The fatal outcome in the case described was unfortunate but was undoubtedly largely attributable to the patient's respiratory condition. The great difficulty which may be encountered in closing the duodenal stump in the presence of massive infiltration must, however, be stressed.

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REFERENCES

- BLACKWELL, J. B., and GILD, A. (1962): Eosinophilic Infiltration of the Stomach. Review of the literature and case report, *Aust. N.Z.J. Surg.*, **32**, 66.
BOCKUS, H. L. (1963): Gastro-enterology, Vol. 1, p. 864-869. London: W. B. Saunders.
ORR, I. M., MILLER, A. A., and RUSSELL, J. Y. W. (1954): Eosinophilic Infiltration of the Stomach and Bowel, *Postgrad. med. J.*, **30**, 485.
PERMYKOVA and LOGINON, E. N. (1961): Eosinophilic Granuloma of the Stomach, *Vop. Onkol.*, **7**, 74.

LONG-TERM REMISSION FOLLOWING METHOTREXATE THERAPY IN A CASE OF HAND-SCHULLER-CHRISTIAN DISEASE

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THE CONDITION now known as Hand-Schüller-Christian disease, derived its title following the descriptions of Hand in 1893, Schüller in 1915 and Christian in 1919, of a symptom complex characterised by defects in membranous bones, exophthalmos and diabetes insipidus. This triad was specifically referred to by Christian in 1919. (Moe and Hansen, 1960).

Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophilic granuloma are related clinically, pathologically and probably aetiologically (Lahey, 1962). They are usually classified together under the heading of the nonlipid reticuloendothelioses (as distinct from the lipid reticuloendothelioses, Gaucher's and Niemann-Pick disease). (Luhby, 1960).

Opinions vary concerning the aetiology of this group of disorders and indeed some doubt exists as to whether they can be truly classified amongst the malignancies of childhood. If it is accepted that all three conditions (Hand-Schüller-Christian disease, Letterer-Siwe disease and eosinophilic granuloma) are varieties of the same essential disorder, then it is convenient to regard Letterer-Siwe as the most malignant and rapidly progressive, eosinophilic granuloma the most benign and easiest to control, while Hand-Schüller-Christian can be considered in an intermediate group. The prognosis of eosinophilic granuloma, which tends to occur in older children, is often excellent whether treated by surgery or radio-

therapy, whilst the prognosis of Letterer-Siwe disease, of rapid onset, is almost invariably poor. In Hand-Schüller-Christian disease the prognosis is extremely variable and survival to adult years has been recorded.

The accepted treatment for Hand-Schüller-Christian disease is radiotherapy to control symptoms due to local tumour formation, chemotherapy in the form of alkylating agents in an attempt to reduce the degree of visceral involvement, and steroids which may on occasion, by their sole use, bring about dramatic remission. (Mermann and Dargeon, 1955).

A case is described of histologically and clinically accepted Hand-Schüller-Christian disease, that prior to his admission to Westminster Hospital had been treated by radiotherapy and alkylating agents and steroids without control, but which underwent dramatic regression of advanced disease immediately following the administration of the antifolic substance, methotrexate (4-amino-N¹⁰-methyl-pteroyl-glutamic acid).

Case Report. This boy (D.C.), aged 10, born 9.5.50 weighing 6 lbs. 8 ozs., only child of healthy parents, was admitted to hospital in December 1959 having previously suffered only from the usual childhood ailments. At the time of admission to hospital, he was complaining of malaise, headaches and backache of only one week's duration. A lump was observed which appeared to be arising from the left frontal bone. Biopsy which was taken from this site

FIG. 1.—Histology.

revealed an appearance characteristic of Hand-Schüller-Christian disease (Fig. 1). Coincident with the lesion in the left frontal bone radiographs demonstrated a deposit in the body of the third cervical vertebra and also a collapse of the 6th dorsal. Both these lesions were treated with high voltage X-rays as were numerous skin deposits and a deposit in the right quadriceps. In fact, 23 of these cutaneous and subcutaneous lesions were treated with high voltage X-rays between January and June 1960. Because of the progression of the disease, chemotherapy in the form of the alkylating agent, Melphalan (Alkeran) (Phenylalanine mustard) was started in February 1960 to a total dose of 25 mg. (orally) in one month. No obvious improvement was noted, therefore in April 1960, prednisone, 5 mg. three times a day, was given for a period of one month, again with no obvious improvement. As the child continued to deteriorate, a further course of Melphalan tablets was given in May 1960, once more to a total of 25 mg. in one month without improvement.

On 13.6.60 the child was referred to Westminster Hospital and admitted on that day with a weight of 44 lbs. 8 ozs., a temperature of 100.6°F and a pulse rate of 160. His Hb was only 43% but the platelets were grossly decreased in spite of a normal total white cell count (4,200).

On Examination. The boy was extremely ill, miserable and in pain being addicted to Nephenthe of which he was having 15 minims 4-hourly. He was clinically anæmic and wasted with flexion contraction of both lower limbs. Examination of the abdomen showed this to be distended with a liver palpable and firm, 2 finger breadths below the right costal margin. There were numerous deposits, mainly over the chest wall anteriorly, arms and abdominal wall. Some were quite firm and others soft. Some were surrounded by areas of brown pigmentation due to previous irradiation. Two small nodules were palpated in the scalp, one of which was situated in the left frontal region. (Figs. 2 & 3). Examination of the central nervous system demonstrated almost absent power in

FIG. 2.—Child on admission to Westminster Hospital 13.6.60.

either leg, the knee and ankle jerks were much exaggerated and there was clonus of both ankles. Plantar reflexes were equivocal. Radiographs of the chest did not show any lung lesions but there was now complete collapse of D6 and erosion of D7 with also considerable erosion of the body of C3. A large bony deficit was shown in the skull radiograph (Fig. 4).

As this child had failed to respond to an alkylating agent, it was decided to try the antifolic drug, methotrexate. This was started on 14.6.60 at the rate of 5 mg. daily. At the same time, prednisone, which had previously been given with no benefit, was restarted, again at 5 mg. three times a day. Within 2 days it was clear that the child was brighter and required less analgesics, and the skin deposits were seen to be diminishing in size. Three days later (19.6.60) it was obvious that the cutaneous nodules were undergoing profound regression.

From that time the child's condition continued to improve steadily and he was discharged from hospital on 27.10.60 with Hb of 100%, having gained 12 lbs. in weight, with a normal temperature and pulse rate. Intensive physiotherapy was given both during his stay in hospital and during subsequent convalescence.

FIG. 3.—Bony deficit in skull 19.7.60.

FIG. 4.—Skull X-ray 11.4.63.

He continued to take methotrexate, 5 mg. and 2.5 mg. on alternate days until his re-admission to hospital on 19.8.61, when he was complaining of nausea and fatigue, swelling of feet and ankles and pain on weight-bearing. Examination showed that the abdomen was grossly distended with ascites. On 4.9.61 an abdominal paracentesis yielded 8½ pints of yellow fluid containing 800 mg. of protein/100 ml. No abnormal cells were detected in the fluid nor was there any abnormality in the liver function tests. It was considered possible that a poor passage of

methotrexate across the blood-peritoneal barrier had allowed activity of disease within the abdominal cavity, particularly as complete control of disease had been achieved elsewhere.

On 7.9.61 the oral methotrexate was stopped and Dianabol (methandrostenolone) 5 mg. t.d.s. was started, together with folic acid, 5 mg. t.d.s. One week later, on 14.9.61, 7.5 mg. methotrexate were administered intraperitoneally followed by abdominal paracentesis on 22.9.61. 16 pints were aspirated. A further 5 mg. of methotrexate was given intra-

FIG. 5.—Patient on 19.8.63.

peritoneally on 23.9.61, this abdominal installation of methotrexate being repeated on 29.9.61 (10 mg.) and 6.10.61 (10 mg.). As an additional controlling measure the entire abdominal cavity was irradiated through a single anterior field on the 2 million volt Van de Graaffe generator to a skin dose of 600r from 26.9.61 to 11.10.61. On 18.10.61 oral methotrexate, which had been discontinued on 7.9.61, was restarted again at a rate of 5 mg. and 2.5 mg. on alternate days. By 24.10.61 there was no detectable ascites. A further complication at this stage was the development of grand mal type convulsions on three occasions but a left carotid arteriogram did not demonstrate any abnormality. The cerebro-spinal fluid was entirely normal on chemical and cytological examination. On 30.11.61, because the total white cell count had dropped to 3,200/cu. mm. the methotrexate was reduced to 2.5 mg. daily. On 5.1.62 the boy was again discharged from hospital for further intensive physiotherapy.

From this time on no further complications occurred, so that now the boy is very well indeed is able to play cricket and football and has delighted both his mother and school teacher by his progress academically. The methotrexate and folic acid were discontinued on 11.4.63, the dianabol on 19.8.63, the prednisone having been gradually withdrawn on this latter date, so that now the boy is having no medication at all. (Fig. 5).

Summary

This child developed a rapidly progressive type of Hand-Schüller-Christian disease at the age of 9 and was treated prior to his admission to the Westminster Hospital by means of steroids, radiotherapy and alkylating agents without control of the disease.

Institution of prolonged methotrexate therapy resulted in remission with one relapse characterised by ascites after an interval of 14 months. This relapse was controlled by the intra-abdominal administration of methotrexate and low dosage abdominal bath irradiation. The boy is now well more than 5 years after his first admission to hospital having completely recovered from the paraplegia present on his first admission. He now takes part in a full range of athletic activities and is said to be an intelligent and industrious pupil.

The usefulness of antifolic drugs in Hand-Schüller-Christian disease is not widely acknowledged in the literature; the only reference we have observed is attributed to Mermann and Dargeon (1955).

Addendum. Bone age corresponds to chronological age. Radiograph taken in 1961 shows a bone age of 11 years 6 months to 12 years. From radiographs taken in 1963, the bone age was 13 to 14 years. (Standards from Radiographic Atlas of Skeletal Development of the Hand and Wrist, by W. W. Greulich and S. I. Pyle (1959), Oxford University Press.)

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REFERENCES

- MOE, P. J., and HANSEN, A. E. (1960): Reticulo-endothelial Granuloma, *A.M.A. Journal Dis. Child.*, **99**, 175.
- LAHEY, M. E. (1962): Prognosis in Reticuloendotheliosis in Children, *J. Paediat.*, **60**, 664.
- LUHBY, A. L. (1960): Reticuloendotheliosis. Chap. 20 in *Cancer and Allied Diseases of Infancy*, Ed. Ariel, I. M., and Pack, G. T., pp. 465-481, London: Churchill.
- MERMANN, A. C., and DARGEON, H. W. (1955): The Management of Certain Nonlipid Reticulo-Endothelioses, *Cancer*, **8**, 112.