already red and injected, the attempt was abandoned. The abdomen was then closed without drainage.

Next day she was much better. Morphine and progesterone were given daily in an attempt to postpone labour, but four days after the operation labour started, and she was delivered spontaneously of a living child weighing 6 lb. (2.7 kg.) after an easy labour lasting 17 hours. She did not complain unduly of any discomfort in the abdominal wound. Her subsequent progress was uneventful. A test meal in the puerperium revealed marked hyperchlorhydria, and a barium meal six weeks after the operation showed that the ulcer was still active and there was some delay in emptying. She was discharged to continue medical treatment, but further surgical measures may be necessary at some future date.

Commentary

This case must be regarded as an exception, for a proved duodenal ulcer was aggravated during pregnancy and perforated at the 36th week. The diagnosis was not difficult once it was realized that an ulcer had existed before pregnancy. A perforated appendix could not, however, be entirely excluded, and for this reason treatment by continuous suction was rejected.

There appears to be no reason why pregnancy should predispose to perforation in the rare cases of active ulceration, but it is possible, in the case of a duodenal ulcer, that rearrangement of the viscera with traction on the mesentery by the enlarging uterus could lead to duodenal ileus. Hurst and Stewart (1929), however, describe the rising uterus supporting the stomach as one of the main reasons for the favourable influence of pregnancy upon the symptoms of ulcer.

The reason for this apparently beneficial effect of pregnancy upon peptic ulcer is not altogether clear. Hurst's explanation was given before the significance of endocrines in pregnancy was appreciated; and while the support of the uterus might benefit a gastric ulcer in the long type of stomach it is difficult to see how it could help a duodenal ulcer in the short high stomach. Two other factors are probably involved: (1) the physiological atony which is believed to occur in the smooth muscle of the alimentary canal during pregnancy—it is even possible that the stomach may pass through similar phases of alteration in tone comparable to those which are known to occur in the ureter; (2) the hypochlorhydria which is so often found during pregnancy.

Way (1945) has investigated the relation between gastric acidity in pregnancy and the presence of gonadotrophic hormone in the urine. His results suggest that the secretion of acid varies inversely with the concentration of gonadotrophic hormone present at the same time in the urine. These two factors, probably controlled by the endocrine system, might operate together to alter favourably for the duration of pregnancy two of the adverse conditions so often present in the ulcer diathesis—viz., hypermotility and hyperacidity.

It is well known that 80–90% of all peptic ulcers in adults occur in men. Differences in mode of living may be partly responsible, but endocrine factors are probably also involved in this very definite sex-incidence. Bockus (1944) suggests a direct relation between pituitary hormones and peptic ulcer apart from pregnancy. He quotes the following evidence as suggestive, but it is still unproved: (1) Pituitary hormones and urinary extracts have prevented experimental ulcer in animals; (2) the occasional occurrence of polyuria in ulcer patients; (3) many female patients with peptic ulcer show masculine endocrine characteristics.

If it could be proved that pituitary hormones are able to reduce the secretion and motility of the stomach a new method of treatment might be established to rival the

popularity of vagal resection. The beneficial effects of pregnancy upon peptic ulcer are therefore worth considering if only to see whether the conditions could be reproduced in the non-pregnant state.

In actual practice the obstetrician faced with the rare association of peptic ulcer and pregnancy need only remember two things; first, to survey the case from the endocrine point of view to exclude masculine characteristics suggesting an android pelvis and possible dystocia; and, secondly, to pay serious attention to any symptoms of indigestion that may occur during the pregnancy.

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APLASTIC ANAEMIA IN SIMMONDS'S DISEASE

REPORT OF A CASE

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The part that the pituitary gland plays in erythropoiesis is uncertain, and although disease of the pituitary may be associated with anaemia its mode of action is unknown. In his review of Simmonds's disease Sheehan (1939) found that there was nearly always a moderate anaemia and that this anaemia is usually hypochromic in the early stages. After many years the hypochromic anaemia may give rise to the hyperchromic variety, and according to Sheehan these hyperchromic anaemias are most often seen in cases in which there is a severe hypothyroid element. Escamilla and Lisser (1942), in their review of 101 typical verified cases, found that in those cases in which relevant data were given the average haemoglobin was 65% (minimum 40%) and the average red blood cell count 3,710,000 (minimum 2,000,000). It is not stated what type of anaemia was present. Snapper *et al.* (1937), describing cases of pituitary and gonadal deficiency, suggest that insufficiency of the anterior lobe of the pituitary may be followed by achlorhydria and that this achlorhydria may induce anaemia after a long interval. The anaemia may be identical with that in pernicious anaemia (Witts, 1942), and in these cases it responds to liver therapy as anticipated. They suggest that anaemia is absent in cases of Simmonds's disease of short duration because the anaemia occurs only after the achlorhydria has been present for a considerable time. However, Simmonds's disease is commonly associated with both hypothyroidism and hypogonadism, and either of these conditions in itself may be responsible for an anaemia. Bomford (1938) and Jones (1940) have described hypoplasia of the bone marrow in hypothyroidism, while recently Watkinson *et al.* (1947), describing two cases of hypopituitarism and hypogonadism, conclude that the long-standing hypogonadism may be responsible for the observed hypocellular bone marrow.

However, although Simmonds's disease may be associated with anaemia, no reference to an associated aplastic anaemia can be found in the literature. In the case to be described a patient with Simmonds's disease of twenty years' duration was admitted with aplastic anaemia, and in view of this complication a report on the clinical and pathological findings may be of interest.

Case Record

A woman aged 45 was admitted in a comatose state on June 26, 1947, and died four days later. The following history was obtained from her mother and husband.

The patient had one daughter, now aged 20. The delivery was a difficult one, and forceps were applied, but there was no clear history of post-partum haemorrhage. She was unable to feed the infant because the "milk dried up." Although before the pregnancy both menstruation and libido had been normal, there was absolute amenorrhoea and complete loss of libido after the birth of this child. Both witnesses observed a marked change in the patient's personality at this stage, for whereas previously she had been active and cheerful she now became too tired to do much, unenterprising, and uncommunicative. She showed an unnatural lack of interest in her daughter and her surroundings, and in later years hardly left the house. Her appetite had been poor, and on occasion she had bouts of vomiting. There was no convincing history of sensitivity to cold. For the last year she complained that her eyes were "funny," but nothing more precise. Eight months ago she had some teeth extracted because they were "septic." Three months ago her gums began to bleed and she was confined to bed. She had never taken medicine, apart from an occasional aspirin, until she was first seen by a doctor some few days before admission.

On admission the patient looked considerably older than her age—in fact, older than her mother. Her complexion was pale and waxy, with a faint malar flush. Her skin was not noticeably dry, but her hair was greying, scanty, and brittle. Her eyebrows were thin and there was an almost complete absence of pubic and axillary hair. Her nutritional state was moderately good and her breasts were not obviously atrophic. There was dried blood round the mouth, and the gum margins were ulcerated and bleeding; many teeth were missing and there were ulcers inside the mouth. She was in a comatose state, but could be roused to obey simple commands. Temperature, 103.6° F. (39.8° C.); pulse, 116; B.P., 100/68, early systolic blowing murmur in all areas. No petechiae present on the skin. No abnormalities were found in the chest, abdomen, or central nervous system.

Investigations

Peripheral blood and sternal marrow examinations were made on June 27 by Dr. Mohun. The blood count showed: red cells, 1,130,000 per c.mm.; Hb, 25% (3.4 g.); C.I., 1.1; white cells, 1,800 per c.mm. (polymorphs 19%, lymphocytes 77%, large mononuclears 4%); packed cell volume, 12%; mean corpuscular volume, 106 c. μ ; mean corpuscular haemoglobin concentration, 29%. Moderate anisocytosis.

The total nucleated cell count of the sternal marrow was indistinguishable from that of peripheral blood—approximately 2,000 per c.mm. Prolonged search of the smears showed extremely few nucleated cells; of these approximately half were lymphocytes, and the remainder consisted of occasional neutrophil polymorphs and intermediate and late normoblasts. The marrow in the sternum was aplastic.

The blood chemistry (June 30) was as follows: Fasting sugar, 64 mg.; cholesterol, 114 mg.; urea, 120 mg. per 100 ml.; Wassermann and Kahn reactions, negative.

Treatment and Progress

Blood was transfused by slow drip; in all she received 2,160 ml. of cross-matched Group A blood. She was also given 50,000 units of penicillin every three hours, 5 mg. of desoxycortone acetate daily, and 1,000 mg. of ascorbic acid intravenously. Glucose drinks were given by mouth.

Her temperature fell slowly almost to normal, but her general condition steadily deteriorated, with deepening coma

and a fall in blood pressure. She was incontinent of urine, but appeared to pass adequate quantities. Her blood picture on June 30, after transfusion of 1,080 ml. of blood, was: red cells, 2,610,000; Hb, 56% (7.7 g.); C.I., 1.1; white cells, 800 per c.mm. (polymorphs 50%, lymphocytes 50%). No nucleated red cells were seen.

The patient died on July 1.

Pathological Report

Summary of Necropsy (No. 3126/47). Simmonds's Disease: Haemorrhage Cyst of Pituitary: Aplastic Anaemia.—Moderate atrophy of heart. Moderate thickening and fibrosis of cusps and shortening and thickening of chordae tendineae of mitral valve; probably slight old rheumatic endocarditis. Slight atheroma of aorta and coronary arteries. Congestion and emphysema of lungs. Focal lymphocytic infiltration and slight septal fibrosis of slightly atrophied thyroid. Parathyroids not enlarged. Oedema and anaemia of liver, with slight fatty change; free iron in some Kupffer cells. Slight myeloid reaction and iron pigmentation in firm congested spleen, enlarged to about twice the normal size. Oedema of kidneys. No abnormality in pancreas, stomach, and intestines. Fibrosis of rather small ovaries. Pale, smooth, atrophic endometrium lining atrophied fibrotic uterus. Hair of head thin and greyish; eyebrows scanty; axillary and pubic hair almost completely absent. A moderately well-nourished woman. The pituitary fossa was occupied by a cyst measuring 2.5 $\times$ 2 $\times$ 2 cm., which pressed on and indented the base of the brain; the optic chiasma was stretched over the surface of the tumour. The sella turcica was widened and the clinoid processes were reduced in size, but there was no erosion of the bone. On sagittal section the wall of the cyst was 0.3 cm. thick and was distended with recent and altered blood. The adrenals were very small and reduced to almost wafer thinness. The larger measured 2.5 cm. long by up to 0.3 cm. thick, and the maximum thickness of the cortex was 0.2 cm. The sternum contained fatty marrow; there were two small haemorrhagic areas at the upper end in relation to the site of a sternal puncture. The marrow throughout the femur was deep red and haemorrhagic.

Microscopical Examination.—Sections of the pituitary cyst, thyroid, adrenals, ovary, uterus, liver, spleen, kidney, lung, myocardium, mitral valve, vertebra, and the marrow from the sternum and upper end and middle of the femur were fixed in 4% saline-formaldehyde, imbedded in paraffin, and stained with Ehrlich's haematoxylin and eosin and with iron haematoxylin and Van Gieson's mixture. The pituitary cyst, liver, and spleen were also stained to demonstrate ferric iron. Sections of the pituitary cyst showed a dense hyaline fibrous wall lined with recent and old organizing blood clot in which cholesterol crystal clefts and a few areas of foreign-body giant cells were present. There was some chronic inflammatory reaction with deposition of free iron and areas of ectopic osteoid tissue in the cyst wall. A little residual anterior-lobe glandular tissue, composed chiefly of chromophobe cells, was present on the outer aspect of the wall, in one place with recent haemorrhage into it, and adjacent to it was part of the posterior lobe, which appeared quite normal. The adrenals showed fibrous thickening of the capsule and slight trabecular fibrosis of the cortical tissue, which was composed of groups of polyhydral cells and showed no differentiation into the normal zones. The medullary tissue was degenerate; the cells stained poorly and their outlines were indistinct. The sternal marrow was almost completely aplastic, consisting of a few scattered primitive haemopoietic cells in fatty tissue. The marrow from the femur and vertebra was aplastic, being composed mainly of fat; scanty small foci of normoblastic and occasionally megaloblastic erythropoiesis and a few groups of haematocytoblasts were present; leucopoiesis was almost entirely absent. The marrow in these last two sites was extensively infiltrated with recent haemorrhage, to which its deep-red appearance was evidently due.

Comment

The onset of Simmonds's disease is usually related to pregnancy, often associated with excessive haemorrhage. The usual pathological finding in these cases is fibrosis and

atrophy of the anterior lobe of the pituitary as a result of necrosis due to thrombosis.

Apart from cystic degeneration in tumours and those arising in association with craniopharyngiomata, cysts of the pituitary large enough to cause pathological symptoms are rare, though small cysts arising in the tubules of the pars intermedia are not uncommon. An unusual feature of this case was the almost complete destruction of the anterior lobe by a haemorrhagic cyst. In view of the definite history of the onset of symptoms dating from the time of a difficult labour there can be little doubt that the pituitary destruction was related to the delivery.

It is difficult to see how haemorrhage alone could cause such a well-defined and circumscribed cyst, and a haemorrhage large enough to produce it would almost certainly have at the time of its occurrence caused severe optic chiasma pressure signs, of which there is no record. It is probable that the cyst was present before the pregnancy, causing some pressure atrophy of the anterior lobe, and that necrosis of this occurred at the time of delivery. There had undoubtedly been haemorrhage into the cyst on occasion; one of these was recent, but fibrosis and organization were too advanced to allow of any estimate of when others occurred. These changes also obliterated any evidence of the exact nature of the cyst.

Complete destruction of the anterior lobe seldom if ever occurs in Simmonds's disease (Sheehan, 1939) and the residual anterior-lobe tissue is usually composed mainly of chromophobe cells as in this case. The recent haemorrhage into this area may well have played a part in the patient's death. This haemorrhage, as also the other recent haemorrhages from gums and into the vertebral and femoral marrow, may have been secondary to the aplastic anaemia.

Cause of the Aplastic Anaemia

The association of the marrow aplasia with Simmonds's disease may be fortuitous, but in view of the absence of any other likely cause, and knowing that Simmonds's disease gives rise to anaemia, it seems reasonable to assume that the long-standing pituitary damage in this case resulted in the aplastic anaemia. It is known that pituitary hypofunction can give rise to a gastrogenic pernicious anaemia, and the aplastic anaemia may be the end-result of such a condition: unfortunately we have no knowledge of the previous state of the blood or whether achlorhydria existed. In this case, apart from the reduced size of the thyroid gland, there was little microscopical evidence of severe atrophy and the acini showed normal colloid formation. It seems unlikely, therefore, that thyroid hypofunction could have been responsible for the marrow hypoplasia. There was atrophy of the adrenals and the ovaries, but, so long as such uncertainty exists regarding the action of the endocrines on haemopoiesis, cases such as this can only give rise to speculation.

Our thanks are due to Dr. C. D. Coyle, medical superintendent of the Archway group of hospitals, for permission to use the clinical notes; and to Dr. Mohun, senior assistant pathologist, Archway group laboratory, for his co-operation and for providing the reports on the haematology and biochemical findings. We also wish to thank Dr. A. B. Bratton and Prof. H. L. Sheehan for their helpful criticism.

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Medical Memoranda

Typhoid Meningitis

A male Chinese aged 25 years was brought into Klang Hospital, Malaya, at 10.30 a.m. on Aug. 9, 1946, complaining of severe headache and pains over his whole body for ten days before admission. Before July 31, 1946, he felt perfectly well.

CASE HISTORY

On July 31 he felt unwell and developed a fever, severe frontal headache, vomiting, insomnia, and a continual aching sensation throughout his whole body, particularly in his legs. The headache was continuous until admission, and he vomited two or three times a day. His appetite was poor and he lost weight. There was neither diarrhoea nor constipation, and micturition was normal.

On Aug. 8 he found that his eyes were very sore in the light. There were no other symptoms.

Examination revealed a well-built Chinese; he was conscious, and showed no skin rash, jaundice, or other abnormalities. He liked to lie curled up on his left side and disliked light on his eyes. The temperature was 103° F. (39.4° C.), pulse 96, respirations 24. There was no neck stiffness, and Kernig's sign was negative. Clinical examination of the central nervous system, chest, and heart revealed nothing abnormal except the photophobia. Loss of weight was evident in both thighs. There was no muscle wasting. Abdomen: no masses or engorged veins were present; no tenderness or rigidity; liver and spleen not palpable; nothing abnormal per rectum.

Investigations on Aug. 9.—Blood film: negative for malaria. Blood count: haemoglobin, 70%; W.B.C., 10,000 (polymorphs, 69%; lymphocytes, 30%; monocytes, 1%). Urine: no albumin; no sugar; film negative. It was decided to observe him and repeat blood-film examinations for malaria.

On Aug. 10 his temperature was 103.4° F. (39.7° C.), pulse 92, and respirations 22. Condition unchanged. Blood films negative. On Aug. 11 temperature was 103.6° F. (39.8° C.), pulse 86, and respirations 22. He suddenly became worse about midday, complaining of a sudden and severe increase in the severity of the headache. His vomiting returned and became much worse. He now had neck stiffness, a positive Kernig's sign, and extensor plantar reflex. On lumbar puncture the cerebrospinal fluid was slightly turbid and under pressure. It was sent to the Institute of Medical Research, Kuala Lumpur, for full examination, and in the meantime the case was treated as a meningitis (our own laboratory film revealing pus cells but no organisms).

Penicillin, 100,000 units daily, was given, with sulphathiazole tablets (initial and second doses being 2 g., followed by 1 g. every four hours). As the patient showed no response, this treatment was discontinued on the morning of Aug. 14. In the afternoon of the same day the I.M.R. report was received.

Report from I.M.R.—Smear: moderate number of pus cells and Gram-negative bacilli. Culture: *B. typhosus* isolated in pure culture. Globulin: Nonne-Apel test positive. Protein: 200 mg. per 100 ml. Chlorides: 680 mg. per 100 ml. Cells: 550, of which 80% are polymorphs.

A sample of blood was taken for Widal and Weil-Felix tests. The result was T 1/480A-O. The Weil-Felix, as expected, was negative. This finding supported a diagnosis of typhoid meningitis.

On Aug. 18 the patient, being treated as a case of typhoid fever, began to improve. On Aug. 31 he developed cystitis and his urine was found to be full of pus cells. This condition disappeared four days later as rapidly as it came.

On Sept. 9 he was much better and complained only of a slight persistent frontal headache. He developed a right facial palsy. His white-cell count was now 11,000 (polymorphs, 73%; lymphocytes, 23%; monocytes, 4%). On Sept. 20 he felt fit except for the right facial palsy, which still persisted. His white-cell count was now 4,500 (polymorphs, 63%; lymphocytes, 32%; monocytes, 3%; eosinophils, 2%).

He was discharged on Sept. 30 fit except for slight facial palsy. Before discharge three consecutive faecal examinations were done, but all were negative.

COMMENT

I have reported this case because true suppurative meningitis due to *B. typhosus* is relatively rare. True, one out of ten patients get meningism in typhoid fever at the onset of the disease, but an actual meningitis is rare. When it does occur, recovery is rarer still, because early involvement of the nervous system, as in this case, is usually an indication that the prognosis is poor.

I should like to thank Dr. R. B. MacGregor, Director of the Medical Services, Malayan Union, for his kind permission to publish this case.

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