with an average of 37.

There is an equal distribution of sex.

The similarity between the symptoms of pancreatic adenoma and epilepsy has been stressed by various authors, notably Nielsen and Eggleston, and it has been suggested that every case of epilepsy should have blood sugar studies. The first of the two cases presented favours this suggestion.

As the ultimate diagnosis depends on blood sugar studies they are naturally of great importance.

Blood Sugar Investigations.

In order to appreciate the abnormal it would be better to consider the normal first.

In man the normal blood sugar level varies according to the time of day and the state of nutrition. Variations in the method of analysis and the source of blood make reported figures not strictly comparable. For example titration methods such as Hagedorn and Jensen give lower readings than colorimetric such as Benedict's and that of Folin and Wu. In addition venous blood readings are lower than capillary. Cavette and Seljeskog compared venous and capillary blood sugars during glucose tolerance tests in 21 normal individuals, who had fasted for 12 to 14 hours and were then given 50 grams of glucose.

	Mean fasting	½ hour	1 hour	2 hours	3 hours
Cutaneous blood sugars	0.095	0.165	0.137	0.097	0.079
Venous blood sugars	0.092	0.151	0.122	0.085	0.078
Difference between cutaneous and venous	0.028	0.014	0.015	0.012	0.015

Hartmann and Jaudon quote Somogyi and confirm from their own records that the difference between 'apparent' and 'true' values in whole blood varies between 23 and 31 mg%, averaging 27, while for the serum the difference is much less, between 6 and 10 mg, averaging 8. Holt and Greisheimer and Campbell, Osgood and Hoskins find the difference between apparent and true values varies between 15 and 20 mgs.

Tungstate acid filtrates give apparent dextrose values, regularly including reducing substances in addition to 'true' dextrose. Joslin (1928) published a table of normal values by seven different methods; the lowest (Bertrand) was 0.070-0.110 and the highest 0.096-0.125 (Lewis and Benedict). He found that readings taken before breakfast in normal individuals were most frequently 0.100%, varying from 0.080 to 0.110%.

Sigwald considered the fasting level to be about 0.100% and the lower limit of the normal 0.090%.

Sippe and Bostock quote Phillips as citing 8 authorities who agree that any reading below 0.090 is hypoglycaemic.

Martin and Hellmuth consider it accepted from the numerous reports in the literature that the normal fasting blood sugar is generally about 100 mg% but that it may vary from 80 to 110 mg.

Pollock and Boshes consider that the concensus of opinion is that the uppermost limit of normal is 120 mg%, but that there is no agreement about the lower limit; Lennox, O'Connor and Bellinger have placed it at 80 mg, Nielsen at 75 mg, Tyson, Otis and Joyce at 80 mg. They say that marked variations occur in supposedly normal subjects to levels below 75 mg. Watson quotes Gray's figures as being widely accepted and considering that the normal fasting level lies between 80 and 120 mg.

Hart and Risa studied 21,000 fasting blood sugars which were all taken 9 a.m. on a fasting stomach and about 16 hours after the last meal. The method was Folin and Wu.

2,371 (11%) had a fasting level below 80 mg. Of these 1620 or 7% fell between 70 and 79. There were 493 or 2% between 60 and 69 mg and 166 or 0.8% from 50 to 59 mg. 74 or 0.35% were from 40-49 mg and 12 or 0.05% between 30 and 39. 6 were found to be below 30.

There were 19 cases with conditions generally thought to produce a low blood sugar.

As a result of these figures the writer considered that routine fasting blood sugars below 80 mg were a common finding. That it was possible that normal individuals may have occasional low blood sugar values with an otherwise normal blood sugar. He concluded "Either spontaneous hypoglycaemia is not a common condition or routine fasting blood sugars are not reliable guides to its occurrence".

From these various figures one may conclude that the normal fasting blood sugar level varies from patient to patient but that the range usually lies between 80 and 120 mg while an occasional level of 60 to 70 mg may occur.

It has been stressed by many authors, particularly Whipple that to diagnose a pancreatic adenoma one must find:

(1) Attacks of nervous or psychic or gastro-intestinal disorder coming on during the fasting state or after exertion.

(2) A blood sugar reading below 50 mg%.

(3) Relief of symptoms immediately after ingestion of glucose.

Where one can get the patient in an attack as in the two cases reported and find a low blood sugar and where as in the second case the response to glucose is immediate the diagnosis is made easier, but it is not always possible to see the patients at these times and Whipple has stressed the fact that "in the

intervals between attacks there are no symptoms except occasional persisting mental retardation or deterioration and the blood sugar is often normal".

It is necessary then, if the symptomatology is suggestive, and one cannot get the patient in an attack, that other diagnostic procedures be adopted. One of the most helpful of these is the Glucose Tolerance Test.

Glucose Tolerance Test.

Gray (1923) considered that the normal blood sugar values were 80-120 mg and after the ingestion of glucose it should not rise above 180 mg (average rise 140 mg) and that at three hours the blood sugar should be equal to or below the fasting level.

Mosenthal considered the curve as normal where the rise was between 120 and 160 mg and which dropped to 120 mg at the end of the second hour. Myers and McKean in an extensive review of the literature considered that venous blood should show a peak below 170 and fall to the fasting level within two hours and in capillary blood should show a peak below 200 and fall below 120 in $2\frac{1}{2}$ hours.

Martin and Hellmuth accept as standard a rise from a control level of about 100 to a peak of 140-180 mg and a fall during the period of the next two or three hours to the fasting level. In the descent (they say) it frequently drops below the control level.

Pollock and Boshes consider that the consensus of opinion is that a normal curve is one that starts at a fasting level below 120 mg, rises to a peak not above 160 mg and returns to the fasting level in less than two hours. Watson in a series of 83 normal young adults showed a fasting level of 90 mg, a rise in half an hour to 134 mg and a fall in two hours to the fasting level.

In estimating the value of a glucose tolerance test various factors must be taken into consideration.

First the age: Children and adolescents tend to have a lower fasting level and a flatter curve.

Weight: Short and Johnston, in a study of 541 cases who appeared healthy and were from Life Insurance records, found that age alone had only a slight effect on the incidence of impaired glucose tolerance, but that there was an unmistakable correlation between the degree of overweight and the incidence of impaired glucose tolerance irrespective of age. A combination of old age and overweight accentuated the incidence of diminished glucose tolerance i.e. the two factors combined have a more decided influence than either alone. They consider it probable that the duration of overweight determines the incidence of impaired tolerance.

Diet: The patient should be on a standard diet as it has been shown by numerous observers that a high carbohydrate diet will

give an increased glucose tolerance and vice versa. (Himsworth, Conn.)

Influence of gastric emptying and intestinal absorption - Hale White and Payne passed a duodenal tube in a healthy young adult on two different occasions, injected 50 grams of glucose in 500 ccs. of water at a uniform rate of 5 ccs. per minute on one day and as rapidly as possible without causing discomfort on another. They took capillary specimens on each occasion at five minute intervals for two hours and found that there was hyperglycaemia as long as sugar was being introduced into the duodenum, but that the blood sugar fell rapidly after the injection was finished. Myers and McKean confirmed this finding in a case of pyloric stenosis on which they did blood sugars before and after operation. (Chart 3.)

From the various authorities quoted a normal sugar tolerance is one that starts from a fasting level of from 80 to 120 and rises in the course of $\frac{1}{2}$ to 1 hour to not above 180 and should fall to below 120 in the case of capillary blood and to its fasting level with venous blood by $2\frac{1}{2}$ hours.

As various authorities have suggested that 6 hour blood sugar tolerance curves should be done in cases of adenoma and only one reference could be found to normal six hour curves a series of 34 six hour blood sugar curves were done on patients, all of whom were surgical cases, the majority fractures. The

type of curve is somewhat flatter than normal but this is in keeping with their diet which contained a relatively high carbohydrate content (about 300 grams).

Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
0.091	0.143	0.127	0.100	0.099	0.091	0.090

(Charts 1 and 2 and Table 1)

As these patients were all resting in bed and as far as possible under basal conditions a further control was done on 10 medical students who fasted from 6 o'clock the previous night and then came up to the laboratory to have their blood sugars done at 10 a.m. on the next morning. As would be expected their curves were flatter still, but conformed with the usual type of curve.

Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
0.085	0.103	0.080	0.080	0.080	0.083	0.083

(Table 2)

All these control cases were on a war time diet and as suggested above this probably accounts for the flat curve. It will be seen that in these normal cases the six hour curve varies very little from the three hour. The estimations were all done by the Folin and Wu method, but the first series were capillary, while the second were venous.

The value of the glucose tolerance curve in the diagnosis of hyperinsulinism has been stressed by various authors, notably Weil, Feiner, Fraser Maclay and Mann, West and Kahn, and Meyer,

Amtman and Perlman. These authors in reviewing the dextrose tolerance curve in pancreatic adenoma all stress the plateau type of curve and Meyer, Amtman, and Perlman show a chart of 44 cases of proven adenoma with this type of curve. (Chart 5) For the purposes of this paper 38 cases have been taken out from the literature and they conform with those of Meyer, Amtman and Perlman, but with this difference, that, where the curves have been prolonged to 6 hours or more, there is a terminal drop to the fasting level or below (Chart 2). This terminal drop had been noted by previous authors, particularly Harris and Weil who said that glucose tolerance tests may bring out a low sugar level, in spite of normal fasting level, especially if the test is carried on for several hours. They suggested that examination of the blood sugar at ½ hour and then hourly for 6 hours should be a standard technique.

The two cases reported both show this plateau type of curve with terminal drop (Chart 1).

The reason given for this type of curve is that either the liver contains sufficient or excess glycogen preventing further deposition (the first case in the literature where islet cell tumour removed - that of Wilder & Co. - had excess of glycogen in the liver when it was examined at autopsy) or else excess insulin inhibits hepatic glycogenesis, though increasing deposition of muscle and tissue glycogen. With reference to this latter

suggestion Bridge showed that when insulin is added in very large doses to a continuous intravenous infusion of glucose the blood sugar rises steadily, the dextrose being given at a rate that would sustain a more or less constant blood sugar level without the added insulin. Accompanying this was a marked interference with the deposition of glycogen in the livers of the insulin treated animals. Livers of rabbits receiving glucose for 6 hours without added insulin contained an average of 9.5% glycogen at the end of the experiment, while the livers from those receiving 4 units of insulin per gram of glucose, at the same rate of injection, only contained 3.7% glycogen. Thus an excess of insulin inhibits hepatic glycogenesis, though increasing deposition of muscle glycogen.

The response to intravenous glucose infusion has also been used as an aid to diagnosis in pancreatic adenoma. Duncan, Hayward and Flick showed that there was an abnormally great ability to remove dextrose from the blood in a case of adenoma, in spite of an increasing rate of dextrose administration by venoclysis from 28 grams per hour at the end of five hours to 36 grams at seven hours to 44 grams at nine hours to 52 grams per hour, yet no increase in blood sugar values was found until after 10 hours of continuous dextrose administration. After operation there was a normal blood sugar level response when dextrose in 15% solution was given continuously at the rate of 28 grams of dextrose per hour.

In a much earlier paper Allan concluded that assuming the average basal heat production of a man is one calory per kilo per hour, if more than 0.25 grams of sugar for each kilo body weight were required where hypoglycaemia was present then the hypoglycaemia must be due to hyperinsulinism.

Insulin Tolerance Test.

Various papers on insulin tolerance tests have been written since the discovery of insulin in 1922 by Banting and Best. Briefly the procedure of the test is to give a dose of insulin intravenously (from 2-10 units) and to observe the reaction of the blood sugar and of the patient in the next two hours. In normal subjects there is a specific curve, the blood sugar usually dropping to its lowest point in about 20 minutes and returning to its original level within the period of two hours. Many papers have been written on this subject but two may be quoted, namely that of Bodansky and Simpson and that of Himsworth. Bodansky and Simpson found that after the intravenous injection of 2 units of insulin the minimum blood sugar is reached at about 18 minutes after the injection. Recovery from the hypoglycaemia begins immediately after the minimum sugar value has been reached. They found that it was complete in lean subjects within 75 minutes but in overweight subjects the rate of recovery was slower. Himsworth found that with an intravenous dosage of 5 units the depression on a high fat diet was much less than on a high

carbohydrate diet. Both curves were at their lowest at from 20-30 minutes and then started to rise again.

In order to confirm the various reports a series of 14 normal patients were investigated. 10 units of insulin were administered intravenously. The curve corresponded with those previously regarded as normal.

F	10'	20'	30'	50'	1.10'	1.30'	1.50'
97	74	51	51	59	72	84	87

(Table 3, Chart 4)

Insulin tolerance curves in spontaneous hypoglycaemia have been reported by various authors. Jones (1935) reported a case of spontaneous hypoglycaemia where the blood sugar fell slowly and had risen very little in two hours. He does not state, however, whether the insulin was given subcutaneously or intravenously.

Hartmann and Jaudon reported three cases of spontaneous hypoglycaemia where, after five units of insulin intravenously, the blood sugar progressively fell (Chart 4).

Fraser Maclay and Mann reported a case of adenoma of the pancreas where five units of insulin were given intravenously and the blood sugar showed no tendency to rise after two hours. After operation the blood sugar rose after 30'.

Greenlee Lloyd and Bruecken stated that if an adenoma of the pancreas were present there was no tendency for the blood sugar to reach normal limits after two hours.

Meyer Amtman and Perlman reported a case of adenoma of the pancreas where after 10 units of insulin the blood sugar was still falling in three hours.

It will thus be seen that the insulin tolerance test may be of some help in the diagnosis of hyperinsulinism but it is not specific for pancreatic adenoma as quite a number of the cases where the insulin tolerance has not risen have either had no operation or no tumour has been found at operation.

A further test to help in the diagnosis of hyperinsulinism was suggested by Liu, Loucks, Chou and Chen who reported a case of pancreatic adenoma where they found increased and faster combustion of carbohydrate before operation as shown by estimation of the basal metabolic rate and the respiratory quotient. This test has been used by Conn who, in reporting cases of hypoglycaemia due to hepatic dysfunction, found in them a normal oxidation of dextrose and not an excessive oxidation as in hyperinsulinism.

HYPERINSULINISM.

Since Seale Harris first suggested that a condition the opposite to diabetes existed there have been many cases described where the symptoms and blood sugar estimations suggested an increase in the amount of insulin produced by the pancreas.

Apart from the more advanced condition of islet cell tumour hyperplasia and hyperfunction of the islet cells have been described.

Hartmann and Jaudon showed that there might be considerable hypertrophy of the islet cells in infants born of diabetic mothers who showed clinical signs of hypoglycaemia.

Campbell Graham and Robinson described a case with typical symptoms suggestive of pancreatic adenoma where the pancreas did not contain an adenoma but where there were large numbers of islets in the pancreas which were made up of very large cells with deeply staining nuclei. A similar type of case was reported by Phillips.

Roscoe Graham in a discussion on a paper read by Le Grand Guerry and George McCutchen mentions a case where no tumour was found but in which the part of pancreas removed contained 8,000 units of insulin per kilo.

It is not possible to distinguish the more severe cases of hyperinsulinism due to pancreatic hyperplasia or hyperfunction from those of tumour, but in the less severe cases it has been suggested that the type of dextrose tolerance curve may be of value. Thus it is suggested by Malamud and Grosh that the response to dextrose gives an indication of the severity of the condition. In the milder cases the tolerance test curve is of the flat type suggesting an overworking insulin-liver mechanism, while in the severe forms in which there is a high plateau curve the insulin-liver mechanism is functioning inco-ordinately.

This attempt to separate the various types of hyperinsulinism in terms of severity seems more logical than to try to arbitrarily divide hyperinsulinism into pancreatic islet tumours and functional hyperinsulinism as has been done by many authors.

Four cases are now shown which appear to grade from mild to severe hyperinsulinism. In three the pancreas was explored but no tumour found. They all appear to have benefited from resection, but in the second case the symptoms have not completely disappeared, and one wonders whether a pancreatic adenoma is still present. In the fourth only the tail was removed and probably a subtotal resection should have been done.

Case 3. K.J., aged 23. Housewife.

History: Was quite well until Christmas 1938 when she went to a party at her works. She had had nothing to eat before she went there and drank several cocktails on an empty stomach. Later on she fell and knocked her head, did not feel the blow, did not lose consciousness and went on dancing. She went to her mother-in-law's home where she felt sick and vomited. She was called at 9.30 the next morning but did not get up. At 11.30 a.m. she was found on the bedroom floor huddled up, clasping her knees with her arms; she resisted movement, seemed stiff; her teeth were clenched. She was put to bed where she lay quite still in a stuporous condition. When spoken to she opened her eyes, obeyed

commands reluctantly. There was no headache, vomiting or incontinence. Though weak she was able to move her arms and legs. There was no noticeable tremor and no complaint of pain. She was sent to hospital where she remained for four days. On admission she resented examination in the receiving room but when left alone she lay quiet as if asleep. She recognised people and spoke drowsily. At times she tried to crawl out of bed and she had screaming attacks.

When she awoke on the third day in hospital her mouth felt very dry and there was a nasty taste in it. She was weak but had no headache. She was discharged the next day, the diagnosis being hysteria.

Between December 1938 and September 1940 she appeared to be quite well. She was married in June 1940. While out for a walk on September 7th, 1940, with a relation, she said that she was feeling very tired, yawned a lot, seemed dazed and detached from her surroundings. She appeared disorientated as to time and place. She did not recognise her husband's name when mentioned in conversation to her. She was taken home and told to go to bed. A few minutes later she came out into the garden saying, 'going there' pointing to the fence at the bottom of the garden. She could not say where there was but kept repeating 'going there'. Later that day she was taken round to her mother's house. She walked like a drunken person, was very weak and again

obeyed commands protestingly. She was put to bed and lay in a stuporous condition: she could be aroused but had to be lifted into a sitting position and fed with a feeding cup as she could hardly hold a teaspoon. After persuasion she would eat what would be given to her. She did not vomit, had no nausea or headache or complaint of visual defect. She could not concentrate and seemed unable to think, but got one word or sentence into her head and kept reiterating it. When her small cousin was allowed to see her she beckoned him towards her bed saying 'hullo love' but did not know his name and seemed to look through him with a glassy stare. There was no incontinence or complete loss of consciousness. Twenty-four hours later she seemed normal again except for a feeling of weakness.

In December 1940 she had a similar attack which lasted four days in the course of which she was admitted to another hospital. She made a similar recovery but on discharge she was told that she was highly strung, but there was no evidence of organic disease.

Early in April 1940 she had a similar attack which was not, however, witnessed. Her fifth ~~and last~~ attack occurred in May 1941 and lasted four days. She seemed more rational than on previous occasions but much weaker for a few days afterwards. Otherwise no fresh observations were made.

Summary of attacks.

They come at any time during the day. They start with a feeling of tiredness - she yawns a lot; there is a feeling of numbness and coldness of the extremities. She feels cold generally and looks pale. When put to bed she lies in a stuporous condition; she can be aroused; protests to commands but with gentle persuasion obeys them. There is no incontinence, no headache, giddiness, visual disturbance or noises in the ears. She only vomited during her last attack when given an egg beaten up in milk. She has to be fed owing to weakness; she is unable to hold a spoon. She cannot concentrate; has marked nominal aphasia. Generally she lies quietly and when roused speaks only in short sentences which are reiterated. The attacks last from 1 to 4 days and are ended by her waking in the morning feeling better. Later, when well, she only remembers her weakness during the attack, but on one occasion she remembers wanting a bed cover but was unable to express her wish.

Past History. During the past few years her sister has noticed that her personality has changed. Whereas she used to be an intelligent and bright individual in the past few years she has lost interest in things and has become difficult and querulous.

Family History. One sister had pulmonary tuberculosis successfully treated by artificial pneumothorax.

Menstrual History. Periods have never been regular and at times they are as much as two to three months apart.

She was admitted to Chase Farm Hospital on 24th May, 1941. Physical examination showed her to be slightly built and thin. Her blood pressure was 90/60. Apart from this nothing abnormal was noted.

Investigations in hospital. On 26th May, 1941, a sugar tolerance test was done, 50 grams of glucose being given.

Fasting	1 hour	2 hours
0.095	0.087	0.095

Lumbar puncture on 26.5.41 showed normal fluid.

Blood count on the same day showed 5,600,000 red cells and Hb. 110%. White cell count normal.

On June 4th, 1941, a further glucose tolerance test was done. This time the dose of glucose was 72 grams (1.75 gram per kilo body weight).

Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
0.119	0.154	0.105	0.077	0.069	0.080	0.080

Two days later sugar estimations were carried out on the patient throughout the 24 hours. The results were as follows:-

8 a.m.	0.083	8 p.m.	0.087
10 a.m.	0.077	10 p.m.	0.090
12 noon	0.105	12 midnight	0.083
2 p.m.	0.100	2 a.m.	0.071
4 p.m.	0.125	4 a.m.	0.074
6 p.m.	0.090	6 a.m.	0.071

An x-ray of the skull showed no abnormality.

The patient was sent home on 8th June, 1941, to be recalled later. She was readmitted on 18th August, 1941, and the following investigations were made:-

27.8.41. Blood count. Red cells. 5,400,000. Hb. 110%. White count normal.

28.8.41. Cholecystogram showed no evidence of defect of liver function.

29.8.41. Further glucose tolerance test. Dose of glucose 72 grams.

Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
0.077	0.105	0.095	0.087	0.067	0.083	0.083

30.8.41. An insulin tolerance test was done, 10 units of insulin being administered subcutaneously.

Fasting	½ hour	1 hour	1½ hours	2 hours	2½ hours
0.067	0.064	0.056	0.059	0.047	0.053

6.9.41. Glucose tolerance test. Dose of glucose 72 grams.

Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
0.062	0.054	0.045	0.050	0.057	0.057	0.077

The patient was advised to have an operation. Throughout her time in hospital she had been a very difficult and temperamental patient. She declined operation and took her own discharge on 7th September, 1941.

On discharge she was advised that if she had any further attacks she should have a blood sugar estimation made. As she was living on the south coast her doctor was advised to this effect.

After her discharge from hospital she was well for 6 weeks but then, one morning, she overslept until 12 noon and felt rather drowsy and dazed for the rest of the day. After this she was quite well until one week before admission when one Saturday afternoon she felt that her arms were weak and heavy and although she could use her hands she was very clumsy. She had very little remembrance of the next two days, waking as usual on the following Tuesday feeling well, but vomited all that day. On the Wednesday on awaking she felt perfectly well.

According to her husband the attack had been similar to the previous ones except that she had been extremely argumentative and very difficult to manage. Unfortunately no blood sugar was taken during this attack. She herself had only very slight recollection of these facts.

On her own request she was readmitted on 12th December 1941. On further investigation the following results were obtained:-

13.12.41. Glucose tolerance test. Dose of glucose 70 grams.

Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	7 hours
0.095	0.124	0.115	0.087	0.064	0.070	0.074

15.12.41. Insulin tolerance test. 10 units insulin intravenously.

Fasting	10'	20'	30'	50'	1 hr.10'	1 hr.30'	1 hr.50'
0.111	0.080	0.041	0.035	0.038	0.047	0.041	0.047

17.12.41. Two hourly blood sugars were done, the patient fasting throughout.

10 a.m.	0.090	10 p.m.	0.100
12 noon	0.090	12 m.n.	0.080
2 p.m.	0.095		
4 p.m.	0.090	4 a.m.	0.100
6 p.m.	0.083	6 a.m.	0.100
8 p.m.	0.080	8 a.m.	0.100

20.12.41. Glucose tolerance test. Dose 72 grams glucose.

Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
0.125	0.182	-	0.095	0.090	0.083	0.087

Operation was decided upon and on 23.12.41 Mr. Galloway operated.

No tumour was found at the operation but the whole of the body and tail of the pancreas were removed. In order to facilitate this a splenectomy was performed at the same time.

Post-operative progress was uneventful.

Four days after the operation the patient's mental outlook was vastly changed and by 12 days after the operation she was bright, co-operative, happy and looking forward to life.

7.1.42. Glucose tolerance test. Dose of glucose 72 grams.

Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
0.090	0.133	0.125	0.090	0.100	0.100	0.111

She was discharged on 8.1.42.

Since her discharge she has felt very much better. She says that she has had one slight attack which was brought on as the

result of her missing a meal and standing in a queue for a cinema. The attack was quickly aborted by her taking some food.

Case 4. P.H., aged 25. Housewife.

Four years before admission, one month after the beginning of her first pregnancy, she developed attacks of breathlessness on exertion, palpitations, trembling and blurring of vision. These attacks lasted about five to ten minutes at a time and at the end of them she felt weak and exhausted for about an hour. At the same time she began to have nausea and was sometimes sick several times a day. She felt tired, weak and unwell and although at times she felt hungry she never ate very much. All the above symptoms were worse in the mornings.

Breathlessness and palpitations.

After a fairly short preliminary period of feeling very cold and tired, and sometimes an accompanying misty, rather darkened vision with a feeling of everything being far away, she would for five to ten minutes become very breathless (even at rest) and would feel her heart pumping very quickly and forcibly and would feel rather trembly and weak at the knees. When this subsided she would still feel cold and tired for some time afterwards. The whole attack lasted about half an hour and when it was finished she would often go into a deep sleep waking up about

half an hour later. These attacks would only come on when she was up and about and were often precipitated by exertion. They were not apparently related to meals.

Giddiness.

While in the street or in the house and feeling quite well she would suddenly find things going round and round, everything would momentarily go black and she would stumble but never fall. This would pass off as quickly again and she would go on feeling well again. The whole attack would last half a minute at the most.

Fainting Attacks.

After feeling very weak and sick for a while she would then see coloured lights in straight, apparently parallel, lines, then she would see a blackness and would sink down unconscious. She thinks that these attacks lasted from five to ten minutes at the end of which time she would wake up feeling weak and shaky.

After two months of these symptoms she was forced to go to bed and remained there until two months after her confinement when she was allowed up occasionally. She was in every way better in bed, although her condition fluctuated greatly from day to day; some days she would feel fairly well and would eat all day without being sick. During her stay in bed most of her attacks occurred after some exertion or other.

She had an easy confinement and felt well soon after. Her attacks decreased but she was still breathless on exertion.

She was kept in bed for eight weeks because of a severe post-partum haemorrhage and then she was allowed up and soon afterwards she went to work.

At the same time as she went back to work she had some financial difficulties and after three months she had a 'nervous breakdown'. This consisted of nightmares, inability to sleep at night, and the development of a stammer and facial tic and she often was very depressed and says that she had suicidal thoughts. When upset she went into hysterical tempers. She again felt ill and was breathless on exertion. Her doctor sent her to a "nerve specialist" who gave her a tonic. At the same time as the tonic was given her financial troubles improved, she changed her occupation for a more congenial one and she felt much better.

She remained fairly well for the next two years but had attacks of breathlessness and palpitations occasionally as before. The attacks occurred mostly in the evenings and were not severe. They would occur about two or three times a week for a month or two and then would ease off for some months. She found that she tired easily and had to have a lot of time off work. She often felt faint and dizzy in the mornings. She had 'hungry feelings' and wanted to eat a little often.

Six months before admission the attacks became more frequent and more severe.

The breathlessness and palpitations became more severe. Almost every evening she had attacks of jerking of the head and neck accompanied by twitching and trembling all over the body which was quite uncontrollable. She never felt nervous when these attacks were taking place. They lasted from five to ten minutes.

In other attacks she had a very severe headache which was throbbing in character and felt as though something was pressing on top of her head. Starting as an ordinary headache before the attack it appeared first over the right temple (constantly) and spread backwards to include both sides of the head though always right more than left. The headache would pass off as soon as the breathlessness and palpitations stopped, merging again into an ordinary headache.

At other times she had epigastric pain which spread upwards and appeared to press on her chest and make breathing difficult and in association with this there was a tight feeling in the throat. These symptoms would only last for the duration of the attacks, that is to say, about five to ten minutes. She has a cramp like pain in the thighs during the breathlessness which proceeds as the attack progresses to a feeling of numbness which creeps up from the toes to the tops of the thighs, round her mouth and from her fingers up her arm. This numbness is sometimes accompanied by pins and needles and lasts a variable time from five minutes to half an hour. When the attack is over she

experiences pain 'as the blood rushes back through her limbs', unless she goes to sleep. The twitching and shaking of the attack is accompanied by nausea but she is not sick until after the attack. She often goes into a deep sleep afterwards and once she saw black and became unconscious, and not rousable for about ten minutes.

For about half to one hour before an attack she often feels hungry and just before an attack she feels tired and cold and weak at the knees.

Backache became apparent six months before admission and has gradually become worse. It was greatly eased by lying in bed but has become more apparent lately, even while lying in bed.

Lately in between attacks she has jumped and raised both hands and held them trembling when the bed is jerked or anything surprises her, but she says that she does not feel in the least frightened.

In the week before her first admission to hospital she often saw double and particularly in the mornings: this diplopia was not related to her attacks but was much more lasting and would become more apparent if she studied something carefully. In this week also she had an ache in her throat which became worse when she entered hospital and she was told that she had an enlarged thyroid. The swelling went down in three or four days.

She was admitted to hospital and there she was found to have hypoglycaemia, having blood sugars as low as 0.033% in her attacks. It was decided, however, not to operate on her and on her discharge from this hospital she was referred to Chase Farm Hospital, where she was admitted on 24.10.41.

On admission when first seen by the receiving room officer the patient was having an attack which consisted of generalised twitching of the whole body. She was quite coherent and explained that she had just had an attack at the nearby railway station and had been given a dose of glucose by a medical student who happened to be on the platform. The glucose was hers as she had been advised to carry some with her. A blood sugar estimation was immediately made and was 0.170%.

When seen in the ward she looked pale and ill. Appeared nervous. Was of small stature and rather plump. All examinations were negative. B.P. 120/80. At the end of the examination the bed was accidently knocked and she immediately cried out, her pupils dilated giving her a staring expression, she had a tachycardia over 120 and her neck pulsated. The attack was soon over. During her first few days in hospital she had several of these attacks, some without stimulus, others when the foot of the bed was purposely knocked.

Description of one of these attacks is as follows:- she appeared to be clutching at her breast, but whether this was due to pain or to muscular twitching was not evident. Periodically

she rubbed her right thigh with her hand. She lay with her head turned to the left and being constantly jerked forwards. There appeared to be pulsation in the neck, but this was not synchronous with the pulse, either at the wrist or by auscultation and seemed more probably due to rhythmic contractions of the sterno-mastoid. During all this time she had hyperpnoea. The pulse was increased (about 120). The attack commenced with her saying that she had a feeling that an attack was coming on. About four minutes later she began to breathe rapidly and quietly. After a minute of this the right arm began to shake followed almost at once by the left. Then the head began to shake. She then threw back her pillows and lay flat. Her arms were drawn up and her hands lay on her chest. The shaking was sufficiently violent to shake the bed and lasted about eight minutes. Then it ceased fairly rapidly and she lay back breathing easily. Occasionally she had a little spasm of shivering. She complained of nausea and vomited up a little fluid.

Special Investigations.

27.10.41. Blood count. Red blood cells 5,300,000. Hb. 98%. White count 10,000.

28.10.41. Serum calcium 11.2 mg%. Plasma phosphorus (inorganic) 2.8 mg%. Plasma proteins 6.7%.

28.10.41. No excess of urobilinogen in the urine.

12.11.41. Cholecystogram; good visualisation of the gall-bladder.

The blood sugar was estimated four hourly during the day and four hourly during the night for five days, the second half of the period the blood sugars being taken at the intervening hours.

28.10.41 Blood sugar at:

8	a.m.	0.082%
10	a.m.	0.098%
11	a.m.	0.095% *
12	noon	0.083%
2	p.m.	0.069%
4	p.m.	0.090%
6	p.m.	0.087%
9	p.m.	0.100%

* after an attack

29.10.41 Blood sugar at:

12	midnight	0.111%
4	a.m.	0.080%
8	a.m.	0.076%
10	a.m.	0.083%
12	noon	0.105%
2	p.m.	0.090%
4	p.m.	0.095% *
6	p.m.	0.093%
9	p.m.	0.154% **

* mild attack
** severe attack

30.10.41 Blood sugars at:

12	mid-night	0.125%
4	a.m.	-
8	a.m.	0.100%
10	a.m.	0.087% *
12	noon	0.133%
2	p.m.	0.100%
4	p.m.	0.105%
6	p.m.	0.083%
9	p.m.	0.085%
12	mid-night	0.061%

31.10.41 Blood sugars at:

4	a.m.	0.090%
8	a.m.	0.062%
1	p.m.	0.125%
3	p.m.	0.090%
5	p.m.	0.108%
7	p.m.	0.114%
10	p.m.	0.108%

1.11.41 Blood sugars at:

5	a.m.	0.095%
9	a.m.	0.102%
11	a.m.	0.125%
1	p.m.	0.114%
3	p.m.	0.111% *
5	p.m.	0.111%

* mild attack

Glucose tolerance tests. (1.75 grams glucose per kilo body weight)

Date	Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
26.10.41	0.077	0.166	0.182	0.125	0.105	0.111	0.080
10.11.41	0.105	0.143	0.143	0.121	0.105	0.110	0.081

Insulin tolerance test.

3.11.41	Fasting	0.100%
	10 units insulin intravenously	
	10 minutes	0.100%
	20 minutes	0.081%
	30 minutes	0.079%
	50 minutes	0.077%
	1 hr. 10'	0.074%
	1 hr. 30'	0.064%
	1 hr. 50'	0.069%

After 20 minutes she had an attack exactly like the one described in detail previously. This was not severe and passed off in 20 minutes. One hour after the injection she sweated profusely and then became drowsy.

At this period the patient had been feeling much better and decided to go home for the week end. Her husband when he brought her back said that the day after she got home she insisted on cleaning up the kitchen, felt very tired and had an attack in which she complained of headache and dizziness and had to lie down. He said the attack was similar to the earlier ones.

When she returned a 24 hour fasting blood sugar test was done.

17.11.41 Blood sugar at:		18.11.41 Blood sugar at:	
2 p.m.	0.105%	4 a.m.	0.090%
4 p.m.	0.080%	6 a.m.	0.087%
6 p.m.	0.077%	8 a.m.	0.069%
8 p.m.	0.077%	10 a.m.	0.071% *
10 p.m.	0.040%	12 noon	0.062% **
12 m.n.	0.105%		

** Immediately after the last specimen was taken the accidental knocking over of a chair provoked an attack.

* Fully developed attack.

9.11.41. Atropine tolerance test.

Fasting	0.085%
1/100 gr. atropine hypo.	
After 15 minutes	0.083%
" 30 "	0.083%
" 45 "	0.079%
" 1 hour	0.077%
" 1 hour 15'	0.079%
" 1 hour 30'	0.078%
" 1 hour 45'	0.077%
" 2 hours	0.083%

Patient was operated upon on 12.11.41 by Mr. Galloway.

No pancreatic tumour was found but the pancreas from ¾" beyond the head of the pancreas was removed. In the process of removal the splenic vessels were torn and it was necessary to ligate the splenic artery and vein.

For the next month after the operation she had some trouble in the shape of tachycardia, fever and attacks of vomiting which was considered to be due to necrosis of the spleen.

By the 12th December she was feeling much better and by the 16th had greatly improved. The pyrexia had finally settled and

she was generally much more co-operative and less excitable and worried. She had had only one attack since her operation (on 24th November) and that was brought about by an accidental kicking of the bed.

On the 21st December she was discharged home, the wound having healed and with few symptoms.

Recently she has developed a pancreatic fistula, which is however slight. When last seen (10.4.42) she was very much better; did not have her previous frightened look and had no tremor. She was, however, fatter and said that she got tired very easily.

Professor Turnbull reported on the portion of pancreas removed and could find no abnormality.

Case 5. H.B., aged 26. Army Private.

History.

Two years before admission while at work, mixing cement by spade, he had a fainting attack in which he felt hot and perspired and then had a sick giddy feeling, with pain in the stomach, lost consciousness and fell down. He does not remember falling. He was unconscious for a short time - a few minutes only. He went on working, although he had a headache. He was quite well the next day. Four months before admission he had a similar attack while on guard. He has occasional attacks of giddiness

in which the head seems to be 'swimming' but there is no definite direction of giddiness.

Five days before admission (6.8.41) while going down the stairs at Old Street station he slipped and fell and lost consciousness, (subsequently he said that he did not recollect slipping). There was slight injury to the right ankle, right shoulder and back of neck, but no evidence of injury to the head. He did not recover consciousness until he was being carried up the ward in hospital. The period of unconsciousness would seem to be about 10 to 15 minutes. On recovering consciousness the eyes felt heavy and he had a slight headache in the occipital and temporal regions.

On admission to hospital he was agitated, his pupils were dilated, there was pain and swelling of the right ankle.

He was kept in bed and later referred to Chase Farm Hospital where he was admitted on 11.8.41.

Physical examination on admission.

Apart from evidence of bruising no abnormality was detected. As the history was suggested of hypoglycaemia, a dextrose tolerance curve was done on 24.8.41. (Dose 1.75 grams per kilo.)

Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
0.100	0.182	0.118	0.077	0.074	0.077	0.080

On the 27th August the patient, while resting in bed on a normal diet, complained of feeling dizzy and of a funny feeling as of tingling in the arms and face. A blood sugar taken at this time was 0.067 mg%. On the 28th August an insulin tolerance test was done. (5 units insulin subcutaneously.)

7.55 a.m.	fasting	Blood sugar	0.100
8.25 a.m.		" "	0.090
8.55 a.m.		" "	0.083
9.27 a.m.		" "	0.080
9.53 a.m.		" "	0.089
10.17 a.m.		" "	0.064

On the 1st September a further dextrose tolerance test was done. (Dose 1.75 grams per kilo.)

Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
0.074	0.111	0.077	0.062	0.067	0.061	0.069

Special Investigations.

Lumbar punctures were performed on 7.8.41 and 18.8.41. On both occasions they were normal.

27.8.41. Blood count. Red cell count 5,100,000. Hb. 98%. White cell count 8,800.

29.8.41. Serum protein 6.0%.

28.8.41. Cholecystogram. Gall bladder fills well with dye.

As the patient had been resting in bed during his previous blood sugar tests for some time before the test was performed the effect of being up and about was tried on 12.9.41 and again on 18.9.41 and 6.10.41.

Date	Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
12/9	0.067	0.071	0.067	-	-	0.071	0.074
18/9	0.090	0.133	0.083	0.090	0.087	0.087	0.083
6/10	0.100	0.095	0.087	0.087	0.064	0.080	0.099

On 17.10.41 an intravenous insulin tolerance test was done (10 units intravenous).

Fasting	10'	20'	30'	50'	1 hr.10'	1 hr.30'	1 hr.50'
0.090	0.045	0.029	0.030	0.037	0.045	0.053	0.061

It was noted that he was developing a marked anxiety state and so he was referred to Mill Hill Hospital. Dr. W.S. Maclay kindly sent me a report on his progress there and the conclusions come to from the psychological point of view are interesting.

There was considerable dispute as to whether he was mentally defective or not, but his Rorschach test and special performance tests showed that he could achieve a mental age of 13 and his I.Q. was rated at not less than 90. He had some curious movements of his arms and legs which were thought to be due possibly to subcortical damage. The diagnosis come to there was anxiety in a patient with focal emotional defect possibly associated with cerebral damage causing motor phenomena.

Case 6. A.E., aged 31. Private soldier.

History.

Since the age of 17 years, that is for the past 14 years, he has suffered from severe headaches. These come on about once a

month, are severe for a day and last about three weeks. Before the onset of the headaches he sees "black spots and bright spots with dark rings round them and bright lights like a rocket bursting in the sky". These spots and lights appear in front of him. They get worse as the attack progresses. The headache usually starts with an aching feeling over the left eye, then across both eyes, and then the headache travels over the vertex and round the temples and when at its worst is like "needles being driven through the head to the back of the neck". At the same time as the headache is at its peak there is pain in the small of the back. These headaches usually come on first thing in the morning but lately have occurred in the afternoon. He is never free from headaches for more than two to three weeks at a time. Sometimes he feels giddy with the onset of the headache. During the severe attacks his eyes get blurred and he gets diplopia. The headaches have been so bad at times that he has had to be away from his work for a week, and has had to stay in a dark room.

Ten months before admission to hospital he joined the army. He managed fairly well until March 1940 when he was sent on an instruction course. Whilst on this course, during which he had to read and study a lot, his headaches became much worse and he began to worry about himself. He has since been very depressed.

When home on leave three months before admission he felt "all in" and had to lie in bed. He quarrelled with his father

over this. In April 1941 he was stationed in Cornwall and at this time he developed difficulty in sleeping. His headaches continued and his appetite became poor. He vomited once or twice in the morning and was admitted to hospital in Cornwall, being discharged from there after two weeks. He was recommended two weeks leave and when he reported back to his unit, his M.O. thought he looked ill and referred him to Chase Farm Hospital.

Past History. He says, and his father bears this out, that he has been depressed since his fiancée was killed in a motor accident eight years ago.

Family History. Negative.

Physical Examination. Negative as far as physical signs were concerned. Appeared very sorry for himself and had attacks of severe headache. Liked to lie in bed with his face to the wall. Resented being disturbed. In view of his history a dextrose tolerance curve was done on 27.7.41.

Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
0.074	0.133	0.041	0.050	0.054	0.095	0.087

At the time when the blood sugar was at its lowest he developed severe headache and saw spots before his eyes "terrific brightness in front of the eyes like searchlights blinding". The symptoms were somewhat similar to his ordinary attacks which he had described but concentrated over a shorter period. He was

now put on a 2,100 calorie diet per day and at the end of a week a further blood sugar curve was done.

Date	Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
7.8.41	0.095	0.133	0.118	0.125	0.111	0.095	0.087

He still felt very depressed and irritable.

It was now decided to try the effect of a very high carbohydrate diet. Accordingly he was given 300 grams of dextrose in the form of two hourly feeds made up as a drink with a little orange essence in addition to his 2,100 calorie diet. At the end of a week on this régime he felt very much better and appeared much brighter. A further blood sugar done on the 18th August was as follows:-

Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
0.074	0.154	0.118	0.111	0.100	0.100	0.100

In view of the severe symptomatology, the low dextrose tolerance on admission, the severe reaction during the dextrose tolerance, and the marked improvement on a high carbohydrate diet with easily assimilable dextrose and the last dextrose tolerance in which after six hours the blood sugar had not returned to the fasting level it was decided to perform a laparotomy.

An operation was performed on 18.8.41 by Mr. Galloway.

No tumour of the pancreas was discovered but a partial pancreatectomy was performed, two inches of the pancreatic tail being resected.

The post-operative progress was interrupted by a post-operative collapse of lung, but this responded well to treatment. There appeared to be considerable improvement subsequent to the operation and he was discharged back to his unit feeling very well. Unfortunately the findings in hospital do not appear to have been communicated to his army medical officer, or else their true significance was not appreciated. He was sent to an infantry training camp, presumably to get toned up again and was put through violent P.T. Naturally he found this too much for him and again developed symptoms, though not as severe as previously. He was seen later by Major Rudd who did a further dextrose tolerance test which showed a suggestive degree of increased sugar tolerance the values of blood sugar after 50 grams of glucose taken every half hour being 110 mg%. Major Rudd further found that he had some extra pyramidal signs suggestive of cerebral damage. (Major Rudd in a personal communication to me mentions that his symptoms were somewhat similar to a case of pancreatic adenoma which he reported with Sir James Walton in October 1941.)

The section of pancreas removed was examined by Dr. Greenfield who reported that "the sections show in all areas pancreatic tissue with an unusually large number of islets, many of which are elongated, as though made up of two or more separate islets.

These measure up to 300 mu × 125 mu. The tissue is otherwise normal". The size of the islet shown in Plate 3 is 375 microns.

McCallum gives size of normal islets as 157 × 146 microns.

(Plate 3)

Cases 5 and 6 appear to be cases of mild hyperinsulinism and in case 6 the question of islet hyperplasia arises.

BRAIN CHANGES IN HYPOGLYCAEMIA DUE TO HYPERINSULINISM.

Malamud and Grosh in reviewing the brain changes in fatal cases of islet cell tumour find that they consist of "cerebral oedema and congestion (Thalheimer and Murphy) perivascular round cell infiltration in the meninges and brain (McClenahan and Norris), atrophy of the cortex and fatty degeneration of the ganglion cells (Terbruggen), moderate diffuse loss of the ganglion cells from the cortex (Wolf) and scattered haemorrhages (Layne and Baker).

Cerebral changes have been reported in several cases who died of 'insulin shock'. Macroscopically Wohlwill described a dry friable brain; other authors (Bowen and Beck, Bodechtel and de Mossier and Mozer) noted cerebral oedema. The histological changes varied from moderate to severe diffuse degeneration of

the ganglion cells in the cortex and basal ganglia. Bodechtel emphasised the focal occurrence of the changes and the prevalence of Spielmeyer's 'homogenious cell disease' in his case. Others (Wohlwill and Terplan) described Nissl's severe change in the neurons and swelling phenomena of the glia and axis cylinders".

In describing a case Malamud and Grosh found that the changes in the neurons of the cortex were predominantly 'Nissl's acute swelling'. The cells and their dendrites were swollen, there was chromatolysis of the tigroid substance and the cytoplasm was pale and homogeneous. The nuclei were swollen. The axis cylinders were reduced in numbers and were often fragmented and swollen. Distinct changes were found in the caudate nucleus and in the putamen and thalamus, especially in the left pulvinar, in which there was great reduction in the number of neurones and the microglia and macroglia had proliferated. Only diffuse swelling was noted in the hypothalamus, cerebellum and brain stem.

Moersch and Kernahan studied the brains of two patients who died in attacks of hypoglycaemia. They found degeneration of nerve cells in both cases, but in addition petechial haemorrhages in the pons. The pathogenesis of the brain changes in hypoglycaemia is still a matter for dispute.

Fraser, Maclay and Mann found that there was considerable disparity between the level of blood sugar and the severity of

hypoglycaemic symptoms and they suggested "that insulin intoxication may supervene when the blood sugar level falls below the critical level of 70 mg% and that the symptoms are dependant on this intoxication - an effect other than its action in lowering the tissue sugar concentration". They found that there was a considerable difference in the symptoms after the injection of insulin in a patient before and after the removal of a pancreatic adenoma. They suggested that there was an excess of insulin in the patient's tissues before operation and that insulin becomes toxic in the presence of low tissue glucose concentration.

Malamud and Grosh considered that the diffuse cerebral degeneration found in fatal cases was due to the direct toxic effect of insulin.

Anoxaemia has been cited as the causative factor in the brain changes. Olmstead and Logan compared the results of hyperinsulinism to those of asphyxia, but later found that there was only a slight fall in the arterial blood Oxygen saturation after insulin and concluded that the convulsive seizures could not be accounted for by such a mild anoxaemia.

Disturbed Water Balance.

Drabkin and Ravdin found that in previously dehydrated animals insulin in convulsive doses failed to cause convulsions, or to raise the C.S.F. pressure. On the other hand, however, they found that in previously hydrated animals convulsions

regularly occurred and there was a rise in C.S.F. pressure. They concluded that insulin convulsions occur only when the sequence of hypoglycaemia, anhydraemia and a rise in C.S.F. pressure takes place and they thought that the anhydraemia was the most important factor.

Yannet studied the effect of prolonged insulin hypoglycaemia on the distribution of water in the brain and found that, in cats, of the animals that survived the injection of a large dose of insulin, about half showed no involvement of the nervous system histologically. Chemically, however, he found a change in cellular composition, there being a significant loss of intracellular potassium. The remaining animals that survived showed widespread cerebral damage. There was a marked loss of cellular water leading to shrinking of the cell and to an increase in extracellular fluid. A proportionately greater loss of cellular potassium was demonstrated, resulting in a decrease in the concentration of intracellular potassium.

Probably the most important factor, however, is that the nerve cell depends primarily on glucose for its nutrition and without glucose the cell is starved.

It is important to remember that, as shown by the excellent results obtained in many of the cases of pancreatic adenoma removed by operation, the changes in the nervous system are

reversable for a time, but if the condition is allowed to go on for too long, then permanent damage may be done. This was well shown in a recent case in which the patient, a diabetic, had gone without insulin for periods and at others taken what he himself thought was the right dose without bothering to obey his doctor's instructions. Eventually he was admitted to hospital in coma. The hospital was an emergency one and there were no immediate facilities for doing blood sugars. The house physician presumed that it was a case of diabetic coma and gave insulin, and on the patient not responding, gave more. When a blood sugar was eventually done it was too low to read. The patient was in deep coma for a week and then from a condition of decerebrate rigidity improved to the mental status of a child a few months old. He eventually reached the mental age of a child of about seven but he has remained there. It appears probable that one or two attacks of severe hypoglycaemia have only a transient effect on the nervous system and that it requires repeated blows over some period of time to do permanent damage. This is suggested in Case 1, where in spite of three pancreatic adenomas and a blood sugar at times as low as 20 mg% the patient only had short periods of unconsciousness and made a good recovery after operation.

HYPOGLYCAEMIA DUE TO HEPATIC DISTURBANCE.

It has been known for some time that severe liver damage may lead to hypoglycaemia, the causative conditions ranging from extirpation of the liver as in Mann's classical experiments to chemical poisons such as hydrazine, phosphorus, chloroform, neoarsphenamine and carbon tetrachloride. Recently (July 1941) Brow and Harvey have reported several cases of spontaneous hypoglycaemia due to drinking denatured alcohol.

It was not until recently, however, that it was appreciated that hypoglycaemia may be produced by conditions such as severe gall bladder disease and that such hypoglycaemia may be cured when the infected gall bladder is dealt with allowing the associated hepatitis to subside. Conn has published several cases of this kind. He found that such patients had an intolerance for fasting with the production of hypoglycaemia. He also found that their blood sugar metabolism as shown by sugar tolerance curves was of great interest.

The liver has three separate functions related to glucose metabolism. There are the functions of glycogenesis, glycogenolysis and the production of glucose and the deposition of glycogen from non-carbohydrate precursors such as glycogenic amino-acids and the glycerol fraction of fats.

In the milder degrees of liver damage the glycogenic function of the liver is impaired. (This has been well shown by Rafsky who studied the blood sugar levels in patients with and without biliary tract disease. He found that a hyperglycaemic response was present in 61.5% of the 52 patients who had gall stone disease and only 22.0% of the 50 patients in the control group. Surgical intervention resulted in an improvement of the carbohydrate tolerance.) Conn considered that this impairment of the glycogenic function was one of rate rather than one of total disability since the blood sugar returns to the fasting level four to five hours after the ingestion of glucose. Conn excludes the question of diabetes in these cases by showing that there is normal oxidation of dextrose during the hyperglycaemic period. Recovery of the glycogenic function takes place with the disappearance of the active infection. When the glycogenolytic function of the liver is impaired, then periods of hypoglycaemia occur. These phases may be differentiated from ones due to hyperinsulinism by again doing respiratory studies and showing normal oxidation in the former.

"It seems then that hyperglycaemia and glycosuria simulating diabetes mellitus may be a manifestation of one phase of hepatic dysfunction and that periodic spontaneous hypoglycaemia may be the manifestation of further hepatic injury in the same patient at different times in the course of hepatitis" (Conn). Conn

further refers to the previous work of Harris on 'dysinsulinism' and thinks that some of his cases who had a previous history of glycosuria and later had alternating periods of hypoglycaemia and hyperglycaemia were due to liver damage. He again stresses the importance of respiratory studies as a differential point.

A case is now reported which may well be a case of hypoglycaemia due to hepatic damage. Operation had been advised as the gall bladder did not appear normal but it was refused and as no facilities were available for doing respiratory studies it must for the moment remain problematical as to whether the liver or pancreas were at fault.

In favour of the hepatic origin is the fact that on the first three occasions when the blood sugars were done they were hypoglycaemic, while the later estimations were mildly diabetic.

Case 7. E.L., aged 52. Merchant.

Admitted to Chase Farm Hospital on September 3rd, 1941, with the complaint of lassitude, headache and increasingly severe periods of headache and dizziness.

Six years before admission he experienced violent temporal headaches as if someone were banging his head with a hammer and when these occurred he was almost unable to concentrate and used to make mistakes frequently in his work and in answering questions.

These headaches were more frequent in the mornings, but more severe when he lay down at night. He attended a neurologist for these headaches and was given medicine with satisfactory result until one year ago when the headaches re-occurred, but were localised to the right side of the head above the ear. They came on in the afternoon and would sometimes persist until he went to bed, leaving him with a heavy feeling on that side of the head until the next morning.

These headaches were infrequent until 9 months ago, when they increased in frequency, and in addition, he developed dizziness on stooping and increasing lethargy as the day went on.

Six months ago, for the first time, he fell asleep at his work in the afternoon. The headaches had meanwhile been increasing in severity, often culminating in his being sick, after which he felt better.

In May 1941 he noticed that he was tired and listless on several mornings when he arrived at his work. By 10.15 a.m. he felt as if he wanted to go to bed. He usually had a good breakfast at 7.45 a.m. On the sixth morning that these attacks of lethargy occurred he went to see his doctor who found sugar in his urine and referred him to the London Hospital. Here glycosuria was again found and on May 30th 1941 a glucose tolerance test was done. A further glucose tolerance was done on 15th August, 1941, and as a result of these tests he was referred to Chase Farm

Hospital for further investigation.

Date	Fasting	1 hour	2 hours	
30.5.41	0.083	0.095	0.080	amount of dextrose given 50 grams
15.8.41	0.077	0.080	0.071	" " " " " "

Past History. Found in 1932 to have a double right ureter.

Physical Examination - negative apart from smooth palpable liver, one finger's breadth below the right costal margin.

The morning after admission a dextrose tolerance test was performed, the dose of dextrose being 125 grams (1.75 grams per kilo body weight). He was fasted for 15 hours before the test.

Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
0.074	0.059	0.064	0.050	0.064	0.062	0.059

Three hours after the test was begun the patient had an attack in which both of his arms went into clonic spasm, both sides of his face were drawn up, and both his eyes turned up. He appeared to be unconscious. This phase lasted about two minutes and at the end of this time he vomited profusely. The attack was seen by the H.P. who had just arrived to take off blood for the next blood sugar test. A further test was done on the 9th September under basal conditions of rest.

Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
0.125	0.200	0.125	0.095	0.095	-	0.100

A cholecystogram was done on the 10th September, the radiologist reporting that there was no visualisation of the gall

bladder up to 18 hours. This test was repeated the next day with the same result.

12.9.41. Red cell count 5,400,000. White cell count 8,600. Hb. 100%.

In view of the hypoglycaemic attack and the possible hepatic enlargement with an abnormal cholecystogram it was decided to perform a laparotomy with a view to exploring the pancreas and gall bladder. The patient requested permission to go home to settle his affairs and this request was granted.

While at home he went to see a diabetic specialist. On the morning of this appointment about 12 noon he felt very weak, then faint, and later had a sudden craving for food. He had to ask someone to do his work for him while he went down to a snack bar and had a chicken sandwich. Immediately after eating this he felt much better. In the afternoon he saw the specialist who reported that he appeared somewhat nervous and excitable.

It was arranged that he return to hospital for further investigations and so he was readmitted on 2.10.41.

Dextrose Tolerance Tests

Date	Fasting	½ hour	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
3.10.41	0.102	0.125	0.129	0.143	0.103	0.100	0.067	0.080
14.10.41	0.100	-	0.154	0.166	0.143	0.074	0.083	0.080

Laevulose Tolerance Tests.

Date	Fasting	½ hour	1 hour	1½ hours	2 hours
4.10.41	0.105	0.133	-	0.125	0.118
15.10.41	0.087	0.095	0.133	0.133	0.139

Insulin Tolerance Test.

Date 2.10.41.

Fasting	0.100
10 units insulin intravenously	
10'	0.100
20'	0.083
30'	0.054
50'	0.053
1 hour 10'	0.071
1 hour 30'	0.074
1 hour 50'	0.090

Adrenalin Test.

10.10.41.	Fasting Blood Sugar	0.133 mg%
	15 mns. adrenalin subcutaneously	
	15'	0.139 mg%
	30'	0.125 mg%
	1 hour	0.133 mg%
	1 hour 15'	0.138 mg%
	1 hour 30'	0.143 mg%
	1 hour 45'	0.138 mg%
	2 hours	0.129 mg%

6.10.41. Hippuric acid test 116% of normal.

4.10.41. Urinary urobilinogen. No abnormal pigment found.

4.10.41. Complete blood count. Normal.

4.10.41. X-ray of skull normal. Sella tursica normal.

During this stay in hospital the patient had no attacks but had some slight headache, more obvious during one of his dextrose tolerance tests. He was discharged home having refused operation.

A further case is reported where the symptomatology was somewhat suggestive of hypoglycaemia and where the sugar tolerance tests were of a mild plateau type with on one occasion a terminal fall to hypoglycaemic levels. Investigation showed that she had some impairment of hepatic function and had diminution in her serum proteins.

Case 8. L.D., aged 29. Married. Typist.

Complaint. Swelling of the legs, especially on standing.

History. For the past two years or more her legs have swollen up when she stands about or keeps on her feet; accordingly they are worse at the end of the day and go right down during the night. She thinks that the condition has got gradually worse since then until now, after a normal day, her ankles are out about half an inch all round her shoes; she has to change her shoes to prevent her feet getting sore from the pressure. She sits down all day as she is a typist.

The legs ache and the feet feel tight and may become sore from the pressure but are not painful. The swelling reaches right up to her knee, but rest in bed always disperses it. She is a little breathless on exertion and has always been so, but can walk up hills etc.

The legs, even when they subside at night, never subside completely - two years ago her ankles were quite normal and now

they are very fat even after several days rest in bed.

Since the onset of oedema two years ago she has developed attacks which occur every month or so. They occur mostly in the mornings, but sometimes in the afternoon. They start with the sudden onset of pain over one eye, usually the left. The pain spreads over the same side of the forehead. After half an hour the pain shifts to the other side and then spreads to most of the head, keeping very severe over both eyes; she feels as if it were 'shutting her eyes up'. A half to ¾ hour from the onset a numb feeling starts in both fingers and hands (equally). The numbness spreads to the face and tongue, then to the legs, taking a quarter to half an hour to do so. Although she can feel a little she does not think she would be able to taste anything. She would have to think very hard when she chewed or swallowed anything, and would have to look at an object and think about it before she could pick it up. Her sight becomes progressively blurred from before the onset of the numbness and becomes very bad. All this eventually forces her to go to bed and within five minutes she is asleep; she does not feel sleepy beforehand. It is a very heavy sleep and may last if not called, up to three days. On one occasion she went to bed on the Wednesday, woke up on the Saturday morning and went to the office thinking it was Thursday morning.

When she wakes she feels tired and exhausted. She gets up and has something to eat, goes for a walk, and is then able to go to bed and get an ordinary night's rest.

Family History. Negative.

Past History. Nil of note.

Physical Examination. Nutrition good. Weight 8½ stone. Pitting oedema of ankles and shins on both sides.

Dextrose Tolerance Tests. (Dose 1.75 grams per kilo.)

Date	Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
9.9.41	0.087	0.166	0.154	0.133	0.100	-	0.090
8.10.41	0.095	0.125	0.125	0.125	0.095	0.095	0.111
23.10.41	0.105	0.158	0.166	0.138	0.129	0.074	0.071

Insulin Tolerance Test. (10 units intravenously.)

Date	Fasting	10'	20'	30'	40'	1 hr.	1 hr 20'	2 hrs.
2.11.41	0.083	0.080	0.055	0.039	0.047	0.050	0.059	0.066

Laevulose Tolerance Test.

4.10.41.	10 a.m.	Fasting Blood Sugar	0.090
		45 grams laevulose given	
	10.30 a.m.	Blood Sugar	0.105
	11.00 a.m.	" "	0.111
	11.30 a.m.	" "	0.125
	12 noon	" "	0.105

Hippuric Acid Test.

16.9.41. 66% of normal.

3.10.41. 76% of normal.

Bromsulphalein Test.

17.9.41. After 30 minutes - trace.

17.9.41 Urinary urobilinogen test - no excess of urobilinogen.

16.9.41. Blood urea = 0.021%

15.9.41. Total blood count normal.

Serum Proteins.

5.10.42. 6.2 mg%.

19.10.42. 7.0 mg%.

Kidney Function Tests.

Normal.

While she was in hospital she was very difficult about her food, seeming to have no desire for anything but bread and butter and green vegetables. She was put on the ordinary ward diet but just didn't eat it.

Because of the relatively short history of oedema and the history suggestive of hypoglycaemia with in addition the plateau type of blood sugar curve it was thought that she might possibly have an adenoma of the pancreas pressing on the inferior vena cava causing partial venous obstruction. (Kepler and Walters reported a case characterised by attacks of mental confusion, sleepiness and numbness of the extremities and tiredness, with convulsive seizures in which an adenoma was found directly over the inferior vena cava and the aorta.)

She was operated upon but at operation no tumour was found. The gall bladder appeared normal. It did not appear justifiable to do a partial pancreatectomy and the abdomen was closed.

In view of her dislike of protein and the low serum proteins after operation she was put on a high protein diet and after a two week interval her serum proteins were again done and found to be raised. She was a distinctly unco-operative individual, this having been a feature of all the hypoglycaemic cases reported here.

Taking all the findings in conjunction - blood sugar tests, liver tests showing mild impairment of liver function and serum proteins - it is possible that this patient has mild hepatic insufficiency partially at any rate caused by insufficiency of diet.

She discharged herself before further investigations on a more balanced diet could be made.

HYPOGLYCAEMIA OF PITUITARY ORIGIN.

Cushing in 1912 reported a case of chromophobe adenoma of the pituitary in which the blood sugar was 0.039%. J. Wilder in 1930 reported two cases of spontaneous hypoglycaemia with clinical and radiological evidence of a pituitary tumour. Foley (1938) made metabolic studies in 26 successive cases of chromophobe tumour of the pituitary and concluded that extensive destruction

of the anterior lobe of the pituitary is necessary before there is disturbance of blood-sugar regulation.

Kepler (1939) found experimentally by traumatic lesion of the hypothalamus that the possibility of hypothalamic lesions eliminating a normally tonic descending innervation could be eliminated as he showed that hypoglycaemia was only occasionally precipitated by what appeared to be identical lesions and that in no instance was it precipitated by lesions severing the dorsocaudal hypothalamic connections.

Young has recovered a diabetogenic substance from the anterior lobe of the pituitary, thus corroborating Foley's statements.

A case is reported of chromophobe adenoma of the pituitary with a blood sugar showing hypoglycaemia.

Case 9. A.S., aged 30.

Admitted to Chase Farm Hospital on 20.8.41. The complaint was of periodic giddy attacks, frontal headaches and failing vision. He felt quite well up till two years ago, but always had poor vision.

In July 1939 he started to get frontal headaches associated with giddy attacks. The giddiness would come on at any time during the day and would last for about five minutes - objective anti-clockwise rotation; there would be noise of machinery in the head in both ears, but no feeling of faintness, nausea or falling.

The headaches which followed the attacks would last from an hour to a day and were always frontal. Aspirin would give relief. Frequency of attacks - about two per month - continuing up till the day of admission. The headaches of late have been more severe and accompanied by a feeling of nausea, but the giddy attacks have remained about the same, the last being two weeks before admission. In November 1940 he was conscripted for the army. Apart from the periodic attacks he felt quite well until April 1941 when he reported to the M.O. complaining of headache and pains in the stomach. The pains were not related to meals, at times they would wake him up at night. A test meal was done and on treatment for ulcer the condition seemed to clear up. However on account of this he was discharged from the army in May 1941.

From May to July 1941 he continued his civil occupation still having periodic attacks of giddiness. On two occasions he fainted and was unconscious for about five minutes, (knows no details of what happened when he was unconscious or the exact time), once while at work and once while in a barber's chair. A 'warning' before the faint lasted about one minute and consisted of a 'queer' feeling, felt very hot. Did not bite tongue or pass urine during the attacks.

For two to three years he has noticed that objects were not to be seen where he expected them to be and three months ago he

obtained his first pair of glasses because of this difficulty in reading. He attended an eye hospital in the beginning of May for new glasses but by the time they had been made for him they were of no use because of his now rapidly failing vision. Early in July his child noticed that his left eye was 'wobbling', (central nystagmus).

Early in July he visited his panel doctor complaining of headaches and fainting. He went to the Miller General Hospital as an out-patient and x-rays were taken which, he said, revealed a tumour. He was referred to Mr. Northfield for further investigation.

Physical Examination. A very pale young man with dark rings under his eyes. Parchment-like skin, very dry. Scalp hair, thick, dry, erect and dark. No axillary hair or hair on arms and legs. Very scanty pubic hair and absence of beard and moustache. No abnormal lumps in head, no bruit, no occipital tenderness, no nuchal rigidity. C.N.S. - bilateral anosmia. No papilloedema; right slight primary optic atrophy with deep cup and well marked lamina cribrosa. Left - same but more marked. Divergent strabismus on looking to the front. Rapid anti-clockwise oscillating movement of the eyeball in all directions - most marked looking 45 degrees to the right and in the left eye more than right. No weakness of ocular muscles - except right eye tends to deviate rapidly. Pupils medium sized, equal, poor

reaction to light - better from nasal side - converges well. No exophthalmos. Corneal reflexes brisk and equal. Well marked lower right facial weakness.

Upper limbs. Right handed. Slight weakness of right upper limb, generally distributed. Hypotonia, right more than left. Jerks increased, right more than left. No tremor or incoordination. No loss to pin prick or to cotton wool. Abdominal reflexes all present and equal.

Lower Limbs. No definite weakness. Right knee and ankle jerks brisker than left. No sensory loss. Joint sense good. Plantars flexor. Weight 11 stone 2 pounds. Height five foot six.

Lumbar Puncture. Pressure 130 mm. On jugular compression rapid rise and fall. C.S.F. 3 ccs. pale yellow fluid. 1 lymphocyte. 275 red cells. 200 mgms. protein. Pandy positive. W.R. doubtful.

6.8.41. Sugar tolerance test.

10 a.m. fasting blood sugar	0.090%
50 grams glucose given	
10.45 a.m.	0.077%
12 noon	0.053%

5.9.41. Fasting blood sugar 0.067%.

9.9.41. Ventriculogram. Large tumour in region of pituitary displacing ventricle upwards and backwards.

Exploration via left frontal flap under local percaine, (60 ccs. 1% solution). Tumour, larger than a walnut, located pushing forward the optic nerve, needled; no fluid withdrawn, therefore probably not a cyst; tumour not removed because of its vascularity and size - subtemporal decompression left on replacing bone flap.

12.9.41. Patient died.

Autopsy. Chromophobe adenoma of pituitary.

TREATMENT OF HYPERINSULINISM.

In the milder forms of hyperinsulinism all that is required is regulation of diet. Waters advised a high fat diet such as carbohydrate 100 grams, protein 60 grams, fat 250 grams, the diet being split up into 6 meals a day. Such mild cases are greatly improved by such a diet but not completely cured. Some patients do not respond to such a diet primarily because it is distasteful to them, but whatever the cause of lack of response there are a certain number of cases who fail on this treatment.

Conn and Newburgh suggested that a high protein diet should be tried on the grounds that there was a slow conversion of glucose from protein and that the liberation was so slow that it did not stimulate the pancreas to produce more insulin in contrast to repeated doses of carbohydrate or glucose.

John suggested that patients with 'functional hyperinsulinism' should be given a high fat diet with 20 units of insulin half an hour after each meal, the rationale of this treatment being that insulin given in this way would gradually dampen down the activity of the pancreas. He suggested that this form of treatment should be carried on for three months and at the end of this time it should be possible to differentiate the 'functional' from the organic, the functional having responded to treatment while the organic should have shown no response.

Whipple recently reported 82 cases, including 19 of his own, where an islet cell tumour was removed at operation. Of these 65 had an islet cell adenoma, 2 an atypical tumour and 15 a carcinoma. The operative mortality was 16%. Of the 69 patients who survived the operation 62 were cured of their hypoglycaemic attacks and of these 36 had been followed for over one year.

These islet cell tumours are not, however, easy to find and Whipple mentions 14 tumours of the pancreas where no tumour was found at the first operation, but found at the second operation in nine cases and at autopsy in the other five. Ziskind, Bailey and Mauer mention a case where two operations were performed without finding a tumour, but at autopsy a tumour was found. Ziskind also mentions a case where a patient was operated upon and no tumour found. A further operation was done two years later

and 2/3 of the pancreas resected. In the resected portion two adenomata were found.

The most common site of the pancreatic adenoma is in the tail of the pancreas, but it may be situated anywhere and of the overlooked tumours mentioned by Whipple 7 were in the head, 5 in the tail and 2 in the body of the pancreas. They may be multiple as in case 1 where three tumours were removed. Typically they are small, usually being about 1.5 cm. in diameter. They are characteristically encapsulated and are reddish in colour, contrasting with the yellowish surrounding pancreatic tissue. Frequently the encapsulation is not complete and on microscopic findings differentiation between benignancy and malignancy has been suggested on the basis of microscopic invasion, variation in morphology of the cells and tumour cells in the vessels. All of these tumours show cells resembling normal islands but with special staining in a large number of cases it can be shown that beta cells preponderate.

Bensley, however, who is the most reliable authority on the pancreas has recently protested at these tumours being called beta cell tumours as he says that in all the cases of islet cell tumour that he has examined the cells have been actually neoplastic cells.

From the figures given it is obvious that the operation is not an easy one and the greatest care must be taken in order not to miss a tumour.

Operation Technique.

Spinal anaesthesia is favoured by the majority of surgeons. The type of incision is still disputed but Whipple favours the transverse believing that a split left rectus fails in the majority of cases to give adequate exposure.

In a personal communication Sir James Walton also favours this type of approach stating that his experience has been that a transverse mid-epigastric incision is very helpful and gives exposure of the whole length of the pancreas which is helpful against injury to the splenic vein.

It is agreed that the initial approach is best made through the gastrocolic omentum, the stomach being elevated with retractors and the colon displaced downwards. The body and tail are now well exposed and the pancreas is then freed from posterior attachment by gentle dissection and the gland is palpated between the index and middle fingers posteriorly and with the thumb anteriorly. When one palpates with one's fingers along the gland, if an adenoma is present one can notice a difference in texture usually feeling an indurated area. To examine the head of the gland properly the duodenum should be mobilised by freeing it from its posterior attachments and then it should be reflected downwards and medially, thus giving access to the entire head. The whole gland should be examined very carefully and also the adnexa,

as shown in the case of Rudd and Walton where the adenoma was found in the gastro-splenic omentum.

Even with the greatest of care as has been shown tumours can be missed. David found 28 cases in the literature where a partial or subtotal pancreatectomy was carried out because of hypoglycaemia and where a tumour was found in the resected portion or at a subsequent operation.

There have, however, been a number of cases where a resection has been carried out and no tumour found. David found 18 cases in which partial pancreatectomy had been carried out, in 15 the pancreas being histologically normal and in the other three hyperplasia of islet cells. Four of the patients died (22% mortality) and of the 14 survivors only three were free from attacks, three were moderately improved and in 8 patients the attacks continued.

At this juncture one should state that it is not possible at the present time to distinguish between a case of severe hyperinsulinism due to pancreatic adenoma and one due to hyperplasia or hyperfunction. Various authors have tried to do so, suggesting that in the so-called functional cases the response to fasting is different, the blood sugar rising instead of falling as in adenoma. These suggestions are not borne out in the cases shown here as on the one hand, in case 1, where there were three adenomas, the blood sugar rose on fasting, and on the other hand

in case 4 the blood sugar fell on fasting, though no adenoma was found.

It thus seems logical to treat the severe cases by operation even though no tumour is found.

The above cases shown by David do not appear satisfactory, but this was probably due to the amount of tissue removed - where recorded it was from 4-41 grams. David contrasts these cases with another 17 where no tumour was found and where a subtotal resection of the pancreas was performed, 35 to 60 grams of pancreas being removed. In 14 of these patients there was a normal pancreas, in two there was islet cell hyperplasia and in one pancreatitis. 11 were relieved of their symptoms and there was only one operative death. As a further contrast David records another 15 cases where 40 to 60 grams of pancreas were removed. Ten of these cases were cured.

In considering the mortality rate of the 23 patients who had a resection of over 30 grams of pancreas David found it to be 4.3%. Comparing this mortality rate with that for pancreatic adenoma where it was 16% David concludes that the operation of subtotal resection is fairly safe. This is borne out in the cases shown, where the three cases in which partial resection was done were little disturbed by the operation itself. It is possible, if one considers cases 4 and 6, that too little pancreas was removed.

DISCUSSION.

Review of English Literature.

The first person to consider hypoglycaemia as a clinical entity in this country was Cammidge who in 1924 published a case with a fasting blood sugar of 45 mg% with hypoglycaemic symptoms which he considered to be due to hepatic dysfunction. That hepatic dysfunction could cause clinical hypoglycaemia was shown by Moore, O'Farrell, Moriarty and Cremin in 1934 when they published a case of hypoglycaemia which had gone to autopsy and in which the liver showed subacute parenchymatous hepatitis, (The post-mortem findings were confirmed by J.W. McNee).

W.G. Barnard in 1932 published the first case of pancreatic adenoma to be observed clinically in this country and he was followed in 1933 by Cairns and Tanner who published a further case, but it was not until 1938 that Fraser, Maclay and Mann reported the first case of adenoma in this country to be cured by operation with removal of the tumour. Since then only one further case has been reported - that of Rudd and Walton.

In 1931 Moore, O'Farrell, Malley and Moriarty published a case of acute spontaneous hypoglycaemia which they considered was due to faulty amylaceous digestion. In February 1934 they published an autopsy report on this patient showing that the

pancreas was normal. In 1932 Ramsbottom and Eastwood published a further case of spontaneous hypoglycaemia where a laparotomy was performed and a gall bladder full of stones was found, but no pancreatic lesion. Six weeks after the operation the patient was no better. A further case was published in 1933 by Griffiths and de Wesselow and also a discussion on it by Cammidge. No definite conclusion was come to but Cammidge favoured a hepatic origin stressing the fact that (in his opinion) pancreatic lesions in hypoglycaemia are secondary to liver dysfunction.

In 1933 Wauchope published an extensive review of the literature on hypoglycaemia.

In 1935 Jones called attention to the relationship between psychological states and hypoglycaemia and published three cases. This same year Berry reported a case of hyperinsulinism on which he had operated with successful result, doing a partial pancreatectomy.

In 1938 Price and Rapier reported a further case of spontaneous hypoglycaemia and since then, apart from the papers already mentioned, little has been written.

It will be seen that compared with the American and continental literature little has been said about the condition of hyperinsulinism in this country and the question naturally arises as to whether the condition is rare here or whether the cases have been missed.

In the course of eight months no less than nine cases have been seen by me in which the diagnosis of spontaneous hypoglycaemia has been confirmed by blood sugar studies and this suggests that these cases are being missed rather than that they are rare.

The most satisfactory type of hyperinsulinism to treat is the case of pancreatic adenoma and the various methods of diagnosing this condition have been discussed in detail. One important observation which was made in Case 1 should be noted and that is the extreme irregularity of the blood sugars while on an ordinary diet. These findings are very suggestive of an irregular liberation of insulin, and not at definite periods as in the cases of so-called 'functional hyperinsulinism'.

It is pointed out that it may be impossible in some instances to differentiate the case of adenoma from that of hyperinsulinism and that in the severe cases operation should be undertaken. If no tumour can be found, then the operation of choice is subtotal pancreatectomy which in good hands produces a successful result.

In the cases of hyperinsulinism reported where an operation was performed, and no tumour found a partial pancreatectomy was done with improvement in all cases after the operation. In Case 4, however, the improvement is only partial and in Case 6 the ultimate result has not been as good as was expected. In Case 4 either an adenoma was missed or insufficient pancreas was removed. In Case 6 where hyperplasia of the islets was present

only the tail was removed and possibly the operation was not sufficiently drastic. Case 3 appears to have benefited considerably but it is too soon to come to any conclusions.

A criticism of these cases of hyperinsulinism which may be made is that they were not given a sufficiently long period of medical treatment either on the lines of Waters, Conn or John. The reason for this was first that the patients were unwilling to submit to dieting for any length of time, and, secondly, that it would have been very difficult to carry out the required dietetic régime on account of the difficulties of war time dieting. Further they were somewhat severe cases and it was felt that they probably would have had to have an operation later on.

The suggestion of Malamud and Grosh that the type of sugar tolerance test gives some indication of the severity of the upset of pancreatic control appears to be a good one and seems to be borne out in the cases reported.

In discussing the symptomatology of pancreatic adenoma it is pointed out that the condition is not usually diagnosed for a period up to three years after the initial symptoms and there may be an interval of up to two years between attacks and therefore particular attention should be made to the type of initial symptoms which are frequently psychological or else vasomotor. The subsidiary tests are described in detail as one is not always lucky enough as in Cases 1 and 2 to get the patients in an attack.

The glucose tolerance test has been discussed at some length because it may be of great value and so may be the insulin tolerance as both Cases 3 and 4 had abnormal insulin tolerances and neither were observed in a definite hypoglycaemic attack. Case 4 is of particular interest as she showed signs of an overactive adrenalin mechanism and it appeared as though she had become so accustomed to react to the need for liberation of glycogen that the slightest disturbance produced a sympathetic response whether she was in an attack or not.

Many authors have laid stress on the response to fasting as a differential point between the organic and the functional type of case. This is not borne out in our cases as the blood sugar rose in fasting in one of the cases of adenoma (Case 1) and fell in one of the cases where no tumour was found (Case 4). It has been suggested that some of the cases of organic hyperinsulinism need to be fasted for 48 hours to produce symptoms and it was in order to obviate this tedious fast that the insulin tolerance test was introduced.

One interesting point arises in reviewing the histories of the cases of hyperinsulinism organic and 'functional' and that is the frequency with which migrainous symptoms are to be found. In Case 7 migraine was one of the outstanding symptoms. The question arises as to whether migraine is associated with a low blood sugar and whether its symptomatology is related to

carbohydrate metabolism. It is interesting to note that Gray and Burtness found that 38 patients had headache when their blood sugar level was between 60 and 90 mgms. and that 22 of these patients suffered from migraine. They further found that complete relief of the headache followed frequent feedings of carbohydrate containing foods and that induced hypoglycaemia reproduced the characteristic headache.

The giving of glucose to cases of migraine in children has been used empirically for some time with good results.

It would be interesting to observe the result of a series of cases treated with insulin as suggested by John, particularly since Gray and Burtness found that his migrainous patients had a flat type of glucose tolerance suggesting that their insulin liver mechanism was over active.

The relationship of the liver to hypoglycaemia is discussed and two cases are reported in ~~the first of~~ which there appears to be some evidence that the liver is at fault. With reference to the differentiation between hepatic and pancreatic hypoglycaemia the estimation of oxygen consumption is discussed this being excessive in cases of pancreatic origin. Unfortunately facilities were not available to do respiratory studies, the hospital being a temporary one.

As evidence of pituitary influence on blood sugar metabolism the sugar estimations in a case of inoperable tumour of the pituitary are given.

TABLE 1.

Control Six Hour Blood Sugar Tolerance Curves.
Method Folin and Wu.

Dose of Glucose 1.75 Grams per kilo body weight.

Patient	Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
1	0.111	0.116	0.154	0.087	0.118	0.133	0.125
2	0.100	0.166	0.105	0.090	0.090	0.087	0.080
3	0.118	0.143	0.102	0.055	0.083	0.109	0.108
4	0.074	0.133	0.087	0.100	0.095	0.083	0.080
5	0.083	0.154	0.083	-	0.095	0.095	0.090
6	0.087	0.125	0.064	0.067	0.085	0.071	0.069
7	0.090	0.200	0.182	0.154	0.143	0.095	0.087
8	0.090	0.182	0.182	0.143	0.143	0.083	0.087
9	0.125	0.133	0.154	0.125	0.090	0.111	0.111
10	0.090	0.125	0.143	0.118	0.090	0.083	0.133
11	0.090	0.105	0.118	0.100	0.095	0.100	0.083
12	0.087	0.095	0.125	0.118	0.090	0.090	0.090
13	0.111	0.240	0.166	0.143	0.118	0.125	0.118
14	0.085	0.118	0.105	0.111	0.095	0.101	0.069
15	0.059	0.100	0.125	0.105	0.062	0.059	0.062
16	0.090	0.184	0.125	0.118	0.111	-	0.090
17	0.100	0.133	0.118	0.100	0.090	0.095	0.090
18	0.083	0.166	0.118	0.098	0.100	0.077	0.077
19	0.083	0.143	0.111	0.100	0.108	0.083	0.083
20	0.080	0.148	0.118	0.108	0.071	0.074	0.080
21	0.077	0.111	0.143	0.133	0.133	-	0.074
22	0.087	0.118	0.133	0.118	0.111	-	0.083
23	0.100	0.133	0.111	0.100	0.077	0.077	0.083
24	0.095	0.133	0.111	0.090	0.083	0.100	0.100
25	0.087	0.143	0.133	0.118	0.118	0.108	0.100
26	0.080	0.133	0.111	0.087	0.083	0.080	-
27	0.090	0.166	0.143	0.133	0.118	0.095	0.090
28	0.095	0.182	0.154	0.143	0.133	0.100	0.100
29	0.090	0.182	0.166	0.133	0.100	0.100	0.095
30	0.095	0.166	0.133	0.105	0.100	0.095	0.095
31	0.109	0.166	0.095	0.105	0.095	0.100	0.105
32	0.090	0.105	0.154	0.083	0.087	0.083	0.095
33	0.074	0.111	0.118	0.105	0.105	0.064	0.077
34	0.095	0.114	0.100	0.111	0.062	0.061	0.071
Average	0.091	0.143	0.127	0.110	0.099	0.091	0.090

TABLE 2.

STUDENTS.

Control Blood Sugar Tolerance Tests (6 hour).
Method Folin and Wu.

Dose 1.75 Grams per kilo body weight.

	Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
C.	0.083	0.118	0.083	0.083	0.071	0.077	0.080
S.	0.087	0.125	0.077	0.080	0.083	0.100	0.090
F.	0.087	0.111	0.090	0.077	0.087	0.083	0.090
P.	0.083	0.083	0.083	0.077	0.083	0.083	0.087
T.	0.090	0.090	0.090	0.069	0.080	0.087	0.080
L.	0.095	0.111	0.090	0.083	0.090	0.087	0.080
E.	0.074	0.100	0.074	0.067	0.074	0.077	0.077
E.	0.080	0.090	0.069	0.080	0.077	0.077	0.080
L.	0.074	0.087	0.067	0.074	0.080	0.080	0.080
S.	0.100	0.111	0.100	0.105	0.062	0.080	0.083
Average	0.085	0.103	0.080	0.080	0.080	0.083	0.083

TABLE 3.

Intravenous Insulin Tolerance Test.

14 normal controls. Dosage 10 units insulin intravenously.

	Fasting	10'	20'	30'	50'	1 hr.10'	1 hr.30'	1 hr.50'
W.	0.095	0.047	0.034	0.034	0.045	0.064	0.077	0.083
F.	0.087	0.062	0.043	0.039	0.054	0.059	0.059	0.067
B.	0.095	0.069	0.050	0.049	0.054	0.064	0.067	0.077
C.	0.100	0.100	0.069	0.055	0.055	0.083	0.083	0.067
D.	0.095	0.073	0.037	0.035	0.059	0.064	0.077	0.079
G.	0.083	0.053	0.045	0.041	0.057	0.062	0.071	0.080
W.	0.095	0.087	0.069	0.060	0.074	0.080	0.087	0.090
B.	0.105	0.070	0.047	0.048	0.059	0.071	0.111	0.105
R.	0.090	0.069	0.064	0.068	0.070	0.083	0.095	0.103
C.	0.100	0.077	0.032	0.034	0.050	0.053	0.056	0.059
D.	0.090	0.070	0.043	0.049	0.069	0.074	0.088	0.083
R.	0.087	0.059	0.044	0.046	0.040	0.074	0.087	0.100
P.	0.147	0.135	0.071	0.090	0.100	0.100	0.118	0.125
R.	0.090	0.059	0.048	0.041	0.053	0.077	0.100	0.105
Average	0.097	0.074	0.051	0.051	0.059	0.072	0.084	0.087

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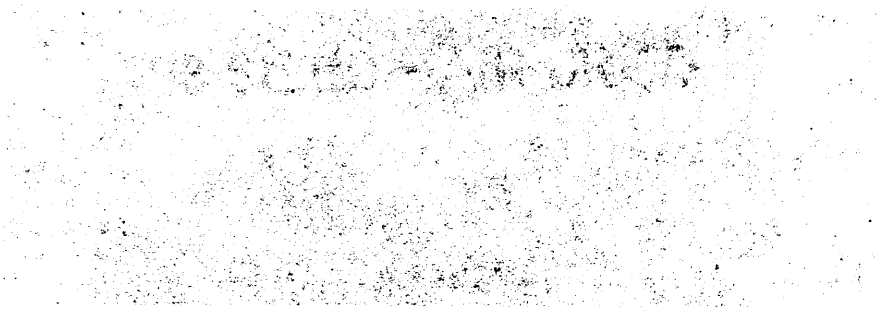
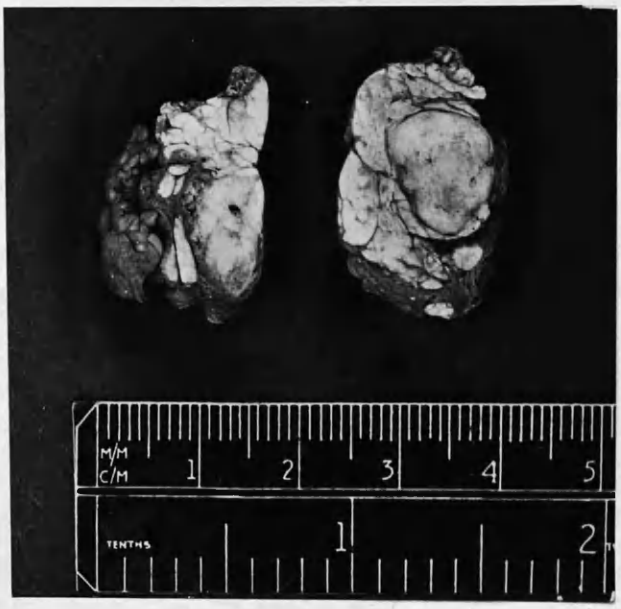


PLATE I. M.H.



ABOVE.

Actual photograph of massive adenoma of pancreas.

Symptoms: Marked hyperinsulinism. Tumour excised.
Result: Disappearance of symptoms.

BELOW.

Microphotograph showing the adenoma with cells typical of islets of Langerhans.

Sections and Photographs by Doctor J.G. Greenfield.

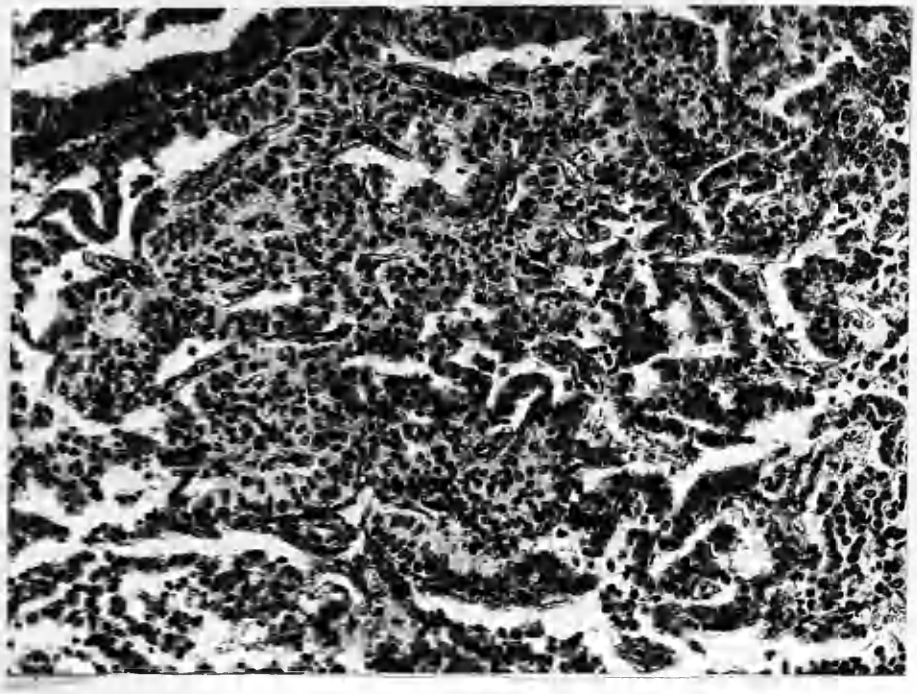
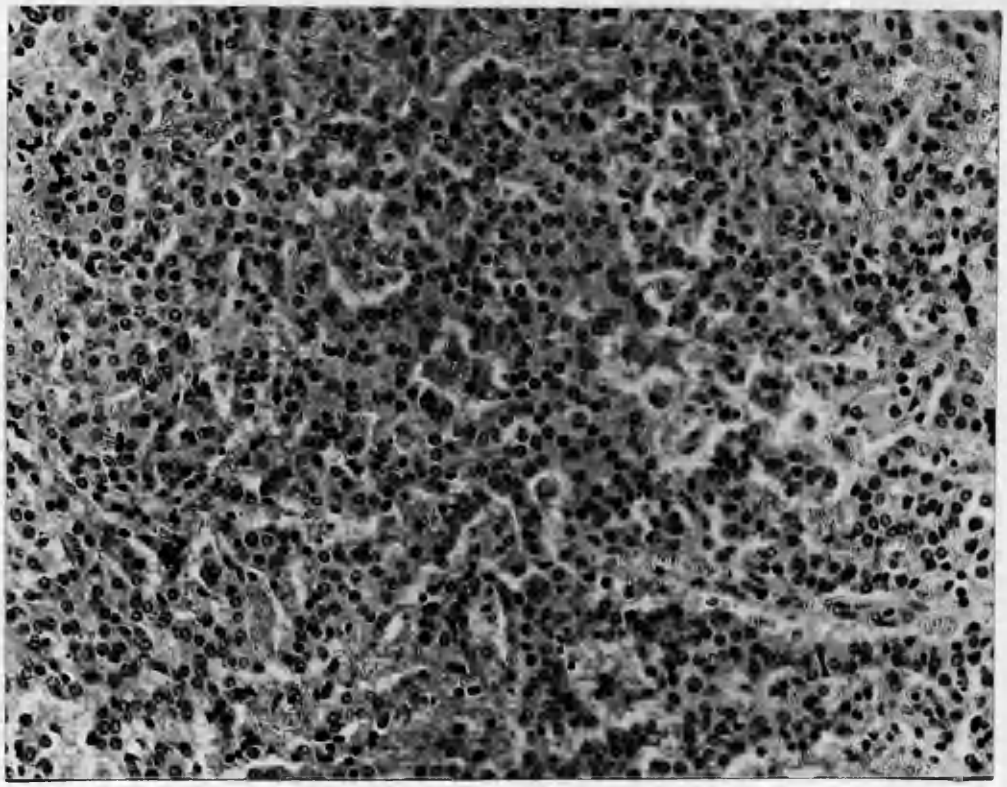


PLATE II. E.S.

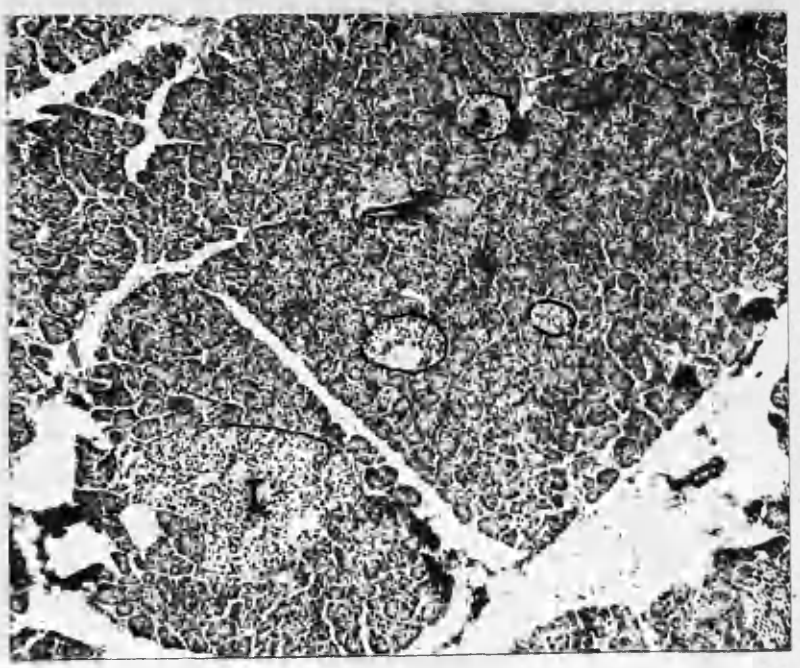


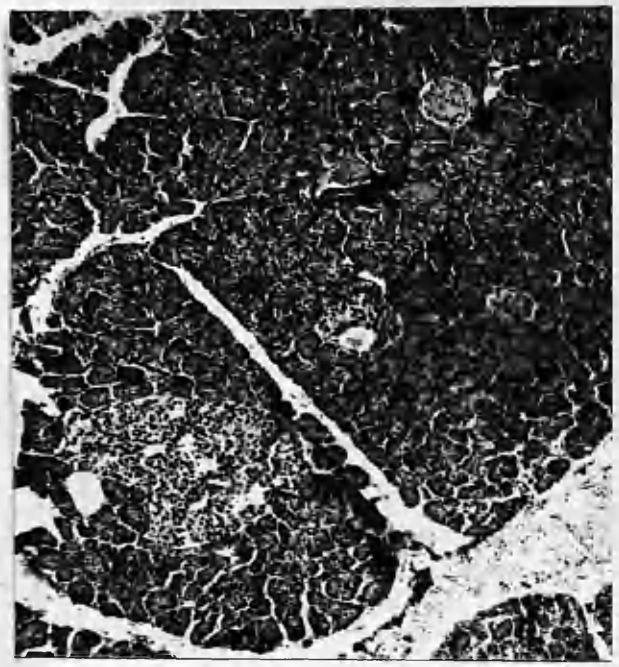
Microphotograph of section of adenoma removed from head of pancreas showing typical mass of cells of exactly the same type and character as the cells of normal islets of Langerhans.

Site of tumour - head of pancreas.
Symptoms. - marked hyperinsulinism.
Removed by operation.
Recovery - complete.

Sections and Photographs by Doctor J.G. Greenfield.

PLATE III. A.E.





Another case of marked hyperinsulinism without palpable adenoma where partial pancreatectomy was carried out with practically complete disappearance of symptoms.

ABOVE.

Microphotograph shows at 1. huge hypertrophy of an islet of Langerhans, of which there were many, at 2. and elsewhere normal islets of Langerhans.

TO LEFT.

Same as above.

Sections and photographs by Doctor J.G. Greenfield.

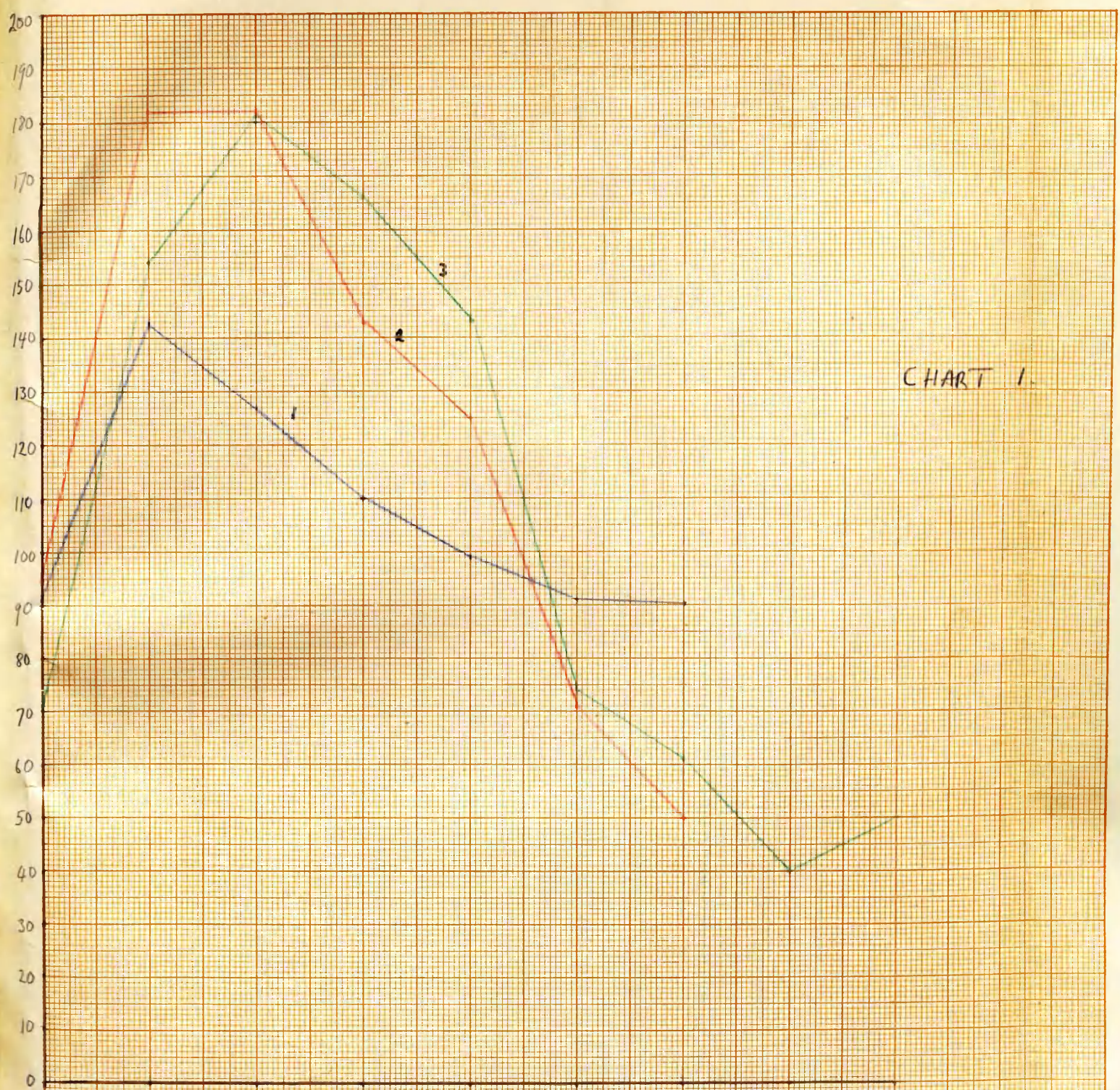


CHART SHOWING NORMAL 6 HOUR GLUCOSE TOLERANCE TEST (1) AND GLUCOSE TOLERANCE TESTS IN CASE 1 (2) AND CASE 8 (3).

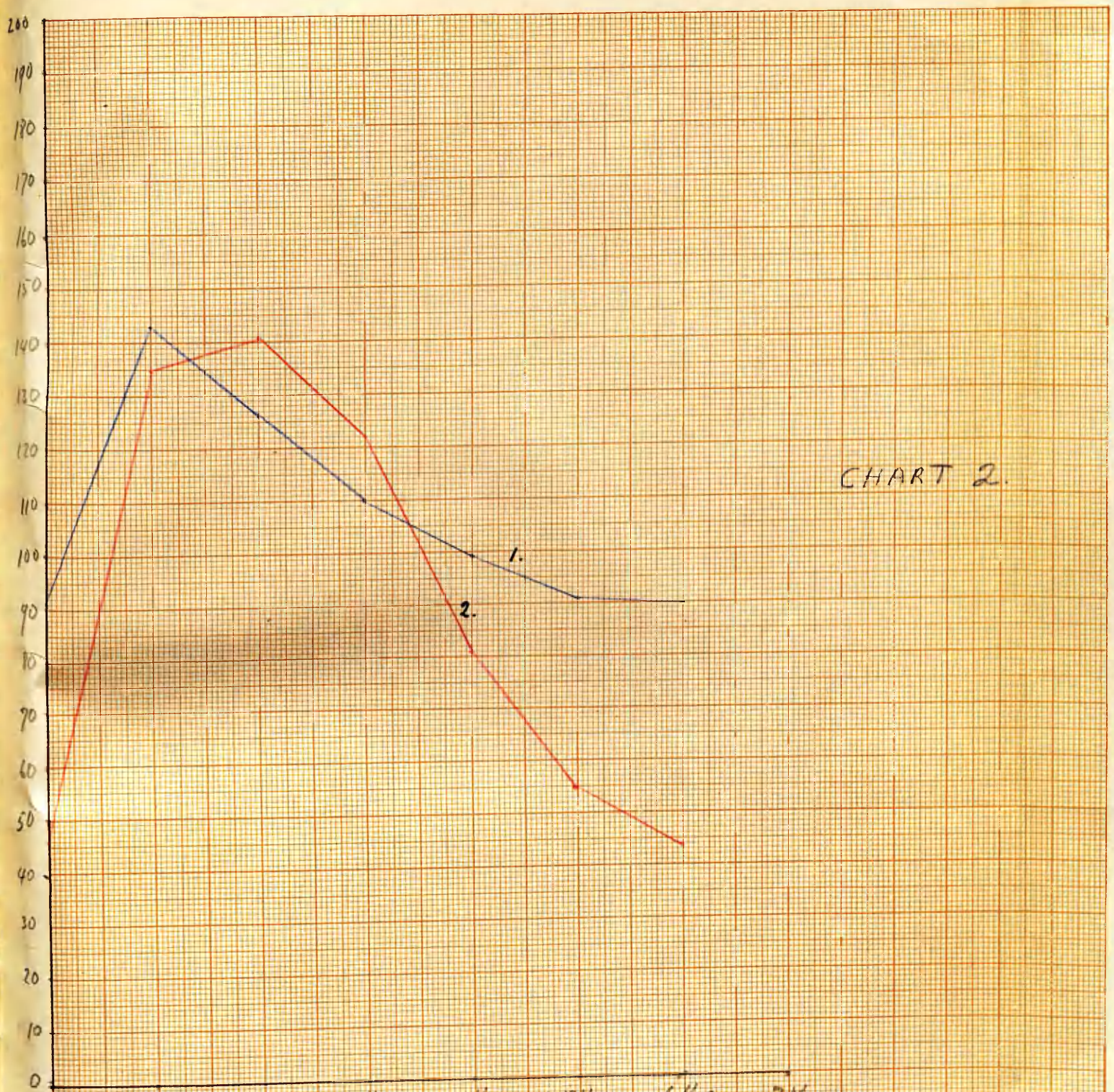
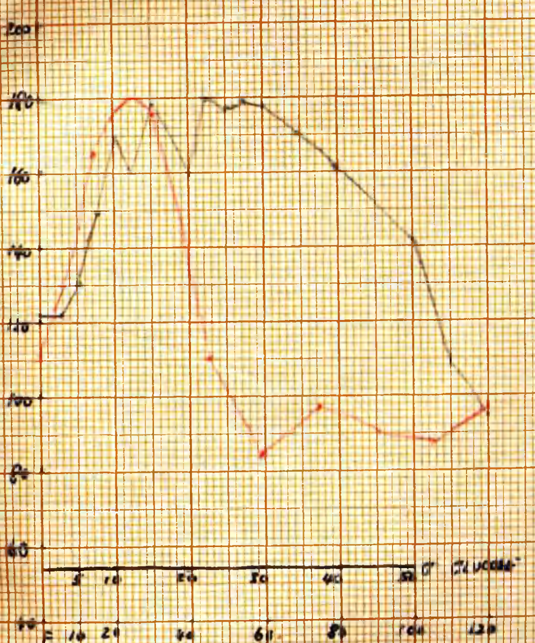


CHART 2.

COMPARISON BETWEEN NORMAL DEXTROSE TOLERANCE CURVE (1.) AND CURVE TAKEN FROM 38 CASES OF PANCREATIC ADENOMA.

CHART 3

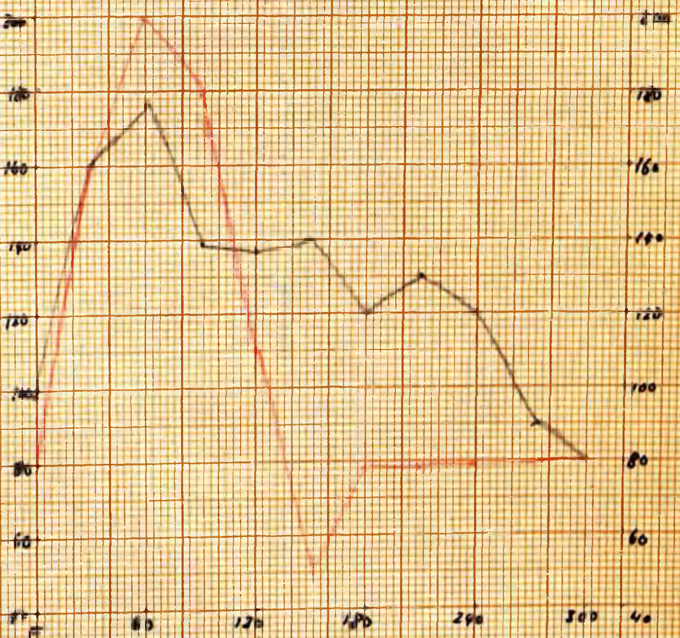


A – Effect of the Intraduodenal Injection of Glucose at different rates on the capillary blood sugar of a Normal Adult.

0.5 G. PER MINUTE FOR 100 MIN.

4.5 G. PER MINUTE FOR 11 MIN

FROM HALE-WHITE & PAYNE



B – Effect of the ingestion of 100 G. glucose on the capillary blood sugar of a case of pyloric stenosis before and after gastro-enterostomy.

AFTER THE OPERATION

BEFORE GASTRO-ENTEROSTOMY

FROM MEYER.

CHART 4.

COMPARISON BETWEEN NORMAL INSULIN TOLERANCE CURVE (1) AND CURVE FROM CASE OF HYPERINSULINISM.

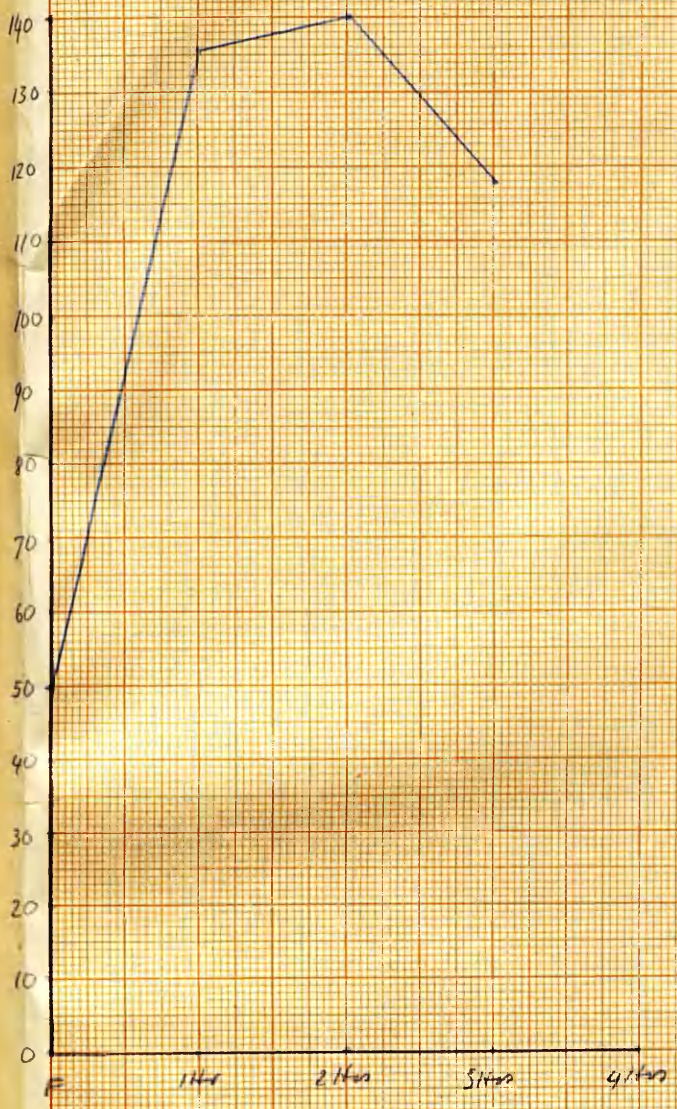


CHART 5.

COMPOSITE GRAPH OF DEXTROSE TOLERANCE TESTS IN 44 CASES OF PANCREATIC ADENOMA (MEYER, AMPTMAN AND PERLMAN).