

## A CASE OF MULTIPLE MYELOMA.

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Multiple myeloma may be defined as a primary neoplasm of the bone marrow, affecting chiefly the sternum, the ribs, the vertebræ, and the skull; the substance of the bone being more or less extensively replaced by the tumor tissue. The neoplasm may invade the neighboring soft parts by continuity of growth, but it probably never forms metastases, as do the common malignant tumors. The disease usually occurs in men in the latter half of life. Probably it has been confounded with osteomalacia in some cases.

The affection was first recognized and described as a definite pathological condition in 1873 by J. von Rustizky,<sup>1</sup> who gave it the name of multiple myeloma. Since that time at least seventeen cases of multiple primary bone tumors, presenting the essential characteristics of multiple myeloma, have been reported. To this number should be added two previous cases, one reported by Bence-Jones<sup>2</sup> and Macintyre,<sup>3</sup> and one by Weber.<sup>4</sup>

From the great similarity of the lesions in these cases it might be expected that the histological characters of the neoplasms would be the same in all the cases. This, however, is not so. A great diversity exists in the results of the histological examinations of the cases in which such examinations have been made. The neoplasm has been called lympho-sarcoma, myelogenous pseudo-leukæmia, lymphadenoma, hyperplasia of the marrow, vascular endothelioma, and different types of sarcoma. Nearly all of the descriptions of the finer details of the cells are inadequate and unsatisfactory, so that it is impossible to determine whether any two of the cases are identical or not in their histological characteristics. In at least eight of the cases, however, the tumors were made

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<sup>1</sup> *Deutsch. Zeitschrift f. Chirurg.*, 1873, Bd. 3, S. 162.

<sup>2</sup> *Philos. Trans. Royal Society*, 1848.

<sup>3</sup> *Med.-Chir. Trans.*, 1850.

<sup>4</sup> *Trans. Pathol. Soc., London*, 1867.

up essentially of cells which were variously described as small round cells, or as lymphoid cells, or as cells like marrow cells, or as cells of round-cell sarcoma, or as round or polygonal cells, 1-2000 of an inch in diameter. The neoplasm in all these cases was probably one and the same in microscopical structure, and it is to this group that the case here reported probably belongs.

An interesting feature of the present case was that the urine contained albumose. The association of albumosuria with multiple myeloma and osteomalacia has been observed in a number of cases since Bence-Jones<sup>1</sup> discovered this substance in the urine of his case. The clinical importance of this fact has been emphasized by Dr. R. H. Fitz<sup>2</sup> in a paper in which the present case is referred to, and also by Drs. Bradshaw and Warrington in a recent paper.<sup>3</sup>

The case here reported was under the care of Dr. R. H. Fitz, who made the diagnosis of multiple myeloma from the presence of a tumor of the sternum, lesions in the ribs, and from the albumosuria. The Röntgen rays proved of great service in recognizing the existence of lesions in the ribs.

The patient, a man 54 years of age, entered the Massachusetts General Hospital Feb. 24, 1898. About a year before entrance he had noticed for the first time a small tumor at about the level of the nipples. This had grown steadily in size. At times, especially at night, he had had pain in the axilla. This pain seemed to the patient to be connected with the tumor.

About four years previously he had noticed that at times he walked like a drunken man. Later he had to use a cane in order to walk. His feet felt numb, but the sense of touch and the muscular sense were retained. There never had been pains in the legs and never spells of severe vomiting. For some time he had had double vision, loss of sexual power, and some incontinence of urine. He gave a fairly good history of syphilis.

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<sup>1</sup> *Loc. cit.*

<sup>2</sup> *Trans. Assoc. Amer. Physicians, 1898. Amer. Journ. Med. Sciences, July, 1898.*

<sup>3</sup> *Trans. Royal Med. and Chir. Society, 1899.*

At the time of admission, or shortly afterward, the following facts were noted: Pupils equal and react to light and accommodation. Slight strabismus of the right eye. In the sternal region at about the level of the nipples a rounded tumor, about four and one-half inches in greatest diameter, elevating the skin. This tumor has a smooth surface, is rather soft, and is slightly pulsating. In the left back near the middle of the vertebral column a small area of dulness about the size of the palm of the hand. In connection with the ribs at the back there are several tumor nodules.

Examination with the Röntgen rays showed changes in the fifth, sixth, seventh, eighth, eleventh, and twelfth ribs posteriorly on the left side, and in the seventh and eighth ribs on the right side between the angle of the scapula and the spine. The knee jerks exaggerated. Pronounced ankle clonus. No disturbance of sensibility. No atrophy. Good muscular power.

Shoes worn at the toes and the outer side of the median line. No increase in the arm reflexes. No fever.

Urine examination: Albumose in abundance. Slight trace of serum albumen. Pus as sediment. Urea, 0.76 per cent.

Blood examination: Hæmoglobin, 60 per cent. Whites, 5,000. Reds, 4,700,000.

During the next four months the condition of the patient remained practically stationary. The tumors of the ribs increased somewhat in size, but the tumor of the sternum did not. In the head, at the junction of the sagittal suture with the lambdoidal suture, a soft tumor the size of a filbert appeared. The urine continued to contain albumose, the analysis by Dr. Edward S. Wood, in March, showing 0.33 and 0.34 grammes in 100 ccm. of urine. In the same quantity of urine there was also 0.03 gramme of serum albumen.

After about four months the patient began to grow rapidly weak and to suffer much pain. Finally he became unconscious and died July 26, 1898.

The autopsy was performed twenty-two hours after death. An abstract of the autopsy records of the pathological laboratory is as follows:

The sternum in its inferior and median portions is much increased in thickness, bulging externally to form a flattened, somewhat fluctuant tumor, about 9 cm. in diameter, beneath the soft tissues, and also bulging internally to form a lobulated tumor mass. A longitudinal section through the sternum shows the bony tissue, except at the extremities of the bone, almost entirely replaced by a tissue which is partly soft, mushy, grayish red to dark red in color, and partly moderately firm, whitish, and semi-translucent. In the superior mediastinum, and loosely attached to the sternum, are two or three soft tumors, the largest the size of a chestnut.

The sixth and eleventh ribs on the left side lose their continuity near the spinal column in a soft, mushy, red tissue, somewhat resembling red marrow. This tissue forms tumor masses beneath the pleura at these points, the largest being about the size of a hen's egg. The tenth rib on the right side and the eleventh rib on the left side present comminuted fractures. There are also callus-like thickenings on the seventh and eighth ribs on the left side, and on the fourth, seventh, and eighth ribs on the right side. The ribs in general seem more friable than normal.

The bodies of several of the dorsal vertebræ are found to contain larger and smaller soft, red masses of material like red marrow, filling cavities in the spongy bone. These masses are chestnut-sized in two or three instances.

In the approximate situation of the spinous processes and laminae of the seventh and eleventh dorsal vertebræ are two masses of soft, mushy, grayish red material, each less than a pigeon's egg in size. These have replaced the bony structure. The spinal cord is not pressed upon by these masses, and in hardened sections showed no definite lesions. The *dura mater* is more adherent than normal to the *pia mater* of the cord. The latter membrane, chiefly in the dorsal region, is thickened, and opaque whitish in color.

The marrow of the shaft of the right femur is yellow and oily.

In the occipital bone there is a circular defect about 3 cm. in diameter, filled with a soft grayish to dark red tissue, and

having a worm-eaten margin. In the frontal bone there is a similar defect filled with a similar red tissue.

Other conditions observed were: broncho-pneumonia and acute pleuritis of the inferior lobe of the right lung; œdema of lungs; senile degeneration of the kidneys; chronic interstitial orchitis.

#### *Histological Examination.*

Most of the material taken for histological purposes was hardened in Zenker's fluid. The remainder was hardened in Flemming's solution. Sections were cut in paraffin and in celloidin.

In preparing sections sufficiently thin for photographing at high magnifications the new Minot-Blake microtome<sup>1</sup> was used with great advantage. The sections were stained in various ways, eosin and Unna's alkaline methylene blue solution, and fuchsin, either alone or in combination with aurantia, being found most useful.

The neoplasms in the sternum, ribs, vertebræ, and skull consist of one and the same tissue. This tissue is chiefly made up of small cells closely crowded together. Interspersed among these cells are rather numerous thin-walled blood-vessels, usually about the size of an ordinary capillary or a little larger. (Pl. XVII., Figs. 4 and 5.) A few delicate fibrillæ are also present among the cells, but these are difficult to see, so that the tissue at the first glance seems to have no supporting framework for its cells except the thin-walled blood-vessels. These fibrillæ are best seen in sections hardened in Flemming's solution, where they appear as delicate strands of irregular course. (Pl. XVII., Fig. 5.)

The cells of the tissue are, as a rule, circular in outline, and are somewhat variable in size. Most of the cells measure six to eight micra in diameter in the hardened section. They seem to have no cell membrane.

The nuclei are round or slightly oval in outline, and have a well marked nuclear membrane. They vary somewhat in diameter, which is usually about one-half or two-thirds that

<sup>1</sup> Francis Blake. A New Microtome. Journ. Boston Soc. Med. Sci., April, 1899.

of the cell. They are often situated eccentrically in the cell. A few are considerably larger than the average.

A striking characteristic of the nuclei is the presence of a variable number of intensely staining chromatin masses, of round or oval outline, continuous with the nuclear membrane and projecting from it into the interior of the nucleus. There is also a well-marked round globule of chromatin in the centre of the nucleus. This, in specimens stained with Unna's alkaline methylene blue solution and eosin, may be sometimes observed to have a distinctly red color, if the blue staining be rather weak, while the nuclear membrane and the globules connected with it are stained blue.

A few cells have two nuclei and a very few three nuclei.

Karyomitosis is not seen in any of the cells, but a very few cells are seen having elongated, or hour-glass shaped, or dumb-bell shaped nuclei; and also cells having two nuclei connected together by a thin band or filament of chromatin, as well as cells having two nuclei, as above described. In view of the absence of nuclear figures these appearances suggest the idea that these cells multiplied by direct cell division. They might, however, be interpreted as the result of degenerative change.

The cytoplasm of the cells is homogeneous, and in some of the sections, after staining with eosin and Unna's alkaline solution of methylene blue, it takes the bluish stain, while in others it takes a purplish tint, or it may be stained with the eosin alone, depending, apparently, on the relative intensity of the staining with the two dyes.

In many of the cells the cytoplasm at the central portion does not stain as deeply as the peripheral portion, so that it appears distinctly paler.

The tumor cells are very different from the majority of the cells of the red marrow. This is shown in Plate XVIII., Figs. 6 and 7.

From the foregoing description, and from the photographs, it should be clear that these cells are, at least, closely related to the so-called "plasma cells" of Unna. Most of these cells have all the appearances of "plasma cells," except that

the cytoplasm does not in all cases show a marked affinity for methylene blue as does the typical "plasma cell." In the opinion of the writer these cells are essentially "plasma cells," or immediate descendants of them, and their deviations from the type of the parent cell are quite analogous to those seen in the cells of other neoplasms.

Most of the blood-vessels of the tissue are made up of endothelial cells only (Pl. XVII., Fig. 5), but occasionally a few fibres of connective tissue may be seen just outside the endothelium. The majority of these vessels are like ordinary capillaries in size; some of them, however, are larger and of variable diameter, but none of them have any muscular tissue in their walls, which at the most have only a little connective tissue outside the endothelium.

In some sections red blood corpuscles in considerable numbers are present among the cells of the tissue. This is regarded either as the result of hæmorrhage or as an artefact produced in removing the tissue from the body.

No necrosis of the cells is to be seen, nor any fatty degeneration.

As above stated, various ribs presented small thickenings and signs of fracture. Sections through five ribs at about the seat of these lesions were studied. All of these show more or less extensive replacement of the red marrow and of the bony trabeculæ of the *spongiosa*, as well as of the cortical bone, in places, by a tissue such as is described above. In one section this tissue has totally replaced the substance of the rib at that point, and has extended beyond its original limits, elevating the periosteum and the pleural tissue, thus forming one of the tumors noted in the continuity of the rib.

Another section shows a mass of the tumor tissue in the *spongiosa* in process of growing through the cortical bone. (Pl. XVI., Fig. 1.) In various places in the *spongiosa* of the ribs, larger and smaller aggregations, or nodules, of tumor cells are present. They are not sharply defined from the surrounding marrow, but merge into it. (Pl. XVI., Fig. 1.) Some of these are microscopic in size.

In thin sections of one of these ribs are seen cells identical with those of the tumors, scattered here and there singly and in groups through the marrow spaces and among the marrow cells.

The cortical bone is absent in many places, or it is represented by strips and islands of a granular, shrunken, abnormally staining bone. In only a few instances were osteoclasts seen associated with this evidently degenerate bone. In two of the sections some of the degenerate bone presents appearances clearly indicative of a new formation of bone at the margin.

One section showed a partly or completely healed fracture with formation of callus.

Sections of the bodies of several vertebræ show that these are more extensively infiltrated with the neoplasm than was apparent at the autopsy. In addition to a few tumor nodules, varying in diameter from a few millimeters to one centimeter or more, many smaller nodules are found scattered through the marrow. One of these is shown in Plate XVI., Fig. 2. They vary in size from one millimeter in diameter down to microscopic groups of cells. The nodules are not definitely separated from the surrounding marrow, but the tumor cells at the margin infiltrate the spaces between the fat cells and take the place of the marrow cells. (Pl. XVI., Fig. 3; Pl. XVIII., Fig. 6.) In thin paraffin sections cells like the tumor cells are found distributed here and there among the marrow cells. Plate XVIII., Fig. 7, illustrates this. The tumor cells are here rather more numerous than usual.

From a study of the sections it seems clear that the tumor nodules have arisen by the aggregation of the tumor cells in the spaces between the fat cells, which spaces normally contain the vessels, marrow cells, and blood; then, by the further multiplication of the tumor cells, the fat cells and other cells and elements of the spongy bone are obliterated.

The occurrence of cells identical with the cells of the tumor scattered singly and in groups among the marrow cells, and the great likeness of these cells to "plasma cells,"



as above stated, suggests the idea that these cells, or "plasma cells," may be one of the varieties of the cells of the normal marrow. In order to test this idea specimens of presumably normal spongy bone of the sternum and vertebræ were examined in paraffin sections. As a result it was found that the red marrow does contain cells which are like those of this tumor, and apparently true "plasma cells," but they are present in smaller number than the similar or identical cells seen in the red marrow in this case. They are found singly, or several in the field of an oil immersion lens. As a rule, they have to be sought for. In Plate XVIII., Fig. 8, is shown a "plasma cell" in a section of normal red marrow. The general appearances of the cells of the marrow are shown, as also their differences from the "plasma cell" and from the tumor cells.

#### CONCLUSIONS.

This case is one of multiple tumor formation, primary in the red bone marrow, and widely distributed through the same.

The cells making up the bulk of the tumors are very like or identical with "plasma cells," which cells are a normal constituent of the red marrow. It therefore seems reasonable to think that the neoplasm, exclusive of its vessels and insignificant stroma, has arisen from an abnormal proliferation of these cells.

Under this view, this case of multiple myeloma is to be regarded as a neoplasm originating, not in the red-marrow cells collectively, but in only one of the varieties of the cells of the red marrow, *i.e.*, in the "plasma cells."

## DESCRIPTION OF THE PLATES.

## PLATE XVI.

- Fig. 1. — Section through the cortex and part of the spongiosa of a rib. The cortical bone is seen invaded by the growth. In two or three places in the spongiosa, the marrow tissue is replaced by areas of tumor tissue.
- Fig. 2. — Section of the spongiosa of a vertebral body. In the centre of the figure a small tumor nodule.

## PLATE XVII.

- Fig. 3. — Section through a small portion of the body of a vertebra. A portion of a small tumor nodule and the adjacent marrow tissue is shown.
- Fig. 4. — Section of a portion of a small tumor in the body of a vertebra. The character of the cells and the general appearances of the tumor tissue are shown. X 1000.
- Fig. 5. — Section through a part of the tumor of the sternum. Magnification 1500, approximately.

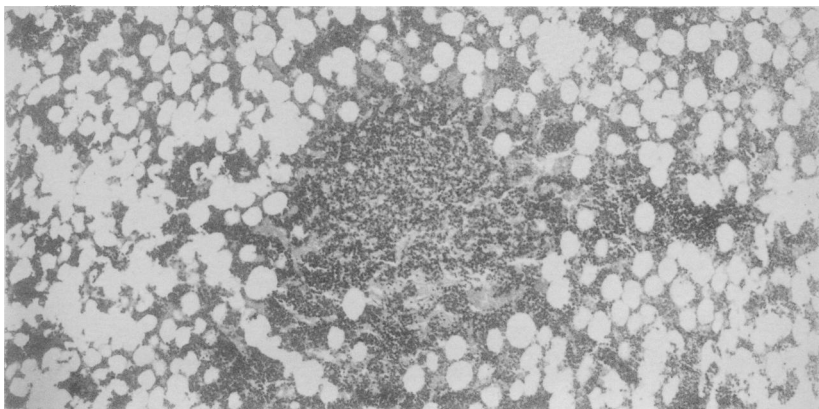
## PLATE XVIII.

- Fig. 6. — From a section of the spongiosa of a vertebral body. An aggregation of tumor cells is seen in the left of the figure. On the right are seen the usual marrow cells between the fat cells. X 1000.
- Fig. 7. — Section of spongiosa of vertebral body, showing tumor cells scattered among the marrow cells. X 1000.
- Fig. 8. — Section of normal spongy bone containing normal red marrow. To the left of the centre of the figure is a "plasma cell." The general appearances of the marrow cells are shown. X 1000.

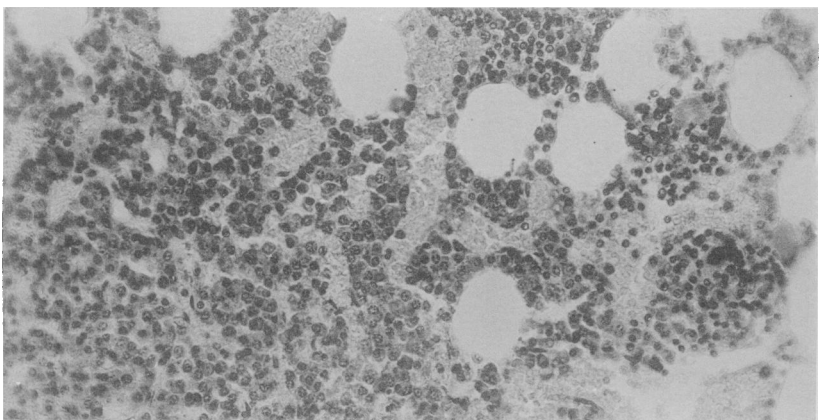
The photographs were prepared with the assistance of Mr. L. S. Brown, in the laboratory of the Massachusetts General Hospital.



*Fig.1.*

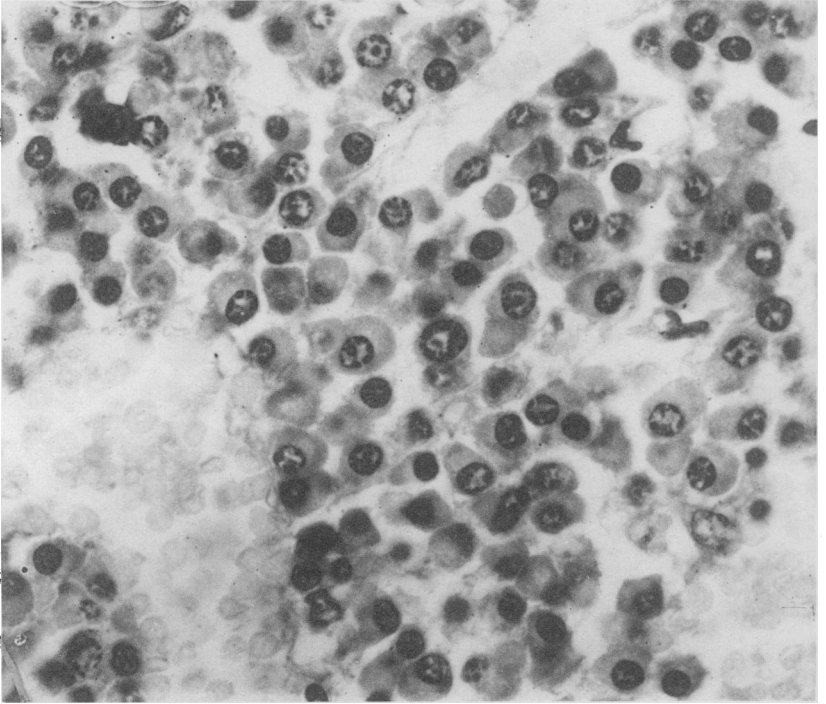


*Fig.2.*

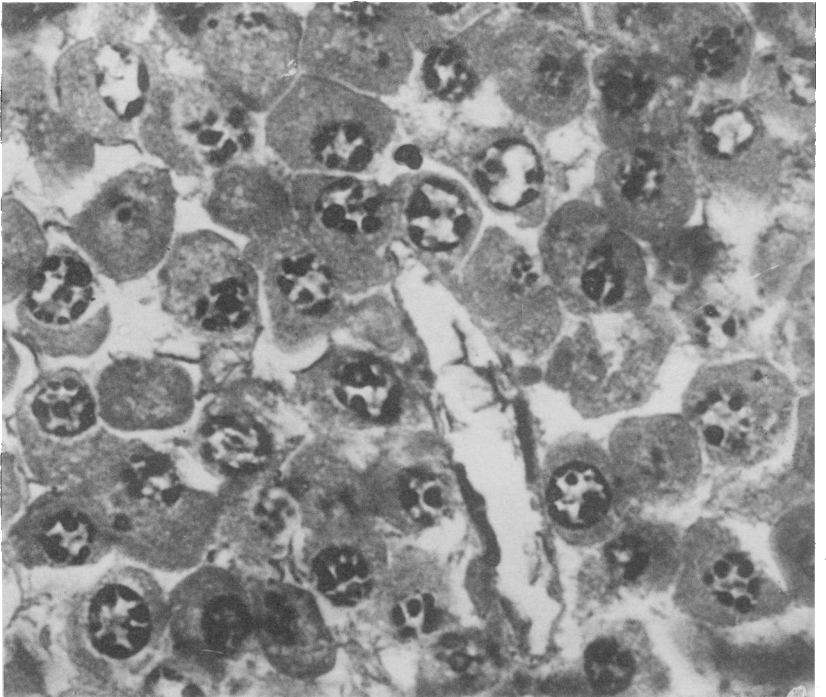


Heliotype Co., Boston.

*Fig.3.*



*Fig.4.*

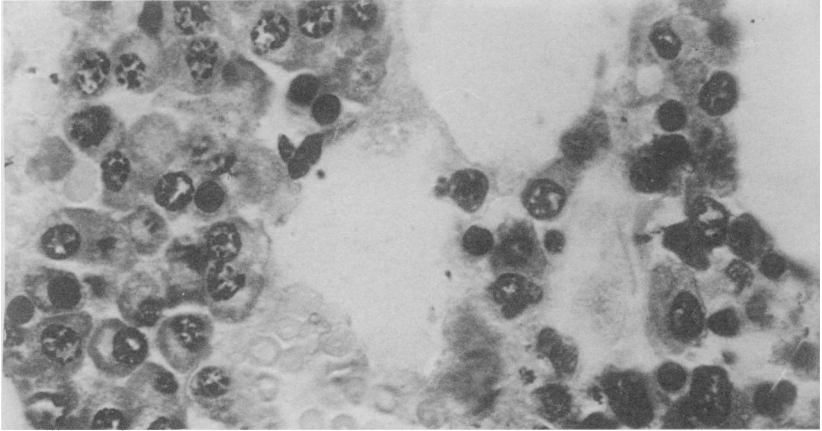


*Fig.5.*

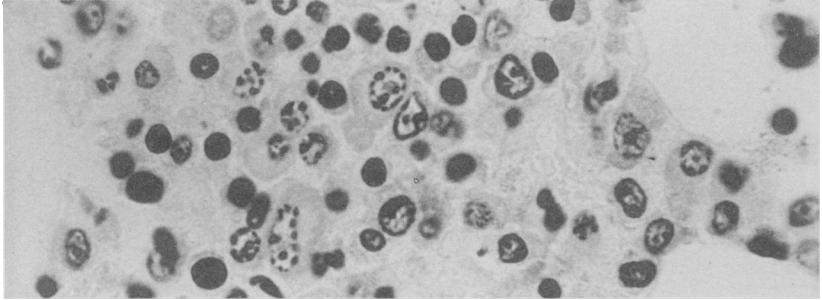
Heliotype Co., Boston.

J.H.Wright.

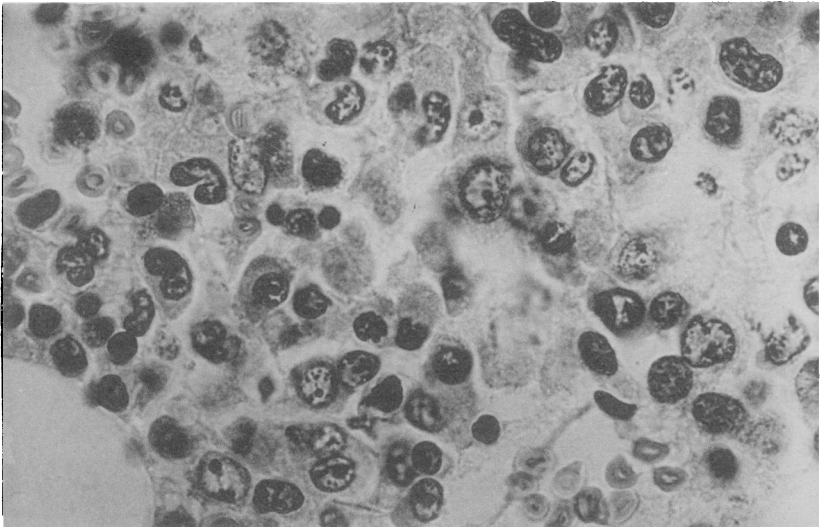
Multiple Myeloma.



*Fig. 6.*



*Fig. 7.*



*Fig. 8.*

Helixtype Co., Boston