TWO CASES OF RETICULOENDOTHELIOSIS—LETTERER SIWE SYNDROME

BY

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Diseases characterized by proliferative changes in the reticulo-endothelial system, other than the leukaemias and specific infections such as tuberculosis and typhoid fever, give rise to three main syndromes in children, but there are many atypical and intermediate forms. Originally described as three separate conditions, these syndromes, namely Letterer-Siwe disease, Hand-Schüller-Christian syndrome, and ‘eosinophilic granuloma’ of bone are now believed by many authorities to have a common aetiology, as yet unknown, and basic pathology. Van Creveld (1951) is of the opinion that a distinction between the first two is unnecessary and at times impossible, and clinical pictures occupying intermediate positions between them and even sharing features of the infectious reticuloses have been described; Siwe (1949) on the other hand, maintained that they were pathologically distinct. Those authors who accept the theory of unity of Letterer-Siwe disease and Hand-Schüller-Christian syndrome do so on the assumption that lipid storage would develop in the former if the disease were protracted; moreover, sequences of the three morbid pictures in one patient on consecutive biopsies have also been described by Bartels (1947), Wentholt and Hadders (1949), Love and Fashena (1948), and Parkinson (1949). That this sequence of events is not always followed has been shown elsewhere and is further demonstrated by the protracted course of one of the cases to be described, but in it account must be taken of the modifying effects of steroids.

Considerable evidence is accumulating on the value of ACTH and cortisone in the treatment of the three syndromes, particularly of the subacute and chronic forms of the Hand-Schüller-Christian syndrome. Karlen (1952) reported disappearance of hepatosplenomegaly and exophthalmos in an 18-month-old girl on cortisone therapy, but relapse occurred when the treatment was stopped on account of severe oedema, and the patient died. Røjel and Lund (1958) described a boy with Hand-Schüller-Christian syndrome aged 14 months at onset, but not diagnosed till 3 years and 9 months, who was pronounced cured after three years’ treatment with ACTH and cortisone, but he was observed for only three months after cessation of treatment, and had received x-ray therapy also.

Sewell (1954) presented a girl of 3 years 10 months to the Royal Society of Medicine who had shown histological features of eosinophilic granuloma of bone and later of Hand-Schüller-Christian syndrome with clinical improvement on cortisone after failure to respond to X-rays; and Flosi, Assis, Coelho Neto, Bloise, Ulhôa Cintra and Barros (1959) described a complete remission after four years almost continuous treatment with cortisone and ACTH in a boy diagnosed as suffering from Hand-Schüller-Christian syndrome when 1 year old, the symptoms having commenced about four months previously. After a year’s treatment with cortisone followed by ACTH, maximum dosage 75 mg. daily, he developed marked features associated with Cushing’s syndrome at which stage treatment was gradually reduced; but bone lesions which were already resolving continued to improve and eventually disappeared after four years’ treatment.

Bearing this evidence in mind, it is necessary to remember the occurrence of spontaneous remission which is the usual outcome in patients with eosinophilic granuloma of bone and is also well recognized in the Hand-Schüller-Christian syndrome.

Moreau (1930) found nine cases of spontaneous recovery amongst 34 cases of Hand-Schüller-Christian syndrome described in the literature, and while Letterer Siwe disease is generally fatal, spontaneous recovery is possible (Lightwood and Tizard, 1954). Recovery from this disease induced by cortisone was described by Cox (1955), and Orrild and Lunding (1953) reported a case of Letterer Siwe disease apparently cured by ACTH.

The object of this communication is to place...
on record two further cases of reticulosus and to
describe the effect of prolonged steroid therapy in
one, the other dying before treatment was properly
instituted.

Case Reports

Case 1. J.E. was 25 months of age when admitted
to hospital in April, 1955, with a history of malaise
following an upper respiratory infection two weeks
previously. For a week he had been drowsy and listless,
inclined to vomit and was thought by his mother to be
having headaches. A few days before admission
puffiness was noticed around the eyes, which for the
past 24 hours had protruded.

He was the second child of healthy parents, born at
term; his birth weight was 7 lb. 11 oz. He was breast fed
for one month only, but he made good progress and his
only illness had been an attack of otitis media treated
with penicillin one year previously. The family history
was uneventful.

Examination. Temperature 99·8°F. He had a pale,
puffy face and proptosis of both eyes, the right slightly
more than the left. In addition to the puffiness of
the eyelids there were also symmetrical, fairly well defined
swellings in the temporal fossae (Fig. 1) and an indefinite
swelling in the right parietal region. The tonsils
were enlarged but not inflamed; cervical and axillary glands
were moderately enlarged; the heart and lungs appeared
normal; liver and spleen were not felt. The optic fundi
showed no abnormality, and the cerebrospinal fluid
was also found to be normal. A blood count was
reported Hb 86% (12·7 g.); colour index, 1·04; W.B.C.s,
6,000/c.mm. (polymorphs 40%, lymphocytes 60%).

A tentative diagnosis of Hand-Schüller-Christian
syndrome was made, but there was no polyuria and urine
specific gravity reached 1,016. Moreover, radiographs
of skull, thorax and long bones revealed no abnormality
apart from opacity of both antra and ethmoid cells.
Because of this finding and the fact that his temperature
fluctuated between 100° and 101°F the possibility of

Fig. 1.—Showing puffiness of eyelids and symmetrical well-defined
swellings in temporal fossae.

FIG. 2.—Blood smear showing vacuolated macrophages. (×480.)

FIG. 3.—Bone marrow showing a foam cell and vacuolated cells.
(×650.)

ethmoiditis was considered, and treatment with anti-
biotics started. No improvement followed, however,
and six days after admission chemosis of both conjunc-
tivae and retinal oedema appeared; there was no real
papilloedema. A second blood count showed a fall
in Hb to 78% (11·5 g.) and vacuolated cells were found
in the smear (Fig. 2). The E.S.R. was 6 mm. in one
hour, platelets 14,000/c.mm. and bleeding time more than
12 minutes. Bone marrow aspiration showed a normo-
cellular marrow containing 'foam cells' (Fig. 3) similar
Cortisone was now added to the treatment but the child's condition deteriorated rapidly. Spontaneous bleeding occurred and he became progressively more anaemic in spite of blood transfusion.

He appeared to be quite blind for several days before he died, two weeks after admission to hospital.

Necropsy. A mass of tumour-like tissue in the anterior fossae of the skull, in the orbits and air sinuses, and invading the upper part of the nose via the cribriform plate was revealed (Fig. 5), but the pituitary fossa appeared intact. A large tumour was found in the lower end of the right femur (Fig. 6). The thoracic and abdominal glands were all enlarged and invaded, and there were small deposits in the heart, kidneys and wall to those occurring in the Hand-Schüller-Christian syndrome; gland biopsy showed complete replacement of the normal architecture by sheets of pale reticulum cells, but no 'foam cells' (Fig. 4).

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**Fig. 4.**—Gland infiltrated with reticulum cells. (H. and E. ×150.)

**Fig. 5.**—Horizontal section through skull showing tumour-like mass in anterior fossae.

**Fig. 6.**—Large tumour in lower end of right femur.
of the small intestine. The liver and spleen appeared normal macroscopically and the lungs showed hypostatic changes only, but histological deposits were noted in lungs, spleen, liver, pancreas, ribs and tonsils. The pituitary gland was normal on section apart from tumour around the capsule. The microscopic picture was of uniform infiltration with sheets and trabeculae of mononuclear cells with pleomorphic nuclei and scanty eosinophilic cytoplasm. No foam cells were found in any of the necropsy sections and no cholesterol was demonstrable in the cells by histochemical techniques.

Case 2. J.C. was 5 years old when admitted in February, 1957, with a history of malaise, loss of appetite, limb pains and irregular fever following an upper respiratory infection one month earlier. He was the third and youngest child of healthy parents, born at term; his birth weight was 6 lb. 10 oz. He was breast fed for three months and his progress had been entirely normal. The family history was uneventful.

Examination. He was a fretful, pale, ill-looking child, with several small bruises and a few petechiae on the trunk. His tonsils were large and unhealthy and tonsillar glands were palpable; there were small discrete glands in axillae and groins, and his liver was easily palpable, his spleen being just felt. No nodules or bony swellings were found, but he resented examination because of muscle tenderness. A tuberculin patch test was negative. Radiographs showed possible erosion of one rib, but no lesion in skull, spine or long bones. Haematological examination revealed Hb 64%, W.B.C.s less than 1,000/c.mm. (polymorphs 11%, lymphocytes 87%, monocytes 2%, platelets scanty); bleeding time more than 15 minutes. Marrow puncture demonstrated the presence in the marrow of many histiocytic cells with slightly foamy cytoplasm, suggesting a diagnosis of Letterer-Siwe syndrome. ACTH in a dosage of 40 units daily was started four days after admission together with penicillin, and a blood transfusion was given the following day, Hb having fallen to 58%; a blood film at this time showed many smear cells.

After four days' treatment the child's general condition had improved remarkably; he lost his muscle pains and became much more cooperative, accepting drugs by mouth which he had previously refused, so prednisolone 12.5 mg. t.d.s. was substituted for ACTH intra-muscularly. He was given another blood transfusion as his Hb had only risen to 66% and four weeks after the beginning of treatment he was symptom-free, had no palpable glands, no obvious enlargement of the spleen and a second marrow puncture showed a normal picture apart from a very few of the abnormal cells originally seen. His liver, however, was still palpable two finger breadths below the costal margin. He had become moonfaced, and his weight had increased by 8 lb. over his admission weight of 29 lb. 5 oz., so prednisolone was reduced to 10 mg. t.d.s. and on this dosage he was discharged to the Out-patient Department at the end of March, his Hb at that time being 75% and W.B.C.s 4,600/c.mm. Dr. Bodley Scott who had seen this child in consultation reported: 'I agree that the primitive cells found in the bone marrow and displacing almost all the normal cells are quite unlike the usual 'blasts' of acute leukaemia. They have irregular nuclei of the reticulum cell type and some have a foamy cytoplasm. Together with the x-ray changes they support a diagnosis of 'Letterer Siwe syndrome'."

He was seen frequently in the Out-patient Department and he remained well but exhibited the appearance of florid Cushing's syndrome. His haemoglobin was maintained and he had no enlargement of liver, spleen or glands. He complained of pain in one ankle but nothing abnormal was found, and as he was markedly overweight (46 lb.) his dose of prednisolone was reduced slowly after two months on 30 mg. daily, until he was taking only 5 mg. a day at the beginning of July. He lost 5 lb. in weight, felt well and began to grow. His Hb was still 96% and blood picture normal; B.P. 110/65 mm. Hg. Prednisolone was again reduced in August to 2·5 mg. daily and continued at this level until in September his tests were noticed to be rather hard and insensitive, and a week later his parotid, submaxillary, axillary and inguinal glands were visibly enlarged and felt firm. Liver and spleen were still not palpable and Hb was 90%, but smear cells were again seen in the blood film (September 24, 1959), as well as a few atypical mononuclear cells. He was admitted on October 1, 1957, for biopsy of a gland and the dose of prednisolone was increased to 10 mg. daily, but he did not improve. The report on the biopsy specimen stated: 'The normal structure of the lymph node has been destroyed, being replaced by a uniform proliferation of medium sized oval cells with scanty eosinophilic cytoplasm and reticular nuclei. The capsule is invaded at one point, and the abnormal cells are infiltrating the fat outside the node. Mitoses are numerous. I regard this tumour as a lymphosarcoma.'

Prednisolone therapy was continued in the same dosage but muscle pains returned and a few histiocytic cells were again seen in the peripheral blood in mid-October, at which time the dose was increased to 30 mg. daily. Rapid weight gain resulted but the symptoms progressed and by the middle of November he was unable to walk on account of general stiffness and tenderness. Radiographs of ribs, pelvis and long bones (November 15, 1957) showed no abnormality.

His condition deteriorated steadily, he became anaemic and leucopenic once more, and developed scattered bruises and petechiae. His weight fell steadily to 36 lb. on December 10, in spite of progressive increase in the dose of prednisolone up to 120 mg. daily and blood transfusion, and by December 20, 1957, his liver had enlarged to three fingers-breadth below the costal margin and spleen and glands were easily palpable. Radiographs (December 19, 1957) showed a little periosteal infiltration in several long bones and slight generalized osteoporosis. He was discharged home for Christmas and re-admitted (December 30, 1957) in severe pain, extremely weak and bleeding from the nose; Hb 40%, W.B.C.s too scanty to count. He was again transfused and another bone marrow puncture was attempted, but
was unsuccessful because he bled too much. For the same reason biochemical investigations were not undertaken, but on January 3, 1958 potassium chloride 1.5 g daily by mouth was started on an empirical basis because of high dosage of prednisolone, general weakness and abdominal distension, steroid therapy being maintained unaltered.

A few days later he was much improved, moving his legs without pain and no longer bleeding spontaneously. At the beginning of February he was once more on his feet, and even running a little. His haemoglobin rose steadily without further transfusion, his white cell count became normal and no histiocytes or smear cells were seen in the blood film; his spleen was no longer palpable but his liver and preauricular glands were just felt.

He was discharged home on February 12, 1958, still on 120 mg. prednisolone daily, and he felt well, but he ate enormously and gained nearly a stone in weight in the next three weeks, reaching 50 lb. His blood pressure rose to 150/90 mm. Hg, having been around 110/60 mm. Hg previously. By the end of March he was too tired to walk and complained of pain in the back, so he was readmitted on March 21, 1958, still with all the signs of florid Cushing's syndrome (Fig. 7). Radiographs showed marked osteoporosis of lumbar vertebrae with flattening and compression of most of the vertebral bodies (Fig. 8) and also slight deformity of the neck of the left femur. Apart from his high colour, obesity and loss of lumbar curve the child seemed well and showed no sign of the original disease. There was now no
anaemia and marrow puncture showed no evidence of any haemopoietic disorder, normal polymorphs being most plentiful, granulocyte precursors numerous, primitive and abnormal cells absent.

He was fitted with a plaster bed and his dose of prednisolone was gradually reduced being combined with ACTH. He appeared well; ketosteroid excretion was satisfactory and blood pressure 120/90 mm. Hg. On May 7, on a dose of prednisolone 20 mg. b.d. and ACTH 40 mg. daily, he was found to have a number of large, slightly tender glands in the neck and a nodule on the occiput, but liver and spleen were still not palpable. On May 12 another marrow biopsy was obtained which showed the marrow grossly infiltrated by large pleomorphic reticulum cells (Fig. 9) the nuclei of which had a coarse chromatin pattern and single prominent pale blue nucleus, the picture being that of reticulum cell reticulosis. A few days later he began to deteriorate rapidly, ecchymoses appearing in the vicinity of the enlarged glands, and liver and spleen enlarging progressively. He became rapidly more anaemic in spite of blood transfusions and died suddenly on June 5, 1958, nearly 18 months after the onset of his first symptoms.

Necropsy. This was performed 24 hours after death. The body was that of a fat boy with the moon-facies of cortisone overdosage, showing massive ecchymosis of the left arm and lower abdominal wall, and numerous small bruises scattered over the rest of the body. There was general enlargement of lymph glands, the tracheobronchial, mediastinal and pre-aortic abdominal glands being dark red in colour and soft. Petechiae were present on the surface of the heart (which was otherwise normal) on the pleura, and in the gastric mucosa. Fresh blood was present in the small intestine, which appeared normal in other respects. The liver was of average size (870 g.) and was pale. The spleen was enlarged (180 g.) and deeply congested; other organs appeared normal. The cortex of all vertebral bodies and of the long bones was extremely thin and the marrow was dark red and prolific.

Histology. Sections of spleen, lymph nodes and bone marrow (Fig. 10) showed replacement of the normal tissue by sheets of pleomorphic reticulum cells. The liver showed subcapsular and portal tract proliferation of these abnormal cells (Fig. 11), but the changes...
were not intense. There was no evidence of lipid storage. The infiltrating cells varied in size and shape, some being rounded, some polygonal and others elongated. Mitoses were scanty, reticulum production slight, but the cells stained with metallic stain and some showed evidence of erythropagocytosis.

Discussion

Diagnosis undoubtedly depends on the histological interpretation of the type of abnormal cell seen in the marrow biopsy and necropsy sections. Cases of the type just described have been published under various names, but the unifying feature is a diffuse infiltration of the marrow by cells of reticuloendothelial type. The two cases under discussion fulfill the clinical criteria advanced by Siwe, but at the same time show certain points of dissimilarity.

Case 1 had marked exophthalmos and foam cells in the marrow biopsy, but the classical triad of the Hand-Schuller-Christian syndrome was lacking. The rapid course of the disease in this case was characteristic of Letterer-Siwe syndrome, though the biopsy picture was more suggestive of the term acute xanthomatous reticuloendotheliosis.

Case 2 conformed more closely to the conception of a malignant reticuloendotheliosis, which was probably what the original authors described as Letterer-Siwe disease, but which in his case was checked over long periods by steroid therapy.

These two cases support a contention made by Lynch, Bain, Stanyon and Crang (1954) that two different disease entities are often confused under this eponym. That steroids influence all varieties of reticulosis there is no doubt; but the possibility of spontaneous remission must not be forgotten. The response to steroids accentuates neither the relationship nor the diversity of the pathological forms.

Summary

Two cases of reticuloendotheliosis of Letterer-Siwe type are described, and the effects of prolonged steroid therapy indicated. A brief review of the literature in relation to steroid therapy of the reticuloses is included.

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Two Cases of Reticuloendotheliosis—Letterer-Siwe Syndrome
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