portal tracts there were more lymphocytes and histiocytes than normal. The fibrous tissue was not increased. The Kupffer cells contained no bile pigment. A diagnosis of biliary obstruction was made.

Laparotomy was performed on May 10. The gall-bladder was normal and the common duct was not dilated. On opening the duct there was only a moderate flow of bile. A probe was passed towards the porta hepatis. However, neither the right nor the left intrahepatic duct could be entered, and it was thought that there was an obstruction at the origin of the intrahepatic portion of the common duct. The common bile duct was drained, using a T-tube. No abnormality was found on palpation of the other intra-abdominal organs.

Apart from a low-grade post-operative fever, due to a pulmonary infection, and mild colicky abdominal pain, convalescence was uneventful. The quantity of bile which drained ranged from 75 to 480 ml. daily from the first to the tenth post-operative days. These figures are within normal limits (Rundle *et al.*, 1955).

Nine days after operation (May 19) a cholangiogram was done. The gall-bladder and bile ducts filled well and appeared normal. The biliary drainage tubes were removed on May 26. At this time the degree of jaundice was lessening (serum bilirubin 3.8 mg. per 100 ml.) and the patient was beginning to regain his appetite and to feel well. The eosinophils had fallen to 5% of 16,300 cells.

Improvement was steadily maintained, and when discharged on June 12 the jaundice had almost completely subsided and the patient was feeling well.

When last seen, on December 23, he appeared to be perfectly well; in the interim further shock treatment had been given. The serum bilirubin, the serum proteins, and the thymol turbidity values were normal, but the urinary urobilinogen was still increased. The total white cell count was 10,950 per c.mm., and 6% of these were eosinophils.

Discussion

Both the patient and his wife were convinced at the time of admission that the illness had resulted from chlorpromazine, and his medical attendants at first thought that he was suffering from hepatitis. It was necessary to distinguish between an obstructive jaundice and a hepatocellular jaundice. In favour of the former were the presence of dark urine containing bile pigments and salts, the pallor of the stools, and the rising level of the serum alkaline phosphatase. However, it was difficult to explain the presence of excess urobilinogen in the urine if this really was an obstructive lesion.

The presence of eosinophilia suggested the possibility of an allergic process. Hodgkin's disease was considered, but there were no enlarged glands and the spleen was not enlarged. Parasitic causes of eosinophilia were sought but were not found.

The results of the liver biopsy suggested an obstructive lesion, but this could not be definitely demonstrated at operation. In fact, the post-operative cholangiogram showed the biliary tree to be normal. A careful review of sections of the liver biopsy has since been made and the appearances are now considered to be those described in the so-called cholangiolitic hepatitis (Watson and Hoffbauer, 1946; Goulston and Smith, 1951).

It would appear, therefore, that this patient was suffering from a form of hepatitis. The biochemical investigations may be explained on the basis of hepatitis with obstruction.

Infective hepatitis must be considered in the differential diagnosis, especially as it is common in the Sydney community at present. Eosinophilia does not appear to have been reported in this disease. On the contrary, it is stated (MacCallum *et al.*, 1951) that eosinophils are commonly absent in infective hepatitis. In this case the total number of eosinophils increased, attaining the high percentage of 58 at the height of the illness.

It is interesting that Lehmann and Hanrahan (1954) have noticed the occurrence of allergic reactions, such as urticaria and asthma. In their series of 71 patients treated over a period of four months with chlorpromazine, 13% showed such reactions. However, they do not mention eosinophilia. In our patient the eosinophilia may have been indicative of an underlying allergic reaction.

Lemire and Mitchell (1954) observed three cases of chlorpromazine jaundice in elderly people. In two of these patients a transient eosinophilia of 7 to 17% was noted. The liver-function tests revealed a hyperbilirubinaemia, an increased serum alkaline phosphatase, and a normal thymol turbidity. Two had liver biopsies performed, and all three were subjected to surgery. The authors consider that their patients were suffering from toxic hepatitis due to chlorpromazine, the mechanism of the complication being unknown. Their findings and conclusions correspond with our own.

Further observations will be necessary to establish whether our patient has sustained permanent liver damage as a result of chlorpromazine therapy. The presence of excess urobilinogen in the urine six months after apparent recovery does suggest this.

Summary

A case of hepatitis following chlorpromazine therapy is reported.

The occurrence of eosinophilia in this illness is discussed.

I wish to thank the General Medical Superintendent of the Royal North Shore Hospital of Sydney for permission to report this case; and Dr. F. A. E. Lawes, Mr. F. F. Rundle, Dr. I. D. Thomas, and Dr. K. Viner Smith for assistance in preparation of the paper.

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Medical Memoranda

Anaesthesia Following Long-term Oral Chlorpromazine Hydrochloride Therapy

A review by Dundee (1954) of the pharmacology and applications of chlorpromazine hydrochloride records the widespread clinical uses of this drug outside hospital practice, and the increasing possibilities of anaesthetists meeting emergency admissions so treated. The following case is put on record so that others may avoid "anaesthetist's distress" in similar cases.

CASE REPORT

A feeble-minded man of 20, weight 11½ stone (73 kg.), was admitted in February, 1955, with a diagnosis of acute appendicitis. He was given ½ gr. (22 mg.) of "omnupon" and 1/150 gr. (0.43 mg.) of scopolamine one hour before operation, and was induced with thiopentone sodium 600 mg., and maintained with gallamine triethiodide, 100 mg., nitrous oxide and oxygen, and ether. There was a delayed return of normal respiration for three-quarters of an hour.

At operation a gangrenous retrocaecal appendix was removed. The operation lasted for one hour and he did not regain consciousness for the next four and a half hours,

tolerating an oro-tracheal airway during this period, the tube being necessary to prevent a valvular obstruction of his larynx by a mobile epiglottis.

His post-operation pulse rate rose to between 130 and 140 for the subsequent two days. There was no post-anaesthetic vomiting and he made an uninterrupted recovery.

COMMENT

The significance of the fact that this patient had been treated with oral chlorpromazine, 25 mg. three times a day, for the fourteen months previous to his admission was not appreciated at the time, and consequently he was given a normal anaesthetic for his age and weight, with the somewhat anaesthetically distressing results. The post-operation tachycardia and absence of vomiting are a well-known feature of chlorpromazine premedication. This case suggests that care should be exercised in giving normal doses of anaesthetic drugs to patients taking chlorpromazine.

My thanks are due to Dr. H. M. Bird for permission to publish this case.

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Prolonged Coma in Simmonds's Disease

Patients with Simmonds's disease often die in coma, which may be induced by various factors, such as the following.

Hypoglycaemia.—A low fasting blood sugar, sensitivity to insulin, and repeated hypoglycaemic attacks are often features of Simmonds's disease (Sheehan and Summers, 1949, 1952; Alexander, 1953). While in mild cases recovery may be spontaneous or may follow administration of glucose, prolonged hypoglycaemia may result in damage to cerebral tissue which is irreversible and fails to respond to glucose. Although the length of hypoglycaemic coma which prevents a full degree of physical and mental recovery must vary from case to case, Lawrence *et al.* (1942) suggest that "coma of one to three hours is usually associated with complete recovery, while longer periods are dangerous." Convulsions in hypoglycaemia have been mentioned as an important factor in preventing recovery from that state (Grayzel, 1934).

Hypothermia.—The profound lowering of the body's metabolic rate that occurs both in Simmonds's disease and in myxoedema may lead to a reduction of temperature sufficient to promote coma. Sheehan and Summers (1952) have shown that in a patient in coma with a very low temperature rapid recovery took place following immersion in a hot bath.

Low Blood Pressure and Loss of Electrolytes.—The adrenals are commonly atrophied in Simmonds's disease, and in some cases coma may be ushered in by marked hypotension and salt depletion, suggesting Addisonian crisis (Sheehan and Summers, 1949; Wolff, 1950).

The case here described makes it apparent that deep coma of 40 hours' duration, associated with hypoglycaemia and convulsions, can be followed by full mental and physical recovery.

CASE REPORT

A woman of 41, who had been unconscious with convulsions since about 1 a.m., was admitted at 2.30 p.m. on June 22, 1953. She was lying deeply comatose, slightly sweating, and with shallow respirations, in a pool of her own excreta. Her limbs were spastic, her trunk in opisthotonos, while every few minutes she was seized with generalized clonic and tonic convulsions associated with coarse grunting noises. Her temperature was 101.6° F. (38.7° C.), pulse 88, B.P. 120/70. Plantar reflexes were extensor, corneal reflexes absent.

The patient was moderately well nourished, with pendulous breasts; her skin was waxy pale, axillary hair was

absent, and pubic very scanty. Following 50 g. of glucose intravenously, the convulsions became less severe, and on receipt of the blood-sugar report as 32 mg. per 100 ml. half an hour later, a further 100 mg. of glucose was administered intravenously with 100 mg. of cortisone acetate and 1 mega unit of penicillin intramuscularly. An intravenous 5% glucose-saline drip was set up. By 6 p.m. the blood sugar had risen to 86 mg. per 100 ml. and, although severe convulsions had ceased, she remained in deep coma, with extensor plantar reflexes. Cortisone, 100 mg. eight-hourly, was continued.

The next morning she was still deeply unconscious, and was incontinent of urine and faeces. The blood sugar was 140 mg. per 100 ml. During the day there were signs of improvement, and by 5 p.m. she had begun to stir and open her eyes. This was 40 hours after the known onset and 26 hours after the institution of treatment, during which she had been given 400 mg. of cortisone intramuscularly and about 260 g. of glucose intravenously.

From then on, progress was uneventful. On a regime of cortisone, 50 mg. daily by mouth, thyroid, 1 gr. (65 mg.), and methyltestosterone, 15 mg., she asserted she had "never felt better."

The electrocardiogram on admission showed low-voltage and flat T waves, later reverting to normal. The electroencephalogram after recovery showed no convulsive organic abnormality.

The history, obtained subsequently, revealed that the patient had had three children, there having been serious post-partum haemorrhage after the last confinement 16 years previously, and subsequent total amenorrhoea. Simmonds's disease was diagnosed elsewhere in November, 1952, and she had been on testosterone and thyroid since then. She had never had fits, but had had one previous short coma, without convulsions, in January, 1953.

COMMENT

Of the known factors which can induce coma in Simmonds's disease, hypothermia and Addisonian crisis can be excluded in this patient, and the question then arises to what extent the hypoglycaemia was responsible for the prolonged coma. In fact, during the latter 24 hours of coma the blood-sugar levels were within normal range, but, as is known in insulin overdosage, the return of the blood sugar to normal may prevent neither permanent mental damage nor a fatal outcome. We have been unable to find a case recorded in which full recovery occurred after hypoglycaemia so deep and prolonged, and it is possible that in our case other factors were partly responsible for maintaining the comatose state.

While cortisone plays an important part in the maintenance therapy of Simmonds's disease, treatment of the coma with cortisone has not been universally successful. Thus Sheehan and Summers (1952) found that intravenous cortisone produced no appreciable effect in two cases of hypopituitary coma, although it is not clear to what extent hypoglycaemia was a factor in those cases. We feel that administration of cortisone as well as glucose to our patient was largely responsible for the successful outcome. Cortisone has been used to combat hypoglycaemia of various causes, such as pancreatic islet tumour and Addison's disease, and we feel encouraged to use it in prolonged hypoglycaemia of whatever aetiology.

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