The Spread of Tumours in the Human Body

THIRD EDITION

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Preface to the Third Edition

The second edition of this book was published 21 years ago, and much new material both in the literature and in my own collection has accumulated since then. I have therefore revised the whole text and re-written many parts of it. It is impossible to read and assimilate the enormous volume of recent publications on the subject, but I hope that the 350 additional references that I have selected for inclusion are fairly representative. I apologize for omitting many other worthy contributions that might have been included, but it is impracticable nowadays to read more than a small fraction of the relevant published work on such a subject, and I have adhered to my rule not to give references to works that I have not personally studied. For reasons of space I have omitted the titles of most of the entries in the *Bibliography* since these often do not convey the particular points that are discussed in the text; but I have retained the full titles of classical works and of those describing important new discoveries or giving good reviews.

I have retained the Appendix, which gives a summary of my findings in the 500 consecutive cancer necropsies that I personally carried out at the Austin and Alfred Hospitals in Melbourne, Australia, and that provided much of the material on which the book was and is based. Most of the additional material now incorporated is filed in the Tumour Reference Collection of the Imperial Cancer Research Fund, London, and I have included the relevant T.R.C. numbers in the text.

I am deeply in the debt of many fellow pathologists for giving me and the Tumour Reference Collection their interesting specimens. They are too numerous to mention individually, but those who have been particularly generous include: Dr. G. R. Osborn, formerly of Derby Royal Infirmary but now in Perth, Western Australia; Dr. R. Salm of the Royal Cornwall Hospital, Truro; and Dr. T. B. Teoh, Director of the Government Institute of Pathology, Hong Kong. In the Imperial Cancer Research Fund, I am very grateful to Dr. Lillian Pang for verifying information in the Tumour Reference Collection, and to Mr. Gerald D. Leach for invaluable photographic help. The courtesy and consideration of my Publishers has greatly lightened the task of revision.

Heswall, Cheshire *Rupert A. Willis*

Preface to the Second Edition

The first edition of this book, published by J. & A. Churchill Ltd., in 1934, was No. 2 of the Monographs of the Baker Institute of Medical Research, of the Alfred Hospital, Melbourne, Australia, where I was Pathologist for 15 years and where most of the material on which the book is based was collected. Now, by kind consent of the Institute and of the former publishers, this new edition is produced by Butterworth & Co. (Publishers), Ltd., in a style similar to that of my *Pathology of Tumours*, to which it now forms a natural supplement.

While the general arrangement of the book remains the same, additions and modifications have been made throughout the text, some parts of which have been completely rewritten. In the 18 years since the first edition appeared, there has accumulated an enormous number of published papers bearing on the spread of tumours; and it has been impossible for me to assimilate more than a small fraction of these. However, I believe that the 260 additional references which I have selected for incorporation in the present edition are fairly representative of recent research in this field. Doubtless I have overlooked some that should have been included; and in excuse I plead the impossibility of a personal perusal of the whole of the relevant literature, and my deliberate adherence to the rule of not including references to papers which I have not personally studied.

The Appendix gives an analysis of the consecutive series of personally performed cancer necropsies which provided my own research material; these were 323 in number in the earlier edition, and are 500 in this.

I repeat my thanks expressed in the earlier edition to Professor P. MacCallum of Melbourne for his interest and help in its launching, and to my wife Margaret for assisting me in abstraction, translation and revision and for preparing many thousands of microsections. In the preparation of the new edition, I am especially indebted to Dr. J. W. Whittick of the Royal Cancer Hospital, London, for his careful reading of proofs and for compiling the Index; to Dr. Teoh Tiaw Bee of Hong Kong for preparing new and better prints of all the illustrations, and for making the photomicrographs for *Figures 80* and *81* from a specimen kindly given by Dr. A. G. Rickards of Lancaster; and to Miss Zaidée Milner for her expert clerical and bibliographic help which greatly lightened my task. *Figure 28* is reproduced by kind permission of the Editor of *Studies in Pathology presented to Peter MacCallum* (Melbourne); *Figures 10, 38* and *66–69* are from my *Pathology of Tumours*, and *Figures 14* and *16* are from my *Principles of Pathology*. To my Publishers I am grateful for their very thorough checking of the text and references and for meeting my wishes in every way.

Leeds *Rupert A. Willis*

Contents

Chapter 1

The Direct Spread of Tumours

DEFINITION OF METASTASIS

Only those growths which are separate from the primary growth and have arisen from detached transported fragments of it are entitled to be called 'metastases'. This essential definition is often ignored, the term 'metastasis' frequently being used for any form of secondary neoplastic disease of a part. The ambiguities which may arise are illustrated in the following inadequate report. 'Carcinoma of the prostate with metastases in the peritoneum, aortic glands, pancreas, left adrenal, liver and lungs.' The report should have read: 'Carcinoma of the prostate extending to the pelvic peritoneum, metastases in the aortic glands, thence contiguity-invasion of the pancreas and left adrenal, discrete metastases in the liver and lungs.' Ambiguities of this kind abound in medical and pathological literature, detracting from the value of the records, and vitiating many statistics. Abbreviated reports should give clear indications of the nature of the individual lesions observed; and, as shown in the example, this can be done without serious loss of brevity.

THE INVASIVE PROPERTIES OF TUMOUR CELLS

Invasiveness is the fundamental and distinguishing attribute of malignant tumour cells, conferring on them their ability, not only to infiltrate the local tissue interstices, but also to penetrate into lymphatics, blood vessels and other preformed spaces and so produce remote metastases by transfer. Let us examine those properties of the tumour cell itself which may be of significance as regards its invasive capacity. These are (1) its power of progressive multiplication, (2) its motility, (3) its loss of adhesiveness, (4) its possible phagocytic properties, and (5) its possible elaboration of toxic or lytic substances.

Progressive multiplication

This is certainly a factor in neoplastic infiltration. Once invasion has begun, at the infiltrating margin of a tumour successive generations of cells are continuously, 'budded out' into the surrounding tissues; and, at the same time, volume increase of the main mass of the growth must provide a *vis a tergo* which literally thrusts the marginal cells of the tumour into all available crevices and crannies of the invaded tissues. The growth of the

tumour resembles that of a root and its attached rootlets; the main root enlarges expansively, while its peripheral rootlets and their fine root-hairs creep and thrust their way along lines of least resistance in the surrounding soil, and the growth and soil-disrupting powers of the whole structure could not occur without the progressive proliferation of its cells. Young (1959) designed experimental models to show the efficacy of tissue pressures and pressure gradients in bringing about the translocation of tumour cells.

But cellular multiplication alone does not account for invasiveness. There are many highly infiltrative tumours which grow slowly and show few mitoses, such as the scirrhous carcinomas of the breast and the signet-ring-cell carcinomas of the stomach; while some other carcinomas of the same organs grow rapidly and to a great bulk, yet show minimal infiltration. The rapid proliferation of many regenerating or hyperplastic tissues, or of transplanted embryonic tissues in adult hosts, does not confer invasive qualities on them.

Motility

Workers of last century reported seeing motile cells in tumours examined fresh after surgical removal (Virchow, 1863; Grohe, 1865; Carmalt, 1872; Waldeyer, 1872; Vierth, 1895). Although these early workers may sometimes have mistaken macrophages for tumour cells, later tissue culture studies proved conclusively the motility of many kinds of tumour cells (Carrell and Burrows, 1911; Hanes and Lambert, 1912; Lambert, 1916; Lewis, 1936; Cox and Cranage, 1937; Russell and Bland, and Bland and Russell, 1933 and 1938; Coman, 1942; Enterline and Coman, 1950; Abercrombie and Ambrose, 1962; Wood, Baker and Marzocchi, 1968). As we might expect, plentiful freely mobile cells are produced in many tumours of mesenchymal tissues. Well-differentiated epithelial tumours tend to grown in compact sheets or clumps in culture; but at the margins of these the cells extend over surfaces with characteristic undulating movements (Abercrombie and Ambrose, 1962), and some cells become detached and amoeboid; and poorly differentiating carcinomas produce many detached motile cells. Enterline and Coman (1950) saw carcinoma cells migrate at rates as high as 4.4 μ per minute, and Wood, Baker and Marzocchi (1968) recorded rates of 6–7 μ per minute. Active migration of the cells of gliomas of various types in culture was described by Russell and Bland (1933), and in greater detail by Lumsden (1971).

Diminished adhesiveness and other surface changes

By micro-dissection Coman (1942 and 1944) showed that the cells of squamous-cell carcinoma adhere to one another less strongly than do their normal counterparts; and by agitation of the tissues McCutcheon *et al.* (1948) found a similar loss of mutual adhesiveness of the cells of adenocarcinomas. Abercrombie and Ambrose (1962) and Ambrose (1968) also reviewed other surface properties of normal and tumour cells in culture, including their negative electric charges as measured by electrophoresis. These charges are high in active tumours thereby increasing the mutual repulsion, and therefore diminishing the adhesiveness between the cells. It is very probable that changes in the complex structure of the surface membranes of the cells underlie the raised charges, diminished adhesiveness, motility and contact relationships of the tumour cells with their neighbours and that these related changes play an important part in determining invasiveness.

Phagocytic activity

The phagocytic powers of tumour cells are debatable. Steinhaus (1891), Stroebe (1892) and others depicted appearances suggestive of included blood corpuscles or stroma cells within tumour cells; but most workers, including myself, have failed to find any unmistakable examples of engulfed host cells. Leucocytes are sometimes seen within tumour cells, not because they have been engulfed by these cells, but because they are themselves actively invading moribund tumour cells. Blood pigments are sometimes taken up by the cells of synoviomas or other haemorrhagic tumours. In mouse-sarcoma cultures *in vitro*, Lambert and Hanes (1913) saw phagocytosis of carmine particles and of dead cells. Kerr and Searle (1972) described how the cells of basal-cell carcinomas may take up dead fragments of cells, to form 'Councilman bodies'. The grounds for attributing to tumour cells any significant powers of active preying on the elements of the invaded tissues are inadequate.

Tumour metabolites

That tumours produce soluble metabolites capable of affecting the surrounding tissues is certain. The high lactic acid output of some carcinomas is well known, and the various stromal reactions in and around tumours point to the influence of diffusible products of the tumour cells (*see* Chapter 10). Some tumours have been found to produce enzymes capable of altering the ground substances of connective tissues, in particular hyaluronidase, and some workers have postulated that these diffuse from the tumours into the tissues and pave the way for their invasion. Cameron (1966) gave an impressive review of the evidence for hyaluronidase as an invasion-promoting factor; and in his later clinical and chemical work he amplified this view and advocated high doses of ascorbic acid as a hyaluronidase antagonist in the treatment of cancer patients (personal communication). This and other investigations on tumour enzymes must be pursued further.

The factors determining invasiveness and their relative importance are still uncertain. Changes in the chemistry and electrical condition of the cell surfaces, with diminished adhesiveness, increased motility and altered contact relationships with neighbouring normal cells, are probably important factors; while continued multiplication maintains an increasing supply of cells with the new chemical and physical endowments. If hyaluronidase or other tissue-damaging enzymes are also a factor, this too might be connected with the changed surface properties of the cells.

THE ROUTES OF LOCAL EXTENSION OF TUMOURS

The paths of neoplastic extension are (1) tissue spaces, (2) lymph-vessels, (3) blood-vessels, (4) coelomic cavities, (5) cerebrospinal spaces, and (6) epithelial cavities. Along any of these paths tumours may extend without loss of continuity over small or great distances; and, by the same routes except the first, discontinuous extension with remote metastasis by carriage of detached tumour fragments also takes place. Local extension and embolic metastasis differ only in the continuity or discontinuity of the spread of the

tumour. Tumour spread in the coelomic cavities and in cerebrospinal spaces is described in later chapters. Here we will consider direct spread by the other routes referred to above.

Tumour infiltration along tissue spaces

Microscopically, it is often apparent that the cells of a tumour have extended by infiltration of tissue spaces, dissecting the tissues apart along planes of anatomical cleavage, and occupying all available nooks and crannies amongst the tissue elements. This is indeed the initial and fundamental mode of spread of most neoplasms. Carcinoma at its inception does not at once penetrate to the lumen of lymphatics and blood-vessels; it must first infiltrate tissue interstices. So also the peripheral extension of well established growths continues to be partly or largely by the process of infiltrative dissection of the structures encountered, without special relation necessarily to vascular or other preformed paths. In sections of the growing edges of many carcinomas, there may be seen clumps of malignant cells in immediate contact with muscle fibres or the parenchymatous elements of epithelial organs, or forming completely investing cuffs around arteries or nerve-bundles *(Figure 1)*. They are invading the tissues by infiltration along potential clefts or planes of least resistance and then by expansive growth are forcing the tissues apart.

In tissues which are physically homogeneous or nearly so, metastatic tumour nodules experience equal facility of extension in all directions and tend, therefore, to assume an approximately spherical shape. This is the usual form of most discrete metastases situated in the substance of the liver, kidney, spleen, lungs, adrenals, brain, myocardium, muscle or bone-marrow. In tumours in these tissues, departures from the spherical shape depend largely on non-symmetrical mechanical impediments encountered by the enlarging tumours. The most striking illustrations of this are seen in tumours situated immediately beneath the capsule of the liver, kidney or spleen. The visceral capsule limits growth in this direction, so that subcapsular metastatic growths exhibit forms intermediate between a sphere and a hemisphere. Microscopic examination confirms the presence of an intact visceral capsule confining the growths on their superficial aspect. It is indeed surprising to observe how primary or secondary malignant tumours in the liver may enlarge the viscus to many times its normal size, and yet the distended capsule may remain intact, and the organ retain its general shape. The tunica albuginea of the testis may long confine testicular tumours, and the sclera intra-ocular tumours.

The fibrous capsules of viscera act not only as barriers confining intravisceral growths, but also as barriers protecting the organs from external growths. Retroperitoneal tumours may widely infiltrate the perirenal tissues and yet the kidney may remain uninvaded by the enveloping tumour. So also, peritoneal deposits from ovarian or other growths may massively clothe the liver and spleen externally, yet fail to penetrate the capsules of these organs.

Periostea, like the capsules of viscera, tend to confine growths within the bones and to exclude external growths. In primary osteosarcoma, and especially in metastatic carcinomas, an intact periosteal layer frequently clothes the surface of the expanding tumour, which thus assumes the form of a smooth boss, or in long bones a fusiform swelling. Neoplastic perforation of the periosteal sheath is followed by infiltration of surrounding muscles and fascial planes, and the tumour then loses its smooth outlines. The pericranium externally and the dura mater internally limit the outward and inward extension

of metastatic tumours in the skull, so that both aspects of these tumours usually present smooth outlines and both the scalp and brain escape invasion.

Periosteum tends not only to confine growths within bones, but also to protect the bones from external growths. In the absence of infection, it is unusual to see neoplastic invasion of bone from contiguous tumours. It is true that necrosis of involved bones commonly occurs in infected tumours, as, for example, the mandible in ulcerating oral carcinomas, but in these cases the bone destruction is often due, not to the tumour invasion, but to pyogenic infection.

Besides visceral capsules and periostea, other compact fibrous tissues which resist neoplastic invasion include ligaments, tendons, fascia, and the dermis. Tumours arising in the ends of the long bones may extend widely into the neighbouring soft tissues and envelop the adjacent joint, which, however, is usually protected from invasion by its fibrous capsule. Intermuscular fibrous septa may long remain relatively intact in a massive tumour, and may play an obvious part in moulding its shape and directing its extension.

Cartilage is another tissue which, largely because of its physical properties, long resists neoplastic infiltration. Bone ends may be totally destroyed by primary or metastatic tumours, yet the articular cartilage often remains intact and protects the joint-cavity from invasion. The costal cartilages may persist when massive tumour-growth affecting the chest wall has destroyed all soft tissues and bony ribs in the area; and the intervertebral discs usually remain intact when extensive metastatic carcinoma has produced total collapse of neighbouring vertebrae.

Tumour extension along lymphatics–lymphatic permeation

We have seen that malignant cells extend into and occupy any available crevices in the invaded tissues. Lymphatics constitute a system of preformed crevices of which many carcinomas freely or even preferentially avail themselves. The part played by lymphatic channels in the direct extension of carcinomas has been recognized almost since the beginning of the histological study of neoplasms. Of the earlier accounts of this mode of spread of tumours, those of Klinger (1857), Waldeyer (1867), Hoggan (1878) and von Recklinghausen (1885) may still be read with profit, and for clarity and accuracy the later accounts by Heidenhain (1889), Vogel (1891), Stiles (1899) and Ernst (1905) have not been surpassed. Handley, whose views are fully described in his book (1922), attributed to lymphatic permeation a degree of importance which most pathologists do not endorse. Handley's views are discussed below and in later chapters.

Macroscopic appearances

Striking macroscopic examples of lymphatic permeation are sometimes exhibited by the serous membranes, the affected area presenting a clearly visible network of white lines of growth which mark out more perfectly than an anatomical injection the pattern of the subserous lymphatic plexus. The best specimens of this condition are seen in the visceral pleura in some cases of primary or secondary carcinoma of the lungs *(Figure 32)*, and in the mesentery in some cases of secondary peritoneal carcinomatosis. It is seen less frequently and less perfectly in other parts of the peritoneum, in the parietal pleura, and the pericardium. The term 'cancerous lymphangitis' for this condition is inaccurate, and the simple title of 'lymph-vessel carcinomatosis' is preferable. In many cases of serosal disease of this kind, there is coexisting permeation of the lymphatics of the subjacent

viscera, for example, of the peribronchial and interalveolar lymphatics throughout part or whole of the lung, sections of which exhibit fine branching lines of growth. In occasional cases of malignant melanoma of the skin, especially of the foot or leg, a striking picture of lymphatic permeation is seen; the affected vessels appear as black cords between the primary growth and the regional lymph glands (Marchand, 1907; Handley, 1906 and 1907; Hertzler and Gibson, 1914; Sutton and Mallia, 1923).

Microscopic appearances

Microscopically, the peripheries of infiltrating carcinomas often provide good examples of the growth of tumour cells along lymphatics; columns of cells occupy distended channels, the endothelial walls of which are still intact *(Figure 2).*

Extent

The extent of centrifugal lymphatic permeation from a single focus of growth is very variable. In many carcinomas it is limited to the immediate neighbourhood of the visible or palpable tumour. With other tumours, on the contrary, it may involve a surprisingly wide area. Thus, from a relatively small area of palpable growth in the mamma, impalpable lines of lymph-vessel cancer, perhaps indicated by scattered outcrop-nodules in the skin, may ramify widely over the trunk and even extend on to the proximal segments of the limbs. Leitch (1922) saw cancerous lymphatics as low as the wrist of a patient with brawny arm from a breast cancer. In my case of parotid carcinoma, No. 56, flat buttons of growth in the dermis were numerous in the neck and thoracic parietes, less numerous in the abdominal walls, while a few nodules were present in the skin as far caudally as the lower parts of both thighs; vertical sections of the skin, subcutis and deep fascia near these nodules indicated their origin by outcropping from the permeated deep fascial lymphatic plexus, in a manner similar to that described for mammary carcinoma by Handley. Lymph-vessel cancer of the serous membranes and subjacent viscera may affect very wide areas. Thus, from a small bronchial growth, or from hilar gland deposits secondary to primary tumours elsewhere, there may arise linear permeation of the subpleural and peribronchial lymphatics of a whole lung or of both lungs. Carcinoma of the stomach may produce almost body-wide lymph-vessel carcinomatosis (Schierge, 1922; Schmücker, 1928), and the primary tumour in the stomach may be relatively insignificant.

Extensive lymphatic permeation, however, does not always proceed centrifugally from a single initial focus. Frequently several or many focal deposits of growth participate, the initially separate permeation zones around these become confluent and so establish a wide permeated area which, though now continuous, was of multicentric origin. Thus the lung from which *Figure 32* was obtained was the seat of many scattered nodules of growth probably of blood-borne origin, and the extensive pleural and pulmonary lymph-vessel cancer doubtless arose, not by progressive extension from any single initial source, but by fusion of the enlarging zones of permeation around these deposits. Similarly, in the peritoneal cavity, transcoelomic transplantation may produce many discrete nodules of growth, and then these may establish linear connections with one another by cancerous filling of intervening lymphatics, so that the final appearance suggests extensive continuous permeation of the subserous plexus with nodes of growth at the intersections. In one of my necropsy cases of carcinoma of the stomach in which

the mesentery was conspicuously affected in this way, other parts of the peritoneum presented discrete asterisk-shaped nodules without linear connections (verified microscopically), thus indicating the multicentric origin of the permeation process. So also in cases of mammary carcinoma with widespread skin nodules, embolic tumour deposits in the axillary, cervical and other lymph nodes, and retrograde embolism of plexus lymphatics, establish auxiliary foci from which the permeation process extends. Before interpreting any instance of extensive lymphatic permeation as a centrifugal process of unicentric origin, it is essential to inquire whether intervening metastatic deposits may not have played a part in providing multiple secondary or tertiary centres whence permeation has proceeded.

The condition of the lymph glands

In an area of presumed lymphatic permeation this is of great significance. Subcutaneous, fascial, subserous and visceral lymphatic plexuses communicate freely with the afferent lymphatics of neighbouring glands; hence, with extensive carcinomatosis of these plexuses, it is inevitable that the proximate lymph glands should be affected, either by continuous permeation or by embolism. Experience confirms this: in cases of breast cancer with extensive fascial and dermal nodules, tumour deposits are invariably present in the cervical, axillary, inguinal, and often also the abdominal and thoracic groups of glands; and with lymph-vessel carcinomatosis of the serous membranes, extensive disease of the abdominal or thoracic glands usually coexists. Hence the absence of lymph-nodal deposits in a territory of secondary growths thought to have arisen as the result of lymphatic permeation is strong presumptive evidence that this interpretation is erroneous. The significance of this consideration respecting the alleged lymphatic route of origin of secondary growths in bones and certain viscera will appear in later chapters.

Size of permeated lymphatics

Lymphatics of any calibre, even the thoracic duct itself, may be the seat of cancerous permeation. In the finest lymphatic capillaries the process is quite impalpable and invisible to the naked eye. Distension of lymphatics by the occluding columns of proliferating tumour cells frequently occurs, so that vessels normally of microscopic dimensions may be brought into prominence as clearly visible fine cords of growth. Permeation of the larger lymphatic trunks, as, for example, the main tributaries and collaterals of the thoracic duct, the larger mesenteric lymphatics, and the peribronchial lymphatics at the hilus of the lung, produces conspicuous cords of growth sometimes 2 or 3 mm in diameter. Cancerous permeation of the thoracic duct, a highly important event in the metastasis of abdominal carcinomas, is given special consideration in Chapter 3.

The fate of cancerous lymphatics

This has been the subject of some debate. Handley described a perilymphatic fibrosis which finally obliterated the invaded vessels and destroyed their tumour content, so that the spreading periphery of the permeated area became separated from the parent primary growth by a widening zone of cancer-free tissue from which the neoplastic cells had been exterminated. According to Handley, the permeation zone was a ring, not a complete disc. Although this idea was widely promulgated in surgical books, it was imaginary. My

experience endorses that of Fitzwilliams (1924), Fraser (1927) and Gray (1939) that, on the contrary, invaded tissues suffer increasing destruction and replacement by the proliferating malignant cells, and the degree of cancerous infestation is at its maximum in the immediate vicinity of the primary site of growth and becomes less with increasing distance from this site. In extensive areas of lymphatic permeation no evidence of wholesale destruction of the neoplasm is to be found. It is true that scirrhous carcinomas evoke fibrosis in the invaded stromal tissue, including that about permeated lymphatics; but this fibrosis never progresses to effective extinction of tumour elements over a wide area.

The general importance of lymphatic permeation

Handley's claim that this is the master key to carcinomatous dissemination did service in focusing attention on a feature of much importance in determining surgical technique. As a tenet of pathology, however, it is unacceptable. Lymphatics constitute only one of several routes of spread, the relative importance of which varies very greatly from tumour to tumour and according to the host tissues invaded. Undoubtedly there are carcinomas which extend preferentially and very widely by lymphatic permeation; but by no means all or even the majority of carcinomas, behave in this way. Extreme instances of predominant lymphatic permeation are no more to be taken as typical of average events than are those other extreme cases in which carcinomas yield extensive blood-borne metastases without exhibiting any extensions by lymphatic channels. Between the two extremes lie the great majority of carcinomas, exhibiting all possible combinations of spread by any or all of the several available routes.

Tumour growth into and along veins

Infiltrating tumours frequently invade the walls of veins, penetrate to the lumen, and proliferate intravascularly. Certain classes of tumours, for example, renal carcinoma, are notorious for their behaviour in this way, and may extend continuously along large veins for great distances. It is, however, important to recognize that venous invasion is not peculiar to any particular class of neoplasms, but is exhibited in greater or less degree by almost all types of malignant growth. The truth of this will be appreciated from the following examples *(see Figures 3–7, 37–39)*.

Facial, oral and pharyngeal carcinoma

Sick (1864), whose paper gave a valuable review of the early literature on neoplastic invasion of veins, described a pharyngeal carcinoma the cervical metastases of which had produced extensive cancerous thrombosis in the internal jugular vein and its tributaries. From the cervical deposits of squamous-cell carcinomas of the tongue Godlee (1881) saw gross invasion of the jugular and innominate veins, and Poland (1885) invasion of both jugulars; both cases had extensive visceral metastases. In a study of 20 necropsies on cases of epidermoid cancer of the head and neck (1930a), I found neoplastic invasion of the main veins of the neck in 12 cases, in 10 of which visceral metastases were present. My subsequent experience accords with these findings: in 64 necropsies on cases of this group, I found invasion of the main veins in 30 cases, and blood-borne visceral metastases in 25 cases (Appendix, page 301). In 31 necropsies in Chinese cases of nasopharyngeal carcinoma, Teoh (1957) found invasion of the internal jugular vein in 11 of 15 cases with remote metastases.

Carcinoma of the oesophagus

Leichtenstern (1891) saw a squamous-cell carcinoma which invaded the azygos vein and grew intravascularly into the superior vena cava and right chambers of the heart. In my case 16, an hepatic metastasis had invaded a large branch of the portal vein.

Carcinoma of the stomach

Späth (1866), whose review of the earlier records of neoplastic venous invasion is a valuable one, described a gastric carcinoma with extensive tumour thrombosis of the gastric, splenic, mesenteric and portal veins. Schlagenhaufer (1909), under the title 'Phlebitis migrans', described a case of gastric cancer, the mediastinal lymph-nodal metastases of which invaded the superior vena cava and produced extensive cancerous thrombosis of this vessel and of the innominate, jugular, subclavian, axillary and cephalic veins. Worringen (1919) saw invasion of the main portal vein and proliferation of tumour cells in the unorganized blood-clot as in a culture medium. My cases 77 and 213 exemplify invasion of main veins (*see* Appendix on page 302).

Carcinoma of the intestine

Kettle (1925, page 31) depicted invasion of a mesenteric vein by an adenocarcinoma of the colon. Invasion of veins was demonstrated in 17 per cent of the surgical specimens of rectal carcinoma studied by Dukes (1940, 1944), and in 70 of 170 necropsy cases of rectal cancer studied by Brown and Warren (1938). Attwood and Giles (1966) reported a remarkable case in which a mucoid adenocarcinoma of the caecum, with recurrent growth in the abdominal wall and diaphragm, invaded the inferior vena cava and extended up in continuity to fill and distend the right atrium and to protrude through a patent foramen ovale into the left atrium. There were no visible metastases in the lungs or other organs, but many pulmonary arterioles contained microscopic tumour emboli. Marangos (1931) described several cases of 'carcinoid' tumours of the small intestine, and remarked on the frequent presence of tumour thrombi in small veins in these growths. Rutishauser (1932, case 5) saw invasion of the inferior vena cava by an adenocarcinoma of the duodenum. In a case recorded by West (1886) the thoracic metastases of a cancer of the gall-bladder invaded the superior vena cava.

Carcinoma of the pancreas

Pancreatic cancers often penetrate main veins. Examples of invasion of the splenic, mesenteric, portal and hepatic veins are recorded by Greenhow (1873), Legg (1876), Rolleston (1899), Adams (1921), Kiefer (1927) and Winter (1931). In Kiefer's case 14, the inferior vena cava was invaded. My case 20 exhibited double invasion of the portal vein without occlusion, and case 244 total occlusion of the vein by growth.

Carcinoma of the liver and hepatoblastoma

Hepatic cancer often shows gross invasion of the portal vein and its branches and the efferent hepatic veins, and it is by these routes that intrahepatic and pulmonary metastases are produced. Noteworthy case-records and valuable reviews of the subject are given by Weigert (1876), van Heukelom (1894), Eggel (1901), Wegelin (1905), Loehlein

(1907), Cruickshank (1910), Goldzieher and Bókay (1911), Winternitz (1912), Rolleston (1912), Lapage (1912), Counseller and McIndoe (1926), Fox and Bartels (1928), Strong and Pitts (1930), Tull (1932), and Berman (1951). In a number of these cases the inferior vena cava was invaded, and in one of Counseller and McIndoe's cases the tumour extended up the vena cava into the right atrium. In Loehlein's third case also the tumour thrombus in the vena cava projected into the atrium, the azygos vein contained growth which projected as a polypus into the superior vena cava, the mammary veins contained growth, and many skin nodules over the front of the chest presented worm-like distended vessels occluded by tumour thrombus. In a peculiar case recorded by von Hippel (1891) there was invasion of portal branch veins by cystic tumours of bile-duct origin and of seemingly benign adenomatous structure. Embryonic hepatoblastomas sometimes invade the inferior vena cava, as in Pang's case (1961;T.R.C. 538) and in T.R.C. 539 in which the growth extended up into the right atrium.

Carcinoma of the breast

Kantorowicz (1893) saw invasion of the subclavian vein, and also of a main pulmonary vein by the pulmonary metastases in the same case. Newcomb (1924) described penetration of the axillary vein. Scheel (1906), using elastic-tissue stains, made a careful study of invasion of small veins in mammary carcinomas. Van Raamsdonk (1921) found microscopic evidence of growth into blood-vessels in 24 of 30 breast cancers. Fraser (1927) depicted tumour occlusion of small veins; and Dawson and Shaw (1937) described cases of 'telangiectatic' mammary carcinoma, with permeation of many small veins. In my cases 4 and 75, large pulmonary veins were invaded by metastases in the lungs.

Carcinomas of the female genital organs

Female genital carcinomas do not often exhibit extension into large veins (Seelig, 1895). I have recorded examples of venous invasion by uterine cancer (1931e), in one of which the retroperitoneal extensions of a cervical carcinoma invaded the inferior vena cava. Microscopically, van Raamsdonk (1921) found growth into vessels in 11 of 30 uterine carcinomas, and Friedell and Parsons (1962) in 49 of 96 carcinomas of the cervix *(see Figure 7)*. Ovarian growths invade the blood-stream only occasionally; Beneke (1890) saw cancerous thrombi in the veins of the broad ligament, and Gibson and Findlay (1923) described a case of papillary carcinoma of the ovary in which a large secondary growth in the neck grew into the subclavian vein and superior vena cava and projected into the right atrium. The special tendency of chorionepithelioma to invade blood-vessels scarcely requires comment.

Carcinoma of the lung

Bronchial cancer frequently penetrates the pulmonary veins or their main tributaries, a feature which is apparent in any adequately recorded series. Sometimes the tumour grows along the lumen of the vein and projects into the cavity of the left atrium (Andrew, 1865; West 1886; Geipel, 1899; Jeannée, 1925; Müller, 1930). Penetration of the innominate veins or superior vena cava is not unusual (*see* my case 182), and the growth may extend into the right atrium (Dana and McIntosh, 1922). Main blood-vessels were invaded in 14 of 27 consecutive cases of lung cancer in my necropsies.