treatment, they rarely degenerated into the lepromatous type of the disease. Through its action on such patients in particular, hydnocarpus oil must have contributed to the decline of leprosy.

The virtue of the isolation of open cases is self-evident. Over the past 20 years several thousands of these have been isolated at settlements in Eastern Nigeria, and this must inevitably have had its effect on the disease. In addition, particularly in Owerri and Rivers Provinces, during the past 15 years approximately 10,000 patients have been isolated for longer or shorter periods in local segregation villages, this number including most of the known cases likely to be infective in the localities concerned. Even though this group of patients enjoyed considerable freedom, and visits home were sometimes frequent, they were for a considerable part of their time removed from the compounds where they formerly lived, and many opportunities for infecting others were thereby prevented. The virtue of the system as an anti-leprosy measure was commented on by Cochrane (1953). There seems to be no doubt about its importance.

Since 1949 the most important leprosy control measure of all has come into play with the general adoption of sulphone treatment. This area provided the first large-scale experiment in the use of oral 4:4'-diaminodiphenylsulphone (D.D.S.) in the field, initiated by the enterprise of Drs. Lowe and Bland. In Onitsha Province it has been reported on by Garrett (1951) and Garrett and Corcos (1952). Since 1951 oral D.D.S. has been the standard treatment for leprosy at all centres, and its effects are now manifest. The long-standing lepromatous cases whose infection lingered on under hydnocarpus treatment are for the most part now discharged. Treatment is extremely popular, attracting patients at an earlier stage of the disease than ever before. Early lepromatous cases speedily become bacteriologically negative. The general public is increasingly leprosy-conscious, and prejudice in localities long resistant to local leprosy control measures has finally succumbed. Relapses hitherto have been unimportant, and there have been no grounds for losing the confident outlook that sulphone treatment engendered. Here, then, is a potent anti-leprosy weapon rendered especially powerful because, thanks to an existing organization, it proved possible to apply it at many centres simultaneously.

The only clue to the relative importance of the four influences antagonistic to leprosy, which have been discussed briefly here, lies in the speed with which change has occurred. Circumstances are unusual, but it is extremely unlikely that natural regression of the disease, the spread of tuberculosis, or a rising standard of living can, either singly or collectively, have produced such profound effects in the space of seven years. They have doubtless played their part, but there seems to be little room for doubt that intense and widespread leprosy control work has been of great importance, that the effort of many devoted leprosy workers has borne fruit, and that the cost of the Leprosy Service to the British taxpayer through the Colonial Development Fund has entirely justified itself.

Summary

Leprosy is a disease of major importance in Eastern Nigeria, where it has a number of unusual features: (a) its incidence as encountered in surveys between 1937 and 1948 was generally high, sometimes phenomenally so; (b) its character is usually mild; (c) highly infective lepromatous cases form only a small minority of total infections, and indeterminate cases are common; (d) the disease affects all age groups; and (e) since 1948 signs of a decline in incidence have steadily increased, and a large-scale reduction in the disease is now evident.

The facts suggest that an epidemic of the disease has occurred which is now waning. In its decline the influence of tuberculosis, improved living conditions,

and leprosy-control measures is probable, and the relative importance of these factors antagonistic to the disease is briefly discussed.

Thanks are due to the Director of Medical Services, Eastern Region, Nigeria, for permission to publish this paper.

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LETTERER-SIWE SYNDROME IN ADULTS

REPORT OF TWO CASES

BY

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Descriptions, from both clinical and pathological aspects, of the commoner lymphatic node tumours are abundant, and their recognition now presents no great difficulty. It is amongst the rarer members of this group of tumours that the greatest difficulty in accurate diagnosis is often encountered. Robb-Smith (1938) has attempted the task of clarifying a most confused group of conditions, and it seems desirable that cases of the rarer types of lymphoid tumours should be recorded, not merely because of their rarity, but in order that the adequate study of such cases may eventually make their clinical and pathological recognition easier.

The cases described below are of the rare Letterer-Siwe syndrome in adult life: they showed several of the clinical features described by Robb-Smith in this condition, with other features not hitherto recorded. The presenting symptoms in each case consisted of a severe macrocytic anaemia with steatorrhea.

Case 1

The patient, a married woman aged 39, was admitted to hospital in January, 1947, for the investigation of a severe anaemia with nausea, anorexia, and rapid loss of weight. A short bout of diarrhoea lasting a few days had occurred

CHART I.—Case 1.

in September, 1946. She was seven months pregnant. Investigations showed a very severe macrocytic anaemia with haemoglobin 24% (Chart I), red cells 1,400,000 per c.mm., with a mean cell diameter of 7.9 μ . A fractional test meal showed the presence of free acid. Marrow biopsy revealed a typical megaloblastic picture. A diagnosis of macrocytic anaemia of pregnancy was made and treatment included blood transfusion, crude liver injections of 2 ml. twice a week, and proteolysed liver and iron by mouth. The patient made a rapid recovery, being discharged from hospital early in March, 1947, with a haemoglobin of 100%. A healthy female child was born in April.

In January, 1948, there was a gradual return of the earlier symptoms of anaemia and loss of weight; the patient now began to suffer from diarrhoea, with frequent pale, watery, offensive motions. She was readmitted to hospital in February, 1948. Her weight was 5 st. 11 lb. (36.7 kg.). The haemoglobin was 46%, red cells 2,000,000, mean cell diameter 8.6 μ . A fractional test meal again showed the presence of free acid; serum calcium was 10 mg. per 100 ml. Total faecal fat was 39.6%—free fatty acid 27.5%, soaps 9.3%, neutral fat 2.8%. A revised diagnosis of idiopathic steatorrhoea was made, and treatment was begun with crude liver injections, 4 ml. daily. Vitamin B, calcium, and iron were also given, and the patient was put on a low-fat, low-carbohydrate, high-protein diet. Response to therapy was good, and the patient was discharged in April with a haemoglobin of 82%, and red cells 4,800,000, having gained a stone (6.4 kg.) in weight. The maintenance dosage of liver was 2 ml. of crude liver weekly. The low-fat high-protein diet was continued.

In December, 1950, a severe generalized eczematous dermatitis occurred, which remained troublesome for some weeks.

By March, 1951, the skin condition had greatly improved, but the patient was now complaining of pains in the back, legs, and right shoulder. Examination showed tenderness over the mid-dorsal spine, and an x-ray film showed wedging of the eighth dorsal vertebra. Serum calcium was 8.4 mg. per 100 ml., serum phosphorus 3 mg. per 100 ml., and serum alkaline phosphatase 14 units. This localized osteoporosis, as it was thought to be, was treated with high dosage of vitamin D, and the pain and disability disappeared completely within a month.

In August small irregular raised nodules, purplish in colour and painful to the touch, began to appear in the skin of her legs and arms. Biopsy of a skin nodule was performed, and sections showed a low-grade tumour of lymphatic or reticulo-endothelial tissue. It now seemed possible that the whole picture might be that described by Robb-Smith as reticulum-celled medullary reticulosis (Letterer-Siwe syndrome) of adults.

In October a sternal marrow biopsy showed a slight increase in eosinophil myelocytes, but nothing else abnormal. By December generalized lymphatic node enlargement appeared. Her weight fell to 5 st. 10 lb. (36.3 kg.) with increasing general weakness. Soon after this, periods of pyrexia of Pel-Ebstein type began and the weakness and loss of weight became even more pronounced. In January, 1952, her weight was 4 st. 11 lb. (30.4 kg.). Abdominal pain of severe colicky type with flatulence and occasional diarrhoea also appeared.

The patient was readmitted to hospital in January. Biopsy of an epitrochlear lymphatic node was performed and the picture, described below, was that of a malignant tumour of lymphatic tissue.

A course of nitrogen mustard was given without any evidence of clinical improvement, although the enlarged lymphatic nodes showed some reduction in size. The pyrexia, cachexia, and abdominal pain continued, and, although there was no sign of further lymphatic node involvement, skin metastases, or bony metastases, her condition steadily deteriorated and death occurred on May 7, 1952.

Biopsy Reports

Skin Nodule.—Biopsy in September, 1951, showed a subcutaneous nodule of densely cellular infiltration, the predominant cell being a fairly well differentiated histiocyte-like cell. There was evidence of active growth in frequent mitotic division figures.

Epitrochlear Node (Fig. 1).—Biopsy in January, 1952, showed the normal gland architecture to be completely destroyed by a malignant neoplasm, the features of which were those of a primary lymphatic tumour. The picture

FIG. 1.—Case 1. Photomicrograph of section of epitrochlear lymph node ($\times 900$.)

varied in different areas of the node, some areas showing predominance of quite well differentiated histiocyte-like cells similar to those seen in the skin biopsy, while larger areas show a pleomorphic picture. Reticulin staining showed a diffuse and considerable increase in reticulin. The general picture was that of a "reticulum-cell sarcoma" as defined by Willis (1948). In the Robb-Smith classification the picture was that of reticulum-celled medullary reticulosis.

Summary of Necropsy Findings

The body was extremely wasted. A few petechial haemorrhages were scattered over the skin of both lower limbs. There were a few small indurated nodules in the skin in both infraclavicular regions. The peritoneum contained about 2½ pints (1.4 litres) of milky fluid. The liver (weight 28 oz.—790 mg.) showed diffusely scattered very small white areas. The spleen (weight 5½ oz.—156 mg.) was also studded with very small white areas (1–2 mm. diameter). The mesentery was crowded with numerous lymphatic nodes up to half an inch (1.3 cm.) in diameter, with large, hard, matted masses of nodes at the root of the mesentery merging with similar retroperitoneal masses. Other organs showed no macroscopic abnormality.

Histology

Both spleen and liver (Fig. 2) contained numerous sharply defined irregularly scattered areas of infiltration by a

FIG. 2.—Case 1. Photomicrograph of section of liver. ($\times 550$.)

neoplasm showing the characters described above in the lymphatic node biopsy. In many of these areas partial or complete necrosis had occurred, but particularly in areas adjoining blood vessels a very cellular picture was seen, the predominant cell being a histiocyte-like cell. The periphery of the pancreas was infiltrated by the same tumour tissue, although here necrosis was widespread and almost complete. Several lymphatic nodes from mesentery, porta hepatis, and inguinal and infraclavicular regions showed replacement of normal lymphoid structure by tumour tissue, very much of which was completely structureless and necrotic, though a few small islands of recognizable tumour tissue with the same predominantly histiocytic cell picture had survived. The mesentery, apart from the numerous enlarged lymphatic nodes, showed diffuse infiltration by necrotic tumour tissue, and many grossly dilated lymphatics.

The affected *dorsal vertebrae* showed no recognizable infiltration, and areas of fibrous tissue represented the original lesions.

Comment

The history falls naturally into three periods. Firstly, a severe macrocytic anaemia of pregnancy in 1947; next a period of three years from 1948 to 1951 during which the clinical picture was that of idiopathic steatorrhoea associated with a macrocytic anaemia; and, finally, the last phase from mid-1951 to 1952 during which generalized spread of a lymphatic node tumour occurred, involving peripheral lymphatic nodes, skin, and bone.

Case 2

A man aged 39 was admitted to hospital on November 5, 1951, suffering from a severe anaemia. He had been well up to a month before, except for two short bouts of diarrhoea and vomiting in July and August, 1951. He had never been abroad. On examination nothing abnormal was found beyond the anaemia and a general pigmentation of skin. There had been no obvious loss of weight. Blood examination showed a very severe macrocytic anaemia, with haemoglobin 34% (Chart II), erythrocytes 1,340,000, and a

mean cell diameter of 7.8μ . Treatment with a refined liver preparation, 2 ml. daily, was begun, but there was no response after 10 days, and a transfusion of 4 pints (2.3 litres) of blood was given. Meanwhile a fractional test meal showed the presence of free hydrochloric acid. Faecal fat estimations showed 50% total fat with normal split/unsplitted ratio. A crude liver preparation was substituted for the refined liver, but no response was obtained, and on December 6 liver therapy was discontinued and folic acid, 25 mg. daily, was given. Response was rapid, a good reticulocyte crisis being obtained, and the patient was discharged on January 16, 1952, with a diagnosis of idiopathic steatorrhoea. His blood picture was nearly back to normal.

He remained in good health on 5 mg. of folic acid twice daily until the end of 1953, when he was readmitted with a relapse of his anaemia and diarrhoea following the stopping of folic acid a month before. Again he responded well to folic acid and was discharged.

On March 2, 1954, he was readmitted to hospital with a two-months history of increasing dyspnoea and cough, with pyrexia and loss of weight. He was gravely ill and had the physical signs of a bilateral bronchopneumonia. Anaemia was not present. No response to antibiotics was obtained, and on radiological grounds a tuberculous bronchopneumonia was suspected. He was transferred to a sanatorium, where he died a few days after admission.

Necropsy Findings (April 3, 1954).—The body was that of a young man showing marked absence of subcutaneous fat. The lungs showed a well-established bronchopneumonic consolidation of gross miliary pattern. The hilar nodes were enlarged, especially on the right side. The liver was enlarged and appeared to be fatty and toxic. The spleen was enlarged and congested, and the mesenteric lymphatic nodes were grossly enlarged.

Histology.—The lungs showed bronchopneumonia. Metastases of a malignant reticulum-cell tumour were present, with central necrosis. There were also scattered miliary areas of recent monilia infection with giant-cell reaction. The reticulum-cell tumour showed well-differentiated histiocyte-like cells predominating, with rather frequent mitotic figures and occasional multinucleated and atypical cells (Fig. 3). *Hilar and mesenteric nodes* showed extensive deposits of the same reticulum-cell tumour as that described in the lung metastases. Much necrosis was present (Fig. 4). The liver had very frequent small miliary metastases of the same reticulum-cell tumour (Fig. 5).

FIG. 3.—Case 2. Photomicrograph of section of lung showing metastases of a malignant reticulum-cell tumour. ($\times 620$.)

FIG. 4.—Case 2. Photomicrograph of section of mesenteric node showing the same reticulum-cell tumour as Fig. 3. ($\times 340$.)

FIG. 4.—Case 2. Photomicrograph of section of liver showing small miliary metastases of the same reticulum-cell tumour as Figs. 3 and 4. ($\times 340$.)

Comment

Death was due to bronchopneumonia following pulmonary, hepatic, and lymph-node metastases of a malignant reticulum-cell tumour, probably arising in the mesenteric lymph nodes.

Discussion

While the cause of idiopathic steatorrhoea (as of sprue) is as yet unknown, it has been recognized for some time that a small proportion of all cases of steatorrhoea are caused by simple obstruction of mesenteric lacteals by a widespread mesenteric lymphadenitis. Ryle (1936) described how such obstruction may occur from tuberculous mesenteric nodes with the production of the sprue syndrome, and Hurst, Payling Wright, and Ryle (1942) describe the history and necropsy of such a case. Hamilton Fairley and Mackie (1937) described a sprue-like syndrome in adults associated with lymphoma, lymphadenoma, and lymphosarcoma of mesenteric nodes, and caused, as they suggest, by defective intestinal absorption from lymphatic obstruction. In two of their four cases anaemia was present, macrocytic in one and normocytic in the other.

For neoplastic disease of mesenteric nodes to produce the sprue syndrome without other evidence of disease it is necessary that the neoplastic condition be a low-grade one, of slow growth, occurring primarily in mesenteric nodes, remaining localized in that area for a considerable interval before becoming generalized and manifesting itself in peripheral lymph nodes or elsewhere. These conditions existed in the two cases here described. That the presenting symptom in Case 1 was that of macrocytic anaemia of pregnancy is not surprising, since pregnancy is a recognized precipitating factor of both sprue and idiopathic steatorrhoea (Morgensen, 1937). That the two cases here described were under observation for four years and two years respectively without developing palpable peripheral lymphatic nodes, hepato-splenomegaly, or other signs of generalized spread indicates the slow-growing, relatively benign nature of the neoplastic process; and careful study of biopsy and necropsy material from these cases has led us to place them in Robb-Smith's category of reticulum-celled medullary reticulosis (Letterer-Siwe syndrome). While this condition has most often been recorded in children (Wallgren, 1940; Varga *et al.*, 1948), where it may be confused with aleukaemic leukaemia, Robb-Smith has observed the condition in adults, in whom a very different clinical picture is produced; the condition runs a much more chronic course, is associated with lymphatic node enlargement, splenomegaly, severe anaemia, and pyrexia; and symptoms of steatorrhoea have been observed. This condition merges with the lesions of the lipoidoses and eosinophil granuloma of bone, in which distinction between a chronic inflammatory condition and true neoplasia is difficult, and, on the other hand, with the more obviously malignant "reticulum-cell sarcoma" of Willis (1948). Willis's Case XII in particular shows some striking similarities to the cases here described.

Summary

Two cases of Letterer-Siwe disease in adults are recorded, with early involvement of mesenteric lymph nodes, giving rise to the sprue syndrome with severe macrocytic anaemia responding only to folic acid. The clinical picture and the pathology of the disease are discussed.

My thanks are due to Professor Payling Wright for helpful criticism; to Dr. J. McMurray for the necropsy report of Case 2, and for providing necropsy material; and to Dr. B. B. Hosford for his co-operation.

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EFFECT OF MITRAL VALVOTOMY ON RENAL FUNCTION

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After surgical intervention some patients with mitral stenosis complicated by congestive heart failure improve to such an extent that they no longer require treatment. Merrill (1946) and Mokotoff *et al.* (1948) suggested that the abnormal renal circulation, which has been demonstrated in patients with chronic rheumatic heart disease both with and without congestive heart failure (Merrill, 1946; Aas and Blegen, 1949; Davies and Kilpatrick, 1951; Werkö *et al.*, 1955), was directly responsible for impairment of salt and water excretion in these patients and for the development of heart failure. Therefore it seemed desirable to investigate renal function before and after mitral valvotomy and to attempt to relate any changes to those in the clinical state.

Material and Methods

Fifteen patients, of whom all but one were female, were studied before and after mitral valvotomy.

The clinical state of the patients was assessed both before and after operation, using the grades of disability defined by Baker *et al.* (1952); these may be briefly summarized as 0, no disability; 1, slight disability; 2, moderate disability; 3, severe disability; and 4, total incapacity. The first post-operative assessment of the clinical state was made six months to one year after operation.

Observations on the renal circulation were made about two hours after a meal with the subjects propped up