the application of heat and cold, and to a degree of heat generated in living tissues, Hunter made the subject of an endless number of investigations, all with the practical view of ascertaining how much or how little should be done to keep damaged human tissues alive.³³ Here was, as we have seen, an experimental physiologist and also an experimental pharmacologist.³⁴ He was a psycho-analyst;³⁵ he tried to inoculate an ass and a bitch with the virus of syphilis.³⁶ He preached the doctrine of operating at the earliest possible stage of a disease, and, placing himself in the position of the patient, said, "Nor do I go further than I now think I would have performed on myself were I in the same situation."³⁷ He performed experiments on the sensitive plant which are now being repeated.³⁸ These are only some of the points in which Hunter has anticipated modern progress.

So much for the past in its relation to our greatest men. What of the future?

THE FUTURE.

As I look forward I like to humour my fancy and indulge my dreams. Imagination, Keats tells us, may be compared to Adam's dream—he awoke to find it truth. The art of the surgeon is the pillar of science, and it is for science to discover how that almost perfect art may now be used to the fullest advantage. We eagerly await the day when disease shall not require to be checked in high career, but shall be blighted at its origin, or even denied existence, when our weapons of war shall be laid aside. That day may yet be far away, but already beyond the distant hills we see promise of the dawn. It does not, perhaps, so much or so deeply concern ourselves as those who soon must take up our task, and lead the hosts whose victory shall attain our high ideal. In due time, and in accord with ancient precedent, this country of ours, the fruitful mother of so many gifted sons, shall raise up in our schools the youths who shall go forth to conquer a crown. They will be best equipped who keep to the course, recall the methods, and are imbued with the ardent spirit of the two famous men whom we praise to-day—the two greatest surgeons the world has ever known.

Our youths must be prepared for self-sacrifice, for arduous discipline, perhaps for the most heart-breaking rebuffs, for the stern or even bitter criticism of their fellows. But there never was a time so rich in promise, so laden with rewards for those who labour with sincerity and truth. They will not travel alone. The whole army of science is in league with them, moving forward with incredible speed, eager to lay at their feet the triumphs of its astounding conquests. The responsibilities which rest on them, the intellectual accomplishments and the dedication of their lives demanded of them, are enough to cause the stoutest heart sometimes to falter. Yet, armed with the sword of the spirit and the breastplate of faith, they will remember that the happiness of life lies in its responsibilities, that true joy is found in the search for what may after a weary journey prove unattainable. Ahead lies the noblest of tasks to which they may consecrate themselves: for the lives of men are in their hands, the love, the happiness, the whole welfare of mankind. We need not fear. They will be worthy of their charge. God counts not result but effort.

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EXPERIMENTAL PRODUCTION OF ACUTE AND CHRONIC ARTHRITIS AND ARTICULAR NEOPLASM BY RADIUM.*

(With Special Plate.)

BY

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A FEW years ago, in a Hunterian Lecture on osteo-arthritis, I ventured the opinion that the peculiar proliferations of bone and cartilage often occurring in the more chronic form of arthritis usually known as osteo-arthritis, some of which attain a very considerable size, were intermediate between a frankly inflammatory process and a genuine neoplasm. The difficulty experienced in distinguishing between the two was so great that some of the loose bodies occurring in osteo-arthritis were designated "synovial chondromata" by Professor Shattock and myself. It is unnecessary to enter now into the histological differences between such forms of proliferation and frankly inflammatory developments. It is interesting to note, however, that the form of chronic arthritis usually known as "rheumatoid arthritis" or "chronic arthritis of the synovial or mixed types" (Fisher) is a frankly inflammatory process, whereas the proliferative changes in the so-called "osteo-arthritis" belong to the peculiar type of proliferation akin to new growth that we are considering. It is interesting to note also that the age incidence of osteo-arthritis or chronic arthritis of the chondro-osseous type is, as a general rule, very similar to that of many forms of malignant change, particularly the carcinomatous—that is, they both occur when the resistance of the body to irritation of moderate degree of intensity is beginning to diminish because the patient has passed the meridian of life. In younger organisms the vascular response to irritation of slight or moderate intensity is marked, and, combined with a moderate degree of cellular proliferation, probably suffices to cope with minor degrees of irritation.

After the meridian of life is past the vascular reaction is not so much in evidence, and a slight but persistent form of irritation tends to bring about a proliferation of cells that are fairly well nourished but degeneration of cells whose nourishment is poor. A good example of this is seen in "osteo-arthritis." The physiological basis for the changes in the latter is that while the central part of the articular cartilage which is devoid of blood vessels is poorly nourished, the extreme lateral portions receive blood vessels from the circulus articulari vasculosus. Irritation, therefore, whether mechanical or toxic, tends to cause degeneration of the central portion of the articular area and proliferation of the lateral portions. We observe this same peculiar admixture of proliferation and degeneration in many forms of true neoplasm, both innocent and malignant. It appears that in new growths we are faced with an essential alteration. There is a breaking down of the physiological harmony between cells and the inhibiting intercellular substance. We can imagine, for example, that prolonged irritation or toxæmia might have, simultaneously, a stimulating effect upon cells but an inhibiting effect upon intercellular substance. On the other hand, inhibition might be at a very low ebb from the degeneration of old age, and might, in a person with suitable disposition, cause a growth to develop. If inhibition is temporarily abolished but eventually recovers, a so-called innocent new growth may result, which after a time ceases to develop actively. If inhibition is impaired a subinflammatory process such as osteo-arthritis develops (compare prostatic adenomata). If it is severely impaired and the irritation is moderate, or if it is slightly impaired and the irritation great, or if irritation is great and inhibition severely impaired, a malignant growth results.

As according to this theory the condition known as "osteo-arthritis" is a stage intermediate between inflammation and new growth, it seemed to me that it might be of considerable interest to ascertain whether it would be

* The expenses of this research were defrayed by the Medical Research Council.

possible to bring about osteo-arthritis and new growth experimentally through the same agency, and for this object tubes containing radium were introduced into the knee-joints of rabbits. The following experiments show the results obtained.

A. Experiments with Radium contained in Glass Tubes.

Fig. 1 represents the left knee-joint of a full-grown rabbit, and shows well marked proliferation of the cartilage of the inner and upper margin of the trochlear surface of the femur.

Experiment 20 (Old Series).—The left knee-joint of a rabbit was opened by an incision upon the internal aspect and under strict aseptic precautions. A glass tube containing 0.0382 mg. of radium bromide was fixed by a catgut suture against the inner margin of the trochlear surface, and the joint carefully closed by suture. The joint was immobilized as far as possible by several layers of gauze saturated with collodion. A glass tube containing 0.15 mg. radium bromide was fixed in a similar position in the right knee-joint. The rabbit remained perfectly healthy, and nineteen weeks later was killed. The left knee-joint revealed the presence of a large chondro-osteophyte similar to those seen in osteo-arthritis (Fig. 1). It had developed from that portion of the articular edge opposite to where lay the radium tube, which had formed for itself an oblong shallow pit in the adjacent part of the internal femoral condyle. The remainder of the joint showed no obvious change beyond localized synovial hypertrophy in the vicinity of the radium tube. The right knee-joint showed similar changes, but to a lesser degree.

Experiment 19 (Old Series).—The left knee-joint of a rabbit was opened as above, and a glass tube containing 0.15 mg. of radium bromide was fixed against the inner border of the internal condyle of the femur. The animal was killed four weeks later, and it was noted that well marked proliferation of the lateral part of the cartilage had occurred at the junction of the internal condyle with the trochlear surface of the femur. A patch of fibrillation of the cartilage had occurred more centrally. Localized synovial hypertrophy was again present.

Experiment 6 (New Series).—A glass tube containing 0.15 mg. of radium bromide was introduced into a similar position in the right knee-joint of a rabbit. Two weeks later the animal died, and it was noted that no alteration in bone and cartilage had occurred, but that a localized villous synovitis was present in the immediate vicinity of the tube.

Experiment 5 (Old Series).—A glass tube containing 0.15 mg. of radium bromide was introduced into the suprapatellar pouch of the right knee-joint of a rabbit. Fourteen months later the animal was killed. The radium tube had created for itself a deep pit above the trochlear surface. Slight osteo-arthritis changes were present. An interesting feature was the fact that the patella had become dislocated, and lay upon the outer side of the femoral condyle. Here an articular surface had developed for the patella with a covering of newly formed articular cartilage (Fig. 4).

B. Experiments with Radium contained in Platinum Tubes.

Experiment 2 (New Series).—The left knee-joint of a rabbit was opened from the inner side under scrupulous aseptic technique, and three platinum tubes containing radium were introduced as follows:

Platinum tube No. 151, containing 1.2 mg., into the outer part of the suprapatellar pouch.

Platinum tube No. 152, containing 0.50 mg., into the inner part of the suprapatellar pouch.

Platinum tube No. 153, containing 0.51 mg., into the lower and anterior part of the joint. Total 2.21 mg.

After an interval of several weeks the animal developed acute destructive suppurative arthritis of a fulminating type, which necessitated its destruction. It is highly improbable that the infection was introduced at the time of the operation owing to the interval that elapsed.

Experiment 1 (New Series).—The left knee-joint of a rabbit was opened from the inner aspect, and platinum tube No. 150, containing 2.44 mg. of radium, was introduced into the joint. The animal was killed eleven months later, and the following conditions were observed (Fig. 2). A condition of chronic arthritis of mixed type or "rheumatoid arthritis" had developed. The radium tube lay in front of the crucial ligaments. The articular ends of both tibia and femur were considerably enlarged from inflammatory thickening of the periosteum. Considerable destruction of the articular surfaces of both femur and tibia had occurred, associated with the formation of chondro-osteophytes at the articular margins. This formation of new bone was particularly well marked from the antero-internal part of the internal tibial condyle, where a

very large osteophyte had developed (see drawing). Adhesive ankylosis occurred in places between the adjacent surfaces of the femur and tibia. The synovial membrane was inflamed, and in places invaded the articular surface in the form of pannus.

Experiment 4 (New Series).—The left knee-joint of a rabbit was opened from the inner side. Two platinum tubes, one containing 0.22 mg. and the second 0.24 mg. of radium bromide, were introduced into the joint cavity (suprapatellar pouch). The animal was killed fourteen months later, and the following interesting conditions were observed (Fig. 3).

The joint was enormously enlarged, partly from a fluid swelling occupying the inner part of the joint and partly from a hard tumour-like mass growing from the lower end of the femur and projecting backwards into the popliteal space, but also inwards. On carefully opening the joint it was seen that the fluid swelling on the inner side was an abscess cavity, containing thick, curdy, purulent fluid, and in which the radium tubes lay. Internally the cavity had a dense fibrous wall, whereas externally the wall of the abscess cavity was formed by the enlarged lower end of the femur. In sagittal section the shape, size, and general relations of the tumour are demonstrated clearly. It is seen to be developing principally from the inner and posterior aspects of the lower end of the femur; to be of a somewhat dense and compact consistency, and to be covered externally by a tough periosteal envelope. Histologically the tumour is clearly an ossifying periosteal sarcoma which has originated from the periosteum covering the intra-articular portion of the diaphysis and the adjacent portion of the epiphysis of the internal femoral condyle.

I am indebted to Professor H. M. Turnbull, Director of the Pathological Institute, London Hospital, for the following report upon the tumour:

The peripheral portions of the mass for a considerable depth consist of a very cellular tissue that is invading and destroying muscle. The cells are spindle-shaped, triangular, polygonal, and spherical, vary greatly in size, but are for the most part large. Deeper in the mass very numerous swollen collagenous fibres appear among the cells, and gradually enlarge to form a close irregular meshwork of very narrow osteoid trabeculae. As still deeper layers are followed the trabeculae become gradually stouter, and enclose larger medullary spaces, in which lie essentially similar, usually degenerated, cells; these trabeculae are of coarse-fibred bone, are for the most part necrosed, and are arranged very irregularly. In the section from the maximal convexity of the mass some large medullated nerves are included in this tissue, and the adventitia of an artery is replaced by the polymorphic cells. The femur as it touches the mass is cut tangentially; the mass replaces the periosteum, but the corticalis is neither necrosed nor interrupted. The medulla of this portion of femur is, however, filled with a close meshwork of trabeculae of necrosed coarse-fibred bone, with some superimposed finely fibrillated bone or osteoid tissue; the medullary spaces contain the polymorphic cells, and these cells show extensive degeneration and necrosis. Similar cells fill some of the inner Haversian spaces and canals of the corticalis.

There are a considerable number of leucocytes within the mass and in places close to it; there are leucocytic thrombi in some large vessels near the mass, and there is much perivascular infiltration with plasma cells in the muscle at a distance from the mass.

The conditions to be separated for a diagnosis are: (1) inflammation leading to bone formation, (2) callus formation following trauma, and (3) neoplasm. The features which I have tried to sketch in the description, particularly the wide peripheral zone of destructive cellular infiltration, make, I think, the diagnosis of osteo-sarcoma undoubted. There is some inflammatory infiltration in the mass and in the tissue beyond the mass, but this infiltration is relatively insignificant, and is such as is frequently found in association with malignant neoplasms. The sections alone do not suffice to settle the origin of the growth, but, taken in conjunction with your pictures, there can be little doubt that the sarcoma arose in the periosteum of the femur, and had invaded the medulla nearer the centre of the mass than the site of the section that includes femur.

I conclude that the condition is an osteo-sarcoma of the periosteum of the lower end of the femur.

It is not claimed that these experiments are anything more than suggestive, and it is obvious that confirmatory evidence will be necessary. The first fact that demands our notice is that, in the series of experiments with small quantities of radium contained in glass tubes, the reaction of the joint elements was slight or moderate and took the form of proliferation of the better nourished edges of the articular cartilage or synovial hypertrophy in the vicinity of the tube. The experiments were conducted under rigid aseptic technique, and suppuration did not occur. The localized proliferations at the edges of the articular

A. G. TIMBRELL FISHER: ARTHRITIS AND NEOPLASM PRODUCED BY RADIUM.

FIG. 1.—Left knee joint of rabbit. Tube containing 0.0382 mg. of radium fixed in contact with inner margin of condyle. Growth of cartilage after nineteen weeks. (Experiment 20, old series.)

Right knee.

Left knee.

FIG. 2.—Rabbit A. 2.44 mg. of radium bromide were introduced into the left knee-joint. Animal died eleven months later. A subacute arthritis is present with a mixture of degeneration and marked bony hypertrophy. The articular ends are greatly enlarged, and below and internal a large detached osteophyte is present. Associated with the degeneration of the central poorly nourished portion of the articular cartilage is definite proliferation of the better nourished lateral portion. (Experiment 1, new series.)

FIG. 4.—Osteo-arthritic changes in knee-joint of rabbit. (Experiment 5, old series.)

FIG. 3.—Periosteal sarcoma growing from the lower end of the femur. Sagittal section of knee-joint (natural size). (Experiment 4, new series.)

M. R. DRENNAN: THE AURICULO-VENTRICULAR BUNDLE IN THE BIRD'S HEART.

FIG. A.—Photograph of the A-v bundle, between the auriculo-ventricular openings (ostrich heart). P.=Pulmonary artery. A.=Aorta. R.O.=Right auriculo-ventricular orifice. B.=Bundle. L.O.=Left auriculo-ventricular orifice.

FIG. B.—Photograph of the right side of the dissected ostrich heart, showing the A-v bundle.

FIG. C.—Photograph of the left side of the dissected ostrich heart, showing the termination of the left branch of the A-v bundle in a complex network under the endocardium.

cartilage were similar to those seen in osteo-arthritis, particularly in the more localized "traumatic" forms.

In the second series of experiments, with larger quantities of radium contained in platinum tubes, a striking fact was the severity of the reaction. Although scrupulous aseptic technique was used, suppuration occurred in a large proportion of cases. It is probable that the suppuration was not introduced at the time of the operation, but was due to auto-infection, for it is known that bacteria settle in damaged tissues.

In Experiment 2 (new series) the total quantity of radium in the three platinum tubes introduced into the left knee-joint of the rabbit was 2.21 mg., and acute destructive arthritis of fulminating type supervened.

In Experiment 1 (new series) one tube containing 2.44 mg. of radium was inserted into the joint, and at the end of eleven months a marked degree of chronic arthritis or "rheumatoid arthritis," with a combination of destruction and hypertrophy, was found.

In Experiment 4 (new series) two platinum tubes containing a total quantity of 0.46 mg. of radium were inserted. At the end of fourteen months a localized abscess was found combined with a large sarcomatous growth.

We have already noted that in the experiments with radium contained in glass tubes changes akin to localized osteo-arthritis accrued. In the three experiments with radium in platinum tubes the results may be summarized as follows:

Experiment 2: Acute suppurative arthritis.

Experiment 1: Subacute arthritis of mixed type similar to "rheumatoid arthritis."

Experiment 4: Localized abscess and sarcoma.

It would be rash to form conclusions from a small series of experiments, but it would appear that the smaller quantities of radium contained in the glass tubes caused proliferative changes only. The larger quantities of radium contained in the platinum tubes caused destructive changes, whereas the smaller quantity in Experiment 4 caused the marked and irregular proliferation of a malignant growth. The resistance of the animal and the time factor are, of course, important.

THE AURICULO-VENTRICULAR BUNDLE IN THE BIRD'S HEART.

(With Special Plate.)

BY

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In fishes, amphibia, and reptiles the muscular wall of the auricles of the heart is continuous with that of the ventricles. In mammals the muscular continuity is almost completely interrupted by the fibrous auriculo-ventricular rings. The very attenuated auriculo-ventricular bundle (bundle of His) is the only direct neuro-muscular connexion between the auricles and the ventricles. The existence of this structure, in a more or less definite form, has now been demonstrated in the whole mammalian group.

In the heart of the bird, however, the presence of the bundle of His has not, so far as I am aware, been established. Keith and Flack (1907), in an important paper dealing with the "Muscular connexions of the primary divisions of the vertebrate heart," seemed to have no doubt that there was an auriculo-ventricular bundle in the birds' hearts which they examined. On the other hand, Mackenzie and Robertson (1910), in a paper dealing with "Recent researches on the anatomy of the bird's heart," state emphatically that "in the bird's heart there is no bundle of His, or other specialized form of muscle tissue connecting the auricles with the ventricles." These same authors state that "Tawara's monograph leaves the impression that the bird's heart resembles the mammalian heart in the possession of a special muscle system. He refers to fibres of the Purkinje type in the region of the blood vessels (of the bird's heart)." Dr. Alexander Morison (1912), in his paper "On the innervation of the sino-auricular node," states in his argument that in birds "most investigators have failed

to find the auriculo-ventricular bundle; not that this fact proves its absence."

The presence or absence of this structure in the bird's heart would seem, therefore, to be "not proven." Yet it seems to me that it is very important that an attempt should be made to decide this question. If the bird's heart can dispense with a bundle of His, it suggests that the physiological importance of the bundle is perhaps being overrated in the mammal. On the other hand, if the bundle can be proved to be present, it brings this heart and its contractile phenomena more into line with that of the mammal, and adds to the significance of this structure in cardiology.

Most workers hitherto have relied on the findings from a microscopical investigation of the hearts of small birds, but it would appear that such an examination is unsatisfactory from the fact that the bundle fibres, if they exist, appear to be little differentiated from the ordinary heart muscle. Keith and Flack¹ state that in birds they "have been unable to find any differentiation of fibres in the bundle; the guide to it being its position and its definite demarcation by fibrous tissue. In the birds' hearts examined (sparrows and goldfinch) the A-V bundle arises from the auricular ring and dives at once into the inter-ventricular septum."

FIG. 1.—Scheme of the distribution of the A-V bundle in the human heart.

FIG. 2.—Scheme of the distribution of the A-V bundle in the ostrich's heart.

I have recently dissected five ostrich hearts with a view to determining whether any trace of a bundle could be detected with the naked eye. The size of these hearts—they are as big as a small ox heart—gave promise that, if there was a bundle, it would be of tangible size. In all of these hearts I have been able to demonstrate a structure which is probably homologous and analogous to the auriculo-ventricular bundle in the mammal.

This structure is not so easily defined as the auriculo-ventricular bundle in the ox, but it is nevertheless as definite as the auriculo-ventricular bundles which I have been able to trace out in the human heart. It arises in the same region as the mammalian bundle, but there is no sign of any definite auriculo-ventricular node at its commencement. In several of the hearts, however, I was able to make out a rich nerve supply to this region from the right coronary plexus. At its commencement this structure is pale and delicate, varying in thickness in the different hearts examined. It is best made out by approaching it from behind, by separating the right and left atrial walls in the region of the interauricular septum (see Plate, Fig. A). It passes through the medial aspect of the right auriculo-ventricular fibrous ring, just under the endocardium, to which it is adherent. As soon as it reaches the interventricular septum it plunges deeply into its substance (see Plate, Fig. B), and runs obliquely towards the left side of the septum. Here, on the septal wall of the left ventricle, it divides at once into a large number of branches, which form a network just under the endocardium (see Plate, Fig. C). The distribution of this part of the avian bundle is very similar to that of the left branch of the mammalian bundle.

In the ostrich heart there is no branch of this bundle tissue having a distribution similar to that of the right