Malignant Tumours in Fishes.

By

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With Plates I and II.

THIS paper contains a general account of about forty examples of tumours, mostly "malignant," found in eighteen species of fishes, all of them marine except two, a Stickleback and a Gold-fish. In all these cases the affection was a very obvious one, attracting immediate attention from the fishermen who caught the specimens, or leading to condemnation of the fish by market inspectors. In some cases the appearance presented by the fish was grotesque, or repulsive in the extreme. I give a list of the specimens dealt with on p. 447–8: all these represent "cancerous" affections. Many other diseased fishes, obtained in the same ways, have been seen and examined. Malformations of development, or growth; large healing scars due to wounds; repulsive ulcers of unknown origin; parasitic tumours and two cases of undoubted piscine tuberculosis (in Cod) have also been examined. Here, however, I refer only to tumours which exhibit the character of malignancy.

LIST OF CASES EXAMINED.*

(1) FIBROMAS.

Plaice (3 examples): On the head, dorsal and caudal fins (1908, 97; 1921, 227).

Halibut: In the body cavity (1912, 33).

Haddock: "Shelled-out" from the body muscles (1910, 39).

Pilchard: On the alimentary canal (1910, 37).

Ray: Myxofibromata in the distended mucous canals (1911, 62).

Conger: Hard nodules in the liver (1913, 50).

* The references are to *Annual Reports of the Lancashire Sea Fisheries' Laboratory*, Liverpool, for the years cited.

(2) Sarcomas.

Cod (3 examples): On the head near the orbit (1913, 52; 1919, 30; 1922, 88); one on the snout (1911, 55); one on the posterior part of the body (1914, 35); one on the stomach.

Haddock: On the head (1921, 227).

Ling: On the orbit (1922, 87).

Cat-fish: On the body behind the head.

Conger: On the orbit (1919, 32).

Turbot (2 examples): On the body (1922, 89; 1923, 99).

Flounder: Lymphosarcoma in the orbit with exophthalmos (1911, 57).

Gold-fish: On the body near the tail (1922, 96).

(3) Melanotic Sarcomas.

Skate (3 examples): On the pectoral fins (1911, 48; 1912, 35).

Skate: Multiple tumours in the flesh (1912, 35).

Ray: On the head near the orbit (1910, 41).

Ray: Multiple tumours in the flesh (1911, 52).

Halibut: Multiple tumours in the flesh (1914, 24).

(4) Cutaneous papillomas.

Halibut: Large multiple growth on the snout (1911, 67).

Turbot: Multiple growths on the body (1913, 47).

Haddock: Multiple warty growths on the body (1923, 101).

(5) Epithelioma.

Whiting: On the lower jaw (1923, 103).

(6) Angiosarcomas.

Stickleback: On the cornea (1914, 41).

Mackerel: On the body (1923, 120).

Cod: On the rete mirabile of the swimbladder.

(7) Ovarian Tumours.

Angler-fish: Numerous cysts on the ovary (1912, 25).

Ling: Papillary cystadenoma of the ovary (1914, 44).

(8) Goitre.

Box vulgaris: Two large thyroid tumours in the opercular cavities (1923, 113).

Sites of the Tumours.

Later on I shall specify more particularly the tissues in which malignant growths have been observed in fishes. The general regions of the body affected are indicated in the above list. Visible tumours, identified generally as sarcomas, occur most frequently in the region of the head, particularly in close proximity to the orbits, and spreading down into the mouth and pharynx. They have been found on the body behind the head on the fins and on the tail. They occur in the body cavity as outgrowths from the peritoneum and underlying connective tissues, on the swimbladder, on the ovary and testis, on the thyroid and in the cornea and choroid coat of the eye. The skin may be affected, but it is not usually the epidermis that is the tissue that undergoes malignant growth: it is rather the underlying layer of coarse ("collagenous") connective tissue fibres that is continuous with the septa that bound the muscle segments or myotomes. In only one case have I seen what may be regarded as an epithelioma. Looking at the above list from the point of view of tissue origin we see only one case of a tumour of hypoblastic origin—that of the goitre found in *Box vulgaris*—and only one case of a tumour of epiblastic origin—the epithelioma on the lower jaw of a Whiting. This is doubtful. In all the other cases the origin is from the mesoblast. Further, they are all "pulp" tissues that have originated from the persistent mesoblastic pulp, or mesenchyme. In Adami's terminology we have to do with "hylic tumours of mesenchymal origin."

The Criteria of Malignancy.

These visible fish tumours certainly belong to that kind of growths called "cancerous." Among them we find both "benign" and "malignant" tumours, and it is convenient to distinguish them in this way, though I think it would be most difficult to establish an absolute differentiation. In general a benign tumour is one which is sharply bounded from the surrounding tissues by a fibrous capsule. It grows very slowly, so slowly that its presence evokes a reaction from the adjacent tissues leading to the formation of the capsule. It grows in all its parts, peripherally and centrally. A benign tumour may lie freely (except for its stalklike attachment to the peritoneum) in the body-cavity, and such lipomas may attain a great size. It may lie in the muscles beneath the skin, and hardly at all attached to the capsule, so that on slitting open the latter the tumour may "shell-out." Biologically the very important distinction between the malignant and benign tumour is this local, *protective* reaction on the part of the normal tissues leading up to the circumscribing of the proliferating cell mass and its partial starvation, so that further growth is almost entirely arrested. It is probable that one important line of investigation, in the near future, will be the endeavour to induce the tissues round a cancerous growth to set up the reaction culminating in the formation of a bounding fibrous capsule.*

The absence of a capsule. First, it is to be noted that tumours have been studied (melanotic, multiple growths in the flesh of a Halibut) where the visible swelling was apparently sharply bounded and had an apparent capsule. But close examination of sections with a high-power lens showed that there was really a continuity between the tumour tissue and that of the adjacent parts, and that typical infiltrative (see below) growth was proceeding (see Fig. 7). The experience of surgeons is that tumours that are apparently benign may ultimately take on the condition of malignancy; the capsule may break down and rapid extension of growth may then become established. The only typically benign tumours seen, among the cases here studied, were two stalked ones (on the dorsal and caudal fins of a plaice). In man these would have been lipomatous, that is, composed mainly of fatty tissues, but in the fish they were loosely fibroid. Because of the narrow stalk by which they were attached to the host extension into the tissues of the latter was difficult or impossible.

Infiltrative growth. Highly typical of the malign tumour is the growing margin of the cell-mass (see later for details). The latter does not grow at all in its central parts, but only at its margins (where cell-division stages can be recognised). Here there is a gradual histological transition between the normal and the abnormal tissues, such that the latter insinuate themselves between, or infiltrate the healthy tissue elements, ultimately destroying the latter. *There is no protective reaction on the part of the organism*, and this is the truly sinister and biologically significant aspect of the process of malignant growth. Because of the infiltration the proliferating tissue may extend far beyond the visible limits of the tumour (say, along the lymph tracts), and so removal of the latter may not eradicate the growth with the result that recurrence may be exhibited. Thus even in removal of a carcinomatous breast, with the lymph glands in the axillæ, the furthest extensions of the roots of the growth may not be dissected away.

Generalisation with metastases. Therefore, we may have a primary growth, or focus, with secondary growths, or metastases. These metastatic tumours become established in this way: fragments of the original tumour become detached and get carried away in the blood- or lymph-vascular channels, become arrested at some place where the calibre of the vessels diminishes sufficiently and then undergo proliferation.

* See a letter in *Nature*, Nov. 10th, 1923, Vol. 112, p. 688, by Dr. J. H. Orton.

Thus the great tendency for metastatic growths to occur in the lungs (in man).

Three examples of such multiple tumours (Skate, Ray and Halibut) are given in the list. In these the condition of metastatic growths is apparently demonstrated in a beautiful way : thus the flesh of the Halibut was simply *full* of tumours which could be felt beneath the skin all over the body. They were melanotic, and so most apparent when the flesh was cut into. Now it is not at all clear that we have, in these examples, true cases of metastatic growth, for it has been impossible to demonstrate the origin of the secondary tumours by the proliferation of detached fragments of the primary growth, carried away in the blood or lymph streams and lodged somewhere as cell embolisms. Nor is it probable that this did occur : otherwise we should expect a certain frequency of sarcomatous tumours in the gills, analogous to the frequency of metastatic growths in the human lungs. I have, so far, seen no tumour on the gills of a fish, and it would be interesting to confirm this negative result by the study of much more numerous cases of malignant growths in fishes, occurring elsewhere than in the gills, liver and kidney : in the two latter organs there are portal circulations affording the opportunities for the occurrence of cell embolisms.

Besides, close study of the growth of the tumours suggests that it is the *condition of proliferation* that extends rather than that healthy tissues become inoculated with tumour fragments : obviously some thoroughgoing experimental work dealing with the results of *implantation* of fragments of fish sarcoma in healthy fish would be highly interesting.

Considered with respect to the three principal criteria : absence of capsulation ; marginal growth with infiltration and generalisation by formation of numerous secondary growths ; the majority of the cases recorded on pp. 447–8 represent malignant tumours.

Histological Nature of the Tumours.

With five possible exceptions we have to deal with sarcomatous growths in fishes : these exceptions may be noticed at once.

(?) *Epithelioma on the jaw of a whiting.* The fish was a small one, about 9 in. in length. On the right lower jaw was a very noticeable tumour about 1 cm. in diameter. It was papillated on the surface. On cutting it open numerous small rounded bodies were seen, and one of the smaller of these is represented in Fig. 20. Here we have something in the nature of an "epithelial pearl," that is a little, spherical body consisting of a nucleus surrounded by concentric fibrous shells. The nucleus consists of round or polyhedral epithelial cells, and the concentric fibrous layers are a *stroma*, that is, a fibrous structure originating in the tissues into which the epithelial nucleus has intruded. Fig. 17 represents several of the "pearls" in situ and part of the adjacent epithelium. Fig. 14 shows a section of the epithelium where it is thickest. Very probably the tumour has originated by down-growths of epidermis. These down-growths have been pinched off, giving rise to the "pearls." This is what the structure strongly suggests, but there is no indication anywhere of the actual connection of the "pearls" with the overlying epidermis.

(?) *Thyroid carcinoma in Box vulgaris.* In a very fine work on fish carcinoma, Gaylard and Marsh describe tumours of the thyroid that (under the name of "throat disease") cause great losses of young Trout and Salmon in fish hatcheries in the United States of America. The disease has been observed elsewhere. It is endemic in some ponds and hatcheries, and it is conveyed by some agent in the water. It is characterised, at first, by simple hyperplasia—that is, numerical increase in the tissue elements (the thyroid gland acini) without any change in their physiological relationships or functions. Then there is great overgrowth of the thyroid, with departure from normal structure, the simple acini becoming converted into cords of glandular cells without normal lumina. There may be typical infiltration of this glandular tumour tissue into the adjacent tissues, with destruction of the latter. In two cases there were metastases (a thyroid tumour on the snout of one fish, and a similar growth on the anus of another). Thus we have what certainly appear to be carcinomatous tumours—malignant growths of glandular tissue elements. In all cases observed so far this carcinoma of the thyroid has occurred among fresh-water fish and such as are either domesticated or artificially reared, or with a history that suggests domestication in the parents. In the case here recorded, a *Box vulgaris* obtained by a collector of the Marine Biological Association, the fish was a typically wild marine one. The affection was a huge overgrowth of the thyroid, probably accompanied by infiltrative growth (I was unwilling to destroy an unique specimen by dissection), but yet a profound hyperplasia rather than a typical carcinoma. A section of part of the growth is represented in Fig. 12.

(?) *Cutaneous papillomas.* Three cases of cutaneous papillomas are recorded here—an Halibut, Turbot and Haddock. These growths are of the nature of skin warts, that is, irregular outgrowths of epidermis having abundant cores of connective tissue. In the Halibut the growth was about the size of a man's closed fist, and was situated on the snout. The Turbot had little slightly raised pigmented spots about 1 cm. in diameter. The entire skin of the Haddock was covered by similar warty growths—a most noticeable thing. Now in none of these cases could the covering of epidermis be recognised, and the substance of the papillomata consisted entirely of the connective tissue cores. But the epidermis of a fish may be remarkably thin and easily abraded by rough handling—especially on raised parts where there is deficient nutrition. So I think that these cases were really cutaneous warts or papillomas, though a perfectly satisfactory demonstration cannot be given.

With these five exceptions all the tumours in the list on pp. 447–8 are sarcomas.

Sarcomatous Tumours.

A sarcoma is usually a rather richly cellular tumour. The cells are of the vegetative type, and are relatively undifferentiated. They have extraordinary powers of proliferation. Typically they form interstitial cell substance, which can usually be seen in such tumours by careful staining (as by Mallory's combination).

Six tumours in the list on pp. 447–8 are called "fibromas," suggesting that fibrous tissue elements, rather than "cells," are characteristic of their histology. But we remember that all fibrous elements are really nucleated cells, and that the "fibre" is to be regarded as drawn out cytoplasmic substance, or, in some cases, perhaps, "interstitial" cell substance. Further, no fish tumour seen so far is entirely homogeneous, and while some regions may present the appearance of almost purely fibrous structure—that is, relatively few nuclei, each being surrounded with a minimal quantity of "cell-body," but with long fibrous extensions of the latter—other regions may contain spindle-shaped, or even rounded cells in fair abundance. Between the type of structure called fibromatous and the typically cellular sarcomatous type there may be insensible transitions even in the same tumour. With the five exceptions dealt with above I therefore regard all the tumours described here as sarcomas. They are essentially connective tissue neoplasms. They are "hylomas," that is, vascular pulp, or mesenchymatous formations rather than epithelial ones—the epithelial tissue, it ought to be remembered, being possibly that of epidermis, peritoneum, alimentary canal or gland.

There are varieties of sarcoma which may now be mentioned—noting that we are dealing with fish tumours. (Though all the kinds of structure represented in Figs. 11 to 22 can easily be seen in the illustrations of any good book dealing with the morbid histology of the mammal.)

Lymphosarcoma (Fig. 22). The case described is that of a Flounder showing startling exophthalmos. On dissecting the orbit it was seen that there was a large tumour of the choroid coat of the eye forcing the bulbus oculi out from the orbit, and destroying both retina and sclerotic. Obviously we have here the structure characteristic of a lymph gland: a reticulum of fibrous tissue, the meshes of which are filled with small spherical cells (of about 2 μ in diameter). This tumour occurred in just such a situation as to suggest that it had originated as a cell embolism. The efferent vessel proceeding from the pseudobranch (the ophthalmic artery) breaks up into capillaries in the choroid gland of the eye, so that cells carried in its blood stream may become arrested in the latter organ. But no traces of a tumour could be found elsewhere in the body of this fish, so that the neoplasm in the eye was probably a primary one and not a metastasis.

Myxofibroma. Like the lymphosarcoma referred to above, this is an exceptional condition. Myxofibroma is a soft "polypoid" tumour substance containing fibrous or stellate cells separated by a mucoid interstitial cell-substance with numerous capillary vessels. The case described here is that of a Ray, in which the mucous canals on the head were enormously enlarged and, here and there, expanded into cysts filled with mucus. The pores were occluded. In the cysts were polypoid bodies attached by stalks to the cyst walls. These bodies had the myxofibromatous structure described above, though it was not quite typical.

Angiosarcoma (Fig. 9). A true angioma is a tumour resulting from the proliferation of either blood- or lymph-vessels. Thus one case referred to in the list—that of a Stickleback—is probably a typical angioma. Little knots of capillaries formed "hæmorhoidal" warts, pendulous on the cornea of the eye and proceeding, of course, from the choroid layer. Two other cases of blood tumours are also recorded. One of these was a growth about as big as a hen's egg on the trunk region of a Mackerel, and the other was a large tumour in the body cavity of a Cod. The skipper of the trawler that sent me this specimen wrote about its markedly *hard* nature, but he was disappointed to find that the growth became much softer after the fish had been kept on ice before dispatch. This observation was very puzzling until, on dissection, the tumour was seen to proceed from the rete mirabile of the swim-bladder and to resemble erectile tissue in its nature.

In these two cases (the Mackerel and Cod) what immediately arrested attention was the richly vascular nature of the tumours. A typical human sarcoma is usually more vascular than a carcinoma and the vessels are thin-walled. But in the *typical* fish sarcomas described here the *bloodlessness* is a feature. It does not appear that in the growth of a "cancer" either blood-vessels or nerves are formed, and when these structures are present they probably belong to the tissues into which the carcinomatous or sarcomatous cells have infiltrated. Now in the two angiosarcomas to which I refer *the* striking feature is just the rich plexus of large and small blood-vessels. Fig. 9 has been drawn from a field that was chosen to show the *margin* of the tumour, so that the blood-vessels are not nearly so numerous as they are in the central part of the growth. Yet there is no doubt that the connective tissue elements—that is, the typically sarcomatous ones—are also highly characteristic. We have here, therefore, a very richly vascular sarcoma. Why, in these examples, a proliferation of the vascular elements should have accompanied a proliferation of the typical connective tissue ones cannot yet be explained.

Melanotic Sarcoma (Fig. 6). Sarcomatous tumours pigmented with the black substance called "melanin" are among the most malignant and rapidly growing of human "cancers." It is of interest, then, to find that such growths occur, in absolutely typical form, among marine fishes, and no fewer than seven cases in the forty quoted are of this nature. Fig. 6 shows a small nodule of actively proliferating melanoma in a Halibut, and it has been chosen to represent the first stage in the development of such a tumour. In the fully developed growths the tissue is coal-black, and the loading of the neoplastic tissues with the melanin granules is so dense that hardly any structural details can be made out. In the first stages the colour may be pink, rapidly passing into dead black.

And just as such melanomas are among the most deadly of human "cancers," so it is, in regard to them in the Skate and Halibut, that the most typical generalisation of the affection has been observed. In one of the Skates seen, and in a Halibut as well, the whole flesh of the fish was full of small and large sarcomatous nodules. (Later on I refer more particularly to the histology of these tumours.)

The forms of typical Sarcoma in Fishes. Premising that a sarcoma is an unco-ordinated (and non-adaptive) overgrowth of connective tissue,* I now proceed to note the varieties of histological structure in such tumours as occur in fishes. The typical structure is probably that represented in Figs. 15 and 18. Generally we have "fibroblasts" developing a meshwork of fibres with, at the nodes, nuclei surrounded by a minimal quantity of cytoplasm of the typical nature. I am, however, unwilling to say much about this tissue, because it has not been well investigated in fishes, and the material I have handled has not been well fixed for fine histological study: also the fact that it is morbid tissue (or, at least, physiologically abnormal) makes one cautious. However, Figs. 15 and 18 represent fairly well the general appearance of most fish sarcomas that are not referred to with some qualifying prefix. In some cases the structure of the tumour is more typically fibroid, and then we may speak of it as a "fibroma," but usually parts of the growth have the characters referred to below.

Large Spindle-celled Sarcoma (Fig. 19). This form of tissue was observed

* The fibrosis, or overgrowth, of connective tissue round an encysted Tapeworm larva in, say, a Halibut, is an adaptation, or protective device.

in one case, that of a Ray that had a coal-black tumour on the head, near one of the eyes. The growth was very soft, and was fixed, hardened and sectioned with some difficulty. When the sections were examined it was extraordinarily hard to make out the histological structure, for not only were the cells loaded with melanin, but large granules of the pigment were crowded into the intercellular spaces. It was found possible, however, to decolourise the tissue by prolonged treatment of the sections with strong hydrogen peroxide, and Fig. 19 has been drawn from such a preparation. The cells are large (about 60 μ in length), irregularly spindle-shaped and often tapering off into fibres that seem to be continuous with a general stroma. The cell substance was loose and fragmented, and took any stains that were tried badly. The nuclei were faint and also stained badly. The cells tended, in many places, to be arranged in rows, lying side by side.

Small Spindle-celled Sarcoma (Fig. 16). The large spindle cells referred to above were only seen in the one case, but the small spindle cells represented in Fig. 16 are rather characteristic of various tumours. The case figured (that of a Halibut) was slightly melanotic, but fields could be chosen for study where the pigment did not obscure the forms and arrangements of the tissue elements. The latter, then, are spindle cells about 20 μ in length, obviously passing, at their ends, into fibrous structures. No tumour seen was wholly composed of such cells, but here and there they were characteristic of the histology. In some places the tissue elements were those called " oat-shaped " cells in the books on morbid anatomy, and always there was, in places, a considerable admixture of the fibroid structures represented in Figs. 15 and 18.

Small round-celled Sarcoma (Fig. 21). This structure is quite distinct from that illustrated by Fig. 22, where we have also a complex of small round cells. The latter are, however, of the type of " lymphocytes "; they are markedly smaller than the cells of a simple round-celled sarcoma, and their arrangement suggests that of a lymph gland. In Fig. 21 we have a very frequent kind of sarcomatous structure : small-rounded cells about 10 μ in diameter, many of them being really the nodes in a fibrous meshwork, while others appear to lie freely in an obscure intercellular substance.

Large round-celled Sarcoma (Fig. 23). The type of structure represented here is quite exceptional. It occurred in a large tumour occupying the whole of the body cavity of a Herring (so that the fish was opened under the impression that it was a ripe female). The tumour was about 8 cm. in length and about 2 cm. in diameter. It included one testis, but the other could not be recognised. The type of structure was that of an angiosarcoma, that is, there were numerous blood-spaces and vessels, and between these lay the morbid proliferating cells. The latter were mostly about 20 μ in diameter; rounded or polyhedral, because of mutual pressure and of the type of undifferentiated epithelial cells. Their arrangement in the proximity of a blood-vessel is interesting, for they there display a marked tendency to a spindle shape, the long axes of the spindles being normal to the circumference of the blood-vessel.

Such are the common kinds of tissues that make up the fish tumours observed. As a rule, however, what the pathologists call the "mixed-cell" type is usually encountered, and the same growth may have different characters according to its degree of development.

Nature of Malignant Growths in Fishes.

Obviously, then, we have to deal with connective-tissue tumours, or sarcomas. The two doubtful exceptions noted above hardly invalidate this conclusion, because the evidence that the growth on the jaw of a Whiting described in Figs. 14, 17 and 20 is not complete, while it would be rather straining the meaning of the facts to call the thyroid tumour represented in Fig. 12 a carcinoma. The only description of a sarcomatous tumour as occurring in a marine fish which I have encountered in the literature is that of a growth in a fifteen-spined Stickleback (see the First Report of the Imperial Cancer Institute). Apparently, then, the sarcomatous type of growth is that characteristic of malignant tumours in marine fishes.

The Mode of Extension of Fish Tumours.

The majority of the tumours described here occur in the "flesh" just underneath the skin, so that they form obvious swellings. If sections are made at the edge of the swelling it is usually possible to discover the growing, or proliferating, margin of the tumour, and so to study its mode of extension. Figs. 1, 4 and 5 represent such sections taken across the growing margin of a tumour, so that on the one side we have nearly normal tissue and on the other tissue that is in process of active proliferation.

Fig. 1 shows the growing margin of a sarcoma that was situated nearly in the middle of the coloured side of a large Turbot. In Fig. 2 the normal skin situated a few cm. away from the edge of the tumour is shown in section, the plane of the latter being nearly transverse to the long axis of the body of the fish. The parts seen are (1) the epidermis, consisting of polyhedral cells; (2) a pigmented layer; (3) a layer of "areolar" tissue containing some coarse fibres; (4) various layers of coarse fibres running in various directions ; (5) another layer of areolar tissue, and, lastly, the underlying systemic muscles. These layers are also shown, in less magnification, in Fig. 1, where it will be seen that the septa that cross the body of the fish obliquely, and provide the attachments for the "flakes" of muscles, are continuous with this sub-epidermal layer of coarse, white, connective fibres. Fig. 2 just indicates, by the stippling between the bundles of fibres, that there is another kind of tissue there : this is what we may loosely call areolar tissue, that is, it resembles the layer just below the epidermis, consisting of an open meshwork of fine fibres with small nuclei at the nodes, small "fibroblasts" and some interstitial ground substance. The coarse, white connective tissue is already specialised, is not "vegetative," and probably never takes any part in the growth of a sarcomatous tumour : it is the loosely, irregularly arranged "areolar" tissue between the fibrous bundles, or just beneath the epidermis, that undergoes active proliferation.

In Fig. 1 the abnormal tissue is represented in dead black. On the left is a region of normal skin. Below are the bundles of muscle fibres (represented by coarse stippling) separated by the connective tissue septa. Now, just at the margin of the swelling the coarse, white connective tissue fibres of the dermis are seen to fray out, so to speak, and finally disappear altogether. This is the result of the active proliferation of the minimal quantity of areolar tissue that lies between the bundles. Thus the latter are forced apart by the growth of substance in between them, are starved and finally degenerate. In the fully developed tumour tissue at a little distance to the right of the field shown in Fig. 1, the coarse fibres, and even the epidermis, would have disappeared completely. The only tissues would be those of the tumour, either bare or covered by a kind of "limiting membrane," which is not typical epidermis.

The margin, or region, of greatest proliferation is represented in Fig. 3. The lower coarsely stippled layer is that of the systemic muscles. The finely stippled region is that of the sarcoma, and this is seen to insinuate itself between the coarse connective tissue fibres and also to grow down in between the muscle fibres as little finger-shaped processes (also seen in Fig. 1).

Figs. 4 and 5 show essentially the same conditions in a Cat-fish (4) and Skate (5). In (4) the epidermis thins out and disappears, and this is also the case with the dermal fibrous layer. In (5) the tumour is situated to the right hand : in this case it had ulcerated and left an excavated sore. The large spaces are probably lymph channels, and there is also shown part of a scute. The epidermis, it will be seen, thins out and disappears, and the tumour tissue is shown infiltrating and destroying the coarse, white connective tissue layer.

Two other kinds of marginal regions are represented by Figs. 6, 7 and 9. Fig. 7 shows (under fairly high magnification) the boundary of a melanotic, sarcomatous nodule in the flesh of a Halibut : this was not visible on the surface, and was seen when the flesh was cut into. Now, the naked-eye appearance here was that of a very sharply circumscribed tumour which was apparently encapsulated : on the other hand, there were very many large and small sarcomatous nodules in the flesh of the fish, so that generalisation (whether by metastases, or otherwise) had occurred, and there seemed to be no doubt as to the malignancy of the growths. And so we see from Fig. 7 that there really was no capsule round the nodule. The tissue normal to the field consists of muscle fibres cut longitudinally, and several such are shown in the figure, some obviously undergoing degeneration. Above and below and between the fibres is the sarcomatous tissue—fibrous, but including many nuclei and some small round cells, and this is seen to be infiltrating the muscular tissue. Above is represented the fully developed sarcoma—here laden with black pigment, both in the cell bodies and between them. The capsulation is apparent only, and a typical process of infiltration is seen when the boundary of the tumour is studied under high magnification.

Fig. 9 represents the superficial part of the angiosarcoma found in a Mackerel, the field chosen being one where the tumour is thoroughly established. The epidermis has quite disappeared, the tumour being bounded by a finely fibrous layer. The pigment layer of the skin is visible, and below it is the usual fibrous layer which is being infiltrated by the abnormal tissue (shown by the fine stippling). Traces of the coarse fibres, and also some degenerating muscle fibres, are shown. The areas represented in black are sections of large and small blood-vessels.

The mode of infiltration may be examined in greater detail. Fig. 6 represents a small sarcomatous nodule (about 1 cm. in diameter) found in the Halibut mentioned above, and this was a very convenient tissue to study, because it was loaded with melanin, and so its extension was easily observable. On the upper surface (for the tumour was not visible in the intact fish) is the skin with all the normal structure. Below the skin are the systemic muscles (the sections of the fibres being shown in black). The smaller bundles are shown, and also one of the transverse body septa. The diameters of the muscle fibres are smaller just beneath the skin than they are deeper down. The densely stippled region represents the sarcoma, and the cell-like spaces were the *loci* of muscle fibres. In many of these spaces degenerating muscle fibres are still present, but others are quite empty. Between the muscle fibres, therefore, active infiltration of the sarcomatous tissue is proceeding.

Now we look at a normal part of the body where the muscles are cut transversely. This is represented in Fig. 8, the black polygonal areas being the cross sections of the fibres. A muscle septum runs obliquely across the field, and this is continuous with a very delicate reticulum, in the spaces of which the fibres are contained. In this field there were no traces of capillaries—fish flesh being relatively bloodless. There is, of course, no trace here of any abnormal tissue.

Compare such a normal part of the flesh of a fish with that represented in Fig. 10. The latter shows the conditions at the growing margin of a large sarcomatous tumour on the region of the body just behind the head in a full-grown Cat-fish (*Anarrichas lupus*). The growth was a fibrosarcoma, that is, the fibrous elements were much more prominent than were the typically cellular ones. The magnification in Fig. 10 is a little higher than that of Fig. 8, and so the muscle fibres are about the same in sectional area. Now two things are to be noted in the figure : (1) the extraordinary development of the interfibrillar connective tissue and (2) the condition that each fibre appears to lie in a space being apparently retracted away from the sheath in which it is seen to be placed in Fig. 8.

Figs. 11 and 13 show this change in the muscular tissue which proceeds upon the development of a sarcomatous tumour : these drawings represent parts of the growing margin of the angiosarcoma of a Mackerel. In Fig. 11 we have a field which is normal but for the presence of an unusually prominent capillary blood-vessel. Each muscle fibre (the stippled areas representing fibres cut slightly obliquely) lies in a sheath, and as the latter is apparently nearly always complete, no matter how the section is made, it must be made up of *sheets* of connective tissue. At the nodes of these sheaths are small nuclei, each surrounded by a minimal quantity of cytoplasmic material. Now if we were to suppose the muscle fibres completely to disappear and the connective tissue meshwork to remain intact the general form of the fish would still be retained : this may almost happen. Fig. 13 is a field from a section of the same material, only taken at the growing margin of the tumour (the fibres are cut rather more obliquely than in Fig. 11, and the magnification is a little higher). Some of the interfibrillar sheaths contain fibres, but most of them are empty, because of the degeneration of the muscle tissue. This appearance of muscle fibres lying in apparently large spaces is most characteristic of many fish sarcomas at their proliferating margins : it is shown in Fig. 6, and it would be seen very strikingly in Figs. 1 and 3 were the magnification high enough. It means that as the abnormal connective tissue grows the muscle fibres suffer in respect of their nutrition, dwindle away and finally disappear simultaneously with the development of the tumour tissue.

The proliferation of the interfibrillar tissue is also to be noted in Fig. 13.

Not only are there nodal cells in the meshwork (as in Fig. 11), but these cell nuclei have been dividing, and now there are numbers of small round cells in the space formerly occupied by the muscle fibres. Fig. 13 shows such small round cells apparently isolated from each other, but I have little doubt that a better preparation would have shown the cell bodies carrying fibrous prolongations and most of them structurally continuous with each other.

The Nature of the Infiltrative Process.

Further light on the precise nature of the process of infiltration of normal tissues by a fish sarcoma is only to be obtained by experimental work—particularly, it would appear, by the study of the physiology of trophic nerves going to the muscle fibres (if there are such ?), and also by tissue growth experiments. But it is difficult to resist interpreting the appearance presented by such sections as I have studied—in this way—the process of infiltration is not the extension, along certain paths, of the products of cell-division (as, for instance, we can imagine a bacterial culture to spread through the meshwork of an agar jelly). It is, rather, *the extension—along the connective tissue framework of the muscle—of the condition of malignancy.* This framework in a normal muscle (as in Fig. 8, for instance) consists of a minimal quantity of supporting tissue, and it is functionally balanced with the quantity of muscle tissue. But in the sarcomatous tumour the balance between the contractile and supporting tissues breaks down, perhaps because there is some general stimulus to proliferation to which the highly specialised muscle cells cannot respond while the relatively undifferentiated connective tissue ones do respond. So we find that in tumours of the nervous tissues it is not the neurones that proliferate, but the neuroglial supporting tissues, or it may be that something like Driesch's idea of the activities of a cell being dependent on its position with regard to other active cells may be in train—failure, in some way, of normal functioning of the muscle fibres may be the stimulus to proliferation of the connecting tissues. Something of this kind has, indeed, been suggested in the older speculations as to the causation of cancerous growths.

Necrosis in Sarcomatous Tumours.

Very commonly the surface of a fish sarcoma breaks through, ulcerates and gives rise to a repulsive sore. One attributes this breakdown of the growth to the rough handling of the fish during transport and capture, and, no doubt, injury is caused in this way. But there is also a process of necrosis going on from about the time when the tumour becomes an obvious growth. In the typical sarcomas described in this paper there are very few blood-vessels (and here we have a difference from the human condition where a sarcoma very often contains many thin-walled vessels). There are no nerves : at least no new ones. If we do find nerves at the growing margin of a tumour it is certain that these were present in the normal tissues into which the sarcoma has been infiltrating. There are no obvious lymphatic channels. What exists is simply the physiologically unbalanced product of proliferation of a tissue which is, elsewhere in the body, present in minimal quantity sufficient, and sufficient only, for the binding together of the other tissue-elements and organs.

The consequence is that the sarcomatous tissue is ultimately badly nourished ; there are, doubtless, excretory products which are not efficiently removed, and the cells begin to be acted upon by these toxic substances and by their own intracellular enzymes. Towards the centre of the tumour the substance becomes soft and then liquefies. Its growth still proceeds at the margins, and so a pressure is set up and the unbroken tumour becomes tense. In this state rough handling almost invariably breaks the stretched surface and a sore results, which then becomes septic.

During this process of necrotic change the minute structure of the tumour alters. In the case of the Cod mentioned in the list as having a large tumour on the body, this change was a very noticeable one. The growth was about the size of a man's closed fist and it felt liquid, yet tense. On cutting it open the contents ran out as a substance with the consistency of soft porridge. Round the margins the growth was firm, and there were solid cheesy lumps embedded in the semifluid central substance. At the margins, and in the cheesy masses, the tissue had the character of a "mixed-cell sarcoma," but the semifluid substance contained, for the most part, unrecognisable cell debris. When smears were made and stained this debris was seen to contain a great variety of cells—small round cells with large nuclei ; "polymorphic" cells ; cells with numbers of chromidial bodies, probably the result of nuclear fragmentation ; multinuclear cells ; cells containing inclusions of the nature of "Russell's bodies," etc. Fibrous elements are very scarce in such necrosed material, and this is, perhaps, a general feature of an old sarcoma : the original, normal *connecting* nature of the tissue becomes lost as the result of the cessation of functioning of the material. The cells assume very peculiar forms, which are, of course, quite aberrant, though they are doubtless responsible for many of the identifications of "cancer bodies" and parasites that have been made in the past.

In the melanotic tumours the necrosis and softening of the morbid substance proceeds even farther. Sarcomas of this kind occurring just below the skin, and so forming visible swellings, have always been broken and ulcerated. The substance remains soft, even on fixing in strong alcohol.

In the angiosarcomas the contents of the larger blood-spaces become greatly altered. The outlines of the corpuscles become obscure and finally disappear, though the nuclei may continue to stain in a typical way. Then even the nuclei disintegrate and disappear, and the blood becomes converted into a colloidal material taking extraordinary colours on staining with Mallory. The walls of the vessels break down and the colloidal contents appear to become organised, but this is due, I think, to the infiltration of the vessels by the intervascular, sarcomatous tissue. The process of thrombosis referred to above *may* be a post-mortem one, but it was too profound, I think, in some of the cases to have been established merely after the death of the fish, and it was, very probably, a process that had begun as a necrotic change during the life of the patient.

The Effect of the Tumours on the Fish.

In some cases the presence of a malignant tumour may go along with an apparently well-nourished fish, but this is unusual and indicates that the tumour is a young, rapidly growing one. Far more general is a condition of emaciation, often striking in the extreme. Thus a Ray suffering from a melanotic sarcoma on the head was so very thin and wasted that all the skeleton of the pectoral fins, even the cartilaginous radialia, could be most distinctly seen when the fish was alive. In this case the tumour was not a very large one, though it formed a deep excavation in the head, due to the ulceration of its substance. The brain, cartilage, stomach, alimentary canal and pancreas were nearly normal in appearance, and the muscles were much wasted, though not otherwise altered. The gills, spleen and liver were coal-black in colour. The liver was very soft, owing to the appearance of large lacunæ between the hepatic tubules. The cells were deeply laden with melanin, and coarse granules of this substance lay between them. On attempting to trace the structure of the liver from sections decolourised with hydrogen peroxide, no success was obtained, and the organ appeared to be in a state of considerable disintegration.

It is not possible yet to make a "clinical history" with regard to a sarcomatous fish. As a general rule the diseased fish comes to us from a market or from an official of the Ministry of Agriculture and Fisheries,* and it is not always even in a fit condition for exact histological study.

* Here I may express indebtedness to many correspondents (market inspectors, collectors of fishery statistics, and naturalists) who have most kindly taken much trouble to forward interesting specimens.

In only two cases has an opportunity occurred for observation of a living fish bearing a sarcomatous growth. In one such case Dr. Orton, of the Marine Biological Association, obtained a large Turbot with a tumour near the dorsal fin. All possible care was taken to keep the fish alive in the Aquarium tanks, but it died, after a few days, and the result was due to the inevitable troubles of captivity in a tank in the case of such a large fish.

In the other case a small Goldfish, about 7 cm. in length, had a tumour about the size of a hazel-nut on the body near the root of the tail. The patient was kept in a small aquarium jar in the Laboratory; the water was changed frequently; the jar cleaned; the fish fed with "ant-eggs" and all reasonable care was taken to keep it alive. We had it for several months, during which time the tumour increased in mass perceptibly. The skin over it became tense and the scales dropped off, though their scars were still recognisable. There was, during the time that the fish was under observation, no evident change in its appearance, and it seemed to be plump and well-nourished. It was ultimately found dead (previously to which its movements in the jar had become more and more languid). It was at once preserved in 10 per cent formalin solution, and still appeared to be normal in its condition—apart from the presence of the tumour, of course. The parts of the body containing the sarcoma and the other regions were cut out and decalcified and dehydrated, and then the tissues collapsed in an amazing way, the body becoming almost ribbon-shaped. When sections were made it was seen that everywhere throughout the body the muscle fibres were degenerating. In the neighbourhood of the tumour they had disappeared and were being replaced by the usual sarcomatous tissue, but even at the other end of the body they were much smaller than normal, while the connective tissues round them had not increased. Even in this degenerate condition the cross-striation of the fibres was still very marked—more so, perhaps, than in the normal state.

We may conclude, then, that the presence of a sarcomatous tumour is detrimental, and that this is so because of the diffusion, through the blood and lymph channels of toxic products resulting from autolysis of the malignant tissue. This is, of course, the justification for condemnation of fish that exhibit abnormal growths: the flesh, in such cases, cannot be regarded as the normal food material that the buyer desires. As to the communication of disease to the person consuming such a diseased fish, there can be no possibility, so far as we know, but just as one rightly refuses to buy a fish that is stale because of incipient putrefaction, so we do not choose to buy a fish the flesh of which is wasting because of the presence of substances that prevent proper nutrition. Nor ought such a fish to be sold as an article of human food.

General Remarks.

First, as to the incidence of malignant disease among marine fishes : Unfortunately no generalisation can yet be made. Nevertheless, it has taken over ten years to collect the forty or so cases referred to in this paper, and the importance of noting the occurrence of "cancerous" growths in fishes has been in the minds of many observers who are highly skilled in respect of the characters of normality and abnormality in these animals. My colleagues and I must, for instance, have actually *handled* many thousands of Plaice, Herrings and Cod during these years, and it is quite certain that no fish displaying a visible swelling could have been overlooked. So also with other naturalists and inspectors, who must have seen very large numbers of fishes. The inspectors, in particular, have abundant opportunities of detecting unwholesome and diseased fish ; they are mostly aware of the importance, or at least the interest, of such conditions that are spoken of here, and it is their job to prevent unhealthy or stale fish from getting into the retail shops. Yet they have seen very few cases of malignant disease. Again, fairly large numbers of living fish are being watched in the various aquaria throughout this country, and the occurrence of animals exhibiting tumours would be sure to be noticed. On the whole we seem forced to the conclusion that malignant disease in marine fishes is very rare—far more rare than it is among men and women.

We ought, however, to note that "cancer" is a disease of mature, or old age. It is certain that the death-rate (or at least, the incidence) must continue to rise in civilised human populations, simply because the tendency of private and public medicine is ever to minimise the occurrence of, and the mortality from, preventable disease. Since we must all die there must be diseases that are not to be avoided or survived, and so the future of medicine must see the postponement of mortal illness until old age—an age, further, which will always tend to increase. As the theory and practice of medicine become more and more scientific and successful, so the incidence and death-rate of *most* affections must decrease, while the incidence and death-rate of a few such diseases as arterial sclerosis, cerebral hæmorrhage and (perhaps) "cancer" will continue to increase.

So as malignant disease may be characteristic of mature or old age we may not have the best of opportunities of observing it among marine fishes, for the most of those that are captured for the public markets are rather young animals. (Was it the case that among the very old Plaice that were taken when the Iceland and White Sea grounds were first exploited, there were many diseased individuals ? That has been asserted, and it would have been interesting if the occurrence of malignant tumours had been noticed.) It is significant that animals which are relatively short-lived (mice and even dogs) seem to be rather susceptible to cancer, while very few (if any) cases of true malignant tumours have been observed among reptiles, which probably live much longer than our experience of these animals in captivity suggests.

Here I must note the prevalence of "carcinoma of the thyroid" in domesticated Trout and other fresh-water fish in the American experience. But it cannot yet be taken as thoroughly established that this affection is quite similar to what we call carcinoma in the mammalian animal, or even that it is a quite typical form of malignant tumour. Many features suggest that the American "throat disease" ought, in the meantime, to be placed in a category by itself: it is endemic in certain cultural establishments; it is epidemic, and the causal agent is contained in the water supply; it can be favoured by some kinds of food and made to regress by other kinds; it can be arrested by adding such substances as contain mercury or arsenic or iodine to the water, and it displays a certain resemblance to epidemics of goitre that occur among the inhabitants of villages in Northern India. If we could find examples of the same kind of illness among truly wild marine fishes some kind of correlation might be set up between habits, food, etc., and the illness; but, so far, the only case of tumour of the thyroid recorded from a marine fish is that of the *Box vulgaris* mentioned above. And I hesitate to describe this as a case of malignant disease in the typical sense.

The causation of Piscine Sarcoma. The number of cases recorded is, of course, far too few to enable us to make any suggestion as to causation. Nevertheless, one cannot help remarking on certain negative results. Perhaps the most widely held opinion among physicians, at present, as to the cause of "cancer" is that the condition of malignancy is initiated because of chronic irritation of some kind or another. Thus there is work on gastric cancer said to be due to irritant parasites; the epithelioma that is said to be due to the use of clay pipes; malignant skin disease among workers in paraffin oil refineries; cancer of the rectum set up by chronic constipation, etc. Now there are beautiful examples of chronic irritation among marine fishes: the parasites *Lernea* (fixed in the ventral aorta) or *Lerneonema* (fixed in the eyes of Sprats); persistent tapeworms in Turbot and Cod; copepod parasites on the gills, in the nasal cavities and on the skin of many fishes, etc. Here we have what appear to be competent causes of malignant growth—if irritation is to be accepted as such a cause. Yet nothing suggests that a sarcoma originating in the skin of a fish has come about as the result of parasitic irritation and no tumour of the gills, or other region of the body specially prone to parasitic irritation, has been observed.

As to the ways in which a piscine sarcoma generalises nothing can be said. In man such a growth forms metastases, and the latter are initiated by fragments of the primary tumour that become detached and are then carried in the lymphatic and blood streams : so much seems to be quite certain. But in fishes we do not (so far) appear to find metastatic growths in the gills—where cell embolisms would be very prone to establishment. As to the possible spread along the lymph tracts I can say nothing, since these are so very imperfectly known in fishes that observations are difficult just yet.

As to the association of malignant disease with the food, habits, etc., of fishes nothing can be said. The data are far too few even for rough and tentative correlations.

SUMMARY.

1. About forty cases of malignant growths have been recorded from British marine fishes.

2. These tumours are nearly all sarcomata. One doubtful epithelioma and a doubtful carcinoma are mentioned.

3. The types of malignant tissue growth are entirely similar to those recorded from man and other mammals. Spindle-celled, oat-celled, round-celled, mixed-celled and fibrous sarcomas are described. Typical melanolic sarcomas are frequent in occurrence.

4. The tumours may generalise, but (apparently) not by the formation of typical metastases.

5. No species or even family of fishes seems to be exceptionally prone to malignant disease.

6. The sites of the tumours are (usually) the dermis and the inter-muscular connective tissues.

7. Carcinomata are very rare, though at least one case is on record (but not in the present collection).

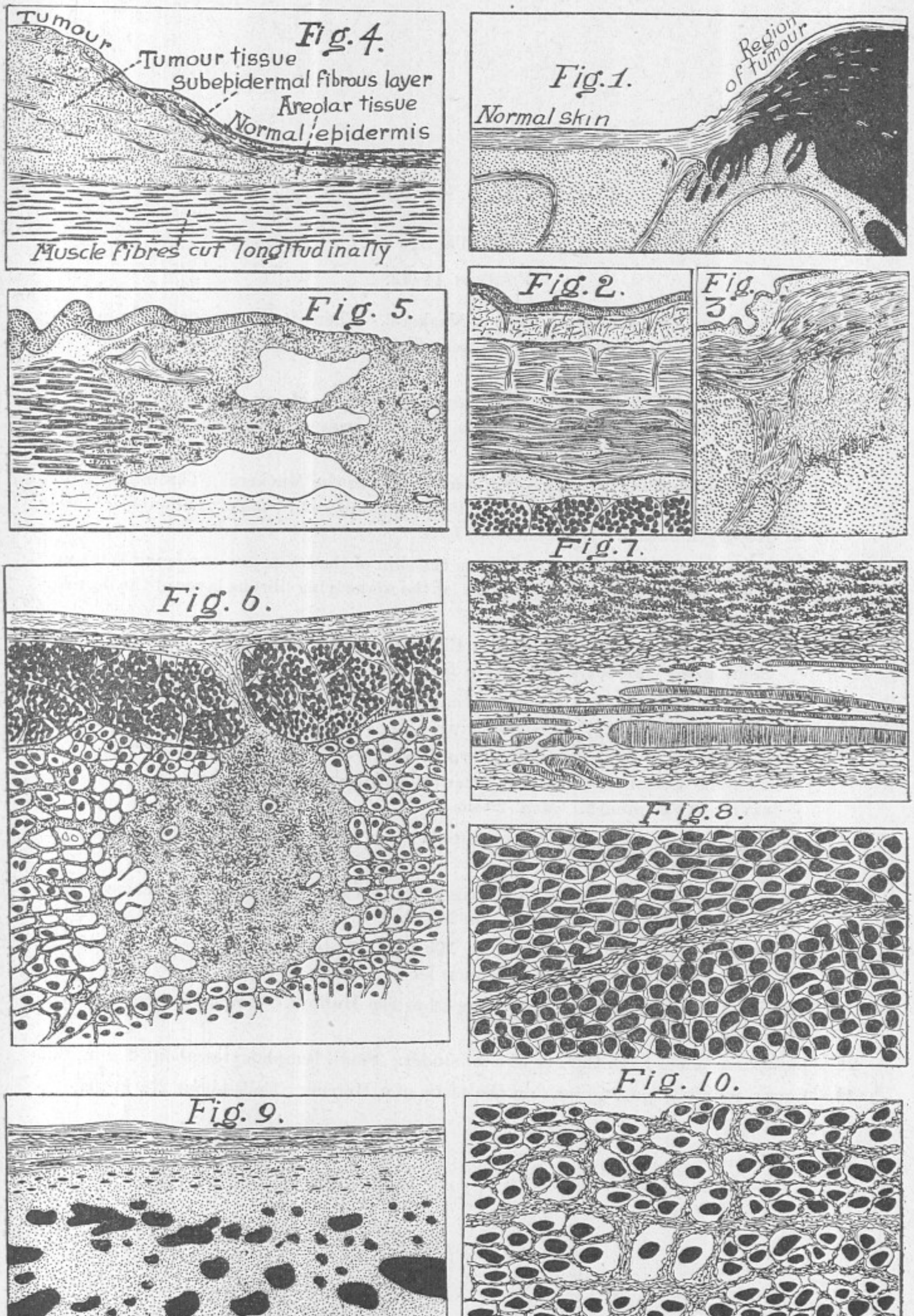
8. No suggestion is made as to causation, but it appears that chronic irritation as a competent cause of malignant growth is not probable in marine fishes.

9. There is need of sustained investigation and record so that correlations may be made. As to causation there is need of experimental work.

PLATE I.

FIGURES 1–10.

1. The growing margin of a Sarcoma in a Turbot; the tumour tissue is black. Mag. 6 dia.
2. The same: the normal skin near the region of active cell proliferation. Mag. 45 dia.
3. The same: the marginal region. The tumour tissue is lightly stippled; the muscle fibres are coarsely stippled. Mag. 45 dia.
4. The growing margin of a Sarcoma in a Catfish; the tumour tissue is lightly stippled. Mag. 40 dia.
5. The growing margin in a Sarcoma from a Skate. The tumour tissue (on the right) is lightly stippled; the epidermis coarsely stippled; the tumour has ulcerated. Mag. 50 dia.
6. A small nodule of melanotic sarcoma in the muscles of a Halibut. Muscle fibres black; the tumour tissue stippled and shown growing in between the muscle fibres, which are degenerating. Mag. 25 dia.
7. Marginal region in a nodule of Sarcoma in the flesh of a Halibut. Muscle fibres striated; tumour tissue fibrous below and densely melanotic above. Mag. 100 dia.
8. Normal muscle tissue in a Turbot, the fibres being cut transversely. Mag. 50 dia.
9. Marginal region in an angiosarcoma from the Mackerel. Blood-vessels black; sarcomatous tissue stippled. Mag. 50 dia.
10. Region of active infiltration in a Sarcoma from the Catfish. Muscle fibres black; tumour tissue fibrous. Mag. 50 dia.



J. J. del.

Sarcomata in Fishes:
growing margins of the tumours.

PLATE II.

FIGURES 11–22.

11. Almost normal muscle tissue from a Mackerel. There is an unusually prominent capillary blood-vessel. The muscle fibres are cut rather obliquely and are stippled. Oil-immersion lens.

12. Tumour of the thyroid in a *Box vulgaris.* The figure shows sections of the gland acini. The other tissue resembles that occurring in inflammatory conditions. Mag. about 10 dia.

13. The region of active infiltration in a Sarcoma from the Mackerel. The interfibrillar connective tissue is proliferating, forming small round cells. The muscle fibres are degenerating. Oil-immersion lens.

14. pidermis (probably proliferating) from the skin of the lower jaw of a small Whiting. A sense organ is showing, also part of the underlying fibrous layer of the dermis. Oil-immersion lens.

15. Sarcomatous tissue from a Halibut. Fibrous tissue with rounded cells 5 μ in dia. Some giant cells. Oil-immersion lens.

16. Sarcomatous tissue from a Halibut. Small spindle cells about 20 μ in length.

17. Epithelioma from the lower jaw of a Whiting. "Epithelial pearls" shown in the tumour tissue beneath the epidermis (which is coarsely stippled). The black area is a section of one of the bones of the lower jaw. The epithelium faces the cavity of the mouth. Mag. 25 dia.

18. Ordinary sarcomatous tissue of the fibrous type. A small blood capillary is shown. Oil-immersion lens.

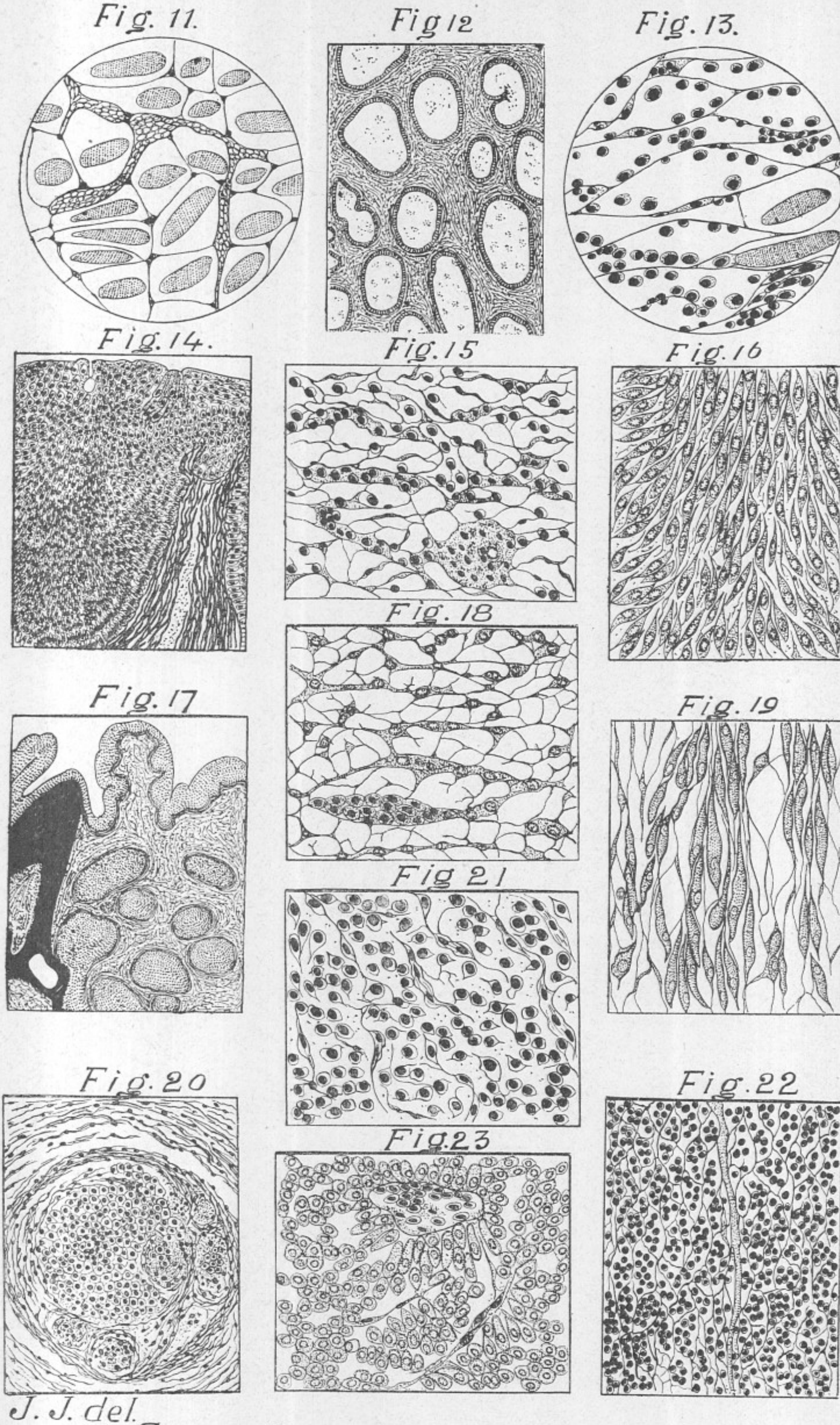
19. Melanotic Sarcoma from a Ray. The tissue was decolourised with hydrogen peroxide. Large spindle-cells about 60 μ in length.

20. Epithelioma from the lower jaw of a Whiting. Details of structure of one of the "epithelial pearls." Oil-immersion lens.

21. Small round-celled sarcomatous tissue from the Halibut. Round cells about 10 μ in dia.

22. Lymphosarcoma from the eye of a Flounder. Small lymphocytes about 2 μ in dia.

23. Large, round-celled Parcoma on the testis of a Herring. Cells about 2 μ in dia.



Sarcomatous and other Tumours in Fishes:
details of the tissues.