THE SYNDROME OF FEVER, ANAEMIA, AND HIGH SEDIMENTATION RATE WITH AN ATRIAL MYXOMA

BY

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[WITH SPECIAL PLATE]

Within the last five years 15 cases have been reported in which a myxoma of the left atrium was diagnosed during life. In one instance the diagnosis was suggested by the clinical findings alone (Kirkeby and Leren, 1952), and in the others it was ultimately made either by angiocardiography (Steinberg *et al.*, 1953; Crafoord, 1954; van Buchem and Eerland, 1957) or during cardiotomy for suspected mitral stenosis. In 12 cases an attempt was made to excise the tumour, but the operation was successful in only four of them (Crafoord, 1954; Scannell *et al.*, 1956; Bigelow *et al.*, 1956; Chin and Ross, 1957). The myxoma was found unexpectedly during exploration of the mitral valve in at least two of the successful cases, and a second operation with a different anatomical approach was then necessary. Pre-operative diagnosis of these tumours is therefore desirable, but their extreme rarity and their tendency to imitate mitral-valve lesions makes this difficult. On this account we report the case below, which, although extensively investigated, was not diagnosed during life.

Differentiating features have been described, but they do not usually appear until the tumour has grown dangerously large. Alterations in symptoms and signs with changes in posture, recurrent syncope simulating Stokes–Adams attacks, systemic embolism without bacteriaemia, variability of the heart murmurs, and progressive failure with rapid cardiac enlargement are recognized as characteristic of this condition (Yater, 1931). Several of these features apeared in the case reported here, together with other abnormalities which have received less attention.

Case Report

A man aged 56 was admitted to Hammersmith Hospital in April, 1953, complaining of increasing tiredness and breathlessness. He had no other symptoms and had never before been ill. He appeared healthy, but was pale and febrile with a temperature of 99.8° F. (37.7° C.). He had a nasal voice due to a highly arched palate, a funnel deformity of the sternum, a small haemangioma on the right shoulder, and an indirect inguinal hernia. His pulse was regular at 80 per minute. His blood pressure was 130/75 mm. Hg. The jugular venous pressure was not raised and there was no oedema. The apex beat was not displaced, the heart sounds were normal, and no murmurs were heard. Haemoglobin, 10.8 g. per 100 ml.; red blood cells: M.C.V. 81 $c\mu$, M.C.H.C. 32%; white blood cells, 9,000 per c.mm.; E.S.R., 110 mm. in one hour (Westergren); serum albumin 2.7 g., serum globulin 5.3 g., per 100 ml.; blood urea, 18 mg. per 100 ml. Sternal marrow normal, except that 8% of the nucleated cells were mature plasmocytes. Sputum culture: no tubercle bacilli. Chest radiographs: slight cardiac enlargement, probably including the left atrium; calcified lesions at apex of right lung. Radiographs of bones normal. Urine: no albumin or proteose.

The patient was discharged two weeks later, and his symptoms disappeared soon afterwards. His haemoglobin rose spontaneonsly to 14.6 g. per 100 ml., and, although the E.S.R. and serum globulin level remained raised, he was well until April, 1954. He then developed a headache and became blind in the right eye for five minutes. His haemoglobin was 9.8 g. per 100 ml. Chest radiography showed further enlargement of the heart with prominence of the left atrium (Special Plate, Fig. 1) and main pulmonary arteries, but an electrocardiogram was normal. Three months later he noticed transient weakness of the left arm. No neurological signs were found, but an apical systolic murmur was heard for the first time. He had breathlessness and palpitations during the next few months, and was readmitted in December, 1954.

He was dyspnoeic at rest and had a short, dry cough. His temperature was 99.4° F. (37.4° C.); pulse rate, 106 per minute; blood pressure, 105/70 mm. Hg. The jugular venous pulse showed "a" and "v" waves filling to 5 cm. above the sternal angle. The apex beat was still not displaced, but a right ventricular lift was felt. The first heart sound in the mitral area was accentuated, and a loud pansystolic murmur was heard, maximal at the apex and conducted to the axilla. The second sound was narrowly split; the pulmonary component was loud, and a faint early diastolic murmur was audible in the third left intercostal space. There were crepitations at both lung bases, the liver was slightly enlarged, and ankle oedema was present. Haemoglobin, 9.3 g. per 100 ml.; E.S.R., 99 mm. in one hour; serum globulin, 6.0 g. per 100 ml.: blood culture repeatedly negative. Sternal marrow unchanged (10% of plasmocytes). Gum biopsy: no amyloid infiltration. Chest radiograph: small left pleural effusion; considerable enlargement of right ventricle and of both atria. Electrocardiogram: moderately large bifid P waves in lead II, and no evidence of right ventricular preponderance.

The cardiac failure responded to treatment, but the persistent fever was unaffected by penicillin and streptomycin. A blood transfusion was given, and the patient was discharged after nine weeks in hospital. A week later he had anginal pain at rest for two days, and in April, 1955, he again noticed weakness of his left arm for ten minutes, subsequently he developed a "frozen" left shoulder. Sudden attacks of giddiness which sometimes caused him to fall, without loss of consciousness, also occurred. He remained breathless and weak, but the oedema did not recur. In February, 1956, he fainted while hurrying, and in the following May a right pleural effusion developed for which he was admitted to hospital.

Temperature 99° F. (37.2° C.); haemoglobin, 11 g. per 100 ml.; E.S.R., 95 mm. in one hour; serum globulin, 5.5 g. per 100 ml. (electrophoretic pattern non-specific; less than 5% of "macroglobulin"). The jugular venous pressure was not raised and the heart signs were unchanged. A faint mitral diastolic murmur was suspected on one occasion, but phonocardiography revealed only the third heart sound. The electrocardiogram was unaltered and a Congo-red test was negative. Cardiac catheterization: P.C.P. 15/3, P.A.P. 55/12, R.V.P. 55/0, R.A.P. +3/−3 mm. Hg. Dye curves showed a cardiac output of 6.7 litres per minute, with evidence of slight backflow on the left side of the heart. The pleural effusion was aspirated, and the patient was discharged a month later.

He remained free from oedema without diuretics until December, 1956, when he was readmitted in congestive failure. He was still febrile and anaemic, and the serum globulin was 5.1 g. per 100 ml. A chest radiograph showed further enlargement of the left atrium and pulmonary arteries, and horizontal septal lines at both lung bases. The heart murmurs were no different, and after two weeks'

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treatment the venous pressure returned to normal. The patient's condition did not improve, however, and on February 8, 1957, he suddenly became shocked and semi-comatose, with intense venous congestion, a blood pressure of 90/60 mm. Hg, and 2:1 heart-block confirmed by an electrocardiogram. He died 12 hours later.

Post-mortem Examination

At necropsy the relevant findings were a right pleural effusion, a recent infarct of the spleen, and a large tumour within the left atrium. Both lungs were oedematous, and there was a small area of fibrosis in the right upper lobe. The left lung was studied by arterial injection, and both lungs were examined histologically. The main and segmental pulmonary arteries, and the primary divisions of the latter, were moderately dilated. The smaller arteries were of normal size. Microscopically, there were moderate medial hypertrophy and mild fibroelastic intimal thickening, but these changes were less severe than in fatal cases of mitral stenosis. There were no significant lesions in the veins and no evidence of any vascular obstruction. A microscopic focus of chronic tuberculosis was present in the fibrotic lesion at the apex of the right lung.

The unopened heart weighed 783 g. The left ventricle and aortic and pulmonary valves appeared normal, but the right ventricle and right and left atria were hypertrophied and dilated. The tricuspid valve ring was 170 mm. in circumference. The tumour measured $105 \times 90 \times 50$ mm., and almost completely filled the cavity of the left atrium (Special Plate, Fig. 2). It was attached by a short pedicle 25 mm. in diameter to the wall of the atrium between the right upper pulmonary vein and the interatrial septum, and its apex lay within the mitral valve cusps. The mitral valve ring was dilated, but the cusps appeared to close efficiently around the tumour, producing a groove upon it. The surface of the tumour was smooth except at the apex, where it was polypoid. On section it was grey and translucent, with dark haemorrhagic areas most numerous near the base and large areas of yellow necrosis beneath the mitral groove. There was no thrombosis on the external surface, and no evidence of endocarditis or of a myocardial lesion.

Sections from six areas of the tumour were stained for reticulin, collagen, and elastic fibres; and with haemalum and eosin, toluidine blue, alcian blue, Southgate's mucicarmine, and the periodic acid–Schiff technique.

Histological Findings

The tumour was covered by endothelium. In the myocardium near its attachment there were numerous thick-walled arteries and veins. The pedicle consisted of irregular bundles of elastic fibres and collagen with the peripheral fibres continuous with those of the superficial endocardium. It was traversed by large distorted vessels, some having a well-developed muscle layer. The body of the tumour showed a constant pattern of malformed blood vessels linked by a network of anastomosing cords of vasoformative cells with abundant intervening amorphous matrix. The vessels diminished in size progressively from base to apex, and all transitions from formed vessels to cords of cells were evident. A minority of the larger vessels showed an incomplete malorientated smooth-muscle layer. The cells of the cords and those forming the walls of the intermediate- and smaller-sized vessels were spindle-shaped with plump vesicular nuclei, and were indistinguishable from the endothelial cells of the larger vessels. Occasional similar discrete cells, more variable in outline, were scattered throughout the matrix. In the apical polypi, where the matrix was relatively more abundant, there were scattered stellate cells giving an appearance resembling a true myxoma. Coarse reticulin and fine elastic fibres coursed in the amorphous matrix. The latter was eosinophilic, giving a reaction which was positive with alcian blue, negative with Southgate's mucicarmine, and faintly positive with the P.A.S. technique. Surrounding some of the vessels there were small pools of basophilic mucin which stained metachromatically with toluidine blue. The necrotic areas contained numerous acicular clefts, and at their periphery there was a narrow zone of macrophages with occasional giant cells. Throughout the tumour there were small collections of plasma cells, lymphocytes, and mast cells, with numerous siderophages and lipophages in the regions of old haemorrhage (Special Plate, Figs. 3 and 4). Sections along the apex of the splenic infarct failed to show tumour embolus.

Comment

The patient developed a loud apical systolic murmur and cardiac enlargement, and he died from an unrecognized myxoma of the left atrium. The deep left auricular impression in the oesophagram provided a clue to the lesion, but its significance was not realized at the time. Tumour embolism possibly accounted for the transient neurological symptoms, and the exertional syncope was probably due to obstructed filling of the left ventricle. Throughout the four years of his illness the patient also had a low-grade fever, variable anaemia, a high E.S.R., and a serum globulin of 5–6 g. per 100 ml. The latter findings were wrongly considered to indicate that he was suffering from a generalized systemic disease.

Discussion

In a brief review of 30 published cases of atrial myxoma Von Reis (1949) pointed out that the E.S.R. was considerably raised in every one of the eight cases in which it was recorded. It was nearly 100 mm. per hour in five instances, and the author's own case had fever and anaemia as well as an E.S.R. of 82 mm. per hour. Fever, anaemia, and a high E.S.R. have been found incidentally in many subsequent cases (Allison and Susman, 1949; Kirkeby and Leren, 1952; Clowes *et al.*, 1954; Gleason, 1955; van Stekelenburg and Jordans, 1956; Lekisch, 1957), but only Kirkeby and Leren commented that their occurrence was not unusual in this condition. No mention is made of such findings in recent reviews of the subject (McAllen, 1950; Prichard, 1951: Martin, 1953; Protheroe, 1957). Although these signs are not invariably present, they appear to occur often enough to be of great diagnostic importance. Had their significance been appreciated in the present case, for example, they might eventually have led to the correct diagnosis. They were evident before the tumour had seriously embarrassed the circulation, and they preceded the other signs by many months. Hyperglobulinaemia, as found in our case, has not apparently been observed before, but it may well have existed in other patients with equally high E.S.R.s.

Why this systemic reaction should occur is uncertain, but Lekisch (1957) suggested that in his patient it was possibly due to degenerative changes in the tumour itself. This explanation is attractive, since haemorrhage and necrosis are very commonly found in myxomata, and similar degenerative changes in uterine myomata are known to cause a febrile reaction. Moreover, the response to breakdown products released from a myxoma might be expected to be both brisk and sustained, owing to the intravascular situation of the tumour. Its exact position within the heart seems immaterial, since fever and anaemia have also been observed when the tumour was in the right atrium (Kendall and Symonds, 1952).

The gross features of the tumour reported here conformed with the accepted characteristics of a

cardiac myxoma, but microscopically the formed elements were clearly angiomatous. Raeburn (1952) has described examples ranging from a classical myxoma to an unequivocal haemangioma. The palatal and other developmental defects in our case were apparently coincidental, since we have found only one other report of a myxoma associated with a congenital abnormality, an atrial septal defect (Paquet, 1946). The rate of growth of these tumours, however, is possibly quite slow, judging from the length of history sometimes recorded. The recent report of a small myxoma found in the atrium of a stillborn infant (Reddy *et al.*, 1956) is therefore of interest.

We wish to thank Dr. C. L. Cope for permission to publish this case; Dr. J. Shillingford for the catheterization and dye studies; and Professor J. McMichael, Professor C. V. Harrison, and Dr. J. F. Goodwin for their interest and advice. We are also especially grateful to Dr. William Evans for much helpful criticism.

REFERENCES

Allison, D. R., and Susman, W. (1949). *Lancet*, **2**, 11.
Bigelow, W. G., Dolan, F. G., and Campbell, F. W. Quoted by Scannell *et al* (1956).
Chin, E. F., and Ross, D. N. (1957). *Brit. med. J.*, **1**, 1447.
Clowes, G. H. A., Neville, W. E., Hopkins, A., Anzola, J., and Simeone, F. A. (1954). *Surgery*, **36**, 557.
Crafoord, C. (1954). Quoted by Goldberg, H. P., and Steinberg, I. (1955). *Circulation*, **11**, 963.
Gleason, I. O. (1955). *Cancer*, **8**, 839.
Kendall, D., and Symonds, B. (1952). *Brit. Heart J.*, **14**, 139.
Kirkeby, K., and Leren, P. (1952). *Acta med. scand.*, **143**, 385.
Lekisch, K. (1957). *Ann. intern. Med.*, **46**, 982.
McAllen, P. M. (1950). *Brit. med. J.*, **1**, 932.
Martin, B. F. (1953). *Ann. intern. Med.*, **38**, 325.
Paquet, E. (1956). *Canad. med. Ass. J.*, **74**, 121.
Prichard, R. W. (1951). *A.M.A. Arch. Path.*, **51**, 98.
Protheroe, R. H. B. (1957). *Postgrad. med. J.*, **33**, 402.
Raeburn, C. (1952). *J. clin. Path.*, **5**, 339.
Reddy, D. J., Rao, T. S., Venkaiah, K. R., Gopalakrishnaiah Gupta, H., Sakuntala Devi, P., and Naidu, N. V. (1956). *Indian J. Pediat.*, **23**, 210.
Von Reis, G. (1949). *Acta med. scand.*, **133**, 214.
Scannell, J. G., Brewster, W. R., and Bland, E. F. (1956). *New Engl. J. Med.*, **254**, 601.
Steinberg, I., Dotter, C. T., and Glenn, F. (1953). *Dis. Chest*, **24**, 509.
Van Buchem, F. S. P., and Eerland, L. D. (1957). Ibid., **31**, 61.
Van Stekelenburg, F. M., and Jordans, G. H. W. (1956). *Ned. T. Geneesk.*, **100**, 1709.
Yater, W. M. (1931). *Arch. intern. Med.*, **48**, 627.

According to the National Food Survey Committee the average weekly amount of money spent on food in this country in 1957 was 28s. 1d. a head, as against 27s. 3d. in 1956. The rise of 10d., or 3%, was the smallest annual increase recorded by the Committee since 1950, a slowing down to be expected once the demand for food had been largely satisfied after many years of restriction. The Committee estimates that 2.4% of the 3% was due to higher prices and 0.6% to an improvement in the standard of purchases as measured by consumer preference. Since 1955 there has been a slight shift in demand from staple foods to what the survey calls "convenience" foods, which can be prepared quickly and easily. Nevertheless British spending habits in relation to the main groups of food have remained fairly stable: in the autumn and winter quarters from October, 1957, to March, 1958, 18% of the total domestic expenditure on food was devoted to milk, cheese, and eggs, 32% to meat and fish, 16% to fruit and vegetables, 26% to cereals, fats, sugar, and preserves, and 8% to all other foods. This compared with 18, 30, 14, 27, and 11% respectively for the corresponding period in 1936–7. All income groups spent more per head on food than in 1956, with the exception of the under £7-a-week group (without other earners in the family). (*Domestic Food Consumption and Expenditure: 1957. Annual Report of National Food Survey Committee.* H.M.S.O., price 8s. 6d.)

DISSEMINATED HERPES SIMPLEX IN THE NEWBORN

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[WITH SPECIAL PLATE]

Herpes simplex virus commonly causes asymptomatic or mild infections, but may produce in some cases a clinical pattern of great variability and severity (Brain, 1956). This is especially so in children suffering from eczema, who may develop a severe generalized infection called Kaposi's varicelliform eruption or eczema herpeticum (Jackson and Dudgeon, 1951). At first this was thought to be only an involvement of the skin, but widespread concomitant visceral lesions have since been described (Pugh *et al.*, 1955; Brain *et al.*, 1957). Another severe form of disseminated visceral herpes occurs in the absence of eczema; this was first reported from the United States (Quilligan and Wilson, 1951; Zuelzer and Stulberg, 1952), and thereafter in England (France and Wilmers, 1953; Pugh *et al.*, 1954) and Australia (Colebatch, 1955; Williams and Jack, 1955).

The post-mortem and histological appearances, as given in these papers, are fairly characteristic, but establishment of the diagnosis depends on the isolation of the virus itself. This has been accomplished in only a few cases; for this reason, and because of certain unusual features, a further case is reported.

Case Report

The patient a male first infant, a full-term normal delivery, was said by the mother to have been "delicate" since birth and a poor feeder who never cried or moved about much. The abdomen was noticed to be rather full during the third week, and on the day of admission to hospital, at 21 days, he became suddenly pale and collapsed, with rolling eyes and continuous moaning, but no convulsions. He was admitted a few hours later, when he was observed to be pale and thin, with involuntary writhing movements of the limbs. There were a large left parieto-occipital cephalhaematoma and a small blister on the back. The abdomen was distended with fluid. The liver was palpable 3 in. (7.6 cm.) below the costal margin, with a firm sharp edge, but there was no jaundice. The spleen was palpable 1 in. (2.5 cm.) below the left costal margin. No abnormality was found in the chest, but breathing appeared to be embarrassed by the large liver. The infant died less than three hours after admission. The clinical diagnosis was cirrhosis, probably due to reticulo-endotheliosis or a storage disease.

Post-mortem Examination (Nine Hours After Death)

The body was that of a poorly nourished male infant, measuring 21 in. (53.3 cm.) from crown to heel but weighing only 7 lb. (3.175 kg.), and showed considerable distension of the abdomen. The umbilicus was healed, and the skin was healthy apart from one small collapsed blister just below the right scapula. There was no jaundice or oedema. There was a large left parieto-occipital cephalhaematoma

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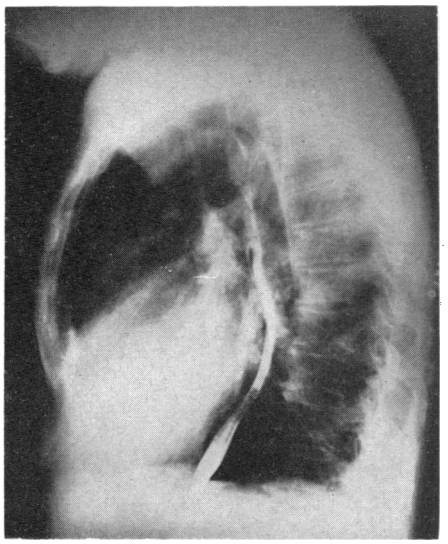

FIG. 1.—Lateral radiograph of chest, showing enlargement of left atrium.

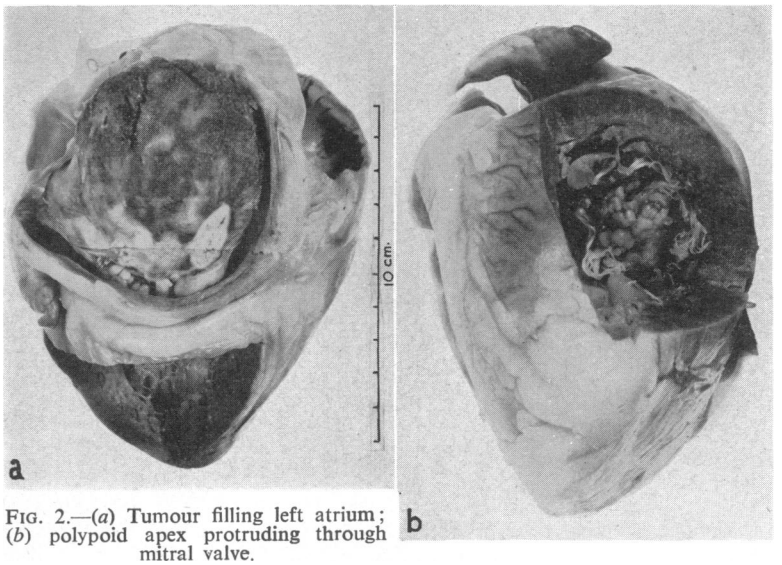

FIG. 2.—(*a*) Tumour filling left atrium; (*b*) polypoid apex protruding through mitral valve.

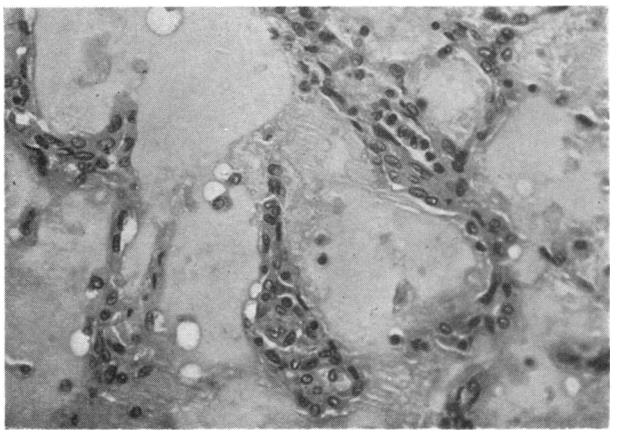

FIG. 3.—Histology of tumour, showing small vessels and cords of spindle cells. (×272.)

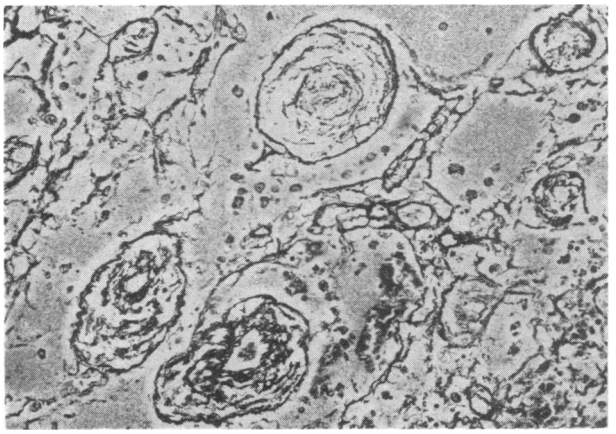

FIG. 4.—Reticular framework of vessels in tumour. (×120.)

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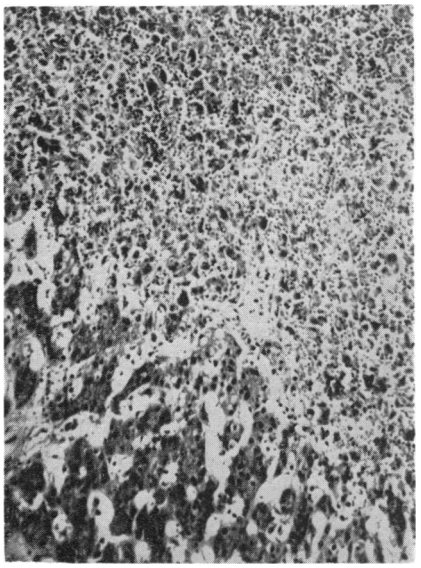

FIG. 1.—Liver, showing the clear demarcation between necrotic and living cells. (Haematoxylin and eosin. ×90.)

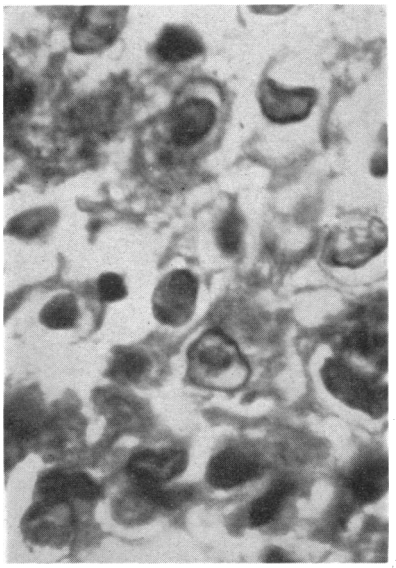

FIG. 2.—The margin of a necrotic area in the liver showing several intranuclear inclusions. (Haematoxylin and eosin. ×500.)

FIG. 3.—One of the necrotic areas in the adrenal cortex containing basophilic material. (Haematoxylin and eosin. ×90.)