onwards into the ventricles; and if there be mitral stenosis, there can be no genuine auriculo-systolic murmur during the last phase of ventricular diastole. In such instances the only obstructive murmur of mitral origin will be an early diastolic murmur.

REFERENCES.—1 Cowan and Ritchie, Quart. Journ. Med., 1910-11, iv. 55. 2 Wardrop Griffith, Heart, 1911-12, ii. 143. 3 Brockbank, Brit. Med. Journ., 1909, ii. 509; Quart. Journ. Med., 1909-10, iii. 345. 4 Pozzi, Policlinico, 1910, xvii. M. 445. 5 Hart, New York Med. Record, 1911, lxxx. 2. 6 Gill, Austral. Med. Gaz., 1911, xxx. 1. 7 Gairdner, Edin. Hosp. Rep., 1893, i. 221. 8 Mackenzie, Quart. Journ. Med., 1907-8, i. 39. 9 Gibson, Life of Sir William Tennent Gairdner, Glasgow, 1912, 683. 10 Wardrop Griffith and Cohn, Quart. Journ. Med., 1909-10, iii. 126. 11 Wenckebach, Deutsch. Arch. f. klin. Med., 1910, ci. 402.

MULTIPLE MYELOMA.

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II.

Before proceeding further it may be of advantage to describe three cases which recently came under my notice, and which possessed characters which seemed to justify their inclusion within the group of multiple myelomata.

CASE I.—For the clinical notes of the first case I am indebted to Dr. Lovell Gulland, Edinburgh.

W. M′K., a male, 57 years of age, was admitted to the Chalmers Hospital, Edinburgh, towards the end of July 1912. He had been ill and unable to work for several months, complaining of pain in the back, shooting down the backs of both thighs, and of weakness of the lower limbs. He had been under treatment for lumbago and Bright’s disease.

On admission he was somewhat emaciated, and stated that he had lost some weight. He was able to walk only with difficulty, and was unable to move about in bed with any freedom. He was able, however, to sit up in bed, to lean forwards, and touch his toes with the arms extended. He had no marked rigidity of the spine, and no tenderness over the spine or along the lines of the sciatic nerves. Examination of the chest and abdomen was negative. Examination of the nervous system showed only exaggeration of the knee-jerks; ankle-clonus, and weakness of the leg moseles; no Babinski; no sensory changes; no optic neuritis. The urine contained a very large amount of albumin, and some Bence Jones’ albumose, but no blood. The blood showed nothing abnormal; the colour index was not low. X-ray photographs of the back demonstrated the presence of disease of the bodies of several of the lower vertebrae.
He remained in hospital for about a month. One evening he developed acute dyspnoea, and the left side of the chest was found to be dull almost to the apex. A large quantity of fluid was aspirated. The centrifugate contained a few red blood corpuscles, but no other cells.

He was transferred to the Longmore Hospital for Incurables, the diagnosis being malignant disease of the lumbar vertebrae—presumably myeloid sarcoma—with secondary deposit in the pleura.

He died on 18th October, and next day a post-mortem examination was conducted by Dr. Harvey Pirie, from whose notes the following extracts are made:

Emaciation extreme. Nodules of hemorrhagic new growth in the ribs of the right side, in right clavicle, and to a lesser extent in the ribs of the left side. Adhesions throughout right pleural cavity; fluid in left pleura. Red fleshy growths infiltrating adhesions on right side. Lungs, no important alteration. Liver shows one or two small nodules, white with hemorrhagic mottlings. Kidneys, subacute parenchymatous nephritis. Spleen large and soft. Spine, a large projection at level of three lowest dorsal vertebral bodies, and others of smaller size on right side of 3rd to 6th dorsal bodies. Bodies of all vertebrae, from 1st sacral to 7th cervical, infiltrated with new growth, and easily divided with the knife. On section several of the vertebral bodies contain rounded brownish-red, soft, circumscribed masses of almost homogeneous appearance, varying in size up to nearly an inch in diameter. Within these areas the spongy bone has completely disappeared. Where some of these impinge upon the cortical layer of bone this has disappeared, and rounded projections of the new growth appear on the surface. There is also diffuse infiltration in all the bodies, with a varying degree of osteoporosis.

From the naked-eye appearances a diagnosis was made of multiple sarcoma of the vertebrae, probably starting in the lower dorsal region.

Histological Examination.—Portions of the new growths were fixed in Pick’s fluid and in corrosive sublimate, and paraffin sections were stained with haemalum and eosin, iron haematoxylin and picric-fuchsin, thionin blue, Löffler’s methylene blue, Borrel’s ripened methylene blue, alcoholic eosin and methylene blue, Ehrlich’s triacid stain, and by Schridde’s azur-eosin-acetone method for demonstration of granules, Leishman’s stain, etc. The appearances, especially of the nuclei, vary slightly with the staining method employed.

In some of the masses the nucleated cells are separated up by numerous diffusely scattered red blood corpuscles, but in others the hemorrhages are not so evident. The nucleated cells practically all belong to one type of cell. This is a rounded cell—or polygonal from mutual compression—on an average about twice the diameter of a
red blood corpuscle, the size of individual cells varying from a little larger than the red blood corpuscle to nearly three times that size. The nucleus, rounded or slightly oval, is eccentric in the majority of instances. With the hematein stains the chromatin seems at first sight to be almost homogeneous, but on careful decolorisation, and if a high magnification be used, it is seen to be made up of minute clumps arranged as a rule somewhat irregularly. In many cells it forms a ring against the nuclear membrane, with several largish granules within the nucleus. Many nuclei show evidence of degenerative changes. When stained with Borrel's blue the chromatin in many of the nuclei shows an arrangement somewhat like that characterising the "plasma cell." The chromatin network is closer in the smaller (younger?) cells than in the larger (older?). Some of the larger cells contain two and three rounded nuclei. The cytoplasm is plentiful as a rule, is basophilic with methylene blue, and frequently condensed at the periphery of the cell. Occasionally small vacuoles are to be made out; there is no distinct cell wall. Large giant cells with the characters of myeloplaxes are to be seen in small numbers, and also a few eosinophil cells; no undoubted nucleated reds. The interstitial fibrous tissue is very scanty, and thin-walled blood-vessels are present in considerable numbers. These contain a few cells corresponding in appearance to the predominant cells of the new-growth.

The nodules in the liver are composed of apparently similar cells.

Hence the appearance of the cells predominating in the new growths, when stained with Borrel's blue and other basic aniline dyes, corresponds to that of the bone-marrow plasma cell of Wright, Christian, and others. But with other staining methods the cells resemble very closely the myeloblasts and myelocytes, especially the former, of the surrounding bone marrow. It is evident that the pathological myeloblast cannot be clearly differentiated from the bone-marrow plasma cell, and to my mind it is an open question whether they are in reality different cells. This case might, in consequence, be placed either with the plasmacytic or with the myeloblastic myeloma, the decision depending to a great extent upon the methods employed in preparing the microscopic sections.

Case II.—The second case occurred in the practice of Dr. Ewing of East Ardsley, Wakefield, whom I have to thank for the excellent notes of the course of the illness, and for the description of the post-mortem examination, in which he was assisted by Drs. Watson and Stewart.

The patient, a man, 51 years of age, had been known to Dr. Ewing
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for some 12 or 13 years as a perfectly healthy man. There was no history of old syphilitic infection, and there was no evidence leading one to suspect it.

On 21st February 1911, when at work in a rather cramped position, engaged in screwing up a nut on a locomotive engine with the aid of a large spanner, he slipped and violently strained the lower part of his spine. Severe and immediate pain was experienced, which was put down to rupture of some part of the erector spinae muscle. The pain was intense in the right lower costal region, close to the spine, and it continued of this severe character up to the middle of April. Owing to the occurrence of slight rises of temperature it was thought that rheumatism might be complicating the condition, but the ordinary remedies afforded no relief. Large quantities of morphia were administered by his medical attendant, with only temporary relief. On 18th April he was examined for malignant disease on account of hemorrhage from the bowel, with continuous pain, general over all the bones, varying in degree, accompanied by some wasting and marked depression, but nothing definite could be determined. Towards the end of the month a little improvement set in, and he was enabled to go out of doors. Soon the pains returned—1st May—and marked wasting set in, with occasional rigors. Malignant disease of the spine or right kidney was suspected. During May, June, and July 1911 the pain was continuous and intense. Some evidence of tuberculosis was found at the right apex. On 11th August the spine in the dorsal region became tender, and the spinous processes prominent. The patient was thence forwards confined to bed. During the remaining months of 1911 the pain continued very severe in the region first attacked, and also all along the spine, with enlargement and marked deformity of the upper dorsal and cervical vertebrae. Spinal caries was suspected. The left hip-joint became enlarged and tender. He was now thought to be suffering from generalised tuberculosis. In January 1912 deformity of the left hip was noticed. This was shown at the post-mortem examination to have been due to spontaneous fracture. From February to November 1912 he suffered from severe pain in the head, neck, back, and in the upper and lower extremities; he was profoundly emaciated; almost all the joints were stiff and swollen. Death took place on 3rd November.

During life the urine was examined repeatedly. It was always transparent. It contained no albumin at any time; it was not tested for albumose.

A post-mortem examination was conducted on 5th November. The brain and the abdominal organs were found to be normal, and there were no evident changes in the cranial bones. Thorax—the thoracic cage was markedly distorted. There was marked pericarditis, old

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pleuritic adhesions, slight evidence of tuberculosis at both apices, but no secondary nodules in the lungs or in any of the organs.

There was marked deformity, with shortening of the thigh to the extent of 2½ to 3 inches. This had been caused by a partly united fracture at the upper end of the femur, about the level of the lesser trochanter. The head and neighbouring part of the shaft were diseased internally. There was lateral curvature of the lower dorsal spine, curvature forwards of the cervical and upper dorsal spine. The bodies of the vertebrae were diseased, the spongy bone being replaced by reddish-brown, soft, sarcomatous-looking masses. Similar changes were found in the ribs and sternum, but there were no prominences on the exterior of any of these bones, and no localised swellings of the ribs. The kidneys were apparently healthy. Dr. Stewart examined the new growth microscopically, and reported it to be a multiple myeloma.

Dr. Ewing adds the following remarks with regard to the causal relationship of the injury sustained to the disease:

"That C. met with an accident which injured some of the structures of the spinal column I think there is not any doubt. His story of the accident was perfectly consistent with the condition found when he was examined first. The persistent localised pain was a marked feature in the course of his disease, and must of necessity have originated on the night of 21st February 1911, as proved by his total helplessness from that moment. His general health to all intents and purposes up to then had not suffered. The bodies of the vertebrae apparently proved to be the primary site of the disease."

Examination of microscopical sections stained with haemalum and eosin shows that the new growth is made up of closely-packed, rounded, or polygonal cells, each with darkly-staining nucleus and a considerable amount of protoplasm, the proportion of which varies in different cells. The interstitial substance is very scanty, but numerous thin-walled blood-vessels ramify amongst the cells. On staining with Borrel's blue and alcoholic eosin the nuclei as a rule stain faintly, the chromatin being in somewhat fine granules and arranged in a peripheral ring, and in small clumps throughout the nucleus. The cytoplasm is distinctly granular, so that one gains the impression that these cells are more closely allied to the myelocytes than are the cells of the other cases examined. I have not had the opportunity of investigating the case histologically to an extent sufficient to enable me to dogmatise on this point.

Provisionally, however, the case may be placed with the myelocytic myelomata.

Case III.—I had hoped to be able to give full details of this case, an adult male native, under the care of Dr. J. R. Morris,
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Bhandara, Central Provinces, India, but I regret that these are not yet to hand, and as I have only the histological evidence to go upon, my reference to the case cannot be anything but meagre and incomplete.

The tissue sent me for examination in September 1912 had been removed from a new growth in the upper end of the humerus. A diagnosis of round-celled sarcoma was made as a result of a former microscopic examination, but on clinical grounds Dr. Morris doubted if this was correct.

On employing methods similar to those used in my first case, the general characters of the cells composing the new growth correspond very closely to those already described in connection with that case, and that description might be again adopted here, with a few modifications. There is a greater number of large cells with two, three, and even four rounded nuclei, all possessing the same characters as those of the mononucleated cells. The chromatin is, as a rule, in a little finer granules, and oftener arranged in a ring against the nuclear membrane, but also scattered throughout the nucleus, in which a nucleolus is easily made out. The cytoplasm is plentiful and finely granular, but not in the sense of Ehrlich-granulation, while with methylene blue it is distinctly basophilic. Many of the smaller-sized cells possess more densely staining nuclei, thus resembling closely the lymphocyte. A considerable number of myeloplaxes were seen.

So far as can be made out, this case may be classed along with the first case.

Discussion.—In discussing a complex subject like myeloma, round about which such a number of apparently discordant views have sprung up, and in connection with which there is in consequence not a little confusion of ideas and judgment, it is essential, in my opinion, to start out from the generally accepted dictum that a true myeloma must be a homologous new formation (quâ the bone-marrow), that is, it originates from bone-marrow parenchyma. It cannot be regarded altogether as a hyperplasia of the marrow, seeing that as a rule only one type of cell is affected, to the exclusion of and displacement of other types of cells normally found in active or reacting bone-marrow. Giant cells with convoluted nuclei (myeloplaxes) are not common, though Börst regards these as distinctive. They were present in small numbers in my first and third cases. Similarly, fully matured cells—the polymorphonuclear series—are awanting, excepting occasional eosinophils, so that a further distinction emerges, namely, that the constituent cells are mainly or wholly unripe cells. The above definition excludes also cells such as
osteoclasts, osteoblasts, and other cells constituting or formed from the so-called endosteum.

In reading the numerous papers on myeloma one must bear in mind that in many of the cases the tissues have not been fixed in a manner suitable to the demonstration of Ehrlich-granulation in the cells, so that under more favourable conditions some of the cases designated myeloblastic or lymphocytic might possibly have been included within the myelocytic group.

In scarcely any case has the oxydase reaction been applied to the fresh tissue, or to tissues recently fixed in formalin. Schütz (1909) states that this reaction, or iodophenyl-blue synthesis, develops exclusively in the granular cells of the bone-marrow series—myelocytes, leucocytes, and mast cells. The cells of the lymphocyte series remain unstained. In a later communication (1910) he states that the granules in the cells of the salivary and lacrymal glands also show the reaction. Nakano gives the latest information with regard to this reaction.

The Myelocytic and Myeloblastic Myelomata.—One may accept it as proved that the great majority of multiple myelomata are composed of cells which correspond either to the myelocyte—as in Sternberg’s case, and probably also in my second case—or more commonly to its precursor, the myeloblast or pre-myelocyte. The latter cell in every respect save the neutrophil granulation resembles closely the myelocyte, but it certainly represents an earlier stage of development. It is recognised that the myeloblast attains to adult size before the granules appear in its cytoplasm (MacCallum). Hence one should expect to find in some myelomas intermediate forms, that is, cells possessing a few granules, and such have been actually reported. Granting that the cells are immature, one should also expect a variation in the size of the myeloblast, so that in some cases smaller cells with a smaller proportion of cytoplasm predominate, whereas in other cases the average size of the cells is greater. Further, immature cells being prone to undergo degenerative changes, some of them may display condensation of the nuclear chromatin with homogeneous deep staining (pyknosis), while in neighbouring cells the nuclei may be vesicular, or the chromatin may be broken up into coarser or finer granules (karyorrhexis), whereas the majority of the cells have the normal appearance already described. Hence, on account of this apparent dissimilarity of the cells, the new growth may be described as composed of several types of cells. It is consequently possible that some of the cases described as lymphocytoma and
plasmacytoma should be included in the myeloblast group, the histological diagnosis depending in great measure on the method of staining employed.

Great difficulty is experienced when we attempt to determine the exact nature and correct position in the classification of the cases which have been described as lymphocytoma and plasmacytoma.

The lymphocytoma is composed of cells resembling the ordinary lymphocyte, but possessing a greater proportion of cytoplasm, so that they correspond rather to the large lymphocyte, an earlier stage of development. The large lymphocyte is with difficulty distinguishable from the myeloblast. The lymphocytoma is stated to originate from the lymphocyte-forming tissue of the bone-marrow, and the new formation takes place without involvement of the lymphocyte-forming centres in the lymphatic glands and of other lymphadenoid foci scattered throughout the body. If this be really so, we have to accept the bone-marrow origin of the lymphocytes of the blood-stream, and to distinguish these from the so-called histogenic lymphocytes of the tissues. The former class should alone be affected in the lymphocytic myelomata, and, reasoning on these lines, many authors approximate the lymphocytoma to the conditions termed in German literature medullary pseudo-leukæmia, the term indicating that the cells do not overflow into the blood-stream. I have never, however, been able to accept this distinction between the members of the lymphocyte class as an absolute one, seeing that the blood lymphocytes are amoeboid, and their ability to emigrate from the blood-vessels has been demonstrated. One cannot assert, therefore, that the tissue lymphocytes have not originally emigrated from the blood, an opinion which is held by many competent workers. Further, the explanation referred to does not account for the lack of reaction in the lymphocyte-forming centres in the lymphatic glands.

Thus if we admit that certain myelomata are formed of cells of the lymphocyte class, and require them to conform to the definition of myeloma as a homologous development of bone-marrow elements, we open up the whole question of the monoplyletic or polyphyletic origin of the blood corpuscles (C. Hart), that is, the derivation of the granular and non-granular cells, including the red blood corpuscles, from one ancestral cell or from different ancestors; and until the supporters of these two doctrines settle their differences, the question cannot be solved. Further, the suitability of the term "myeloma" as connoting all the different new formations included under it remains in doubt.
If it be finally proved that the lymphocyte of the blood actually originates in and proliferates in the marrow, as distinct from endosteum—and Hart points out that this is rendered probable by the recent investigations of Hedinger and Oehme—then the medullary lymphocytoma is correctly placed with the true myelomata. This would not dispose of the difficulty already mentioned of explaining why the other lymphocyte-forming centres in the body are seldom affected to any appreciable extent. When these are affected, as is the case in exceptional instances—for example when the lymphatic glands are enlarged—this enlargement can usually be explained as due to the influence of intercurrent disease.

If, on the contrary, the lymphocyte be proved to have an origin exclusively foreign to the marrow, then the lymphocytoma occurs in the marrow as a heterologous new formation, and its inclusion under the true myelomata becomes of doubtful expediency. It may be noted that in this class are included some cases which show apparent metastasis, and in which “lymphoid” nodules are found in the fatty marrow in the interior of the shafts of the long bones. These cases recall irresistibly the microscopic appearances found in a case of chloroma which I examined and described in association with Dr. Melville Dunlop. The cells of chloroma closely resemble the large lymphocyte, and it is still uncertain whether they develop exclusively from the osteogenetic layer of the periosteum or from the bone-marrow as well. This similarity is referred to also by Adami. He considers chloroma closely allied to myeloma, and agrees with Dock and Warthin that its cells are of the type of the large lymphocyte, or “more accurately of the myeloblast type,” that it is an aberrant form of myelomatosis. Chloroma, however, differs in the invasion of the blood by the cells, and in the formation of secondary nodules in many organs. This, moreover, affords support to an explanation of the lymphocytoma which had occurred to me independently, and had appealed strongly to my mind, before I encountered the statement of Adami just quoted, namely, that the lymphocytoma, so-called, is composed of cells which are in reality myeloblasts of comparatively small size. This explanation, provided it be the correct one, yields the simplest solution of the difficulties already discussed, and, further, the homologous nature of the new formation is at once evident.

The Plasmacytoma.—Similar difficulties have to be met in dealing with the plasmacytoma. In myelomata of this variety, the cells resemble closely Unna’s plasma cells of inflammatory
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They may be somewhat larger than the myeloblast—a rather unreliable criterion. The nuclear chromatin of the plasma cell is arranged in blocks against the nuclear membrane, so that the clearer parts of the nucleus present a radiating appearance like the spokes of a wheel—"wheel-nucleus," "Räd-kern." There is also a finer network throughout the nucleus, and usually a central coarse granule or granules of chromatin. The finely granular or homogeneous cytoplasm is strongly basophilic with methylene blue and allied stains; it is condensed towards the periphery of the cell, so that a faintly stained or clear ring or "halo" surrounds the nucleus. The nucleus is usually excentric. Christian, Hoffmann, and Weber and Ledingham figure cells which completely correspond to this description. Many of the cells in my first case, in sections stained with ripened methylene blue and strongly decolourised, display the same characters. I think there is no doubt that the plasmacytic myeloma forms a not inconsiderable proportion of cases of myeloma, though all the cases described as plasmacytoma are not necessarily authentic. That this opinion is prevalent is evident when one notes how many authorities show a tendency to regard the plasma cell appearance as specially characteristic of myeloma.

J. H. Wright, who first described the plasmacytoma, regards the cells constituting it as in some respects differing from the ordinary plasma cell, and Christian, while admitting that in some cases the apparently authentic medullary plasma cell does not altogether correspond to Unna's cell, argues that the slight differences found are insufficient to brand it as a totally distinct cell, and names it the "bone-marrow plasma cell." Hoffmann discusses the plasma cell question in very full detail and from every aspect, also Weber and Ledingham, and Ghon and Roman. Other writers who describe plasmacytomata are Aschoff, Quackenboss and Verhoeff, Verebély, Lubarsch, Berblinger and Simmonds.

The "bone-marrow plasma cell" has a central or excentric rounded or oval nucleus, just as in the case of Unna's cell; but the chromatin may be scattered in coarse or fine granules throughout the nucleus, and though the cytoplasm is basophilic there is no halo, or only a very imperfect one surrounding the nucleus. Several authors remark that this basophilia is somewhat relative, depending upon the extent to which the decolourising process is carried. Further, it is well recognised that basophilia is a characteristic of young cells, which are not necessarily plasma cells. I have observed similar characters in the cells of my
own cases, particularly the third of these. I would also place emphasis on the fact that whereas many cells, as in my first case, display characters indistinguishable from those of the true plasma cell, all transitions can be discovered, even in closely neighbouring cells, and more especially near the periphery of the circumscribed masses, between that cell, a cell corresponding to Christian's bone-marrow plasma cell, cells admittedly myeloblasts, and even those apparently authentic myelocytes. As a matter of fact it seems unjustifiable to separate all these cells into strict compartments of their own. Different methods of staining may bring out different appearances in the same cell. One example of this may suffice. Ehrlich's triacid stain may give indication of an apparently greater amount of cytoplasm than is demonstrable by, say, haemalum and eosin, the same section being used, one stain being removed before applying the next.

In fact, I believe that it is probable that the so-called bone-marrow (medullary) plasma cell is not very far removed from the myeloblast.

Even granting this, however, we must accept as authentic, as already stated, the myelomata composed of cells possessing characters indistinguishable from those of the true plasma cells.

But here, again, the question of the homologous nature of this new formation, relative to the bone-marrow parenchyma, presents a difficulty, seeing that the origin of the true plasma cell is still in doubt. Hodara, Naegeli, Pappenheim, Wright, Christian, and others state that the plasma cell occurs in the normal human bone-marrow, though it is not absolutely clear that all these authors refer to the same cell, and their statements are subject to the criticisms already brought forward, that is, if we discuss the plasma cell as a homologous cell, relative to the bone-marrow parenchyma. Most authors regard the plasma cell as related to and probably derived from the lymphocyte; others derive the plasma cell of the marrow and other tissues from the endothelial cells or fixed cells of connective tissue, which would make the plasma cell a cell foreign to the bone-marrow proper, and the plasmacytoma a heterologous formation. Enough has been advanced to show that the nature and position of all the formations described as plasmacytoma are still in doubt, and that the plasmacytoma can be accepted as a true myeloma only with certain reservations.

Erythroblastoma.—Very little can be said with regard to Ribbert's unique case of myeloma composed of cells of megaloblastic type, which he named erythroblastoma. There is no
reason why a new formation of this kind should not occur; it would be homologous. We must await reports of similar cases. One must note, however, that Christian points out that his bone-marrow plasma cells may become soaked with haemoglobin diffusing out from degenerating red blood corpuscles, and suggests that the cells in Ribbert's case may possibly not have been erythroblasts at all. It is interesting to note that Schridde reports a rather anomalous variety of myeloma, the erythromyeloblastoma.

I shall not discuss the relationship of myeloma to the leukæmias, in which the blood invasion is pathognomonic, and to the pseudo-leukaemias (e.g. Hodgkin's disease), in which the lymphatic glands and other lymphadenoid tissue are markedly and characteristically altered, or the distinctions which exist between it and malignant growths of bone. One may dogmatically assert that in true myelomata no one mass, even though of larger size than the others, can be regarded as necessarily the primary focus and all the others as secondary. There is no instance in tumour growth in which the skeleton is exclusively affected, as is the case in myeloma. The available evidence supports the opinion that myeloma is more nearly allied to the system diseases than to the tumours, or, as Adami and Lubarsch put it, it belongs to the group of blastomatoid states rather than to the true blastomata. "Myeloma is becoming, to an increasing extent, regarded as a system disease of a malignant type; the malignancy expressing itself in part in the rapid course of the disease, and in the great destruction of the spongy bone and cortical layers; the deleterious influences based upon the special marrow changes, which cause proliferation of cells which never become fully ripe and never fully functionate" (Berblinger). But in the phenomenon of an apparently simple hyperplasia becoming transformed into an unlimited proliferation, Hart recognises the near relationship between a so-called malignant system disease and true tumour formation.

Etiology.—The arguments which have been advanced by different authors with regard to the etiology of multiple myeloma tend to support the concept of a system disease rather than of a tumour growth. Many of the reported cases have shown a syphilitic history, or one of chronic alcoholism, or one of exhausting work and overstrain, frequently associated with poverty and consequent malnutrition. In a majority of cases, chronic nephritis has been present. In one family two brothers were attacked by myeloma; in another instance one member of a family suffered
from myeloma, while another suffered from pernicious anaemia. A congenital weakness or insufficiency of the haematopoietic apparatus may possibly be the fundamental cause in some cases, so that if this apparatus be exposed to the action of malign toxic influences, such as syphilis, chronic nephritis, or chronic alcoholic poisoning, serious disorganisation of its function results. There is no available explanation of the remarkable phenomenon of the assumption of excessive proliferation by one cell type, coincidently with the cessation of proliferation of the other cell types of the marrow. Hart, indeed, suggests that the different cell types possess a varying degree of dignity in their "vita propria"; but this is an unsatisfactory way out of the difficulty.

Klebs and Waldstein hold that a primary anaemia is concerned in the etiology, but the proliferative changes occur practically exclusively in active marrow, and not as a reaction of quiescent yellow marrow. Moreover, blood examinations show that anaemia is a feature of the disease in its later stages only. Nor can the osteoporosis be regarded as of etiological significance, seeing that in true myelomata this change is always secondary to the marrow changes, and localised to the situations in which these are taking place.

The disease in many cases appears to have originated as a direct sequel of a mechanical injury, as, for example, in Dr. Ewing's case which I report, and in Wm. Mackenzie's case.—Trauma is now accepted as of etiological importance in many cases of tumour growth, particularly sarcomata. Nevertheless, while admitting that, in the present state of our knowledge, it is impossible to disprove the correctness of this opinion, one is justified in asserting that it is equally difficult to prove the absence of the disease in an early stage at the time when the injury was sustained.

No one would willingly admit that in a normal healthy adult any conceivable strain or twist could so act upon deeply-seated and protected bones, such as the bodies of the vertebrae, as to produce a system disease of the bone-marrow contained, and that its influence is sufficient to bring about the mysterious rapid overgrowth of one special element in the marrow of many bones simultaneously.

The etiology, therefore, of multiple myeloma, apart from the probable action of obscure toxic influences, is still quite unknown.

Conclusions.—1. Multiple myeloma appears to be a system disease of the haematopoietic apparatus, of malignant nature; blastomatoid rather than true blastoma.
Fig. 1.
Section from mass in body of vertebra in Case I.; stained iron-hematoxylin and picro-fuchsin. The larger cells show something of the "plasma cell appearance," better seen in Fig. 2. Red blood corpuscles scattered between the cells. (x 600.)

Fig. 2.
Section from mass in body of vertebra in Case I.; stained alcoholic eosin and Borrel's blue, to show "plasma cell appearance" of the cells; and, further, the transitions which can be traced between neighbouring cells, e.g. from a through b, c, and the cell to its left side, to d, e a degenerating cell. A cell near the centre of the field possesses two nuclei. (x 880.)
Fig. 3.
Section from Case II.; stained with alcoholic eosin and Borrel's blue.
To show principally the granular cytoplasm of the cells. (x 880.)

Fig. 4.
Section from new-growth in Case III.; alcoholic eosin and Borrel's blue, showing characters of the cells as described in text. Two cells with two nuclei in each, and one with three nuclei, are seen in the lower part of the field. (x 620.)
2. It is questionable whether all the different varieties of myeloma described in the literature of the subject can be clearly differentiated from each other. Possibly the apparent differences are due to the variability of one cell type.

3. The apparent metastases do not result from embolism of cells of the new formation in the marrow, but are due to simultaneous transformation of foci of haematopoietic tissue present in the organs or to direct local extension.

4. Nothing definite or trustworthy is known with regard to the etiology of the disease.

5. Finally, the nomenclature in common use clinically should be amended.

The name Myeloma should be either restricted so as to indicate only the disease which is the subject of this paper, and for which it was introduced by Rustizky, and it should not be employed to designate all new formations in the interior of bone, including the myeloid or giant-celled sarcoma and other central sarcomata of bone, the cells of which are not derived from bone-marrow parenchyma; or, the term Myeloma should be given up completely, seeing that the termination -oma suggests to many tumour formation, and the term Myelomatosis, which has been proposed, should be adopted generally in place of it, seeing that this term connotes a definite pathological alteration, sui generis, of bone-marrow proper.

Additional References.—Myeloma.—Adami, General Pathology, 1st ed., London, p. 677. Kaufmann, Lehrbuch, 1907, 4te Aufl. S. 727. Klebs and Waldstein, cited by Berblinger, Oechi and Versc, both cited by Ghon and Roman. Orth, Pathologisch-anatomische Diagnostik, 1909, 7te Aufl. S. 739. Simmonds, Münch. med. Woch., 1911, Bd. ii. S. 2528. Ziegler, Spez. pathol. Anat., 1906, 11te Aufl. S. 118.

Oxydase Reaction.—Winkler, Fol. Hämatolog., 1907, Bd. iv. S. 323; and 1908, Bd. v. S. 17. Schüttze, Münch. med. Woch., 1909, Bd. i. S. 167; and 1910, Bd. ii. S. 2171. Nakano, Fol. Hämatolog., 1913, Bd. xv. Teil i. Archiv. Heft 1, S. 123.

The Plasma Cell Question.—Ghon and Roman, Fol. Hämatolog., 1913, Bd. xv. Teil i. Archiv. Heft 1, S. 72. Pappenheim, Virch. Archiv., 1901, Bd. clxv. S. 365, and Bd. clxvi. S. 424; also frequent communications in Fol. Hämatolog. Sinclair and Shennan, Trans. Ophthalmolog. Soc., 1908, vol. xxviii. (Parinaud's Conjunctivitis).

Chloroma.—Melville Dunlop, Pathological Report by Shennan, Brit. Med. Journ., 1902, vol. i. p. 1072.