PLASMA CELL TUMOURS

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This review is based on fifteen cases of plasma cell tumours which have been seen in recent years at the Westminster Hospital. In studying the widely different clinical features an attempt has been made to demonstrate various manifestations of this disease-process. The term multiple myelomatosis is used in this paper when a number of bones are involved. Single tumours are described as solitary plasmocytoma, either of bone marrow or of soft tissue according to their origin. An attempt will be made to correlate these newly reported cases with others already reported in the literature and in so doing to make a comprehensive classification of the disease.

HISTORY

William McIntyre (1850) reported the first case of this condition under the name of mollities ossium. A microscopical report was given by Dalrymple, and Bence-Jones showed the presence of an unusual protein substance in the urine. Rustizky (1873) writing twenty-seven years later, has been credited with the first histological definition and seems to have been the first to recognise the disease as a specific affection of the bone marrow. Kahler (1889) is cited as the first to describe the clinical condition. Only the name of Bence-Jones remains from the original trio as being responsible for the discovery of a protein substance found in the urine in many cases.

Since that time numerous case reports have appeared in the literature, and good early reviews were made by Martiri (1915), Wallgren (1920), and Geschickter and Copeland (1928). The disease was usually known as multiple myelomatosis, and at the time of Geschickter and Copeland's paper only five cases of disease in a solitary bone focus were to be found in the literature. Multiplicity of tumours was regarded as a cardinal symptom, and 90 per cent. were shown to have involvement of ribs, sternum, clavicle, and lumbar spine.

More recently it has been shown (Cutler *et al.* 1936, Willis 1941) that the condition often arises in a single focus which may reach considerable size before spreading to other bones. More cases have also been described where solitary tumours of bone remain without any other organ being involved.

A tumour, at first sight somewhat different from those described above, arising in the soft tissues of the nasopharynx but with a histological appearance similar to the bone tumour, is now recognised as belonging to the same disease group. Many of these cases have now been described, some remaining confined to soft tissues, and a smaller group associated with bone marrow tumours. Extramedullary soft tissue tumours have also been described outside the nasopharynx, and Hellwig (1943) who reviewed all extramedullary tumours reported since 1905 was able to find thirteen examples, the sites being the pleura, mediastinum, spermatic cord, thyroid, ovary, intestines, kidney, and skin. Gordon and Walker (1944) reported a case occurring in the lung, and Ulrich (1939) reported one arising in the testis.

Microscopically all these tumours, whether intra-medullary or extramedullary in position, are most commonly composed of plasma cells, the majority of which are mature, but with a certain number of intermingled immature forms. The histological details and cell types will be discussed later but mention of this point is made here in order to introduce the final and most rare variety of the disease in which plasma cells appear constantly in the peripheral blood, with or without associated bone tumours, but always with diffuse bone marrow infiltration of cells of the plasma cell type.

Subgroups of the disease—It is seen, therefore, that various subgroups of the disease can be enumerated, and an attempt will be made to present our cases in such a manner as to demonstrate these groups:

1. *Bone Marrow Tumours*—
   - (*a*) Multiple at onset.
   - (*b*) Solitary at onset, with subsequent multiple spread.
   - (*c*) Solitary bone marrow tumours.
2. *Extramedullary Tumours*—
   - (*a*) Confined to the nasopharynx.
   - (*b*) Primary in nasopharynx but associated with lymph node involvement.
   - (*c*) Primary in nasopharynx but associated with bone marrow involvement.
   - (*d*) Very rare examples occurring in other tissues, *i.e.*, pleura, testes, skin, etc.
   - (*e*) Confined to the conjunctiva.

     (A somewhat doubtful group probably of granulomatous origin; for examples see Hellwig 1943).
3. *Generalised Spread* (from 1 or 2 above)—
   - (*a*) Spread to viscera, liver, spleen, etc.
   - (*b*) Plasma cell leukaemia.

Case Histories

Case 1. J. B., male, aged 60 years. Under care of Dr S. P. Meadows. Admitted to hospital December 13, 1945, complaining of pain in chest, and back between shoulder blades, three months' duration. Two months before admission noticed tearing pain in chest associated with cracking sound " as if a rib had broken." This occurred twice. For one week before coming into hospital aware of hard, painless lump on left side of head. During this week suffered several severe epistaxes. *On examination*—Thin and pale. Signs of congestion of bases of lungs. Abdominal mass felt in right epigastrium. Hard nodule felt over left temporal region and another just below left nipple, both apparently attached to bone. Patient's general condition very poor. Went steadily downhill and died December 26, 1945. *Investigations*—Radiographic examination showed clear oval areas in fourth and eighth right ribs, and in third, sixth, seventh, and eighth left ribs. Body of eighth thoracic vertebra collapsed. Bence-Jones protein found in the urine on several occasions. *Post-mortem examination: Skeleton*—One tumour found in calvarium lying over the vertex, half-inch in diameter; another seen in left temporal bone; they were soft and purple on the cut surface. Similar bony tumours, some more frankly haemorrhagic, found in second, third, fourth, fifth, sixth, and seventh right ribs. Masses all lay near the angles; pathological fractures had occurred through each deposit. The fifth and eighth left ribs showed similar appearances. All vertebrae contained small haemorrhagic tumours. Body of eighth thoracic vertebra collapsed and over its anterior aspect was a white fleshy tumour. Sternum was fractured through the body and on section contained many similar deposits. *Post-mortem examination: Viscera*—All organs normal with the exception of: *Trachea*—Reddened; large laminated blood clot at the carina blocking both main bronchic lot showed organisation. *Lungs*—Both lungs grossly oedematous; bronchi contained fluid blood. *Liver*—Weight sixty-eight ounces; not obviously enlarged but many small white deposits both sub-capsular and in depths of the organ. *Spleen*—Weight seven ounces; appeared normal to naked eye with exception of patchy capsular thickening. *Cause of death*—Oedema of lungs following large epistaxis. *Microscopic appearances—Ribs*—Tumours composed of masses of cells, lying in scanty trabeculated stroma and completely replacing normal bone architecture; the majority closely resembled plasma cells; some binucleate and larger forms present. *Liver*—The masses seen naked eye were composed of cells similar to those in the bone tumours (Fig. 28); diffuse infiltration of plasma cells throughout the sinusoids. *Spleen*—Some congestion; groups of plasma cells seen lying in the sinuses (Fig. 30).

Case 2. W. M., male, aged 52 years. Under care of Mr E. P. Brockman. First seen complaining of pain in back, present six weeks. *On examination*—General condition poor. Radiographic examination revealed multiple clear-cut, punched-out areas in skull, ribs, vertebrae, femora, and ilii, scattered diffusely throughout the bones. *Investigations*—Bence-Jones proteinuria positive on numerous occasions. Patient deteriorated rapidly; died eight weeks after onset of symptoms. *Post-mortem examination*—Cause of death—Scattered broncho-pneumonia, Multiple small, soft, purple tumours found in bones enumerated above (Figs. 1-2). No other abnormalities found. *Microscopic examination* of tumours revealed masses of plasma cells in scanty but vascular stroma.

Case 3. C. T., male, aged 45 years. Under care of Sir Stanford Cade. First seen April 1932, complaining of intermittent pain and stiffness in the back progressing to severe pain and inability to bend forward. Symptoms present two years. *On examination*—Firm swelling found in the back just lateral to second and third lumbar vertebrae. No loss of sensation or power in lower limbs. Radiographic examination showed osteolytic process in second and third lumbar vertebrae but no other bone lesions. *Treatment and subsequent history*—Forty-eight radon seeds, each 1 millicurie, inserted into the tumour by Sir Stanford Cade; resulted in complete loss of pain and diminution in size of tumour. Symptoms recurred September 1932. Radiographs then showed osteolytic lesions of punched-out type in skull, fourth, fifth, sixth, seventh, ninth, and tenth right ribs, sixth and seventh left ribs, and right ilium (Figs. 3–4). *Investigations*—Blood counts normal. Repeated examinations for Bence-Jones protein always negative.

FIG. 1

Case 2. Longtiudinal section of femur and ilium showing multiple haemorrhagic deposits.

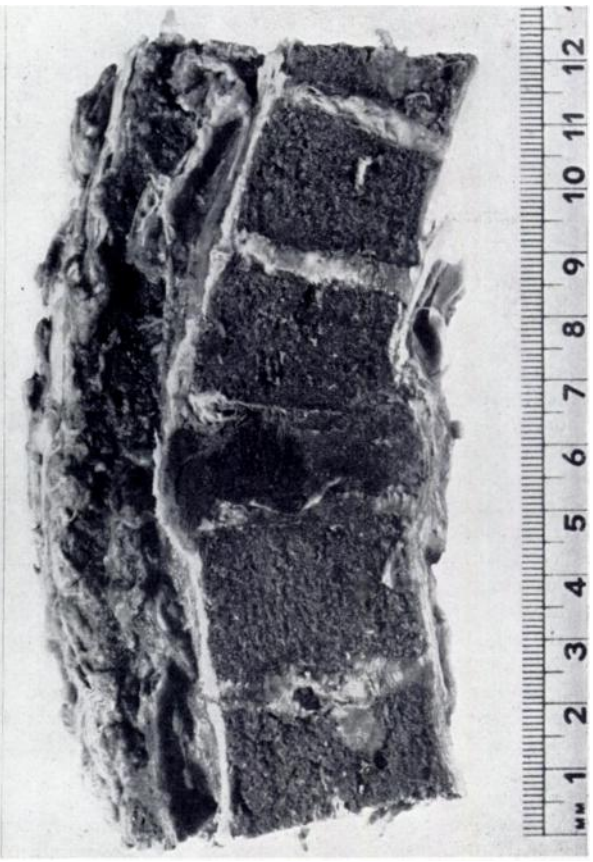

FIG. 2

Case 2. Longitudinal section of vertebrae showing haemorrhagic tumour and collapse of vertebral body with transgression of intervertebral disc.

Biopsy of tenth rib November 2, 1932, showed tumour composed entirely of cells morphologically similar to plasma cells, both mature and immature (Fig. 19). General health at this time reasonably good. Patient discharged. Remained well for some weeks when he began steady downhill course and died February 1933, three years after onset of symptoms. No autopsy performed.

Case 4. J. P., female, aged 55 years. Under care of Mr E. P. Brockman. Admitted February 19, 1947, complaining of pain in right arm. Gave history of having fallen on outstretched hand six months previously. Radiographs showed fracture of upper end of humerus passing through what was considered to be an osteoclastoma (Figs. 7–9). *On examination*—No abnormal signs other than wasting of muscles round right shoulder girdle, and a pulsating hard swelling fixed to bone over anterior aspect of upper end of humerus with a distended vein running over it. All shoulder joint movements restricted. Towards the end of February patient complained of pain in the low back. Followed a downhill course and died March 15, 1947, with left sided broncho-pneumonia and empyema. *Investigations*—Wassermann and Kahn tests negative. Blood counts normal. Repeated tests for Bence-Jones proteinuria negative. Radio-

graphs at the end of February showed change in the tumour of the humerus towards an osteolytic appearance of malignant type. In the spine, collapse of body of third lumbar vertebra noted. No other bone tumours found. *Post-mortem examination*—Left sided empyema confirmed and found to be extensive, penetrating the interlobar septum; underlying broncho-pneumonia. At the base of the brain was a collection of green pus, similar in appearance to that in the chest; spread had evidently occurred from the chest through site of twelth thoracic vertebra which was collapsed and replaced by soft red tumour, thus laying open the spinal canal. The third lumbar vertebra was also collapsed. Small red nodules seen in the majority of the vertebrae. No other tumours found except that in the humerus; upper half of bone replaced by pink-grey mass showing areas of haemorrhage, with pathological fracture at lower end of lesion. Cut surface of sternum showed marrow increase of purple appearance but no actual tumours. *Microscopic examination* — Tumours showed aggregations of cells, the majority with eccentric nuclei of typical plasma cell appearance; binucleate and large forms common.

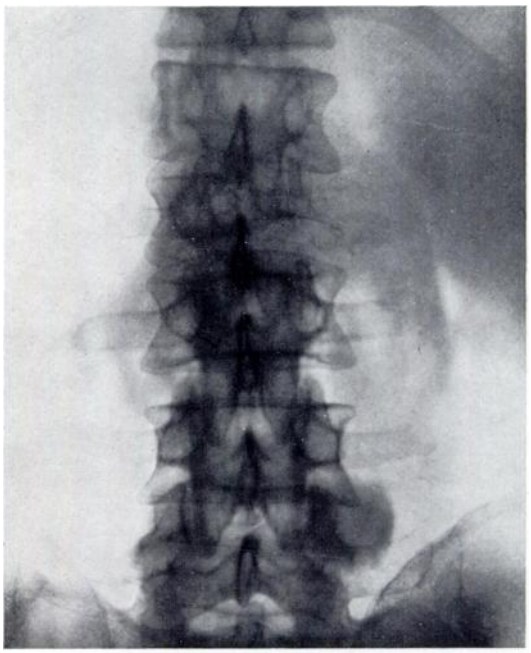

FIG. 3

Case 3. Vertebral column showing destruction and collapse of second lumbar vertebra.

Case 5. P. B., male, aged 41 years. Under care of Sir Stanford Cade. Complained of intermittent pain in right shoulder for three months, becoming so severe that he could not lift his arm. Sleep impossible. *On examination*—February 1946, large firm, slightly tender swelling under right deltoid muscle extending anteriorly across shoulder joint halfway along the clavicle and posteriorly across lateral border of the scapula. Tumour fixed to bone. Biopsy performed and diagnosis of plasmocytoma made (Fig. 22). *Investigations*—Numerous tests for Bence-Jones protein and albumen in the urine negative. Wassermann negative. Radiographs March 1946 showed multiple small round areas of decalcification in upper end of right humerus and acromion process (Fig. 5). Multiple small areas of cortical destruction also extended down inner side of humerus. Considerable soft tissue swelling of whole shoulder region. Skull and other bones showed no other abnormality. Further radiographs May 27, 1946, showed changes similar to those in the humerus in right ischium, right inferior pubic ramus, neck and greater trochanter left femur. One week later considerable thinning of anterior and posterior clinoid processes of the skull noticed. *Subsequent history*—General condition on admission very poor. Gave history of loss of weight up to the time of admission. Followed a downhill course while in hospital. Died June 22, 1946. A few days before death further tumour noticed in skull just above right orbit. No autopsy performed.

Case 6. V. B., female, aged 30 years. Under care of Sir Stanford Cade. First complained of pain in the back between shoulder blades 1942. Radiograph of spine at that time showed collapse of fifth and sixth thoracic vertebrae. Treatment for tuberculosis of spine by plaster jacket with periods of rest in bed (on one occasion for twenty months, April 1942 to January 1944) continued until August 1946 when she developed motor and sensory loss of both lower limbs. December 1946 laminectomy performed, including removal of large mass of red tumour material from region of fourth, fifth, and sixth thoracic vertebrae which were grossly eroded. Patient's condition not good enough to permit bone grafting; plaster jacket applied. After operation weakness of lower limbs improved; patient was able to move her legs; sensation returned. Admitted to the Westminster Hospital for radiation therapy January 18, 1947. Microscopy of tumour showed typical plasma cells with large binucleate varieties (Fig. 21). *Investigations*—January 23, 1947—Plasma inorganic phosphates 6·3 mg. per 100 c.c. Plasma urea 21 mg. per 100 c.c. Serum alkaline phosphatase 6 units. Serum calcium 9·8 mg. per 100 c.c. Thymol turbidity and flocculation tests negative. Serum albumen 5 g. per 100 c.c., globulin 2·1 g. per 100 c.c., total 7·1 g. per 100 c.c. Repeated tests for Bence-Jones proteinuria negative. Proteose present precipitated by salicyl-sulphuric acid; not by heat. Wassermann reaction negative. *Radiographic examination*—Radiographs on six occasions between 1942 and the end of 1945 showed no skeletal lesion other than collapse of the thoracic vertebrae (Fig. 10). On January 2, 1946, a clearly demarcated osteolytic lesion was seen

in the neck of the left twelfth rib. On February 21, 1947, the following lesions were found in radiographs taken in Westminster Hospital: multiple clear-cut, punched-out areas of complete translucency in calvarium of skull (Fig. 6), in fourth, fifth, seventh, eighth, and ninth left ribs, both pubic rami, upper end of right femur and both ilii. *Subsequent history*—Patient is alive at present time and although she lies in a plaster case her general condition remains satisfactory.

The importance of this case lies in the fact that it demonstrates the long time interval, in this instance four years, which may elapse between onset of the primary tumour and involvement of the bone marrow of many bones, with a radiographic appearance which is identical ultimately with that of typical multiple myelomatosis. It should also be observed that Bence-Jones proteinuria was first noticed thirteen months after the second bone lesion and approximately at the same time as the development of multiple tumours. This sequence of events shows that the diagnosis of a solitary bone tumour is justifiable only after a long follow-up period. Willis (1941) stated that any bone marrow plasmocytoma remaining solitary for more than one year could be accepted as a true solitary tumour, but this case shows that it is not possible to give any specific time interval, and that all solitary tumours should be followed up for many years with the possibility of spread to other bones always in mind.

FIG. 4

Case 3. Radiograph of pelvis showing large deposits in the ilium.

Case 7. J. K., male, aged 48 years. Under care of Sir Stanford Cade. Complained of sharp intermittent pain at back of left thigh. When seen July 1946, ten months after onset of symptoms, pain so severe and persistent that he was unable to bear weight. *On examination*—Smooth, round, hard swelling with ill-defined edges visible just below left greater trochanter, fixed to femur but not to skin. Hip movements full. Biopsy performed. Diagnosis of plasmocytoma made (Fig. 13). *Investigations*—Serum alkaline phosphatase December 23, 1946, December 30, 1946, and July 8, 1947—8 units. Serum acid phosphatase December 23, 1946—4·9 units. (all alcohol-stable). Plasma inorganic phosphates December 23, 1946—4·4 mg. per 100 c.c., and July 8, 1947—3·4 mg. per 100 c.c. Serum calcium December 23, 1946—10·3 mg. per 100 c.c., and July 8, 1947—10·2 mg. per 100 c.c. On December 30, 1946, serum proteins were raised: albumen 4·8 g. per 100 c.c., globulin 3·9 g. per 100 c.c., total 8·7 g. per 100 c.c. Thymol and colloidal flocculation tests positive, 3 plus and 5 plus respectively. On July 8, 1947, after treatment, all these values had returned to normal. Serum proteins—albumen 4 g. per 100 c.c., globulin 1·9 g. per 100 c.c., total 5·9 g. per 100 c.c. Flocculation tests negative. Numerous tests for Bence-Jones proteinuria and albuminuria consistently negative. Radiographs of all bones in the body, December 22, 1946, and January 6, 1947, showed no abnormalities except in upper end of left femur where osteolytic changes in neck and trochanter extended slightly down the shaft (Figs. 17–18). Repeat radiographic examinations January 16, 1947, and January 24, 1947, showed little or no change. *Treatment and subsequent history*—Treatment undertaken with high voltage X-rays only, using two ports of entry with skin dose 2000r to one, and 2800r to the other. Tumour dose, 3000r. General condition of patient while in hospital and during follow-up to present time has remained excellent. Now has no pain whatsoever in leg.

Case 8. H. N., male, aged 72 years. Under care of Mr E. Stanley Lee. History of slowly increasing pain in hips and legs and of solitary sacral tumour. General health good for one year from onset of symptoms, at which time uraemia developed. Death three weeks later. *Investigations*—Bence-Jones proteinuria present each time a test was made during last two months of life, but serum globulin was

never raised. Wassermann reaction negative. *Post-mortem examination*—Diagnosis of solitary tumour of the sacrum confirmed by careful post-mortem examination of entire skeleton, and negative radiographic findings in all bones of the body excluding sacrum, three weeks before death. Tumour of the sacrum large (8×8×6 cm.), fleshy, replacing entire bone and undergoing central necrosis (Figs. 15-16). Local invasion of posterior surface of rectum had occurred. *Microscopic examination*—Tumour composed almost entirely of typical plasma cells with some larger and binucleate forms lying in loose trabeculated matrix (Figs. 11–12). Cause of death—uraemia following renal tubular block, the association of which with myelomatosis will be discussed later (Figs. 25-26).

The presence of Bence-Jones proteinuria with a solitary tumour is most unusual and no other reference to it can be found in the literature. This case has been published in detail by one of us (Lumb, G., 1947).

Case 9. E. B., female, aged 66 years. Admitted to hospital March 1946 under Mr E. Stanley Lee, complaining of choking feeling in the throat for one year and difficulty in swallowing for three months. *On examination*—Large red nodular growth, ulcerated at one point, affecting right vallecula and extending across posterior third of tongue to left vallecula, and laterally into pharyngeal wall on right side. No enlarged cervical glands. *Investigations*—Wassermann and Kahn tests negative. Blood count normal. Urine examination no abnormality. Biopsy April 8, 1946: tumour composed entirely of typical plasma cells. At the point of ulceration, there was infiltration with inflammatory cells, including polymorphs. *Treatment* by high voltage X-rays and teleradium total dosage 3100r to the tumour. In May 1946 mass had completely disappeared. Up to present time patient has been in normal health; no recurrence.

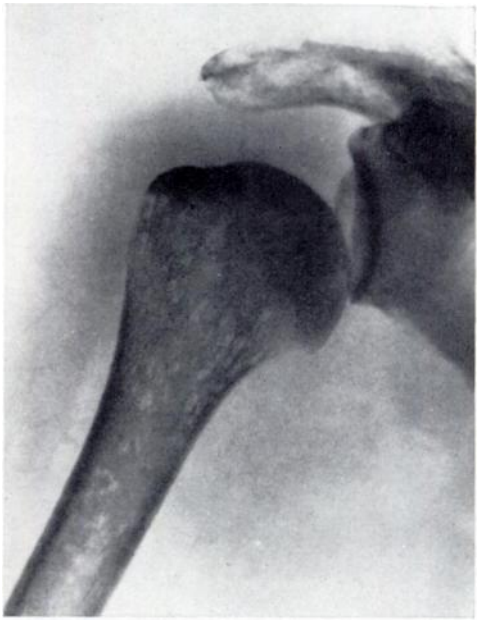

FIG. 5

Case 5. Radiograph of right humerus showing multiple punched-out areas.

Case 10. S. F., male, aged 34 years. Under care of Sir Stanford Cade. January 1945 first complained of cough and dyspnoea not relieved by treatment. *Investigations*—March 1945 biopsy performed of small subglottic tumour, 1 cm. in diameter, situated below posterior part of right vocal cord. Microscopic diagnosis of plasmocytoma made. Wassermann and Kahn tests, blood counts and urine tests all normal. After treatment by teleradium with tumour dose of 5000r, mass disappeared, and he remained well with no recurrence of symptoms until last seen February 1947. Then went to live in Edinburgh. We have received following report from Edinburgh Royal Infirmary: "On examination of the larynx June 18, 1947, when the patient reported complaining of increasing breathlessness for six weeks, a swelling was seen in the subglottic region protruding into the lumen from the anterior wall. Dyspnoea increased and tracheotomy was performed later the same day. A piece of tumour was removed for biopsy and the histologist reported a plasmocytoma. A further

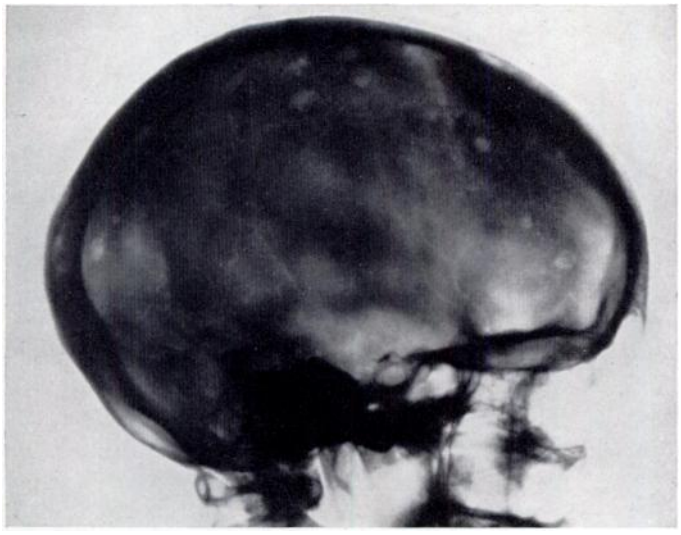

FIG. 6

Case 6. Radiograph of skull showing multiple punched-out areas.

course of irradiation is contemplated. Urine is still negative for Bence-Jones protein. Radiographs of the entire skeleton show no bony tumours and there are no enlarged cervical glands. The patient's general health remains good."

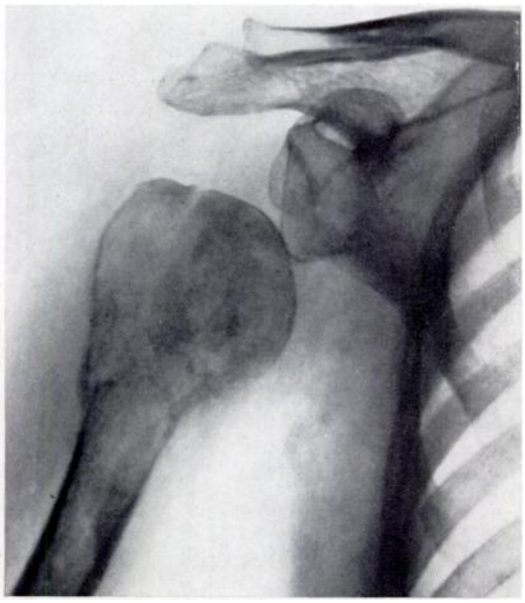

FIG. 7

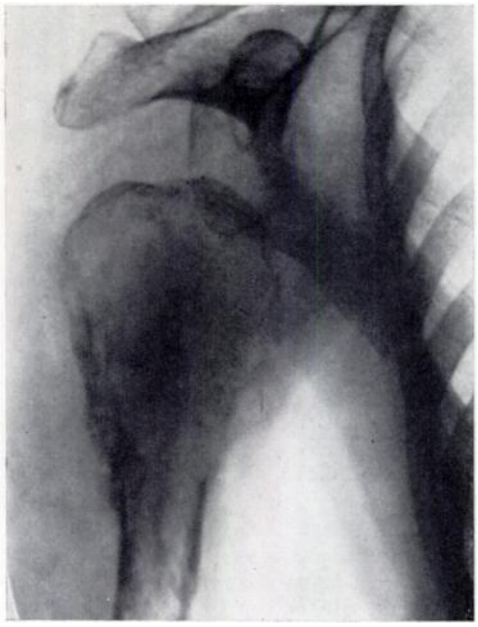

FIG. 8

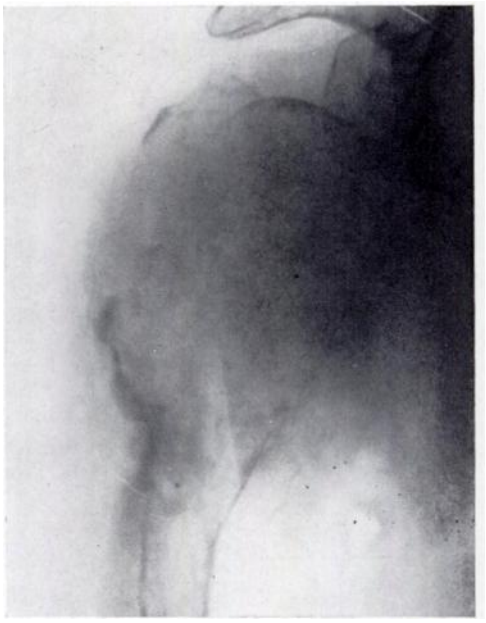

FIG. 9

Case 4. Fig. 7 is radiograph of right humerus showing a lesion resembling an osteoclastoma and including a pathological fracture. Fig. 8, radiograph of same bone one month later shows osteolytic change in the lesion. Fig. 9, four months after the original radiograph, shows complete osteolysis.

Case 11. Soldier, aged 20 years. Under care of Sir Stanford Cade and Dr F. M. Allchin. History, seven years' duration, huskiness and difficulty in breathing, not severe enough to warrant treatment until January 1944 when thyrotomy was performed in the Army and a mass removed from right vocal cord. Microscopic examination of this tissue showed sub-epithelial accumulation of plasma cells, but the general appearances were considered to be those of a chronic inflammatory process. Repeated Wassermann tests negative. No evidence of tuberculosis or leprosy. Gram and Ziehl-Neelsen staining of sections revealed no organisms. Possibility of lichen planus excluded. In succeeding years no definite diagnosis made. Further small masses appeared so that March 12, 1947, when seen for first time in Westminster Hospital he showed following lesions: *On examination*—*Tongue*—Multiple cracks and fissures with induration and underlying firm areas. *Palate*—Extending round labial aspect of teeth a red raised area firm and not tender. From the hard palate extending on to the soft palate, two raised, firm, non-tender, red patches. *Larynx*—Epiglottis and arytenoids thickened and the surface heaped up producing an appearance similar to that in the palate. In right subglottic region further similar plaque of red rough heaped-up epithelium; the lumen of glottis stenosed. *Investigations*—Further biopsies from tongue and palate showed aggregations of plasma cells lying under epidermis. A number of binucleate forms seen. Clumps of cells infiltrated deeply but no invasion of epidermis and no ulceration (Fig. 20). Sections stained Gram and Ziehl-Neelsen showed no micro-organisms, and in view of remarkable uniformity of cell-type, unusual in inflammatory changes, it was considered that neoplastic origin was more probable. Teleradium therapy in conjunction with high voltage X-rays instituted, with tumour dosage of 5500r. June 25, 1947, all lesions had disappeared leaving only some oedema of arytenoids. Urine tests for Bence-Jones protein repeatedly negative. Serum proteins 7·5 g. per 100 c.c. Blood chemistry in other respects normal.

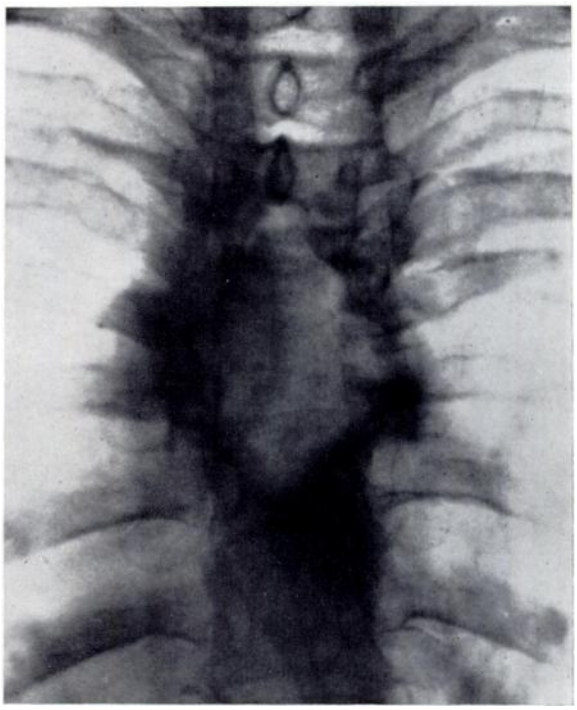

FIG. 10

Case 6. Radiograph of spine showing complete osteolysis of thoracic vertebrae.

Case 12. P. E., female, aged 24 years. Under care of Sir Stanford Cade. First complained March 1941 of swelling in left cheek and left side of face with difficulty in breathing through left nostril. *Investigations*—October 1941 Caldwell-Luc operation performed with extensive removal of soft growth in left lateral nasal wall. Routine examination showed positive Wassermann and Kahn reaction. Congenital syphilis diagnosed, and anti-syphilitic treatment instituted. Microscopy of the tumour showed it to be composed entirely of plasma cells and, despite associated syphilis, the diagnosis of plasmocytoma was thought likely. *Treatment and subsequent history*—Teleradium therapy instituted. Radiographs showed no bone tumours in skeleton. Remained well and in October 1945 was delivered of normal child. Wassermann test at this time negative and has remained so since. Continued well until July 1946 when again developed epistaxis from left nostril, with recurrence of soft tumour in left lateral nasal wall and antrum. Readmitted to hospital September 1946 and further course of irradiation given. October 23, 1946, operation performed for removal of antro-nasal wall and ethmoid tissue, including the tumour mass. Microscopic examination showed tumour to be a plasmocytoma (Fig. 24). Repeated tests for Bence-Jones proteinuria negative. Has remained well until present time.

Case 13. G. P., male, aged 44 years. Under care of Sir Stanford Cade and Dr F. M. Allchin. First complained of sinusitis January 1944 at which time a nasal polyp was removed with complete relief until June 1945. *On examination*—Right side of nose obstructed, with associated discharge and epistaxis. *Investigations*—September 1945, Caldwell-Luc operation performed and numerous polypi removed. Two months later epistaxis recurred. January 12, 1946, examination revealed friable bleeding mass arising

from mid-meatal region causing depression of inferior turbinate bone. January 28, 1946, biopsy showed a tumour composed entirely of plasma cells (Fig. 23). Repeated urine tests failed to demonstrate Bence-Jones protein. After teleradium treatment with tumour dosage of 5450r, the tumour disappeared and patient was well until enlargement of upper deep cervical glands on right side occurred. This swelling disappeared completely after further teleradium treatment, and patient remained well until November 1946 when he complained of left sciatic pain. Radiographs of lumbar spine and pelvis February 17, 1947, showed no bone lesions. Patient went to South Africa, March 1947. Rectal examination at this time showed no evidence of enlargement of prostate nor was there any clinical evidence of prostatic disease. Patient admitted Groot Schuur Hospital in Capetown April 9, 1947, and they report general condition at this time poor; deteriorated rapidly; complete paralysis with all signs of cauda equina lesion; sensory loss to level of groins including saddle area; complete incontinence. Left seventh and right eighth ribs showed swellings anteriorly, with radiographic evidence of loss of bone structure and expansion. Patient died May 4, 1947. *Post-mortem examination* refused, but one involved rib removed and showed microscopical evidence of plasma cell tumour. Other investigations showed haemoglobin 13 g. per 100 c.c., red blood corpuscles 3,490,000 per cu.mm., white blood corpuscles 17,600 per cu.mm., neutrophils 78 per cent., lymphocytes 16 per cent., monocytes 2 per cent., eosinophils 4 per cent. No plasma cells seen. Sternal marrow showed no abnormalities. Lumbar puncture showed complete block—protein 140 mgm. per 100 c.c., globulin increased, one lymphocyte per 100 c.c. Blood chemistry normal. Wassermann reaction negative. Bence-Jones protein present in urine.

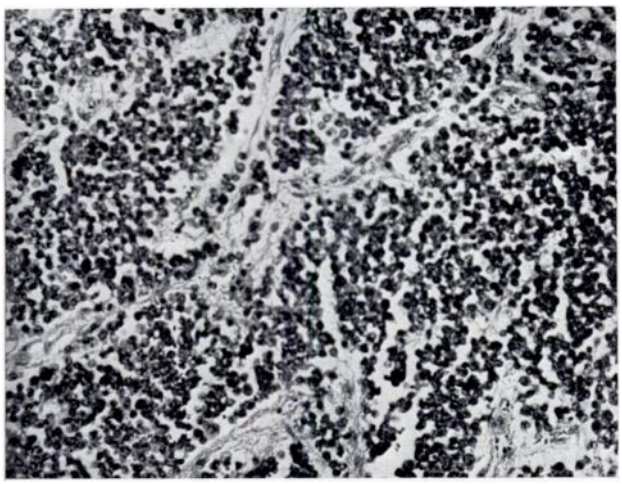

FIG. 11

Case 8. Photomicrograph showing general trabeculated appearance of tumour. Magnification ×60.

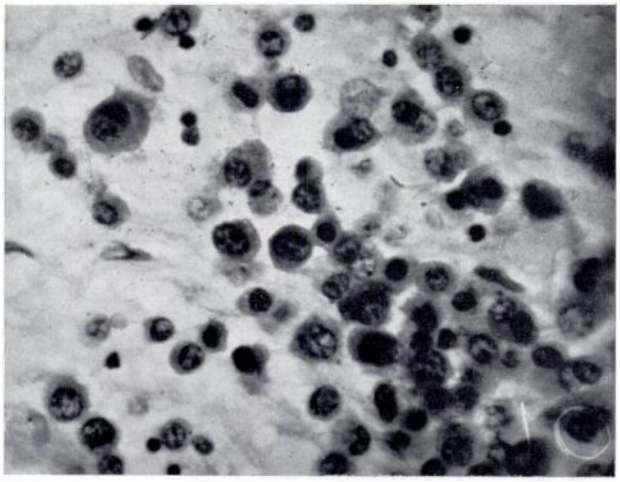

FIG. 12

Case 8. High power view of same tumour as Fig. 11. Magnification × 240.

Case 14. A. G., male, aged 77 years. Under care of Dr S. P. Meadows. First seen November 1945, with six months' history of shortness of breath and aching pain in chest. Also had productive cough and indefinite abdominal pain. Had lost two stones in weight during preceding two years. *On examination*—Emphysematous with basal chronic bronchitis and slight oedema both ankles. *Investigations*—November 7, 1945, peripheral blood showed haemoglobin 25 per cent., red blood corpuscles 1,600,000 per cu.mm, colour index 0·8, white blood corpuscles 5400 per cu.mm., neutrophils 13 per cent., lymphocytes 52 per. cent., monocytes 4 per cent. Remaining 31 per cent. of cells, after peroxidase staining and demonstration of motility with supravital dyes, labelled monoblasts. December 3, 1945, blood count much the same—haemoglobin 36 per cent., white blood corpuscles 12,100 per cu.mm.,

neutrophils 17 per cent., lymphocytes 22 per cent., monocytes 9 per cent., monoblasts 52 per cent.; count of 500 bone marrow cells showed 30 per cent. normal looking plasma cells (Fig. 14). Distribution of other cell types normal. Urine tested repeatedly; showed each time presence of Bence-Jones protein and albumen. Blood proteins November 12, 1945—albumen 3·61 g. per 100 c.c., globulin 3·82 g. per 100 c.c., total 7·43 g. per 100 c.c., and blood urea 42 mg. per 100 c.c. Radiographic examination of the entire skeleton November 12, 1945, November 30, 1945, and December 7, 1945, showed no bone tumours. While in hospital patient's general condition became weaker and after gradual decline signs of right subdural haemorrhage appeared December 10, 1945. Died December 12, 1945. *Post-mortem examination*—Large subdural haematoma lying over right parieto-occipital region causing depression of underlying brain which was otherwise normal. Heart showed left ventricular hypertrophy but was otherwise normal. Liver weighed sixty-eight ounces; adherent to anterior abdominal wall over right lobe by old adhesions involving area two inches square. Spleen enlarged and congested. Several lymph nodes of coeliac and para-aortic group enlarged. Sternum, ribs, vertebrae, and shaft of right femur showed hypertrophic purple marrow with oval cyst three-quarters by half-inch containing soft purple marrow substance in neck of right femur. *Microscopic examination—Bone marrow*—Sections from various areas showed plasma cells of typical appearance in clumps among other marrow cells. *Liver*—Areas of fatty degeneration. Principle change was congestion of sinusoids, all of which were wide open, thus spreading liver cells apart. In the sinusoids, apart from erythrocytes, were numerous typical plasma cells. Kupffer cells not generally enlarged but there were deposits of haemosiderin in some (Fig. 29). *Spleen*—Congested. Occasional plasma cells seen in the sinusoids but no true invasion demonstrated. *Lymph node* from para-aortic group—normal architecture but sinuses widely distended and contained numerous plasma cells (Fig. 31).

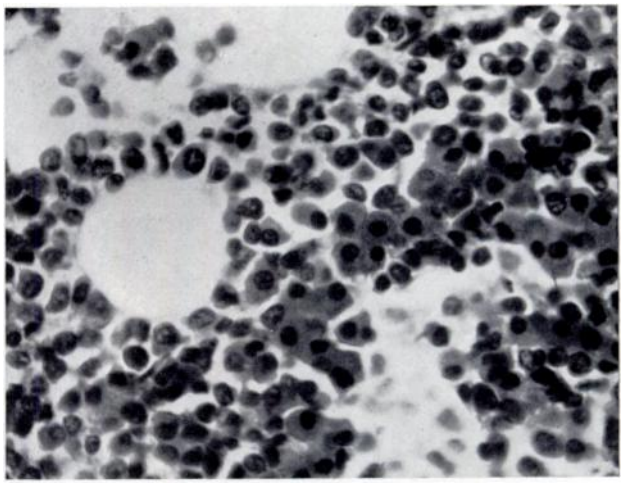

FIG. 13

Case 7. Photomicrograph showing typical plasma cell appearance. Magnification ×160.

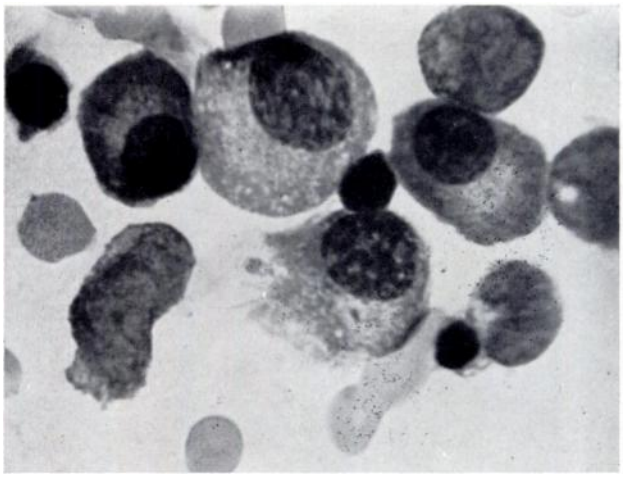

FIG. 14

Case 14. Photomicrograph showing high power view of sternal marrow smear. Magnification ×800.

This case is most interesting in that despite the large number of plasma cells in the bone marrow and their presence in viscera such as the liver, spleen, and lymph nodes, the abnormal cells in the peripheral blood appeared to be monoblasts. This phenomenon is well recognised in other types of leukaemia where differing cell varieties appear in the marrow and the peripheral blood. The case may be described as an example of aleukaemic plasma cell leukaemia.

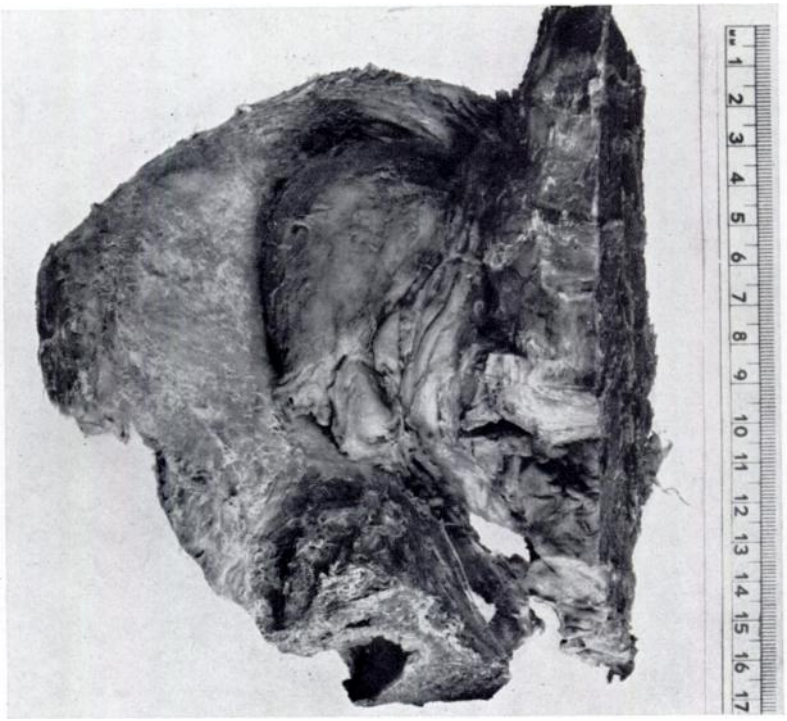

FIG. 15

Case 8. Specimen of sacral tumour removed at autopsy showing complete destruction of sacrum and spread of tumour over anterior surface of right ilium.

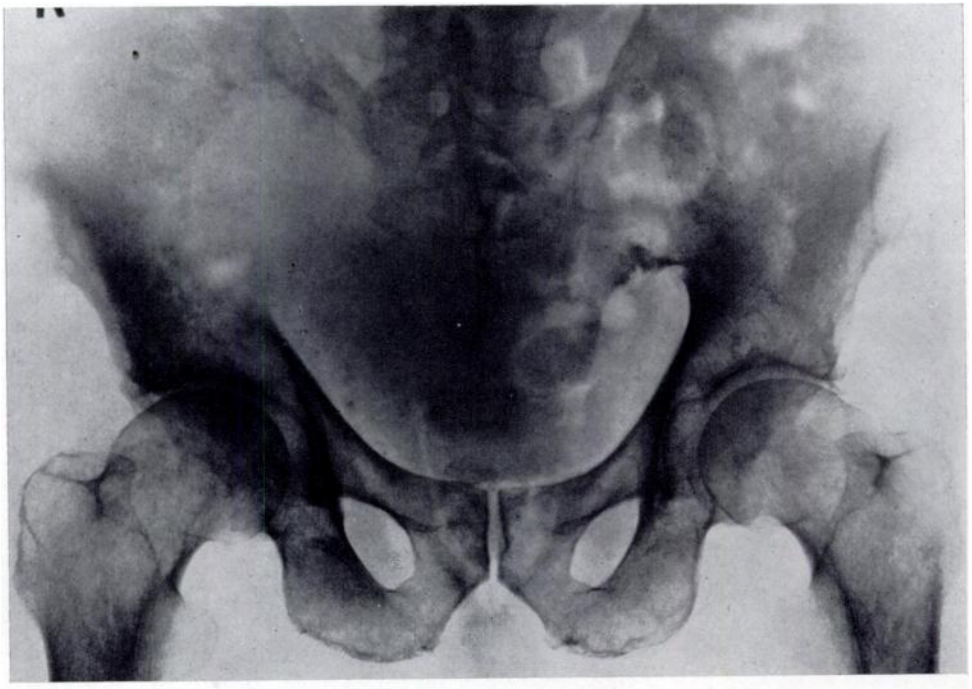

FIG. 16

Case 8. Radiograph of pelvis showing osteolytic tumour destroying the sacrum.

Case 15. S. M., male, aged 57 years. First admitted under care of Dr W. E. Lloyd, December 5, 1941, with one month history of dizziness, head pains, cough, and pain left loin. *On examination*—Signs of bronchitis both bases. Liver and spleen palpable at two fingers breadth below costal margin. No lymph node palpable. Mass felt on left side in region of left kidney. *Investigations*—Urine contained albumen and Bence-Jones protein January 28, 1942, and gave positive results in numerous subsequent tests. Serum proteins January 30, 1942, albumen 5·1 g. per 100 c.c., globulin 1·1 g. per 100 c.c., total 6·2 g.

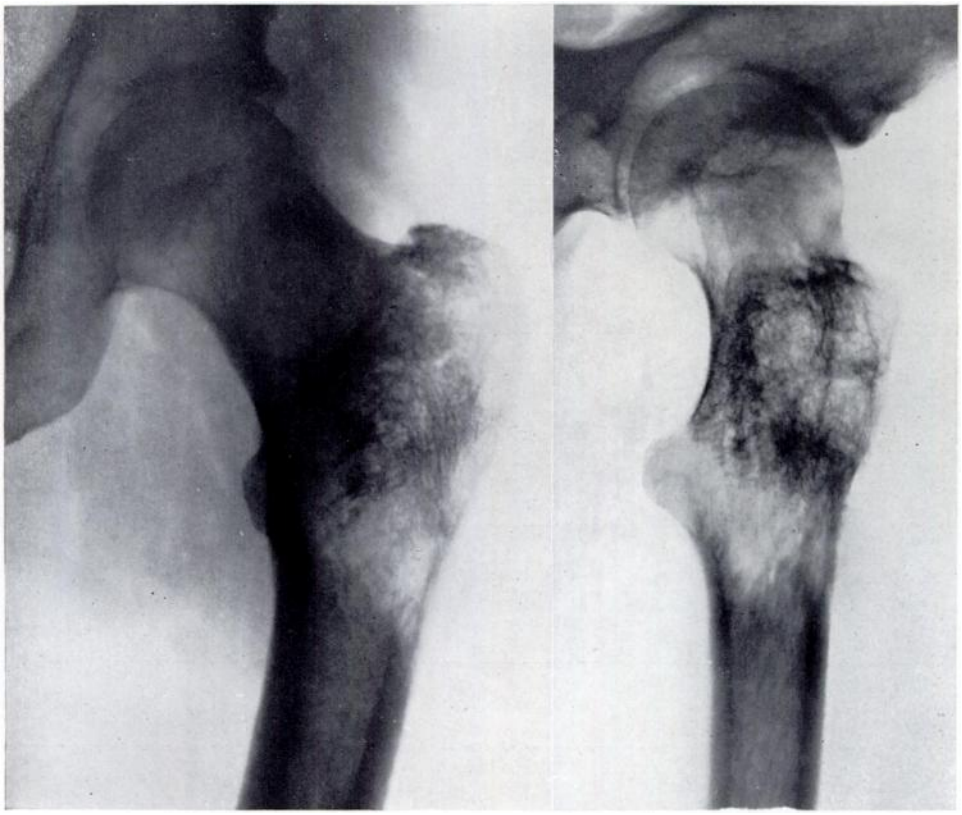

FIG. 17 FIG. 18

Case 7. Radiographs of left femur showing solitary osteolytic lesion at upper end of the bone. Fig. 17 antero-posterior projection. Fig. 18 lateral projection.

per 100 c.c. Sternal marrow puncture January 27, 1942, 32·6 per cent. plasma cells in a count of 500 cells. Despite this great increase in number of plasma cells the only other abnormality was relative reduction in erythrogenic tissue. Peripheral blood examination January 13, 1942—haemoglobin 62 per cent., red blood corpuscles 3,000,000 per cu.mm., colour index 1·0, white blood corpuscles 7200 per cu.mm., neutrophils 46 per cent., lymphocytes 35 per cent., monocytes 11 per cent., plasma cells 8 per cent. Blood examination January 26, 1942—haemoglobin 63 per cent., red blood corpuscles 3,150,000 per cu.mm., colour index 1·0, white blood corpuscles 9200 per cu.mm., neutrophils 36 per cent., lymphocytes 49 per cent., monocytes 5 per cent., plasma cells 10 per cent. Radiographs of lumbar and thoracic vertebrae showed no bone tumours. Renal function test on December 24, 1941—blood urea 36 mg. per 100 c.c., urea clearance test 57 per cent. of normal. Patient was discharged February 16, 1947, and died shortly afterwards at home. Unfortunately no autopsy performed. Despite lack of post-mortem examination the diagnosis of myelomatosis is assured in view of the sternal marrow findings and it provides a good example of the rare condition of typical plasma cells occurring in considerable numbers in the peripheral blood (Fig. 27) which may well be termed plasma cell leukaemia.

A résumé of various points from the case histories is shown in Table I.

TABLE I

Case No.	Sex	Age in yrs.	Bones involved	Soft Tissues involved	Radiographs	Bence-Jones Proteinuria	Serum Protein		Survival
							Albumen	Globulin	
1	M.	60	Ribs, sternum, vertebrae	Infiltration by plasma cells of sinusoids of liver and spleen	Punched - out areas in ribs; and collapse of vertebrae	Repeatedly positive	—	—	3½ months
2	M.	52	Skull, ribs, vertebrae, femora, ilii	None	Punched - out areas in affected bones	Repeatedly positive	—	—	2½ months
3	M.	45	Skull, ribs, vertebrae, right ilium	None	Osteolytic lesions in second and third lumbar vertebrae	Repeatedly negative	—	—	3 years
4	F.	55	Humerus and vertebrae	None	Tumour in humerus first resembling an osteoclastoma later becoming osteolytic	Repeatedly negative	—	—	8 months
5	M.	41	Humerus, ischium, skull	None	Multiple punched - out areas in affected bones	Repeatedly negative	—	—	10 months
6	F.	30	Skull, ribs, vertebrae, pelvic bones, femora	None	Punched - out areas in affected bones	Unusual proteose present	5·0 g. per 100 c.c.	2·1 g. per 100 c.c.	Alive now after 5 years
7	M.	48	Femur only	None	Osteolytic lesion at upper end of the left femur	Repeatedly negative	4·8 g. per 100 c.c. in Dec. 1946, 4·0 g. in July 1947	3·9 g. per 100 c.c. in Dec. 1946, 1·9 g. in July 1947	Alive now after 24 months
8	M.	72	Sacrum only	Kidney (tubular blockage)	Large osteolytic lesion of sacrum	Repeatedly negative	5·1 g. per 100 c.c.	2·5 g. per 100 c.c.	13 months
9	F.	66	None	Pharynx	No bone tumours	Negative	—	—	Alive now after 20 months
10	M.	34	None	Larynx	No bone tumours	Negative	—	—	Alive now after 2½ years
11	M.	20	None	Tongue, palate, larynx	No bone tumours	Negative	—	—	Alive now after 7½ years
12	F.	24	None	Lateral nasal wall	No bone tumours	Negative	—	—	Alive now after 6 years
13	M.	44	Ribs and vertebrae	Lateral nasal wall	Osteolytic lesions in ribs	Became positive after 3 years	1·8 g. per 100 c.c.	2·0 per g. 100 c.c.	3½ years
14	M.	77	Diffuse infiltration of bone marrow	Liver, spleen, and para - aortic lymph nodes	No bone tumours	Repeatedly positive	3·61 g. per 100 c.c.	3·82 g. per 100 c.c.	7 months
15	M.	57	Infiltration of sternal marrow	Unknown	No tumours seen in lumbar and thoracic spine	Repeatedly positive	5·1 g. per 100 c.c.	1·1 g. per 100 c.c.	4 months

Note 1.—Plasma cells were found in the peripheral blood of Case 15.
Note 2.—Wassermann reaction was negative in all cases except Case 12, which had a positive reaction for a period.
Note 3.—Sternal marrow smears were examined in Cases 4, 5, 6, 7, 8, 13, and 14. All were normal with the exception of 13 and 14 which showed 30 per cent., 32·6 per cent. of plasma cells respectively.

CLINICAL FEATURES

Bone tumours—*Incidence*—Multiple myeloma is the most rare malignant tumour of bone. The incidence is stated to be 0·03 per cent. of all malignant disease (Geschickter and Copeland 1936) and it constitutes only 3 per cent. of all bone tumours (Cade *et al.* 1947). Solitary plasmocytoma of bone is even more rare, and in a search of the literature only seventeen proved cases have been found (Lumb 1947). In this series, of the seven cases of multiple myeloma five were males and two were females. This is in agreement with other recorded series which show a preponderance of males over females in the region of two to one. It is a disease of adult life, occurring usually between the ages of forty and sixty, but it can appear in young adults (Case 6). Kaufman (1945) also reported a case of solitary tumour of the skull in a boy aged fourteen years.

Site of multiple tumours—In multiple tumours the flat bones are chiefly affected, especially the bones of the thoracic cage—ribs, vertebrae, sternum, and after that in order of frequency the skull, femora, pelvis, and clavicle. Occasionally any bone may be

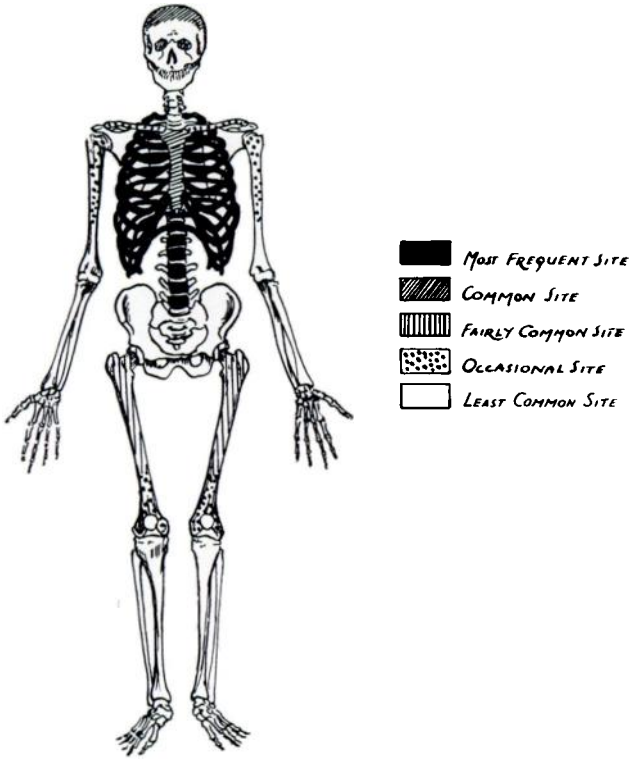

DIAGRAM 1
Site and frequency of multiple tumours.

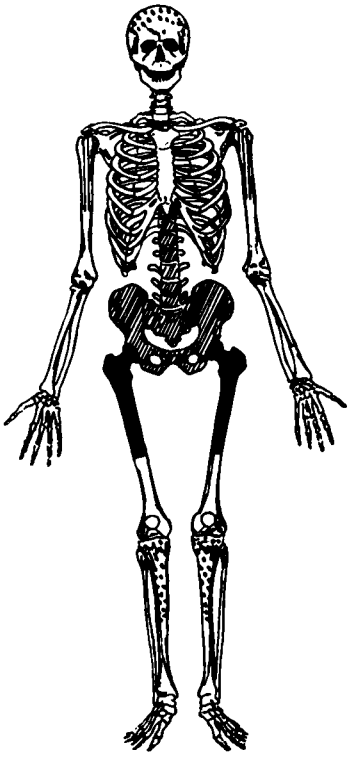

DIAGRAM 2
Site and frequency of solitary tumours.

involved (Diagram 1). Any part of the spinal column may be the site of the disease. In this series there was one case with disease in the lumbar vertebrae and one in the dorsal vertebrae. The body and the processes of the vertebrae may be involved. At first the tumours are usually small, but occasionally they grow to the size of a pigeon's egg and sometimes become much larger (Case 4).

Bone tumours originate in the cells of the bone marrow, but it is important to realise that any site in the bone may be attacked. Round or oval clear-cut masses of grey or purple

tumour tissue appear. Multiplicity of lesions is characteristic of the condition. In the skull and ribs the tumours may be palpated or even seen. Larger tumours of course are plainly visible, more especially after they have transgressed the bone and involved soft tissues (Cases 4, 5, and 8). Indeed, in this condition so much bone may be replaced by tumour that pathological fracture occurs, and when tumours involve the vertebral column, pressure on the spinal cord may give rise to compression paraplegia (Case 6).

Site of solitary tumours—Solitary tumours tend to be larger than any individual mass of the multiple disease. Moreover the order of frequency of bones affected is different (Diagram 2). Thus of eighteen proved cases in the literature, six were in the femur, five of which were in the upper third (Zdansky 1927, Martin *et al.* 1928, Rogers 1929–30, Harding and Kimball 1932, Rutishauser 1933, and Case 7 in the present series); four were in the vertebral column (Walthard 1924, Cutler *et al.* 1936, Willis 1941, Lumb 1947); four in the bones of the pelvis other than the sacrum (Cutler *et al.* two cases 1936, Leedham-Green *et al.* 1938–39, Gootnick 1945); two were in the humerus (Shaw 1923, Stewart and Taylor 1932); and one each in the tibia (Chesterman 1935–36) and the skull (Kaufman 1945).

Differentiation of solitary tumours from generalised disease—In assessing cases which can truly be termed solitary plasmocytoma of bone, we agree with the criteria for diagnosis laid down by Willis (1941). Thus the possibility that the tumour is merely an initial sign of generalised disease must be excluded. This may call for observation over several years (Case 6). We believe that all solitary tumours should be held suspect and that careful follow-up should be continued indefinitely. Other important features in diagnosis are histological examination of the tumour, repeated radiographic examination of all bones in the body, and repeated tests for Bence-Jones proteinuria. If all these factors are insisted upon, a very large number of cases reported in the literature as solitary tumours must be excluded. It is in this way that we have arrived at our total of eighteen proved cases.

Symptoms and signs of bone tumours—The local symptoms and signs of tumours, whether single or multiple, are identical and can be discussed together. *General symptoms* are found only when the tumours are multiple. An exception is to be noted however in Case 8 which is most unusual, and so far as we can discover the only example of its type so far described (Lumb 1947). *Pain* is without doubt the most frequent symptom. In the majority of cases pain is also the earliest manifestation. In our cases of bone disease it occurred without exception and in all it was the first symptom. It may, however, occur only after injury, which is often trivial but which may lead to pathological fracture of an already diseased bone. Ulrich (1939) states that from a study of the history of 259 cases of multiple myeloma there was freedom from pain in only 4·6 per cent., while clinical recognition of the tumour was possible in 36·7 per cent. The onset of pain is insidious and often intermittent, becoming gradually more severe and continuous. This is well marked in most tumours of the spine. It should be noted that pain may precede the appearance of a tumour by many months (Cases 3, 7, and 8). In the later stages of the disease there is general *malaise*, weakness, and anaemia, progressing to *cachexia*. During this period the pain becomes increasingly widespread and severe. *Anaemia* may be an important concomitant, doubtless due to extensive bone marrow replacement. Occasionally, unexplained anaemia may lead to bone marrow investigation and radiographic examination with recognition of the condition. *Complications*—The usual complications of the disease are pathological fracture of a bone, and compression paraplegia in the case of vertebral tumours.

Extra-medullary plasma cell tumours—*Incidence*—These tumours, although occurring with greater frequency than solitary plasmocytomata of bone, are nevertheless rare. In the great majority of cases they arise in the larynx, air sinuses, and upper air passages. They may easily be mistaken for the much more common, and more grave carcinomata and sarcomata which arise in this situation, or they may be mistaken for chronic inflammatory conditions. Of our cases, three were males and two were females. In other reported series

there has been an even greater preponderance of males, ranging from five to one, even up to thirteen to one (Hellwig 1943). It is a disease of adult life, usually reported between the ages of forty and sixty, but two of our cases were less than twenty-five years of age.

Site—The tumour occurs most frequently in the mouth and upper air passages. All our cases have been in this situation, one in the subglottic area, two in the lateral nasal wall involving the inferior turbinate bone, one in the vallecula, and one involving the tongue, palate, and larynx. Hellwig (1943) reviewing 127 cases from the literature found sixty-three in the air passages, forty-seven in the conjunctiva, four in the lymph nodes, and thirteen in other organs—the pleura, mediastinum, spermatic cord, thyroid gland, ovary, intestines, kidney, and skin.

Symptoms and signs of extra-medullary tumours—When the tumour is in the nasal passages the classical symptoms are: 1) nasal obstruction; 2) discharge from the nose; 3) epistaxis; 4) tumour in the nose; 5) deformity of the nose, face, or palate; 6) pain. Of these, the first three are cardinal symptoms of the disease. The discharge at first is clear and watery, becoming thicker and purulent, and later blood-stained. *Epistaxis* may be repeated and severe. In both our cases of nasal tumour it was an early symptom. *Deformity* depends upon the position of the tumour and the direction of spread. One of our cases (Case 12), in which the growth had extended forwards, showed swelling of the cheek. The tumour may involve the antrum, spread backwards into the nasopharynx or pterygo-maxillary region, grow upwards displacing the nose or eye, or downwards to present in the roof of the mouth. *Pain* is not a common symptom in the early stages but indefinite dull aching in the region of the growth is frequent, and in both our cases a provisional diagnosis of " sinusitis " had been made. When the tumour is situated in the larynx *huskiness* and *dyspnoea*, with or without cough, are invariable symptoms.

Clinical appearances—Examination of the nose reveals a red, friable, often ulcerated, and partly necrotic, bleeding mass, obstructing the airway; without biopsy it is sometimes very difficult to differentiate from carcinoma of the antrum. We have observed that the vascularity of the plasmocytoma group tends to be greater than in the case of other tumours occurring in this area. When tumours are found elsewhere than in the upper air passages the clinical appearances are much the same. Soft, red, polypoid tumours are found (Case 10). Sometimes there is an associated submucous thickening of the nasopharynx, epiglottis, and larynx, with subsequent stenosis (Case 11, and Vogt 1912, quoted by Blacklock and Macartney 1932). It should be stressed that these tumours may be single or multiple in their distribution. Thus in our series Cases 10, 12, and 13 were single, and case 11 was multiple.

Clinical course—It has been indicated (Stewart and Taylor 1932, Blacklock and Macartney 1932, and Hellwig 1943) that these tumours may follow various courses: they may be completely benign and without recurrence; they may show local malignancy in the form of invasion and destruction of adjacent tissues, and a tendency to local recurrence following treatment; and finally cases have been described where invasion of adjacent lymph nodes has occurred with ultimate bone involvement indistinguishable from multiple myelomatosis (Case 13).

RADIOGRAPHIC APPEARANCES

1. Multiple myelomatosis—In typical cases the tumours produce multiple circumscribed areas of destruction involving both cortex and medulla, in which the bone texture has completely disappeared. The lesions occur in any part of the bone and typically they are found in vertebrae, ribs, sternum, and skull, eventually affecting any or all bones of the skeleton (Diagram 1). The areas appear as clear-cut, punched-out, oval or round patches of complete translucency, from 1 to 3 cm. in diameter, a characteristic feature being the lack of new bone formation either in the bone itself or in the periosteum. Fractures, and when

the lesion is in the vertebrae—areas of collapse, are common. Collapse of vertebrae occurs at an early stage and is associated with destruction of the intervertebral disc, in contradistinction to metastatic carcinoma where collapse occurs later and the discs are not involved. Kyphotic deformities are frequent, and differentiation from tuberculosis of the spine may be difficult in so far as this disease is also characterised by destruction of the intervertebral disc. Deficiencies in the skull often simulate those seen in xanthomatosis, but this condition is most frequent in children and young people, and the deficiencies have an irregular outline forming " map-like appearances." Translucent areas in the skull are also found in osteomalacia and osteitis fibrosa which must be excluded.

2. Solitary plasmocytoma—Solitary plasmocytoma of bone marrow, and multiple tumours beginning in solitary foci, may be considered together from the point of view of radiographic appearances. Two different types of lesion have been described, the histological appearances being identical (Gootnick 1945, Paul and Pohle 1940). The first type is cystic and trabeculated, closely resembling an osteoclastoma. The lesion is large, of reduced density, and sharply limited; within it are thickened irregular trabeculae. It is usually found in the medullary portion of the pelvis or long bones, frequently expanding the cortex. There is often pathological fracture (Figs. 7, 8, 9). The second type of lesion is purely destructive and very similar in appearance to the osteolytic metastasis of a carcinoma, or an osteolytic type of osteogenic sarcoma. It is sharply demarcated, homogeneously rarified in appearance, and seldom shows expansion. The vertebrae are often involved (Figs. 10, 16, 17, and 18).

In our series, Case 4 was an example of the first type. This variety is the more rare form of tumour. Cutler *et al.* (1936) describe one case, and Gootnick (1945) reported another. Paul and Pohle (1940) suggested that in the case of a solitary tumour with these radiographic changes the prognosis is better than in other varieties. This has not been our experience, for in Case 4 which was of this type, death occurred within seven months of the onset of symptoms. Examples of the second type of radiographic appearance are seen in cases 5, 7, and 8, showing bone lesions which were purely destructive, and with marked osteoporosis or complete lysis of a large area of the involved bone, with no evidence of new bone formation either within the bone itself or under the periosteum. This appearance may be extremely difficult to differentiate from that of other destructive lesions of bone.

Radiographic examination, therefore, although of the utmost importance in the diagnosis of solitary and multiple myelomatosis, cannot be said to be pathognomonic for all cases.

DIFFERENTIAL DIAGNOSIS

Soft tissue plasma cell tumours in the upper air passages must be distinguished from carcinoma and sarcoma with which they can easily be confused. The degree of vascularity of the plasmocytoma seems to be the most significant clinical differential feature. Biopsy with microscopical identification of plasma cells can exclude the more malignant conditions, but the differentiation of chronic granulomatous diseases may be difficult. (See Microscopy of Tumours, on opposite page.)

The differential diagnosis of plasma cell tumours in bone must include all the bone lesions; it is of primary importance to decide whether the tumour is solitary or multiple. Radiographic appearances are not pathognomonic. In fact no single diagnostic point is infallible and it is only when clinical appearances, radiographic changes, microscopic and biochemical evidence, are considered together that the positive diagnosis can be made.

No mention has been made of those rare examples where the disease occurs in some other soft tissue or viscus, because the differential diagnosis is essentially that of the particular organ involved.

MORBID ANATOMY AND MICROSCOPY OF TUMOURS

The tumours are soft, mainly red or purple in colour, very vascular, and bleed freely when cut. When large in size, central necrosis may take place (case 8). When the tumour is situated in the bone marrow local invasion causes thinning of bone and ultimately pathological fracture. Soft tissue tumours, either of primary origin, or after bursting the boundaries of the bone, show local invasion of surrounding structures such as muscle, mucous membrane, or even skin.

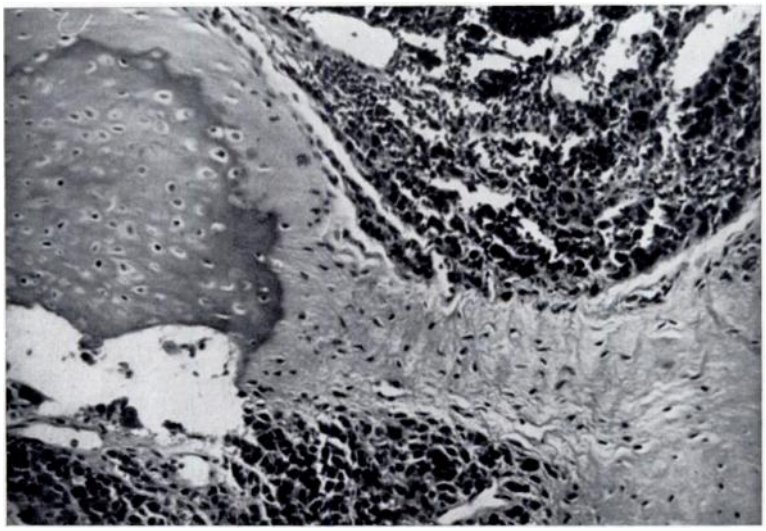

FIG. 19

Case 3. Low power view to show erosion of bone. Magnification ×60.

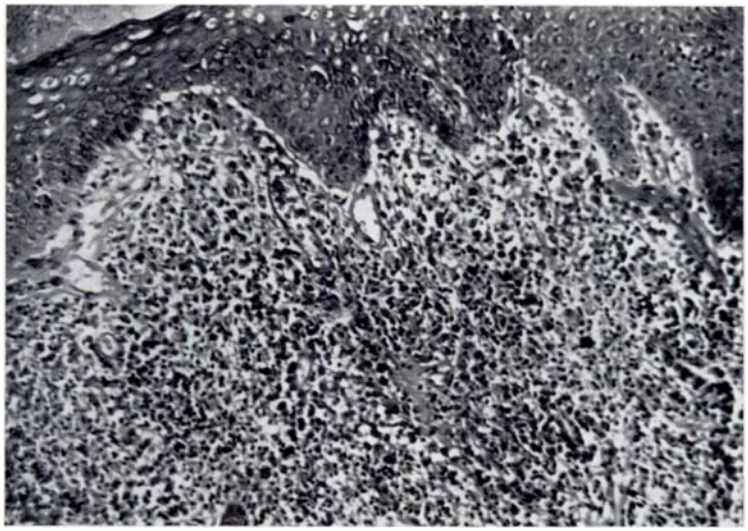

FIG. 20

Case 11. Low power view of soft tissue tumour lying beneath squamous epithelium but not invading it. Magnification ×60.

The microscopic appearances of the tumours described in our series are so essentially similar that they can be discussed together. The commonest cell type in all cases measured ten to fourteen microns in diameter and was ovoid, polygonal, or pyriform in outline, with a nucleus containing a well-marked nucleolus, and often eccentrically placed. The nuclei were

composed of dense chromatin, arranged in masses around the periphery to give a "cart-wheel" or "clock face" appearance. A perinuclear halo, best demonstrated when stained with iron haemotoxylin, was seen in many cases. The cytoplasm was plum-coloured when stained with eosin, and in some cases a carmine colour was produced with pyronin methyl green (Cases 8 and 12). Difficulty was experienced in the majority of our cases in obtaining positive Pappenheim reactions with pyronin methyl green. In this connection Geschickter and Copeland (1928) state that: "these cells . . . do not take the typical plasma cell stain by the Unna Pappenheim or polychrome methylene blue technique." Morison (1941) also failed to obtain positive results in myelomatosis with the Unna Pappenheim method. Stewart and Taylor (1932), however, obtained typical results in four cases. It would appear, therefore, that although the commonest cell type in these tumours has all the morphological characteristics of the plasma cell, it does not always react in the same way as the inflammatory variety of cell to pyronin methyl green staining.

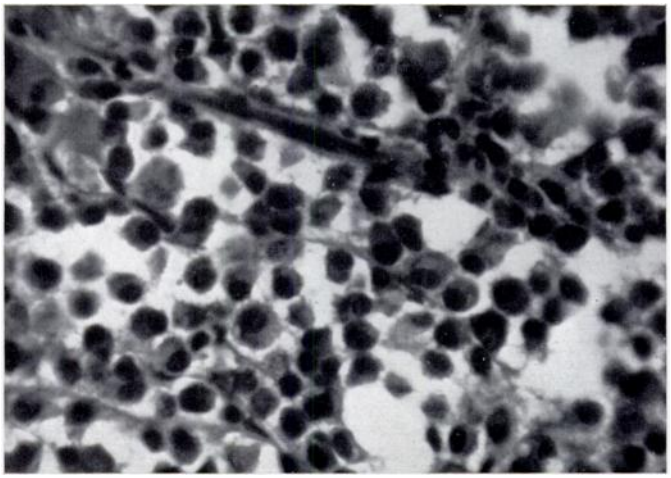

FIG. 21

Case 6. Photomicrograph showing trabeculated tumour. Magnification ×160.

In addition to the cells described above many larger forms, frequently with two or more nuclei were seen (Figs. 12 and 24), but these cells always retained an essentially similar general nuclear structure and are regarded as of similar origin. Mitotic figures were not frequent in our series but were found in small numbers in the majority of cases. Cells tended to remain discrete in most areas but were sometimes closely packed together. The stroma was invariably scanty, consisting of fine trabeculae interspersed with numerous small blood-vessels. Histological evidence of invasion could be obtained in all cases where spread occurred and examples of muscle and bone invasion are seen in Figs. 22 and 19.

FIG. 22

Case 5. Low power view of tumour to show invasion of muscle fibres. Magnification ×60.

In Case 4 the greatest variation from plasma cell type was seen, and some difference of opinion might exist as to whether this case of myelomatosis should be classed as of "plasma cell type." Ewing (1940) used the term "myeloma" to describe tumours arising from specific bone marrow cells, and recognised the following types histologically: 1) plasma cell myeloma; 2) myelocytoma,

derived from granular leucocytes; 3) lymphocytoma, derived from lymphocytes; and 4) erythroblastoma, derived from nucleated red cells. Whether any such clear-cut differentiation is justifiable is not fully established.

Some authors have attempted to differentiate the cell types by means of the peroxidase staining reaction (Beck and McCleary 1919) and others by means of the Unna Pappenheim reaction (Aschoff 1905). Many authors, in describing different cells in cases of multiple myelomatosis, have been uncertain whether to class them among the plasma cell or the myelocytic group, and some have thought the apparent difference was due to fixing or staining methods (Berblinger 1911, Shennan 1913).

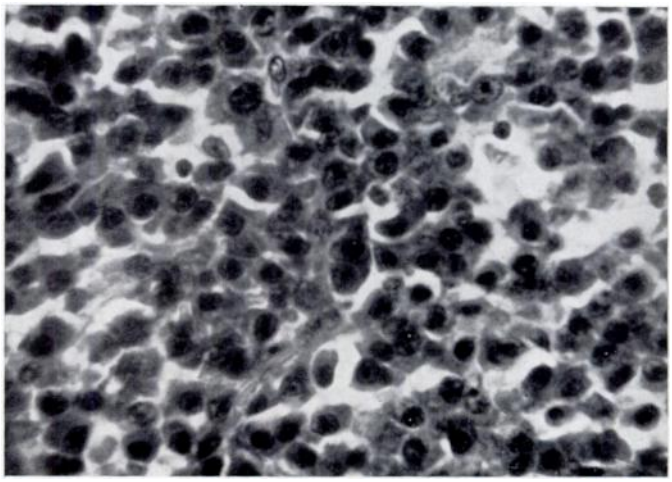

FIG. 23

Case 13. Soft tissue tumour showing plasma cells, some large and some binucleated. Magnification × 160.

Christian (1907) in a most careful histological description of six cases, felt that the tumour cells showed a greater resemblance to plasma cells as found in the bone marrow than to any other type of cell, and concluded that a group could be defined within which the cells of individual cases showed no greater variation than occurs in other tumour groups. This belief has been confirmed by most workers in later years and is borne out by the cytological findings in our series.

It may be noted that in recent years the number of reports of plasmocytoma, as compared with other types, has increased. Wallgren (1920) found only three cases reported as plasmocytoma out of twenty-five cases reported between 1900 and 1904, whereas fifteen cases out of thirty between 1905 and 1909, and fifteen cases out of twenty-five between 1910 and 1914, were labelled plasmocytoma. Fleischhacker and Klina (1936) diagnosed nine of their ten cases as plasmocytoma with the remaining one doubtful. Similarly in most other reports this tendency is noticeable, whilst in accounts of soft tissue tumours, cells histologically resembling plasma cells have always been described, and in our series this finding was confirmed.

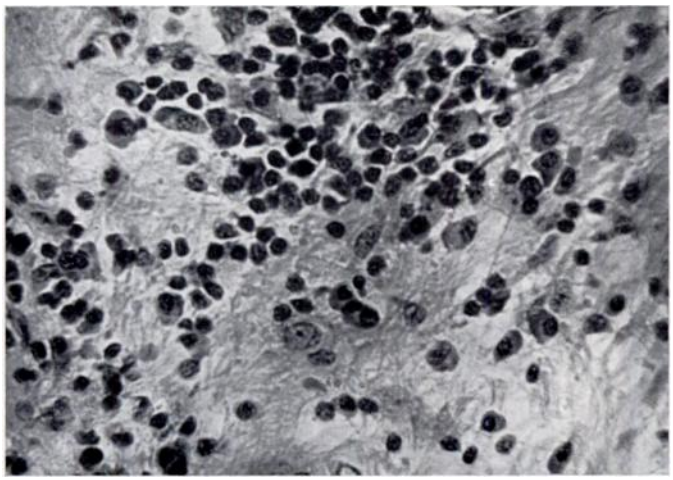

FIG. 24

Case 12. General view of soft tissue tumour. Magnification × 140.

Microscopic evidence of the degree of malignancy in these tumours is usually estimated by the degree of variation of cell type, the frequency of mitotic figures, and evidence of local

invasiveness. It is true that in our cases which showed multiplicity these features were more marked than in the solitary cases.

Many authors have thrown doubt on the truly neoplastic nature of the nasopharyngeal tumours which remain confined to their site of origin. It has been argued that the plasma cell is commonly seen in chronic granulomatous conditions, and that an inflammatory etiology is likely. In this connection our Case 11 may be cited, because in this patient a granulomatous origin was considered seriously. This case closely resembles one reported by Blacklock and Macartney (1932) and we draw the same conclusion, namely that, in view of the uniform cellular pattern, the absence of organisms, and the failure to invade the surface epithelium, a neoplastic origin is the most likely (Fig. 20). This fact is further substantiated by rapid disappearance of the tumours after irradiation.

BIOCHEMICAL FEATURES

Bence-Jones proteinuria—Since the discovery by Bence-Jones in 1848 of an unusual substance of protein nature in the urine of patients suffering from multiple myelomatosis, considerable importance has been attached to its presence as a diagnostic feature of the disease. Bence-Jones protein is precipitated below 60° C. but disappears on boiling, only to reappear on cooling again to 50°–60° C. It may be separated from albumen, also present so frequently in the urine of myelomatosis cases, which starts to come down at 70° C. and flocculates at 80°–100° C. Care should be taken in testing for Bence-Jones proteinuria to use filtered urine, the pH of which has been made neutral or faintly acid.

While the presence of this protein substance in the urine is a strong indication of multiple myelomatosis, it must be remembered that Geschickter and Copeland (1928), surveying a large number of cases, found the test positive in only 65 per cent. Hellwig (1943) found 61·8 per cent. positive in a series of 259 cases which he reviewed. Moreover Bence-Jones proteinuria has been reported on rare occasions in other conditions, notably metastatic carcinoma in bones, multiple bone sarcoma, senile osteomalacia, fibrocystic disease of bone, chronic lymphatic and myelogenous leukaemia, and polycythaemia rubra vera (Bayrd and Heck 1947).

It has usually been stated that in solitary plasmocytoma of bone Bence-Jones protein does not appear in the urine, and this is true of the majority of cases. In our series, however, Case 8, a proved solitary tumour, gave positive tests for Bence-Jones protein on numerous occasions. It is our view that the presence of this substance in the urine may well be associated with the total bone marrow involvement by tumour. In Case 8 a very large mass was present. No record of Bence-Jones proteinuria has been made in cases of soft tissue tumours without bone involvement, a fact borne out in our series.

Abnormal serum protein—Ellinger (1899) first recorded abnormal protein, precipitated by heat at 56° C., in the serum of myelomatosis cases. Since then frequent reports are available of raised serum protein, in one example the figure being as high as 18·4 grammes per 100 c.c. (Atkinson 1937). It is generally considered that the protein appearing in the serum is of the same chemical composition as the Bence-Jones protein found in the urine, although in referring to our own cases, and those in the literature where tests for both substances were recorded, no correlation between blood protein and the presence or absence of Bence-Jones proteinuria can be made.

Blackman *et al.* (1944) have shown that the abnormal protein is a globulin, and they have thought it most likely to be a beta globulin. The positive flocculation tests in one of our cases (Case 7) suggest the possibility of a gamma globulin also playing some part in the make-up of the substance. Gutman *et al.* (1941) have shown that the globulin does not react in the usual way to the salting-out process used for estimating the albumen and globulin fractions in the total serum protein. Thus abnormally high albumen or globulin fractions may

be recorded, or on the other hand normal or even apparently reduced levels may be found. These findings have been borne out in our series.

Certain blood changes thought to be associated with the abnormal serum protein have been recorded. Stewart and Parkes-Weber (1938) noted failure of clot retraction, auto-haemagglutination, increased viscosity, accelerated erythrocyte sedimentation rate and spontaneous thrombosis.

Amyloidosis—The association of amyloidosis with multiple myelomatosis has frequently been noted. Magnus Levy (1931) reported the phenomenon, Atkinson (1937) collected forty cases from the literature, and Blomberg and Fischbach (1945) reported one other. Amyloid

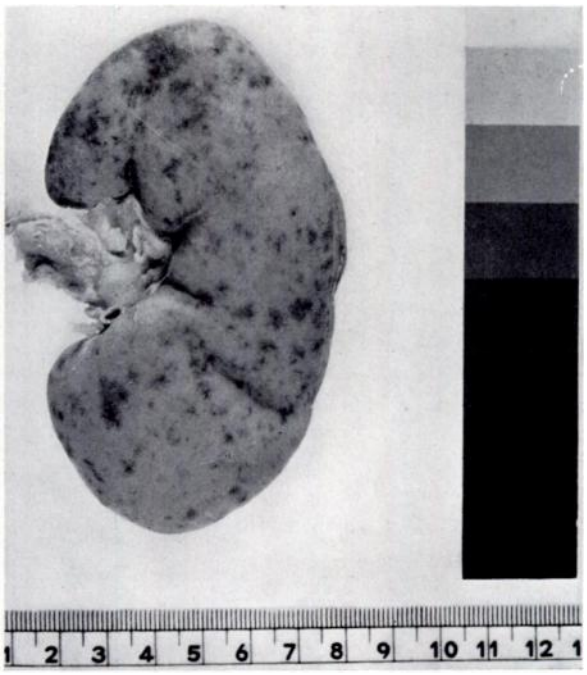

FIG. 25
Case 8. Kidney removed at autopsy showing surface pallor with haemorrhagic splashes.

substance is deposited through the body and has been noted particularly in the kidneys. It does not always give typical staining reactions, and has been considered as being produced by abnormal protein metabolism following myelomatous permeation of the marrow. We have no case associated with amyloidosis, but an example already fully reported by Stewart and Parkes-Weber (1938) was under the care of Sir Stanford Cade in the Westminster Hospital. In this case the amyloid deposits were found in particular around the joints.

KIDNEY CHANGES

Renal changes in multiple myelomatosis have been described (Lohlein 1921, Bell 1933, Forbus *et al.* 1935, Holman and Hill 1939, Morison 1941, and Newns and Edwards 1945). Bell studied eleven such cases. All authors describe tubular blockage as the principle lesion. Glomerular changes are minimal or absent, and the general appearances are similar to those found in the acute uraemia of crush anuria, mismatched transfusions, and sulphonamide poisoning. The substance blocking the tubules is thought to be Bence-Jones protein. Blackman *et al.* (1944) brought evidence to show that albuminuria does not damage the tubules

but that when beta globulin is present in the urinary filtrate, tubular blockage occurs. This condition leads to uraemia with considerable nitrogen retention as demonstrated by the blood urea and non-protein-nitrogen levels. It was found in our Case 8 where the kidney was

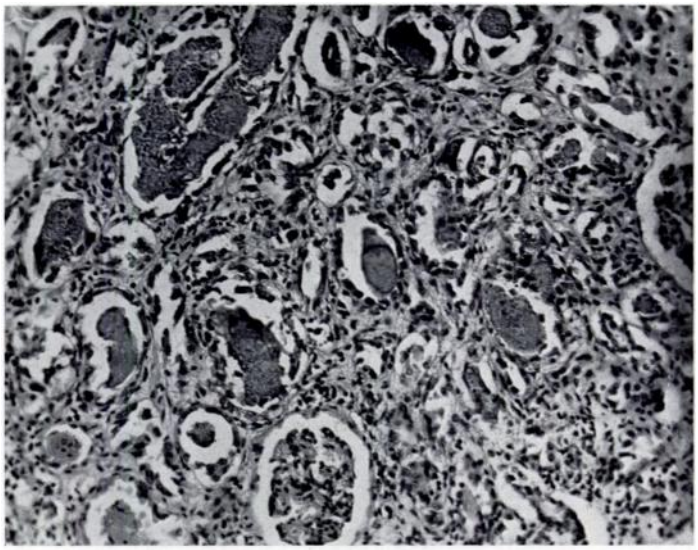

FIG. 26

Case 8. Photomicrograph to show plugging of kidney tubules. Magnification × 60.

pale and splashed with haemorrhages (Fig. 25) and microscopically showed the typical appearances described above (Fig. 26). One of us has already reported this case (Lumb, G., 1947) noting the unusual findings of renal blockage in a case of solitary tumour.

PERIPHERAL BLOOD CHANGES

Anaemia—There is often some degree of anaemia during the later stages of multiple myelomatosis, due to purely mechanical replacement of erythrogenic tissues by myeloma cells. In solitary bone tumours, and in soft tissue tumours without multiple bone involvement, there are no specific peripheral blood changes.

Plasma cells in the blood stream—The finding of plasma cells in the peripheral blood in cases of multiple myelomatosis is unusual but has been recorded, first by Aschoff (1905) and more recently by Patek and Castle (1936) who were able to find eleven cases in the literature while reporting one new case. Where plasma cells are a constant feature in the peripheral blood, in association with other signs of myelomatosis such as bone marrow invasions and Bence-Jones proteinuria, the term plasma cell leukaemia is used. Plasma cells may appear in the blood stream in such conditions as rubella, glandular fever, myeloid leukaemia, metastatic carcinoma, and Hodgkin's disease. Their appearance, however, is usually transitory and they are seldom found in large numbers.

The total leucocyte count in plasma cell leukaemia is seldom very high and 15,000 to 30,000 per cu.mm. is a common finding. Muller and McNaughton (1931) reported a case with a leucocyte count as high as 60,000 per cu.mm. The total number of plasma cells is also not very great, a percentage of five to twenty being the most common finding. So-called aleukaemic varieties with total leucocyte counts within normal limits have been recorded (Ghon and Roman 1913, Micheli 1904, Maresch 1909, and our Case 15). It is debatable whether or not the term leukaemia is justifiable in these conditions in view of the relatively

low total leucocyte count. However, the generalised nature of the disease, and its course, are similar to that seen in other leukaemias. This group of cases simply demonstrate one of the many varieties possible in an essentially multifocal disease, and the use of the term leukaemia is of value only as a reminder that generalised blood invasion can occur.

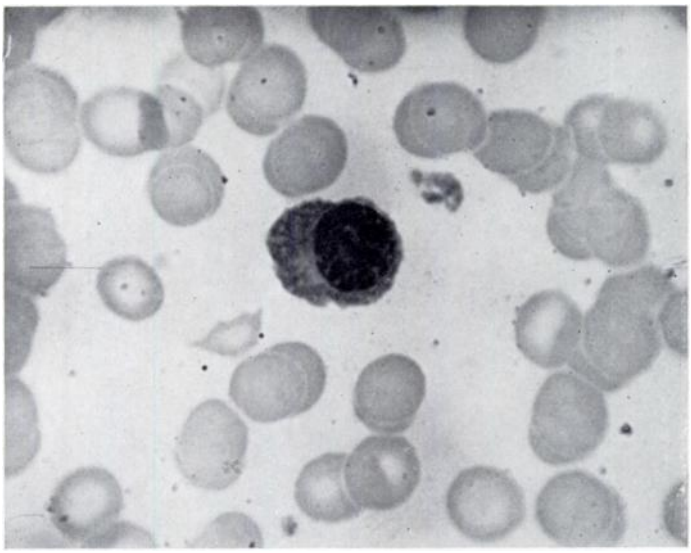

FIG. 27

Case 15. Photomicrograph of peripheral blood smear showing a typical plasma cell. Magnification ×800.

Plasma cell invasion of liver and spleen—In myelomatosis with peripheral blood involvement it is common to find plasma cell invasion of such organs as the liver and spleen. Lymph node infiltration is seen and in fact any organ may be involved. In our Case 14, liver and lymph node invasion was well demonstrated (Figs. 29 and 30) but although at autopsy the spleen was seen to be enlarged and congested, no true plasma cell invasion could be demonstrated microscopically. Spleen invasion was seen in Case 1 (Fig. 30).

TREATMENT AND PROGNOSIS

When it has become multiple, treatment of the disease can be only palliative, for a fatal termination is inevitable. The duration, when multiple invasion of bones has occurred, varies. Geschickter and Copeland (1928) quote two years as the average. In our series four patients (Cases 1, 2, 4, and 5) were dead within months, while Case 3 lived for three years. Case 6 is interesting in that four years elapsed before the bone tumours became multiple and she is still alive and in good general health five years after the onset of disease, and one year after the development of multiple tumours. Individually the tumours are very radio-sensitive, and irradiation with high voltage X-rays or radium provides the only useful form of therapy; 2500 to 3000r is delivered to each tumour treated over a period of three to four weeks. In order to avoid skin damage two or more ports are used, employing fractions of 150 to 200r at each treatment. After such a course of therapy, there may be radiographic evidence of regression of tumours with areas of recalcification. Treatment is particularly valuable when applied to the spine. The pain and discomfort of compression paraplegia may be obviated if treatment is given before vertebral collapse occurs, or alleviated if it is given later. The relief of pain is often very dramatic.

For solitary tumours some authors have claimed the merits of surgery, either alone, or followed by irradiation, as an alternative to irradiation alone. Thus Stewart and Taylor (1932) reported a case with a successful eight-year follow-up after forequarter amputation

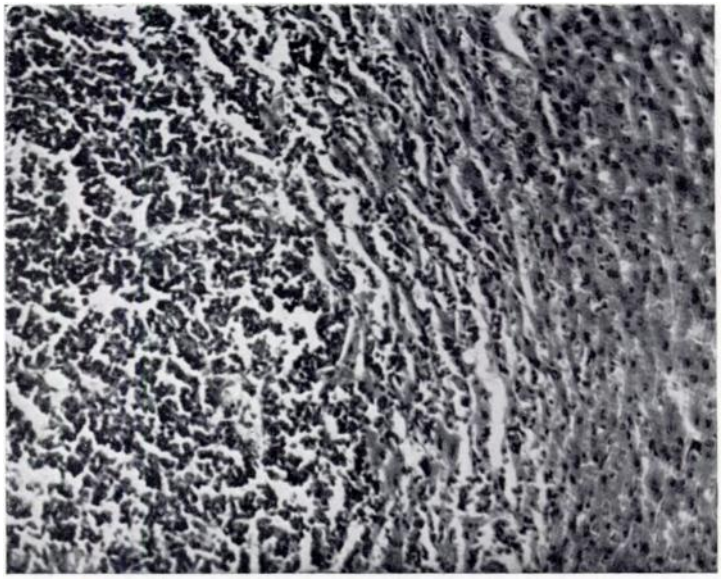

FIG. 28

Case 1. Photomicrograph showing nodule of plasma cells lying in the liver. Magnification ×60.

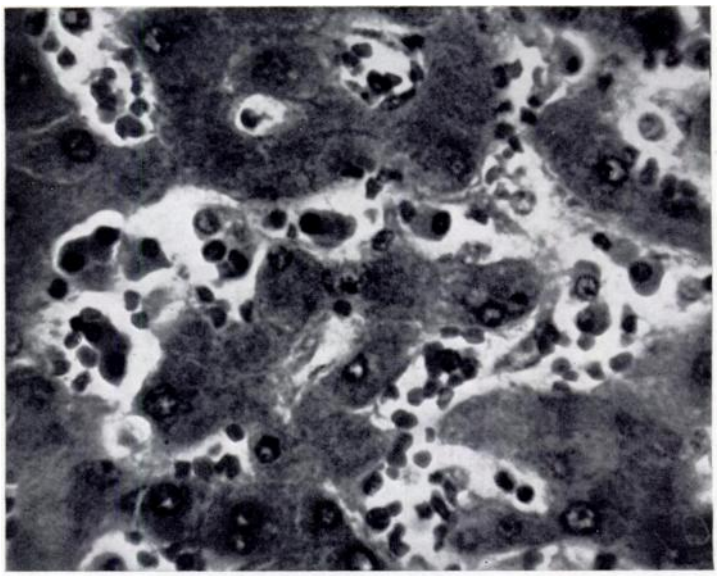

FIG. 29

Case 14. Photomicrograph showing plasma cells lying in the liver in sinusoids. Magnification ×160.

for a solitary plasmocytoma of the humerus. Shaw (1923) described a case alive and well after curettage and bone graft of the tibia. Rogers (1930) reported a case of plasmocytoma of the femur treated by curettage and radium insertion. The limb was later amputated because of sepsis, and the patient was alive and well three years later. We consider the

treatment of choice to be irradiation using high voltage X-rays through multiple ports, so that a dosage of 3500 to 4000r is delivered to the tumour over a period of four to six weeks. It may be added that the efficacy of any form of treatment for truly solitary bone tumours

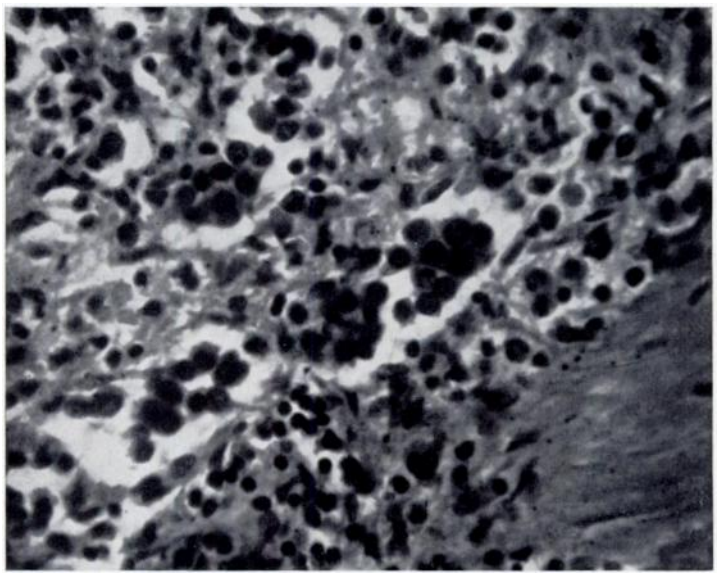

FIG. 30
Case 1. Photomicrograph of spleen showing plasma cells lying in sinusoids. Magnification ×160.

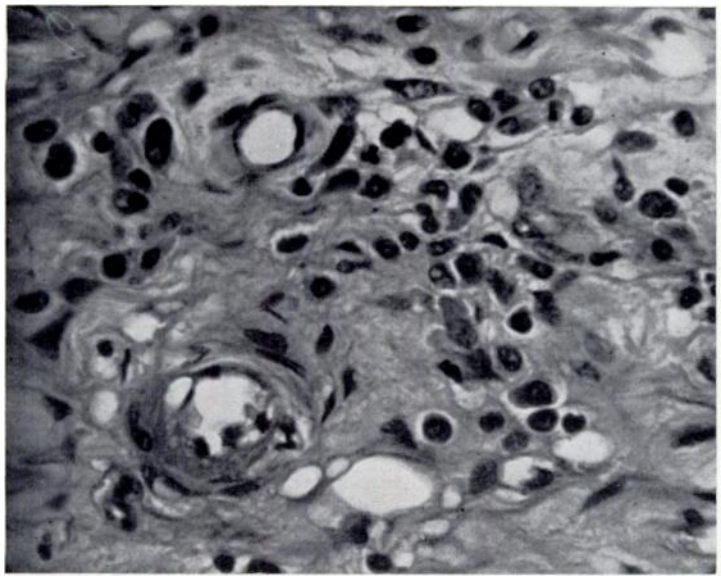

FIG. 31
Case 14. Photomicrograph of lymph node trabeculum showing plasma cells lying in sinusoids. Magnification ×160.

must be estimated in the light of the knowledge that most of these tumours seem to be essentially benign. Thus the case reported by Willis (1941), which was discovered only at autopsy, and for which no treatment had been instituted, showed a tumour of a cervical vertebra which probably had been present for at least twenty years. The hope, therefore,

in treating a solitary tumour is that later bone spread such as occurred in case 6 may be prevented, and other complications such as renal blockage (Case 8) may be averted. The general prognosis of solitary bone tumours is good, but the possibility of late onset of multiple tumours (case 6) can obviously affect the expectation of life very seriously.

In our opinion the treatment of choice for soft tissue tumours in the upper air passages excluding the larynx, is a combination of excision with irradiation, because the results of this technique are better than when either method is employed alone. Certain of these tumours, it should be stated, are extremely radiosensitive and success may be achieved with irradiation alone. In the case of tumours of the larynx irradiation without surgery, using teleradium, is to be recommended. A total tumour dose not exceeding 6000r is given over a period of five to six weeks. For cases treated by the combined method a small dose of not more than 3000r on the skin is given pre-operatively through multiple ports, either by high voltage X-rays or teleradium. Such a dose temporarily arrests growth and causes shrinking. The tumour remnants are then removed with a diathermy loop, and a post-operative course of irradiation with total dosage of 5000 to 6000r is given over a period of three to four weeks by teleradium. In cases where the antrum and ethmoid air cells are involved and removal is found necessary the cavity should be packed with gauze into the folds of which is placed up to 40 mgm. of radium in numerous foci; these are left in place for two to three days; at the end of two weeks further irradiation is given by intra-oral prosthesis carrying the radium foci. The ultimate prognosis of plasmocytomata in the upper air passages is good as compared with carcinoma or sarcoma. Treatment usually results in temporary arrest of disease although treatable local recurrences are common (Cases 10 and 12). Some show generalised spread to lymph nodes and bones with a fatal result. Case 13 is an example. Hellwig (1943) in reviewing sixty-three tumours from the upper air passages found nine invading lymph nodes and nine more invading bone.

RELATIONSHIP OF THE VARIOUS TYPES OF PLASMA CELL TUMOURS

We have now discussed the clinical types and manifestations of plasma cell tumours wherever they occur in the body. Hitherto, some authors have maintained that solitary and multiple plasma tumours of bone represent two separate entities, and Willis (1941) rightly maintained that too few proved solitary tumours have been studied adequately to make any dogmatic pronouncement. However, certain features in the cases of our series are significant. Thus Case 8 was a patient with a proved solitary bone tumour in whom death occurred as the result of a renal condition previously described only as a complication of multiple myelomatosis. In Case 6 a solitary tumour existed for four years, during which time many radiographic examinations of the skeleton were made, and then general spread occurred typical of multiple myelomatosis. With reference to the association of soft tissue and bone tumours, the following facts are of interest. Case 13 demonstrated spread from soft tissues to bone with an interval of two years between the appearance of the tumours. There are also many examples to be found in the literature, the most impressive in view of the long time-lag before bone involvement being Jackson *et al.* (1931), Piney and Riach (1931), and Ringertz ninth and fourteenth cases (1938) where intervals of eight and a half years, two and a half years, twelve years, and six years elapsed between the appearance of upper air passage tumours and the discovery of bone spread. Blacklock and Macartney (1932) also agreed that spread to bone can occur. In Case 13 of this series two years elapsed between the appearance of the soft tissue tumour and the paraplegia.

A final word may be said on the general spread which may occur during the terminal phase of all varieties of the disease. Any viscus in the body may be involved, but the liver, spleen, and lymph nodes are most frequently affected. In the liver and spleen, lesions consist of intra-sinusoidal collections of plasma cells, and in the lymph nodes plasma cells are found in the sinuses and inter-follicular tissue, the lymphoid structure remaining intact in all these organs (Cases 1 and 14). Lowenhaupt (1945) suggested that in view of these findings,

together with the bone marrow involvement, and the occasional leukaemic type of distribution, plasma cell tumours present a diffuse reticulo-endothelial proliferation.

The generalised nature and spread of the disease provides interesting data for speculation as to the nature of the cells involved in plasma cell tumours. Ewing (1928) said that " multiple myeloma is a specific malignant tumour arising probably from a single cell type." Wallgren (1920) expressed similar views. This hypothesis is attractive when one considers the similarity in cellular appearance between the majority of tumours (Christian 1907, and thirteen of our fifteen cases).

Other workers, whose conclusions are summarised by Ewing (1940), tend to favour multiple varieties arising from the various specific bone-marrow cells (*vide supra* Ewing 1940, page 327). Examples which seem to favour this theory are seen in Cases 4 and 14 of this series.

However, it is clear that no dogmatic statement can yet be made as to the exact origin of the cells in plasma cell tumours; whether from a single cell, either in the bone marrow, or diffusely in the reticulo-endothelial system which in our view is the more likely; or from different specific bone marrow cells, *i.e.*, lymphocyte, granulocyte, and erythrocyte precursors.

We believe that the disease should be regarded as of multifocal origin, as opposed to any theory of spread by metastasis as suggested by Cutler *et al.* (1936), and that it may exist in a wide variety of forms which should not be regarded as distinct diseases, but as gradations in extent and activity of the same disease process.

SUMMARY

1. Fifteen new cases of plasma cell tumour are reported with a review of the literature.

2. Case examples are quoted to show the gradual merging of the different clinical and pathological syndromes into one entity.

3. A comprehensive analysis of the various manifestations of the disease is made.

4. An attempt is made to correlate the widely differing features of the disease-process and a classification is given.

5. It is considered that metastasis plays no part in this condition.

6. The variety of forms of plasma cell tumours are shown as gradations of an essentially similar disease-process, and are not regarded as separate conditions.

Our thanks are due to the members of the Honorary Staff of the Westminster Hospital (London) for their permission to make use of case records; to Professor N. F. Maclagan for biochemical reports; to Dr J. G. Humble for haematological reports; to Dr Peter Hansell of the hospital photographic department; to Messrs Ilford & Co. for Fig. 16; to Dr Greenblatt of Cape Town, South Africa, for his follow-up report on Case 13; and to Dr Simpson Hall of the Edinburgh Royal Infirmary for the follow-up report on Case 10. More especially our grateful thanks are due to Sir Stanford Cade and Professor R. J. V. Pulvertaft without whose constant help and advice this paper would not have been possible. We wish to acknowledge that part of this work has been carried out with the assistance of a grant from the British Empire Cancer Campaign to the Westminster Hospital.

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