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EDITORIALS AND ANNOTATIONS

THE CLASSIFICATION AND ANNOTATIONS

It is over thirty-five years since the late Dr Codman was asked by the relatives of a patient suffering from a malignant tumour of bone, whether there were any cured cases of this condition and if so, what treatment had been adopted. Dr Codman could not answer these questions and so he was given a thousand dollars to find out. This was the origin of the Bone Sarcoma Registry of the American College of Surgeons and, as is so often the case in medical advances, it was based on a false assumption, for when the patient died at the end of 1920, he was found to have been suffering from a metastatic carcinoma from an unknown primary and not a bone sarcoma at all.

Nevertheless, this revival of collective investigational research—for it was a method of medical research advocated by Francis Bacon, and used by John Locke and the elder Heberden—inspired critical interest in bone tumours and set the example for the establishment of registries for other types of neoplasms and uncommon conditions.

In assessing prognosis and therapeutic results in any condition, one is immediately faced with problems of classification and identification, for unless one is reasonably confident that one is comparing like conditions, conclusions must be of little value. In the present issue of the Journal Thomson and Turner-Warwick report the results of a review of 179 cases of primary bone tumours, and it is of some interest and importance to consider the evolution of the classification of these tumours in the last quarter-century.

In 1922 Dr James Ewing discussed the problem of classification in the paper which contains the first account of the "endothelial myeloma," by which he is now eponymously commemorated. Ewing at that time suggested that malignant bone tumours should be classed as:

Osteogenic sarcoma
- periosteal (extraperiosteal)
- solid, medullary and subperiosteal
- telangiectatic
- sclerosing

Endothelioma
- angioendothelioma
- solitary
diffused
- multiple

Myeloma
- plasma-cell
- lymphocytic
- myelocytic
- erythroblastic

In agreement with Bloodgood's dogmatic assertions, Ewing accepted the giant-cell tumour as benign, but, with regard to osteogenic sarcoma, he felt it was unfortunate that it was necessary to distinguish the periosteal osteogenic sarcoma from the medullary variety "but the facts demand the sacrifice of simplicity in the interests of more accurate knowledge." He had found that the periosteal osteogenic sarcoma had a much better prognosis than the
medullary varieties and could readily be distinguished histologically from the periosteal fibrosarcoma.

Ewing introduced the term "osteogenic sarcoma" as a more specific term than the collective term osteosarcoma and in preference to periosteal bone sarcoma; he used it in the sense of a sarcomatous tumour derived from primitive malignant cells analogous to the osteoblast; it was, in fact, an osteoblastoma and was not used in the sense of a bone-forming tumour. The malignant cells might remain undifferentiated and induce ostolysis or, with greater differentiation, there might be "myxoid," chondromatous or osteoid stromal formation.

When the Bone Sarcoma Registry was established, Codman, on the advice of a committee of the American Pathological Society and the College of Surgeons, adopted a classification which was almost identical with Ewing's, although the periosteal fibrosarcoma was specified and an undifferentiated type of osteogenic sarcoma was also recognised; nevertheless, Codman (1924) himself questioned the desirability of subdividing the osteogenic sarcomata according to anatomical site.

The establishment of the Registry stimulated interest in this field of surgical pathology; Christensen (1925) analysed a thousand cases of bone sarcoma, mainly drawn from the Registry, studying the location, age and sex, but did not attempt any study of prognosis; and Codman (1926), after five years, could report only thirteen cases of "cured" osteogenic sarcomata and emphasised the high proportion of metastatic bone tumours which had been mistaken for primary neoplasms. Kolodny (1927) presented a detailed study of the 700 cases then in the registry, but suggested that the classification was unnecessarily complex and that a grouping into five categories, without subdivisions—osteogenic sarcoma, Ewing's sarcoma, myeloma, an unclassified residuum of sarcomata, and giant-cell tumour, was sufficient for all practical purposes. However, his views as to prognosis were not very cheering: "In bone sarcoma as in other malignant tumours, the question of therapy is still awaiting its answer. It is a strange fact that with our knowledge of minute details of the histopathology of bone tumours the progress along the practical therapeutic road is almost in the same stage that it was in some fifty years ago. As a rule, malignant bone tumours are fatal and we know of no therapeutic method to prevent death from this disease." In the following year the Bone Sarcoma Registry revised their classification, but rather than following Kolodny's suggestion of simplification, they included the periosteal and medullary fibrosarcoma under the heading of osteogenic sarcoma and added a sixth variant, the periosteal or capsular type, but omitted the undifferentiated osteogenic sarcoma.

The majority of surgeons and pathologists, both in the United States and in this country—for example, Muir (1929), Ogilvie (1929)—accepted the classification of the Registry, but there were heretics. As early as 1923 Coley (1924) had questioned Bloodgood's assertion that the giant-cell tumour was benign, and he reiterated this in 1927 and 1932, pointing out that in most cases it was possible to differentiate the benign from the malignant varieties on the basis of clinical, radiological and histological evidence; in a way, this was a return to the views of Virchow and Gross but supported by more critical clinico-pathological evidence. However, an even more important paper was that of Phemister (1930), who called attention to the existence of the chondrosarcoma which could be distinguished from the osteogenic sarcoma group both on radiological and histological grounds, and the distinction was more than justified by reason of its very much better prognosis; in this country, Platt (1932) had come to the same conclusion.

In 1931 appeared Geschickter and Copeland's monumental Tumours of Bone based on the Bloodgood collection of Johns Hopkins Hospital; the classification was somewhat complex as it was based on histogenesis, but the importance of this work is that, for the first time, the natural history of the individual types of tumour was correlated with therapeutic effects and embraced not merely osteogenic growths but all types of tumours arising in bone.

In 1937 a discussion on malignant tumours of bone was held at the Royal Society of
Medicine, and Scarff put forward what he described as a fairly simple classification, which clearly had affinities both with the classification of the Bone Sarcoma Registry and with that of Geschickter and Copeland. His classification was as follows:

- Giant-cell tumour.
- Osteogenic sarcoma.
- Infiltrating chondroma.
- Medullary fibrosarcoma.
- Periosteal fibrosarcoma.
- Myeloma.
- Ewing's tumour.
- Angio-endothelioma.
- Chordoma.

Scarff discussed his reasons for distinguishing these types of bone tumour, some of which were well defined entities whereas others were specified for their significance in differential diagnosis.

In 1939 Ewing reported on the revised classification adopted by the Bone Sarcoma Registry. The rather curious subdivisions of osteogenic sarcoma were maintained, but the chondrosarcoma was recognised as an entity. A malignant as well as a benign form of giant-cell tumour was admitted and a system of grading was suggested, which was soon to be superseded by Jaffe, Lichtenstein and Portis's (1940) masterly paper, which not only set out a system of grading based on stromal differentiation, but emphasised that the so-called variants have little in common with genuine giant-cell tumours or with one another; these "variants" have subsequently been defined as the benign chondroblastoma (Jaffe and Lichtenstein 1942), chondromyxoid fibroma (Jaffe and Lichtenstein 1948) and aneurysmal bone cyst (Lichtenstein 1950), while the so-called giant-cell tumours of tendons and synovia are probably granulomata rather than neoplasms. This work on the giant-cell tumour, which has been accepted with few dissentients (Willis 1949) has at last placed this much debated condition in a proper perspective as a comparatively uncommon tumour of adult life.

The 1939 revised classification of the Registry also recognised the reticulosarcoma of bone, first defined by Parker and Jackson (1939) and the rather questionable liposarcoma.

One of the most important papers in relation to nomenclature and classification of bone tumours was contributed by MacDonald and Budd (1943), who reviewed the 118 cases with a five-year cure which had been classed as osteogenic sarcoma or chondrosarcoma on the Registry files. On re-examining these cases they decided that only fourteen (11.8 per cent) could be classed as osteogenic sarcoma, whereas ninety-seven (82 per cent) had been so classed in the Registry; on the other hand, they found that fifty-six (47.5 per cent) of the cases were chondrosarcoma as against the Registry classification of twenty-one (17.8 per cent) and that there were thirty-seven (31.4 per cent) of fibrosarcomata which had not been distinguished in the Registry classification from the osteogenic sarcomata. A preliminary study of the fatal cases (interrupted by the exigencies of war and so far as is known not resumed) showed that 40 per cent were osteogenic sarcoma, 40 per cent were chondrosarcoma and only 15 per cent were fibrosarcoma.

If MacDonald and Budd's conclusions are accepted (they are strongly supported by Thomson and Turner-Warwick's findings in the present number of the Journal) it is an admirable example of the dangers of drawing conclusions with regard to prognosis, etc., in relation to conditions classified in one system or another, unless the nomenclature and descriptive definitions are so clear as to leave no doubt that the categories which are being compared are truly homogeneous; it would seem very doubtful if the actual classification of cases in the Bone Sarcoma Registry can be regarded as reliable, and therefore any statistical analysis of this material must be suspect, although this in no way diminishes the immense value of the thousands of cases in the Registry when used for critical study.
The problems of identification of the various types of bone tumour has been largely resolved by the publication of Lichtenstein's monograph (1952), which not only adopts a logical and simple classification, but also provides admirable clinical, radiological and histological description of each type of tumour and furthermore includes a description of the majority of benign lesions which are liable to be confused with the more malignant tumours.

In regard to nomenclature, MacDonald and Budd did not appear to have been so critical as they were in classification, and they suggested a reversal of usage in respect of the terms osteogenic sarcoma and osteosarcoma; they proposed that osteogenic sarcoma should be a collective term to include the osteomucoid-forming tumours, the chondrosarcomata and the fibrosarcomata, and that osteosarcoma should be restricted to those tumours in which there is formation of an osteomucoid matrix; this seems undesirable as osteosarcoma is an old term whose meaning has always been non-specific, whereas osteogenic sarcoma was introduced by Ewing to mean a tumour of osteoblasts and not necessarily a bone-forming tumour, and certainly not in the vague sense of originating in bone; in the interpretation of terms, etymology should not take precedence over semantics.

Price (1952) of the Bristol Bone Tumour Registry has put forward a system of grading osteogenic sarcoma which has been used by Tudway (1953) in his study of the results of external irradiation. Price's grading is restricted to the tumours which other pathologists would class as osteogenic sarcoma and fibrosarcoma, and differentiation is based on the mitotic activity of the tumour cells; it is natural that with such a system many tumours showing great mitotic activity would have a poor prognosis, but, as both Price and Tudway admit, the correlation is often poor and this is probably due to the lack of distinction of the fibrosarcomata from the osteogenic group.

Thomson and Turner-Warwick's classification put forward in this number of the Journal appears attractively simple, for there are only five categories—osteosarcoma, chondrosarcoma, fibrosarcoma, spindle-cell sarcoma, and giant-cell tumour. However, it must be recognised that this classification is restricted to the skeletal sarcomata arising from connective tissue and excludes the malignant tumours of vascular and haemopoietic tissue, Ewing's sarcoma, chordoma, liposarcoma and the "adamantinoma" of limb bones.

The classes, with the exception of the spindle-cell sarcoma, correspond to those in the revised 1939 Classification of the Bone Sarcoma Registry and used by Lichtenstein (1952), but the particular interest of this paper is the excellent demonstration it provides that this type of classification is meaningful in relation to prognosis; it is based on all the cases seen at the Middlesex Hospital since 1925.

In regard to terminology, Thomson and Turner-Warwick follow MacDonald and Budd (1943) in misunderstanding Ewing's usage of the term osteogenic sarcoma and substitute for it the old ill-defined term osteosarcoma; if it is felt that the term osteogenic sarcoma is open to misinterpretation, then it would be quite legitimate to use the term "osteoblastic sarcoma" whose connotation could not be in doubt.

Each of Thomson and Turner-Warwick's categories has a very different natural history. The "osteosarcoma" group are the most malignant, with three-quarters of the cases fatal within a year of treatment, whereas in the chondrosarcomata there is a 50 per cent five-year survival and 40 per cent fifteen-year survival. The fibrosarcomata were intermediate in prognosis, with half the cases fatal within two years, while the spindle-cell sarcomata—a category which has not been segregated by other workers—have a curious survival pattern in that half the patients died in less than six months and the rest have survived between five and fifteen years. The giant-cell tumour group illustrates the increased gravity of this condition if the "variants" are omitted, as half the cases showed local recurrence and a quarter died from distant metastases.

The histological criteria on which the classification is based are set out very clearly and should be of great assistance to pathologists, for the follow-up results reveal that if such a classification is adopted an accurate prognosis can be given. The designation of a tumour is
significant only if the microscopist follows the rules of recognition that the authors have adopted, and it is essential to recognise, for example, that cartilaginous islands may be found in a tumour of osteoblasts and ossification may occur in a chondrosarcoma or fibrosarcoma, but in these cases they are reactions in the tumour matrix and not part of the malignant process.

With regard to grading, Thomson and Turner-Warwick have not found cytological grading of value in the osteoblastic group but they do not mention the periosteal (juxtacortical) osteogenic sarcoma (Dwinnell, Dahlin and Ghormley 1954) which is of very low malignancy and possibly corresponds to Ewing's (1922) description of the periosteal osteogenic sarcoma.

In the chondrosarcoma group, histological grading was of definite prognostic import, but no attempt was made to follow Geschickter and Copeland (1931) and Lichtenstein (1952) in distinguishing primary and secondary chondrosarcomata.

The periosteal fibrosarcoma which is not invading bone was excluded from the series, and in the fibrosarcoma grading was only of value in separating the rather uncommon, well differentiated form which has a much better prognosis. Thomson and Turner-Warwick express some doubt as to whether the spindle-cell sarcoma should be treated as a distinct type from the fibrosarcoma, even though the histological appearances are quite characteristic; they tended to occur in rather younger individuals, but it must be confessed that it would seem to the reviewer that they are probably only a variant of the fibrosarcoma.

In the giant-cell tumours, Thomson and Turner-Warwick followed the grading proposed by Jaffe et al. (1940) and confirm their conclusions as to the importance of stromal differentiation in the prognosis of these tumours.

It is always difficult to assess the relative merits of surgery or radiotherapy, alone or in combination, as it is necessary to know the criteria which determined the form of treatment to be adopted. All that can be said is that in the "osteosarcoma" the patients who survived three years or more had received combined surgery and radiotherapy; all the patients with chondrosarcomata who received radiotherapy alone have died, whereas 58 per cent of those who received surgery alone are still alive; in the fibrosarcoma all those treated by radiotherapy alone have died and the longest survivals are in the group treated by surgery and radiotherapy; and although the number of spindle sarcomata was small, a similar pattern of therapeutic response was observed.

In the giant-cell tumours the findings are more complex, but it seems that the worst results were obtained by curettage alone, indifferent results were obtained with radiotherapy alone, and the cases with the longest survival were treated by a combination of surgery and radiotherapy.

It is clear that if a patient nowadays asks a surgeon what is his expectation of life with a primary bone tumour, a much more accurate prognosis can be given than Dr Codman could offer thirty-five years ago, but this must be based on a critical appraisal of the clinical features, and the radiological and histological appearances. As to which form of therapy is likely to give the best result, there are as yet only general indications, and it is hoped that the study of cases in the many bone sarcoma registries that now exist will in the future also provide this answer.

A. H. T. ROBB-SMITH.

REFERENCES