the ulcer seen for the first time with a long recurrent history—particularly if its position in the stomach is then on the more distal lesser curvature.

The Duodenal Ulcer

But what of the duodenal ulcer?—variously estimated as three times more common than gastric ulcer in London, five times more common in the country as a whole, seven times more common in the Army, and ten times more common in America. There is here, if anything, a slight swing of the therapy pendulum to the medical side, and this from a logical point of view I find hard to understand. Admitted that it is not such a fatal disease, that the bogey of carcinoma is absent, and that probably, at all events in the earlier stages, the periods of natural remission of symptoms are longer—even so, most duodenal ulcers eventually follow a similar pathological course to that of gastric ulcers, including one feature not common to gastric ulcer—obstruction. A young patient with duodenal ulcer, with a relatively short history and mild symptoms, particularly if his ulcer is uncomplicated and he himself a neurotic, is going to call for medical measures. But I can see no reason for varying the course previously mentioned for gastric ulcer should the response not be both definite and rapid. To let a duodenal ulcer, simply because it is unlikely to be fatal, become intractable and complicated is to let it be intolerable to the patient and a reflection on his medical attendants. When surgery becomes a necessity in such a case the technical and mechanical difficulties are often far greater than those of the largest gastric ulcer. It is a question, as so often is the case in medicine, of being forewarned and forearmed.

Having mentioned obstruction as an ultimate outcome of duodenal ulceration, I might briefly consider, and perhaps slightly lament the passing of, the operation of gastro-jejunostomy. Twenty years ago it was the accepted surgical treatment of peptic ulceration. Many thousands of patients have obtained permanent relief from it. But many series of figures in other countries have shown that on this scale it will have a 25% failure rate—obviously too high to balance its slightly (now only very slightly) lower mortality rate than procedures which have succeeded it. It looked as though vagotomy might give it renewed popularity. But there is still a small group of patients with duodenal ulcer who, if carefully selected, will benefit as much from gastro-jejunostomy as they would from gastrectomy.

Assessment of Surgery

And now, what of the results of surgery? The mortality from gastrectomy should now be less than 2%. For this we have to thank the advances in anaesthesia in the last 10 years, the greater appreciation of the need for adequate pre- and post-operative treatment (particularly in respect of hydration and blood chemistry), and the wider application of the antibiotics and sulphonamides. It may be asked whether 2% is still not too big a risk. As the overall morbidity rate of peptic ulceration is very little less, and would appear to be rising, I should say it is not. If, as I have advocated, (a) an effort is made to bring ulcers earlier in their course to surgery, and (b) so far as is possible a standardized and simplified operation is evolved, then the operation should become still safer.

The question of the assessment of results is a very difficult one. Any firm and scientific basis is almost impossible to find. Both physical and psychological factors have to be evaluated and integrated. One of the most satisfactory results of a good gastrectomy is not so much the actual disappearance of pain as the mental reaction of the whole patient's make-up to this absence.

And so to be successful we must get rid not only of the patient's ulcer but also of his fear of the ulcer. Failure in either of these two respects accounts for the two great groups of post-gastrectomy complications—the recurrent ulcer, and that series of mechanical, nutritional, and meta-

bolic disturbances nowadays included under the term "the dumping syndrome." In assessing results, therefore, we must discover not only that a patient has lost his pain but that his weight is improving, that he is not anaemic, that he can take a reasonable-sized meal at reasonable intervals and enjoy it, that he has no untoward and unpleasant post-prandial symptoms, and that he is in himself happy and contented. This admittedly is a very empirical basis for assessment of success, or lack of it. I hope I am not being unduly optimistic in suggesting that 95% of patients who have a gastrectomy are satisfied—very roughly, 75% completely so, and 20% sufficiently so (despite some minor residual symptoms) to be glad they had had the operation. It is the remaining 5%, of course, who should really interest us as surgeons—as doctors. Why is every one in twenty a failure? There are probably three main causes for this: one due to the surgeon, faulty technique; one to the patient, that peculiarly labile psychological make-up common in the ulcer patient; and one due to neither, intercurrent disease.

Whether these defects, except for the first, can be corrected lies in the future; and by then we may have ceased carrying out a major operation, however safe and however successful, for a condition the aetiology of which is still wrapped in mystery.

THE VARIABILITY OF ENDOCRINE DYSFUNCTION IN POST-PARTUM HYPOPITUITARISM

BY

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It is largely due to the work of Sheehan (1937, 1939, 1940) that the clinical picture of post-partum hypopituitarism (Simmonds's disease) is becoming more widely recognized. Six such cases have been investigated over a period of six months, and an attempt has been made to determine the value of certain investigatory procedures which have been introduced in recent years. Cook *et al.* (1951) have described seven severe cases of post-partum hypopituitarism seen during the 15-year period 1935 to 1950. Six of these had been diagnosed during the last two years. As they point out, this indicates an increased awareness of the condition rather than a greater incidence, since the liability to post-partum pituitary necrosis should have fallen with better ante-partum and natal care.

In 1942 Escamilla and Lissner laid down "four cardinal characteristics" before they would accept the diagnosis of Simmonds's disease. These were (1) loss of weight, (2) loss of sexual function, (3) asthenia, and (4) a basal metabolic rate below -20%. However, Sheehan (1948) has shown that loss of weight is unusual in hypopituitarism, and when present may be due to some complicating factor. By definition, Escamilla and Lissner (1942) were restricting their material without knowing what the real clinical picture should be, for it is only on a pathological basis that this can be decided.

The one essential criterion for the diagnosis of hypopituitarism is evidence of destruction of the anterior pituitary (Simmonds, 1914; Sheehan, 1948). In the case of post-partum hypopituitarism one must have a definite history of haemorrhage and collapse at the time of delivery followed by failure of lactation and amenorrhoea. Further symptoms develop which have

been adequately described elsewhere (Sheehan and Summers, 1949) and are further illustrated by the following case reports.

Case 1

A woman aged 59 complained of asthenia, pallor, intolerance to cold, and occasional oedema of the ankles after a difficult labour 24 years previously. At that time she was delivered of a stillborn baby weighing 16 lb. (7.3 kg.). This resulted in post-partum haemorrhage followed by complete amenorrhoea. Since then there had been a gradual loss of 4 st. (25.4 kg.) in weight. During the past six years the knees had become painfully contracted.

On examination she was seen to be obese, cerebraation was slow, and many blankets were required to keep her warm. The skin was very pale, smooth, and glistening. The eyebrows were thinned, especially the outer portions, and axillary and pubic hair was completely absent. The knees showed gross signs of osteoarthritis, with ankylosis in a position of 90 degrees flexion. In addition there was a severe delusional psychotic state. Five days after having been seen in the out-patient department she was admitted urgently because of severe abdominal pain, vomiting, and diarrhoea. The pain was chiefly localized to the left iliac fossa, and had been present for two days. The blood pressure was reduced to 90/60 mm. Hg. In spite of increasing abdominal tenderness, rigidity, and distension there was no pyrexia or leucocytosis. Operation revealed a ruptured appendix with peritonitis. Careful pre- and post-operative treatment with glucose-saline, adrenal cortical extract ("eucortone"), and streptomycin enabled the patient to make an uneventful recovery. There has been a great clinical improvement as a result of treatment with methyl testosterone, sodium chloride, and small doses of thyroid.

Case 2

A woman aged 47 attended the out-patient department because of the recent onset of left-sided pleural pain. There were no clinical signs of pulmonary disease; x-ray examination of the chest was negative, and the pain soon disappeared. She also complained of mild asthenia, intolerance to cold, pallor, anorexia, "bilious attacks," and occasional ankle oedema. These symptoms had developed after a difficult labour 16 years previously in which there occurred retention of the placenta, post-partum haemorrhage, and collapse. She had been unable to suckle the baby, and complete amenorrhoea followed this pregnancy. She had not experienced hot flushes, and there had been no loss of weight.

On examination she was quite bright and co-operative. The skin was smooth, yellowish, and pale. The areolae were depigmented. There was no loss of the eyebrows, but the axillary hair was absent. Some pubic hair was still present. Treatment with methyl testosterone has caused a gain in weight of 1 st. (6.4 kg.) in six weeks. Her appetite has improved, she has more energy, and no longer complains of the cold.

Case 3

A woman aged 30 had had recurrent attacks of headache during the past nine years. These were occasionally associated with fortification spectra, paraesthesiae, and vomiting. During this period there had been some diminution of energy and increased sensitivity to cold but no loss of weight. These symptoms, along with amenorrhoea, followed a post-partum haemorrhage due to retained placenta. She had been unable to suckle her child, and had noticed a gradual loss of axillary hair and eyebrows. The pubic hair had failed to grow after having been shaved. It is of interest that six years after the post-partum haemorrhage the patient was operated on for acute appendicitis, and the operation notes stated that the uterus was infantile in size.

On examination she was bright and intelligent. The skin was pale and smooth. Erythema ab igne was present. The

eyebrows were thinned, and there was no axillary and very little pubic hair. The breasts were atrophic, and the areolae were very pale in spite of the dark scalp hair.

Case 4

A woman aged 47 was admitted urgently because of vomiting, dizziness, and lumbar backache of 24 hours' duration. Three weeks previously an "influenzal illness" had caused an exacerbation of her asthenia and coldness. She stated that following a difficult labour 13 years ago she had never been her normal self. The chief complaints were asthenia, amenorrhoea, and undue sensitivity to cold; and aching pains in the knees had recently developed. There had been no loss of weight or hot flushes.

On examination the temperature was 101.4° F. (38.6° C.), and she was drowsy and lethargic. The skin was dry and smooth. The eyebrows were scanty, and there was almost no axillary or pubic hair. The blood pressure was 90/55 mm. Hg. There was slight ankle oedema, and the knees were held in a position of flexion. The blood chemistry was not investigated as an urgency, and the patient recovered when given glucose-saline drinks.

Case 5

A woman aged 59 was admitted complaining of severe asthenia, intolerance to cold, and painfully contracted knees. Eighteen years previously she had had a difficult labour followed by puerperal fever and amenorrhoea. Since that time she had been subject to attacks of vomiting, delirium, pyrexia, hypotension, and coma. These attacks seemed to be precipitated by mild infection, and lasted for two or three days. During the past seven years they had necessitated her admission to one hospital on no fewer than seven occasions. Unfortunately, during these attacks blood analysis was not done. There had been no loss of weight. The affection of the knees was of only six months' duration.

On examination there was pronounced apathy and depression. Questions were answered slowly in monosyllables. She appeared extremely pale and her skin was smooth, shining, and yellowish. The eyebrows were scanty, and the axillary and pubic hair was almost completely absent. The knees were painful, somewhat swollen, and ankylosed in a position of flexion. There was depigmentation of the areolae. During her stay in hospital she developed an attack in which the blood pressure dropped from 180/110 to 95/75 mm. Hg, the temperature rose to 102° F. (38.9° C.), and coma supervened. The blood sugar was 60 mg. per 100 ml., the serum sodium 270 mg. per 100 ml., and the plasma chloride 390 mg. per 100 ml. The urine contained 4 g. of chloride per litre. She soon recovered when given intravenous glucose-saline, eucortone, and deoxycortone acetate. A week later she had a further attack, in which she was restless, screaming, and irrational. The blood sugar was now found to be 15 mg. per 100 ml. There was a prompt response to intravenous glucose. During the next three weeks she was in and out of hypoglycaemia in spite of the administration of intravenous glucose-saline and eucortone.

Case 6

A woman aged 32 was admitted urgently in a stuporous state. Two weeks previously she had had a similar attack of confusion and drowsiness, from which she recovered spontaneously. She had been quite well until three months previously, when she had had a severe post-partum haemorrhage with retention of the placenta. She was very severely shocked and required blood and plasma transfusion. The haemoglobin dropped to 5.5 g. per 100 ml. and the blood pressure was 70/35 mm. Hg. There was a failure of lactation followed by amenorrhoea. Marked asthenia, increased sensitivity to cold, anorexia, and a loss of 1 st. (6.4 kg.) in weight supervened.

On admission she was pale, drowsy, and irritable. Her skin was dry and rather smooth. The eyebrows were scanty and there was almost no axillary or pubic hair. The areolae

were still pigmented, and erythema ab igne was present. The blood sugar was only 41 mg. per 100 ml. She responded rapidly to glucose-saline and eucortone. During the next 10 days the blood sugar varied between 24 and 76 mg. per 100 ml.

Variation in Severity of Clinical Picture

A summary of the biochemical findings in the six cases is shown in Table I. The symptoms and signs are explicable by damage to the anterior pituitary followed by secondary failure of the thyroid, adrenal cortex, and ovary. It is important, however, to recognize that there may be a selective defect, one gland being affected more than another, and thus we have the introduction of such terms as "pituitary myxoedema" (Means *et al.*, 1940; Lerman and Stebbins, 1942) and "pituitary Addison's disease" (Lang, 1946).

TABLE I.—Laboratory Data on Six Patients with Simmonds's Disease

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Haemoglobin (g./100 ml.)	10.7	10.1	14.2	11.0	11.0	9.0
Basal metabolic rate (%)	-65	+1	+15	-15	-10	-20
Blood cholesterol (mg./100 ml.)	200	280	290	192	125	186
Serum sodium (mg./100 ml.)	336	334	320	310	314	317
Serum potassium (mg./100 ml.)	19.2	20.6	31.6	16.0	24.0	20.0
Kepler test	Positive	Negative	Positive	Positive	—	Positive
Kepler factor	10	—	35	10	—	—
Insulin-tolerance test (120-minute blood sugar expressed as percentage of fasting blood sugar)	Hypoglycaemia Unresponsiveness 82	Normal	Border-line result	—	—	—
17-ketosteroids (mg./24 hrs.)	4.2	7.0	3.4	1.7	1.9	4.9
Gonadotrophins (mouse units/24 hrs.)	<5	<3	27	<3	<3	19

Certain clinical features are common to all cases—asthenia, intolerance to cold, diminution of libido, and amenorrhoea. The skin, which is smooth and glistening, has a peculiar waxy pallor out of all proportion to the degree of anaemia. The eyebrows are usually thinned and the axillary and pubic hair is absent or nearly so. The areolae are usually depigmented and the external genitalia atrophic. Gallavan and Steegmann (1937) comment on the frequency of arthritis of the knees in these patients.

There was a marked variation in the severity of the clinical picture in the six cases. Two of these (Cases 2 and 3) were exceptionally mild and first presented with symptoms (pleural pain and headache respectively) presumably unrelated to the hypopituitarism. The degree of asthenia was slight in these two cases, and both patients were able to do their own housework, and, in addition, Case 3 was capable of working in a light occupation. In two of the others (Cases 1 and 5) the condition was very severe and both were bedridden, the first patient for six years and the second for six months. Marked arthritis of the knees was present in both of them, and it was also present, but to a less degree, in Case 4. This last patient came with backache, vomiting, pyrexia, and hypotension, probably due to an adrenal crisis. Case 5 had many attacks of a similar nature, and marked lowering of the serum sodium and plasma chloride was found. In addition she had a prolonged spontaneous hypoglycaemic attack. Case 6 also presented with hypoglycaemia.

The severity of the clinical picture does not appear to be entirely related to the duration of the disease process. Thus the hypopituitarism in Case 6 was quite severe in spite of the fact that the condition had been present for only three months. The amount of haemorrhage and degree of collapse at the time of delivery are probably of supreme importance. It is, however, difficult to obtain an accurate retrospective assessment of the severity of blood loss and degree of shock.

Discussion of Investigatory Procedures

On investigation a normochromic anaemia is the usual finding, often associated with lymphocytosis and sometimes with eosinophilia. The leucocyte changes are presumably related to the diminution of 11-oxycorticosteroids secreted by the adrenal cortex.

The basal metabolic rate is usually much reduced—in fact, Escamilla and Lissner (1942) described this as one of their "cardinal characteristics." In the present investigation the two mildest cases (Nos. 2 and 3) had normal values even after repeat estimations had been performed. In this connexion it is interesting to note that in discussing the diagnosis of myxoedema Asher (1949) states: "I have found the basal metabolic rate of little help." Recently I have seen two cases of myxoedema due to Hashimoto's disease, both of which had elevated basal metabolic rates in spite of the fact that there was little or no radioactive iodine uptake by the thyroid after a tracer dose. The blood cholesterol in hypopituitarism is either normal or slightly elevated and does not reach the high values found in primary myxoedema.

The serum sodium and potassium usually show little change except when an adrenal crisis develops, in which case the former is reduced and the latter may be raised. It was certainly surprising to find a marked elevation of the serum potassium in Case 3. This was found on several occasions, and the urinary potassium excretion was only 0.6 g. in 24 hours. There were no electrocardiographic changes attributable to the hyperpotassaemia.

The Kepler test (Robinson *et al.*, 1941) has been of great value in assessing adrenocortical insufficiency—primary or secondary. Levy *et al.* (1946) have found positive values in 11 cases of pituitary insufficiency, and in each patient the Kepler factor was less than 30. Simpson (1948) obtained similar results in four patients. In the present series five cases were investigated, with positive results (failure of water diuresis) in four. In one of the mildest cases (Case 2) the test was negative, and in Case 3 the factor was over 30. In Case 6 the delay in water diuresis was so pronounced that calculation of the factor was impracticable.

The insulin-tolerance test (Fraser and Smith, 1941) was carried out on three of the patients, full dosage of insulin (0.1 unit per kg. body weight) being used; the results are shown in the Chart.

The test was not carried out if the fasting blood sugar was below 70 mg. per 100 ml. Case 2 failed to show the usual "hypoglycaemia unresponsiveness," and Case 3 gave a borderline result. Fraser and Smith (1941) in investigating 10 cases of pituitary insufficiency found hypoglycaemia unresponsiveness in each patient. The 120-minute blood sugar varied between 47% and 80% of the fasting level, with a mean of 63%. More recently Forbes *et al.* (1950) failed to demonstrate hypoglycaemia unresponsiveness in two patients with hypopituitarism. This test was also negative in a male case verified at necropsy (Paschakis and Cantarow, 1951). Dangerous hypoglycaemia may result from intravenous insulin in these patients (Hausmann *et al.*, 1951), but there seems to be little doubt that mild cases of hypopituitarism will not show the expected hypoglycaemia unresponsiveness.

It has been repeatedly emphasized that the excretion of 17-ketosteroids in hypopituitarism is extremely low. In fact, Fraser *et al.* (1941) found zero readings in 13 out of 15

Insulin-tolerance curves on three of the cases. Case 1, "hypoglycaemia unresponsiveness." Case 2, normal. Case 3, borderline result.

patients, and the other two averaged only 1.4 mg. and 1.8 mg. a day. The values obtained in the present series, although low, are much higher than those found by other workers. This may be due to the method used, but is more likely the result of investigating mild cases. O'Donovan (1948) also comes to the conclusion that this test is not very helpful in mild or borderline cases, in which the adrenal secretion may not be significantly reduced. Simpson (1948) records one undoubted case of hypopituitarism with an excretion of 12 mg. a day. Tucker *et al.* (1950) suggest that the determination of 17-ketosteroid excretion, and also the insulin-tolerance test, although extremely useful, may not disclose instances of partial anterior pituitary failure.

One expects the gonadotrophin excretion, as a direct indication of the activity of the anterior pituitary, to be extremely low in these patients. Klinefelter *et al.* (1943) found the excretion to be below 3 mouse units a day in seven out of nine patients. All 14 patients whom they investigated had excretion levels below 6.6 mouse units a day. Surprisingly enough, two of the present series had normal excretion values. Oelbaum and Wainwright (1950) have recorded a normal gonadotrophin output in a male case of hypopituitarism, verified at necropsy.

Conclusions

We can now see that the various laboratory investigations give a most interesting combination of results. One of the mild cases of hypopituitarism (Case 2) shows only a deficiency of gonadotrophin excretion with apparently normal thyroid and adrenocortical function. On the other hand, the other mild case (Case 3) has a normal gonadotrophin output and normal thyroid function, but a slight reduction of adrenocortical activity as witnessed by low 17-ketosteroid excretion, a positive Kepler test (but high factor), and borderline insulin tolerance. Case 1 has severe thyroid failure and much adrenocortical damage. Cases 4, 5, and 6 all appear to have severe adrenocortical insufficiency and also some degree of hypothyroidism (see Table II). It is certainly surprising to find hypertension in Case 5 when there is such adrenocortical damage.

TABLE II.—Variation in Degree of Damage to Hormone Production

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Gonadotrophin ..	+++	++	0	+++	+++	0
Thyrotrophin ..	+++	0	0	++	++	++
Adrenocortico- trophin ..	++	0	+	+++	+++	++

0 = no damage. + = mild damage. ++ = moderate damage. +++ = severe damage.

Paschkis and Cantarow (1951) have noted a similar variation in functional damage to the thyroid, adrenal cortex, and gonads as a result of pituitary tumours. Moreover, they also found a dissociation in the results of the three broad spheres of adrenocortical activity even in the same patient. Thus in one patient there was a normal 17-ketosteroid excretion in the presence of hypoglycaemia unresponsiveness, in four patients the converse was found, and in two patients the salt excretion was abnormal in the presence of a normal response to insulin.

As in all branches of medicine, it becomes obvious that biochemical tests can be interpreted only against the background of past history, symptoms, and physical examination. If one waits until all the biochemical characteristics are present, then milder cases of the disorder under question will be missed. I cannot do better than quote O'Donovan (1948): "If we have to achieve a more frequent diagnosis of partial pituitary necrosis we must include amenorrhoea and uterine atrophy, dating from a pregnancy, even in the absence of all the other clinical and biochemical characteristics of Simmonds's disease. Finally, it appears that biochemical and metabolic investigations are not of great assistance in diagnosis, as they are positive only in

the gross manifestations of the syndrome, when the clinical diagnosis is already obvious to at least the more initiated observer."

Summary

Six cases of hypopituitarism due to post-partum necrosis are described. The biochemical findings have been analysed, and it has been shown that there may be a marked dissociation in the degree of functional impairment of the thyroid, adrenal cortex, and gonads. The diagnosis of hypopituitarism can be made in mild cases even when most of the results of investigatory procedures are normal. The clinical features are of paramount importance in the detection of partial anterior pituitary failure.

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Operations for the control of tuberculosis and malaria are to begin shortly in Sarawak with the help of the World Health Organization. A team of specialists in B.C.G. vaccination and a malaria adviser have just left Manila, headquarters of the W.H.O. Regional Office for the Western Pacific, to assist the Sarawak authorities. The B.C.G. team will stay in Sarawak about nine months to demonstrate the most suitable methods of tuberculin-testing and mass B.C.G. vaccination and to train local staff to carry on the work. The malaria adviser will remain there for two years, directing a pilot project to determine whether D.D.T. residual spraying in houses is effective in controlling malaria in this territory, where three species of anopheles mosquitoes are suspected of transmitting the disease. Tuberculosis is said to be the most urgent problem confronting the medical department of Sarawak. The B.C.G. team is to carry out a survey as well as protective vaccination of about 50,000 people in major centres of the colony. Equipment and supplies for the malaria project will be provided by W.H.O. under technical assistance, while further material will be made available by the Government of Sarawak. The technical personnel of the B.C.G. campaign is provided by W.H.O. subject to reimbursement by Unicef; Unicef and the Government will also furnish equipment for this work. In both the antituberculosis and antimalarial operations parallel teams working with the international advisers will be provided by Sarawak health authorities.