Europ. J. Cancer, Vol. 16, pp. 203–217
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0014-2964/80/0201-0203 $02.00/0

The Vascular Pattern of the Spontaneous C3H Mouse Mammary Carcinoma and its Significance in Radiation Response and in Hyperthermia

P. FALK

Medical Research Council Cyclotron Unit, Hammersmith Hospital, Ducane Road, London W12, Great Britain

Abstract—*The vascular pattern of the spontaneous C3H mouse mammary carcinoma develops from a capillary network into an afferent system lacking arterioles and consisting only of capillary-like vessels and an efferent system characterized by large sinuses. Lack of correlation between the growth of stroma and parenchyma leads to a circuitous and uneven supply of blood and to a high degree of occlusion of the efferent system with consequent reduction in the rate of flow of blood.*

The parenchyma consists of tubules formed of single or multiple layers of cells between which capillaries do not penetrate. The diffusion pathway of oxygen and nutrients to the inner cells of the multi-layered tubules is considerably longer than that to their outer cells or to the cells of the single-layered tubules. Consequently it is in the former parts that anoxia and severe hypoxia are likely to prevail. The pattern of necrosis agrees with this supposition. It is predicted that radiation and hyperthermia will act differentially and in opposite senses on these two tumour components, hyperthermia being more effective on the former, radiation on the latter.

INTRODUCTION

THE MOUSE C3H mammary carcinoma has been extensively used in studies of response to radiation, hyperthermia and ultra-sound and yet no detailed account of the architecture of its vasculature appears to have been published. This paper is an attempt to fill the gap. The importance of the vascular architecture in these studies follows from the role of blood in the supply and removal of metabolites to and from the tumour cells and its additional role as a conveyor of heat between the tumour and the rest of the body. Maldistribution of blood within a tumour may cause local hypoxia and so lower the response to radiation, while a restricted circulation may reduce the distribution of heat from a tumour during and after local heating and thereby increase the effectiveness of hyperthermia.

Accepted 18 May 1979.

The vasculature of tumours in many cases differs widely from that of normal tissues and in older C3H tumours is particularly bizarre. The system, however, originated as a simple network of capillary-like vessels and if the development of these is followed, the pattern in older tumours is more readily understood. The development, however, cannot be followed in isolation since to a considerable extent it is determined by the growth of the tumour itself and, since tumour growth is a modification of normal growth, the starting point adopted here is the organisation of normal, resting mammary gland.

MATERIALS AND METHODS

Mice

Mice of the C3H/He strain obtained from the MRC Laboratory Animal Centre at Carshalton have been bred at Hammersmith since 1973. In these animals, tumours start to appear in the females at the age of 36 weeks

and continue with a frequency of about 1% per week increasing to 3% after 60 weeks. (P. H. Warren, personal communication.)

Extraction of tumours

Mice were selected from this colony, either because they had visible or palpable tumours of the desired size or because they were of an age when tumours too small to see or feel might be present. The mice were killed with ether and, before fixation in neutral buffered formalin, were dissected only so far as to allow rapid entry of the fixative and to prevent compression of tumours by skin shrinkage. After 6 weeks fixation, visible tumours were excised. Smaller tumours, hidden by the fat surrounding the mammary glands, could only be detected by removing the whole glands for subsequent dehydration and clearing. The glands of 100 mice so explored yielded 3 tumours.

Preparation for examination

A detailed account of preparing tumours for three-dimensional examination of their blood vessels has already been published [1]. In outline, either thick sections (200 μm) were cut by cryostat or the tumours were cut by hand into halves or thick slices. The products were then stained in benzidine followed by H_2O_2 giving the blood an intense blue-black colour. Fast green F.C.F. or eosin were used as counterstains.

The half tumours and slices after dehydration were immersed in a special resin (formerly Resin 4116, now renumbered 8116, produced by B.I.P. Chemicals Ltd., Warley, Worcs., U.K.). This resin is both a clearing agent and a mountant, solidifying after addition of a catalyst. The specimens embedded in it were examined either directly or with a microscope. They were of particular value in examining large areas, but also supplied considerable microscopic detail. Mammary glands found to contain small tumours were similarly stained and mounted in resin.

For three-dimensional examination, the thick sections were traced onto acetate sheeting and the tracings, supported by sheets of glass, were stacked on an X-ray viewer one above another, with spacers of appropriate thickness between, the alignment being given by the larger blood vessels. When viewed from above, a three-dimensional picture of the blood vessels was obtained. For detailed histological examination, the thick sections were supplemented by thin (5 μm) sections stained in haematoxylin and Van Gieson's fluid.

Three-dimensional model

Although the stacked tracing technique had proved satisfactory in a previous study of rat sarcomas [2], abrupt expansion of the main drainage vessel in the mouse carcinoma obscured the branching and anastomosis occurring below so that no clear picture of this part of the tumour was obtained. A solid model that could be viewed from the side was therefore constructed (Fig. 7). Tracings of the vessel and its branches were copied onto thin card, and these copies then cut out and mounted one above another with spacers of polystyrene between them of the requisite thickness to make the vertical and horizontal magnifications the same. The structure was made rigid by a light coating of resin (Cl 202 PA, obtained from Trylon Ltd., Wollaston, Northants., U.K.) and when this had hardened the gaps were filled with a modelling resin (PR 160, also obtained from Trylon Ltd.), which could be shaped with a scalpel or smoothed with carborundum paper.

RESULTS

Normal resting mammary gland

Normal resting mammary gland is a compound tubulo-alveolar gland, divided into lobes and lobules (Fig. 1a and 1b). Each lobule is supplied with an inconspicuous nerve and conspicuous artery, vein and milk duct, the milk duct being formed by the union of the tubules. Within the lobule, the artery and vein lie side by side and the capillaries, which connect the arterioles and venules, form almost closed circles round single tubules and loops round individual alveoli. Capillaries never penetrate between the cells of a tubule or alveolus. In fixed material, the capillaries are well filled with blood and stand out clearly. Although in general the vascular system of each lobule is independent of that of its neighbours, occasionally a capillary originating in one lobule traverses the interlobular space and connects with the venule of an adjacent lobule.

Transformation and the growth of the neoplasm

The smallest tumour found measured 3 × 1.2 mm (Fig 2a). Considerable develop-

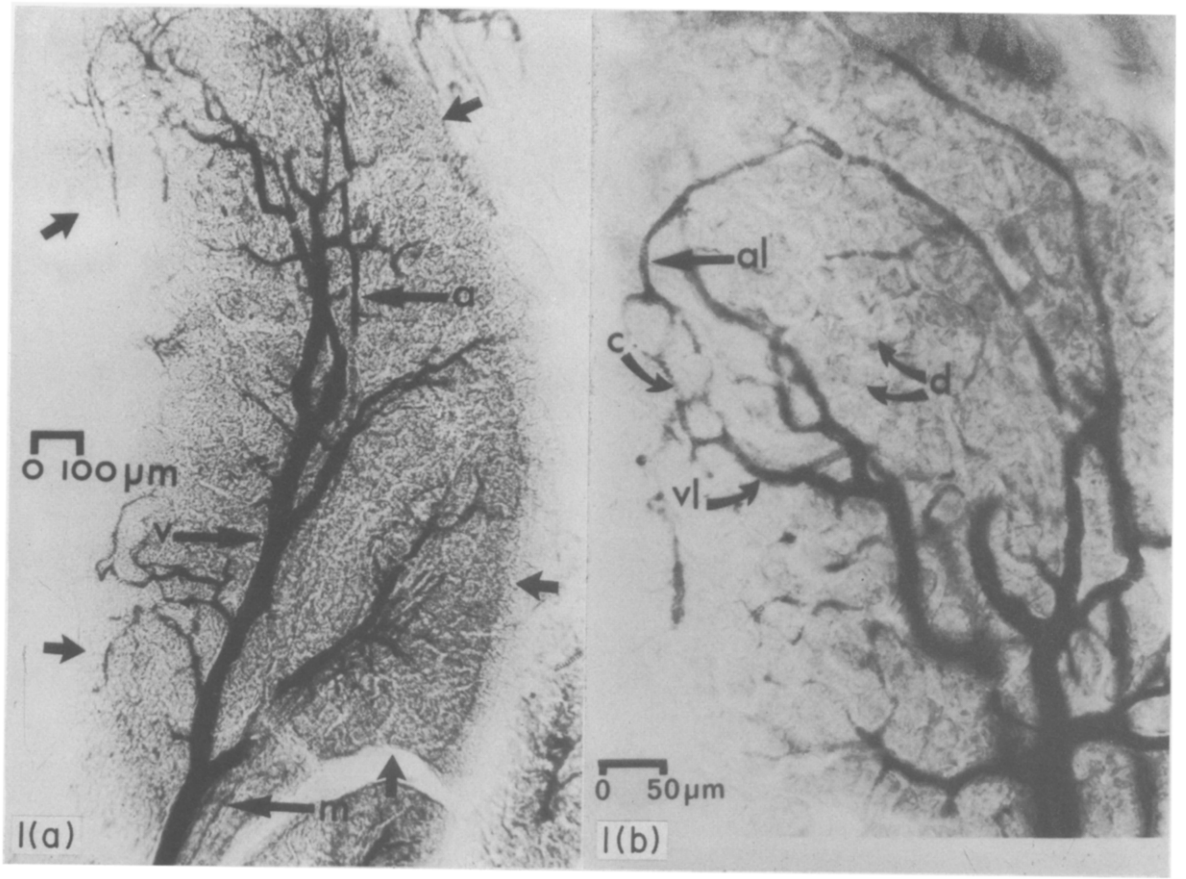


Fig. 1a. Normal resting mammary gland; 200 µm *section, stained in benzidine and hydrogen peroxide and counterstained in eosin. The outlines of a single lobule are marked by arrows. The artery (a), vein (v) and milk duct (m) run side by side.*

Fig. 1b. The same at greater magnification to show ducts (d), an arteriole (al), a venule (vl) and the well-filled capillaries (c).

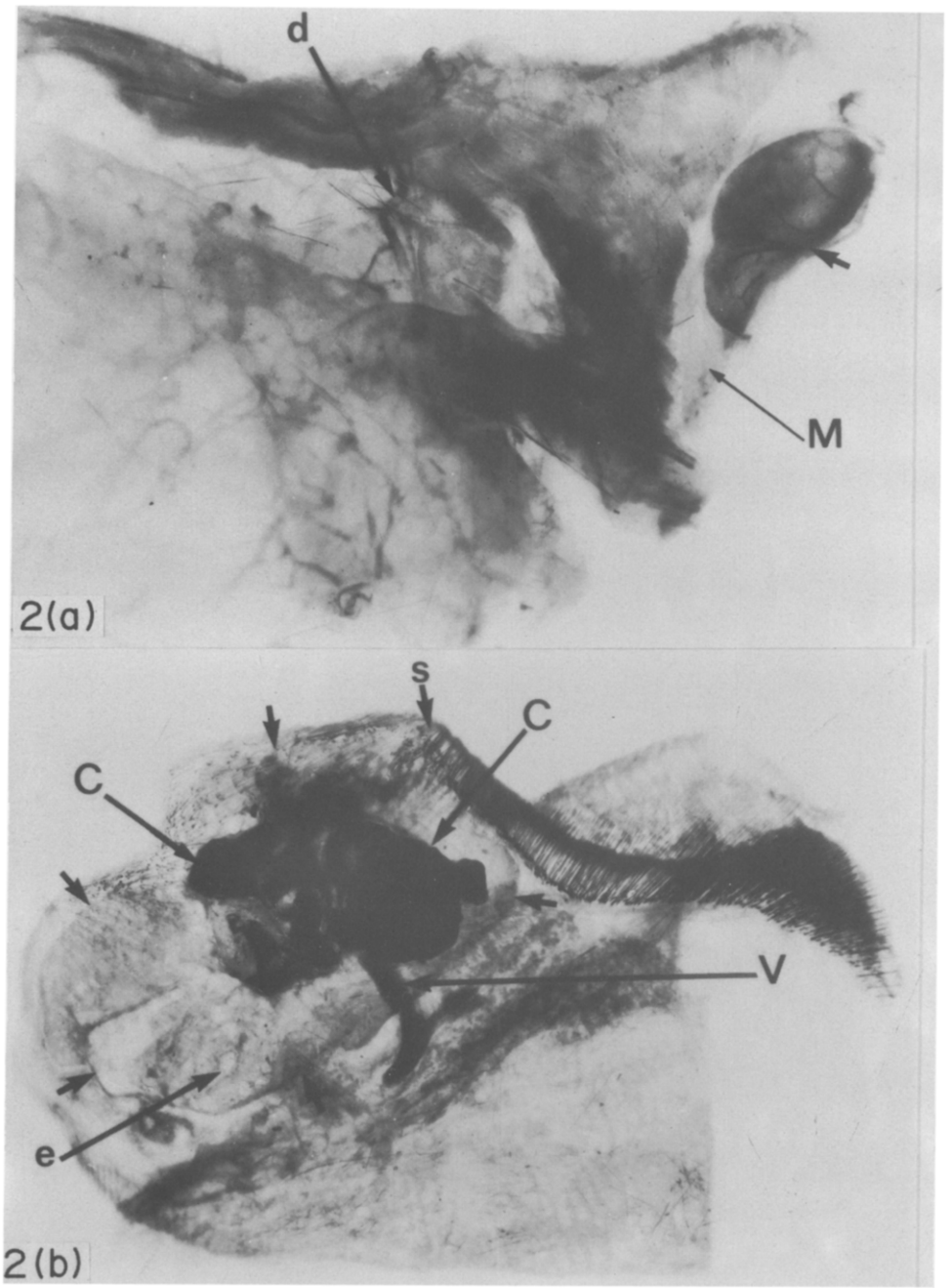


Fig. 2a. Tumour 3 mm *long* × 1.2 mm *high* × 1 mm *wide, stained in benzidine and hydrogen peroxide, counterstained in fast green FCF and mounted in resin. The tumour was tightly pressed against the anterior face of the humerus and lies obliquely on the mammary gland* (*M*), *the pedicle* (*in line with the head of the arrow*) *being obscured by the right hand margin of the tumour. All vessels visible are efferent. The base of the left lobule was removed in an attempt to make the internal vasculature clearer.* (*d*) *milk duct.*

Fig. 2b. Outside slice (2 mm *thick*) *of a tumour*, 12 mm *broad* × 8 mm *high* × 10 mm *wide, stained in benzidine and hydrogen peroxide, counterstained in fast green FCF and mounted in resin. The lateral lobules have not yet occluded the central vessel, which lay in the adjacent slice. The vertical vessel* (*V*) *is the drainage vessel, which will survive after occlusion of the central vessel. The dense mass above it consists of overlapping circumferential vessels* (*c*). *The vessels of the left lobule are not filled, though some of their empty channels show in section* (*e*). *The walls of the tumour are indicated by arrows.* (*S*) *skin.*

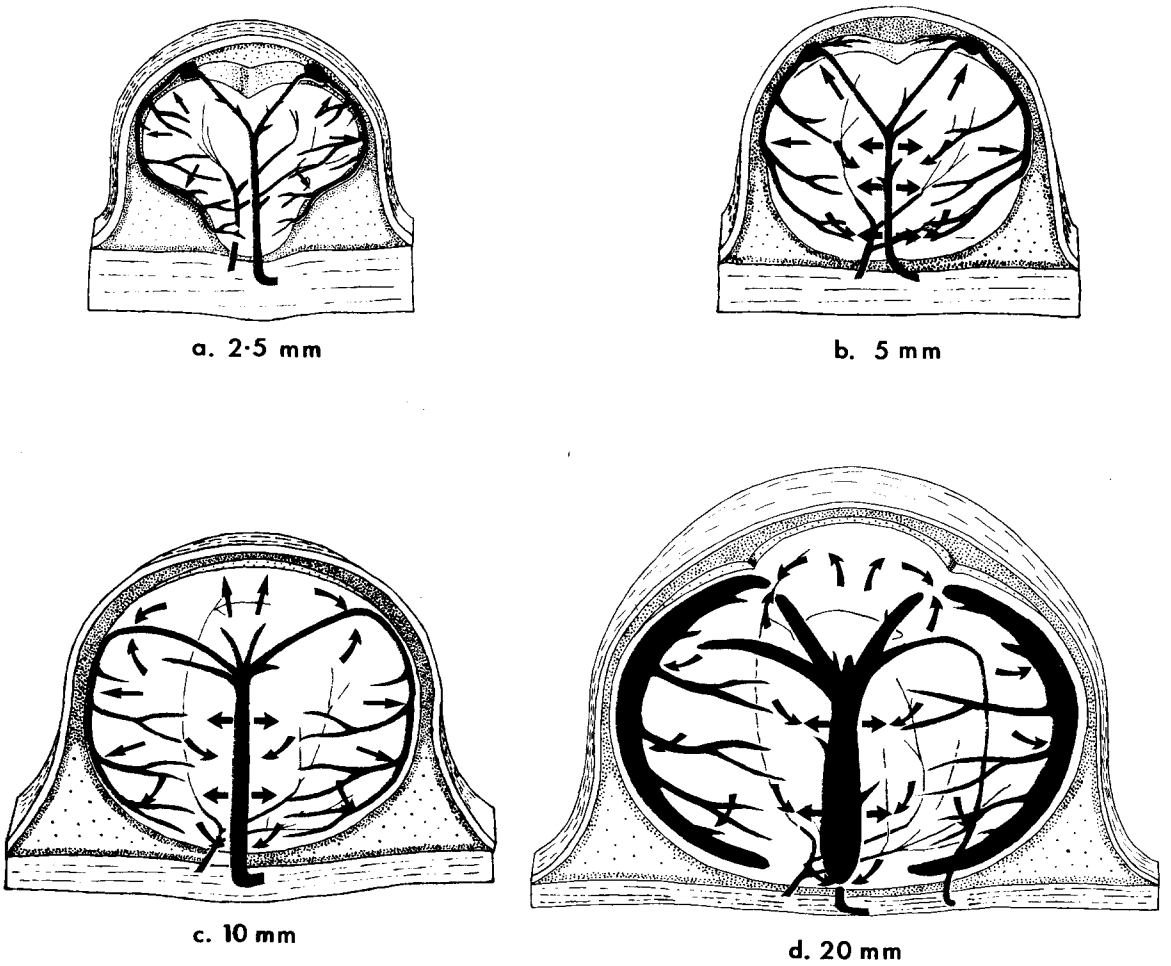


Fig. 3. *Development of the efferent system. Each drawing represents a tumour halved vertically with skin above and mammary gland and supporting tissue below. Only those efferent vessels (blue), lying on or near the cut surface are represented, whereas the afferent vessels (red) have been continued to the far wall of the tumour. Figures in* mm *refer to the diameter of the tumour. Arrows indicate pressures caused by growth. A pair of lateral lobules grows outwards (a) and expands outwards and downwards (b) and (c), pressing against the central column, which also expands. A third lobule grows vertically upwards (d) and presses against the lateral lobules. The pressures at first constrict and finally occlude the central vessel and the circumferential vessels. A single narrow drainage channel usually persists. Drainage otherwise is by capillary-like vessels.*

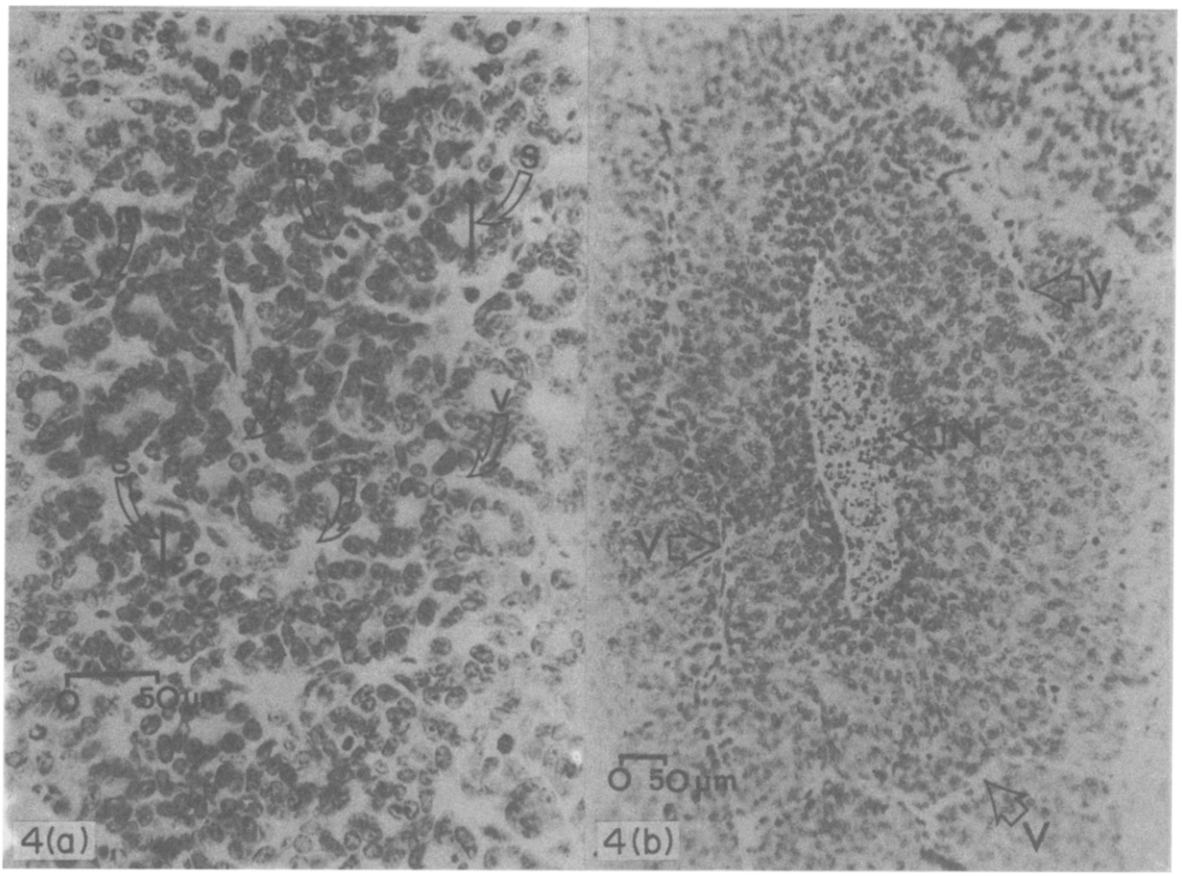


Fig. 4a *Thin (5 µm) section of tumour containing only single-layered tubules (S) and blood vessels (V). (m) mitotic figures; (c) erythrocyte.*

Fig. 4b. *Thin section showing a single multi-layered tubule, the limits of which coincide with the blood vessels (V). (N) necrotic central area.*

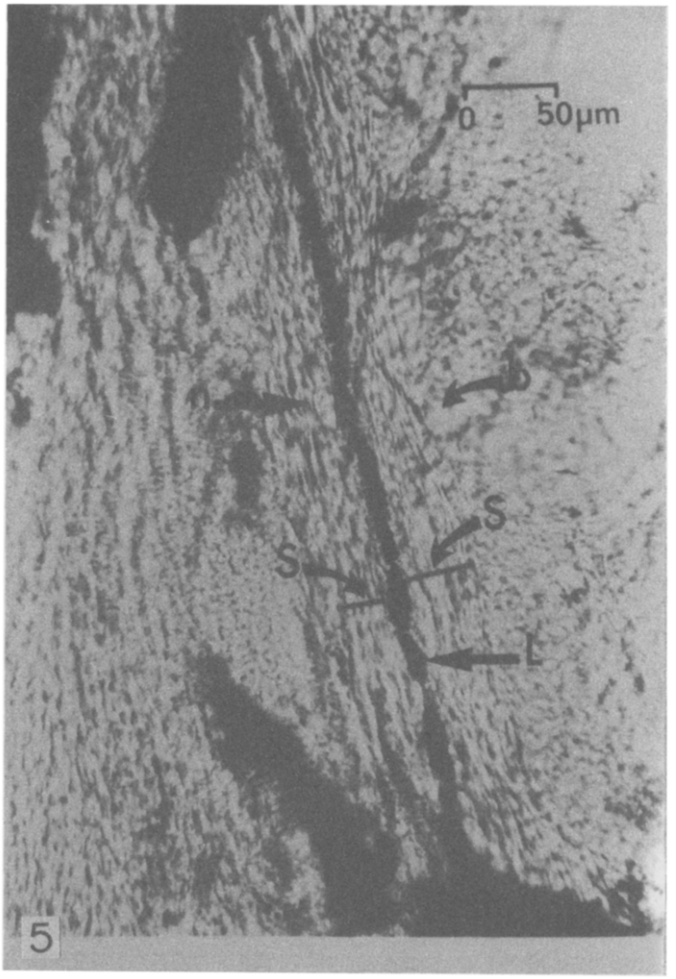


Fig. 5. Thick (200 µm) section through an afferent blood vessel, stained in benzidine and hydrogen peroxide and counterstained in fast green FCF. The lumen (L) of the vessel is well filled. The sheath (S) is composed of fine closed vessels lined with squamous cells and supported by collagen. The nuclei (n) of the endothelium are visible as dashes. One fine branch (b) is just visible leaving the vessel. All other visible vessels are efferent.

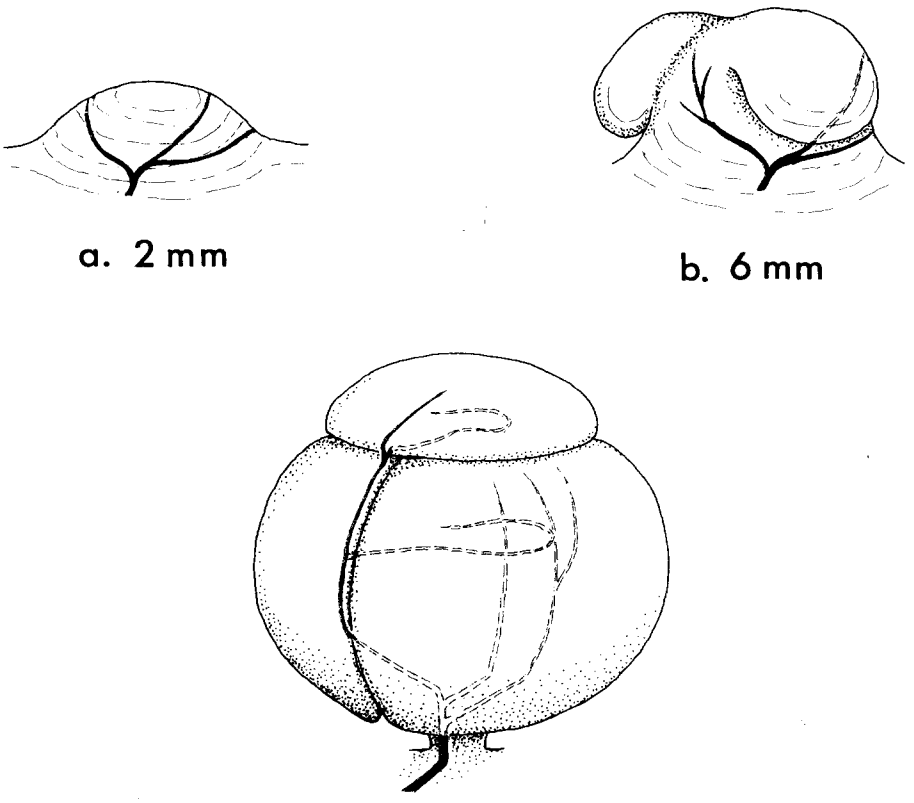


Fig. 6. Development of the afferent system. (a) Three pathways of the original network of capillary-like vessels develop into the three main afferent channels (b) The lateral lobules grow out above the level of these vessels, one of which has been trapped, the broken lines depicting its course below the lobule. A second is about to be trapped, but the third escapes between the two lobules. In (c) the dashed lines represent the course of the vessels within the tumour. The two right-hand vessels are held down until they have reached the far wall of the tumour and in consequence oxygenated blood is extremely unevenly distributed.

ment had already occurred, but an outline of the process of transformation could be inferred from it and from serial sections of later tumour stages. These latter showed that transformation occurs within a single lobule in which normal development has been completed. Neoplastic proliferation produces a small tumour mass that expands towards the skin but retains its contact with the lobule from which it arose by means of a short pedicle. Further development appears almost as a caricature of that of normal gland, the division of lobes into disparate lobules in the latter being paralleled in the neoplasm by branching of the tumour mass into lobes, which remain united centrally and, as growth proceeds become increasingly closely packed together. Thus at 3 mm diameter, the tumour mass is slightly bilobed; at 4 mm, the lobes stand out on either side at the head of a central trunk and at 5 mm they have grown downwards and become pressed against the trunk (Fig. 3). At 10 mm, a third lobe starts to develop towards the skin and from then on, additional lobes arise irregularly, giving the tumour its characteristic warty appearance.

Histology and incidence of necrosis

The histology of the tumour was found to fit well with the description of mouse mammary tumours in general given by Dunn [3]. The principal types of tissues are: single-layered tubules, Dunn's adenocarcinoma type A, and a miscellaneous collection of multi-layered structures grouped together by Dunn as adenocarcinoma type B. The single-layered tubules appear in transverse section as tightly packed, closed rings of glandular epithelial cells, with nuclei at the outside and much central cytoplasm (Fig. 4a). Two variants of this type are those with patent ducts and those having cells with conspicuous vacuoles. The commonest type of multi-layered tubule is shown in Fig. 4b, but there are also types showing little organisation into tubules and others still which are loosely packed and contain cystic or papillary ingrowths. All tumours examined contained both a single-layered and a multi-layered tubular component, each forming scattered blocks within the tumour and never restricted to one lobe only. No exact estimate was made of the frequency of the two types, but it appeared that the single-layered is the commoner in small tumours and the multi-layered in large.

An important observation, noted also by Dunn, is that islands of necrosis occur at the centre of some of the multi-layered tubules, but never in the single-layered. Twenty-five measurements were made from 5 different tumours of the distance between the edge of a necrotic area and its nearest blood supply. The mean distance was found to be 62 μm with a maximum of 110 and a minimum of 30 μm. The significance of this pattern of necrosis will be commented on later in connection with the blood supply to the two tissue types.

The origin of the tumour vasculature

The earliest stages of vascularisation of a C3H tumour have been described and figured by Reinhold [4]. Working in an Algire chamber, he implanted a small fragment of tumour on to the subcutaneous tissue of a specially prepared dorsal air sac. The tumour fragment grew and was invaded by capillary sprouts from the tissue of the host. These anastomosed and gave rise to a network of irregular capillaries. About 2 days later an arterial supply was established.

Though in Reinhold's work the tumour was implanted, the earliest stages of vascularisation seen here in spontaneous tumours suggest that the process is identical. Serial sections show that the tumour vasculature is not derived from that of the transformed lobule, from which the tumour originated. The arterial supply can be traced to an interlobular artery, which supplies both the tumour and several adjacent normal lobules. The main drainage vessel, which leaves the central column at its base, is similarly derived from an interlobular vein, though not the vein paired with the supplying artery.

The further course of vascularisation consists of the modification of the network thus formed. No differentiation occurs into arterioles, capillaries and venules, and consequently throughout the paper the terms 'afferent vessel,' 'capillary-like vessel' and 'efferent vessel' are used.

The afferent system

The afferent vessels of the tumour are peculiar both in their structure and in their distribution. In a 20 mm diameter tumour, the supply consists of a single vessel with an internal diameter of 100 μm and a normal muscle coat 16 μm thick. The vessel enters obliquely at the base of the tumour. Immediately after entering, it divides into three and at this point the muscular investiture is replaced by dense, homogeneous collagen,

which persists along each branch 2–3 mm before giving place to collagen fibres enclosing lines of flattened cells which from thin sections can be identified as endothelial cells forming blood vessels originating as branches of the main vessel (Fig. 5). In the fixed material, these vessels are closed, but since their endothelium is invariably supported by collagen, they can be traced with certainty in sections stained in Van Gieson's fluid. For the first part of their course, they accompany the main afferent vessels, forming a sheath round them, but at frequent intervals bundles of them leave the sheath and pass into the tumour mass where they run between ducts.

As each of the three branches crosses the tumour, its lumen becomes progressively narrower and, when the tumour wall is reached, the lumen is lost altogether, the branch being reduced to nothing more than a bundle of fine vessels. The bundle ramifies over the tumour surface, giving rise to smaller bundles, each of which enters the tumour again, passing through the interlobular connective tissue before finally breaking up into individual vessels and penetrating between the tubules (Fig. 8).

The distribution of the three branches is remarkable, since however large the tumour, two running almost horizontally and close together ascend only 1 mm before reaching the tumour wall, while the third, though separating from the first two and rising obliquely, reaches the tumour wall on the opposite side from them and only another 1 mm higher. The larger part of the tumour, therefore, is not supplied by major vessels and has to rely on a circuitous blood supply by means of capillary-like vessels. The probable explanation of this curious distribution is shown in Fig. 6, in which two of the afferent channels which developed from the original capillary network are seen to have been trapped by the outgrowth and expansion of one of the first pair of tumour lobes. A third channel, which lay between the expanding lobes was free to rise for a short distance before it, too, was forced to the tumour surface.

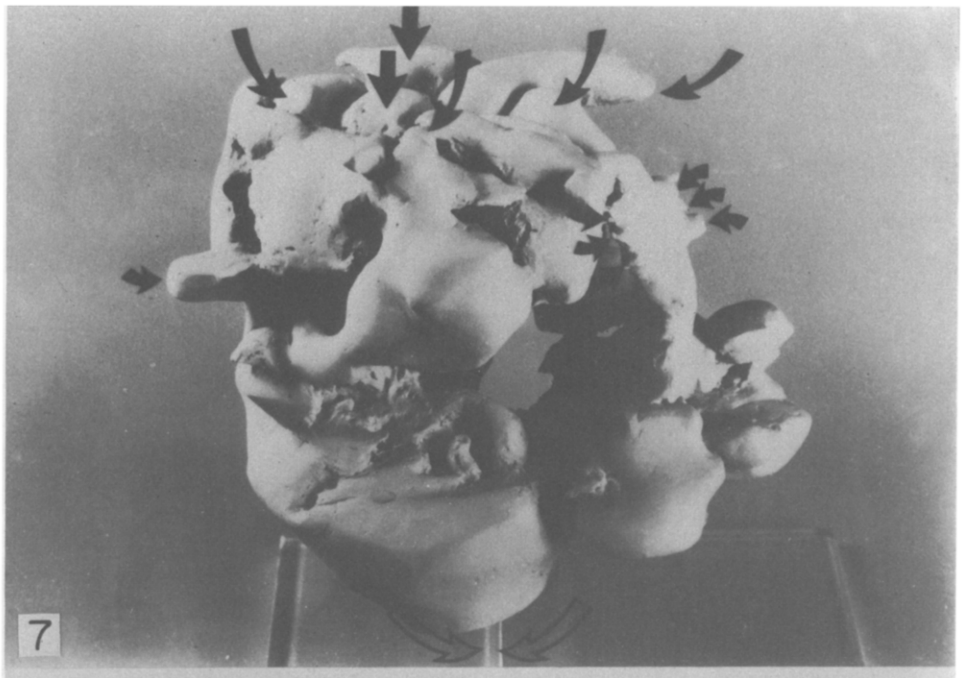
The efferent system

In tumours of less than 15 mm diameter the capillary-like afferent vessels running between the ducts eventually widen with occasional angular swellings and after some anastomosis form the conspicuous radial vessels seen in Fig. 3. The radial vessels drain into circumferential vessels which turn inwards at the apex of the tumour and unite forming a single, central drainage vessel. This leaves the tumour through its pedicle and joins an interlobular vein of the mammary gland below. The central vessel is also supplied by lateral vessels.

At a diameter of between 15 and 20 mm, the drainage pattern of the tumour is profoundly modified. The two lateral lobes, which grew out first sideways and then downwards, press inwards against the expanding central column (Fig. 3c). Outward expansion of the tumour is restricted by its covering of collagen, so that the pressure of the lateral lobes at first constricts the base of the central vessel and then occludes it completely. Meanwhile the outgrowth of a third lobe at the apex of the tumour, which presses on the two lateral lobes, leads to a similar constriction and occlusion of the circumferential vessels just above the point where they unite to form the central vessel. The occlusion of the central vessel and of the circumferential vessels leads to the remarkable dilatation of both (Fig. 3d). After occlusion, their natural drainage route is lost and though one circumferential vessel usually persists, giving some direct escape for blood from the central channel, drainage otherwise is by capillary-like vessels to the tumour surface and thence still in narrow vessels to the efferent system of the mammary gland below.

The dilated radial and circumferential vessels are shown in section in Fig. 8 and the dilated central vessel by the model in Fig. 7. The model represents the vessel in a tumour 19 mm in diameter in which occlusion was complete at the base and at the apex. The point of occlusion at the base is marked by hollow arrows and the points of entry of supply vessels by solid arrows. Both the vessel and the branch at its side are grotesquely swollen, but the whole system comprises a single blood-filled space with a wall averaging 80 μm in thickness. The volume is 15 mm^3.

In addition to the radial vessels and the circumferential sinuses, a third type of efferent vessel occurs. These drain laterally into the central drainage channel and consist of chains of flattened polyhedral sinuses united to each other by a dense network of capillary-like vessels. The polyhedra may be as much as 1.5 mm long, but not more than 100 μm in depth. They occur where the pressure between surrounding neoplasmic tubules appears lowest.



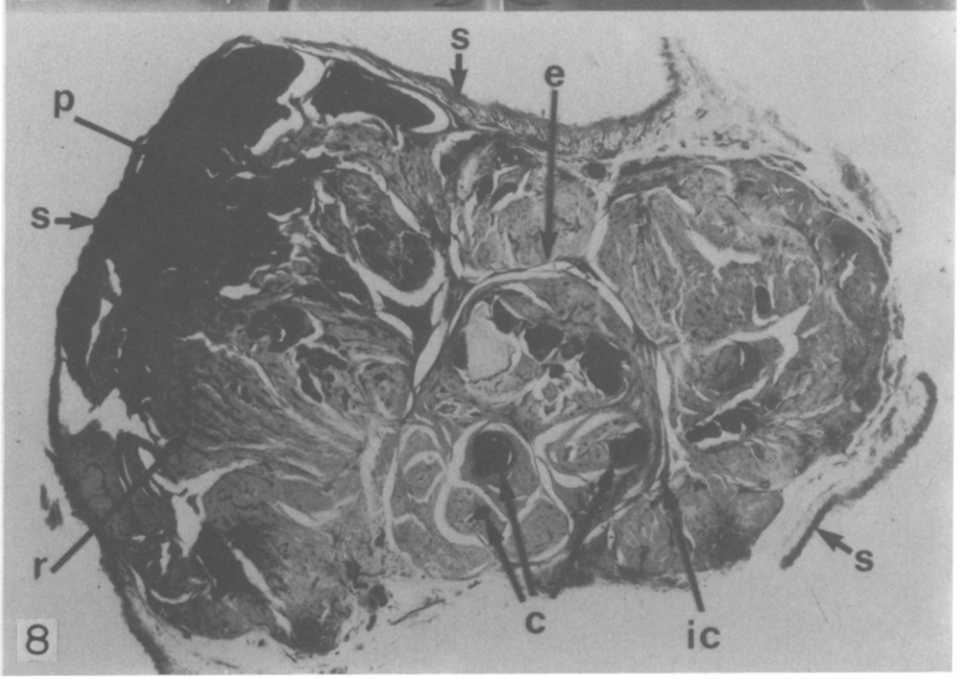


Fig. 7. Scale model of the central drainage vessel of a C3H tumour, 20 mm *in diameter. The original model is* 20 cm *high and constructed to a scale of* 50:1. *The main vessel is on the left with a broad branch on the right. Anastomosis occurs freely between them. The internal cavity is entirely blood-filled and the thickness of the wall is* 80 μm. *The hollow arrows at the base of the model indicate the point where the tumour's lateral lobules press together and have completely occluded the vessel. The broad arrows indicate the points of entry of the circumferential vessels, now largely occluded and above their broad bases represented only by very numerous capillary-like vessels. The smaller arrows represent the bases of vessels returning blood laterally into the main channel.*

Fig. 8. Thick section (200 μm) *through a* 19 mm *diameter tumour stained in benzidine and hydrogen peroxide and counterstained in dilute eosin. The section is cut horizontally about two thirds of the way up the tumour below the level where the central column branches to give the two lateral lobules. The central lobule occupies the lower central third of the section and has divided into smaller lobules. The large vessels in it combine at a lower level to form the central drainage channel. The lateral lobules on either side of it are also starting to divide. (P), circumferential vessel: (r), radial vessels: (c), central vessels: (e), bundle of afferent vessels: (ic), interlobular connective: (s), skin.*

The blood supply to the tumour

Since the tumour has a single blood supply, the diameter of which can be measured, the possibility exists of estimating the relative rates of supply to the tumour and to normal, resting mammary gland. The volume of the tumour described above with a diameter of 19 mm and a supply artery of 100 μm internal diameter, was found to be 2000 mm^3. The largest artery that could be found supplying mammary gland and no other type of tissue, had an internal diameter of 40 μm. The volume of gland supplied was 9 mm^3. Assuming that the rates of flow of blood are directly proportional to the fourth power of the radius [5], the rate of flow in the tumour is approximately 40 times that in the artery supplying the normal gland. In proportion to volume, therefore, the blood supply to the tumour is slightly less than a fifth of that to normal, resting gland.

Variation in tumour vasculature

The only variation found in the vascular pattern resulted from the frequency with which the tumour divided into lobes. A 20 mm diameter tumour may have as many as 12, or as few as 3, externally visible lobes. The only difference in vascular pattern of these two extremes is that in the former the circumferential sinuses are divided into more and shorter segments.

DISCUSSION

The vascular pattern and its development

The early development of the vasculature of the C3H tumour occurs under the influence of a chemical factor, T.A.F. (tumour angiogenic factor), produced by the neoplasmic cells. Later the characteristic pattern of the vasculature is imposed largely, if not entirely, by the stresses and strains of tumour growth. In other respects there seems to be no correlation between parenchyma and stroma.

Folkman [6] and Ausprunk and Folkman [7] have shown that T.A.F. induces the endothelial lining of preformed vessels in the proximity of a tumour to migrate towards the tumour and also stimulates these cells to divide. This dual action leads to the formation of the initial capillary network and, once an arterial supply to this is established, its vessels become either afferent or efferent. In the C3H tumour, neither the afferent, nor the efferent, vessels acquire a muscular investiture, presumably because no equivalent to T.A.F. is formed to stimulate the muscle cells of the vessels in the tumour's proximity to divide and to migrate. Except for a short distance at their start, the afferent vessels, though elongating greatly, remain capillary in form, and their efficiency is reduced still further by their circuitous course. In the efferent system, in contrast, 'preferred channels' widen to form an apparently efficient, well-organised drainage system, but this efficiency is short-lived, since pressure between the expanding tumour lobes leads to the occlusion of the main vessels and reversion to a system of capillary drainage.

In contrast with the pattern of vascularity of normal mammary gland with its neat arrangement of afferent and efferent vessels lying side by side, united by a compact capillary network precisely related to the tubules it supplies, the vasculature of the tumour consists of little more than extremely elongated capillaries with few cross connections between them, and large sinuses, occupying a substantial part of the tumour volume, but playing almost no part in circulation. The failure of the vascular system to provide an adequate supply of metabolites to all cells of the tumour is shown by necrosis, which is invariably present in larger tumours and is at first confined to the centres of multilayered tubules. This pattern of distribution seems to result from the difference in the length of the pathways along which oxygen travels by diffusion. Since capillaries run alongside tubules, but do not penetrate them, the pathway between the innermost cells of a multi-layered tubule and the nearest capillary inevitably traverses many cell layers and is considerably longer than that to the outer cell layers or to the cells of a single-layered tubule.

The effect of the length of the diffusion pathway has been considered in detail by Thomlinson [8]. In his model, a gradient of oxygen tension occurs in the cells surrounding a capillary, the tension decreasing as the distance from the capillary increases and, if the blood is saturated in the first instance, reaching zero at about 160 μm from it. If because of the length of the capillary or for some other reason the blood were not fully saturated, oxygen tension would be reduced to zero at less than 160 μm. Applying these considerations to the present case, in which the distance between the margin of the necrotic area and the nearest capillary varied from 110 to 30 μm with a mean of 60, it can be concluded firstly that the blood on arrival was never fully saturated, and secondly that

the extent to which its oxygen load had been depleted varied, presumably in accordance with the length of the capillary pathway.

Vascular pattern and radiation response

Three predictions concerning the radiation response of the C3H tumour can be made from a knowledge of the pattern of its vasculature. Firstly, the anoxia and severe hypoxia which result from the vascular pattern will make the tumour relatively resistant to X-irradiation. All the investigations that have been made confirm this prediction. Howes [9] found that for mice with tumours about 6 mm in diameter and breathing air, a single dose of 4910 rad was required to give a TCD_{50} at 150 days. Hill *et al.* [10] tentatively concluded from the results of their radiation experiments that the tumour contains only a small proportion of well oxygenated cells and that the majority of the remaining cells are at intermediate oxygen tensions as regards radiosensitivity.

Secondly it can be predicted that radioresistance will increase with increasing tumour volume and that there will be a sharp rise at a diameter of 15–20 mm when the main drainage vessels become occluded, thereby reducing the rate of blood flow. This prediction appears not to have been tested over the whole range of tumour size required. Suit and Maida [11] investigated the effect of volume on the oxygen status of small tumours. They showed that even in tumours of about 1 mm diameter, a few anoxic or severely hypoxic cells were present and that in tumours of 8 mm diameter, breathing high pressure oxygen (44 psi) was not effective in bringing the oxygen to aerobic levels in all parts of the tumour.

The third prediction is that all parts of the tumour will not respond uniformly to radiation, the inner cells of the multi-layered tubules with their greater degree of hypoxia being more resistant to X-irradiation than their outer shells or than single-layered tubules. No evidence is available to confirm or refute this prediction. If it were found in a series of tumour transplants from the same origin, that the proportion in which the two classes of tissue are present is statistically constant for a given tumour size, the prediction might be tested and, if confirmed, the way might be open for a new method for the investigation of radiation damage.

The vascular pattern in relation to hyperthermia

The two important findings in this context which emerge from the study of the vascular pattern of the tumour are the existence of large blood sinuses, through which the circulation must be very slow, and the extent of anoxia and severe hypoxia. Since the circulation of blood is the most effective mechanism for the exchange of heat between the tumour and the rest of the body, a large volume of almost stagnant liquid within the tumour must greatly reduce the rate of heat exchange, but the significance of this clearly depends on how heat is supplied to the tumour. It is hard to see how a reduced rate of circulation can cause a significant difference in the temperature of the tumour and of the surrounding tissues if whole body heating is used, but if a satisfactory means of local heating is found, it seems likely that both during heating and for a period afterwards, the tumour temperature will be above that of the surrounding tissues. Since the effect of hyperthermia is dependent both on the temperature to which the tumour is raised and on the time for which it is maintained at the higher temperature [12, 13], this might prove an important consideration.

The relevance of the high proportion of hypoxic and anoxic cells follows from the findings that hyperthermia is most effective in conditions of low pH [14, 15], nutrient deficiency [16] and low oxygenation [17, 18]. Hence it seems likely that hyperthermia would cause most cellular destruction in the inner parts of the multi-layered tubules, the region most insensitive to radiation, and, in addition, that there would be a marked increase in its effectiveness in tumours above 10–15 mm diameter.

Implications of the vascular pattern in the interpretation of tumour growth and physiology

It is generally accepted that neoplasms differ from the normal tissues of the body in their lack of organisation and of correlated development. The vascular pattern of the C3H tumour strongly supports this view. So inefficient a system could not exist in a structure subject to natural selection, but tumours by their nature are not subject to natural selection. Providing their component parts function well enough to support the life and development of the tumour as a whole, no influence exists to improve the parts further.

This conclusion has practical, as well as theoretical, implications since it follows that a

degree of teleology that would be justifiable in the interpretation of the physiology of normal tissues would be quite unjustifiable in the approach to neoplasms. Where correlation between stroma and parenchyma is so slight that the parenchyma can largely occlude the whole drainage system, it cannot be assumed that activities such as vasoconstriction are other than an inevitable consequence of the mode of development. They may be quite unrelated to the tissue's needs.

Acknowledgements—Many members of the Medical Research Council Cyclotron Unit have helped in the production of this paper. I am grateful to all of them and in particular to Mr. P. H. Warren, who bred the mice, and to Mr. F. Paice, the photographer. My greatest debt is to Dr. R. H. Thomlinson of the Regional Radiotherapy Centre, Mount Vernon Hospital for his constant help and encouragement.

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