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CARCINOMA AND CUSHING'S SYNDROME

BY

J. R. BILLINGHURST, B.M., M.R.C.P.
Medical Registrar, University College Hospital, London

A. K. THOULD, M.D., M.R.C.P.
Medical Registrar, University College, Hospital, London

O. P. GALPIN, M.B., M.R.C.P.
Senior Medical Registrar, Manchester Royal Infirmary

AND

J. M. HINTON, B.M., B.Ch.
House-physician, Whittington Hospital, London

[WITH SPECIAL PLATE]

Though it is common at necropsy to find adrenal metastases from primary bronchial carcinoma, these do not usually give rise to any clinically recognizable endocrine disturbance. On the other hand, patients with bronchial carcinoma may very occasionally manifest the biochemical or even full clinical features of Cushing's syndrome. This subject has recently been fully reviewed by Allott and Skelton (1960), and mention has been made of primary sites of carcinoma other than the bronchus. It is worth drawing attention to this association between carcinoma and adrenocortical overactivity, partly to avoid the erroneous diagnosis that the primary neoplasm lies in the adrenal cortex, and partly to prevent the patient undergoing a fruitless adrenalectomy when a primary neoplasm elsewhere is unsuspected. Bagshawe (1960a) has pointed out that the finding of marked hypokalaemic alkalosis in a patient with adrenocortical overactivity should arouse strong suspicion of a primary neoplasm, most commonly in the bronchus.

Two further cases of this association are reported here. In each it was considered at one time that the primary carcinoma might be present in the adrenal.

Case 1

The patient, a housewife aged 57 years, was admitted to Harefield Hospital on October 23, 1959, chiefly because of mental disturbance. Over the preceding three months there had been a gradual and progressive change of mood with alternating bouts of depression and elation, sometimes with aggressive outbursts, sometimes with grandiose delusions of wealth and largesse. The first physical symptom noticed by the patient was swelling of the legs and arms in May, 1959, followed later by swelling of the face. Treatment by diuretics led to some improvement in the arms, but her legs became progressively larger, as did her face. Her weight greatly increased and she became much more breathless on exertion. She noticed a dry mouth, but did not mention undue thirst or polyuria. There was no complaint of muscular weakness. She smoked 20 to 30 cigarettes daily, and had suffered from a cough for 20 years. No relevant past or family history was obtained.

On admission she was garrulous and sometimes confused. There was marked generalized pigmentation of the skin, largely racial in origin, but considered by her husband to have increased from its previous level. The buccal mucous membrane was not pigmented. Extensive purpura was present over both forearms, and purple striae were noted in the skin of the abdomen and buttocks. There were typical fatty deposits over the trunk, face, and neck. Hirsuties was not marked. Pitting oedema of the lower limbs was not associated with raised jugular venous pressure. The blood-pressure was 150–190/90–110 mm. Hg. Hess's capillary fragility test was negative. Crepitations were heard over the left lower lobe of the lung. Both ankle-jerks were absent, but no sensory abnormalities were detected. The urine contained 2% of sugar and a trace of acetone.

Investigations

Investigations showed marked hypokalaemia (serum sodium 150, potassium 2.3, chloride 99 mEq/l.). The salivary potassium concentration was 23 and sodium 5.6 mEq/l., giving a Na/K ratio of 0.24. The blood sugar was 316 mg. per 100 ml. 1½ hours after a meal, and a glucose-tolerance test showed a fasting level of 166 mg. per 100 ml., rising in 1½ hours to 253 mg. and falling in 2½ hours to 205 mg. per 100 ml.; all specimens of urine contained sugar. Urinary 17-ketosteroid excretion was 60.2 mg. and 17-ketogenic steroids 30.8 mg. in 24 hours. Other findings were as follows: Hb 11.2 g. per 100 ml.; M.C.V. 98 $c\mu$; M.C.H.C. 32%; white cells 7,000 per c.mm. (85% neutrophils); platelets 120,000 per c.mm.; normal bleeding and clotting times; E.S.R. 60 mm. in first hour (Westergren); blood urea 45 mg. per 100 ml. Chest radiographs initially showed only cardiac enlargement, but subsequently patchy consolidation of the left lower lobe appeared. Prednisone did not significantly reduce the daily output of 17-ketosteroids, and this feature, together with the finding of a raised β-fraction, was considered to suggest an adrenal carcinoma as the cause of her clinically diagnosed Cushing's syndrome.

Progress

Potassium chloride by mouth in increasing doses up to 10 g. daily resulted in only a slight rise in the low serum level, though never to normal, the highest being 3.5 mEq/l. Glycosuria was controlled by soluble insulin, the daily requirement ranging between 20 and 60 units. Penicillin was given for the apparent infection in the left lower lobe of the lung, which was associated with a low-grade fever, and the signs improved, though not completely. Three weeks after admission there was an episode of right-sided colic associated with the passage of blood-clots in the urine. A hard, fixed mass was felt deep in the right loin, and a hard mass arising out of the pelvis. Hirsuties became more marked, extensive fresh purpura developed, the platelet count decreased progressively to 35,800 per c.mm. four weeks after admission, and the haemoglobin fell to 8.5 g. per 100 ml. Blood transfusion was refused.

She was transferred to Hillingdon Hospital on November 22, a month after her original admission, for further investigations with a view to adrenalectomy. Coarse crepitations were still present over the left lower lobe, where the percussion note was moderately impaired and breath sounds were diminished. Investigations confirmed the persistent hypokalaemia (3.5 mEq/l.), not associated, however, with alkalosis (serum bicarbonate 25 mEq/l.). For the first time some myelocytes were seen in the peripheral blood. The urine grew a *Proteus* on culture. Shortly after transfer her temperature and pulse rate rose rapidly and her general condition deteriorated. A blood-stream infection was suspected and subsequently confirmed, a *Proteus* being grown. Tetracycline, penicillin and streptomycin, and erythromycin were variously given without avail and she died on November 28, 1959.

Necropsy Findings

The relevant findings were as follows. About 300 ml. of blood-stained fluid was found in the left pleural cavity. There was an infiltrating white tumour 3×2×2 cm. arising in the left lower-lobe bronchus and extending up into the wall of the main bronchus. The left lower lobe was collapsed. There were several small secondary deposits in the right lung, one in the upper lobe being associated with an infarct. Hilar, mediastinal, and both groups of deep cervical lymph nodes were enlarged and invaded. The liver was studded with small secondary deposits up to 2 cm. in diameter, and there were a few minute subcapsular secondary deposits in both kidneys. The uterus was grossly enlarged (12×8×8 cm.) by secondary tumour, and also contained two degenerate fibroids up to 5 cm. in diameter and an endometrial polypus. The left lobe of the thyroid gland contained two small deposits. The bodies of all the lumbar vertebrae were riddled with tumour deposits. The suprarenals were grossly enlarged, the left measuring 8×3.5×2 cm. and weighing 25 g., and the right measuring 7×3.5×2 cm. and weighing 22 g. The enlargement was due to bilateral cortical hyperplasia, each cortex having a mottled brownish-yellow colour. On the left side there were also three tiny "pin-head" secondary deposits. The pituitary was grossly normal except for a tiny secondary deposit in the posterior lobe adjacent to the anterior lobe. The left ventricle was moderately hypertrophied. Severe bilateral haemorrhagic pyelitis and slight acute cystitis were present; the ureters were only slightly dilated. The spleen was slightly enlarged and very congested and oedematous.

Histology

The tumour arising from the left lower-lobe bronchus was an oat-cell carcinoma. Secondary carcinoma was confirmed in liver, thyroid, uterus, and a vertebra, in which reactive hyperplasia of haemopoietic tissue was noted. Microscopical examination of the suprarenals showed marked hyperplasia of the zona fasciculata of the cortex, many cells being laden with lipoid, and in addition there was one gross and several small foci of secondary carcinoma. In the pituitary there were extensive hyalinization of the basophil cells and secondary carcinoma in the boundary zone of the posterior lobe.

Case 2

A 52-year-old married woman was admitted to the Whittington Hospital on April 11, 1960, with a four-weeks history of polyuria, polydipsia, and nocturnal frequency. During this time she had also noticed pain and weakness of the right arm and leg, together with slight pain in the left leg. Ten years previously she had had a hysterectomy for uterine prolapse, but had otherwise been in good health. Her son had died of leukaemia at the age of 28. There was no family history of diabetes mellitus.

On admission she was observed to be obese and kyphotic, weighing 168 lb. (76.2 kg.) and 5 ft. (1.5 m.) tall. There were many pale abdominal striae and she had much hair on the upper lip. Her blood-pressure was 190/100 mm. Hg. There was no papilloedema, and the retinal vessels were normal. She had a systolic murmur at the apex, conducted into the neck. In the right arm there was marked weakness of the triceps and wrist and finger extensors, moderate weakness of the biceps, and slight weakness of the finger flexors, together with an absent triceps jerk. In the right leg there was slight weakness of the dorsiflexors of the foot. There was a moderate degree of wasting in the affected muscles. There was no sensory loss.

Investigations

The haemoglobin was 11.5 g. per 100 ml. and E.S.R. 19 mm. in the first hour (Westergren). Chest radiographs revealed a mass at the left upper hilum with a raised left diaphragm. There was marked glycosuria, and a glucose-tolerance test showed a diabetic-type curve, rising from a fasting level of 284 mg. per 100 ml. to a level of 375 mg. per 100 ml. at three hours. There was little ketosis, but all specimens of urine contained sugar. Serum sodium was 144 mEq/l., and the lowest recorded potassium was 3.6 mEq/l. The serum bicarbonate was normal. The 24-hour urinary 17-hydroxycorticosteroid excretion was 64 mg., 90 mg., and 72 mg. on three separate occasions, and 17-ketosteroid excretion per 24 hours was 34 mg. There was no appreciable suppression of 17-hydroxycorticosteroid output in the urine after prednisolone, 5 mg. 6-hourly, was given for 24 hours. The urinary 24-hour calcium excretion was 100 mg.; serum calcium was 10.2 mg. and serum inorganic phosphorus 2.5 mg. per 100 ml. Her 24-hour urinary creatine excretion was 400 mg. and 220 mg. on two separate occasions, and urinary creatinine excretion on the same occasions was 800 mg. and 540 mg. respectively. The serum glutamic oxalacetic transaminase was normal. Her cerebrospinal fluid was normal, under a pressure of 300 mm. of water. A radiograph of the cervical spine showed diminution of the disk spaces between C4–5 and C5–6 vertebrae. Radiographs of the lumbar spine showed considerable osteoporosis. An intravenous pyelogram showed the right kidney to be low and rotated, with a large soft-tissue shadow above it.

Progress

The diabetes was controlled with a mixture of soluble insulin 30 units and protamine-zinc insulin 15 units daily. On bronchoscopy the left upper-lobe bronchus was seen to be almost completely occluded by pressure from without. A biopsy was negative for carcinoma cells, as were three specimens of sputum. Three weeks after admission she developed pain and weakness in the left arm, and a small nodule appeared in the region of the umbilicus. This was excised, and histological examination showed it to be composed of cells typical of an oat-cell carcinoma. The abdominal striae became purple. She went downhill rapidly, developed ascites, and died of peritonitis on June 13, 1960.

Necropsy Findings

Necropsy was performed on the morning she died. A carcinoma was found arising from the bronchus of the upper lobe of the left lung with secondary growth involving the hilar lymph nodes in a mass 9 cm. across. Some growth was surrounding the left pulmonary artery, causing stenosis. There was congestion and oedema of both lungs. Carcinoma also involved the pericardium and the base of the heart. There was moderate hypertrophy of the left ventricle, with some atheroma of the coronary arteries. The left pleural cavity contained 200 ml. of clear fluid. In the abdomen there was a generalized fibrino-purulent peritonitis, with a litre of purulent fluid. Carcinomatous growth was observed in the liver and in the upper abdominal and aortic lymph nodes. The pancreas was involved with secondary growth, and showed changes of chronic pancreatitis with fat necrosis. The posterior abdominal wall was also extensively infiltrated, as was the perinephric fat surrounding the left kidney. There was growth in the cortex of this kidney and in the bladder wall. Both adrenal glands appeared to be largely replaced by carcinomatous tissue. The brain, hypothalamus, spinal cord and pituitary appeared normal. The spleen was congested. The ovaries were atrophic.

Histology (Dr. Stansfeld)

Sections of the lung tumour showed a highly cellular malignant epithelial growth, the morphological features of which suggested a poorly differentiated primary adenocarcinoma of bronchial origin. A similar type of structure was seen in metastatic tumours in the liver, pancreas, kidney, and a lymph node. In some sites the tumour showed very little differentiation of acinar structure and the appearance approached that of an undifferentiated "oat-cell" carcinoma.

Sections of a tumour present in one suprarenal gland showed clearly that metastatic carcinoma of the same type

as the lung tumour was present in a pre-existing cortical adenoma of the suprarenal. In spite of existing extensive destruction of one pole of the suprarenal tumour by secondary carcinoma, there was still a large amount of the cortical adenoma remaining.

In the light of these findings it seems highly probable that the features of Cushing's syndrome noted in this case were the result of the primary cortical adenoma of the suprarenal, and were not attributable to the bronchial carcinoma. Sections of both ovaries, pituitary, midbrain, spinal cord, and brachial plexus showed no significant changes.

Comment

Case 1

The presenting symptom in this case was a florid psychosis, and the diagnosis of Cushing's syndrome was made on the finding of trunk obesity, plethora, purple striae, increased pigmentation, hypertension, and glycosuria. Though the patient did not complain of muscle weakness, hypokalaemia was profound and resistant to relatively large amounts of potassium by mouth (up to 134 mEq daily). Urinary aldosterone estimations were not carried out; an isolated salivary Na/K ratio was low at 0.24, but as the normal range is wide this is uncertain evidence for excess aldosterone excretion. Edmunds *et al.* (1958) record a case of Cushing's syndrome in which the average salivary Na/K ratio was 0.27, rising after partial adrenalectomy to 0.35. In Bagshawe's review (1960a) of patients with frank Cushing's syndrome showing this order of hypokalaemia none had adrenal metastases (other than those with a primary adrenal carcinoma) and one had a pituitary metastasis. Both of our cases had adrenal metastases, and Case 1 had a metastasis in the pituitary as well as adrenocortical hyperplasia.

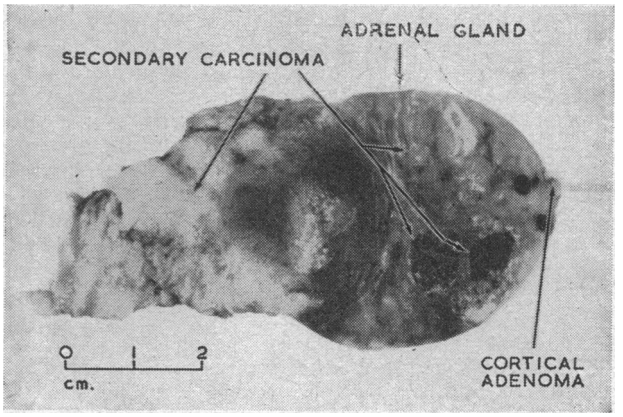
During life, however, the first suspicion of malignancy was aroused by the discovery that the purpura, not in itself unusual for Cushing's syndrome, was due to thrombocytopenia. The high urinary steroid excretion, raised β-fraction, and failure of prednisone to suppress 17-ketogenic steroid output seemed to lend further support to the diagnosis of a primary adrenal carcinoma, perhaps metastasizing widely, though in fact very high urinary steroid excretion can occur in benign tumours and even cortical hypertrophy, and suppression by prednisone can be reliably diagnosed only if urinary cortisol is estimated (Cope and Black, 1959).

Case 2

This case is of interest because of the presenting symptom of asymmetrical muscular weakness. This had been present for a month before admission—as long as the total length of the history—and predominantly involved the righ arm, and to a less extent the right leg, without sensory loss. Later the left arm was affected, though never to such an extent as the right. Examination of radiographs of the cervical spine revealed no evidence of metastatic spread from the bronchial carcinoma. Subsequently at necropsy, though the brachial plexus and spinal cord were carefully dissected out, no metastases were discovered involving either. No cerebral secondary growths were seen. In view of the presence of a bronchial carcinoma a peripheral neuropathy of the purely motor type was naturally suspected (Brain and Henson, 1958). It is unusual, however, for it to be so asymmetrical, and the cerebrospinal-fluid protein in these cases is frequently raised, though it was not in this case. The serum potassium in this case was not so low as in Case 1. The calcium excretion is sometimes raised in Cushing's syndrome (Albright, 1938), but we found no evidence of this in this case.

Discussion

As Allott and Skelton (1960) report in their review of the literature, 36 cases have been previously reported in which a non-endocrine malignant tumour (by which they mean a tumour arising in organs other than the pituitary, adrenal, or ovary) has been associated with hyperactivity of the adrenal cortex. They add two further cases, and Bagshawe (1960a) a third. To these may be added the case of Parrish (1960), where this overactivity was associated with a primary neuroblastoma arising from the sympathetic chain at the thoracic inlet, and the case of Farrant and Insley (1960),



Case 2. Adrenal gland showing carcinomatous metastases and small cortical adenoma.

where the malignant tumour was an islet-cell carcinoma of the pancreas. We add a further two cases, making 43 in all. Of these, 19 (44.2%) are in females and 22 (53.5%) in males, and in one the sex is unknown. This is a high incidence of female involvement, as Allott and Skelton point out, especially as five of seven cases of carcinoma of the pancreas were in women, and of 21 cases of carcinoma of the bronchus (including our two) eight were in women. The previously reported cases tended to occur at a younger age than is usual for that type of carcinoma, and our two patients were rather young.

In cases previously reported the rapidity of onset of symptoms of adrenal overactivity has been a characteristic feature, and the two cases we describe are no exception. Obesity, gain in weight, hypertension, thirst, polyuria, and hirsuties have been previously reported (Allott and Skelton, 1960) as notable features. Our two cases show most of these, though neither was very hypertensive. Others have been reported as showing marked muscular weakness (Bagshawe, 1960b), relieved by increased potassium intake, but none so far as having the marked, asymmetrical neuromyopathy shown by our Case 2.

Great emphasis has been placed on the hypokalaemia and metabolic alkalosis seen in these cases (Bagshawe, 1960a). Both our cases showed a low or low-normal potassium (2.3 mEq/l. in Case 1 and 3.6 mEq/l. in Case 2), but no significant alkalosis. Another feature of Case 2 is that a cortical adenoma was found in one adrenal gland, and a metastasis from the primary neoplasm of the bronchus was present in the adenoma

as well as in the adrenal cortex. Crooke's change was present in the basophil cells of the anterior pituitary of the first case, but not in Case 2. Certainly there was time in Case 1 for the full picture of Cushing's syndrome to develop, and it is interesting that this hyalinization of the basophil cells was so marked. In Case 2 it would appear that there was not time for this to develop. As Allott and Skelton (1960) point out, this finding has been an inconstant feature of previously reported cases; it probably takes some time to develop, and is therefore absent from those cases in which the disease is rapid in onset and progression.

At least four theories may be advanced to account for this observed association of carcinoma with adrenal overactivity. (1) It may be due entirely to chance. Against this is the observation that these cases fall into a distinct pattern, with variations from the usually observed incidence in females of the carcinomata concerned, together with an unusual age distribution. (2) The carcinoma is stimulated by adrenal overactivity. There is little evidence that this should be so. Though the experimental evidence of Pomeroy (1954) in mice supports this theory, neither Kaliss *et al.* (1954) nor Fisher and Fisher (1959) were able to find experimental support for this in rats. (3) There may be stimulation by the cancer of the adrenal glands or adrenal cortical adenomata to hyperactivity. It is tempting to suggest that this may have happened in Case 2, where metastatic carcinomatous growth occurred in an adrenal cortical adenoma. Such adenomata are not uncommonly seen at necropsy in patients not suspected clinically of having Cushing's syndrome, and are presumably often, therefore, non-active. (4) Representatives of any or all of the above explanations may be found in any series of patients showing this association. Though increased aldosterone production has been postulated as a possible explanation of the findings of this association (Spaulding *et al.*, 1955), only one case has so far been reported where this has been found to be so (Webster *et al.*, 1959). Conceivably Case 1 could be explained on this basis on the somewhat tenuous evidence of the low Na/K ratio, but this is doubtful, to say the least of it.

We are no nearer to explaining the mystery of why hypokalaemic Cushing's syndrome should occur in association with malignant disease involving such widely separated organs as the thymus (Duguid and Kennedy, 1930), colon (Warren, 1945), bronchus (Brown, 1928), and prostate (Webster *et al.*, 1959). We feel, however, that it is important to go on reporting these cases as they occur, since by comparing their similarities and differences a common factor may emerge to explain this syndrome.

Summary

Two cases in which carcinoma of the bronchus was associated with Cushing's syndrome are reported. They are compared with similar cases in the literature where this association between malignant disease and adrenal overactivity has been observed. These two cases are of interest because one presented with a florid psychosis and purpura, which proved to be due to bone-marrow metastases, and the other with an asymmetrical neuromyopathy. Various theories are advanced in an endeavour to explain this association.

We thank Dr. M. G. Ashby and Dr. E. Idris Jones for permission to publish information about their patients; also Dr. A. G. Stansfeld, of St. Bartholomew's Hospital, for the histological report and photographs of Case 2, and Dr. Jones-Williams, of Mount Vernon Hospital, for the α- and β-fraction estimations on Case I. Thanks are also due to Dr. J. D. O'D. Lavertine for the post-mortem report on Case 1, and Mr. Macdonald for the photographs of this case, taken at Harefield Hospital.

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ACUTE CARBON TETRACHLORIDE POISONING

TRANSAMINASE AND BIOPSY STUDIES

BY

J. K. DAWBORN, M.B., B.S., M.R.A.C.P.
Drug Houses of Australia Research Fellow

MARY RALSTON, M.B., B.S., D.C.P., M.C.P.A.
Pathologist to the Clinical Research Unit

AND

S. WEIDEN, M.Sc., Ph.D.
Biochemist to the Clinical Research Unit

From the Walter and Eliza Hall Institute of Medical Research and the Royal Melbourne Hospital

[WITH SPECIAL PLATE]

Many features of acute carbon tetrachloride poisoning are well established (Cameron and Karunaratne, 1936; Council on Industrial Health, 1946; Hardin, 1954). However, the following case of carbon tetrachloride poisoning provided a unique opportunity for studying the course of hepatic damage by means of serial estimations of the serum glutamic oxalacetic transaminase (S.G.O.T.) level (method of Reitman and Frankel, 1957) and serial liver biopsies.

Case Report

A storeman aged 22 years accidentally swallowed a mouthful of carbon tetrachloride. Immediately his head began to throb, he felt faint, and two hours later he vomited and passed dark urine. The following day he suffered increasing anorexia and abdominal pain. On the third day he was admitted to hospital, and clinical examination disclosed pronounced tenderness and rigidity in the epigastrium. The urine contained granular casts, and there was moderate proteinuria but no bilirubinuria. The initial biochemical analyses were as follows: serum bilirubin 1.4 mg. per 100 ml.; serum albumin 2.7 g. and globulin 2.3 g.

J. R. BILLINGHURST *ET AL.*: CARCINOMA AND CUSHING'S SYNDROME

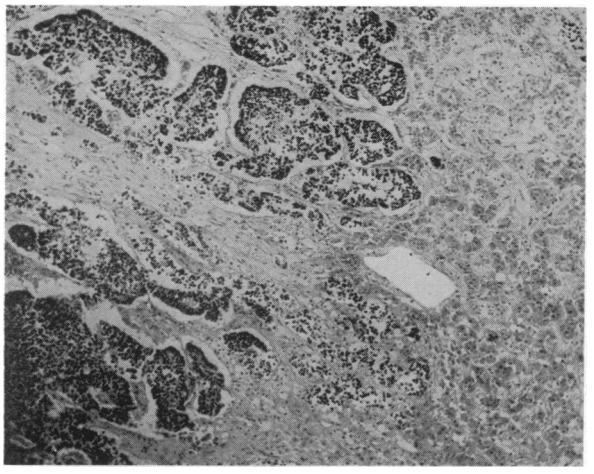

FIG. 1.—Case 2. Secondary carcinoma in adrenal gland. (H. and E. ×45.)

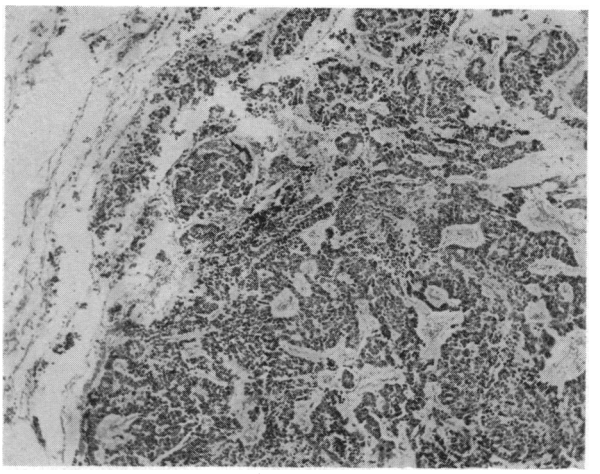

FIG. 2.—Primary bronchial carcinoma. (H. and E. ×45.)

J. K. DAWBORN *ET AL.*: ACUTE CARBON TETRACHLORIDE POISONING

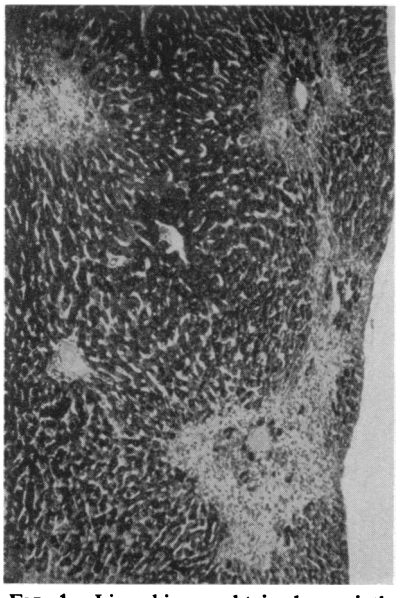

FIG. 1.—Liver biopsy obtained on ninth day after swallowing carbon tetrachloride. There is pronounced centrilobular zonal necrosis. (Periodic acid-Schiff. ×80.)

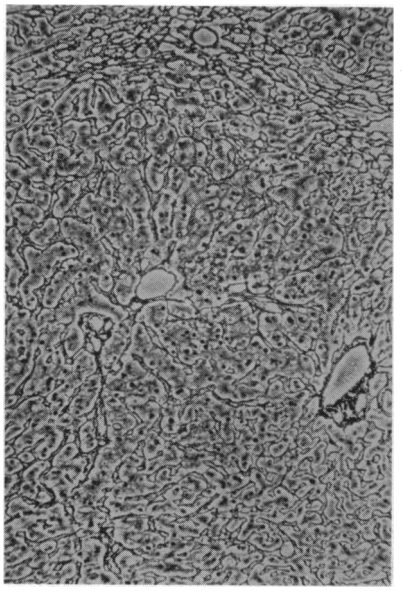

FIG. 2.—Section of liver biopsy obtained on ninth day, showing preservation of reticulin framework despite cellular necrosis. (Silver impregnation stain. ×80.)

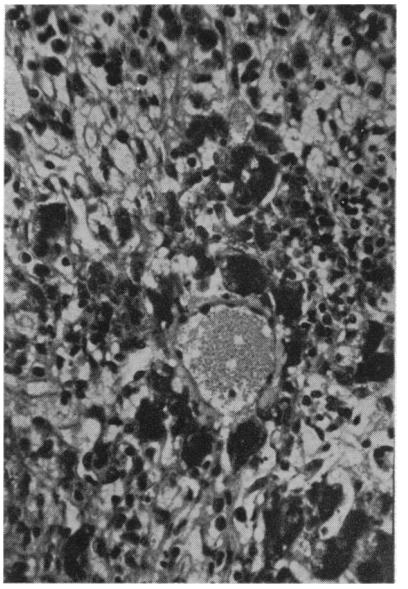

FIG. 3.—Section of liver biopsy obtained on 28th day. There are large regenerating liver cells with hyperchromatic nuclei and considerable inflammatory-cell infiltrate. Final biopsy on 70th day showed restoration of normal liver histology. (H. and E. ×400.)

C. N. BEST AND P. B. COOK: MESENTERIC RETICULOSARCOMA AND STEATORRHOEA

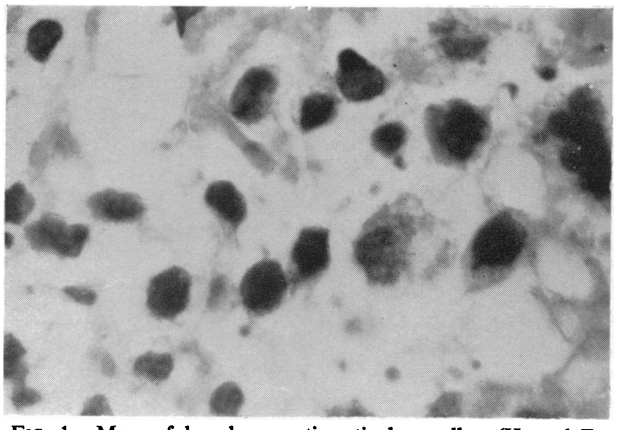

FIG. 1.—Mass of largely necrotic reticulum cells. (H. and E. ×700.)

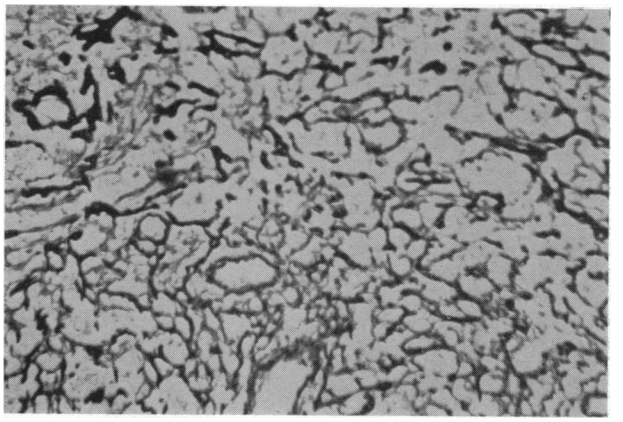

FIG. 2.—Reticulin preparation, showing dense network. (×130.)