

RETICULOENDOTHELIAL GRANULOMA : A REVIEW WITH A REPORT OF A CASE OF LETTERER-SIWE DISEASE

BY

ALBERT E. CLAIREAUX, M.D., M.R.C.P.Ed., and IAN C. LEWIS, M.B., Ch.B., M.R.C.P.
From the Department of Child Life and Health, University of Edinburgh

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Granulomatous lesions affecting the reticulo-endothelial system produce a group of disorders having certain striking clinical features. The condition known as Hand-Schüller-Christian disease is one of this group, and the well-known Schüller-Christian triad of exophthalmos, diabetes insipidus, and multiple lesions in the skull was for many years considered to be pathognomonic. More recently Otani and Ehrlich (1940) and Lichtenstein and Jaffe (1940) have described a condition which has come to be known as 'eosinophilic granuloma of bone.' Multiple skeletal lesions may be present, but there is, as a rule, little evidence of systemic upset and recovery is the usual outcome. The rarest and most severe condition in this group is that known as Letterer-Siwe disease. It affects infants, frequently within the first six months of life, and invariably proves fatal.

Farber (1941) and Green and Farber (1942) have suggested that the underlying pathological changes in eosinophilic granuloma of bone are similar to those in Hand-Schüller-Christian disease and in Letterer-Siwe disease. Jaffe and Lichtenstein (1944) agreed with this concept and believed that the three conditions were 'different clinical expressions of the same basic disorder'. On the other hand, Siwe (1949) is unwilling to be so definite. He admits that they are all diseases of the reticuloendothelial system but does not feel justified in assuming that anything more than a family relationship exists.

The following case is an example of the acute form of reticuloendothelial granuloma known as Letterer-Siwe disease.

Case Report

Clinical Findings. The patient was a female infant, the second child of healthy, unrelated Gentile parents. She was born spontaneously at term on February 22, 1949, and weighed 6½ lb. at birth. She made normal progress until, at the age of 14 weeks, she became listless and vomited her feeds. She appeared to recover but

two and a half weeks later she developed diarrhoea which was treated by a course of sulphonamides. The child had little appetite and became very irritable but the diarrhoea ceased. The mother thought the infant was teething but the doctor noticed that she was becoming very pale and sent her to hospital. She was admitted on August 2, 1949, aged 22 weeks, six weeks after the onset of symptoms. The patient was a very fretful, quite well-nourished baby weighing 11 lb. 4 oz. The skin and mucous membranes were pale; there was no clinical icterus. The two lower central incisors had erupted. A few shotty glands were felt in the left groin.

The spleen was enlarged and was palpable 2 in. below the costal margin. It was smooth, firm, but apparently not tender. The liver was palpable. There was considerable disturbance in temperature (Fig. 1). No other

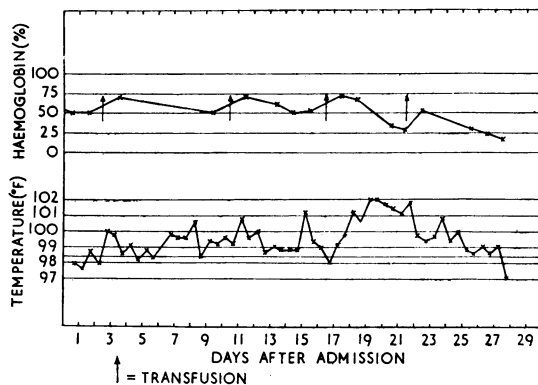


FIG. 1.—Chart showing temperature and haemoglobin.

clinical signs were present. The haemoglobin levels were estimated by the Sahli method (14 g.=100%), and indicated the progressively severe anaemia (Fig. 1). The anaemia was uninfluenced by transfusion.

The parents' and child's blood were Rhesus positive. The Wassermann reaction and Mantoux test (1/1,000) were negative. No pathogenic organisms were isolated from the stool. The blood cholesterol level was 125 mg. %.

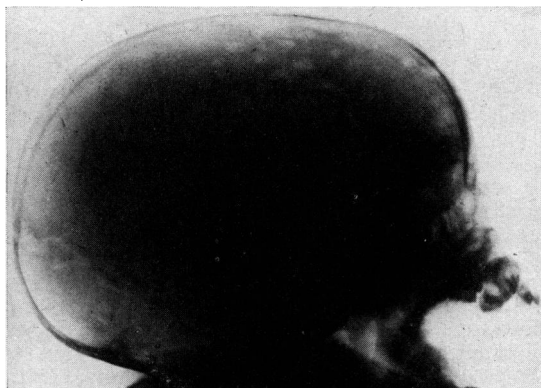


FIG. 2.—Radiograph of skull; multiple defects in calvarium.

Cerebrospinal fluid, obtained by lumbar puncture, was normal. Urine analysis was normal. The results of the liver function tests were: serum thymol turbidity, 6 units; serum gold sol, 1; serum cephalin cholesterol flocculation, ++; serum alkaline phosphatase, 11 units; serum bilirubin, 1 mg. %.

Frequent attempts to obtain bone marrow were unsuccessful.

Radiological Examination. Radiographic examination of the skull revealed numerous areas of rarefaction in the calvarium (Fig. 2). These areas were circular in outline and varied considerably in size. The defects gave the skull the 'map-like' appearance which has been described in Letterer-Siwe disease.

Radiographs of the lower limbs showed cyst-like defects in the lower ends of the femora and in the upper ends of the tibiae (Fig. 3). In addition to these lesions, the femoral shafts were unduly broad and the cortex was rather dense. This suggested that subperiosteal formation of new bone had occurred.

X-ray examination of the chest was negative.

Since admission, the liver, spleen and lymph nodes had increased slowly in size (Fig. 4). Sixteen days after admission a purpuric rash appeared over the trunk, neck, and limbs, and persisted for three to four days before fading.

Blood transfusions of 120-180 ml. each were given on the third, eleventh, seventeenth, and twenty-third days after admission. These caused only transient improvement (Fig. 1).

The baby died on August 29, 1949, 28 days after admission and ten weeks after the onset of the disease.

The clinical diagnosis was Letterer-Siwe disease.

Necropsy Report. The body was that of a rather small, extremely pale infant aged six months and weighing 9 lb. 10 oz. The skin over the chest was wrinkled and there was little subcutaneous adipose tissue. No skin lesions were found. The abdomen was distended, and the liver and spleen were easily felt.

HEAD. The skull showed numerous circular, semi-translucent areas over the vault of the skull and in the temporal and occipital bones. They varied in size, the

average diameter being 0.5 cm. The larger lesions were yellowish in colour and soft, almost gelatinous. The brain showed no abnormality. The pituitary fossa was of normal size. The pituitary gland was normal.

THORAX. The pharynx, oesophagus, and thyroid gland showed no abnormality. The thymus gland was enlarged and firmly adherent to the surrounding tissues. The gland was irregularly shaped and on section showed numerous yellow, pultaceous areas. The trachea and bronchi were healthy. The lungs were well-expanded and reddish-pink except for the lower lobe of the right lung which was dark purple and unusually firm. There was no pneumonia. The pericardium was healthy. The heart was normal in size, but the myocardium was extremely pale. There were no congenital lesions. The coronary arteries were healthy.

ABDOMEN. The peritoneum was healthy. No abnormalities were found in stomach, small or large intestine. The liver was enlarged and weighed 226 g. The capsule was smooth and the organ was pale yellow-brown. Numerous areas of fatty degeneration were seen on the cut surface. The gall bladder and bile ducts were healthy.

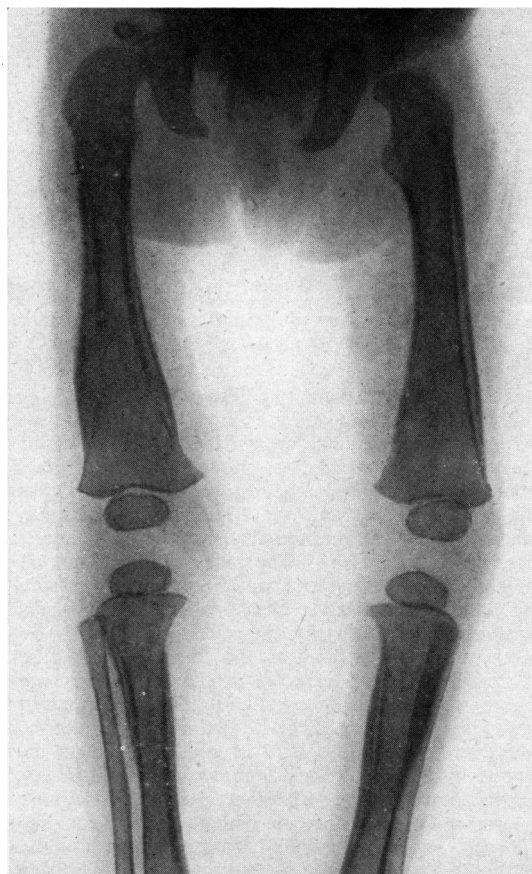


FIG. 3.—Radiograph of lower limbs. Defects in lower ends of femora and upper ends of tibiae.

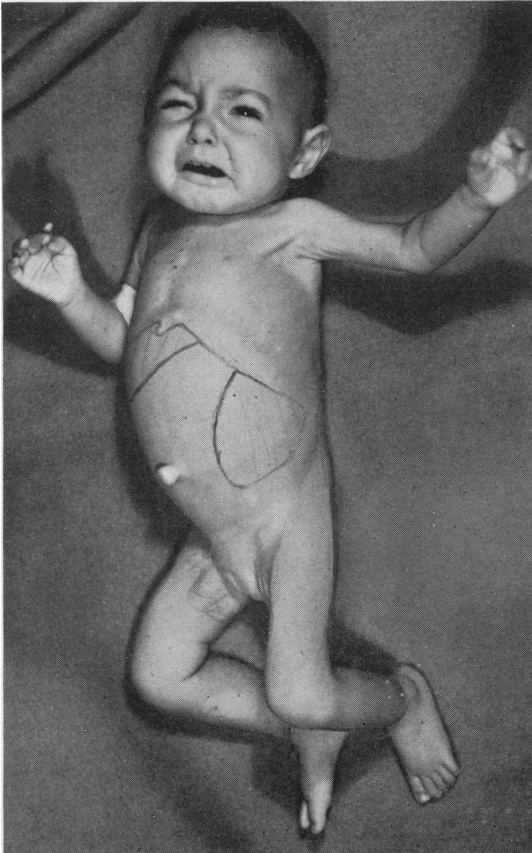


FIG. 4.—Patient 26 days after admission. Note enlargement of liver, spleen, and inguinal lymph nodes.

At the porta hepatis there was a group of enlarged lymph nodes which were pale yellow and rather soft. The spleen was greatly enlarged and weighed 126 g. The capsule was thickened and partly adherent to the lateral abdominal wall. The organ was firm. On section the pulp was dark red and the Malpighian bodies were prominent. The suprarenal glands and pancreas appeared to be healthy. The kidneys were of average size and shape. On section no abnormality was found. The ureters and bladder were healthy. The inguinal lymph nodes were enlarged and soft.

SKELETON. In addition to the changes in the skull, all the ribs showed areas of rarefaction, which were largest just lateral to the costo-chondral junction, and in a few cases the cortex of the rib had been expanded into a fusiform swelling 2 cm. in length. On section they were seen to consist of a gelatinous, semi-fluid mass of yellow material. The left femur also showed circular, punched-out areas, 0.5 cm. in diameter, which contained yellowish, gelatinous material similar to that found in the ribs. The lesions were primarily situated in the cancellous bone but some erosion of the cortex had also occurred. Similar lesions were found in the sternum.

Microscopy Report. The capsule of the liver was normal. The liver cells, particularly those in the inner zones of the lobules, showed severe fatty change. In addition to the fatty degeneration, numerous small granulomas were found throughout the parenchyma. These varied slightly in size but the average was that of a miliary tubercle. They were not encapsulated but the surrounding liver cells were compressed to form a pseudo-capsule. The granulomas were composed of large, pink-staining reticuloendothelial cells surrounded by a few lymphocytes and plasma cells. The central part of the lesion was, in some cases, undergoing hyalinization. Sections stained with Scharlach red showed that the lesions contained no fat although the surrounding liver cells were filled with fat droplets (Fig. 5).

The capsule of the spleen was slightly thickened. The trabeculae were normal. There were numerous granulomatous areas throughout the pulp. These areas were similar in character to those in the liver but were larger, more numerous, and less discrete. Many of the Malpighian bodies had been partially replaced by granulomatous tissue. The granulomas were composed of pink-staining reticuloendothelial cells, lymphocytes, plasma cells, and a few eosinophil leucocytes. Some of the larger granulomas showed central necrosis. They contained no fat.

Large portions of the thymus gland had been replaced by granulomatous tissue similar to that already described, but in addition to pale reticuloendothelial cells a number of giant cells were seen (Fig. 6). A few eosinophil leucocytes were also found. Many of the granulomatous areas had undergone necrosis and at the periphery of the gland replacement fibrosis had occurred. Sections stained with Scharlach red showed that many of the histiocytes in the granulomatous areas contained fat but this was almost confined to the cells in the margins of the necrotic areas.

The capsule of the lymph node was normal. The node had been largely replaced by granulomatous tissue (Fig. 7). These lesions were more discrete than those found in the spleen and thymus, and necrosis was not a pronounced feature.

The pleura was healthy. The lungs were well expanded, and the bronchi were healthy. Numerous granulomatous areas were found throughout the interstitial tissue (Fig. 8), and bore a superficial resemblance to miliary tubercles. A number of small lesions had coalesced to form larger granulomas of which a few were undergoing fibrosis. Many of the surrounding alveoli contained histiocytes.

Sections from the skull, ribs, and sternum showed similar changes. The bone had been partially replaced by granulomatous tissue which consisted of sheets of pale-staining histiocytes together with small groups of lymphocytes and polymorphonuclear leucocytes. Here and there multinucleated giant cells were found. A few eosinophil myelocytes were seen.

Section from the left femur showed more advanced changes. The cancellous bone had been replaced by granulomatous tissue similar to that found in the ribs and skull but occasional areas of frank necrosis were present. These necrotic zones were surrounded by

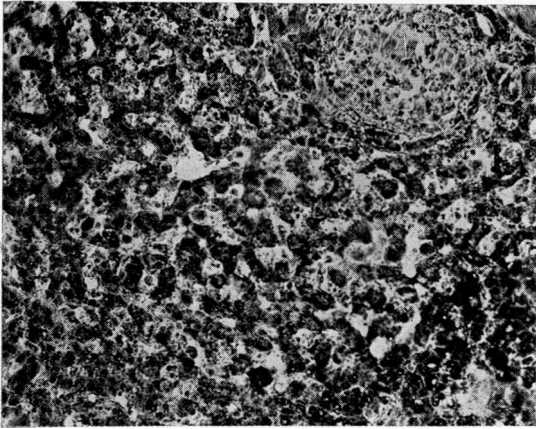


FIG. 5.—Fat droplets in parenchymal cells of liver showing fatty degeneration. The granulomatous lesion is free from lipoid. Scharlach red. $\times 100$.

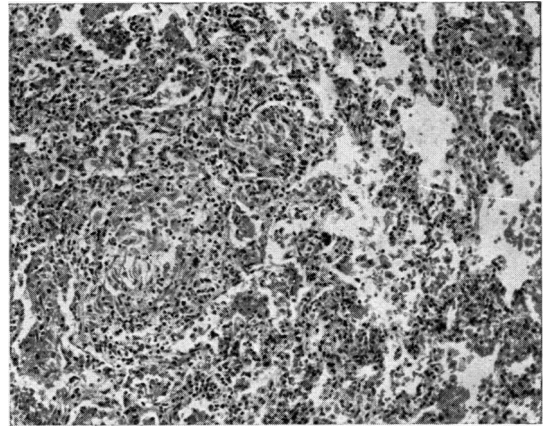


FIG. 8.—Granulomatous nodule undergoing fibrosis in interstitial tissue of lung. Numerous histiocytes in surrounding alveoli. Haematoxylin and eosin. $\times 100$.

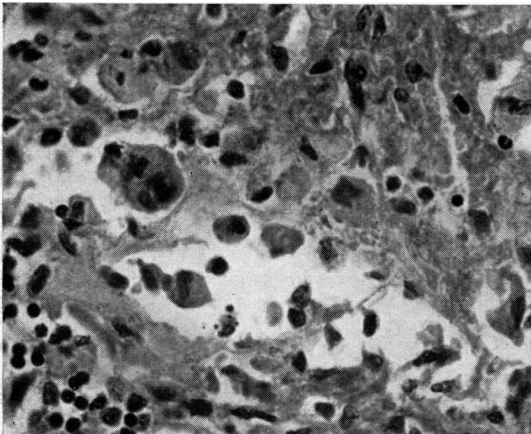


FIG. 6.—Margin of granuloma in thymus showing multinucleated giant cells. Haematoxylin and eosin. $\times 400$.

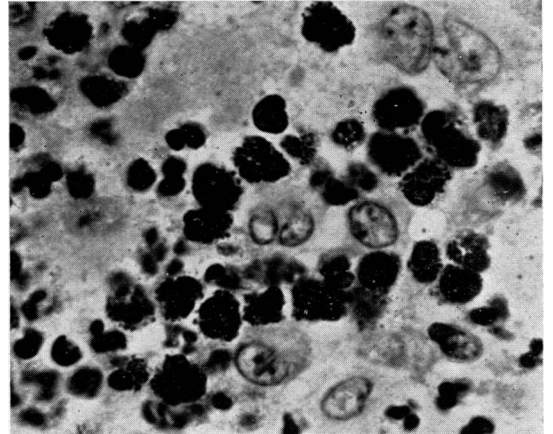


FIG. 9.—High power view of ileum to show numerous eosinophil leucocytes. Haematoxylin and eosin. $\times 850$.

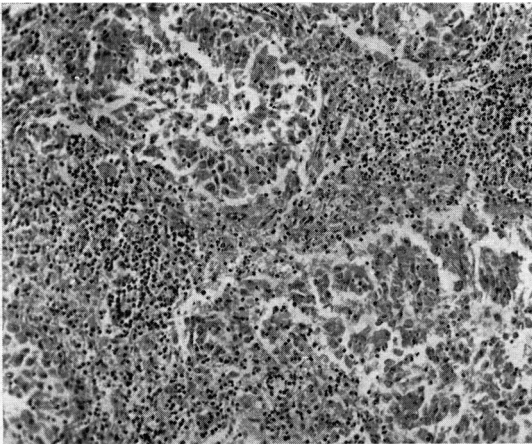


FIG. 7.—Large discrete granulomas in lymph node. Haematoxylin and eosin. $\times 100$.

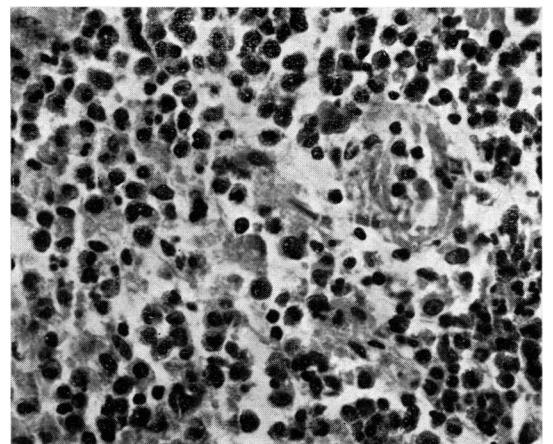


FIG. 10.—Scapula, showing eosinophilic granuloma of bone and dense collection of eosinophil leucocytes. Haematoxylin and eosin. $\times 400$.

numerous histiocytes, giant cells, and foam cells, which were seen only close to the areas of necrosis.

The pathological diagnosis was non-lipoid reticulo-endothelial granuloma: Letterer-Siwe disease.

Discussion

The first record of a similar case was made by Letterer (1924) who believed that he was dealing with 'aleukaemic reticulosis.' Between Letterer's first report and the present day some 20 cases have been recorded, the most recent being that of McKelvie and Park (1950). There also have been reported some 13 cases transitional between Letterer-Siwe disease and Hand-Schüller-Christian disease.

Siwe (1933) had regarded the disease as a non-lipoid reticuloendotheliosis of unknown origin and had described the following diagnostic criteria:

- (1) Marked splenomegaly with moderate to pronounced enlargement of the liver.
- (2) A haemorrhagic tendency, chiefly manifested as petechiae or purpura.
- (3) Generalized enlargement of lymph nodes which are discrete and not tender.
- (4) Localized defects in bones which may be detected only by radiographic examination or at necropsy.
- (5) The blood picture is that of a progressive, non-regenerative anaemia.
- (6) The disease is neither hereditary nor familial, and occurs exclusively in infants. The onset is acute and the outlook is unfavourable. The duration varies from a few weeks to a few years. The aetiology is unknown.
- (7) The characteristic pathological lesions show generalized hyperplasia of histiocytes in various organs, especially the spleen, liver, lymph nodes, thymus gland, skin, and bone marrow.

The case we have described presented these clinical features. In our patient the haemorrhagic tendency was manifested by a transient purpuric rash. There were no true cutaneous lesions of a seborrhoeic or eczematous nature. Skin lesions of a similar nature have been described in Hand-Schüller-Christian disease by Herzenberg (1928), by Lane and Smith (1939), and more recently by Curtis and Cawley (1947) in a case of eosinophilic granuloma of bone. Such lesions are frequent but not invariable accompaniments of systemic reticulo-endothelial granuloma.

The pulmonary lesions are of some importance. In our case the lesions were mostly small and only the larger granulomatous areas were undergoing fibrosis. Gross and Jacox (1942) have described a case with severe pulmonary fibrosis and cyst formation.

The progressive anaemia is the result of widespread replacement of haemopoietic tissue by the granulomas.

McKelvie and Park (1950) also review briefly the pathology and the reported cases of eosinophilic granuloma of bone, and its relationship to Letterer-Siwe disease. We will therefore pass on to other theories of the mechanism of Letterer-Siwe disease, particularly those concerned with metabolism and infection.

Rowland (1928), after describing the clinical and pathological features suggested that the disease resulted from a primary disturbance of lipid metabolism. This hypothesis was further strengthened by the work of Epstein and Lorenz (1930), who had studied the chemical nature of the deposits in Gaucher's disease, Niemann-Pick disease, and Hand-Schüller-Christian disease. The last thus came to be regarded as a disorder of the cholesterol metabolism related to Gaucher's disease and Niemann-Pick disease. This view was accepted by Sosman (1930, 1932), Chester (1930), von Gierke (1931), and Hilton and Eden (1941). Chester (1930) and Chester and Kugel (1932) thought that Hand-Schüller-Christian disease was 'a chronic non-infectious, abacterial, inflammatory granuloma due to the deposition of various lipid substances in the involved tissues.' They called the lesion a 'lipogranuloma' and described its characteristic features. Strong (1936) questioned the existence of a definite relationship with a disorder of lipid metabolism. Thannhauser and Magendantz (1938) were opposed to the idea of an upset in lipid metabolism as the fundamental cause of the condition. They maintained that the deposits of cholesterol occurred as secondary changes in granulomatous lesions composed of proliferated histiocytes. Unfortunately, they classified Hand-Schüller-Christian disease as a normocholesterolaemic type of essential xanthomatosis in spite of the fact that a number of patients with this disease have had a high blood cholesterol level. Gross and Jacox (1942) in a review of the literature found 45 cases where the blood cholesterol had been estimated. In 23 cases it was over 200 mg. % so the term 'normocholesterolaemic' should not be applied to the disease. Nevertheless, these workers were able to show that the hypothesis of a primary lipid metabolic disorder was not firmly based, and they attracted attention to the importance of the granulomatous lesions.

If the presence of granulomatous lesions largely composed of histiocytes is accepted as the fundamental lesion in Hand-Schüller-Christian disease the connexion between the latter and Letterer-Siwe disease becomes more obvious. As Wallgren (1940) remarked, the lesions tend to affect similar structures in both diseases in a similar manner. There is little difference between the skeletal lesions in the two diseases of large numbers of foam cells in biopsy

or necropsy specimens from patients with Hand-Schüller-Christian disease. If, however, these foam cells are not considered of fundamental importance, the two conditions may be regarded as variants of a single pathological process.

Many workers have suggested that eosinophilic granuloma of bone, Letterer-Siwe disease, and Hand-Schüller-Christian disease are variants of a common basic disorder. This view has not passed unchallenged. Siwe (1949) has discussed the features presented by the reticuloendothelioses in children. He states that 'the concept of uniformity is correct only in so far as the reticuloendothelial system is involved in all cases.' He points out that eosinophilic granuloma of bone is a localized condition confined to the skeletal system, whereas Letterer-Siwe disease is a systemic disorder. With regard to Hand-Schüller-Christian disease, he considers that the presence of foam cells is the most important feature and is not shown by the other forms to the same extent. He does not regard the presence of these cells in all organs to be essential. Siwe considers that the cases reported by Flori and Parenti (1937) and Freund and Ripps (1941) and others are atypical examples of Hand-Schüller-Christian disease and are not transitional cases between it and Letterer-Siwe disease. He is doubtful if any such cases exist. Wallgren (1940) had suggested that the nature of the lesion might depend upon its age, foam cells only being found after a considerable period of time. Siwe is unable to accept this theory and states that neither the age of the patient nor the duration of the disease process can influence the course. We are of the opinion, however, that the evidence submitted by Green and Farber (1941) and Jaffe and Lichtenstein (1944) in favour of a common basic disorder underlying these three conditions is at least as convincing as the contrary view suggested by Siwe (1949). From a pathological point of view all three conditions result from granulomatous lesions composed of histiocytes. In the acute form these histiocytes occupy the whole lesion. In eosinophilic granuloma of bone the picture tends to be dominated by eosinophil leucocytes and in Hand-Schüller-Christian disease by foam cells, but the basic lesion is similar in all three. Furthermore, skin lesions of a similar nature have now been reported in all three disorders and radiographical differentiation of the skeletal lesions in this group would not be possible. The recent reports of lymph node involvement in eosinophilic granuloma of bone would suggest that this condition is not so localized as Siwe (1949) believes.

The transitional cases present a problem of classification. It is difficult to accept Siwe's view that they are atypical examples of Hand-Schüller-

Christian disease. In the case reported by Merritt and Paige (1933) the histological appearances of many of the lesions were very similar to those found in the case we have reported. Foam cells were found in the thymus and femur but early lipid changes were present in these sites in our case also. It is difficult to believe that the two types of lesion can occur in the same patient without there being some change from one to the other.

We believe that further clinical and histological study will accentuate the similarity between these three types of reticuloendothelial granuloma. The problem will not, of course, be solved until the aetiology is completely understood.

Aetiology. The aetiology of the reticuloendothelial granulomas is still obscure. Farber (1941), Green and Farber (1942) and other recent workers in this field are inclined to take the view that the conditions are the result of an infectious agent.

Green and Farber (1942) have stated that all attempts to transmit the disease to laboratory animals have so far failed, but they also believe the condition to be infective in origin and suggest a virus as the agent.

The pathological features of the granulomatous lesions are in keeping with an underlying inflammatory condition. The lesions in the liver and lungs in our case bore a faint resemblance to those of tuberculosis, and it will be remembered that Hand (1893) thought that he was dealing with a case of atypical tuberculosis when he first described the condition which now bears his name. If we are in fact dealing with an infectious disease further work is required to identify the causal organism.

Diagnosis. Letterer-Siwe disease, the acute form, is characterized by hepatosplenomegaly, enlargement of lymph nodes, fever, severe anaemia and changes in the skull, ribs, and long bones demonstrable radiographically. Not infrequently skin lesions of a haemorrhagic, purpuric, or eczematous nature are also present. An interesting feature in our case was the early eruption of teeth. The child had two teeth when admitted to hospital at the age of 22 weeks. Wallgren (Case 1, 1940) also noted that the teeth may erupt early in this disease. His patient had three teeth at the age of 3½ months.

The disease usually appears before the age of two years and runs an acute course ending fatally in a few weeks or months. Frequently a case, such as that reported by Merritt and Paige (1933) and others, may run a subacute course for many months, and the condition in the later stage tends to resemble the lipophagic form known as Hand-Schüller-Christian disease. The blood cholesterol is usually normal, but in the case reported by van Creveld and Ter Poorten (1935) the blood cholesterol was

596 mg. %. Pulmonary lesions are common. They resemble miliary tuberculosis in the early stages and fibrosis occurs as the disease progresses. Pleurisy and pneumothorax have been known to occur. Secondary infections such as otitis media, bronchitis, and bronchopneumonia are common. Letterer-Siwe disease is not familial or hereditary.

The pathological features of the acute form are exemplified in the case we have described. In addition to the organs affected in our case similar lesions in the pancreas, suprarenal glands, pituitary gland and Peyer's patches of the small intestine have been reported by various writers. Grady and Stewart (1934) have reported the occurrence of large cystic areas in the liver. On histological examination, the lesions were composed of masses of pale-staining histiocytes with a few lymphocytes and plasma cells. In our case the lesions in the liver and lungs were well-defined while those in the spleen, lymph nodes, and thymus gland were more diffuse. Necrosis was especially pronounced in the latter. Phagocytosis of fat droplets is not a conspicuous feature of this form and foam cells were only found near areas of necrosis. Eosinophil cells were scanty and giant cells were limited to the neighbourhood of necrotic tissue.

Hand-Schüller-Christian disease, the chronic lipophagic form, occurs chiefly in children and young adults and is neither familial nor hereditary in character. Kellog (1940) found that the majority of cases occurred in the first decade. Sosman (1932) reported a case in a male aged 55 years and Hertzog *et al.* (1940) described their findings in a male aged 54 years. These cases are exceptional.

This form of reticuloendothelial granuloma is commoner than the acute type. Gross and Jacox (1942) reviewed the literature and found 84 examples of the condition, and added a case of their own. Since then 24 cases have been reported in the literature bringing the total up to 109.

The clinical features are variable. The classical triad of multiple skin lesions, diabetes insipidus, and exophthalmos was regarded as pathognomonic of the condition by Schüller (1915). Sundelius (1936) stated that skull lesions, diabetes insipidus, and exophthalmos occurred in that order of frequency; the classical triad was the next most frequent occurrence. Horsfall and Smith (1935) classified symptoms and signs according to the frequency of their appearance, and found the classical triad was most frequent. This was followed by dwarfism, gingivitis and carious teeth, pain over bony lesions, discharging ears, lymphadenopathy and the adiposogenital syndrome. It was soon recognized that the presenting symptoms and signs would depend on the site of the granulomatous lesions. Many cases

have now been reported where the classical triad was absent. Hand-Schüller-Christian disease can appear under many guises. Snapper and Parisel (1933) have reported a case which closely resembled osteitis fibrosa cystica, and Hampton (1942) one in which the outstanding clinical sign was severe jaundice. The occurrence of dystrophia adiposogenitalis has been described in detail by Schüller (1915), Schüller and Chiari (1930), and Chester and Kugel (1930). Dwarfism was a feature noted by Rowland (1928) and Snapper and Parisel (1933).

Deafness may result from lesions in the petrous-temporal bone and mastoid processes. Dyspnoea can occur as a result of severe fibrosis, and cor pulmonale with acute right-sided failure may result.

Chester (1930) described the occurrence of xanthelasma of the eyelid in one of his patients, while Snapper and Parisel (1935) reported spontaneous fractures of both femora in a patient with multiple granulomatous lesions in the long bones.

Headaches and localized scalp tenderness are common (Imler, 1946). Freund and Ripps (1941) reported a case where great enlargement of the cervical lymph nodes gave the patient a bull-necked appearance. It is thus obvious that in the absence of the classical triad there may be some difficulty in reaching a diagnosis.

Radiological investigation is essential. The lesions in the skull, ribs, pelvis, vertebrae and long bones have the characteristic appearance common to all types of reticuloendothelial granuloma. In the skull they are more clear cut than those elsewhere (Imler, 1946).

The radiographic appearance of early chest lesions resembles that of miliary tuberculosis. In later cases fibrosis and emphysema are found. Nearly all the fatal cases have shown extensive pulmonary lesions.

Laboratory investigations should include a differential leucocyte count and estimations of the blood cholesterol. The latter is frequently normal but in a number of cases it is markedly raised. A moderate degree of eosinophilia is commonly found.

Transitional cases between Letterer-Siwe disease and Hand-Schüller-Christian disease occur from time to time. These almost invariably end fatally. The disease tends to be more acutely progressive in very young children and the outlook is unfavourable in such cases. In older children and adults the condition is more chronic and the prognosis is better. According to Sosman (1932) the mortality in Hand-Schüller-Christian disease is 30%.

The pathological features of this form are variable. If the lesions are present in the orbits and in the region of the pituitary, exophthalmos and diabetes may ensue (Schüller, 1915; Schüller and Chiari,

1930). Frequently other skeletal structures are affected. Lesions have been reported in the petrous-temporal and mastoid region, in the mandible, scapula, clavicles, ribs, pelvis, vertebrae and in the long bones. Considerable attention has been paid to the location of the granulomatous deposits which could have caused diabetes insipidus. Thompson, Keegan, and Dunn (1925) reported inflammatory changes in the brain near the tuber cinereum and in the pituitary gland, while Dietrich (1913) had also found granulomatous tissues around the hypophysis. Horsfall and Smith (1935) thought that diabetes insipidus resulted from granulomatous lesions in the region of the tuber cinereum and not in the sella turcica. The most complete neuropathological report is that of Davison (1933). He found that in the case reported by Chester and Kugel (1932) the capsule of the pituitary gland was invaded by foam cells and the tuber cinereum showed areas of gliosis.

The histological features of the lesions in Hand-Schüller-Christian disease are so striking that the examination of a biopsy specimen will provide the diagnosis. The granulomas are composed of masses of histiocytes, many of which contain fat droplets and cholesterol and have assumed the appearance of foam cells. Cholesterol clefts may be found. Eosinophil leucocytes are frequently present in the more cellular areas but seldom in such great numbers as in the eosinophilic form (Fig. 9). In older lesions some scar tissue may be found.

Eosinophilic granuloma of bone is the least severe of this group of diseases. Patients rarely succumb unless some intercurrent infection supervenes. The lesions may be solitary but multiple lesions are frequently found, and are often silent and only revealed by radiographic examination following the discovery of a lesion which has given rise to symptoms. Any bone in the body may be involved except those of the hands and feet. Multiple skull lesions are common and cannot be distinguished radiographically from those of the acute or chronic lipophagic types. Lymph node involvement has been reported but is not a common occurrence.

Jaffe and Lichtenstein (1944) reviewed the literature, and their review has been extended by McKelvie and Park (1950).

The pathology of eosinophilic granuloma of bone has been described in great detail by Green and Farber (1942) and by Jaffe and Lichtenstein (1944). The histological appearance of the lesion is characteristic (Fig. 10). Masses of eosinophil leucocytes are found in granulomatous lesions composed of solid sheets of histiocytes. There has been considerable speculation concerning the part played by the eosinophil leucocytes in this condition. They are

less conspicuous in the acute form or in the lipophagic form. They are usually present in the bony lesions and not in the viscera (Ackerman, 1947), but Love and Fashena (1948) have found them in large numbers in cervical lymph nodes. The production of these eosinophil leucocytes may be the response of the organism to an infectious agent or to some products of tissue destruction caused by the granulomatous lesions.

Green and Farber (1942) have suggested that in eosinophilic granuloma of bone the lesion proceeds through a lipophagic stage and thereafter reverts to normal. Engelbreth-Holm, Teilum, and Christensen (1944) also believe that various histological stages occur in the progress of the lesion towards healing. They define the stages as (1) a hyperplastic proliferative phase, (2) a granulomatous phase, (3) a xanthomatous phase, and (4) a fibrous or healing phase. There may be cases which show these transitions but they do not necessarily occur in every instance. Jaffe and Lichtenstein (1944) have described a case where the lesion apparently healed by resolution. We have also seen a case where the granuloma was undergoing fibrosis and healing without the intervention of a lipophagic phase.

Treatment. Letterer-Siwe disease is almost invariably fatal and no treatment has any influence on the outcome. It is possible that x-ray therapy would have some effect on the subacute or transitional cases but no reports of this are available. Blood transfusions, as was found in our case, are merely palliative measures and have little effect on the final outcome.

Treatment of Hand-Schüller-Christian disease can cause a remarkable improvement both in the general health of the patient and in the repair of the lesions. Sosman (1932) has suggested a high protein, low fat, high carbohydrate diet, and recommends the use of 10 units of soluble insulin daily to promote an appetite. The patients under this regime gain weight and show an improvement in general well-being. Patients with polyuria improve after injections of pitressin, but Sosman (1932) has had even better results with x-ray therapy. He believes that the latter not only has a good effect on the bone lesions but is equally effective in controlling the diabetes insipidus. All workers agree that there is a rapid symptomatic response to deep x-ray therapy. The skeletal lesions repair more slowly in adults than in children (Sosman, 1932; Hilton, and Eden, 1941). The exophthalmos is refractory to radiotherapy. The pulmonary lesions have to be treated with care. If they are in the early miliary stage therapy may aid resolution. If, however, fibrosis has already occurred this may be increased by x-ray therapy. In cases where diabetes insipidus is a prominent

feature, little benefit can result from radiotherapy if the granulomatous lesions in the region of the pituitary have already undergone fibrosis. Imler (1946) recommends a total dosage of 600 r measured in air to the pituitary and 400 r to the bones.

Hand-Schüller-Christian disease, unlike Letterer-Siwe disease, is subject to spontaneous remissions. Such remissions have been noted both in the skeletal and pulmonary lesions (Imler, 1946).

Like Hand-Schüller-Christian disease the lesions in eosinophilic granuloma of bone may undergo spontaneous resolution. Solitary lesions respond well to surgical curettage (Hill, 1949) and both solitary and multiple lesions respond well to radiotherapy. The latter, with or without surgical curettage, is the treatment of choice in eosinophilic granuloma of bone. It is especially useful in preventing pathological fractures which are a danger if the lesions are allowed to remain untreated.

Summary

A case of Letterer-Siwe disease is presented and the clinical and pathological features are described.

The relationship between Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophilic granuloma of bone is discussed and it is suggested that these three conditions are all examples of reticuloendothelial granuloma. Letterer-Siwe disease is the most severe and fatal form and the prognosis is uniformly bad. Eosinophilic granuloma of bone is the mildest type and frequently occurs as a single lesion. Hand-Schüller-Christian disease occupies an intermediate position, and the outlook is better than in Letterer-Siwe disease, but less favourable than in eosinophilic granuloma of bone.

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