LECTURES ON CYSTIC TUMOURS OF THE JAWS, AND ON THE ETIOLOGY, GENERAL CHARACTERS AND RELATIONS OF TUMOURS.

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LECTURE III.*

AT a time when the test of direct experiment is being applied for the elucidation of many of the complex problems of animal life and its modification by disease, it would be surprising if the mystery of tumour formations had not been attacked from the same direction. Although no conclusive results, yet some suggestive facts, have already been arrived at by this method.

In dealing with the subject it will be more convenient to consider, first, the changes which portions of normal tissues undergo when implanted into various parts of the bodies of animals; and, secondly, the results of the implantation of portions of tumours.

To John Hunter, the founder of this great museum, we owe the first facts with regard to the behaviour of implanted tissues. You are doubtless all familiar with the experiments by which he succeeded in transplanting human teeth and cock's spurs into the combs of cocks; I will therefore only remind you, in passing, of the remarkable growth of the spurs when transferred to this highly vascular soil.

Many other experimenters have been at work in this field, but it is to an exhaustive series of investigations by Leopold†, that we owe the more complete knowledge now possessed.

Van Dorremal, Goldzieher, and Zahn, found that portions of such tissues as the epithelium of the lower lip, of the conjunctiva and of the nasal mucous membrane, grew to a slight extent when placed in the anterior chamber of the eye of animals, rabbits being generally used. Epithelium was also produced from the under surface of a portion of cornea implanted in the lymph sac of a frog.

Leopold implanted into the anterior chamber portions of costal and epiphysal cartilage, and unstriated muscular tissue, from rabbits, either fully grown or half-a-year old, with the result, that in the fully grown animals not the slightest tendency, and in young animals only a trace of growth, was observed in the implanted tissue. I am, however, able to state, that portions of the intermediary cartilage, with the periosteum attached, of recently born animals, will increase to eight to ten times their original size, when transplanted into the anterior chamber; but they finally become reabsorbed.

Cohnheim and Maas sought to ascertain if portions of fresh normal tissues would grow and produce new formations within the blood-vessels. They inserted portions of the periosteum of rabbits into the jugular veins of dogs and chickens. These, lodged in the branches of the pulmonary artery, became vascularised in the same manner as a simple thrombus, and produced within two weeks first cartilage and then true bone. But these portions of bone began, without exception, to disappear within the next week, and after the fifth week not a trace of them remained.

The experiments on the transplantation of tissues from adult animals show, therefore, that fully formed tissues, such as cartilage, cornea, and nerve, are absorbed; but growth is observed when such tissues are used as periosteum, and the deep layers of epithelial surfaces, which more nearly resemble foetal tissues. Growth also takes place when tissues from very young animals are used.

Experiments on the transplantation of embryonic tissues were first performed by Zahn, and they have since been supplemented by Leopold's researches. Leopold used, in different groups of experiments, minute portions of various tissues from embryo rabbits, twenty-four, twenty-one, and seventeen or eighteen days old. The portions were inserted into the anterior chamber of the eye, the peritoneal cavity, and the subcutaneous tissue of rabbits. The best results were obtained when portions of cartilage were inserted into the anterior chamber; but growth also ensued, as a rule, when the same tissue was implanted

in the peritoneal cavity. Minute portions of the epiphysal cartilage, when introduced into the anterior chamber, became adherent to the iris; from this structure, minute vessels passed to the cartilage, and soon invested it with a delicate network. In one of the most favourable cases, the implanted cartilage began to grow in eight days; and at the end of fifty days the cartilage had increased forty to sixty times its original size. By the nineteenth day, the tumour filled the anterior chamber, and was nodulated and tuberculated. By the hundred and twentieth day, the tumour almost completely filled the anterior and posterior chambers, and had reached its greatest size. On the hundred and eighty-eighth day, the animal was found dead from pneumonia, the portion of cartilage having increased three hundred times its original size. The implanted portion of cartilages became ossified to a greater or less extent, whether placed in the anterior chamber or in the abdominal cavity. Microscopic examination showed that the formation of bone and cancellous spaces took place in the same manner as under the natural conditions; and, in the portions examined, abundant evidence of proliferation of cartilage-cells was obtained. By the introduction of portions of embryonic cartilage into the pulmonary circulation, Leopold obtained much the same results as those previously recorded by Zahn. Eight days after the introduction of four small portions into the pulmonary circulation, only two unaltered portions were found in the branches of the pulmonary artery. In another similar experiment, one cube of cartilage was found lying in a much thickened vessel; but in another portion of the lung the finest divisions of the pulmonary artery contained numerous minute grains and knobs of scattered particles of hyaline cartilage.

These experiments of Leopold's were undertaken in order to apply the test of experiment to Cohnheim's theory, that all tumours are derived from latent rudiments of embryonic tissue. As regards the congenital tumours, the result is extremely favourable, for the greater power of growth possessed by embryonic than by adult tissues is distinctly demonstrated; but the perfect ossification of the implanted cartilage, also indicates its capability of development, and thus separates it from the elemental tissue of the tumours of later life, the chief characteristic of the majority of which is the imperfection of their power of organisation. This difference is also seen in other respects: in the most successful experiments the masses of cartilage had ceased to grow by the hundred and twentieth or the two hundred and fifth days respectively; and in another experiment the cartilage became reduced by absorption to one half the size it had attained, a phenomenon almost unknown in the history of tumour-formations. We must, therefore, conclude that the continuous and destructive growth of the more malignant tumours, among which some forms of enchondromata may be reckoned, depends on some other property than their supposed embryonic nature.

Considering the favourable results obtained by the implantation of embryonic tissues, it might be expected, from the supposed analogy of structure, that portions of tumours would also grow when transferred to the bodies of animals. But in spite of the greatest care and precaution exercised in performing the experiments, especially by Billroth, it cannot be said that the transplantation of a tumour has been satisfactorily accomplished. The small nodules, found in the lungs by Langenbeck and Föllin, after the injection of cancer juice, were evidently due to embolism. Billroth's results were negative, in three cases of inoculation of portions of tumours, chiefly cancers, from men to dogs; and in six cases, in which portions of similar tumours were injected into the veins of dogs. He thinks that possibly better results may be obtained with sarcomata. After the injection of the juice of a medullary cancer of the upper jaw into the femoral vein, by Otto Weber, in sixteen days a mass of medullary granulations, of the size of a fist, consisting of small round cells, grew up in the wound. Finally, the tumour became necrosed, and disappeared. The dog escaped and, therefore, no *post mortem* examination could be made. The same results followed a similar experiment performed on a cat. The nearest approach to satisfactory results were obtained by Goujon. In one experiment, a small portion of an encephaloid tumour was placed under the skin of a guinea-pig. The animal died twenty-five days subsequently, and a knot, about the size of a pea, consisting of epithelial cells like those composing the encephaloid tumour, was found in the operation wound. The lymphatic glands were thickened, hard, and showed, on section, specks, which were found to be composed of epithelial-like cells. In another experiment, a deep ulcer with an everted edge, followed the injection of the substance of a tumour into the femoral vein. After cicatrization of the ulcer, small knots or tubercles remained. The animal escaped two months after the operation. Owing to the strong tendency to the formation of tubercle, which

* Given at the Royal College of Surgeons, June 1882. The latter part of the Lecture, treating of the relations of tumours to each other, has been extended, but the conclusions have not been altered.

† Virch. Arch., Band xxxv., page 263.

guinea-pigs exhibit, even after slight injuries, the results of these experiments must be accepted with considerable hesitation. Zahn introduced particles of an enchondroma, from an old woman, into the anterior chamber of the eye, and into the circulation; but no growth ensued, except in one instance, when a small portion of cartilage in the lung was found to have increased. Negative results have also followed the transplantation of tumours from one animal to another of the same species.

The failure in all these experiments to produce a permanent tumour-formation, except perhaps in one of Goujon's experiments, may probably be referred to two causes. In the first place, a fully formed portion of the tumour may have been taken, for no growth might be expected to take place, unless a portion of the advancing or growing part of the tumour were implanted. It is, however, also probable that a favourable condition of the tissues in which the growth is implanted is required, such as may be assumed to exist in the highest degree in advanced age. That the tissues and organs themselves possess a varying resisting power to the growth of pathogenic materials when introduced into the circulation is shown by the experiments of Grawitz. When various cultivated fungi, such as penicillium, were introduced into the circulation, he found that they affected different organs, in an inverse proportion to their nutritive activity. Those organs, such as the lungs and brain, which possessed the most rapid circulation and the highest nutritive activity, showed the greatest immunity from the fungus-disease, and were only affected by highly malignant forms. Perhaps the same resisting power is shown by the lungs to the formation of cancer; secondary deposits being found, not uncommonly, in the liver, kidney, and bones, while the lungs remain perfectly free, although the cancer elements must have passed through the pulmonary circulation in order to reach the organs first named. In such cases, small fibrous nodules are occasionally met with in the lungs, which, like those in Langenbeck's and Follin's experiments on the inoculation of cancer, may be considered probably as cancer emboli which have not grown, but have given rise to a formation of fibrous tissue around them. The lungs, on the other hand, apparently offer more favourable conditions for the growth of sarcoma, as they are frequently the seat of secondary deposits in cases of sarcoma of the bones.

The failure of all experiments to inoculate animals with tumours from man, or from other animals of the same species, stands out in remarkable contrast to the daily evidence we have of the auto-inoculation of tumours, either by transference of nuclei of the tumour-cells by means of the blood-vessels and lymphatic vessels to other organs, or by direct implantation. Direct implantation is frequently observed, as in case of cancer or papilloma of the peritoneum, secondary to disease of the ovary or Fallopian tube; and it occasionally occurs in cystic adenoma of the ovary. In a case of cystic adenoma of the ovary, which had ruptured, Mr. Knowsley Thornton found a minute cyst implanted in the peritoneum, which was an exact miniature of the tumour of the ovary. Sometimes a primary or secondary cancer of the peritoneum even extends through the lymphatics of the diaphragm, and affects the pleura, just as is sometimes observed in tubercle.

Sir James Paget quotes a case in which a tumour appeared in the abdominal walls in the course of a puncture, by which the abdomen was tapped for cancer of peritoneum. Mr. Cripps has recently described a case in which an ulcer, having the appearance of an epithelioma, formed on the inner side of the elbow of a woman, whose arm had, at this point, been kept for two months in constant contact, by means of bandages, with an ulcerated cancer of the breast. The precise nature of the ulcer, however, was not ascertained by microscopic examination.

Permit me now to call your attention to a theory of the mode of origin of tumours, which has been advanced by Professor Cohnheim.* He endeavours to prove "that a fault, an irregularity of the embryonic rudiment, is the true cause" of the tumour-formations; that, at an early stage of embryonic development, more cells are produced than are necessary for the formation of the affected part; so that a certain quantity remain over unused, of perhaps only the minutest dimensions, but having a great proliferative capability, on account of the embryonic nature of the cells. The period of the excessive production of cells may probably be referred to a very early stage of development, possibly to the period between the complete differentiation of the blastodermic layers, and the perfect formation of the rudiments of the particular organs. Possibly, the superabundant cell-material is distributed more or less generally over a histo-

genetic embryonic layer, or is confined to a single spot, so that the morbid growth may affect an entire system, such as the osseous or cutaneous; or may be confined to a single organ. He concludes "that a fault, an irregularity of the embryonic rudiments of the organs and tissues, is the true cause of the later tumours."

The tumour-rudiment may remain latent for an indefinite period, until stimulated to growth by an increased blood-supply, from any cause whatever. A diminished resistance in the surrounding tissues, as in the atrophy of advancing age, is also supposed to favour the growth of a tumour rudiment.

Professor Cohnheim supports his theory by reference to the teratoma and many congenital tumours, as moles, angiomata, and multiple enchondromata, fibromata and lipomata of the subcutaneous tissue, which he has observed in new-born infants; also, other tumours occurring in the earlier period of life, as the muscle-tumours of the kidney, gliomata of the retina, and sarcomata and cancers of various organs. The most conclusive example is furnished by the dermoid cysts of the subcutaneous tissue. Although their existence can be made out by dissection in infants, they rarely attract attention until puberty. These cysts, lined with epidermis, and often containing hair, are probably, as Lücke pointed out, derived from an abnormal involution of the external layer of the blastoderm into the middle layer; this displacement occurs in those localities where there is a normal involution of the epiblast, or where the closure of fissures or folds takes place in the embryo, as around the orbit, in the lines of the branchial fissures, or in the median line of the thorax.

He ingeniously applies his theory for the elucidation of many of the obscurities surrounding the origin and causation of tumours. The following are among the principal conclusions at which he arrives. This theory renders comprehensible the occurrence of tumours in any tissue, whether capable of production during the whole of life as epithelium, or as connective tissue; or such as only increase on the application of a physiological impulse, as the muscular and glandular tissues of the uterus and breast.

The liability of particular localities to cancer, such as the lips, orifices of the stomach, the rectum, the os uteri, upon which Virohow founded his hypothesis of irritation, receives an ingenious explanation, by the supposition that a reason exists in the embryonic development of the part. Cohnheim points out that at or near these orifices a complication occurs in development, either an invagination of the epiblast, an union of this with another epithelial layer, or a transition from one form of epithelium to another; in these parts, he thinks a slight irregularity may easily come about, leading to the formation of an excessive mass of epithelium, which may furnish the elements of a tumour. Further, the origin of the heterologous tumours, viz., those which differ in their structure from the tissues in which they lie, is explained by the theory of *displacement* of embryonic tissue; as, for example, the dermoid cysts of the skin already mentioned; the striped muscle tumours of the kidneys, which he believes to be produced by a faulty segmentation of the protovertebræ; and certain heterologous tumours occurring in some of the principal organs of the urogenital system, as the enchondromata of the testicle, and the dermoid cysts of the ovary, testicle, and pelvis; the origin of these is attributed to the close connection existing between the Wolffian body, with the epiblast in the one side, and the protovertebræ in the other, a relation which may lead to the admixture of embryonic cells formed in excess from either of these structures with the rudiments of the urogenital organs. In a similar manner, an explanation of the enchondromata of the parotid gland is furnished by the inference, that they are derived from misplaced portions of Meckel's cartilage. Again, the supposed embryonic nature of the tissue comprising the sarcomata is referred to the early stage of development at which their rudiments are believed by Cohnheim to be cut off; he observes, that the histological prototype of a spindle-celled or round-celled sarcoma must be sought in the first beginnings of the development of the connective-tissue organs. The tumour-rudiments cannot, he thinks, be expected to form tissue as perfect as the normal structures, owing to the differences existing between the conditions of their growth, both as regards the time and the place of their development.

I have endeavoured, as far as time will permit, to give an impartial account of Cohnheim's exposition of his theory, and the manner in which he applies it for the explanation of the origin of tumour-formation.

Some facts on which the theory is based, render it highly probable that the rudiments of a large number of tumours appearing in the earlier part of life are congenital, perhaps of a larger number than we are disposed at present to admit.

Maas has found, among 278 cases of tumours, 26, that is 9.3 per cent.,

in children, which must be considered congenital. But no facts have at present been brought forward, which even remotely indicate that the sarcomata and cancers of later life originate from pre-existing rudiments formed in the embryo.

Such an assumption appears to me altogether incompatible with our knowledge of the life-history of the individual structures and elements of the body. For from the time of their earliest formation until death, growth, and even development, of the individual units formed by growth goes on continuously in the epithelial and glandular tissues of the mucous and cutaneous surfaces. It is in these structures, and especially in the breast and uterus—which possess until late in life a remarkable reserve of formative activity—that tumour-formations most commonly occur. The reparative power is capable of producing in the most advanced age highly organised tissues such as bone, connective tissue, and epithelium, in a manner conforming to the general type and outline of a part, as is seen in the union of fractures and the healing of wounds; and surely, such a cellular activity would, under certain conditions, be capable of forming a tumour, which truly possesses the greatest capacity for growth, with the most limited power of development. The following facts, also, appear to me to be opposed to Cohnheim's theory. All cartilaginous tumours of bone are not composed of embryonic cartilage, nor do they all originate from the centre of the shaft or the centre of the epiphysis, as those congenital tumours composed of fetal cartilage invariably do. For many cartilaginous tumours are hyaline, and originate from the intermediary cartilage, and others originate in the periphery of the shaft. Again, if all tumours of bones were derived from embryonic rudiments, they would begin in the long bones, either near the centre of the shaft or that of the epiphysis; for any embryonic rudiments of the foetal shaft would gradually be separated from the epiphysal line by the growth of the extremities of the diaphysis, and from the surface by the formation of fresh layers of bone beneath the periosteum. Similarly, a rudiment remaining in the epiphysis would gradually be separated from the line of junction with the diaphysis, and from the surface by a similar increase of the peripheral structures. But, on the contrary, we observe that by far the larger proportion of the sarcomata of bones originate in the latest formed parts, viz., either beneath the periosteum, or at the line of junction of the epiphysis and diaphyses; in fact, precisely in those positions where embryonic rudiments would be least likely to be placed.

Nor is it necessary to go back to embryonic life to find the elements from which the sarcomata of bones are formed. These tumours much more nearly resemble the imperfect stages in development of the structures formed in the processes of repair and inflammation, than those which we may presume would be produced from the embryonic round cells, constituting the rudiments of the connective tissues, and which, Cohnheim observes, are only found at the earliest period of embryonic life; these, embryonic cells, if tending to a higher type of development, would produce foetal cartilage and not osseous tissue, as is observed in most sarcomata.

Further, the history of the development of the breast renders it inconceivable that the rudiment of an adenoma or a cancer can be actually formed at an early stage of foetal life; the first rudiment of the gland itself does not appear as a bud-like ingrowth of the epiblast until the fifth month of foetal life, and it is only represented at birth as "a delicate rosette of radiating rudimentary gland tubes.* And if the rudiment of a cancer actually be congenital, how is it that it does not develop under the physiological incitement of puberty?

(To be continued.)

* See Kölliker and A. A. Bowlby, BRITISH MEDICAL JOURNAL, 1882.

OIL OF WINTERGREEN IN THE TREATMENT OF ACUTE RHEUMATISM.—Dr. F. P. Kinnicutt draws the following conclusions from the results obtained in twelve cases of acute rheumatism, treated by oil of wintergreen. 1. In the oil of wintergreen we possess a most efficient salicylate in the treatment of rheumatism. 2. In its efficiency in controlling the pyrexia, the joint-pains, and the disease, it at least ranks with any of the salicyl compounds. 3. The best method of its administration is in frequently repeated doses, continued in diminished doses throughout the convalescence. 4. Its use possesses the advantages of being unattended with the occasional toxic effects, the frequent gastric disturbance produced by the acid or its sodium salt, even when prepared from the oil of wintergreen; that its agreeable taste, and finally its comparative cheapness, are further recommendations in favour of its employment.

ABSTRACT OF LETTSOMIAN LECTURES

ON

THE TREATMENT OF SOME OF THE FORMS OF VALVULAR DISEASE OF THE HEART.

Delivered before the Medical Society of London.

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LECTURE III.—MITRAL STENOSIS.

Pathology and Etiology of Mitral Stenosis—Points of Difference from the Lesion which induces Regurgitation—Compensation—Special Treatment in Mitral Stenosis—Complications—Embolism and its Treatment.

I PROPOSE now to consider the morbid conditions associated with a structural change at the left auriculo-ventricular aperture, a change which narrows this outlet, and impedes the influx of blood into the left ventricle during the period of diastole. No disorder of function can bring about such a condition as this. The lesions are always organic. We will first glance at the morbid anatomy of the affection. If the mitral aperture be viewed from the auricle, it may, in many cases, be seen that a smooth septum presents itself between auricle and ventricle, crossed by a narrow slit, almost straight but inclining to be crescentic; such slit may be no larger than a sixpenny piece, or a shirt-button, will pass through; and, from its appearance, the orifice has been termed the "buttonhole orifice." The natural form of the curtains may be entirely lost, their place being occupied by a thick fibrous structure, welded at its circumferential attachment with the cords and fleshy columns, which may all be transformed into a dense tendinous mass. In certain cases, this fibrous material, as well as the septum, is infiltrated with calcareous salts to such degree, as to make it closely resemble bone.

Another, but less frequent form of obstruction is that in which the mitral orifice, as seen from the auricle, resembles a hollow cone. This is known as the "funnel-mitral;" its ventricular outlet may be so small that it will scarcely admit the point of the little finger. Dr. Hilton Fagge has recorded forty-six examples of the buttonhole to one of the funnel form of construction; Dr. Hayden thirteen of the former to one of the latter. And of my own records of twenty necropsies in cases of mitral stenosis, two only were "funnel-mitral." M. Lancereaux has described a case of mitral stenosis, in which, amongst the vegetations which surrounded the thickened orifice, he discovered hard granules, which were shown by chemical tests to consist of urates. When treated with nitric acid, they gave rise to a yellowish product (alloxan); and this, on the addition of ammonia and distilled water, gave the characteristic red colour of murexide or purpurate of ammonia. The granules when dissolved in acetic acid crystallised in the characteristic rhomboids of uric acid. I draw attention to this observation, because it may have an important bearing on the question of etiology and treatment. I have myself met with a case of mitral stenosis in which there were abundant gouty deposits in the joints, some of which suppurated and gave exit to uratic deposits intermixed with the pus.

It is obvious that the great difficulty created by such alterations as these is the due filling of the ventricle from the auricle. In addition, there is, however, in many cases necessarily a reflux into the auricle at the systole of the ventricle. In proportion as the slit is narrow, the possibility of such reflux is less, and in extreme cases of stenosis it appears probable that no regurgitation is possible. In all cases, the main difficulty is the obstruction; that of regurgitation is subsidiary though frequently coexistent. It requires only a slight consideration to be convinced that quite a different set of conditions obtains in mitral stenosis to that manifest in mitral regurgitation. Morbid anatomy teaches us that in stenosis the left ventricle is usually not dilated; it has its normal capacity, or is even smaller than natural. We should expect so: for the difficulty is not that the ventricle is habitually overfilled, as in regurgitation, but that it is insufficiently supplied owing to the imposed obstruction.

Upon the left auricle, the consequences of mitral stenosis are very manifest. It is usually not only dilated, but hypertrophied. When