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## SOME POINTS IN REGARD TO THE GENESIS OF MESOBLASTIC TUMOURS.

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THE experiments to be recorded here have reference to the effect of intraperitoneal inoculation of coal-tar into fowls. One object in performing them was to test the effect of this substance on the bone marrow in relation to blood formation.

As described elsewhere,<sup>1</sup> the peritoneal cavity in fowls is in direct communication with the marrow of the medulla of the bones. It was hoped thus to introduce the tar directly into the marrow as one had previously introduced powdered glass.<sup>1</sup> The inflammation set up, however, by the tar closed the stomata to the marrow and prevented this. In actual fact, with the exception of a slight anaemia in one case, cock 14, no symptoms referable to the blood system were produced in any of the inoculated fowls. This aspect, therefore, except for a further passing reference, need not be further dealt with.

In a previous case already referred to, where sterile powdered glass had been injected intraperitoneally into a fowl,<sup>1</sup> a large mesoblastic tumour, the size of a Jaffa orange and attached by a fine pedicle to the duodenum, had developed. Another object, therefore, in performing these experiments was to test the effect of such a carcinogenic agent as tar in this direction.

The coal-tars used were, in the first place a dehydrated crude sample, produced from Scotch coal in vertical retorts in Aberdeen Gas Works and, secondly, one which, in the hands of Professor Archibald Leitch, had produced, by painting the skin, carcinomata in mice. Both were diluted to a 10 per cent. solution in Paraffinum Liquidum (B.P.) before injection. All of

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the birds received inoculations with the first tar sample, some in addition were treated also with the second one. All received multiple inoculations at weekly intervals.

With the exception of the slight anaemia already referred to, none of them, even after a long period and many injections, showed any symptoms that could be regarded as evidence of poisoning by the tar. It was thus possible to keep the birds for observation for some considerable time.

Some details of the more important points in the experiment may now be given. It lasted from the beginning of September 1928 to the middle of January 1929. White leghorn cocks, aged six months at the beginning of the experiment, were employed. Eleven were inoculated, numbered consecutively from 10 to 20. To each of them, at the beginning, was administered intraperitoneally, by means of a syringe, from 2 to 4 c.c. of the 10 per cent. solution of Aberdeen tar in liquid paraffin. This was repeated at weekly intervals. Meanwhile, on or about the 20th November, four of them, namely cocks 15, 18, 19 and 20, were killed by weasels. On the 23rd November and again on the 29th, those remaining, namely cocks 10, 11, 12, 13, 14, 16 and 17, received 2 c.c. of a 10 per cent. solution of the London tar instead of the Aberdeen material. After the last date, no further injections were given.

The appearances present on the naked eye examination of the various birds will now be described. Of the cocks killed by weasels, only two were available for examination. The others had been entirely devoured by rats, the bones only being left. Cock 20 had been attacked but the gizzard and part of the intestine were still left undamaged in the abdominal cavity. They showed a uniformly greatly thickened peritoneum and a round, smooth nodule of the size of a pea and pure white in colour on the anterior surface of the gizzard. Cock 15 was intact. Its abdomen was filled with an oily brownish fluid; the peritoneal lining was uniformly thickened and there was a solid exudate over the surface of the liver and gizzard, rendering both adherent to the anterior abdominal wall. The other organs showed nothing abnormal.

Cock 17 was found dead on 2nd January 1929. The only lesions of importance in this case were some peritoneal exudate, a uniformly thickened peritoneal lining which was also studded all over with rounded smooth nodules the size of a pea, most of them white, some, however, slightly blackish.

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Between the 14th and 18th January, the remainder of the birds, namely cocks 16, 13, 11, 10, 14 and 12, none of them obviously out of condition, were killed. In all, there were peritoneal effusion and uniform great thickening of the peritoneum. In cocks 13 and 16 there was in addition a mass of tissue behind the gizzard, rendering this adherent to the surrounding organs. This contained some black pigment. In cocks 10, 11, 12 and 14, further to the findings already described there occurred numerous tumours, attached often by a thin pedicle to the peritoneum. They varied in size from that of a small pea to one of the size of a plum, which occurred in cock 10. They had a characteristic appearance, being round, smooth and of a porcellanous whiteness. In addition, the tumours had a very mucoid, slimy consistence, evidenced in one direction by their eluding the grasp of the forceps when an attempt was made to hold them for cutting up. These characteristics have often been observed in others of the less malignant type of Rous tumours, encountered as sporadic occurrences.

It should be emphasised at this stage that, in several of these fowls, while the whole of the peritoneal surface was subjected to the same irritant, three different conditions were found present as a result, often in the same fowl. Thus there occurred a uniformly thickened peritoneum, thickened adhesions between various organs and isolated tumours on free surfaces. The possible significance of this will be discussed later.

Cock 14 exhibited a special pathological finding in that it showed considerable development of cysts in the marrow of the long bones. During the period 23rd October to 3rd December it presented evidence of anaemia. The haemoglobin percentage, 45 per cent. at the beginning of the period, improved, however, to normal towards the end.

The microscopic appearances of the various lesions present will now be described. This has reference in the main to the conditions found in the peritoneal cavity, as this alone appeared to be affected.

The earliest stage found present appeared to partake of the nature of a granuloma. There was a dense tissue matrix forming a background. It consisted largely of a collection of polymorphonuclear leucocytes together with a very few stellate, branching, reticular cells. These latter were slender structures with branching arms and at this stage entirely without vacuoles.

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In the matrix just described were embedded numerous, multi-nucleated, very vacuolated giant cells. These were rounded in outline and enclosed in their centre a much larger single vacuole. At the same time there were present also numerous larger spaces, enclosed by a thin sharply defined limiting membrane, which showed often a single flattened nucleus (Figs. 1 and 2).

The vacuoles were for the most part empty—a few exceptionally contained a little black pigment derived from the tar. Thus Fig. 3 shows carbon pigment inside some of the vacuoles. The smaller collections of tar are inside multi-nucleated giant cells. Possibly all the vacuoles at one time may have contained tar or oil. This may have disappeared spontaneously or by being dissolved out in the process of making sections. The origin of the larger spaces would seem to have been by distension and thinning from the multi-nucleated giant cells, which in turn appear to arise from the reticular stellate cells already described.

The next stage appears to be associated with the disappearance of the polymorphonuclear infiltration and of the multi-nucleated giant cells as such, and with the appearance of a large number of very vacuolated reticular cells forming a network (Figs. 4 and 5). Such cells are typical macrophages or free-histiocytes. The tissue has a sponge-like appearance from their presence and from the persistence of the larger vacuoles previously described.

Groups of histioblasts or resting-wandering cells are also present on occasion at this stage (Fig. 6). They are characterised by angular outline, unstained nucleus, and deeply basophil cytoplasm. From these are derived many of the macrophages or free histiocytes already referred to.

In the next stage the tissue evolves in one of two directions. Thus it may become ordinary connective or scar-tissue (Fig. 7). This especially occurs in regions of adhesion.

On the other hand, on the free surfaces of organs it may develop into rounded tumours. Histologically, these are of the nature of fibromata and are without the vacuolisation or other appearances already described (Figs. 8, 9, 10). The occurrence of these fibromata on free surfaces and on surfaces subject to friction and slip may be emphasised in passing.

The appearances of a tumour produced by the intraperitoneal injection of powdered glass into a fowl may now be described for comparison. Fig. 11 shows a section of part of this tumour which, it will be seen, contains vacuoles and

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vacuolated giant cells and corresponds to the vacuolated tar tumour described above. Fig. 12, on the other hand, shows a portion practically entirely fibromatous, while Fig. 13 from the same tumour shows a network of macrophages, corresponding to that seen in the tar condition. Thus the powdered glass has produced the same effects as the tar.

For comparison, two illustrations from sporadically occurring fibromata in fowls are submitted. Fig. 14 is from a section of a spontaneous tumour in the leg of a fowl (hen 140) which, naked eye in its whiteness, smoothness, non-infiltrating character and its mucoid slimy consistency, resembled the tumours in the tar fowls above. In this case there was a secondary growth in the heart and the tumour was transplanted for one generation but was lost in the second.

Fig. 15 is from a section of a tumour on the under-surface of the wing of a fowl (hen 35) caused by a weasel-bite. This tumour had extensive secondary growths in the thorax and abdomen.

Without an extensive discussion of the matter, it would seem possible to draw the conclusion from the cases described that in the tar cases we are dealing with the occurrence of a granuloma which, in part, has developed into ordinary connective or scar tissue and in part into a definite tumour, a fibroma. The appearance of the tumour refers of course to its initiation only: once initiated it progresses, tumour tissue giving rise to tumour tissue without having to pass through a granulomatous stage.

Such a happening would seem to have a bearing on a commonplace in the discussion of such conditions, namely the question as to whether such lesions are granulomata or tumours. Both views are held. The truth would seem to be that, in many cases, the granuloma may be a stage towards the development of a fibroid mesoblastic tumour and that, in certain tumours, there may be found a mixture of the two conditions persisting together.

A possible deduction from the occurrences described in the tar fowl is, having regard to the granulomatous condition and its dual fate, that tumour formation in the mesoblastic tissues is repair gone wrong. This would seem to be warranted inasmuch as in the peritoneal cavity of the same fowl subjected to the same conditions part of the granulomatous tissue has become normal scar tissue while another part has become a fibromatous tumour.

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While the full reason for this differential development may not be to hand, its occurrence should be emphasised. There is a possible hint as to causation in the fact observed, namely that, while adhesior tissue became eventually normal scar tissue, tissue on a free surface, although capable of forming scar tissue as in the thickened peritoneum, tended in places to develop towards fibroma formation. In the latter case there would be an absence of tension phenomena between the two adhering surfaces during the process of maturation of the tissue. In addition there would be the presence of an unwonted factor, namely, that of "slip" between the opposing surfaces of the peritoneum. It is possible that as connective tissue is developed to sustain tension, the absence of this tension, due to these two factors, during its development might give the tissue a push in the wrong direction.

This last consideration raises the general question of the possible determining cause of tumour formation. The majority regard it as due to some form of irritation : a minority, however, look on it as due to specific cancer producing substances, as apart from irritation. They argue that in those cases where there is gross naked eye injury done to a tissue by an irritant, tumour formation rarely occurs : and that carcinogenic substances may produce cancer without much evidence of "irritation." Such a statement of the case limits the possible results of irritation to something gross and palpable. Naturally the phenomena of inflammation, an affair in the main of the connective tissues, and which appears to be taken as an index of the amount of irritation, would be much less in the case of an irritant affecting an intact epithelial surface than in the case where the epithelial surface had been broken through and a bacterial invasion had taken place.

Ewing<sup>2</sup> would seem to state the case fairly where he remarks that nearly every variety of influence capable of disturbing the nutrition and equilibrium of the cell has been connected with the origin of some form of cancer. It would seem therefore to be unnecessary to substitute a multitude of different specific cancer producing bodies for the finer gradations of cell irritation, that is those having to do with the interfering with the normal life of, and with what one might call, a constant "nagging" at the cell. All tumour producing substances would appear to have this in common that in order to produce their effect they must all pass through the gateway of irritation.

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As the subject has been discussed elsewhere<sup>3</sup> very little need be said at this stage regarding the nature of the supposed ultimate cause of tumour formation, except to state that there is no evidence for this being of the nature of a living multiplying virus. Apart from evidence discussed elsewhere and not germane to the present issue, in the instances dealt with here, tumours have been produced by such things as tar and powdered glass, where the presence of such a virus should not come into question. The occurrence of a tumour following on a weasel bite only serves to emphasise the present point of view. The inflammation occurring here, due to the organisms present, whatever these were, produced a non-specific irritation and interference with the development of normal repair, which in its turn led to the production of the tumour.

So far one has been discussing the question of tumour production as contrasted with the phenomena of normal repair. In parenthesis it may be said that, in this communication, one is dealing solely with mesoblastic tumours of a fibromatous type as they occur in the fowl. The question arises whether such tumours are all of the same nature differing possibly only in degree.

Examination of a considerable number of them, of the spontaneously occurring and experimentally produced types, leads one to conclude that they can be regarded in this light. The aetiological evidence, such as it is, leads one to this conclusion. Histological examination shows that, although they may vary considerably in architecture, even in different areas of the same tumour, parts being very dense while others are of more open texture, they are all modifications of connective tissue, using this word in its broadest sense, the more common varieties conforming readily to the category of fibromata.

Such a statement refers equally to simple and malignant tumours. The question now arises how these two types are to be distinguished. Histologically the more cellular a tumour is and the more embryonic in type the cells are, the more likely it is to be malignant and conversely. The main distinction, however, between the two groups is a biological one. Malignant tumours grow much more rapidly, invading other tissues meanwhile, and are liable to produce secondary growths in the animal's own body or by transference in the bodies of animals of the same species.

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The greater rapidity of growth and invasive power is merely an indication of the cellularity, etc., and need not be further discussed. The power of producing secondary growths requires, however, further elaboration.

The cells involved in these tumours are of the monocytic or macrophagic and the fibroblastic lineage of the reticulo-endothelial system. This has been shown in addition to other evidence quite definitely by the work of Carrel, Fischer, Haagen, etc., on tissue cultures from such tumours.<sup>3, 4</sup> The microscopical appearances in the tar and glass tumours in the above fowls lends support to this view, inasmuch as the two main types of cell active there, as already shown, are the macrophages and the fibroblasts.

In parenthesis, a word may be said regarding the great importance of the reticulo-endothelial system in connection with the subject under discussion. The authority on this matter is Maximow. A glance at the diagram in his paper,<sup>5</sup> p. 588, will show how the many types of macrophagic cells all end up by becoming fibroblasts. The phenomena of repair can be written practically in terms of these two types of cell. This subject is discussed more fully elsewhere.<sup>3</sup>

Carrel, Fischer, Haagen, and others have shown by tissue cultures from such mesoblastic tumours as the Rous tumour, arsenic and indol tumours that the agent, by which the tumour can be transferred to other fowls, exists and multiplies in the macrophage but that it is absent from the fibroblast. In later work, however, Carrel,<sup>6</sup> dealing with rat sarcoma No. 10 of the Crocker foundation and with the Jensen rat sarcoma, has shown, also by tissue culture, that the fibroblast is capable, as well as the macrophage, of carrying and producing the infecting agent.

It appears, therefore, that the cells involved in these fibroid mesoblastic tumours, the macrophage and the fibroblast, may produce and carry a substance which enables them on inoculation to reproduce the tumour. This substance in fowl tumours can be separated from the cells which contain it by filtration through porcelain filters and, thus purified, is able still to reproduce the disease on injection.

Various views have been held and are still held regarding the nature of this agent. Some, like Gye, regard it as an absolutely necessary adjuvant to a non-specific living cancer virus. The majority, however, now regard it as a chemical

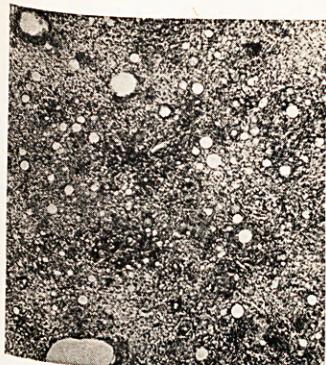


FIG. 1.—Cock 11: coal-tar inoculation into peritoneum: low power: thickened peritoneum: granulomatous tissue, showing a background of polymorphonuclear leucocytes and a few stellate reticular cells, in which are set round spaces of various sizes and multinucleated vacuolated giant cells—the darker spots.

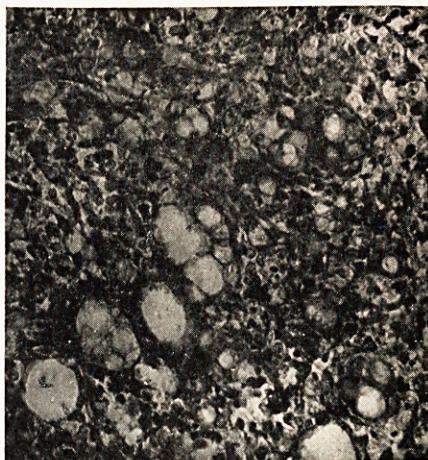


FIG. 2.—Cock 11: high power of same, showing especially the multinucleated, vacuolated, giant cells (round the larger vacuoles).

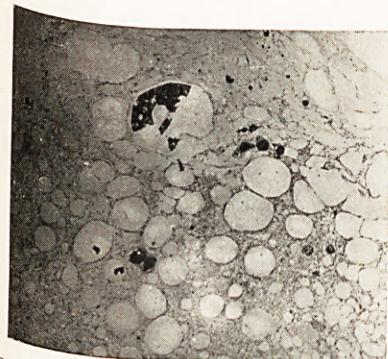


FIG. 3.—Cock 12: tar inoculation as before: low power: thickened peritoneum, showing numerous round spaces in the granulomatous tissue, a few of them containing tar: the smaller tar patches are inside multinucleated giant cells.

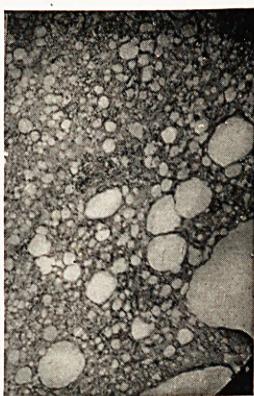


FIG. 4.—Cock 14: tar inoculation as before: low power: later stage than in Fig. 1, showing a network of vacuolated cells—macrophages—enclosing larger spaces.

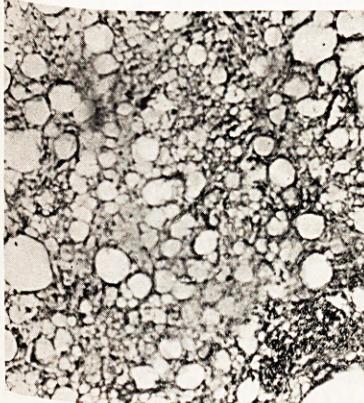


FIG. 5.—Cock 14: high power of last; showing vacuolated spongy-cells, the macrophages: absence of polymorpho-nuclear leucocytes.

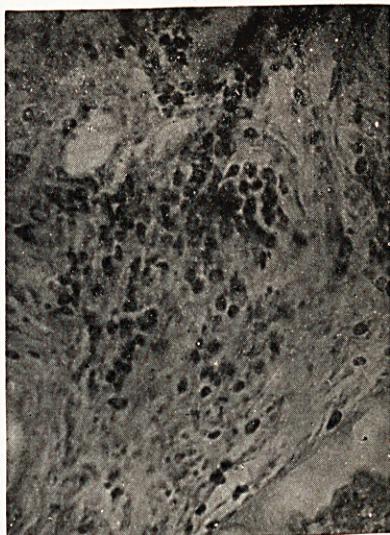


FIG. 6.—Cock 12: tar inoculation as before: high power: macrophagic tissue as in Figs. 4 and 5, showing a nest of histioblasts (resting-wandering cells of Maximow: note angular shape, unstained nucleus: deeply stained basophil cytoplasm).

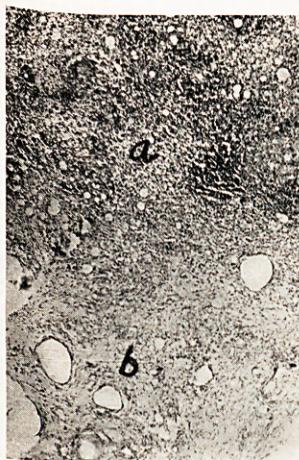


FIG. 7.—Cock 14: tar inoculation as before: low power, showing junction of granulomatous tissue *a*, with scar tissue, *b*.

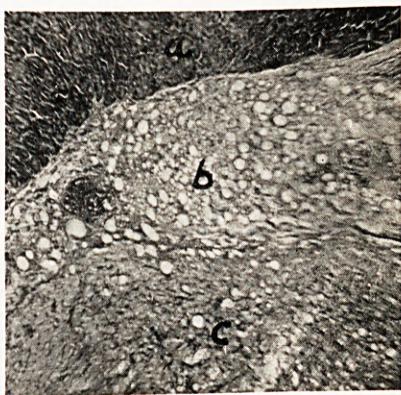


FIG. 8.—Cock 14: tar inoculation as before: low power, showing junction of granulomatous *b*, with fibromatous *c*, tissue: *a* is pancreas.

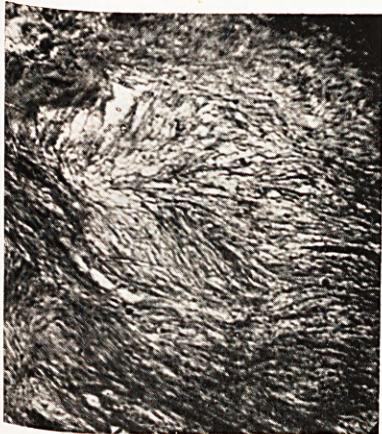


FIG. 9.—Cock 10: tar inoculation as before: low power: section from fibromatous tumour the size of a plum.

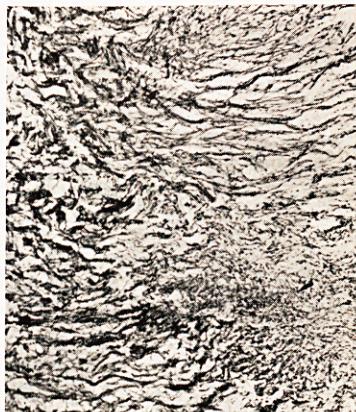


FIG. 10.—Cock 20: tar inoculation as before: low power: section of fibromatous tumour.



FIG. 11.—Cock 91: glass powder inoculated intraperitoneally: section of part of resultant tumour, size of Jaffa orange, showing a granulomatous condition with formation of vacuoles and macrophagic giant cells.

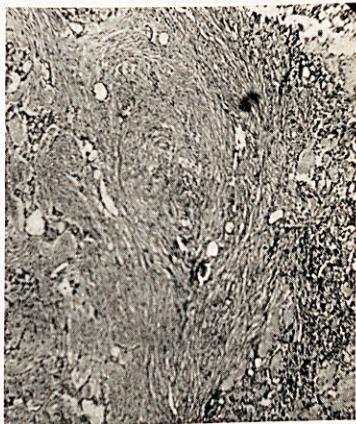


FIG. 12.—Cock 91: section of another part of tumour showing a more fibromatous condition: low power.



FIG. 13.—Cock 91: section of another part of tumour showing branching vacuolated macrophages: high power.



FIG. 14.—Hen 140: encapsulated spontaneous fibroma from leg of fowl: secondary growth in heart: transplantable for one generation: low power showing fine fibrillæ and at other parts the tumour more densely fibromatous.



FIG. 15.—Hen 35: section of fibroma from wing of a fowl, due to a weasel bite: secondary growths in thorax and abdomen: low power showing fine fibrillæ.

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substance, capable in itself alone of instigating tumour formation. Different ideas, however, exist with regard to the nature and mode of action of this chemical substance. This matter is discussed elsewhere<sup>3</sup> and a short summary, of the conclusions arrived at, alone is necessary here.

As already mentioned, these tumours are to be regarded as belonging to the monocytic or macrophagic lineage of the reticulo-endothelial system. Evidence was adduced from a consideration of leukæmic and other tumour conditions in the fowl that, when a primary tumour of this nature is formed, having been led up to by non-specific irritation of some type or other, there is a tendency for the formation, by the cells of the primary tumour of a specific chemical substance. So far, one is in accord with the more recent views.

This chemical substance, which was designated a "stimulin," was conceived as having the power, on its being absorbed and distributed by the blood, of stimulating embryonic non-developed cells of the reticulo-endothelial system throughout the body to develop along the lines of the originating cells. In this way an attempt was made to explain the secondary growths of the malignant tumours of this type in various regions in a single animal's body. They are regarded as growths within a system, the reticulo-endothelial system. They are not true metastases for these arise from cells set free from the original tumour which are carried by the blood, lymph, etc., to different parts of the body, where they proliferate and form new growths.

It is a commonplace with regard to such tumours that, in the beginning, they can be transferred by implantation to blood relations only of the host, but that after several such transferences they can be successfully transferred to members of the same race other than blood relations, and thereafter to members of other races or to the species in general. They cannot, however, be transferred beyond this to animals of a different species.

These occurrences have relation to the important question of the "specificity" of such tumours and the following deductions were drawn from them. Such a progression was regarded as one from the reticulo-endothelial system of the single fowl through that of blood relations to that of the race and species. Concurrently with this the "stimulin," which at first could only affect the reticulo-endothelial system of the host

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of the tumour was supposed to become gradually able, by "acclimatisation," to provoke tumour growth in the reticulo-endothelial system of the species.

The *modus operandi* of the spread of the tumour in the individual case, of the "specificity" of the tumour in the early transfers, and the subsequent partial breakdown of this "specificity" would appear to have been satisfactorily accounted for thus.

These remarks have reference only to the types of tumour dealt with here. There seems to be no reason whatever why the same views should not hold with regard to all true sarcomata, in which case their metastases would have to be regarded from an angle different from the usual one.

As has been said, the word "stimulin" was used to designate the chemical substance obtained from tumours with the qualities just delineated. This word, however, is used with other significations and it seems expedient to use a term with a meaning more or less restricted to the sense required here. The word "Cledone" might be appropriate. Originally, as  $\kappa\lambda\eta\delta\omega\nu$ ,\* it implied a message sent from Zeus which caused certain of the inhabitants of the world to comport themselves according to a certain fashion. By liberal substitution it might be made to imply here a chemical substance produced by a set of master-cells at one part of a system and sent out by them into the circulation, and which would cause undeveloped cells of this system at distant parts of it to comport themselves like the originating cells.

The literature appropriate to the present subject may be dealt with quite briefly. There has been a considerable amount on the question of the production of sarcomata in fowls by means of injection of extract of fowl embryo in conjunction with such substances as arsenic, indol, tar, etc. These are beside the point here and need not be further discussed.

The production of sarcomata by the injection of tar is discussed by Woglom in his monographic article.<sup>7</sup> He refers there to the production of a fibromyxoma by Yamagiwa, Suzuki and Murayama and by Yamagiwa and Murayama by the injection of tar and hydrous wool fat into the breast of a female rabbit. Lacassagne and Monod are mentioned as having produced a sarcoma in the testicle of a rabbit by injection of tar. Russell similarly is recorded as having produced a

\* I am indebted to Mr Andrew Gordon, M.A., for suggesting the use of this word.

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spindle-celled sarcoma in mice by subcutaneous inoculation of tar. At page 711 *et seq* the question of sarcoma production by the painting of tar on the surface of the skin is discussed. The difficulty of distinguishing such sarcomata from spindle-celled carcinomata produced under similar circumstances and so establishing their separate existence is stressed.

The subject is also discussed by Lewin in his Monograph on Tumours.<sup>8</sup> He mentions that cases of formation of sarcomata after the exhibition of tar have rarely been recorded. Many of the cases so chronicled have occurred in association with carcinoma. The question is thus complicated, as has already been indicated, by a difficulty in determining whether many of the so-called sarcomata thus encountered are not in reality carcinomata with fusiform cell formation by the epithelium.

From the discussion by these two authorities it would seem that the cases of sarcoma production following tar administration, especially tar inoculation, recorded in the literature are few in number.

From a survey of subsequent literature one has not been able to find much in the way of additional cases. Löwenthal<sup>9</sup> injected mice intraperitoneally with tar dissolved in oil and found in three out of forty-two the production of a sarcoma at the pylorus and root of the mesentery. Melzer<sup>10</sup> claims to have produced an alveolar sarcoma in rats by the inunction of tar. Choldin (quoted by Lewin) succeeded in producing in a hen by subcutaneous injection of an oil solution of tar, a true sarcoma which was transplantable.

The relation of inflammation and granulation tissue to the production of cancer is discussed by Ewing (*loc. cit.*, p. 5). He refers to the fact that often inflammatory growth passes by insensible gradations into neoplastic proliferation. He states that the conclusions of the older clinicians are justified in that cancer rarely arises on a previously normal tissue but only in tissues altered by chronic inflammation. He regards the neoplastic process as the correlative of the inflammatory one and believes that the latter may pass by insensible gradations into the former.

Lewin (*loc. cit.*, p. 24) also discusses this aspect of the subject. He refers to the work of Podwyssotzki and others on the production of granulomata and subsequently tumours by the injection intraperitoneally into guinea-pigs, rabbits, dogs, etc. of kieselguhr. He discusses also Stieve's work on kieselguhr

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tumours and concludes without sufficient reason, however, it would seem in some cases, that transitions from such granulomata to true tumour conditions occur.

The reaction of the tissues to an irritant with the production at first of a granuloma seems also to be the basis of the production of tumours in association with such macroscopic parasites as *Tænia crassicollis*, etc., and such microscopic infections as *Bacillus tuberculosis* and those causing syphilis, Hodgkin's disease, etc. This subject is discussed by Ewing (*loc. cit.*, p. 4) and Lewin (*loc. cit.*, pp. 84 and 88).

**Summary and Conclusions.**—Where coal-tar was injected intraperitoneally into fowls, granulation tissue or a granuloma was at first formed. Thereafter scar tissue was formed in some places while in others definite fibromata appeared. A possible reason for this differential development is suggested, while the fact of its actual occurrence is stressed as significant in regard to tumour formation.

It is emphasised that fibroid mesoblastic tumours appear to be of the nature of perverted repair processes.

The tumours here produced are compared with other like tumours. The general aetiology is discussed and a view previously stated is reaffirmed, namely, that such mesoblastic tumours (and possibly the majority of true sarcomata) are tumours within a system, the reticulo-endothelial system. Metastases in such cases are not regarded as true metastases.

The part played by the "stimulin" is rediscussed, and for reasons given a new designation, "Cledone," is suggested for this principle.

I am indebted to Professor Archibald Leitch for a sample of carcinogenic tar; to Mr James Ironside for preparing the photographs; and to the Carnegie Trust for the Universities of Scotland for a grant towards their reproduction.

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