At operation the median nerve was found swollen above and constricted beneath the transverse ligament (Fig. 4). The ligament was incised. Three months after operation there were no pins and needles and no pain. Power had improved little but the patient was entirely satisfied.

MULTIPLE MYELOMATOSIS

A Clinico-Pathological Review, with a Report of a Case of Myeloblastic Type

By Harwood Stevenson, M.D., M.R.C.P.

Visiting Physician, The Royal National Orthopaedic Hospital, Stanmore

'Bear this disease in mind when treating pains of the limbs of an obscure and intractable character.' This was said by Thos. Blizard Curling, F.R.S., Surgeon to the London Hospital, to William Macintyre 100 years ago. The quotation is from the paper in which Macintyre published at his leisure in 1850 the clinical history of a case which had been noted to have 'urine of high density containing much animal matter, but without dropsy or cerebral disturbance.' The animal matter had been found to have unusual properties. The urine clouded on heating, cleared on boiling and coagulated on cooling again. Furthermore, it did not coagulate with nitric acid until it had stood for an hour or two. Then the coagulum cleared on boiling but solidified again on cooling. This strange behaviour had already been reported by Dr. Bence-Jones in 1848. It is of great interest to read the original papers including the still earlier description of the morbid anatomy of the same case by Dalrymple in 1845. The combined reports of the clinician Macintyre, the pathologist Dalrymple and the biochemist Bence-Jones made this the most completely reported case at that time and have led to its designation as the first definite case of multiple myelomatosis.

Macintyre tells the story of his patient with the humanity and feeling which at that period had not been banished from scientific papers. The account is a model of accuracy and clarity from the moment when his patient while on holiday 'vaulting out of an underground cavern' falls to the ground with great pain in the chest and severe dyspnoea—his first spontaneous fracture—to the day when the story is completed by the pathologist. The ribs, sternum and spine were found to be soft and brittle and the latter collapsed to such a degree that the bodies of the lumbar vertebrae were scarcely thicker than those of the cervical. Dalrymple found the tumours which had so largely replaced the bones to contain 'oval cells with a faint grey nucleus and a bright and distinct nucleolus.' He also described and illustrated with wood-cuts cells with two, three or four such nuclei. He commented that there was no new bone formation as in osteo-sarcoma. He differentiated these cells from pus cells by their power of self-reproduction and described them as 'nucleolated nuclear cells capable of reproducing their kind.' He thought the disease was truly malignant.

These three papers all refer to earlier reports of cases of Mollities Ossium, a term which covered a considerable group of conditions. Macintyre's references show the difficulty of accurate differential diagnosis without biochemical aids. He refers to the term 'Medullary Gout' said to have been used by Saillant of Paris in 1792, which suggests no more than pains in the bones with hollow spaces. We are on firmer ground, however, when we come to Howshipp (1826).

He described a woman of 35 whose history lasted for six years with 'stooping rolling gait,' pain in the bones, tenderness of the ribs, spontaneous fractures of both femora and massive albuminuria of undetermined type. At necropsy the femora, pelvis, lower parts of the tibiae, bodies of lumbar and dorsal vertebrae, ribs and sternum, could all be cut freely. The cortical bone was in many places reduced to egg-shell thickness and the bones contained cavities filled mostly with soft material varying in colour from dark blood to liver. The combination of pain, fractures, the bones affected, their cavitation and the length of history make either hyper-

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parathyroidism or myelomatosis the only likely diagnosis. There is insufficient evidence for absolute certainty but I favour the latter.

Finally there are two cases detailed by Mr. Samuel Solly in 1844. Solly himself agreed with Blizard Curling that the disease he was reporting differed from rickets. He preferred, indeed, the very apt descriptive title of 'Osteomalacia Rubra et Fragilis' from the colour of the matter in the cystic spaces and the fact that the bones broke and did not bend. One of his cases is illustrated here by reproductions of his lithographs, through the kindness of the Librarian of the Royal Society of Medicine (Fig. 1).

This second patient, Sarah Newbury, aged 39, showed some aspects suggestive both of multiple myelomatosis and of hyper-parathyroidism. Her illness lasted 34 years. It commenced with sudden pain in the back while stooping, followed by paraesthesiae in the right leg. A year later she began to complain of pains in the bones, general weakness and feebleness of gait. Again a year later both femora fractured suddenly when her husband was lifting her out of bed. Her extreme deformities can be seen from the lithograph (Fig. 1). The hands and fingers were said to be swollen and soft. The urine contained three to four times the normal amount of phosphate of lime and the left kidney at autopsy contained a calcium phosphate stone. This would seem to favour hyper-parathyroidism although there is frequently a high urinary calcium excretion in multiple myelomatosis; oddly enough, however, I can find no mention of stone occurring in the latter condition. The cortex was egg-shell thin in the long bones, ribs and spine, all of which cut easily. The sternum contained cysts but without loss of its general firmness, a point against hyper-parathyroidism. Further the femur illustrated was so replaced that while the head had a shell of cortical bone, the shaft was left with only a periosteal covering. Some of the cysts, including that in the head of the bone, were filled with a clear yellow serum and there was also a very red and vascular layer \( \frac{1}{6} \) in. thick deep to the articular cartilage at the lower end of the femur. These points must be said to favour osteitis fibrosa cystica.

The main interest for us lies in the fact that Macintyre believed that Solly was describing the same disease as himself. It would seem to have been many years before it was realized that 'the strange animal matter' when present really differentiated his case from many other diseases grouped together as Mollities Ossium (Kahler, 1889).

Without detailing all the reports in the 19th century, one should mention the papers of Rustitzky (1873) who recognized that the tumours arose from hypertrophy of the marrow and proposed the name multiple myelomatosis; of Kahler (1880) who recognized the frequent association of Bence-Jones protein with multiple myeloma and after whom the condition has been known as Kahler's disease; and of Ewald (1897) who removed a solitary myeloma of plasma cells from a patient with proteosuria. In 1898 Bradshaw made the first definite ante-mortem diagnosis, confirmed after death.

Statistics

Atkinson (1937) has surveyed the literature and produced some useful figures. He found that of 596 cases the proportion of men to women was 420 to 186. This proportion remains reasonably constant in the various age groups, which were as follows:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>9</td>
</tr>
<tr>
<td>11-20</td>
<td>8</td>
</tr>
<tr>
<td>21-30</td>
<td>18</td>
</tr>
<tr>
<td>31-40</td>
<td>70</td>
</tr>
<tr>
<td>41-50</td>
<td>130</td>
</tr>
<tr>
<td>51-60</td>
<td>196</td>
</tr>
<tr>
<td>61-70</td>
<td>114</td>
</tr>
<tr>
<td>Over 70</td>
<td>22</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>567</strong></td>
</tr>
</tbody>
</table>

Over 80 years passed before the disease was reported in a child under 10 years (Jacoby, 1930). The extremes of age are recorded as 16 months (Hager, Roen and Peterson, 1933) and 80 years (Hallermann, 1929).

The history from the first symptom to death commonly lies between two months and two years, but is sometimes three to seven and has even been as long as 16 years (Davidson and Balsr, 1937). To give some idea of frequency it may be mentioned that at three large hospitals the figures for post-mortem incidence were given as \( \frac{3}{4},000, 4/9,000 \) and \( 9/6,000 \), making a combined figure of \( 16/19,000 \).

The tumours have been said at times to disappear and reappear (Thomas, 1901). As many as 82 myelomatata have been counted in one case. Fractures were noted in the histories of 175 cases in the following proportions:—Ribs, 57; femur, 35; humerus, 38; sternum, 13; clavicle, 11; vertebrae, 6; radius, 5; ulna, 4; tibia, 3; scapula, 3; pubis, 1; sacrum, 1; ilium, 1.

Solitary myelomatata have been noted growing from the skull, ethmoid, sphenoid, mastoid, frontal bone, maxilla, clavicle, shoulder, humerus, rib, vertebrae, ilium, femur and tibia. The references to such cases may be obtained from Atkinson's paper already quoted. To close the question of single tumours, he further mentions that solitary plasmacytomata have also been found in many soft tissues, among other sites the nostril, uvula, upper air passages, cornea, breast, conjunctiva and the floor of the mouth.

Histology

At the turn of the century, J. H. Wright of Boston (1900) recognized both the likeness of myeloma cells to the plasma cells described by
Fig. 1.—Illustrations from Solly’s article written in 1844.
Fig. 2.—The presenting lesions in the lower ends of the femora. See case report page 280.

Fig. 3.—A later stage with pathological fracture.
FIGS. 4 and 5 show extensive deposits in the bones of the trunk with numerous pathological fractures.
Fig. 6.—Showing numerous deposits in the skull.

Fig. 7.—Showing the marrow film from sternal puncture.

Figs. 8a and b.—Showing enlargements of the predominant cells in the marrow film.
Marshall (1895), and also the frequency of staining abnormalities. The discussion about the precise origin of the 'myeloma plasma' cells then began. The crux of the matter lies in the facts that myelomata are by no means of constant cell type and that the tumours in a particular case may be composed of cells of more than one 'marrow type.' While in most cases the tumour cells are more or less like plasma cells—mostly more than less—others have been labelled myeloblastic, myelocytic, lymphocytic and erythroblastic according to the appearance of the predominant cell (Parkes-Weber and Ledingham, 1909). Atkinson (1937) found cases where the histological type of the predominant cell had been stated in the following numbers:

<table>
<thead>
<tr>
<th>Type</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmacytoma</td>
<td>207</td>
</tr>
<tr>
<td>Lymphocytoma</td>
<td>16</td>
</tr>
<tr>
<td>Myeloblastoma</td>
<td>27</td>
</tr>
<tr>
<td>Myelocytoma</td>
<td>24</td>
</tr>
<tr>
<td>Erythroblastoma</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>279</td>
</tr>
</tbody>
</table>

The questions of interest arising out of the above facts then are three:—Firstly, what is the origin of the plasma cell? Secondly, is the myeloma cell a true plasma cell or a modification or relation of it? Thirdly, are the cells in tumours classified as myeloblastomas, lymphocytomas, etc., true myeloblasts, lymphocytes, etc., or not, and what is their relation to the 'myeloma plasma' cell?

1. Scott, Stanton and Oliver (1933) describe the typical tumour plasma cell as 'oval or angular, about 10 microns in diameter, with basophilic cytoplasm, a central vacuole, and an eccentrically-placed round nucleus with the chromatin arranged peripherally in coarse masses like the spokes of a wheel.' They say further that this is also the description of the mature plasma cell defined accurately by Marshall in 1895 and originally named by Unna in 1891. Valuable papers on the origin of the plasma cells have been written by Michels (1931), Finey (1928), Maximow (1932), Scott, Stanley and Oliver (1933), Cunningham, Sabin and Doan (1925) and Miller (1931).

From a study of the references given it may be concluded that the normal plasma cell arises from the reticulum cell of the haemopoietic and general connective tissues and that it is closely related to the lymphocyte series. Also that it occurs mainly in lymphoid tissue or as part of a lymphoid reaction, and is found in marrow as a direct offshoot from the marrow reticulum only in small numbers, giving 1–2 per cent. in a marrow count.

2. The second question:—Is the 'myeloma plasma' cell a true plasma cell? Doan has expressed the opinion that the myeloma plasma cell is a development of the reticulum cells under abnormal stimulation to tumour formation into a cell closely related to the lymphocytes. Churg and Gordon (1942) believe that the myeloma cell differs frequently in size, staining reactions and other criteria from the Marshall plasma cell and that it is derived from the marrow reticulum. They also point out that even in plasma-cell myeloma many of the cells may resemble myeloblasts and that in their own material they found transitional cells between myeloblasts and plasma cells. Further useful references may be found in the papers written by Williams (1932), Morse (1920), Geschichter and Copeland (1928), Rohr (1940) and Ulrich (1939).

Naegeli and also Rohr believe the myeloma plasma cell to originate from the marrow reticulum. Scott, Stanton and Oliver in their paper already quoted claim to have seen in the reticulum framework of myelomata some of the cells 'rounding-up' to become free cells; they call these young cells plasmoblasts and describe them as nucleolated cells difficult to distinguish by staining methods from myeloblasts or erythroblasts.

There seems a reasonable opinion to be drawn therefore that the myeloma plasma cell is a reticulum-derived cell like the Marshall plasma cell. It does not always fully conform to the descriptive criteria of the latter, though it must be remembered that it is a tumour cell and not therefore a normally functioning cell. But it should be noted that whereas the concensus of expert opinion favours the origin of the normal plasma cell from the lymphocytes and from the reticular cells mainly outside the bone marrow, the myeloma plasma cell would seem to arise from the reticular stem cell of the haemopoietic and lymphoid tissues, i.e. the cell which gives rise to both the 'myeloid' and the 'lymphoid' series, and this mainly in the bone marrow. In other words the myeloma plasma cell is produced from the multi-potential cell further back in the series than the cell from which the non-pathological plasma cells commonly arise.

3. The third question is the relationship between the various types of myeloma cell. It is clear that while all are agreed that the majority of these cases have tumours composed of plasma cells, there have been many cases reported upon by competent pathologists with other labels. Valuable references may be found in the papers written by Scott, Stanton and Oliver (1935), Cappell (1929), Menten (1920), Wood and Lucke (1923), Wallgren (1919), Ewing (1928), Hirschfield (1910), Stewart and Parkes-Weber (1936) and Rosenblum and Kirschbaum (1936).

But the question at issue is whether it is really correct to speak of a myeloblastoma in the sense
of a tumour or system disease arising among the mature myeloblasts of the haemopoietic tissues throughout the body; or whether the condition is one which arises among the reticular cells with all their potentialities to various types of haemopoiesis. This latter idea seems gradually to be finding favour. The condition is a neoplastic disease lying between a frank malignant tumour and a diffuse systemic hyperplasia. It arises in primitive marrow cells which are capable of differentiation in more than one direction, though commonly doing so to form the cells resembling plasma cells as we have seen. Further references may be found in the papers written by MacCallum (1901-5), Christian (1907), Symmers (1918), Smith and Silberburg (1936), Chirg and Gordon (1942) and Ulrich (1939).

Alice Stewart and Parkes-Weber (1938) reported, among others, a case which displayed an unusual (macrocytic) anaemia, at first moderate and later extreme; tenderness of the lower ribs and lower spine; no Bence-Jones proteosuria or raised blood protein or altered albumin-globulin ration; a generalized rarefaction of all bones, at first with the cystic clear areas visible only in the skull; later cystic areas in the long bones and pelvis; lymphoblasts were obtained in small numbers from sternal puncture. At necropsy the skull, sternum, ribs, femur, etc., contained tumours consisting of ‘round nucleated cells indistinguishable from those of lymphatic leukaemia or lymphosarcoma.’ These cells were also found in the liver and kidneys with some metastatic calcification in the latter. This case must be accepted as a lymphocytic multiple myeloma of recent date and is important as the existence of this type has been denied by others.

To summarize the histological position, plasma cells arise from or with lymphocytes and can arise from reticulo-endothelial cells. Myeloma plasma cells arise from the marrow reticulum cells. These being multi-potential, can and sometimes do differentiate into other cells of the myeloid or lymphoid series, or even into cells of the erythrocyte series. It is therefore not strictly correct to think of a myeloblastic multiple myeloma as a disease of the normal myeloblasts in the marrow but as a disease of the marrow reticulum, which in this case gives rise to myeloblasts. This view unifies multiple myelomata but cannot be considered as absolutely proven. It does not explain why in this disease the reticulum cell should so commonly give rise to a subsidiary cell which is normally an off-shoot several stages down one of the three series possible to the parent cell; and further, why it gives rise to that particular subsidiary cell which is normally so scantily present in bone marrow, where this disease commonly originates and mainly spreads.

Radiology

In essence the radiological picture is one of multiple round or oval areas of translucency in the bones. The cortical bone may be greatly thinned and expanded. There is no bone reaction except occasionally to the spontaneous fractures, which are of course common. Ribs, calvarium, spine, sternum, pelvis and the upper limb girdle and long bones may all be affected by tumours varying in size from millimetres to centimetres. Single myelomata do occur. Generalized osteoporosis rarely precedes the cystic appearances and occasionally the diffuse form of the disease may never give rise to localized myelomata (Abrikossoff and Wulff, 1927, and Stewart and Parkes-Weber, 1938). But in general the absence of diffuse rarefaction is a useful point in differentiation from hyper-parathyroidism with osteitis fibrosa cystica, though a case simulating the latter condition has been reported (North, 1936). In the spine the collapse of the bodies may be distinctive; when it is uniform the discs may be thickened and lenticular in the lateral view.

Bence-Jones Proteinuria

The significant animal matter is usually stated to be present in a little more than half the cases, but by modifying the tests for its presence it can be found much more frequently. Two such modifications may be mentioned:—

1. Fifteen drops of 25 per cent. salicyl-sulphonic acid are added to 1 in. of urine in a test tube. The contents are boiled for 30 seconds. If the precipitate is due to Bence-Jones protein it will clear with the boiling.

2. To 5 cc. of urine 1 cc. of 50 per cent. acetic acid is added and then 3 cc. of 30 per cent. sodium chloride. Bence-Jones protein comes down on the addition of the latter. But globulin will also behave so and must be borne in mind.

Bayrd and Heck (1947) give a good clinical survey and make the point that Bence-Jones proteinuria, which is probably due to a class of globulins of small molecular weight (about 30,000), can occur in other conditions than myelomatosis, e.g., chronic lymphatic leukaemia and carcinoma with bone secondaries. Boggs and Guthrie (1912) reported similarly upon a case of carcinoma of the stomach with bone secondaries; they mention other cases in which the same findings had been reported. Nevertheless such cases are evidently very rare.

Bence-Jones proteinuria may be present and absent at different times in the same case. It is
usually associated with a normal or low blood protein level (Freund and Magnus Levy, 1932). Cantarow (1935) claimed that it was associated rarely with a high blood protein.

**Hyper-proteinæmia**

Short and Crawford (1929) made the first step in diagnosing a case of myelomatosis by discovering Bence-Jones protein in a specimen of serum. It is true that the precise identification of proteins in serum is rendered more difficult by the fact that their temperature of precipitation and solution are influenced by the concentration of the protein, the pH, the quantity of electrolytes and urea present, etc. (Wintrobe and Buell, 1933). But Bence-Jones or no, *the total plasma proteins are frequently raised in multiple myelomatosis*.

Magnus Levy (1933) collected 18 cases and added 3 more with figures over 8 per cent. for total blood proteins. Atkinson (1937) found 60 cases reported in the literature with figures ranging from 8.7 to 18.4 per cent. Feller and Fowler (1938) write also of hyper-proteinæmia in this condition. Briefly, the total blood proteins and differential blood proteins are normal in about half the cases. In others there is a rise of the total mainly produced by a great increase of the globulin fraction; or there may be a normal total but an increase of the globulin and a fall of the albumen fraction.

Hyper-proteinæmia, which may also occur in cirrhosis of the liver, lymphogranuloma inguinale, kala-azar, leprosy, malaria and filariasis, gives rise to other subsidiary evidence of its presence, e.g. auto-haemagglutination and excessive rouleaux formation (Reimann, 1932), failure of clot retraction, clumping in the pipette with Hayem's solution, increased E.S.R., high blood viscosity, positive Takata-Ara reaction and very rarely spontaneous thromboses (Wallgren, 1920).

Wuhrmann, Wunderley and Wiedermann (1948) have found that by electrophoretic analysis they can differentiate cases of hyperproteinæmic multiple myelomatosis into those displaying an increase of α, β or γ globulin. This may lead to the reason for the variable response to urethane treatment to be noted later.

The blood fibrinogen is often slightly raised but has been found very much increased. Reimann (1928) found the highest figure of 5.48 per cent.

**Hypercalcaemia**

Charlton (1927) and Gutman, Tyson and Gutman (1936) have shown and others have confirmed that in about two-thirds of the cases the serum calcium is raised. (The latter reported an increase in 48 out of 68.) The figure may be even between 15 and 20 mgm. per cent. but the level may not be constant. Calcification may occur in kidneys, lungs or stomach (Stewart and Parkes-Weber, 1938). The serum alkaline phosphatase is usually normal or moderately raised as is the serum inorganic phosphorus. It will be remembered that the phosphorus in hyperparathyroidism is lowered. But a case has been reported with raised serum calcium and lowered serum phosphorus simulating hyperparathyroidism (Cabot, 1937). The acid serum phosphatase has seldom been estimated, but it has been normal whenever recorded.

**Renal Effects**

As the blood pressure is usually normal and the circulatory system unimpaired, the occurrence of uraemia and even anuria needs explanation. Holman (1939) found blockage of the renal tubules, i.e., the loops of Henle, with protein casts. It will be noted that this is the part of the nephron associated with resorption of water. Further he found dilatation of Bowman's space and some degree of giant cell reaction. There were no lesions of the glomerulus itself. *The essence of the renal failure is simply tubular blockage and the consequent nephronic hydronephrosis.* This blockage by acidophilic protein casts is not necessarily associated with the excretion of Bence-Jones protein, though of course it may be. Those cases with hypercalcaemia have also an increased urinary excretion of calcium, though stone formation is not reported. Further reports on renal changes may be found in papers by Foord and Randall (1935), Bell (1933) and Morison (1941).

**Amyloidosis**

Atkinson (1937) was able to list 40 cases of this complication in the literature from the first reported by Dowse (1872). They varied from a little microscopic amyloid in the renal glomeruli to most extensive deposits in the kidneys, tongue, bowel, spleen, joints, muscles, etc. Stewart and Parkes-Weber (1938) give the history of a case which they call unique in that the man developed amyloid masses varying in size from small knobs to a grapefruit. He developed a condition simulating rheumatoid arthritis with lumps about the joints, in the abdominal muscles, on the ribs and the skull. This description is very like the illustration of Sarah Newbury from Samuel Solly's paper of 1844 (Fig. 1). In at least two cases intestinal obstruction has been caused by amyloid disease (Bell, 1933, and Randall, 1933). This complication, which occurs in about 5 per cent. of cases, seems to be more likely to arise in those excreting Bence-Jones protein according to Magnus-Levy (1933).
The Blood Picture

There is usually a normo-chromic or low colour index anaemia of very varying degree, with a normal or low total white count and a normal differential count. Cases have been reported with no anaemia and at the other extreme we find haemoglobin values of under 20 per cent. Hyperchromic and macrocytic anaemia has also been reported simulating Addison's anaemia by Stewart and Parkes-Weber (1938) and by Protto (1939), but this form does not respond to liver.

Abnormal white cells of the myeloid series and less commonly plasma cells appear in small numbers (1-10 per cent.) in the peripheral blood with moderate frequency, especially later in the course of the disease.

Sternal Puncture

Beizer, Hall and Giffin (1942) strongly urge the value of sternal puncture when this disease is suspected. Their indications for this minor operation are so clear that they may well be detailed:

1. Inexplicable anaemia with malnutrition.
2. Inexplicable pains in bones with normal X-ray photographs.
3. X-rays suggesting bone secondaries without an obvious primary.
4. 'Nephritis' with hyper-proteinanaemia and normal blood pressure.
5. Hyper-proteinanaemia without cirrhosis or nephrosis.
6. Questionable hyper-parathyroidism.
7. Auto-haemagglutination and rouleaux formation in blood smears.

Varadi (1937) in detailing seven cases also pleads for sternal puncture. It certainly clinched the matter in our own case, and may give the diagnosis when there are no positive X-ray findings (Weissenbach and Lievre, 1939).

Neurological Complications

These are common and mainly due to the effects of pressure upon the spinal cord or nerve roots as a result of the collapse of vertebrae. It is possible that involvement of the spinal vessels may cause demyelination of the posterior columns and to a lesser extent of the lateral and anterior columns. Involvement by encasement or invasion of the cranial nerves II, III, V, VI, VII and VIII has been reported. Aronshu (1931) has reported a case of Diabetes Insipidus secondary to involvement of the base of the skull. Castleden (personal communication) had a patient with what appeared at necropsy to be a solitary myeloma in the fourth cervical vertebra, who died suddenly as a result of its collapse. Further interesting references to neurological complications may be found in the papers by Davison and Balser (1937), Norme (1921), Kreuzar (1926) and Thomas (1901).

Cerebro-spinal Fluid

The cerebro-spinal fluid has not often been reported upon, but Cabot (Case 20031) found a cerebro-spinal fluid with protein value 95 mgm. per cent. and a gold curve 5 5 5 5 5.

A Haemopoietic System Disease or a Malignant Neoplasm?

The skin has been involved by nodules (Sasaki, 1939). The spleen, liver and glands are usually macroscopically normal at autopsies but microscopic infiltration is by no means uncommon and gross involvement of glands does undoubtedly occur as in Churg and Gordon's (1942) case, where the abdominal glands were as large as 3 cm. in diameter and there was also macroscopic nodular involvement of the spleen. A case has been reported with involvement of the para-aortic glands following direct spread to the pleura; the latter may of course give rise to effusion, sometimes bloodstained. Churg and Gordon found six cases reported in the literature with splenic nodules. As far back as 1906 Norris wrote of a boy of 16 who had involvement of liver, thyroid, heart, pleura, thymus, adrenals, kidneys or lymph-glands. Ulrich based his paper upon a case which presented as a tumour of the testicle and was found also to be a diffuse myelomatosis. Secondary masses, i.e. tumours that could not possibly have arisen in any haemopoietic tissue, have also been found in the pulmonary artery (Funkenstein), pituitary (Piney and Riach) and in the uterus, pancreas and lungs. Both testicles and ovaries have been involved.

Angela Heffermann (1947) reported a case from which only one conclusion is possible. It presented an abdominal tumour which gave rise to duodenal obstruction. The patient had Bence-Jones proteinuria but no radiological evidence of myeloma. The mass proved to be a large plasmacytoma diffusely infiltrating the pancreas and involving all coats of the duodenum. At autopsy two small myelomata in bone ½ in. in diameter were found in the right first and second ribs. There was local infiltration through the periosteum into the adjacent connective tissue and voluntary muscle. This case must be admitted to be an example of genuine malignancy.

Enough has been said to show that, apart from involvement of the haemopoietic system and extension to those organs which contain haemopoietic tissue at some stage of development true
metastasis does occur. It will be remembered that in 1846 Dalrymple said the disease was malignant.

Classification

Before attempting to classify multiple myelomatosis it would be well to mention a few more cases which throw additional light upon the matter. Plasma cell leukaemias for instance are by no means rare. Thus Osgood and Hunter's patient had 48 per cent. of plasma cells out of a white cell total of 34,000, diffuse thickening of the skull and infiltration of the marrow spleen, liver and lymph glands with plasma cells. Miller and McNaughton (1931) describe two cases of multiple myelomatosis, one with 53 per cent. of 16,000 plasma cells in the blood and the other with 65 per cent. of 65,000. Piney (1924) reports a similar case and they are now known to be by no means excessively rare. Relevant cases have been reported by Aschoff (1906) and Gluzinski and Reichenstein (1906).

Jackson Parker and Bethea (1931) gave an important paper discussing plasmacytoma and their relationship to multiple myeloma. Two of their five cases may with value be summarized:—

1. Plasmacytoma of tonsil removed. Eight years later the patient developed multiple myelomatosis of the bones with Bence-Jones proteinuria and local and glandular recurrence.

2. A lump in the neck was proved to be a plasmacytoma. The patient later developed multiple myelomatosis and a retroperitoneal mass.

A plasmacytoma may therefore arise in lymphoid tissue and later invade the bones, or vice versa. Also the nodular and diffuse types of bone involvement can occur in the same case.

Ulrich (1939) made the point that myeloma could occur solitary, diffuse and multiple with secondary metastases and with blood steam involvement of leukaemoid type. Piney and Riach advance a very similar series of possibilities. It must then be agreed that myelomatosis can occur in the following forms:—

1. As a tumour of bone of low malignancy.
2. As a soft-tissue plasmacytoma later producing multiple myeloma in bone.
3. As a system disease confined to the marrow.
4. As a system disease of marrow and other haemopoietic tissues.
5. As a malignant tumour with true metastases.
6. As a leukaemia.

Treatment

Palliative treatment may be necessary for pain, anaemia and the spontaneous fractures. Deep X-rays (Betts, 1940) are sometimes valuable, though one has to weigh the pain it is hoped to relieve against the side-effects of radiation.

Transfusion has been used when anaemia was severe; iron may raise the haemoglobin. The rare hyperchromic macrocytic anaemias do not respond to liver.

Snapper (1937) on the analogy of kala-azar, which also produces hyper-proteinaemia, proposed treatment by stilbamidine and pentamidine. He found that pain was relieved, though without any other effect upon signs or symptoms. Alwall (1947) reported a case which confirms this statement; in a personal letter he describes how the patient felt quite well for a further three months, with only slight pain, till she died suddenly from cerebral haemorrhage. Later work by Snapper and others (1947) has shown that stilbamidine and pentamidine only relieve pain when the patient is on a low animal protein diet. The dosage schedule and diet suggested may be found in Snapper's articles given in the list of references.

The possible values of radioactive phosphorus or strontium have not yet been adequately tested. The nitrogen mustards appear to be ineffective in myelomatosis (Jacobson, 1946). Laminectomy for apparently solitary or early cases developing a spinal level may be justifiable (Batts, 1939).

Urethane in Treatment

Paterson et al. (1946) treated two cases with urethane without improvement. Alwall (1947) tried urethane on one case for three months also without benefit. He did, however, treat a second case with urethane with most dramatic improvement. She recommenced housework, the anaemia and albuminuria cleared, the E.S.R. dropped from 140 mm. to 2 mm. and the blood proteins, total and differential, returned to normal. The sternal marrow, which had contained 33 per cent. myeloma cells, contained none after 3½ months. The radiological translucencies in bone after eight months of treatment remained unchanged.

In March 1948, Dr. Alwall very kindly wrote the following progress report on this most promising case, and has allowed me to publish it here:—

The second patient was given i gm. of urethane every four days from June to September 1947, and calcium and vitamin D orally. On re-admittance to the clinic in September 1947, though she had begun to feel tired, her condition was on the whole objectively unchanged. The sternal puncture revealed numerous myeloma cells, but not as many as on the first examination one year earlier. Ever since then the patient has been given i gm. of urethane three times daily. The increase of the urethane dosage soon brought about subjective improvement which still persists. She feels quite fit, is
perfectly capable of working, and has no pain.

On examination in December 1947, sternal puncture revealed the following:—
'The marrow is fairly rich in cells, but one now has to look long before finding one cell of suspect myeloma character. Without knowledge of the earlier diagnosis one would scarcely be able to diagnose myeloma' (Professor C. G. Ahlström, M.D.).

The blood findings were normal, and there was no proteinuria. The X-ray examination showed no change. The time of these observations was about 16 months from the beginning of treatment.

This would appear to be the first case in whom treatment has brought about more than symptomatic improvement.

History of a Case of Myeloblastic Type

J.P. was first seen in April 1947. She was a girl of 11⅔ who had complained for six weeks of pain when standing or walking in the lower and inner part of the right thigh. There was no history of injury. X-ray examination showed 'a rarefying lesion about an inch and a half across in the lower end of the femur with some slight periosteal reaction.' This was thought to be a focus of low-grade osteomyelitis. A few days later she developed chicken pox and was admitted to a fever hospital. After three weeks she was transferred to the Royal National Orthopaedic Hospital, Stanmore. There had been no development of the condition in the leg, and from the fever hospital there were notes that the white cell count was 8,000, the Wassermann and Kahn tests were negative and that she was free from pain at rest in bed.

On admission she was found to be a thin and sallow but active child. There was some tenderness above the medial condyle of the right femur and a very slight swelling deep to the muscle. There were no enlarged glands. The spleen and liver were not enlarged. The chest, heart and C.N.S. showed no abnormality. The temperature chart was normal.

The urine contained no albumen or sugar. Bench-Jones' and Bradshaw's tests were negative. Pus cells were present to the extent of four per 1/100 in. field in a centrifuged specimen and red blood cells 40 on the whole slide. W.R. negative. E.S.R. 7 mm. in the first hour. The blood pressure was 105/65.

The blood picture was as follows:—R.B.C.s, 4,700,000; Hb, 92 per cent.; W.B.C.s, 9,000; polymorphs, 66 per cent.; lymphocytes, 28 per cent.; mononuclears, 6 per cent. No abnormal white or red cells were seen.

The whole skeleton was X-rayed for the first time. The films showed large numbers of rounded or oval punched-out areas clearly visible in the skull, ribs, pelvis and larger long bones. None were seen in the spine, below the upper thirds of the radius and ulna, or a similar level in the legs. There was no generalized rarefaction. It was decided that the slight periosteal reaction seen originally was probably due to a small crack or pathological fracture and in view of these findings the original diagnosis could not be upheld.

The blood chemistry was investigated with the following results:—

- Serum alkaline phosphatase, 34 units per cent.
- Serum calcium, 16.8 mgm. per cent.
- Serum inorganic phosphorus, 3.9 mgm. per cent.
- Serum cholesterol, 186 mgm. per cent.
- Plasma protein, 7 per cent. (globulin, 3 per cent.)
- Blood urea, 54 mgm. per cent. (The blood urea was taken at the end of a long bout of vomiting; later results were normal.)

Biopsy was performed on the lower end of the femur and finally a sternal marrow puncture. The material was kindly examined by Dr. Hamilton Paterson of the Redhill County Hospital, Edgware, to whom I am indebted for the following reports:—

<table>
<thead>
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<th>Per cent.</th>
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<tbody>
<tr>
<td><strong>Myelogram:</strong></td>
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<tr>
<td>Myeloblasts</td>
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<td>Premyelocytes</td>
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<td>Myelocytes</td>
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<tr>
<td>Metamyelocytes</td>
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<tr>
<td>Neutrophils</td>
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<tr>
<td>Eosinophiles—polymorph</td>
</tr>
<tr>
<td>Normoblasts—basophil</td>
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<td>Normoblasts—polychromat</td>
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<tr>
<td>Normoblasts—eosinophilic</td>
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<tr>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Plasma cells</td>
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<tr>
<td>Monocytes</td>
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Similar cells, myeloblasts, were found in the biopsy material from the lower end of the femur in approximately the same proportion. Figs. 7 and 8 show the marrow film and enlargements of the predominant cells.

The girl was not in any serious amount of pain so that it was judged not worth while submitting her to deep X-ray therapy. In July 1947, she returned home at her parents' request.

**Progress:** Portable X-ray films were taken on several occasions. Figs. 2 and 3 show the lower ends of one femur displaying the original presenting lesion and a late stage. Figs. 4 and 5 show late stages of the more severely affected portions of the skeleton. Pathological fractures of both femora and humeri developed.
Urine was obtained on several occasions after her discharge home but did not show Bence-Jones protein. There was, however, a moderate albuminuria of 30 mgm. per cent.

A normocytic anaemia developed with the haemoglobin level at 54 per cent. This rose to 72 per cent. on giving iron by mouth.

The serum calcium at the end of July, 1947, was 11.6 mgm. per cent. The alkaline phosphatase had risen to 43 units. The blood proteins were still normal with a total of 6.75; fibrin, 0.38; albumen, 4.00; globulin, 2.38 per cent. The blood urea was then 25 mgm. per cent.

Further biochemical observation was not possible as the parents were anxious that she should not have blood specimens taken. The blood films up to November 1947, did not show any abnormal white cells. In January 1948, she 'caught a cold' and died within 48 hours. A post-mortem examination of even minor extent was refused.

I am indebted to Mr. H. Jackson Burrows under whose care the patient was admitted to Stanmore for permission to publish this report.

The Full Diagnostic Picture

Age: Commonest in the fourth and fifth decades, but occurs from infancy to extreme old age.

Sex: More common in men by approximately two to one.

Hereditary, Family and Race: These play no part in the aetiology.

Pain: Very common (90 per cent.) and may be severe, especially in the long bones, loins and pelvis.

Weakness and Cachexia: Practically constant.

Pathological Fractures: Common and frequently multiple, especially of ribs, clavicles and femora.

Radiological Changes: Found in most cases but none in about 10 per cent.

Neurological Symptoms: Probably 15 per cent. suffer from spinal fractures and compressions.

Anaemia: Present in more than half the cases with a normal or low colour index, but varying greatly in degree.

Abnormal Cells in Peripheral Blood: Detected in small numbers in about 10 per cent. at some stage of the disease.

Bence-Jones Proteinuria: Present in more than half the cases.

Hyper-proteinaemia and/or Hyper-globulinaemia: Present in about two-thirds of the cases, with consequent effects upon sedimentation rate, viscosity, etc.

Hyper-calciaemia: Present in about two-thirds of the cases.

Renal Dysfunction: Present in over half the cases from nephronic hydronephrosis secondary to tubular obstruction.

Amyloid Disease: Present in about 5 per cent. but varies much in extent.

Serum Alkaline Phosphatase or Inorganic Phosphorus: Normal or moderately increased.

Biopsy and/or Sternal Puncture: Often of great diagnostic value.

Autopsy: There may be evidence of genuine malignant metastasis; more commonly there is microscopic involvement of the haemopoietic tissues only, or the condition is confined to the bones.

Definition

Multiple myelomatosis is a system disease of the reticular cells commonly but not exclusively of the marrow, giving rise to proliferation in one or more of the directions possible to those multipotent cells. The commonest product of such proliferation is the myeloma plasma cell, which is related but not precisely similar in origin to the normal plasma cell. Occasionally true malignant metastasis to non-haemopoietic tissues occurs and rarely leukaemoid invasion of the peripheral blood stream.

ACKNOWLEDGMENT

I would specially like to thank Dr. Alwall for his kind permission to publish the progress report upon his patient who is under treatment with urethane.

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FUNKENSTEIN, quoted by Harbitz, and then by Atkinson q.v.


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Dr. GORDON T. CALTHROP

We regret to announce the death, after a long illness, of Dr. Gordon T. Calthrop, an honorary life member of the Fellowship of Post-Graduate Medicine, and a former member of the Executive Committee. Some of the older members of our Committee will remember him in the days before his increasing ill-health prevented his attendance at our meetings, and will have personal cause to regret the loss of a very charming and much respected colleague.
Multiple Myelomatosis: A Clinico-Pathological Review, with a Report of a Case of Myeloblastic Type

Harwood Stevenson

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