HEREDITARY BONE TUMOURS IN MICE

BY

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AND

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(WITH SPECIAL PLATE)

It should no longer be disputed that a tendency to cancer is often inherited. While there is ever-accumulating evidence to show that this is so in man, of which probably every practitioner must have seen examples, most of the experimental proof has been obtained by animal breeding. The inheritance of mammary cancer in mice is being very fully investigated, chiefly by American workers. Certain strains which have been inbred for many generations are characterized by a definite and constant cancer incidence, high in some strains, intermediate or low in others. Once these characters are established such strains are used extensively for investigating the origin of mammary carcinoma. Other inbred strains have proved the inheritance of a leukaemic tendency, while in others there is a regular production of tumours of the liver or lung.

In 1929 a pair of mice from the Simpson strain (developed by Dr. Burton J. Simpson of Buffalo from the Lathrop-Loeb stock) was given to us by Dr. T. Lumsden. From this pair we have bred more than 5,000 descendants. The general incidence of mammary carcinoma is over 50 per cent. (in some inbred lines it is considerably higher). Lung tumours are very frequent, and other lines have a high incidence of leukaemia. Angiomata, epitheliomata, and other neoplasms are less numerous.

Sarcomata

Sarcomata were known to occur but rarely in the strain. The first six cases in our stock appeared in 1933, three of these being of bone and three subcutaneous. Mouse 100, the first to produce a bone tumour, had a sarcoma of the sternum in addition to a mammary carcinoma. The relations and descendants of these sarcoma mice were

bred from; certain lines were inbred brother to sister, others were outcrossed in an attempt to increase the sarcoma incidence. During the next two years there were forty-two cases of bone tumours, mainly sarcomata, in this group. One of these, a female of 5½ months, had a hind limb amputated for a sarcoma of the tibia and was paired to a sarcoma-bearing male. The descendants from this mating, together with those from three other double-sarcoma pairings, formed the nucleus of our present inbred sarcoma strain, now in its seventh generation. The sarcoma incidence in one line is shown in Fig. A.

The sarcoma incidence in the ordinary Simpson stock is approximately 1 per cent. During the first four generations of inbreeding it increased to 10 per cent. In our inbred strain from the double-sarcoma pairings it is just over 50 per cent. At the time of writing there have been ninety-six cases of bone tumours in the inbred strain

among 188 mice which have died over the age of 5½ months. There is a curious difference in incidence in the sexes, the females producing three times as many sarcomata as the males.

FIG. A.—The pedigree of one line of the sarcoma strain, showing the high incidence of sarcoma. The age of the mouse at death or appearance of the tumour is given in months. Where no age is given the mouse is still living.

○ = female; ● = sarcoma-bearing female; □ = male; ■ = sarcoma-bearing male; leuk. = leukaemia; Sim. = Simpson stock.

Sites Affected and Types of Tumour

We have now examined over 260 bone tumours, mainly sarcomata, from the descendants of the original pair of Simpson mice. In the majority of cases clinical recognition is easy. There is a thickening or tumour found in one of the long bones (Fig. B), while paraplegia is

usually the first indication of a vertebral tumour. Large tumours about the pelvis may impede locomotion or parturition, while in others intracranial growths may be suspected. Diagnosis has been confirmed in some cases by

FIG. B.—Right femur and tibia from mouse 3754; osteogenic sarcoma of femur; slight changes in tibia.

x rays, which are a ready means of revealing multiple lesions or metastases (Plate, Fig. 1). An analysis of the sites shows that any bone may be affected (in one mouse the whole skeleton was altered), but the more common

sites are the femur, tibia, and spine, and occasional tumours of the jaw, skull, humerus, ribs, or sternum are met with.

The main types recognized are osteomata, composed either of compact or of cancellous bone, alone or in varying proportions, and in some cases associated with chondrification or rapidly growing soft tissue. The cancellous osteoma, local or diffuse, is the most common type.

Histology

Histological examination demonstrates all stages in the development of bone tumours. The earliest phase consists of proliferation of the osteoblasts, forming local hard or cancellous tumours (Plate, Fig. 2), single or widely distributed throughout the skeleton. This change may be confined to a small area, but more often it increases in extent until most of the bone is affected. At any time this proliferation may pass beyond the limits of the periosteum and invade the surrounding tissues. Again, at any point proliferation may show giant-celled tissue or may pass into a purely spindle-celled rapidly growing sarcoma (Plate, Fig. 3). Metastases are found in the lungs, liver, kidneys, and spleen. Like the parent tumour they show all grades of bone formation.

The essential feature of the tumours seems to be a varying degree of neoplasia of the osteoblast. In their varying degrees of differentiation and malignancy they show an exact analogy with the mammary tumours, which range from a single adenoma through all the stages to a generalized carcinoma of the whole mammary tissue.

Conclusion

With the possession of this inbred sarcoma strain, which reproduces many of the bone lesions known in human pathology, it may be possible to investigate the proximate cause of bone tumour formation and perhaps solve other problems concerning bone neoplasia.

Research into this subject and the investigation of rarer types of bone pathology are proceeding.

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C. Coggi (*Ann. Ostet. Ginec.*, February 28, 1938, p. 107) discusses the aetiology, morbid anatomy, symptomatology, and treatment of necrobiosis of uterine fibromyomata during pregnancy. Six personal cases he describes include three cases of total aseptic necrosis, and one case each of partial aseptic necrosis, red degeneration, and septic necrosis. As a result of his investigations he comes to the following conclusions: (1) Aseptic necrosis in uterine fibromyomata during pregnancy is fairly infrequent, and is chiefly found in primiparae of a relatively advanced age; the immediate cause is ischaemia. (2) The symptoms consist chiefly of pain in the hypogastrium accompanied by tenderness on pressure over one particular spot and general disturbance which may range from slight pyrexia to cachexia and even acute peritonitis. (3) Expectant treatment is dangerous and unreliable and should only be adopted in special cases. (4) Myomectomy is the treatment of choice whenever possible; the fear of myomectomy being followed by abortion should not prevent the performance of this operation, since the patient will be in a better state to face another pregnancy. (5) The prognosis is always grave, and whatever be the treatment adopted necrobiosis is dangerous for the mother and in most cases fatal to the foetus.

A CASE OF ABDOMINAL PREGNANCY

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(WITH SPECIAL PLATE)

Although many cases of abdominal extra-uterine gestation have been reported in recent years the condition is one of interest and is uncommon enough to justify the presentation of yet another case. That recognition is difficult is evinced by the fact that in a comprehensive review of the literature Cornell and Lash (1933) found a correct pre-operative diagnosis to have been made in only 35 per cent. of the 236 cases collected. Before proceeding to report the case recently under my care it will be relevant briefly to review the present knowledge of this condition. For information I am greatly indebted to the exhaustive survey by Cornell and Lash quoted above.

Present Knowledge of the Condition

Abdominal pregnancy has been reported in women whose ages range from 15 to 64 years, the 64-year-old patient having carried her foetus forty years. Under 2 per cent. had previously suffered ectopic pregnancy, and the condition was seldom complicated by other diseases or tumours. The leading symptom was abdominal pain, and this was often associated with slight vaginal haemorrhage and attacks of fainting or vomiting. On abdominal palpation the ectopic foetus may be felt separate from a moderately enlarged uterus and lying higher than the normal foetus. The cervix, though soft, is less so than in a case of normal pregnancy, and it is often high up behind the symphysis pubis. Exploration of the uterine cavity with a sound, or hystero-graphy after lipiodol injection, has been found of considerable diagnostic value.

Deformities are the rule in the baby; these are often due to pressure, only eight cases out of 236 having been reported as normal. The foetal mortality is high: in eighty-six cases in which the baby was born after six months the mortality was 22 per cent., whereas in sixty cases in which the baby was born alive in the eighth and ninth months the mortality was 35 per cent.

The maternal mortality was 14 per cent. in the 236 cases, shock, haemorrhage, and peritonitis accounting for the majority of deaths. It has been taught that in abdominal pregnancy operation may be profitably delayed until the foetus is dead and the placenta thrombosed and relatively avascular, but Cornell and Lash have shown that in the cases so treated the maternal mortality was 33 per cent., thus forcing one to the conclusion that such a teaching is erroneous. These authors also point out that operative treatment should include the removal of foetus, membranes, and placenta *in toto*, as the mortality of such a procedure—being 10 per cent.—compares very favourably with a mortality of 20 per cent. in cases treated by leaving the placenta, with or without marsupialization. However, it may be that the high mortality of the latter policy may be partially accounted for by its being adopted in the more advanced cases or with more seriously ill patients. Certain other writers, on the other hand, consider non-interference with the placenta to be the wisest course and report its complete absorption in a few months.

Upon the question of the optimum time to operate for the safety of the mother and child, the conclusion is that as the policy of delay has been shown to be fraught with

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FIG. 1.—Radiograph of mouse 2773, showing osteogenic sarcomata of both tibiae and one lumbar vertebra; also large bony metastases in liver.

FIG. 2.—Longitudinal section of femur from mouse 2121: osteogenic sarcoma with some normal marrow still remaining. Haematoxylin-eosin: Ilford green filter (Micro 3). Obj. 2/3"; eyepiece $\times 5$.

FIG. 3.—Mouse 3155. Transverse section of humerus, showing osteogenic sarcoma within shaft, surrounded by osteogenic and spindle-celled sarcoma, rapidly growing and infiltrating muscle. Van Gieson: Ilford blue and yellow filters (Micro 2 and 4). Obj. 1"; eyepiece $\times 5$.

K. L. JAMES: RUPTURE OF OVARIAN DERMOID

Photograph of the tumour in section. Note fatty sebaceous material (A); green jelly-like secretion (B); matted hair (C); and a tooth (D).