I am grateful to Dr. W. M. Jamieson, Dr. R. N. Johnston and Mr. R. J. A. Fraser for access to case notes, and to Dr. K. N. V. Palmer for helpful comments.

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NONMETASTATIC NEPHROGENIC HEPATOSPLENOMEGALY AND EPILEPSY

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IN RECENT years a variety of general systemic manifestations and unusual syndromes have come to be recognised as presenting features of an otherwise occult neoplasm. Their diversity has included the purely dermatological manifestations, including acanthosis nigricans, dermatomyositis and erythema gyratum repens; a variety of neuromuscular syndromes; skeletal disturbances including clubbing, pulmonary hypertrophic osteoarthropathy and pachydermoperiostosis; thrombophlebitis migrans and phlebothrombosis; erythrocytosis and red cell aplasia; and various hormonal and metabolic disturbances (Greenberg, Divertie and Woolner, 1964). Familiarity with such manifestations are of dual importance; firstly, as diagnostic pointers and secondly, in the frequent observation that successful removal of the primary lesion may lead to complete regression of these features.

Creevy (1935) recorded three patients with hypernephroma presenting with clinical features suggesting cirrhosis of the liver. Stauffer, at the

1961 annual meeting of the American Gastroenterological Association drew attention to non-metastatic hepatosplenomegaly from renal carcinoma. The published abstract (Stauffer, 1961) mentions five cases, but Greenberg and others (1964) ascribe 10 such cases to the author; four with splenic enlargement and all with grossly abnormal results of liver function tests. The abnormal findings returned to normal after nephrectomy. Such a favourable response is well recognised for renal polycythemia and is at times noted with proven pulmonary metastasis. That this should obtain on occasion with hepatosplenomegaly is of considerable interest as wider appreciation of this phenomenon would lead to more of these cases being offered operative treatment despite markedly deranged liver function, with a prospect of effecting complete cure. The frequency with which such an outcome may be expected is unknown and accordingly a case of renal carcinoma recently encountered by us and diagnosed only at necropsy but who showed

marked derangement of liver function with prominent hepatosplenomegaly in life, without macroscopic or microscopic abnormality of the liver at death, is described. The case is of further interest on account of epileptiform seizures for several months pre-terminally without demonstrable intracranial pathology at autopsy.

Case Report

A farmer's wife, aged 47 years, was admitted on 10.7.62 and remained under our care until her death on 12.11.63. Her symptoms throughout the illness were largely constitutional: weight loss, tiredness, lassitude and excessive sweating, with from time to time additional non-specific features of a marked anaemia (Fig. 1).

There was evidence of weight loss and continued low grade fever. Small shotty nodes in the left axilla remained the sole adenopathy in the accessible sites throughout the illness. A firm mass, two to three finger-breadths in size, with a "notch" in the anterior border was readily palpable in the left hypochondrium. It was possible to get "behind" the mass but not "above" it. It was dull to percussion and moved with respiration. It was regarded as a splenic enlargement. Very soon the liver, too, became readily palpable.

Investigations: ESR 85-140 mm./hr. (Westergen), Hb. 55% (7.9 g./100 ml.); PCV 28%; MCHC 28%; slight hypochromia and microcytosis of the red cells; reticulocytes <1% and 1.4%; tests for occult blood and quantitative and qualitative tests for excess urinary urobilinogen negative; urinalysis chemically and microscopically normal; Coomb's test negative; WBC 4000-7000/cu. mm. with normal differential counts; platelets 150-300,000/cu. mm.

Bone marrow examination in July 1962 produced aspirates of normal cellularity with normoblastic hyperplasia as the only abnormality but a further examination a few weeks later showed a shift to the left of the granular series with marked increase of the premyelocytes. No abnormal cells were seen.

The liver function tests showed moderate impairment with the alkaline phosphatase 13 and 16 KA units; serum albumin 3.88, globulin 3.72 and 4.45 g./100 ml.; increase in the α_1 , α_2 and γ globulin in the electrophoretic strip; 20% retention of bromsulphalein at 45 minutes. Serum bilirubin and seroflocculation studies were normal. Tests for LE cells and antinuclear factor were negative. A deformity of the stomach by extrinsic pressure from the "spleen" was noted on a barium meal and an enema examination was reported as showing a displacement of the sigmoid flexure and the upper descending colon by the splenomegaly. A chest X-ray and a skeletal survey were negative.

An abdominal reticulosis, possibly of the Hodgkin type was thought to be the likeliest diagnosis and the alternative possibility of a pre-leukaemic condition was also considered. Aspiration liver biopsy was precluded on account of persistently elevated prothrombin time (17-18 seconds; control 13.5 seconds) despite intensive treatment with vitamin K₁. Supportive treatment with packed red cells was given in July and again in September.

During the latter months of 1962 she remained in relatively good health with increase in energy and absence of night sweats. Her weight, however,

continued to fall at the rate of 1.5-2.0 lbs. per month. The haemoglobin after an initial slight fall stabilised at 65-75%. A course of oral iron was given on account of persistent hypochromia and microcytosis but this was without benefit. The hepatosplenomegaly became a little more marked and the alkaline phosphatase rose to 28 KA units.

Towards the end of 1962 she defaulted attendance at the clinic and when seen again late in February 1963 her condition had deteriorated considerably with continuing weight loss, tiredness, lack of energy and excess sweating. There was progressive increase in both the hepatic and splenic enlargement with further deterioration in the liver function tests (Fig. 2). A repeat bone marrow aspirate on 14.3.63 was of normal cellularity. The erythropoiesis was normoblastic, slightly hyperplastic, and with some features of iron deficiency. The myeloid series was reported as showing "a marked preponderance of cells which look like premyelocytes, but, considering the discrepancy in numbers between these cells and the myelocytes, many of the cells may be reticulum cells. There are also a few non-granular, more primitive cells of the reticulum cell—monoblast type". A bone marrow trephine biopsy was reported by the pathologist as being cellular and showing an increase of eosinophils. Joint review of the two sets of films failed to take the diagnosis further. A surgeon could not be persuaded to undertake a laparotomy with a possible open liver biopsy as the procedure was considered too hazardous in view of the impaired liver cell function.

She received supportive treatment with further blood transfusions with some subjective improvement. Because of the strong clinical suspicion of a reticulosis, treatment with nitrogen mustard, chlorambucil, corticosteroids and local irradiation to the spleen was given over the ensuing months but all were singularly without any benefit.

From June 1963 she became subject to recurrent major convulsive seizures. An electroencephalogram showed trains of theta waves over both temporal areas with frequent mixed spike and wave discharges from the right cerebral hemisphere with maximal disturbance over the right inferior fronto-temporal area. A lumbar puncture showed no alteration in the cellularity, chemistry or dynamics of the cerebrospinal fluid. The seizures were treated with phenobarbitone and later with phenytoin sodium and primidone with moderate success. With the inexorable progress of her cachexia she gradually lapsed into coma and died on 12.11.63.

Necropsy. Apart from the cachexia, the following features were of note:—

Examination of the intracranial contents including multiple sections of the brain failed to reveal any naked eye or microscopic abnormality of the meninges, brain substance or the blood vessels. There was bronchopneumonia with slight non-specific enlargement of the hilar lymph nodes. The liver (1000 g.) was not enlarged and appeared normal both on naked eye and histological examination. The spleen was slightly enlarged (300 g.) and showed congestive changes and haemosiderin-laden macrophages. The organ was pushed forward by a large tumour mass replacing the upper pole of the left kidney, which had all the typical features of a hypernephroma on histological examination. All the intra-abdominal lymph nodes and the renal veins were free of tumour deposits.

FIG. 1.—Note the progressive cachexia, recurring anaemia, progressive hepato-splenomegaly, and increasing evidence of liver cell dysfunction.

Discussion

The protean manifestations of renal tumour are well recognised. Constitutional disturbances with fever as the only presenting features have been frequently recorded but Weinstein, Geraci and Greene (1961) draw attention to the relative infrequency of prolonged fever as the sole clinical manifestation. Marked to moderate elevation of the ESR (Melicow and Ulson, 1960; Bottiger, 1960a) and non-specific alterations in the serum globulins (Bottiger, 1960b) have also been noted in a proportion of patients. There were no relevant renal symptoms in the present case and well over 20 urine specimens over the prolonged illness failed to reveal any biochemical or microscopical abnormality. Melicow and Ulson (1960) noted atypical presentation in 183 of 537 cases with renal carcinoma and in 60% of the former red blood cells were absent from the urine throughout the illness.

The diagnostic confusion in the present case was compounded by the presence of classical clinical and radiological features of a splenic enlargement. At death, the spleen was certainly enlarged though much less than in life and whilst this may have been an agonal feature, it seems more probable that the "notch" observed along the anterior border was due to the composite mass presented by the spleen and the enlarging renal tumour. The hepatomegaly with pronounced liver cell dysfunction, the non-specific anaemia and the striking though atypical features in the bone marrow directed diagnostic considerations towards a reticulosis or a pre-leukaemic process. The absence of liver enlargement at autopsy was likely due to the pronounced cachexia in the latter part of the illness.

The most interesting feature of the case was the striking absence of histological abnormality of the liver despite the pronounced functional im-

pairment during life. Had the diagnosis been made during life and the tumour resected, there is a strong presumption in the light of Stauffer's experience that complete resolution of the abnormal features may have occurred. This is important as many such patients are probably refused operative treatment at present on the grounds that the abnormality of functional efficiency of the liver denotes a disseminated lesion. The present case emphasises the need to undertake pyelographic examination in patients presenting with unexplained hepatomegaly with or without splenic enlargement and liver cell dysfunction and raises the optimistic note that even a severe degree of functional impairment of the liver need not necessarily be a bar to surgical treatment in that complete resolution of the abnormal features may follow a successful nephrectomy.

Epileptiform seizures in the absence of a demonstrable intracranial abnormality, as in this case, should probably also be regarded as a non-metastatic lesion likely to resolve after successful removal of the primary malignant disease. Judging by recent reviews of nonmetastatic manifestations of malignant disease (Pinals and Krane, 1962; Greenberg and others, 1964), epilepsy of this type does not appear to have been described previously.

Summary

A case is described of a woman of 47 who suffered from a fatal illness for 18 months, characterised by constitutional disturbance, weight loss, fever, non-specific anaemia, progressive hepatosplenomegaly and increasing liver cell dysfunction and preterminally grand mal epilepsy. Autopsy, which revealed a hyperne-

phroma of the left kidney, failed to show macroscopic or histological abnormality of the liver, brain or the intracranial vasculature. It is suggested that this was a case of nonmetastatic hepatosplenomegaly and epilepsy in whom resolution of these features could conceivably have occurred if the renal tumour had been identified and resected during life. Further information on the frequency of such manifestations would be helpful in the diagnosis and management of renal carcinoma.

I am grateful to Professor A. G. Macgregor for permission to study this case who was admitted under his care and to Professor A. C. Currie for the post-mortem examination.

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TWO PATIENTS WITH CARDIAC MYXOMA:—ONE PRESENTING AS BACTERIAL ENDOCARDITIS, AND ONE AS CONGESTIVE CARDIAC FAILURE

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TUMOURS of the heart may be primary or secondary, the latter being 20-40 times commoner than the former (Prichard, 1951). Thorel in 1903 found no primary tumours in a series of 3,300 autopsies. Ravid and Sachs (1943) found one such tumour in every 1,888 consecutive autopsies and Straus and Merliss (1945) reported 18 in 480,331 autopsies. Of the primary tumours nearly half are myxomata.

The clinical manifestations of these tumours are protean, and as with other conditions which are uncommon the diagnosis is sometimes not made because it is not considered. Even when considered it is not always easy to establish. This is unfortunate because although most myxomata may be removed with comparative safety, if they are not, once symptoms have begun, death will follow sooner or later (Goodwin, 1963).