THE BIOLOGICAL SIGNIFICANCE OF OVARIAN TUMORS IN THE FOWL

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During the last two years, 40 cases of the occurrence of tumors in fowls, in an annual population of 800, have been observed. About 25 per cent of these were of ovarian origin and it is proposed to discuss their significance in this paper.

As a preliminary, some remarks may be made on the structure of the ovary of the fowl. It is not proposed to deal here with the gross anatomy, general physiology, or embryology, as these are fairly fully discussed elsewhere, (Lipschütz (1), Lillie (2), McGowan (3)). The present survey will deal rather with the types of cell to be found, in view of these being potential sources of tumor formation.

Germinal cells, in the shape of ova in the ovarian follicles, are of course a numerous cell type. Next in importance are the cells of the *membrana granulosa*. As discussed elsewhere (3) (4), these are probably derived from ordinary peritoneal epithelium and are essentially of the same nature as the *interstitial* cells which constitute at times a large portion of the ovarian stroma. Both types of cells are mesoblastic in origin and correspond to the macrophages or free histiocytes, found elsewhere in the body in connective tissues, etc. Similar cells are found in large numbers also in the *theca externa* of the egg follicles. Besides these, and forming the ground work of the stroma, there is an ordinary connective tissue basis.

Pearl and Boring (5) in discussing the histology of the ovary of the fowl describe two special types of cell. The first variety, they state, is crowded with eosinophile granules and this they term the "interstitial" cell. They describe a second type, which they call the "lutear" cell, from an alleged resemblance to the

lutein cells of the mammalian ovary. This cell, they state is about three times as large as the "interstitial" cell. When follicular atresia is completed, it is said to contain a yellow pigment and for this reason Pearl and Boring designated it a "lutear" cell.

Elsewhere (6) it has been pointed out that, in all probability, these so called "lutear" cells are macrophages containing iron pigment, a substance for which Pearl and Boring did not however examine. It was questioned, therefore, if true lutein cells, such as occur in the ovary of the mammal, existed here. The cell in question would seem rather to be a variety of the ordinary *interstitial* cell or ovarian macrophage as already described, which in this case has participated in the removal of haemorrhages, obtaining in this way a supply of iron.

With regard to Pearl and Boring's "interstitial" cell with eosinophile granules, it was also suggested that these, in all probability, were cells of haematopoietic origin (myelocytes). This view was already arrived at before one was aware that papers on this subject had been published by Goodale (7) and by Nonidez (8). These authors had pointed out that they considered the granule bearing "interstitial" cells of Pearl and Boring to be modified blood elements without, however, defining them more closely. Nonidez further considered that the "lutear" cells of Pearl and Boring were derived from degenerating sexual cords.[1] If by this is meant a direct derivation, then, of course, this view differs from the one already suggested above on this point.

The question arises for discussion and may be dealt with at this point as to how the ovary in the fowl comes to be supplied with haematopoietic cells. In this connection it may be pointed out in the first place, that the organs of the genito-urinary system are derived from a definite well-defined portion of the mesoblast, called the *Nephrotome* or *Intermediate-cell-mass* (Lillie, *loc. cit.*, 190), a point the significance of which will be discussed immediately. Jolly (9, p. 598) emphasizes the fact that the presence of haematopoietic tissue, specially interested in the formation of myelocytes, is common in the genital glands of certain fishes and

[1] *Vide*, however, Rasmussen, Special Cytology (Cowdry), 1928, Vol. ii, p. 1222, for a considered negation of this view.

batrachians. In *Protopterus* this tissue is directly continuous with that of the kidney and has the same composition. Here it occurs chiefly on the periphery of the kidney and is continuous with a mass of the same kind which binds the two kidneys on their dorsal aspect. He shows that, in this situation, the haematopoietic tissue, which entirely surrounds the genito-urinary system, is continuous with that which surrounds the intestine. These considerations have a bearing not only on the present question, but also on that of the frequency with which blood-forming tissues are found in the kidneys of mammals, including man, in disease conditions. The renal-portal system, embryonic in birds, permanent in some other vertebrates, together with the sinusoidal character of the blood vessels of the mesonephros of birds is only another aspect of this same haematopoietic relation.

Even stronger evidence for the mode of origin of the haematopoietic cells of the ovary of fowls is obtained by a consideration of the method of blood formation in Teleostean fishes. In these, as Jolly (*loc. cit.*, 550) points out, blood formation is exceptional in that the blood *anlage* forms inside the body of the embryo and not extracorporeally on the wall of the yolk sac. Its site of formation is in the *Nephrotome* or *Intermediate-cell-mass* already referred to, which lies in the embryo between the *Somites* and the *Lateral-plate*. As already mentioned this structure also gives rise to the genito-urinary apparatus. In other words, therefore, blood formation and the formation of the kidneys and the genital glands, all occur in one and the same area of the mesoblast. Having regard to the fundamental essential similarity in development of embryonic forms, it is easy to see therefore how the ovary of the fowl should be endowed with haematopoietic tissues. In this connection Jolly (*loc. cit.*, 553) points out that this mode of blood formation in the Teleostean fishes is merely a variety of the extra corporeal blood formation in the yolk sac found in other vertebrates. Intermediate cases between the two extremes occur. It should be noted moreover that in all the cases, even the extreme ones, blood formation is still virtually occurring on the wall of the primitive gut.[2]

[2] Blood formation in the liver and spleen of vertebrate embryos is another aspect of the same subject.

These haematopoietic cells, as found in the ovary of the bird, usually occur in the form of myelocytes. They may however, be present in more embryonic form as, for instance, in the form of histioblasts, premyelocytes, etc., or more rarely in a more developed form, the polymorph. As already pointed out elsewhere (10), the true *interstitial* cell of the ovary is a macrophage and its presence in the ovary in such large numbers is due to its phagocytic capabilities, coupled with the opportunities that are afforded in the ovary in the shape of aborting egg follicles, etc., for its displaying them. Together, these two types of cell give the stroma of the ovary the appearance of granulation tissue.

Vestigial remnants of the Wolffian body, etc., may be present in the ovary and may afford cells from which tumors could arise. It may be mentioned in passing, however, that no tumor corresponding to such a source has been found in the present series.

In the literature, one has been able to find only one reference dealing with the frequency of spontaneous tumors in the domestic fowl. Unfortunately neither the types of tumors nor their site are recorded. Schneider, (11) who writes the paper in question, finds an increase of tumors in the second half of the pullet year over the first half. He thinks that there is some evidence to indicate that heavy antecedent egg production is associated with a rise in the tumor rate. The normal annual tumor rate for fowls between the ages of six and eighteen months he gives as about two to three per cent.

The present series of cases is not large enough nor have they extended over a period long enough to warrant deductions of the nature of Schneider's being drawn. One has concentrated rather on the types and situations of the tumors found, to see if these offered anything towards a solution of their occurrence.

During the last two years, as already mentioned, in an annual population of 800 hens, 40 cases of tumor occurrence have been observed. These will be considered under the headings, ovarian and extra-ovarian. Of the extra-ovarian cases, which will not be further dealt with here, there are 28 and all these are cases of leucosis with tumor formation. Many of these in addition have ovarian involvement, inasmuch as leucosis is a system disease. The twelve cases left are, however, of primary ovarian occurrence.

The nature of these last cases may now be considered in a general fashion. No *Germ-cell* tumor was observed. Such if it occurred would probably be of the nature of a teratoma. "Epithelial" tumors, of a cystic or solid cell mass type and arising from the *membrana granulosa* of the ovarian follicles, were rare—two cases. Such growths, though superficially epithelial in type, are of course essentially mesoblastic. Two cases showed tumors formed of myelocytes or premyelocytes.[3] Growths consisting of more embryonic cells of the myelocyte lineage occurred in the ovary, only however as secondary to primary affection elsewhere. The most frequently occurring tumor (eight cases) was of the *Rous sarcoma* type. This arises in all probability from the macrophages or true *interstitial* cells.

Omitting the myelocytic cases as being of the nature of leucosis, the tumors of the ovary represent 25 per cent of all the tumors found in the fowls of this series. This is a high percentage and the proportion becomes relatively much greater if one considers that the extra-ovarian tumors found here are all of the myelocytic leucotic type, while the ovarian ones under consideration are of a fibro-sarcomatous nature. One therefore investigates to see if any reason can be assigned for the greater frequency of occurrence of these fibro-sarcomatous tumors in the ovary.

The modern type of fowl, especially the White Leghorn with which the present observations have to do, has been developed along the line of egg laying capabilities. Instead of laying 30 eggs in the year, as fowls in their undeveloped state do, such breeds produce anything up to and exceeding 300 eggs in the same period. This must involve very greatly increased metabolic activity in the ovary of the latter as compared with the former. Already Schneider (*vide supra*) has drawn attention to a possible relation between egg laying and tumor formation in his series of cases. Whether the tumors referred to occurred in the ovary and whether he attributes their origin to the exhaustion of egg laying or to a local effect, he does not state.

If attention is confined to the *Rous type* of tumors in the above

[3] Myelogenous leukaemia or leucosis is usually regarded as having a central or marrow origin. The cases in the ovary of the fowls would seem to indicate that at times the origin may be peripheral.

series and if the condition of the ovary is regarded in the light of their occurrence, some important considerations arise. The greatly increased activity of the gland must bring about a greatly augmented process of removal of debris and detritus (such as aborted egg follicles, their remnants after the yolk is extruded, blood, etc.), from the ovary and hence greater activity on the part of the cells directly concerned, the macrophages or free histiocytes. It does not surprise one to find, therefore, that microscopical examination of the ovary reminds one forcibly of a granulomatous condition and in particular of the granulomatous condition already described as appearing in the peritoneum of fowls the subjects of tar injection intraperitoneally (12). In the latter case, after a preliminary granulomatous stage, fibromatous tumors of the *Rous type* appeared in a considerable proportion of the cases. It does not seem too far fetched to suppose that the *Rous tumors* in the present instance have a similar pathogenesis.

In both cases it would seem that the presence of an irritant is involved basically. In the ovarian cases, it is of the nature of an abnormal intensive physiological stimulus which produces locally all the effects attributable to a local irritant; in the other, an actual concrete irritant itself is operative. In both cases there is an increased functioning of certain cells of the part to perform a necessary operation, namely, the removal of material which is or has become of a nature foreign to the part. In both cases, possibly from an effort to cram too much work into too little time, the operation would appear to have got out of hand, the process has become chaotic and perverted, and a tumor has resulted.

So far one has dealt with one aspect only of the activities going on in the ovary, namely those having relation to the removal of disintegrated products. Very intensive anabolic changes, however, are going on at the same time in connection with the building up by the "epithelial" lining of the follicles, of the material in the egg follicles of the greatly increased number of eggs produced. Here again one may suppose that the process breaks down under the time limit and tumors of an "epithelial" type result from cells performing an epithelial function.

It might seem from these observations that, if the cells of a

tissue are stimulated to a prolonged, abnormal and unnatural degree of functioning, whether by a local irritant or physiological impulses, there is a possibility, especially if cells, with a considerable reserve of developmental potentialities either in them or behind them, and of an embryonic nature, are involved, that there will be hasty and irregular improvisation of the cell machinery to meet the call. The finely adjusted balance of the activities of the tissue cells to one another and to the body as a whole of ordinary conditions will be upset and a state of disorder, anarchy and disharmony ensue, which may easily lead to tumor formation, that is, to a continuous piling up of cells which, owing to their mode of origin, are in reality useless and unable to perform their intended function.

Behind this view is, of course, the idea that *Function* dominates the life and activities of the cells, that they have a purpose in life, and that they react to all and any type of stimulus by attempting to exhibit, in whole or in part, their specific function. This signifies also that hypertrophy passes by easy gradations into tumor formation. In the condition of limited progression, from which the name is derived, hypertrophy occurs most typically in tissues the cells of which have no reservoir of cells with developmental potencies behind them and where time is allowed for a stabile edifice to be constructed.

As local "irritation" of a tissue is less likely to be co-ordinated to the wants of the body as a whole than central, nervous or hormonic, stimulation, it would seem to be more prone to bring about tumor growth inasmuch as the resultant activity will be by this of a more disharmonious order. In the case of the ovary, both influences may quite well be operative.

Some of the considerations previously discussed may have a bearing on the elucidation of the occurrence of special disease conditions in human beings. Thus the association of the kidney with haematopoietic tissues in the embryo throws light on the appearance of blood forming tissues as tumors, in leucosis, etc., in the kidney of the adult.

Round celled sarcomata are especially common in the ovary and the testicle. The explanation of their occurrence, difficult

under ordinary circumstances, possibly becomes easier if regard is had to the inclusion in them in the embryonic state of haematopoietic tissue. In this connection it may be mentioned that Muir (13), sensing that a special explanation is required, suggests that such tumors do not arise from ordinary connective tissue, but possibly from undifferentiated embryonic cells or possibly from the *interstitial* cells.

The occurrence of the *interstitial* cells of the ovary and testicle, as disposed around blood vessels, is stressed by such authors as Lipschütz (14), Sharpey-Schafer (15). While this may indicate, as these authors suggest, a ready means of absorbing an internal secretion, it is equally justifiable to suppose that it is a periarterial arrangement of the cells with its usual implications. Sharpey-Schafer (*loc. cit.*, 362) would seem to question here the ductless gland idea, for he says that the cell masses, although arranged in a suggestive manner around the blood vessels, are not especially vascular, indeed far less so than is the case with most endocrine organs. Such considerations may afford a basis for an explanation of the frequency of occurrence of peritheliomata in the ovary and testis as mentioned by Ewing (16).

SUMMARY

An examination of the ovary of the embryo and adult fowl shows that haematopoietic tissues are important constituents of its stroma. The bearing of this on tumor formation, etc., is discussed.

The ovary in modern breeds of fowls is in a state of great functional activity owing to the increased egg production. On the one hand, there is great productive, on the other, great removal, activity. In respect of the latter function, the actively functioning ovary may be said to be in a condition of lasting *granuloma*.

Tumors of the ovary of the fowl are relatively very common. This seems to be correlated to its great functional activity. The possible bearing of this conception of the genesis of tumors in general is discussed.

The idea underlying the present view is that unnatural hyper-

stimulation, whether by means of a general nature such as nerve impulses, hormones, cledones[4] etc., or locally by irritants, leads through hypertrophy and hyperfunction to a condition of perversion of growth and dysfunction or absence of function. To stimuli of very varied nature the organ, tissue or cell reacts uniformly by increasing the machinery for functioning and thereafter exhibiting increase of its intrinsic and specific function. As in other machinery, however, persistent and erratic overworking leads to break-down and disintegration. This conception applies not only to tumors, including leucosis, but also to other disease conditions of which pernicious anaemia may be cited as an example.

It is pointed out that the occurrences in the ovary of the fowl may have an important bearing on the interpretation of certain tumors of the ovary and testicle in man.

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[4] *Vide* McGowan. Edin. Med. Journ, 1929, 36, 645.