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CONCERNING THE MODE OF SPREAD OF CARCINOMA.

A Pathological Study of a Series of Cases with Special Reference to the Route of Spread to the Liver and to the Factors that Determine the Mode of Spread within that Organ.

- by -

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Preface.

The investigations in this thesis were conducted in the Pathology Department of Stobhill Hospital.

The research owes its initiation to Dr. F.L. Reynolds who has granted every facility for observation in his department, and whose constant helpful criticism and suggestions I have greatly appreciated.

I am indebted to Dr. A. McL. Watson of the Department of Physiology of the University for examining some of my microscopical preparations and for discussing and criticising my deductions from the structural arrangement.

I would also express my thanks to Professor Noah Morris for his kind encouragement and advice and for many of the clinical summaries of the cases on which post mortem examinations were performed.

To Dr. A.D. Briggs, the Medical Superintendent of Stobhill Hospital I am grateful for giving permission to avail myself of the cases quoted in this piece of work.

Finally, the constant co-operation of the technical Staff of the laboratory and the preparation of the microphotographs by Mr. H.W. Boot have been greatly appreciated.

PART I.

PART I

1. The Source of the Material Examined.

The cases dealt with in the present paper comprise all those in the Glasgow Municipal Hospitals in which autopsies had been conducted during the period January 1937 to December 1942. They number 141 and represent 7.5 per cent of the total number of 1,828 autopsies performed and 47.7 per cent of the total number of 292 cases of carcinoma on which autopsies were performed during that period.

R.A. Willis, in his Monograph on "The Spread of Tumours in the Human Body" (1934) gives statistics, compiled from several authorities, of the comparative occurrence of metastatic tumours in the liver in fatal cases of all classes of malignant tumour. These figures varied from 24 per cent (Colwell 1905) to 36 per cent (Willis 1934 - after examination of 323 cases of malignant tumours) of all cancers.

Of the 141 cases of intrahepatic malignant disease, 133 were determined as being secondary to primary carcinoma outwith the liver, five were recorded as primary "liver cell" carcinomata, and three as arising primarily from the bile duct epithelium within the liver. In the present series of cases metastases were present in the liver in 133 of the 292 cases examined; this represents 45.5 per cent of all cancers. The great discrepancy between these percentage figures and those of the authors quoted above is naturally due to selection of cases for post mortem examination.

2. Secondary Carcinoma in the Liver - One Hundred and Thirty Three Cases.

Of these, 87 were male and 46 female cases. The average age incidence of the group was 57.0 years, the youngest of the series being 23 years, whilst the oldest was 86 years.

From the microscopical examination of the sections and from the autopsy records of the 133 cases the following data have been obtained:

(I) The Primary Site of Growth: Having regard to the conformation, size, and other features of the neoplastic growths, the pathologist had determined the site of the primary tumour as recorded below; the numbers in the first column record the cases in which secondary growths occurred in the liver:

Oesophagus	2	out	of	a	total	of	9
Pyloric end of stomach	22	"	"	"	"	"	33
Cardiac end of stomach	5	"	"	"	"	"	8
Transverse Colon	1	"	"	"	"	"	4
Descending Colon	2	"	"	"	"	"	3
Pelvic Colon	8	"	"	"	"	"	17
Rectum	1	"	"	"	"	"	2
Extrahepatic Bile Ducts	3	"	"	"	"	"	4
Gall Bladder	8	"	"	"	"	"	8
Pancreas (Head)	20	"	"	"	"	"	40
Pancreas (Tail)	1	"	"	"	"	"	3
Trachea	1	"	"	"	"	"	1
Bronchus (Right)	14	"	"	"	"	"	44
Bronchus (Left)	17	"	"	"	"	"	37
Pleura ("Endotheliomata")	2	"	"	"	"	"	4
Kidney (Right)	3	"	"	"	"	"	4
Kidney (Left)	2	"	"	"	"	"	3
Urinary Bladder	1	"	"	"	"	"	3
Prostate Gland	7	"	"	"	"	"	10
Ovary	1	"	"	"	"	"	3
Thyroid Gland	1	"	"	"	"	"	2
Adrenal Gland	1	"	"	"	"	"	1
Mammary Gland (Right)	3	"	"	"	"	"	6
Mammary Gland (Left)	3	"	"	"	"	"	7
Undetermined (Pelvic and abdominal but unspecified)	4	"	"	"	"	"	8

In/

In one case of gastric carcinoma the primary tumour growth had been removed at operation one year before death had occurred. In one case of mammary carcinoma the primary tumour growth was removed several years before death. In no case was there any indication that the carcinoma had arisen from more than a single focus.

(II) General Characters: In 25 of the 133 cases the hepatic involvement was confined to the right lobe of the liver and in 3 cases to the left lobe. In 105 cases more than one lobe was involved.

In 18 of the 133 cases the liver was greatly enlarged, moderately enlarged in 45, and of average size in 70.

Of the 133 cases the secondary tumour growths had been described as "large and numerous" in 22, "large and few in number" in 18, "small and numerous" in 41, and "small and few in number" in 40. Direct extension, owing to contiguity, had occurred in 12 cases; of these 6 showed "satellite" nodules in the hepatic substance around the main tumour mass.

Necrosis within the secondary tumour nodules had occurred in some 17 of the cases examined. In 4 cases haemorrhage had occurred into the substance of the tumour nodules in the liver.

Invasion of the regional lymphatic glands, that is, those in the hilum of the liver, in the gastro-hepatic omentum, the coeliac, the para-aortic and the pancreatico-duodenal groups, and the lymph nodes in the suspensory ligaments of the liver, by neoplastic growth had occurred in 121 of the 133 cases. In

44 cases in which I performed the post mortem examination there were 25 in which the associated liver hilar lymphatic glands were enlarged and involved in the carcinomatous process and 11 in which the lymphatic vessels in the capsule of the liver and in its suspensory ligaments were invaded by cancerous tissue.

Massive involvement by tumour growth of the portal vein and its branches was observed in 3 cases. Fibrosis of the liver was a prominent feature in 7 cases.

Histological examination revealed small round mononucleated cell infiltration in relation to the tumour nodules or in the periportal tissues in 17 of the 95 cases in which sections were available for microscopic examination. Pigment was present in the periportal tissues in 4 cases.

Jaundice of the obstructive type and of varying intensity was described in 35 cases. In 27 of these the obstruction had occurred in that portion of the bile duct system outwith the liver substance.

Ascites was present in 46 cases but in only 12 of these did it occur alone; in the remaining 34 cases effusions were also present in the pleural or pericardial cavities or in both. The presence of fluid in the abdominal cavity associated with secondary carcinoma of the liver need not necessarily be the result of portal obstruction and in fact was more often due to widespread/

widespread blockage of the lymphatic vessels in the peritoneum by carcinomatous tissue. In 3 cases the peritoneal effusion was blood-stained and in a similar number it was purulent.

(III) Prominent Associated Hepatic Lesions: Of these fibrosis had occurred in 7 cases, bacterial infection in 2, chronic venous congestion in 3, distension of the intra-hepatic bile ducts (as a result of extra-hepatic obstruction) in 4, and marked necrosis of the hepatic tissue in 1 case.

(IV) Metastases present in other organs: After routine examination of all the organs of the body, with the exception in some cases of the brain macroscopical secondary involvement was recorded as follows:-

	No. of cases.
Regional Lymphatic Glands.....	121
Diaphragm.....	13
Pleura.....	28
Lungs.....	36
Pericardium.....	7
Adrenal Glands.....	21
Kidneys.....	16
Spleen.....	8
Skin.....	3
Ovaries.....	3
Skeletal System (Skull bones 2)	8
Brain.....	3

The term "regional lymphatic glands" applies to those situated in the hilum of the liver, the pancreatico-duodenal group, those in relation to the pyloric and cardiac ends of

the stomach, those in relation to the inferior vena cava immediately below the diaphragm, the para-aortic and coeliac groups of lymphatic glands, and those in the suspensory ligaments of the liver.

(V) Pre-existing General Diseases: Of importance in determining death there were recorded cardio-vascular degeneration in 10 cases, chronic bronchitis in 3, bronchiectasis with associated brain abscesses in 2, pernicious anaemia in 1, osteomyelitis of the skull bones in 1, recto-vaginal fistula in 1, "haemachromatosis" in 1, and cholelithiasis in 1 case.

This data was obtained by examination of the clinical histories of the cases submitted for post mortem examination.

3. Some anatomical and histological considerations.

Before proceeding further it is necessary to examine some salient points in the anatomy and histology of the liver and its vascular supply and lymphatic drainage with special reference to their relative importance in the spread of carcinoma to the liver.

(I) The Development of the Liver: The liver, as it develops as a diverticulum of the ventral surface of the foregut at its junction with the vitelline duct, grows upwards and forwards into the septum transversum and derives its connective tissue from the included mesenchymal cells of this septum. The liver, coming to lie as it does in this ventral mesogastrium, derives/

derives its falciform and coronary ligaments from the anterior portion of the latter (vide Gray's Anatomy page 167, figure 215). The posterior portion of the ventral mesogastrium forms the lesser omentum - the anterior wall of the bursa omentalis.

The pancreas, an organ closely related to the common bile duct and a relatively common site of primary carcinoma in this series of cases, develops in two parts, one dorsal and the other ventral. The dorsal portion arises as a diverticulum from the dorsal wall of the duodenum and grows upwards and backwards in the mesoduodenum to enter that part of the dorsal mesogastrium which goes to form the posterior wall of the bursa omentalis. This dorsal portion forms the body, tail, and part of the head of the pancreas. The ventral portion arises as a diverticulum from the primitive bile duct at its opening into the duodenum, grows round the duodenum, and finally fuses with the dorsal portion. By fusion of the dorsal mesogastrium and the posterior parietal peritoneum to form the posterior wall of the bursa omentalis the pancreas becomes retroperitoneal.

Hence it is probable that the connective tissues, lymphatic channels, and blood vessels of the pancreas develop from the posterior mesogastrium, the duodenum thus forming a possible "watershed" between the lymphatic drainage of the pancreas and the liver.

Consideration of these points in the development of the pancreas and also of the subsequent description of its lymphatic/

lymphatic supply may go some way to explain the relatively late involvement of the liver by secondary carcinoma when the primary neoplasm is in the pancreas (see page 11).

(II) The Lymphatic System of the Liver: The superficial lymphatics may be grouped into those on the convex or superior surface, and those on the concave or inferior surface. They are present in the capsular tissue over the entire liver surface.

On the convex surface posteriorly they reach their terminal lymphatic glands by three routes.

The vessels of the middle set, five or six in number, pass through the vena caval foramen in the diaphragm and end in one or in two lymphatic glands around the terminal part of the inferior vena cava; a few lymphatic vessels from the left side pass backwards towards the oesophageal hiatus, terminating in the pericardial group of superior gastric lymphatic glands; the vessels from the right side pass along the abdominal surface of the diaphragm, cross its right crus, and end in the pre-aortic lymphatic glands around the origin of the coeliac artery. From the surface of the right and left lobes, adjacent to the falciform ligament, the lymphatic vessels converge to form two trunks, one which accompanies the inferior vena cava to the lymphatic glands around its terminal portion, the other running downwards and forwards round the sharp anterior margin of the liver along the upper part of the ligamentum teres, to end in the upper hepatic lymphatic glands. From the anterior part of the convex surface/

surface a few additional vessels reach the upper hepatic glands again passing around the anterior margin of the liver.

On the inferior surface the lymphatic vessels mostly converge to the porta hepatis and there, together with the deep lymphatics, enter the hepatic lymphatic glands; one or two lymphatic vessels from the posterior parts of the right and caudate lobes accompany the inferior vena cava to the glands around its termination.

Schafer (1912) has stated that the connective tissue capsule of the liver is apparently devoid of lymphatic channels but that an efferent lymphatic vessel passes round from the portal fissure into the suspensory ligaments and conveys part of the lymph from the liver towards the diaphragm.

Hass (1936) maintains, however, that there are capsular lymphatic capillaries which drain directly through the diaphragm but that they have very slight communication with these in the depths of the liver. This last point is of considerable interest, as it will be seen in certain of the present series of cases that this is probably correct and has a bearing on the distribution and site of the secondary carcinomatous nodules in the peripheral hepatic substance.

The few communications which are present occur in the attachments of Glisson's capsule to the main hepatic capsule.

The deep lymphatics of the liver converge to form ascending and descending trunks. The ascending trunks accompany the hepatic veins and after passing through the diaphragm reach the glands around the termination of the inferior vena cava. The descending trunks emerge at the porta/

porta hepatis and end in the hepatic lymphatic glands; these are situated chiefly along the course of the portal vein.

The lymphatics of the gall bladder intercommunicate freely with those of the liver. They drain into the lymphatic glands close to the duodenum at the head of the pancreas (Hass 1936). They also pass to the cystic lymphatic gland and the hepatic lymphatic glands. Those of the bile ducts drain into the hepatic glands situated along these ducts; those from the lower part of the common bile duct enter the upper pancreatico-duodenal group of lymphatic glands.

(III) The Relationship of the General Lymphatic System to the Liver: The pelvic visceral lymphatic vessels form the afferents of the hypogastric lymphatic glands and include vessels from the membraneous and prostatic portions of the urethra. The efferents of the hypogastric lymphatic glands end in the common iliac group of glands. Thence the lymph flows into the right and left lateral aortic groups which also receive lymphatic vessels from the generative organs, kidneys, and adrenal glands. Their main trunks enter the cysterna chyla, but others enter the pre-aortic lymphatic/

lymphatic glands, which include the coeliac group, and some pierce the crura of the diaphragm and enter the lower end of the thoracic duct.

The pre-aortic glands are the drainage centres of the visceral lymphatic vessels which accompany the coeliac and superior and inferior mesenteric arteries.

The above, together with the retro-aortic group, are all inter-connected and constitute the lumbar lymphatic glands which in turn are connected with the hepatic lymphatic glands.

The visceral lymphatic glands associated with the coeliac artery form three sets - gastric, hepatic, and pancreatico-lienal groups.

The hepatic group, including the cystic lymphatic gland, receive efferents from the stomach, duodenum, gall bladder, and a few from the pancreas, as well as those from the liver.

The main lymph drainage of the pancreas is to the pancreatico-splenic lymphatic glands and thence to the coeliac group. This may go some way to explain the relatively infrequent or late involvement of the liver by secondary spread from primary carcinoma of the pancreas. It may well be that the main lymphatic channels must become blocked by carcinoma to produce an alteration in the direction of the lymph flow; this lymph flow is diverted through the few lymphatic channels passing by way of the small group of pancreatico-duodenal glands to the/

the hepatic lymphatic glands and thence to the liver.

The hepatic lymphatic glands are also inter-connected with the several groups of gastric glands and especially with those in relation to the pylorus and to the lesser curvature of the stomach. The lymphatic drainage of the small and of the large intestines is indirectly connected with that of the liver in the lumbar group of lymphatic glands.

Of the parietal lymphatic glands of the thorax the sternal or internal mammary group, four or five in number, are situated along the internal mammary artery at the anterior ends of the intercostal spaces. They receive afferents from the medial portion of the mamma, from the deeper structures of the anterior abdominal wall above the level of the umbilicus, and from the upper surface of the liver by way of a small group of lymphatic glands lying behind the xyphoid process.

The diaphragmatic group of parietal lymphatic glands of the thorax lie on the thoracic surface of the diaphragm, and consist of anterior, middle, and posterior sets. The anterior set consists of a group of lymphatic glands behind the base of the xyphoid process which receives afferents from the convex surface of the liver, and one or two lymphatic glands which receive vessels from the anterior part of the diaphragm. Their efferents pass to the sternal group of lymphatic glands. The middle set lying in the fibrous wall of the pericardium receives/

receives lymphatic vessels from the middle of the diaphragm and those on the right side receive efferents from the convex surface of the liver. Their efferents end in the posterior mediastinal lymphatic glands around the oesophagus and the termination of the inferior vena cava. The posterior group are connected with the lumbar lymphatic glands and the posterior mediastinal glands around the aorta at its point of exit from the thorax. The diaphragmatic pleural plexus anastomoses freely with that on its abdominal (peritoneal) surface, which in turn anastomoses with the lymphatic vessels of the liver. The right sub-diaphragmatic lymphatic plexus enters the glands around the right inferior phrenic artery and right lateral aortic lymphatic glands; that of the left side passes to the lateral aortic, pre-aortic, and terminal oesophageal lymphatic glands.

Of the visceral thoracic lymphatic glands the posterior mediastinal group receives lymphatic vessels from the oesophagus, diaphragm, convex surface of the liver, and posterior pericardium, and sends efferents to the tracheal and bronchial glands, which in turn drain the lungs, bronchi, thoracic part of the trachea, and visceral pleura. The latter group of lymphatic glands also sends out efferent vessels which unite with those from the internal mammary and anterior mediastinal lymphatic glands, the latter group having received afferents from the sternal lymphatic glands.

Thus/

Thus it will be realised that the intra-hepatic lymphatic system is intimately connected with that of the parietal and visceral systems of both thorax and abdomen (fig. 1). This is partly because of the anatomical position of the organ and its relatively large size; furthermore the liver is closely associated with the portal and caval veins in the abdomen and with the inferior vena cava in the thorax and therefore with their accompanying lymphatic networks.

(IV) Arterial Supply: The hepatic artery is a branch of the splenic artery, the main branch of the coeliac axis. It branches off at right angles to the splenic vessel and is smaller than the latter. Two of its branches are the gastro-duodenal and right gastric arteries. The hepatic artery then divides into the branches to the right and left lobes of the liver and gives off the cystic artery - usually from its right branch - in the hilum of the liver. The hepatic artery supplies little nourishment to the parenchyma of the liver.

(V) The Portal Venous system of the Liver: The portal system includes all the veins which drain the blood from the abdominal part of the digestive tube with the exception of the lower part of the rectum and the anus; it also drains the spleen, the pancreas, and the gall bladder. Within the liver the portal vein ramifies like an artery and ends in the capillary-like sinusoids/

sinusoids; it carries the main supply of nourishment to the hepatic cells.

The portal vein enters the liver by way of the porta hepatis at the transverse fissure of the liver; there it divides into right and left branches and these accompany the corresponding branches of the hepatic artery into the substance of the organ. On its way towards the liver the portal vein is surrounded by the hepatic plexus of nerves.

Lastly the accessory portal system of Sappey includes small veins which pass into the round and falciform ligaments; these small veins unite with the epigastric and internal mammary veins, and also with the azygos vein through the diaphragmatic veins.

(VI) Venous Drainage: The hepatic veins begin as the intra-lobular or central veins of the liver lobules; these receive the blood from the liver sinusoids. The intralobular veins join to form the sub-lobular veins, which in turn join to form the hepatic veins. The latter open in upper and lower groups into the inferior vena cava as it lies in a groove in the posterior surface of the liver. The upper group usually consists of three large veins, a right, a middle from the caudate lobe, and a left vein; the lower group vary in number, are much smaller, and drain the right and caudate lobes.

(VII) The Histology of the Liver: The liver lobule is a polygonal/

polygonal prism. Running through the centre of the lobule, and in its long axis, is the central vein, while at the periphery of the lobule are the interlobular bile ducts, the branches of the hepatic artery, and those of the portal vein (the interlobular vein) with their associated networks of lymphatic channels and spaces.

That the true liver unit in man is the anatomical lobule centred around the central vein follows logically upon the consideration of the liver as predominantly an endocrine gland (Maximow Bloom 1930), and also in the light of comparative anatomy.

The liver cells are arranged in cords which radiate from the central vein to the periphery of the lobule. The cords consist of double columns of hepatic cells; they may branch slightly and anastomose with nearby cords but nevertheless their general direction is towards the periphery. They are separated by the blood sinusoids.

The thin walled bile capillaries run through the length of liver cell cords, where they receive short lateral branches, and drain into the bile ducts viâ the "ducts of Hering". These bile capillaries are intercellular and run between the two adjacent columns of cells of the liver cell cords. They frequently anastomose with each other.

The blood sinusoids, lined partly by flattened endothelial cells/

cells and partly by the stellate cells of Küpffer, link up the inter-lobular branches of the portal vein with the intra-lobular or central veins. This is the only route by which the portal and hepatic vessels are connected; there are no valves in either system of vessels. It has been noted (Maximow Bloom) that the finest branches of the hepatic artery enter the sinusoids at the periphery of the lobule.

The lymphatic vessels of the liver begin in the periportal connective tissue around the terminal ramifications of the portal vein. They are also found in the supporting connective tissues in relation to the branches of the hepatic artery, bile ducts, and hepatic vein (fig. 2). None are present within the liver lobules. Lymphatic vessels are also present in the capsular tissues of the liver, but have little communication with the deeper vessels (see page 9).

The periportal collagenous connective tissue continues directly into the fibrous reticulum which surrounds the blood sinusoids. Of the latter fibres the larger ones usually run parallel to the sinusoids while the smaller ones form an interlacing network of cross fibres around the sinusoids. This is well demonstrated in sections prepared by Hortega's silver impregnation method for connective tissue:- (figs. 4 - 7):-

HORTEGA'S SILVER CARBONATE METHOD for Connective Tissue.

The following method of Hortega is how in use and was the actual technique carried out in the present investigation. It is a recent method used by Hortega when in Oxford. It has the advantage over the previous method in that it takes less time and that the same solution of Silver carbonate (Hortega's Ordinary Silver Carbonate) is used in this and the method for Neurofibrils, Axis-cylinders and nerve-endings.

Best results after long fixation in F.A.B.
Although good results have been obtained after 15% Formol.

1. Cut frozen sections 15 - 20 microns thick.
   Receive sections in Ammonia water (8 - 10 drops in 50 cc of Dist. water).

2. Wash in 2 changes of dist. water, 1 - 2 minutes in each.

3. Treat with 0.25% Pot. Permanganate for 5 - 8 minutes.

4. Bleach in 10% Oxalic acid, several changes. Time about 15 minutes.

5. Wash well in several changes of dist. water.

6. Heat for 10 minutes at 50°C in 2% Silver Nitrate plus 6 - 8 drops of Pyridine to every 10 c.c. of silver.

7. Without washing place in Hortega's Ordinary Silver Carbonate and heat till bottle brown.
   Temperature about 45 or 50°C. Add 3 - 4 drops of Pyridine to the Silver sol. to prevent a scum forming.

8. Wash in dist. water for about a half-minute.

9. Reduce in 10% Formol. Tone in Gold Chloride and fix in Hypo.

10. Wash and mount on a clean slide. Blot with alcohol moistened filter-paper, dehydrate in abs. alc., clear in Carbol-Xylol.
    Mount in balsam.

Hortega's/

Hortega's Ordinary Silver Carbonate is prepared as follows:-

To 5 cc of 10% Silver Nitrate add 20 cc of 5% Sodium carbonate. The resultant precipitate is dissolved by adding strong Ammonia drop, by drop. There should be no excess of Ammonia.

Make up the total volume to 50 cc with dist. water.

Not only is this intra-lobular reticulum well demonstrated in the adult in pathological and non-pathological conditions but also in livers taken from subjects only a few months old in which no structural changes have occurred in the organ.

The continuous tissue space present in this reticulum is available for the intra-lobular collection and transference of lymph (Mallinow Bloom, 1930, - Drinker and Yoffy , 1941).

Lee (1923), after examination of the relationship of lymphatic vessels to blood capillaries in the mammalian liver, stated that "Lymphatic vessels form a rich plexus in Glisson's sheath and in the liver capsule, extend up to but not within the liver lobule, form many anastomoses between the portal units, and establish abundant communications with similar vessels in the walls of the hepatic veins. One must consider that fluid and solutes leave the blood sinusoids in the lobules and are, for a time, tissue fluid between the liver cells and the walls of the sinusoids. This fluid, in so far as it is removed as lymph, remains extravascular until it reaches the lymphatic capillaries at the periphery of the lobule and until these capillaries in their turn deliver it to the trunk/

trunk vessels."

In the present series of cases an examination was made of histological preparations showing the fibrous reticulum in the liver lobules. Tissue was prepared from post mortem material from subjects less than twelve months old and from adults in whom no lesion was seen in the liver. The following observations were made:-

(1) The reticular fibrous tissue in the hepatic lobules is a definite entity and is in relation to the sinusoidal network, embracing the blood sinusoids, and sending out a small number of fine fibrils over the surface of the columns of liver cells.

(2) The fibrous reticulum is closely associated with the sinusoids and forms at least an imperfect "basal membrane" in which there are potential if not actual tissue spaces. The latter may be exaggerated in histological sections owing to the unavoidable shrinkage which takes place in post mortem material and in the process of fixation.

(3) There is no marked increase in the fibrous reticulum in the liver tissue in which carcinomatous metastases are present when compared with that in "normal" hepatic tissue. Exceptions to this are seen in cases of primary carcinoma of the liver associated with cirrhosis or in cirrhotic livers in which secondary carcinoma is present; in these cases, however, the increase/

increase in supporting tissue occurs mainly in Glisson's sheath.

Schafer (1912) asserts that there are no lymphatic spaces between the sinusoids and the hepatic cells, but in the 14th Edition (1938) of his book it is agreed that the Küpffer cells are in intimate relationship with a fine framework of reticular fibres lying between the Küpffer cells and the hepatic cells. These reticular fibres appear to grade imperceptibly into the callogen fibres of the portal sheaths and of the hepatic capsule.

4. The Route of Spread.

(I) Spread to the Liver: In dealing with the spread of secondary carcinoma within the liver it is essential in the first place to examine the site of the primary neoplasm and the possible and most probable routes of spread of the carcinoma from the primary focus to the liver.

Examination was made at each autopsy to determine, as far as possible macroscopically, the route of spread of the carcinoma from the primary focus to the liver. In many cases the post mortem appearances were confirmed by the microscopical examination of selected portions of tissue.

Irrespective of the site of the primary neoplasm a few almost constant features were apparent and these agree with the statements made in the literature concerning the spread of carcinoma in the body, and for the most part, with particular references to the spread to the liver.

In/

In the present series of cases those occurring above the level of the diaphragm, in which metastases were present in the liver, included primary carcinomata of the thyroid gland, mammary glands, trachea, bronchi, lungs, pleura, and oesophagus. In these cases the regional lymphatic glands were invariably markedly involved in the neoplastic process, and invasion had occurred along one or more of the groups of lymphatic channels entering the upper part of the abdomen, for as already described there is free communication between the lymphatic systems of the mediastinum, parietes, deep structures of the neck, and those of the diaphragmatic and retroperitoneal tissues.

For example, in Case 4, one of primary carcinoma of the right lobe of the thyroid gland in a woman aged 54 years, the regional cervical, the mediastinal, and the upper abdominal lymphatic glands were invaded by carcinoma. A few scattered neoplasms were present in the abdominal cavity; several small whitish tumours were encountered in the thick layer of subcutaneous fatty tissue.

In the anterior portion of the right lobe of the liver, and immediately below the capsule, was a secondary growth rather less than 1 cm. in diameter.

In this case secondary tumour nodules were also present in both adrenal glands, and in the upper pole of the left kidney.

After a consideration of the cases of primary bronchiogenic carcinoma examined there was little doubt that the route of metastatic spread was by way of the lymphatic system (figs. 8, 9, 10, 11, 14, and 19). A description of several of these cases will serve to demonstrate this.

In Case 254, a male aged 35 years, the primary neoplasm arose in relation to the main bronchus entering the left lung. "Radiations" of the primary tumour mass, accompanied by a considerable increase in fibrous tissue, were present in both lobes of the left lung. The substance of these lobes was firm, partially collapsed, and studded with small tumour nodules, pinhead in size.

The hilar and mediastinal lymphatic glands had been grossly invaded by carcinoma and formed a large mass which partially encased and compressed, but did not invade, the aorta and oesophagus. The left parietal and diaphragmatic pleura was diffusely infiltrated by tumour tissue. Under the pleura of the right lung were several flattened tumour growths. Spread had been along the lymphatic channels.

The sub-clavian lymphatic glands at the root of the left side of the neck were enlarged and grossly invaded by carcinoma.

One large lymphatic gland, 1 cm. in diameter was present in relation to the inferior vena cava on the abdominal side of the diaphragm. Several enlarged lymphatic glands invaded by tumour were present along the lesser curvature of the stomach and extended in a continuous line into the hilum of the liver (fig. 21) where several small secondary tumour nodules were present in the contiguous portion of the hepatic substance.

The retro-peritoneal lymphatic glands around the inferior vena cava and upper portion of the abdominal aorta were greatly enlarged and their substance replaced by neoplastic tissue.

Small tumour nodules varying in size from 0.3 to 0.5 cm. in diameter were present throughout the substance of the liver.

Microscopical examination of the material taken at the post mortem confirmed the observation that spread had occurred by the lymphatic system.

In a case of bronchial carcinoma, too recent to be included in the present series, and occurring in a female aged 53 years, the neoplasm had arisen in relation to the bronchus entering the upper lobe of the right lung. Wide-

spread/

Widespread lymphatic invasion had occurred, as in the above case, but in addition the lymphatic channels in the suspensory ligaments of the liver were involved in the carcinomatous process. Furthermore, the distribution of the metastases in the liver substance was clearly divided into two groups, (a) those in the superficial liver substance having arisen in relation to the capsular lymphatic channels and (b) those in the deep hepatic substance having arisen in relation to the branches of the portal vein.

In the latter group careful macroscopical examination was made to ascertain whether or not the lumina of the branches of the portal vein were invaded by carcinoma; it was seen that the tumour nodules were in the supporting tissue of the veins and at no point had the lumen been invaded, although several of the tumour nodules measured up to 2 cms. in diameter.

Metastases were also present in both adrenal glands and a single secondary nodule was present in the peripheral substance of each kidney.

The two cases just described were extreme examples of lymphatic involvement but the same was true for cases in which the carcinoma had not produced such widespread lymphatic invasion. Much depended on such factors as the site of the primary neoplasm in the bronchial tree, on the invasive power of the carcinoma cells, and in some cases on the occurrence of pre-existing lesions involving the lymphatic system.

One/

One case, in which no metastases were seen in the liver, is of interest in this respect. The primary tumour growth had arisen in relation to the bronchus entering the upper lobe of the left lung. The lymphatic glands at the hilum of this lung, the mediastinal, the left para-aortic, and the left femoral group of lymphatic glands were invaded by carcinoma.

Several of the mediastinal lymphatic glands, especially on the right side, and the coeliac and the right para-aortic lymphatic glands were enlarged and calcified. These were the site of a healed tuberculous lesion. This afforded a probable explanation of the "selective" spread of the carcinoma in this case, and a possible explanation of the fact that no metastases were present in the liver. It is not proposed to draw any definite and general conclusions as to the spread of carcinoma from this particular case but it will be considered when the factors that determine the mode of spread are discussed (page 80).

In Case 263, a male aged 73 years, the primary neoplasm was considered, after microscopical examination and as no other probable primary focus was seen, to be a "Pleural endothelioma"; it had arisen in relation to the pleura on the right side. Both the visceral and parietal layers of the pleura were greatly thickened and white in colour owing to diffuse malignant change. Greatly thickened bands of tumour tissue extended between the surface of the lung and the chest wall and diaphragm. The lung was collapsed.

Infiltration by the carcinoma had occurred through the lymphatic channels of the right dome of the diaphragm into those of the suspensory ligaments of the liver (figs. 16 and 17) and into those on the related hepatic surface. Invasion of/

of the liver was not determined macroscopically but on examination of sections prepared for histological investigation it was seen that infiltration of the superficial hepatic substance had taken place.

Invasion of the lymphatic channels in the parietal pericardium was also present.

In other cases of so called "pleural endothelioma" varying degrees of infiltration by way of the lymphatic channels had occurred through the diaphragm and into the suspensory ligaments of the liver but not all showed actual involvement of the liver substance (fig. 15).

Many investigators have discussed the route of spread of mammary cancer. Sampson Handley has demonstrated that there may be continuous extension of tumour cells by way of the lymphatic channels downwards through the abdominal wall to the epigastric region and thence by the falciform ligaments to the liver, or that spread may be through the deep lymphatic vessels of the chest or abdominal wall to those in the pleura, diaphragm, and peritoneum. The tumour cells may reach the surface of the liver and produce superficial infiltration of that organ. Alternately the viscera may be invaded through their main lymphatic vessels with the formation of tumours situated deep in the substance of the organ. In this way the liver is involved through the falciform and round ligaments, or by way of the portal lymphatic nodes. Handley believed that the general dissemination of the carcinoma was by continuous permeation. Whether this is so or whether lymphatic/

lymphatic embolism is the more frequent mode of spread it still remains that the majority of investigators agree that the main route by which carcinoma of the breast spreads is by the lymphatic system.

The following case provides a suitable illustration of this.

In Case 100, a female aged 31 years, the primary neoplasm was in the right breast. This breast was much scarred as a result of X-ray therapy. Multiple small tumour growths were present in the opposite breast and underneath the skin at the root of the neck; many small growths were scattered throughout the subcutaneous tissues of the rest of the trunk.

The pleura covering the upper lobe of the right lung was welded to that of the chest wall. Numerous adhesions passed between the layers of pleura of the middle and lower lobes of the lung on this side; these lobes were partially collapsed and the visceral pleura covering them was thickly studded with flat secondary tumour growths little more than pin head in size. The parietal pleura in the lower part of the cavity showed similar lesions. One of them was larger, being 1 cm. in diameter, and had extensively involved the underlying rib. The pleura had been invaded by continuous growth from the primary focus. On the left side numerous pleural adhesions were present. The lung was large, firm, and oedematous. The visceral pleura on this side was studded with small secondary growths similar to those on the opposite side. Carcinomatous involvement of the lung substance had not occurred.

The condition of the peritoneum was similar to that of the pleura; it was studded with small secondary growths and the omentum was contracted, hard, and nodular.

Both ovaries were enlarged, and numerous small growths were found within them.

In the right lobe of the liver, just below the anterior surface, and towards its upper part was a large secondary growth, 3 cm. in surface measurement by 2 cm. deep. Another secondary growth, globular in shape and 1.5 cm. in diameter, was present in the adjacent but deep liver tissue. Throughout/

Throughout all the hepatic lobes were numerous secondary growths varying in size from that of a pinhead to 1 cm. in diameter.

In another, (Case 52), a female aged 78 years, in whom the primary neoplasm was in the right mamma, a similar spread had occurred and a few scattered tumour nodules were present in the liver.

The primary carcinoma in a third, (Case 136), a female aged 49 years, was situated around the indrawn nipple of the left mamma. In addition to the invasion of the parietal and diaphragmatic pleural surfaces, as seen in the last two cases, the deep and peripheral substance of both lungs was thickly studded with small secondary tumour growths. A few pinhead secondary tumour nodules were seen in the subcapsular hepatic tissue of the anterior surface of the liver. A single carcinomatous nodule was present in the tail of the pancreas and another in the right adrenal gland; small growths were present in the peripheral substance of each kidney.

This case is of particular interest in that some authorities consider that metastases occurring in the liver are frequently secondary to lung metastases and that they are conveyed to the liver in the arterial blood stream; this will be discussed later (page 87).

Continuing the examination of typical cases it is convenient, at this point, to consider those in which the primary neoplasm had its origin in some part of the alimentary canal. As the oesophagus is included in the supra-diaphragmatic group of organs it will be considered first.

In Case 29, a male aged 62 years, the lower end of the oesophagus was greatly thickened by carcinomatous infiltration; considerable ulceration had occurred extending in the longitudinal direction some 8 cm. upwards along the oesophageal lining. From the primary site on the anterior wall the carcinoma had spread upwards in streaks to the level at any rate of the cricoid cartilage. The carcinoma had not only thickened the wall of the lower end of the oesophagus but had spread/

spread out into the surrounding tissues.

At various points at which adhesions passed between the lungs and the chest wall, neoplastic nodules were present. On the surface of the lung on the right side, numerous firm white nodules varying in size up to 0.5 cm. in diameter, had occurred along the lines of distribution of the lymphatic vessels of the thoracic wall and especially along those in association with the 7th, 8th, and 9th intercostal spaces.

At the junction of the oesophagus with the stomach, two lymphatic glands below the level of the diaphragm were present, each 2.5 cm. and 3 cm. in diameter. They had been invaded by carcinoma and had indented the wall of the stomach. The left one had caused ulceration of the over-lying gastric mucous membrane, and from this haemorrhage had occurred.

A few cancerous nodules were present immediately under the pleural surface of each lung and a certain number of nodules were present in the liver; none of the latter were of great size, the largest measuring no more than 1.5 cm. in diameter. Certain of the retroperitoneal lymphatic glands in the upper and middle portions of the abdomen were involved by carcinoma.

This case was a very good example of spread by the lymphatic system and resembled in some respects that in two of the cases of primary bronchiogenic carcinoma already described.

Microscopical examination demonstrated that the carcinoma was composed of a squamous type of epithelium (fig. 34).

Primary gastric carcinoma was one of the more common neoplasms to produce secondary nodules in the liver. The primary tumour growth arose in any part of the organ but usually it was situated in relation to the lesser curvature of the stomach near its pyloric end. The chief route of invasion by lymphatic channels varied somewhat according to whether the primary growth was nearer the pyloric or the cardiac /

cardiac end of the stomach or whether it had arisen in relation to its lesser or greater curvature. Ultimately the carcinoma cells reached the liver by way of the hepatic hilar lymphatic glands, or, as occurred especially when the lymphatic glands at the cardiac end of the stomach were invaded, by the capsular lymphatic channels. These facts were exemplified in the following cases.

In Case 286, a male aged 65 years, a carcinomatous ulcer, about 3 cm. in diameter was present in the wall of the lesser curvature of the stomach towards its pyloric end.

The lymphatic glands along the lesser curvature of the stomach and the periportal lymphatic glands were enlarged, firm in consistency, and white in colour. These and the hilar lymphatic glands of the liver, the para-aortic lymphatic glands, and those in relation to the left adrenal gland, were involved by carcinoma.

Firm fibrous adhesions passed between the liver and the surrounding tissues. Numerous large secondary tumour nodules were present in the substance of the liver; these nodules were whitish in colour, and they showed central necrosis. The secondary carcinomatous growths distributed throughout the liver were mainly in relation to the portal venous system and to the suspensory ligaments of the organ. No tumour tissue was seen in the lumina of the hepatic blood vessels.

In another case, (Case 132), a female aged 39 years, two large ulcers were present in the pyloric end of the stomach. Both were in relation to the lesser curvature, one on the anterior and the other on the posterior wall of the viscus. The former was 3 cm. in diameter and part of its floor was necrotic. The latter was 5 cm. in diameter. In both instances the edges were thick and they, together with the peripheral part of the floor, were formed of white neoplastic tissue.

The liver was greatly enlarged. It extended far to the left/

left of the middle line and in a downward direction reached the middle of the abdomen. The organ contained great numbers of secondary growths varying in size up to 1 cm. in diameter. A few of them reached 1.5 cm. in diameter but none were greater than this. The outline of the growths was crenated. The surface of the organ was smooth and glistening.

Around the bile ducts in the hilum of the liver the tissues contained a number of small white crenated growths and similar growths were present in the retro-peritoneal tissues in the middle line of the upper part of the abdomen.

No other secondary growths were found in the body.

In one, (Case 209), a male aged 63 years, the primary neoplasm had its origin immediately to the right of the oesophageal opening into the stomach, and on its lesser curvature. The deeper part of the tumour had become adherent to the posterior parietal tissues. The neoplastic tissue had spread into the lymphatic glands in the lower mediastinum.

The liver was large and throughout its substance were numerous secondary growths varying in size up to 5 cm. in diameter. A considerable amount of necrosis had occurred in the larger masses. The larger secondary tumours, which were situated immediately below the hepatic surface, were umbilicated.

No other secondary growths were found in the body.

It was apparent in this case that the route of spread of the neoplasm was by way of the lower mediastinal lymphatic glands and the lymphatic channels in the suspensory ligaments passing to the surface of the liver.

In a further case (Case 278), a male aged 56 years, a firm tumour mass about 6 cm. in diameter had arisen in the wall of the pyloric end of the stomach, enveloped the head of the pancreas, the first and second parts of the duodenum, and the common/

common bile duct. By direct invasion the neoplasm had involved the lumen of the portal vein. The tumour mass was also adherent to the transverse colon.

Within the stomach the mucous membrane in relation to the mass was ulcerated. The ulcer was about 6 cm. in diameter; its margins were firm and fungating; its base was deep and covered by much necrotic material.

The coeliac, pancreatico-duodenal, and liver hilar lymphatic glands were involved in the neoplastic process.

The tumour had directly invaded the portal vein and the lumen of this vessel was distended with neoplastic tissue up to its entry into the liver.(fig. 3). One small secondary nodule was present in the hepatic substance immediately below its diaphragmatic surface.

No secondary tumours were found in the other organs of the body.

This case is of particular interest in that, although massive invasion of the portal vein had occurred, only one small metastasis was present in the liver. Furthermore microscopical examination demonstrated that this secondary tumour nodule had its origin in relation to the capsule of the organ. It is most probable that the tumour cells reached the position in which the solitary metastatic nodule developed along the capsular lymphatic channels which communicate with the lymphatic glands in the porta hepatis. It seems justifiable to assume, in the absence of proof to the contrary, that had this metastasis occurred as a result of blood spread, other metastases would have been present in the organ.

This, however, will be discussed further when the spread of carcinoma within the liver is considered (page 57).

Carcinoma of the large intestine is of relatively common occurrence/

occurrence, and frequently gives rise to secondary growths in the liver. Although the most common site of the primary neoplasm is towards the distal end of the descending colon, it not infrequently arises at other sites. Several cases may be quoted from the present series.

In Case 291, a female aged 75 years, the primary carcinoma was in the anterior wall of the transverse colon. The neoplasm formed a flattened mass about 6 cm. in diameter; its substance was firm in consistency and white in colour.

The abdominal organs were firmly matted together and both layers of the peritoneum were adherent to each other. The subperitoneal collections of lymphatic tissue and mesenteric lymphatic glands were the site of widespread carcinomatosis. Other than the liver, in which only superficial invasion was present, involvement by carcinoma of the abdominal organs themselves had not occurred.

Several neoplastic nodules were present in the connective tissue around the blood vessels in the hilum of the liver.

It is obvious in this instance that infiltration of the superficial hepatic substance was by way of the peritoneal and capsular lymphatic channels.

In Case 80, a male aged 63 years, in the descending colon, and situated some 10 cm. distal to the splenic flexure, was a circular carcinomatous ulcer, 2.5 cm. in diameter and occurring rather to the medial side of the lumen of the bowel. The edges of the ulcer were thickened and its floor was adherent to a neighbouring loop of small intestine but invasion of the latter by tumour tissue had not occurred.

Numerous carcinomatous nodules, pinhead in size, were scattered thickly over the visceral and parietal peritoneal surfaces.

Many of the retroperitoneal glands were enlarged and had/

had been invaded by carcinoma.

The liver was half as large again as the average, owing to extensive involvement by neoplastic growths. These were nodular, white and firm, and varied in size, but few of them were more than 1 cm. in diameter; little hepatic substance remained. The omental tissue had been almost entirely replaced by small round hard tumour masses and was continuous downwards with the mass of the liver.

In another, (Case 273), a female aged 80 years, in which the primary neoplasm was a "ring" carcinoma of the descending colon, the para-aortic lymphatic glands had been invaded by tumour growth. On the left side they formed a hard nodular mass nearly 15 cm. long and about 4 cm. wide. The lymphatic glands in relation to the hilum of the liver were enlarged and firm; they had been extensively involved by carcinoma.

The mediastinal lymphatic glands had been similarly involved and a few secondary nodules were present in each of the lungs.

The liver was much involved by firm white neoplastic growth. This formed a layer 2 cm. or rather more in thickness over much of the lower anterior surface. In the remainder of the liver were many rounded growths varying in size from a pinhead to 2 cm. in diameter.

In a third (Case 24), a female aged 32 years, the pelvic colon over a distance of 10 cm. was the site of carcinoma. The neoplasm largely occluded the lumen of the bowel and the wall of the colon in this area was much thickened. The appendices epiploecae had been invaded by the growth and the retroperitoneal lymphatic glands, especially in the lower part of the abdomen, were the site of secondary invasion by neoplastic tissue. Both ovaries were enlarged, especially that on the left side. This ovary was attached to the primary neoplasm and had been invaded by cancer. In the right ovary several small neoplastic growths were seen.

The liver contained numerous neoplastic nodules. They were firm but not hard, varied in size from 1 to 4 cm. in diameter, and were white in colour.

Microscopical examination demonstrated that the neoplasm was an adeno-carcinoma in type.

In a similar case, (Case 174), a female also aged 52 years, the secondary carcinomatous nodules were arranged in two groups, those in the superficial hepatic tissue immediately under the liver capsule, and those in the deep substance of the organ.

Not all cases of primary carcinoma of the large intestine showed such obvious lymphatic spread as has been described above, and in passing it is of interest to note that, apart from the "senile" types of carcinomata in which invasion of the lymphatic glands and metastases were often absent, the carcinomata which tended to fungate into the lumen of the bowel did not give rise to such widespread lymphatic involvement and metastases as did those which were scirrhous in type and showed little or no fungation. This observation has been made by several authorities (Craig & MacCartney 1923 - quoted by Willis).

Case 39, one of primary carcinoma of the rectum in a male aged 64 years, is worthy of note. A large mass was present in the rectum, involving the proximal portion of its wall. Numerous secondary tumour nodules were scattered throughout the peritoneum; one larger nodule had involved the wall of the splenic flexure. The lymphatic glands in the mesentery and the pancreatico-duodenal group were invaded by carcinoma.

The liver was enlarged, greenish in colour, and scattered throughout its substance were numerous tumour nodules varying in size from 1 to 3 cm. in diameter; central necrosis had occurred in many of them.

The mediastinal lymphatic glands, the lymphatic vessels in the visceral pleura of the right lung, and those in the lower intercostal spaces on the right and in the second intercostal space just to the left of the sternum, were involved by carcinoma.

Thus it was most probable that spread had occurred by

way/

way of the lumbar group of lymphatic glands and ultimately reached the liver (see fig. 1).

Primary carcinoma of the pancreas comprises one of the larger groups of cases examined in the present series. Some authorities consider that the occurrence of metastases, especially in the liver, is a late manifestation of the condition. In this series of cases it may be noted that of the total number examined, less than half have given rise to secondary tumour nodules in the liver. This may be compared with the figures for cases of primary gastric carcinoma in which not less than two thirds showed secondary growths in the liver. It is not the concern of this paper to investigate this problem, but such factors as development, the main route of lymphatic drainage, and possibly the age incidence, may be of considerable importance.

The following cases are representative of those in which secondary involvement of the liver by carcinoma occurred.

In a recent case, a male aged 59 years, a tumour mass 5 cm. in diameter had replaced the tissues of the head of the pancreas. The carcinomatous growth was firm in consistency and pale yellowish-white in colour. The neoplasm was adherent to the posterior wall of the stomach in the region of the pylorus but had not invaded the gastric wall. The body and tail of the pancreas were not involved in the carcinomatous process.

Widespread invasion of the regional lymphatic system had occurred; the coeliac and pancreatico-duodenal lymphatic glands, those along the greater curvature of the stomach at its pyloric end, and those in the hilum of the liver were much enlarged and contained carcinomatous tissue.

The liver was somewhat enlarged and dark green in colour. Numerous secondary tumour nodules, varying in size from 0.2 to 1.5 cm. in diameter, were present throughout the peripheral hepatic substance and also in the portal tracts of the liver; no tumour tissue was seen in the lumina of the veins or in the lumina of the other hepatic blood vessels.

The suspensory ligaments of the liver, the diaphragm, the diaphragmatic pleura on the right side, and the peritoneum covering the transverse colon were invaded by carcinoma.

In another, (Case 105), a male aged 64 years, a large, hard, nodular mass occupied the head of the pancreas. Large, hard, adherent lymphatic glands surrounded the common bile duct from the head of the pancreas into the hilum of the liver; the cystic duct was surrounded by neoplastic growth which had invaded the lymphatic gland at the neck of the gall bladder. The pancreas and hilum of the liver were encased in adherent omentum which was studded with hard tumour nodules. The liver was grossly enlarged and studded with a great many secondary nodules.

The abdominal aorta and its coeliac and superior mesenteric branches were surrounded by hard masses of densely matted lymphatic glands showing invasion by tumour growth. The lymphatic glands were involved as far as the bifurcation of the aorta at the brim of the pelvis.

The peritoneal lining of the anterior abdominal wall in the epigastric region, and that on the under surface of the diaphragm, the posterior mediastinal lymphatic glands on the right side, those along the internal mammary blood vessels on the left side, the diaphragm on the right side and the visceral pleura covering the contiguous portion of the right lung, were also invaded by carcinoma; the last named structure was adherent to the diaphragmatic pleura.

In several cases of primary carcinoma arising in relation to the head of the pancreas the neoplasm had become adherent to the surface of the liver, and in these cases direct invasion of the hepatic substance had occurred. Lymphatic spread, however, was also present and could be traced into the lymphatic glands in the porta hepatis.

Several cases of primary carcinoma arising in relation to the genito-urinary system may now be examined.

In Case 139, a female aged 34 years, the right ovary was replaced by a tumour mass, 13 cm. in diameter. The right Fallopian tube and its fimbriae could be defined and were isolated from the tumour mass. The neoplasm was situated behind the anterior layer of the broad ligament, was for the most part retroperitoneal in position, and was lying over the lower part of the right ureter at the level of the brim of the pelvis. Thrombosis had occurred in the ureteric and also in the renal and mesenteric veins.

The lymphatic glands in the pelvis and around the abdominal aorta were the site of secondary carcinomatous invasion. Several small nodules were seen under the peritoneal covering of the uterus. In the pouch of Douglas a small secondary growth was found. Near the pyloric end of the stomach, and attached to its greater curvature, was a tumour mass similar in every appearance to the others; it was 4 cm. in diameter. This mass did not involve the wall of the stomach but was adherent to it and to several loops of small intestine. In the hilum of the liver was situated a large tumour mass which had to some extent invaded the substance of the right lobe of the liver, and encroached on the cystic duct, gall bladder, and common bile duct; the duodenum was adherent to this mass. The tumour was whitish in appearance, but had become bile-stained.

The liver was grossly enlarged and projected some 10 cm. below the costal margin. A single mass, about 12 cm. in diameter, was found within the substance of the organ; it was in the right lobe and had caused partial compression of the common bile duct.

Numerous secondary carcinomatous growths were seen in the substance of both kidneys.

Three tumour nodules were present in the bones of the skull.

In this case there was no evidence of "seeding" on the peritoneal surface and there was no doubt that the various tumour masses in the sub-peritoneal tissues were in fact lymph/

lymph nodes invaded by carcinoma. Furthermore, the lymphatic glands invaded followed the route of lymph drainage from the generative organs to the coeliac region and thence to the liver.

Again in Case 61, a male aged 72 years, the primary neoplasm had its origin in the prostate gland. The lateral lobes were greatly enlarged; they had become fused together and consisted of a hard white mass which was obviously carcinomatous. The carcinoma had spread into the surrounding tissues and had formed a mass of considerable size round the right internal iliac blood vessels.

In the lower part of the abdomen the lymphatic glands on the right side were still discrete but were much enlarged owing to carcinomatous invasion.

The liver was small and brown in colour. Immediately under the anterior surface were two small white nodules, one being about 1 cm. in diameter, the other the size of a large pinhead.

In a similar case, (Case 70), a male aged 73 years, numerous round white tumour nodules varying in size up to 1.5 cm. in diameter were present throughout the liver. One nodule in the hilum of the liver constricted the common bile duct and the gall bladder. The wall of the bile duct was not invaded by tumour growth

The varying distribution of the tumour nodules in the liver in the last two cases may well be explained by the fact that in the first the carcinoma cells reached the liver by way of its superficial lymphatic channels, whereas in the second the spread to the liver was by way of the liver hilar lymphatic channels.

One case will serve to demonstrate the spread of carcinoma/

carcinoma in primary carcinoma of the urinary bladder with secondary involvement of the liver.

In this, (Case 277), a male aged 67 years, two fungating masses were present in the trigone of the bladder in the region of the right ureteric orifice which was occluded. The bases of these tumour masses were broad and firm; they had invaded the entire bladder wall posteriorly. The prostate gland was not enlarged.

The regional pelvic lymphatic glands were involved in the neoplastic process. The carcinoma had also invaded the deep inguinal, aortic, and coeliac lymphatic glands and those in relation to the portal vein and the neck of the gall bladder in the hilum of the liver.

The liver was somewhat enlarged. Numerous large secondary tumour nodules were present throughout its substance. These nodules had occurred in relation to the branches of the portal but not to those of the hepatic veins. Carcinomatous tissue was present in the lumina of the branches of the portal vein, including its largest branches, but again, not in the hepatic veins. In one portion of the liver a small nodule protruded from the liver substance through the wall of a large branch of the portal vein into its lumen; the luminal surface of this nodule was smooth, white in colour, and firm in consistency.

Numerous secondary tumour nodules were present in relation to adhesions between the diaphragmatic and visceral layers of pleura on the right side.

Several significant facts emerge from this case. Firstly, on microscopical examination of sections of material taken from the hilum of the liver, the lymphatic glands in relation to the portal vein were invaded by carcinoma. Furthermore, tumour tissue was present in the lymphatic spaces of the connective tissue between the lymphatic glands, portal vein, and bile ducts in the porta hepatis, and also in the peri-neural lymph spaces/

spaces of the nerves accompanying the portal vein in this region (fig. 20).

It was apparent from the examination of this series of microscopical sections that the liver had been invaded by carcinoma along the lymphatic vessels entering the liver at the porta hepatis. In this the carcinoma cells were present in the lymphatic glands, in the connective tissue between them and the liver, in the capsule of the liver adjacent to it, and finally had invaded the contiguous portion of the liver substance. Secondly it will be demonstrated, when the spread of carcinoma within the liver is considered, that the tumour tissue in the lumen of the branches of the portal vein was the result of secondary permeation along these veins from the metastases already established in the liver and had occurred after invasion of the branches of these veins within the secondary tumour nodules; it is not, therefore, the initial stage in the production of metastases in the liver.

Last to be considered in this group are the primary malignant neoplasms of the kidney. Some are designated malignant "hypernephromata", others adeno-carcinomata. We, however, are concerned only with the presence of secondary tumour growths in the liver in these cases.

In Case 288, a male aged 64 years, the right kidney was about three times the average size. Its substance was almost entirely replaced by tumour tissue and was whitish-yellow in colour; in several small circumscribed areas it was dark red in colour. The renal pelvis and the lumen of the right ureter were dilated and contained necrotic tumour tissue; the wall of the/

the ureter was not invaded by the neoplastic tissue. In the region of the upper pole of the right kidney the tumour was firmly adherent to the posterior part of the peritoneal surface of the diaphragm, to the right lobe of the liver, and to the hepatic flexure of the large intestine; a flattened circular tumour mass about 4 cm. in diameter was present in the contiguous portion of the diaphragm.

The anterior and lateral aortic lymphatic glands were greatly enlarged and their substance replaced by tumour tissue; this was especially so in the region of the right renal artery. The lymphatic glands in relation to the vessels in the hilum of the liver were also invaded by neoplastic cells.

The liver was much enlarged, being about one and a half times its average size. In its substance were several large tumour nodules. These nodules were whitish in colour and firm although the largest showed central necrosis; two of them, on the surface of the liver, were umbilicated.

The right adrenal gland could not be demonstrated; the left was invaded by tumour tissue. Several mediastinal lymphatic glands were slightly enlarged and contained neoplastic tissue. In the peripheral substance of both lungs were numerous secondary tumour nodules about 1.5 cm. in diameter. They were more numerous in the right lung and especially in the subpleural substance of the base of its lower lobe; this was firmly adherent to the diaphragm.

Again there was well marked involvement of lymphatic glands and the invasion was easily traceable into the porta hepatis. There was also a probable direct spread from the primary neoplasm to the liver at the point at which they had become adherent to one another but if so this would be a late manifestation and only a subsidiary pathway.

Spread by the blood stream might well be considered a possibility in this case. As is usual in such cases the neoplasm presented dark red areas due to haemorrhages. Rupture of blood vessels, together with the disintegration of tumour tissue would tend/

tend to facilitate the entry of tumour cells into the blood stream. Furthermore, secondary tumour nodules were present in the lungs indicating as a possibility a venous spread to these organs from the kidney and thence to the liver. Such a sequence has been suggested by some authorities.

It should be noted, however, that the involvement of the lymphatic glands was massive, also that the distribution of the tumour nodules in the lung substance was indicative of the lymphatic spread by way of the diaphragmatic and, to a lesser extent, the mediastinal lymphatic channels rather than a blood spread. Again, if the great discrepancy in the size of the tumour nodules be taken as the criterion of their relative age then those replacing the aortic lymphatic glands and those in the liver were older than those in the lung substance. This is against dissemination to the liver by the blood stream, as it would necessarily have to occur by way of the pulmonary circulation.

In Case 74, a male aged 70 years, the left kidney was represented by a large mass measuring some 25 cms. in length and 12 cms. in breadth. A few centimetres from it the ureter was completely obstructed by a calculus. The lower portion of the mass consisted of two large communicating cysts. Their lining was smooth and they represented the pelvis of the kidney; they contained thin dark brown fluid. The upper part of the mass was composed largely of a closed cyst containing fluid blood and blood clot. On the inner wall of this cyst was a yellowish tumour mass about 5 cm. in diameter. At the inner margin of the mass was a firm white neoplastic nodule 1 cm. in diameter. The yellowish portion of the tumour was necrotic. No evidence of the adrenal gland on this side could be found.

Several of the para-aortic lymphatic glands were much enlarged owing to neoplastic growth within them.

The visceral pleura of both lungs was thickly studded by tumour nodules varying in size up to 1 cm. in diameter. On the right side a nodule, 2 cm. in diameter was present in the hilum of the lung. Only an occasional nodule was seen in the deep substance of the lungs.

In the right lobe of the liver in the substance of its sub-diaphragmatic portion were two small neoplastic growths, one little more than a pinhead in size, the other 0.5 cm. in diameter.

No secondary tumour nodules were seen in the other organs of the trunk.

The neoplasm was of a papilliferous type of adenoma and hence from its histology there was no doubt but that it arose in relation to the renal substance.

This was an example of carcinoma arising in the upper part of the left kidney in which lymphatic spread had occurred first to the para-aortic and thence to the mediastinal and pleural lymphatic glands and ultimately reaching the liver had spread along its superficial lymphatics. The neoplastic cells most probably reached the liver by the lymphatic channels in the suspensory ligaments. The situation of the secondary tumour nodules in the hepatic substance, their size relative to those in the substance of the lung, pleura, and lymphatic glands, are indicative of this being the probable route of spread. Assuming that the route of spread had been by the blood vessels via the lungs and hepatic artery it is highly improbable that the secondary nodules in the liver would have been distributed only in the superficial portions or that they would have reached the liver at such a late stage in the process of neoplastic extension.

Lastly, eight cases of primary carcinoma of the gall bladder and three cases of primary carcinoma arising in relation to the extra-hepatic bile ducts were examined.

It has already been noted that there is free intercommunication between the lymphatic capillary vessels of the contiguous portions of the liver and gall bladder (page 10). Hence it would be rational to assume that invasion of the liver substance by carcinoma arising in the gall bladder might well occur along these channels. That this in fact is so may be demonstrated in any one of the cases now considered.

For example, in Case 280, a male aged 75 years, the gall bladder was replaced by a large white tumour mass in which a considerable amount of fibrous tissue was present. The neoplasm had involved the contiguous portion of the liver by direct invasion and several discrete but small tumour nodules were present in the hepatic substance. The bile ducts within the liver were dilated and cystic and contained dark green fluid bile.

The supporting tissues around the blood vessels in the porta hepatis were infiltrated by tumour tissue but no invasion of their lumina was seen (fig. 18).

The liver was adherent to the under surface of the diaphragm and numerous flattened carcinomatous nodules were present in the peritoneal and pleural aspects of the right dome of the diaphragm.

No involvement of the coeliac or mediastinal lymphatic glands was seen, nor were secondary tumour nodules present in the lungs.

It was confirmed by microscopical examination that the hepatic substance had been invaded by permeation along the lymphatic channels and tissue spaces between the liver and the gall bladder (fig. 24). Furthermore, spread through the

diaphragm/

diaphragm had occurred from tumour nodules in the subcapsular liver substance; the neoplastic cells had invaded the lymphatic channels and tissue spaces in the capsule of the liver (fig.12), in the suspensory ligaments, and in the diaphragm itself.

This tends to confirm the opinion advanced in several cases already instanced, that this was the route by which invasion of the liver had occurred.

One case demonstrated that secondary involvement of the liver can occur in primary carcinoma of the gall bladder in the absence of massive direct invasion.

In this case, (Case 77), a male aged 73 years, a firm tumour mass was associated with the gall bladder. The viscus was small and shrunken; its lumen was almost completely occupied by an oval calculus measuring about 2 cm. in its long diameter. The lining of the gall bladder was dark red in colour. The neoplasm was contiguous to the head of the pancreas and second part of the duodenum but it did not involve these structures.

The liver in proximity to the gall bladder had been replaced by nodular masses of neoplastic tissue. The nodules, however, were small and continuous massive involvement of the liver had not occurred. A few small tumour growths were scattered here and there throughout the organ.

No carcinomatous growths were found elsewhere in the body.

Microscopical examination confirmed the diagnosis made at autopsy. In parts the neoplastic epithelium was columnar in type and tended to line spaces. Furthermore, the spread of the carcinoma could be traced into the liver substance and

was/

was confined to the peri-bile duct and peri-portal lymphatic channels. No tumour tissue was seen in the lumina of the portal or hepatic blood vessels.

To complete this group of cases, one of primary carcinoma of the extra-hepatic bile ducts may be quoted.

In this case,(Case 253), a female aged 60 years, the carcinoma had arisen from the common bile duct and formed a firm whitish tumour mass in the shape of a horse shoe in the wall of the second part of the duodenum in the region of the ampulla of Vater. The duodenal surface of the mass was fungating and ulcerated. The neoplasm was adherent to but had not invaded the substance of the head of the pancreas.

As the result of obstruction by the neoplasm at its distal end the common bile duct was dilated, being more than 0.5 cm. in diameter.

The coeliac and pancreatico-duodenal lymphatic glands and those in the porta hepatis were enlarged and contained tumour tissue.

The liver was enlarged; its substance was yellowish-green in colour, soft, and friable. The bile capillaries were greatly dilated and in many cases cystic; they contained dark green bile. Numerous very small whitish tumour nodules were present throughout the hepatic substance.

There is little doubt that spread to the liver had occurred along the peri-bile duct lymphatic channels. This was borne out by the invasion of the lymphatic glands in the porta hepatis and by the histological demonstration of carcinomatous tissue in the lymphatic channels in Glisson's capsule (fig. 22).

(II) Spread from the Liver - Eight cases of Primary Hepatic Carcinoma: At autopsy primary hepatic carcinoma was diagnosed only after careful search had been made to exclude the presence of/

of a primary focus in the other organs of the body.

Five of these cases were diagnosed, after microscopical examination, as primary liver cell carcinomata; the remaining three had arisen in relation to the intra-hepatic bile ducts.

These cases have been included in the present investigations for the following reasons:

(a) There is a marked similarity between the route of spread of carcinoma from the liver and that of the spread of carcinoma to that organ.

(b) They illustrated certain features of the mode and route of spread of secondary carcinoma within the liver.

It is not the purpose of this paper to discuss the aetiology of primary carcinoma of the liver. Several of the factors at issue, however, should be mentioned. Firstly, the relationship of cirrhosis of the liver to primary malignant disease in that organ has not been definitely ascertained. Secondly, some authorities consider that primary carcinoma of the liver may arise simultaneously in several foci, and not from one single focus. Lastly, there may be considerable difficulty in ascertaining the exact structure from which the carcinoma has arisen, that is to say, whether it has arisen in relation to the hepatic parenchymal cells, or to some portion of the intra-hepatic network of biliary channels.

The following cases may be instanced to demonstrate such points as are relevant to the present discussion.

In Case 279, a male aged 69 years, the liver was more than/

than three times its average size. The surface was finely nodular, and fine fibrous adhesions were present between the surface of the right lobe and the peritoneum covering the disphragm.

The right lobe was diffusely infiltrated by small tumour nodules, white in colour, and varying in size up to 0.5 cm. in diameter. The left lobe was less diffusely infiltrated by more discrete and larger whitish tumour nodules; these varied in size up to 1.0 cm. in diameter. The hepatic substance remaining was brownish green in colour. Gross luminal permeation of the intra-hepatic portal veins had occurred.

In the hilum of the liver, and around the main portal vein at some distance from its entry into the liver, were several enlarged lymphatic glands varying in size up to 2.0 cm. in diameter. They had been invaded by carcinoma and the neoplastic tissue was firm and whitish green in colour.

Secondary spread had also occurred throughout the diaphragm. The suspensory ligaments of the liver and diaphragmatic pleura on the right side were studded with small secondary tumour growths. These had spread into the right mediastinal pleural lymphatic vessels.

Fine fibrous adhesions were present between the contiguous pleural surfaces of the lower lobes of both lungs and the diaphragm.

Several small neoplastic nodules were present in the pleura covering the base of the right lung and, to a lesser extent, in that covering the base of the left lung. Only the lung substance in relation to the pleura had been involved in the carcinomatous process.

One small secondary neoplastic nodule was present in the peripheral substance of the spleen contiguous to the liver; another was seen in a similar position in the subcapsular substance of the right kidney.

Microscopical examination confirmed the diagnoses of primary liver cell carcinoma and that the neoplastic tissue in the periportal lymphatic glands and other nodules described/

described was, in fact, derived from the primary hepatic neoplasm.

Well marked lymphatic spread has been demonstrated in this case and it is worthy of particular note that invasion of the lung substance had occurred only peripherally in relation to the tumour nodules in the pleura indicating a lymphatic rather than a blood spread to the lungs.

In Case 155, another example of primary liver cell carcinoma, the pancreatico-duodenal and para-aortic lymphatic glands in the upper part of the abdomen had been grossly invaded by the neoplasm. No metastases were present in the lungs and hence this case also is opposed to the theory of metastatic spread of this type of neoplasm by the blood stream.

In Case 120, a male aged 75 years, a large carcinomatous mass was present in the left lobe of the liver. It also encroached on the right lobe of that organ. The neoplastic tissue was yellow in colour and in the centre of the tumour were broad whitish bands of tissue apparently related to the bile ducts in Glisson's capsule. The tumour was composed of spherical masses which had coalesced. Smaller tumour growths were present in the right lobe of the liver; they varied in size from 0.5 cm. to 4 cm. in diameter. No evidence of cirrhosis was seen in the hepatic tissue which remained.

The wall of the gall bladder was thin and the viscus was distended with greenish-yellow bile. The cystic duct and extra-hepatic ducts were not thickened and were not involved in the carcinomatous process.

The carcinoma was confined to the liver and micro-

scopical/

microscopical examination showed that the neoplasm most probably had arisen from the epithelium lining the intra-hepatic bile ducts or capillaries.

That the spread of carcinoma was confined to the liver and that secondary invasion of the right lobe had occurred from it is not satisfactorily explained as being blood spread, as the blood supply to the lobes of the liver is to some extent separated before entering these lobes. On the other hand infiltration could occur in this direction along the lymphatic capillaries and tissue spaces of Glisson's capsule.

The age factor in this case may explain the absence of secondary tumour spread outwith the liver, and indeed several authorities have stated that metastatic invasion is unusual in cases of primary malignant tumours of the liver and that when it does occur it is seldom widespread.

(III) Spread within the Liver: An examination of the cases of the series revealed several features in the pathology of secondary carcinoma in the liver which were, for the most part, in agreement with the observations made by previous investigators.

Gross enlargement of the liver was not an outstanding feature of secondary carcinomatous invasion, for as has already been mentioned, in approximately half the number of cases little or no enlargement had occurred; in only eleven cases was there great enlargement, and in the remaining

number/

number it was only of a moderate degree. Furthermore, in cases in which the liver was diffusely infiltrated by small tumour growths, as for example in some cases of primary carcinoma of the head of the pancreas, it was seldom greatly enlarged, nor was it altered in shape.

Some of the largest livers seen in the present series of cases were those in which the primary neoplasm had arisen in relation to the parenchymal cells of the organ itself.

The right lobe of the organ was more often grossly involved by secondary tumour growth than the left and quadrate lobes. This is primarily due to the anatomical fact that the right lobe is the largest and consequently its lymphatic and blood supply is greater than that of the other lobes.

The secondary tumour nodules deep in the hepatic substance were invariably spherical in shape; those occurring in the superficial substance were hemispherical, being limited on one aspect by the capsule of the liver. The latter showed little or no tendency to protrude beyond the surface, but where the metastatic tumour nodules were of considerable size, as in those from primary gastric carcinomata, and when present in considerable numbers replacing the greater part of the liver substance, the surface of the organ was at times irregular, the neoplastic nodules projecting from the surface beneath the hepatic capsule.

In most cases the outline of the tumour nodules was crenated/

crenated. Their colour and consistency was almost always similar to that of the primary neoplasm. On the occasions when jaundice had occurred the nodules were bile-stained. They varied from pinhead in size up to several centimetres in diameter. Some of the largest were seen in cases of primary gastric carcinoma. Those in primary carcinoma of the bronchial tree, large intestine, and genito-urinary system were sometimes of considerable size but more often they were not more than two to three centimetres in diameter. Diffuse infiltration by small tumour nodules, little more than pinhead in size, occurred in a considerable number of cases; this was a common though not invariable feature of primary carcinoma of the head of the pancreas.

Central necrosis was a relatively common feature and was related to the size of the nodule. Again, this was most commonly seen in the secondary growths in cases of gastric carcinoma although it also occurred in cases of bronchial, renal, and pancreatic carcinomata, and in carcinoma arising in the large intestine.

Haemorrhage into the tumour nodules was a relatively uncommon occurrence and when it did occur was rarely extensive and was usually confined to one particular nodule. For example, in a case of carcinoma of the head of the pancreas (Case 290), haemorrhage had occurred into one of the small secondary nodules in the liver.

The distribution of secondary tumour growths in the liver would appear to be confused where gross involvement has occurred, but in the cases in which they are relatively few in number they may be divided into two main groups (a) secondary tumour nodules occurring in the tissues of Glisson's capsule; (b) secondary tumour nodules occurring in the tissues of the hepatic capsule.

Group (a), the larger group, was that in which the tumour nodules occurred in relation to the periportal tissues of Glisson's capsule; here the lymphatic drainage is to the lymphatic glands in the hilum of the liver. Macroscopically in the majority of cases of this group these nodules had not invaded the lumen of the portal blood vessels. On microscopical examination where invasion of the smaller branches of the portal vein had occurred, it was confined to the lumen of these vessels and could be traced as an unbroken column of neoplastic cells from an already established secondary tumour nodule. This was particularly well exemplified in Case 277, in which the primary carcinoma had arisen in relation to the trigone of the urinary bladder (figs. 27, 28, and 29). Serial sections of a tumour nodule which had occurred in relation to a branch of the portal vein within the liver demonstrated that the carcinoma cells had infiltrated the tissue spaces of the adventitial and medial portions of the vessel wall, and a

solid/

solid mass of neoplastic cells was present in the lumen of the blood vessel. At the junction of this vessel with a larger branch of the portal vein a thrombus had formed and was covering the carcinomatous cells in the lumen of the smaller vein. The connective tissue around the vessel and the neighbouring liver substance was diffusely involved by carcinomatous growth.

Similar appearances were seen in many other cases in which the secondary tumour growths were situated in relation to the portal venous system within the liver. Furthermore, in these cases, invasion of the branches of the hepatic artery was a late manifestation of the carcinomatous process and had occurred in a similar manner to that just described with regard to the invasion of the portal vein. In no case of the series could it be demonstrated that a metastatic tumour nodule had arisen from an actual embolus arrested in a branch of the artery. This is not in agreement with the contention put forward by Willis and certain other authors and the subject will be discussed more fully later (page 88).

It was a striking fact that the bile ducts were more resistant to carcinomatous invasion than any other structure in the liver and in many cases were seen as distinct entities in the substance of a secondary tumour nodule in which the liver cells, portal vein, and hepatic artery had been destroyed/

destroyed and were no longer recognisable as such. A similar observation has already been made by Sheehan (1930) in his description of the spread of a primary embryonic neoplasm of the liver. Spread, however, did occur by the peri-bile duct lymphatic channels and tissue spaces (fig.33), and had occurred especially in the cases of primary carcinoma arising in relation to the gall bladder and extra-hepatic bile ducts. For example, in Cases 280 and 287, both cases of carcinoma primary in the gall bladder, infiltration had occurred along the lymphatic channels around the bile ducts as well as along those in relation to the branches of the portal vein in Glisson's capsule.

A sub-group of this class of case calls for notice. In several cases the secondary tumour growths occurred in relation to the central veins and collecting branches of the hepatic veins. Again, these nodules were situated in the peri-vascular connective tissues and in most cases did not invade the lumina of the veins.

In Case 215, one of bronchial carcinoma, one such tumour nodule was present in the connective tissue around a larger branch of the hepatic vein within the liver (figs. 35 and 36). The lumen of the vessel was not invaded. Spread in relation to the larger hepatic veins was less common than that by other routes, and the explanation most probably is that the connective tissue sheath of these veins is relatively scanty and therefore has fewer lymphatic channels and tissue spaces by

which/

which the carcinoma cells can reach the liver substance.

Group (b), the second of the main groups of tumour nodules were those which occurred in the substance of the liver immediately beneath its capsule. As has already been described (page 8) there are several groups of capsular lymphatic channels which pass along the superficial tissues of the liver and drain either into the lymphatic glands in the porta hepatis or by the lymphatic channels in the suspensory ligaments, through the diaphragm, and thence into the several groups of lower mediastinal and substernal lymphatic glands. In cases in which invasion of the liver had occurred by this route alone, the secondary tumour nodules were rarely numerous and indeed often occurred singly. This is to be explained by the fact that the superficial lymphatic capillaries have very few communications with those of the deep hepatic substance.

For example, the capsular lymphatic channels were infiltrated by carcinoma cells in a case of bronchial carcinoma (Case 278, figs. 8 - 11) and also in a case of gastric carcinoma (Case 268). In one case of carcinoma of the head of the pancreas the subcapsular lymphatic channels in relation to a secondary growth were infiltrated by tumour tissue (fig. 13).

Irrespective of the site of the primary carcinoma, whether it is above or below the level of the diaphragm,

a/

a secondary lymphatic spread to the liver may occur by all or any one of the routes described above. The present series of cases, however, demonstrated that the site of the primary neoplasm did influence the route of spread. For example, in a case of "pleural endothelioma" (Case 263), the spread was more or less confined to the lymphatic vessels passing through the diaphragm and only the superficial hepatic substance was involved. On the other hand, bronchial carcinoma may reach the liver by the suspensory ligaments or by the liver hilar lymphatic glands; this depended on whether invasion of the pleural or the mediastinal and upper abdominal lymphatic channel was predominant.

When considering the invasion of the liver by carcinoma several authorities differentiate between metastases and direct spread by contiguity. However this may be, when direct invasion did occur the primary neoplasm first became adherent to the contiguous portion of the liver capsule. It then invaded the subcapsular tissue spaces and lymphatic channels and ultimately the tumour cells reached the substance of the liver along the tissue spaces and lymphatic capillaries of Glisson's capsule. The commonest examples were those of malignant tumours arising in relation to the gall bladder (fig. 24), but it was not an infrequent occurrence for those arising in the stomach, the head of the pancreas (fig. 23),

or/

or in the upper pole of the right kidney, to invade the liver in a similar manner.

Direct invasion of the liver was seen, for example, in Case 287, one of carcinoma of the gall bladder. Here direct infiltration had occurred through the contiguous portion of the liver capsule; masses of carcinomatous cells were present in the lymphatic channels around the bile ducts and portal vessels of Glisson's capsule and had invaded the peripheral substance of many of the liver lobules (fig. 39). The lumina of the blood vessels in Glisson's capsule had not been involved in the carcinomatous extension. A similar appearance was seen in Case 36, one of primary carcinoma of the upper pole of the right kidney, and in several cases of gastric and pancreatic carcinoma (fig. 38) where direct invasion of the liver had occurred.

Discrete "satellite" nodules were sometimes seen in the liver substance around the larger and presumably older tumour masses, and, in neoplasms involving the liver by direct invasion, in the hepatic substance adjacent to the primary growth. These were invariably located in Glisson's capsule and although in most of them the lumen of the branches of the portal vein contained tumour tissue, the tissue spaces and the lymphatic channels around these blood vessels were also invaded by tumour cells; it was from the latter that infiltration had occurred/

occurred into the surrounding hepatic substance. In many areas where permeation had been confined to the portal vein no "satellite" tumour nodules were seen. The lumina of the hepatic artery and the bile duct were seldom invaded in the neoplastic process in the smaller "satellite" nodules.

Thus in one case of primary bronchial carcinoma (Case 239) many small "satellite" tumour growths were present at some little distance from the larger nodules in the liver. This occurred in Glisson's capsule and tumour tissue was present in the lumina of the branches of the portal vein in these "satellite" nodules but not in the lumina of the hepatic artery or bile ducts.

Fibrosis may accompany neoplastic invasion of the liver and it may occur in one or more of three forms. Firstly, that affecting the liver generally - cirrhosis - was not a marked feature of secondary involvement but was of common occurrence in primary tumours of the liver and especially those arising in relation to the bile ducts. When this form did occur as an accompaniment of carcinoma in the liver it was rarely gross, usually was only seen on microscopical examination, and took the form of an increase in the fibrous tissue elements in Glisson's capsule.

Secondly, in a considerable number of cases an increase in fibrous tissue was present in the pseudo-capsule around the/

the periphery of the metastatic nodules (fig. 25). This was most commonly seen in cases in which the secondary tumour nodules were relatively slow growing and compact.

Thirdly, a varying amount of fibrous tissue was present within the substance of the tumour nodules. This took the form of fibrous trabeculae which had undergone more or less hyaline change. It varied greatly from case to case and depended largely upon the nature of the primary tumour, that is to say, whether or not the primary growth tended to be scirrhous in type - a condition found in many mammary cancers. It also depended upon the relative activity of the tumour cells in the secondary neoplastic nodules; the more rapidly multiplying tumour cells were less likely to be separated by such massive strands of fibrous tissue as were the less active groups. There was little doubt that this increase in fibrous tissue whether outside or within the tumour nodules was derived, as is generally accepted, from the hepatic connective tissue and not from the neoplasm itself.

The following cases may be taken as examples of fibrous hyperplasia. In two cases, one of primary carcinoma of the right ovary (Case 139), and the other, a primary carcinoma of the head of the pancreas (Case 276), a general fibrous tissue increase was present in relation to Glisson's capsule. This was also very marked in two cases of primary gall bladder carcinoma (Cases 280 and 287), and amounted to a unilobular cirrhosis; in these cases the carcinoma cells had/

had infiltrated along the tissue spaces in the interlobular bands of fibrous tissue.

In a case of primary carcinoma of the upper pole of the right kidney (Case 36), in which direct invasion of the liver had occurred, there was a considerable local increase in the fibrous tissue of Glisson's capsule for some little distance around the periphery of the main invading tumour mass and also around the isolated metastatic nodules.

In one case of primary carcinoma of the sigmoid colon (Case 91), and in another arising in the transverse colon (Case 291), broad fibrous trabeculae were present within the secondary tumour nodules in the liver.

A similar condition was also well exemplified in the hepatic metastases of a case of carcinoma of the prostate gland (Case 70).

Most of the points dealt with up to the present stage of these investigations could be demonstrated with little difficulty at autopsy. Microscopical examination, however, revealed some additional data which will now be considered. The structural differentiation of the neoplastic cells within the secondary tumour nodules varied greatly when compared with that of the primary growth and in the majority of cases it was necessary to refer to the observations made at autopsy in order to determine with any degree of certainty the site

of/

of origin of the neoplasm. This was especially so in carcinoma arising in relation to the bronchial tree, pancreas, adrenal glands, kidneys, prostate gland, and ovaries, and it was a factor of considerable importance when demonstrating the local spread of nodules within the liver in that the mode of infiltration was more clearly followed in those cases in which the tumour cells had not reached a high degree of structural differentiation.

It is not the purpose of this paper to deal with the reproductive activity of the neoplastic cells of metastases in the liver as compared with that in the primary neoplasm. In passing, however, it may be noted that no features were observed to contradict the statement that the reproductive activity of the tumour cells in the metastatic nodules in the liver is greater than in the primary growth.

One of the greatest difficulties experienced in determining the mode of spread of carcinoma within the liver was that in the majority of the cases coming to autopsy the carcinomatous process was well advanced and therefore it was not always possible to obtain material which could be considered as representing the earliest stages in the metastatic invasion of that organ. A few such cases, however, were available and in them, where the secondary tumour nodules were small, the secondary growths had arisen mainly in the connective tissues of Glisson's capsule either

deep/

deep in the liver or in the subcapsular region. Less commonly they occurred in relation to the perivascular tissues of the branches of the hepatic veins. In many of these cases, as well as in those in which the metastases had been established for some considerable period of time, columns of tumour cells were present in the tissue spaces and lymphatic capillaries in close proximity to or continuous with the periphery of the tumour nodules (figs. 31, 32, and 40).

For example, in Case 291, one of primary carcinoma of the transverse colon, the secondary tumour growths were in the subcapsular hepatic substance. On microscopical examination the capsule of the liver was indented and thickened over one of these tumour nodules. The columns of neoplastic cells had radiated into the liver tissue along the tissue spaces and lymphatic channels in the connective tissues surrounding the branches of the portal vein, and bile ducts.

Along the invading margin of the secondary neoplastic nodules a variety of appearances were seen depending for the most part on whether the marginal tumour cells were compact and invading the contiguous liver substance "en masse", or whether they were invading the hepatic tissue in separate, almost villous-like, columns. In the former group the surrounding liver substance was compressed and formed a pseudo-capsule around the tumour nodules. Immediately

adjacent/

adjacent to the margin of the neoplastic growth this pseudo-capsule consisted solely of the fine fibrous reticulum of the collapsed blood sinusoids - the liver cells having disappeared. In some instances an increase in fibrous tissue was present in this portion of the pseudo-capsule. Around this again the hepatic parenchymal cells were arranged in concentric layers and showed varying degrees of atrophy. They were elongated and flattened; their cytoplasm was more deeply stained and was not vacuolated; their nuclei were smaller and stained darker than the normal liver cells. The columns of liver cells in this area were separated by collapsed and partially collapsed blood sinusoids. Beyond this region the parenchymal cells were swollen, vacuolated, and their cytoplasm was faintly stained; the blood sinusoids were dilated and often congested (fig. 25). The histological picture just presented varied from case to case. In those in which the compression of the liver tissue was not so extreme, the tumour cells had either invaded the "spaces" presumably previously occupied by the columns of liver cells or infiltrated between the columns of partially atrophied liver cells and the endothelial walls of the collapsed blood sinusoids (figs. 44 and 46). For example, in Case 286, one of primary carcinoma of the lesser curvature of the stomach, a pseudo-capsule was present around the secondary tumour nodules in the liver. It consisted of collapsed and partially collapsed sinusoids, their reticular supporting tissue, and flattened and elongated/

elongated liver parenchymal cells concentrically arranged. These liver cells had undergone atrophy and necrobiotic changes.

At the invading margin of the tumour nodule in particular the lumina of the blood sinusoids were patent and not invaded by tumour cells. The neoplastic cells, however, were infiltrating between the columns of liver cells and the walls of the blood sinusoids; they were in direct contact with and were replacing the liver cells.

In the cases in which the marginal tumour cells were invading in villous-like columns there was little or no pseudo-capsular formation and in these the neoplastic cells had insinuated themselves between the columns of liver cells and the walls of the blood sinusoids and tended to collapse still further the lumina of the sinusoids (figs. 41 - 45). This was most clearly seen in histological sections prepared by Hortega's silver impregnation method for fibrous reticulum and counterstained by haematoxylin and eosin to differentiate between the hepatic parenchymal and neoplastic cells. The process was especially well exemplified in one case of primary bronchial carcinoma (Case 239). One small secondary tumour growth had occurred in relation to Glisson's capsule and at its invading margin the carcinoma cells had infiltrated between the columns of liver cells and the reticular tissue surrounding the/

the blood sinusoids (figs. 47 - 50). The liver cells of these columns were pressed together and were more darkly stained than the liver cells at some distance from the nodule. The tumour cells were in direct contact with the liver cells and no reticular fibrous tissue was present between them. The lumina of the blood sinusoids at the periphery of the invading tumour mass were narrowed but patent and only a few red blood corpuscles were present in them; in no instance were tumour cells seen in the lumina of the blood sinusoids. These sinusoids remained patent and uninvaded for some little distance in the peripheral substance of the tumour nodule but eventually deeper in the neoplastic mass they became completely collapsed, distorted, and unrecognisable as blood channels.

These histological appearances were also clearly defined in sections of material from Cases 290 and 257, two cases of primary pancreatic carcinoma, in Case 288, one of carcinoma arising in relation to the right kidney, and in numerous other instances.

On the other hand in many instances the blood sinusoids were invaded by the neoplastic growths but in the majority of cases this had been preceded by infiltration along the columns of liver cells. This phenomenon and its significance in relation to the other modes of spread will be discussed, together/

together with the factors which govern the mode of spread of secondary carcinoma in the liver, in the second part of this paper.

One further point which may be mentioned is that, in a number of cases infiltration by small round mononucleated cells had occurred in relation to the secondary neoplastic invasion (figs. 24, 39 and 40). It was present in the tissues of Glisson's capsule and either preceded or accompanied the invasion by the neoplastic cells. This feature is well recognised as being not uncommonly associated with primary and secondary malignant tumours in other organs of the body.

The histological picture of the relationship of the neoplastic to the non-neoplastic cells in the cases of primary hepatic carcinoma differed little from that already described in secondary involvement of that organ (figs. 26, 30, 37, and 51). For example, in Case 189, one of primary parenchymal cell carcinoma, the non-malignant liver cells formed a pseudo-capsule around the periphery of the nodules of neoplastic tissue and the carcinoma cells were infiltrating along the columns of liver cells. In a second case (Case 279), infiltration by malignant cells had occurred both along the periportal lymphatic channels, without involvement of the lumen of the portal vein in this particular area, and between the columns of normal liver cells and the endothelial lining/

lining of the adjacent blood sinusoids. In one area direct invasion of the lumen of a central vein was seen; in this case, as described previously (page 49) massive luminal involvement of the portal venous system had occurred. In yet another case (Case 285), in which the neoplasm had arisen most probably in relation to the intra-hepatic bile duct epithelium, carcinomatous infiltration of the lymphatic channels and tissue spaces in Glisson's capsule, especially of those around the periphery of the liver lobules, was a prominent feature; the lumina of the branches of the portal vein, hepatic artery, and hepatic veins were not involved in the carcinomatous process. Infiltration by small round mononucleated cells had occurred in the tissues of Glisson's capsule in the neighbourhood of the groups of neoplastic cells and a unilobular cirrhosis was present.

Microscopical examination rarely failed to demonstrate numerous instances of the various pathological changes described above; several of them were usually present in each case and only varied in their degree of prominence.

PART II.

PART II

I. Concerning the Factors that Determine the Route of Spread.

(I). Some General Considerations: It is commonly accepted that of all the organs of the body the liver is the most common site of secondary carcinomatous invasion. Several theories have been enunciated to explain this observed fact. The most commonly quoted is that of "tissue predilection" which Ewing defines as the particular susceptibility of a tissue to develop secondary tumours. This, however, is merely stating the phenomenon in other words. Again, Warburg 1930 - quoted by Willis - states that the metabolism of cancerous tissue is characterised by (1) a high glycolytic power and (2) the ability to metabolise sugar under relatively anaerobic conditions. Since the liver is a carbohydrate store constantly bathed by portal blood rich in sugar, and since it is one of the most poorly oxygenated tissues of the body,- it receives only 12 - 26 ccs. of arterial blood per 100g. per minute (Newman) - it is a very favourable "soil" for the growth of malignant neoplastic cells. There are, however, obvious objections to this theory; among them the fact that not all secondary tumours in the liver grow with equal rapidity or show equal activity and structural differentiation; rapidity of growth and structural differentiation are essentially functions of the neoplasm itself and are little, if at all, influenced by the particular organ in which the secondary neoplasm is growing.

It is possible that in a general way the highly nutrient portal blood tends to facilitate the survival of the tumour cells but there is as yet little evidence to support this theory.

There is not much doubt that the anatomical position of the liver and its relationship to wide areas through the lymphatic and vascular systems account for the occurrence of the greater number of metastases in it as compared with other parenchymatous organs of the body. Further, the lymphatic arrangements bring the liver into close relationship with parts where primary carcinoma is common. This opinion, based on anatomy, is supported by Ewing and many other authorities. Certainly the distribution of the tumour metastases as seen in the present series of cases tends to confirm this explanation.

Though local reaction by the tissues of an invaded organ does undoubtedly occur and tends to modify the structural form of the tumour nodule, this largely coincides with the degree of structural differentiation of the cells of the parent neoplasm; that is to say, whether they have differentiated little or whether they have reached a high stage towards structural perfection. The former tend to grow more diffusely than the latter.

The increase in the fibrous tissue elements of an invaded organ may occur as fibrous trabeculae within the tumour/

tumour nodule, as part of the pseudocapsule around it or, in the case of the liver, as a generalised fibrous tissue increase of Glisson's capsule. This may be due to several factors. Firstly the presence of fibrous trabeculae within the secondary neoplastic nodule is almost always associated with a similar fibrous tissue increase in the primary neoplasm and it is apparently a property of certain types of malignant tumours to stimulate the development of fibrous tissue; to such tumours the term "scirrhous" is applied. There may also be an increase in the fibrous tissue elements in the invaded organ outwith the tumour nodule but here, and especially where the increase is confined to the pseudo-capsule around the neoplasm, the fibrosis may be the expression of a process by which the tissues endeavour to repair the damage caused by the growing tumour. Where a generalised fibrous tissue increase, affecting more or less the whole liver, has occurred the underlying cause seems more obscure. Handley has suggested, in justifying his theory of continuous lymphatic permeation, that breaks in the tumour cell cords may occur as the result of perilymphatic fibrosis, due to some irritant related to the tumour process. It may thenbethat a similar process has occurred in the liver; certainly in those cases in which permeation of the lymphatic channels in Glisson's capsule is demonstrated either locally for some distance around a tumour nodule, or throughout the hepatic/

hepatic substance, it is invariably accompanied by a widening of Glisson's capsule due to an increase in its fibrous elements. Be this as it may, tumour cell permeation is not seen in all cases in which diffuse fibrosis is present and in these it may be that the fibrosis is pre-existing.

Many authorities consider that the condition known as cirrhosis of the liver is an important factor in the aetiology of primary malignant tumours of the organ but this primarily concerns the parenchymal cells of the liver and is an entirely different subject from that of secondary carcinomatous invasion.

There are a number of cases, however, of metastatic tumour involvement in which there is no reason to suppose that fibrosis had occurred prior to invasion of the organ and in which no histological evidence of permeation of the lymphatic channels or infiltration of the tissue spaces of Glisson's capsule has occurred and yet diffuse fibrosis is present. Theoretically it is possible in such cases that the products of the neoplastic cell metabolism, percolating along the tissue spaces and lymphatic channels of Glisson's capsule, may act as "toxic irritants" and set up a tissue reaction which is ultimately expressed in the proliferation of fibrous tissue elements.

The excretion of specific toxic substances by cancer cells has not been demonstrated and theories based on this are not generally accepted. Nonethe less, there can be no doubt that the necrobiotic changes observed in the parenchymal cells/

cells in the areas surrounding tumour growths are in part due to the effects of the effete products of metabolism from the tumour cells. These effete materials - "fluid excretions" - differ in chemical composition from the normal fluid bathing the tissue cells; by reason of this and of the fact that these fluids are not so rapidly removed by the usual drainage system, since it has become partially obstructed by the presence of the neoplasm, changes occur in the cells of the organ - in this case the parenchymal cells of the liver - owing to the "foreign" fluid surrounding them. (Reynolds and Slater).

It has been observed in the present series of cases that where the secondary tumour nodules are surrounded by a pseudo-capsule consisting in part of liver cells, these cells are compressed with consequent flattening or elongation. Their cytoplasm is more deeply stained, most probably as a result of concentration of the stain absorbing elements, and it contains no vacuoles. Further, their nuclei are small and deeply stained. On the other hand the liver cells beyond the "capsular" area are swollen, have not taken up the cytoplasmic stain so well, and contain large vacuoles. The reason for this may be that the "capsular" parenchymal cells are undergoing true pressure atrophy and furthermore are deprived of nourishment owing to the local anaemia caused by the obliteration of their related blood sinusoids whereas, in the hepatic tissue beyond the "capsular" area, the blood sinusoids are dilated and there is a certain stases of the blood/

blood in them thus allowing the toxic excretions of the tumour to concentrate, and to bathe the hepatic parenchymal cells for a considerable period of time.

It has also been noted (page 65) that the liver cells in the pseudo-capsular areas become altered in shape, atrophied, and disappear. This disappearance is probably due to lysis of the liver cells after they have reached a certain degree of atrophy. A similar process can be well demonstrated in cells of the central nervous system in certain specific lesions, such as in General Paralysis of the Insane.

Another observation related to the toxic excretions of tumour cells is the small round mononucleated cell infiltration which is often marked and which in a considerable number of cases precedes or accompanies malignant cell invasion and is a feature in the histological appearances of the precancerous condition. In this respect it is of interest to recollect that a similar small round mononucleated cell infiltration is characteristic of protozoal as opposed to bacterial infections; the protozoa in contrast to the bacteria belong in fact to the animal kingdom. It may be that the reaction provoked by the malignant cell is of a similar nature; this, however, still remains a problem to be elucidated.

Lastly, stimulation to proliferation by small amounts of toxic excretions of malignant cells may account for many of/

of the changes seen in lymphatic glands recently invaded, or about to be invaded, by carcinoma. These changes are the result of a "toxic irritation" and are not necessarily a preparation of the "soil" for subsequent tumour cell invasion.

In regard to the spread of carcinoma to an organ there are two possible routes; firstly, by way of the lymphatic channels and tissue spaces and secondly by way of the blood vessels. In addition to these two pathways, in the case of the liver spread within the organ might occur by way of the bile ducts. Some writers advocate that in the peritoneal sac, dissemination may be by the process known as transplantation.

A constant difficulty experienced in the investigation of secondary carcinomatous invasion of the liver is the late stage in the process at which cases come to autopsy. Much, however, may be learnt from examination of the routes of spread from the primary focus to that organ.

A considerable number of investigators in the past have differentiated between "true" or embolic metastases, invasion by permeation, and direct extension from a primary focus in an adjacent organ e.g. gall bladder, stomach, pancreas, and right kidney. However this may be, once malignancy has supervened the further growth and spread of the neoplasm are essentially due to the progressively multiplying tumour cells. They/

They infiltrate along the lines of least resistance. Thus, growing out along the tissue spaces in the primary growth, they come presently into contact with the capillary networks of the vascular and lymphatic systems. It is at this stage in the neoplastic process that the various theories on the mode of metastatic spread to the liver tend to differ. Although most observers are agreed that the local spread of a primary neoplasm is chiefly by way of the tissue spaces and lymphatic channels, Sampson Handley (1906), in his study on the spread of mammary cancer, and E.H. Kettle (1916), considered that continuous lymphatic permeation was the most important process in the formation of metastases. On the other hand R.A. Willis (1934) has stated that the main process is by the dissemination of blood borne emboli which reach the liver by way of the hepatic artery and portal vein, while Ewing (1931) and others emphasize the importance of spread by tumour emboli along the lymphatic channels.

The relative ease of invasion along the lymphatic channels in contrast with that of the venules, and more especially the arterioles, may be explained by the structural differences in their walls; the walls of the former consist of nothing more than a layer of endothelial cells with their basement membrane, whereas/

whereas those of the latter are well formed structures. Furthermore, in certain pathological conditions, as in the present instance, the lymphatic radicles become distended and present no difficulty in their recognition, whereas on examination of histological sections of normal tissue they, unlike small blood vessels, are collapsed and not easily demonstrated. Thus from the anatomical considerations alone it would seem justifiable to conclude that a malignant tumour as it invades can erupt into the lumen of a lymphatic channel with greater ease than into that of a corresponding blood channel. Applying this argument to the early formation of metastases by embolic spread, it would be logical to assume that if the tumour cell embolus lodges in a small lymphatic vessel the rupture of its wall, and the subsequent invasion of the surrounding tissues, would occur more easily and rapidly than in a similar event occurring in a corresponding blood vessel. Another factor to be considered is the nature of the blood flow as compared with the movement of the lymph. Whereas that of the blood is a relatively rapid flow, driven through the arterial network under a rhythmically varying positive pressure and draining away from the capillary bed by a similar rhythmic but alternating positive and negative pressure, that of the lymph is more in the nature of a percolation. Further, in addition to being slower, the movement of lymph in the lymphatic vessels occurs in a desultory manner and much of it is of a to-and-fro nature.

Moreover/

Moreover, should a lymphatic channel of even moderate size become occluded the flow of lymph is readily reversed and the fluid carried away through associated collateral channels. Thus a single tumour cell, arrested in the lumen of a lymphatic capillary, is less likely to be dislodged and so is able to multiply and form either a solid column of neoplastic cells within the lumen or, by eventually rupturing its wall, form a secondary tumour growth; on the other hand a single tumour cell reaching the lumen of a blood vessel is more liable to be washed away and destroyed by the natural mechanism present in the body for destroying effete and foreign cells. Again, should it become arrested it will be confined for a longer period to the lumen of the blood vessel and destruction there may be effected.

The blood sinusoids of the hepatic lobule fall into a rather different category from the blood capillary network of the other organs of the body; many of their lining cells - the cells of Küpffer - have become highly specialised. That the endothelium lining these sinusoids is complete is still disputed by several authorities. Maximow Bloom ("Histology" 1930) however, considers that the evidence put forward against there being a complete sinusoidal lining has been the result of faulty technique in the use of experimental injection methods and that there is in fact a complete endothelium lining the blood/

blood sinusoids. Histological examination in the present investigation tends to confirm this view. The sinusoidal endothelium is, as already demonstrated, supported by a fine fibrous reticulum which separates it from the liver parenchymal cells. Because of this, and in so far as the rate of the blood flow in the blood sinusoids is slowed down, when a tumour embolus reaches the lumen of a blood sinusoid and is arrested there it is more likely to behave in a manner similar to that of a tumour embolus lodged in a lymphatic capillary than as in an ordinary blood vessel.

Regarding the spread of carcinoma in general it has been observed that certain pre-existing pathological conditions involving the lymphatic system may influence the distribution of the secondary tumour growths. Several authorities consider it possible that changes in the lymphatic glands and lymphatic channels, such as those due to chronic inflammation, may have a significant bearing on some of the variations seen in the route of spread of carcinoma. Such an occurrence is illustrated in one case of bronchial carcinoma, included in the first part of this paper (page 25). In this it seems reasonable to conclude that the extensive pre-existing tuberculous infection of certain of the mediastinal lymphatic glands and those in the coeliac and right para-aortic groups had resulted in obstruction to the lymphatic vessels draining directly into them; invasion of the lymphatic glands by carcinoma did not occur; on the other hand the/

the left para-aortic and left femoral glands had been invaded. The absence of metastases in the liver may have been the result of the alteration in the route of spread in the lymphatic system. In this event the case, like many others in the series, illustrates spread by lymphatics as opposed to spread by the blood stream.

Furthermore, it has been observed that carcinomata, occurring in subjects in whom senile changes are well advanced, show little tendency to invade extensively the deeper tissues surrounding the primary growth, and still less to form metastases in other organs. It is possible that the fibrosis and subsequent hyalinisation, which is characteristic of many malignant tumours of the aged, obliterates tissue spaces and lymphatic channels in the part and so tends to prevent the local extension of the carcinomatous process. Again, the generalised fibrosis of organs which is observed in advanced years will have a similar affect in preventing metastatic distribution. In young subjects, in contrast to this, carcinomatous involvement of the lymphatic system is usually exceptionally well marked.

(II) The Route of Spread by Lymphatic Channels and Tissue Spaces: From the consideration of the anatomical distribution of the lymphatic system of the liver, and from the naked eye appearances in the cases in which secondary tumour growths were present within that organ, there is little doubt that carcinomatous/

carcinomatous invasion of the liver is, for the most part, by way of the lymphatic channels.

By the time a case comes to autopsy involvement of the general as opposed merely to the local lymphatic system has usually occurred, and in those cases in which secondary growths are present within the liver at least one group of lymphatic glands associated with the organ is almost always invaded by carcinoma. This was well exemplified in the cases quoted in the first part of this paper and was amply substantiated by microscopical examination. This route of invasion has been noted by J. Maxwell (1930) in his investigations on primary malignant intra-thoracic tumours, and by Ewing (1931) in regard to primary pancreatic carcinoma.

Furthermore, the widely differing relative size of lymphatic glands invaded by carcinoma may be taken as one of the criteria indicating the time at which they were invaded. It was generally the case that those nearest the primary malignant focus were the larger and consequently the older and those in relation to the liver were the smaller and therefore the more recently invaded.

In many of the microscopical sections the lymphatic glands in the hilum of the liver, and the perivascular lymphatic channels in the suspensory ligaments were so conspicuously invaded by malignant cells as to give a clear demonstration of the significance of this mode of spread. Occasionally

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in both these regions the perineural lymphatic vessels had been similarly invaded.

The mode of spread of carcinoma by way of the lymphatic channels and tissue spaces may take one of three forms (1) embolic, or so called "true" metastatic spread, (2) spread by continuous permeation along the lymphatic channels, and (3) spread by direct extension from the primary malignant growth.

The transport of a tumour embolus along a lymphatic channel to the liver, or indeed to any organ, is by no means an expression of spread retrograde to the normal direction of the lymph flow; it is due rather to the fact that as the general spread of the carcinoma involves any one group of hepatic regional lymphatic glands and consequently blocks the various lymphatic vessels passing to that group, the lymph flow is reversed and drains into some other associated or collateral group. For instance, when the lymphatic glands into which drain the perivascular lymphatic vessels of the intrahepatic branches of the portal vein and hepatic artery become grossly invaded by carcinoma, the afferent lymph flow to them is arrested. The lymph is then deviated into the lymphatic vessels in Glisson's capsule and, entering the capsular and perivascular (hepatic vein) lymphatic systems, eventually/

eventually drains into one of the mediastinal or other associated groups of lymphatic glands by way of the suspensory ligaments and diaphragm.

In less advanced cases, where death had intervened before gross involvement of the liver had occurred, the distribution of the secondary neoplastic growths was in most cases in relation to the ramifications of the branches of the portal vein; in others it was confined to the subcapsular substance of that organ, and in a few cases, although this was of least common occurrence, the distribution of these secondary tumour nodules was related mainly to the larger branches of the hepatic veins. As these nodules were discrete and as widespread permeation of the associated lymphatic channels was not seen on histological examination it seems probable that the neoplasm had reached its position in the liver as a cell embolus along the lymphatics. In a number of the smallest secondary nodules, which were taken as having but recently begun to invade the hepatic substance, the perivascular and subcapsular tissue were invariably invaded by the neoplasm whereas the lumen of the associated branch of the portal vein was not always involved, and the hepatic artery seldom involved, in the neoplastic process.

Hence it seems justifiable to assume that a tumour cell embolus which has become separated from a proliferating mass of neoplastic tissue either in a regional lymphatic gland/

gland, or in a lymphatic vessel in relation to the primary malignant growth itself, is carried along the lymphatic channels into the liver where it is arrested in the terminal portion of a lymphatic capillary, proliferates, and by rupturing into the surrounding tissue, forms a secondary tumour nodule.

"Satellite" tumour nodules were seen around the larger metastases in a number of cases. From histological examination there is little doubt that their occurrence is the result of a process exactly similar to that by which the carcinoma reaches the liver.

In contrast to this, continuous permeation to the liver along the lymphatic channels occurred in a small number of cases. Most notable of these were the cases of "pleural endothelioma"; in many of these the microscope demonstrated extensive and continuous spread to have occurred along the perivascular and other lymphatic channels from the pleura through the diaphragm and suspensory ligaments to the sub-capsular lymphatic channels in the peripheral hepatic substance. Primary carcinomata of the gall bladder and of the extra-hepatic bile ducts tended to invade the liver in a similar manner, either through the communicating lymphatic channels present between the gall bladder and liver or along the peri-bile duct and perivascular lymphatic capillaries entering the liver in the porta hepatis. In these cases the blood vessels were seldom involved/

involved in the carcinomatous process. Within the liver permeation of the lymphatic channels in Glisson's capsule was a constant feature and, where secondary foci occurred, they had invaded the liver lobule from the terminal portions of the lymphatic channels at their periphery.

In some cases of primary gastric and pancreatic carcinoma and in those arising in relation to the upper pole of the right kidney direct spread by continuity occurred. In these, the process of invasion of the liver was of a somewhat different character. In the first place the neoplastic mass became adherent to the contiguous surface of the hepatic capsule. Theoretically this may occur in one of two ways, either by mechanical abrasion of the peritoneal covering of the liver resulting from slight but repeated movement of the organs concerned, or by the irritation of that peritoneal covering by the "toxic excretions" from the tumour cells. In either case serous exudation occurs from the denuded surface, coagulates, and so leads to adherence between the opposing surfaces. Later there is organisation of the serous coagulum as in the natural process of repair but in addition tumour cells infiltrate along the tissue spaces of the newly formed fibrous tissue and so gain access to the liver directly through its capsule. Subsequent spread within that organ in such cases, is by direct extension and infiltration along the tissue spaces and lymphatic channels. Discrete "satellite" tumour growths

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were often seen in the hepatic substance at some little distance from the main mass of the invading tumour. They had invariably arisen in relation to the tissues of Glisson's capsule and, in a number of the smallest of these nodules, no tumour tissue was seen in the lumina of the associated blood vessels, that is, in the branches of the hepatic artery and portal vein; hence it is justifiable to assume, as in the case of metastatic invasion of the liver from outside the organ that the tumour cells reach the local site of growth either by direct extension along the tissue spaces and lymphatic channels or, as tumour emboli transported along the lymphatic channels in Glisson's capsule.

(III) Spread by Way of the Blood Vascular System: When the lumina of the blood vessels in relation to the primary neoplasm have become invaded by carcinomatous tissue, there is little doubt that cell emboli are separated from the neoplastic mass and are borne by the blood stream to other organs, there to proliferate, forming secondary growths. This is expressed by the occurrence of metastases in the brain, since this organ has no lymph drainage system communicating with the general lymphatic system of the body. It is, however, difficult to understand how a venous embolus passes through the pulmonary capillary bed to reach the arterial side of the vascular system and so far no convincing explanation has been advanced.

The liver not only receives an arterial blood supply but also through it passes the entire volume of the portal blood. Furthermore, although lymphatic vessels are present in the perivascular tissues surrounding the branches of the portal vein, hepatic artery, hepatic veins, and bile ducts, and although they are known to extend into the perilobular tissues, no lymphatic vessels as such are present within the liver lobule itself. These facts, together with the appearances and distribution of secondary malignant growths within the liver are considered by many authorities to indicate that the spread of carcinoma to the liver is, for the most part, by blood borne tumour cell emboli.

If Willis' (1930) explanation of the mode of transmission of cancer cells from the venous to the arterial systems through the lungs is correct, it would support this view; he states that although the uninterrupted passage of single tumour cells through the blood capillary network in the lungs is not of frequent occurrence, numerous cell emboli arrested in the lungs proliferate and eventually invade the vessels of the pulmonary venous circulation and so form a new source of blood borne embolic spread. These emboli are disseminated throughout the systemic circulation and are carried to the liver via the hepatic artery. Schmidt (die Verbeitungswege der Karsinome, Jence 1903, quoted by Kettle), however, has demonstrated that while cancer/

cancer cell emboli lodge frequently in the lung capillaries they are usually ineffectual since in the majority of cases they become surrounded by thrombus which, undergoing organisation, destroys or successfully encapsulates them.

In the present series of cases there was no evidence to indicate that lodgement of malignant cell emboli in the terminal branches of the hepatic artery was of common occurrence. In fact, when tumour tissue was seen in the lumen of this vessel, it was evident that invasion had occurred through the wall of one of its smaller branches within an already established secondary growth and played no part in the initial invasion of the liver or in the local dissemination of the tumour within that organ.

On the other hand frequent luminal invasion of the portal venous system had occurred within the liver. Here again, however, histological examination revealed that, in the majority of cases, the initial invasion had occurred from tumour growth already present in the tissues surrounding the smaller branches of the portal vein, especially where these vessels were enveloped by the expanding neoplastic nodule, and not from emboli lodged within their lumina.

Regarding the manner in which the neoplastic cells invade the blood vessels the process was clearly demonstrated in serial sections showing invasion of a small portal vessel in the peripheral substance of a secondary tumour growth within/

within the liver. At one level the tissue spaces of the adventitia were invaded; from there the malignant cells had spread into the media and then into the intima where proliferation of the invading neoplastic elements had caused considerable disruption. Eventually the cells had erupted into the lumen of the vein and were filling it. Finally the tumour mass continued to extend along the lumen of the vessel, its advancing margin being covered by a layer of thrombus; apparently the thrombosis had preceded the further extension of the neoplastic cells.

It seems conceivable that the thrombus formed over the endothelium of a blood vessel in the process of invasion by carcinoma may result from the initial damaging of the endothelial cells by the metabolic excretions of the malignant cells. Thus when the tumour cells actually invade the lumen of the blood vessel it may well be that the damaged endothelium forms a much less effective barrier to their progress.

Histological examination not infrequently revealed continuous extension of the tumour cells along the lumen of the smaller and larger branches of the portal vein within the liver; this occurred for varying distances around the secondary tumour nodules. In some cases it was so widespread that the main portal vein itself was involved. Indeed, in one case of primary liver cell carcinoma, it had extended

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along that vein as far as the pancreas. This accords with the fact, often observed elsewhere in the body, that a malignant neoplasm frequently invades and spreads along the veins. Hugo Ribbert ("Geschwulstlehre" second edition) states that continuous carcinomatous growths may occur for considerable distances along the lumen of a vein without the formation of intermediate growths in the surrounding tissues. This was well exemplified in the present series of cases and was seen most frequently in the portal network of blood vessels within the Liver. Less commonly but in a similar manner the larger branches of the hepatic veins were involved in the neoplastic process.

(IV) Spread by way of the Bile Ducts: Invasion of the lumina of the bile ducts must be extremely rare as in almost all the invaded areas they persisted while every other tissue of the liver had disappeared. When invasion of the bile ducts did occur it was by way of the associated lymphatic channels around their wall.

(V) Spread within the Liver Lobule: Once a secondary malignant growth is established within the liver, irrespective of the route by which it has reached that organ, invasion of the hepatic lobule is not long delayed.

Accepting that the initial involvement of the liver is along the lymphatic channels it is highly probable that the lobule/

lobule is invaded by the eruption of the proliferating neoplastic cells from the terminal portion of a lymphatic radicle in Glisson's sheath, and subsequent infiltration along the tissue spaces between the collagen fibres which enter the peripheral zone of the lobule. Thence further extension is by the infiltration of malignant cells between the columns of liver cells and the endothelial lining of the blood sinusoids. Some of the sections of the present series demonstrated endothelial cells of Küpffer separating the tumour cells from the lumen of the sinusoid.

Several authorities have questioned the existence of tissue spaces between the liver parenchymal cells and the blood sinusoids. The examination of sections leaves little doubt that such are present but that normally they are only potential spaces. Muir has observed that in congestion and dilatation of venous channels, the walls of the capillary vessels in the neighbourhood become more permeable; fluid transudes into the tissues, and to remove this excess of fluid the tissue spaces and lymphatic channels become opened up. Moreover he states that in obstruction by carcinoma, due either to compression or invasion, this process occurs. It is conceivable that this, together with the obstruction of the lymph flow by invasion of the regional lymphatics in relation to the liver leads to an opening up of the potential tissue/

tissue spaces between the liver cell columns and the blood sinusoids, and thus facilitates their invasion by the carcinoma cells.

As the infiltrating neoplastic cells extend within the liver lobule they multiply in three dimensions and so tend to obliterate or rupture into the thin walled sinusoids. In many cases the columns of tumour cells were seen extending along the lumina of the blood sinusoids at the periphery of a secondary neoplastic nodule. From the observations previously noted it must be taken that the initial invasion of the liver lobule had occurred in these instances, along the perilobular tissue spaces.

In some cases small clumps of carcinoma cells were seen lying "free" within the lumina of the blood sinusoids. Assuming this was not an artefact, there can be little doubt that a number of small tumour cell emboli are arrested in the sinusoids; this is especially so where the primary carcinomatous focus is in one of the organs drained by the portal system. There was no evidence that this played any material part in the local dissemination of the tumour.

Variations occurred in the general histological picture presented by the invading margin of the tumour growth within the hepatic lobule; it would seem that these depend upon the rate of growth within the nodule as a whole, upon the invasive power of the malignant cells, and to some extent upon the degree of structural differentiation attained by the/

the neoplastic cells. Thus in slow growing "compact" carcinomatous nodules in which the cells, squamous or glandular, showed a considerable degree of structural differentiation, the growth expanded as a whole and was usually surrounded by a well formed pseudo-capsule. On the other hand, where the growth was rapid, and the malignant cells least well differentiated, there was little or no pseudo-capsular formation; it was in the latter that the process of local infiltration of the liver lobule was best seen. Between these two extremes were many gradations in the histological picture, depending upon the relative predominance of one or other of the factors concerned in the nature of the peripheral expansion of the carcinoma.

(VI) Transplantation or " seeding" within the Peritoneal Cavity: This is only a subsidiary mode of spread of carcinoma to the liver and is usually confined to the subperitoneal tissues covering its surface. In the majority of cases the outer aspect of these "seeded" malignant tumour nodules is covered by peritoneum. It seems, therefore, that they have reached their position by the subperitoneal lymphatic channels.

In the small number of cases in which true "seeding" occurs, it is probable that the process of invasion is similar to that already described with regard to direct extension of a primary malignant neoplasm when the latter becomes adherent to the contiguous surface of the liver. In "seeding", however,

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it is usually only a small secondary nodule on the adjacent peritoneal surface which becomes adherent to the opposing surface of the liver. Once the tumour cells are established there, the adhesion between the apposed serous surfaces stretches and eventually only a fine fibrous strand exists between those on the liver surface and those of the original nodule.

It seems inconceivable that cancer cells, lying free within the peritoneal cavity, could become implanted on its serous lining unless, at the point of implantation, there had been pre-existing damage, either mechanical or "inflammatory", to the peritoneum.

2. CONCLUSION.

Long before the advent of the microscope it was recognised that malignant tumours not only invaded the tissues in their immediate neighbourhood but also that they metastasised to distant organs. In the past century the solution of the problem of the spread of cancer within the human body has commanded the attention of many pathologists and has presented little difficulty to such investigators as Ribbert, Paget, Muir, Kettle, Handley, and many others whose knowledge of the science of descriptive pathology is irreproachable. It is, however, desirable periodically to test the hypotheses and discoveries of the past.

In the present investigations, general and microscopical examinations were made on 133 consecutive cases of carcinoma in which secondary spread to the liver had occurred. The 8 cases of primary hepatic carcinoma were included for the purpose of comparison.

Various authorities have stressed, from time to time, the relative importance of the lymphatic system and the blood vascular system in the general dissemination of carcinoma throughout the body, and it was with this in view in regard to the liver that the present investigation was undertaken.

It has many times been suggested that the spread of carcinoma to the liver and especially within that organ is for the most part by way of the blood stream. Chief among the/

the factors submitted in support of this view were the passage of the entire portal blood in addition to arterial blood through the liver, the absence of lymphatic capillaries within the hepatic lobule, the probable frequent dislodgement of malignant cell emboli into the blood stream, the distribution of discrete secondary tumour growths in relation to the ramifications of the blood vessels in the capsule of Glisson, and the often gross luminal involvement by carcinoma of the branches of the portal vein within the liver.

In the present series of cases, although there was evidence to suggest that blood borne tumour emboli did play a part in the secondary neoplastic invasion of the liver it was only of minor importance. It has been amply confirmed that spread to that organ occurred chiefly along the lymphatic channels entering the liver by the porta hepatis or by the surface route. It was apparent that in the majority of cases dissemination had been effected by malignant cell emboli dislodged either from a regional lymphatic gland or from the primary neoplasm itself; the former seemed more probable. In a small number of cases continuous permeation of the lymphatic capillaries and in others direct extension from the primary focus were the routes taken.

Whilst neoplastic cells frequently gain access to the lumen of the blood vessels within the liver and permeate extensively along their lumina, it has been emphasised that the/

the malignant cells arrived in the first place by way of the perivascular lymphatic vessels. This luminal spread was most often seen in the interlobular branches of the portal vein around the secondary tumour nodules and was not a common source of further neoplastic invasion of the hepatic tissues.

Although in the local extension of an established secondary malignant growth luminal invasion of the blood sinusoids occurs and results in rapid spread within the hepatic lobule, the initial invasion of the lobule is by the insinuation of the carcinoma cells between the columns of liver cells and the endothelial lining of the blood sinusoids.

APPENDIX

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(I) - Cases of Secondary Involvement of the Hepatic Substance.

Pr.-Peritoneal; Pl. -Pleural; Pd. -Pericardial; R -right; L -left.

No.	Sex	Age	Primary Source	Liver Involvement (Metastases)	Lymphatic Involvement	Metastases in other Organs.	Jaundice	Diffusion into body Cavities
2	M	61	Common Bile Duct.	Liver enlarged. R. lobe - one large. L. lobe - several small.	Liver Hilar.	-	+++	Pr. + (bile stained) L.pl. + (bile stained)
4	F	54	Thyroid Gland	R. lobe - one small.	Mediastinal Upper Abdominal.	Lungs. R. Kidney. Adrenal Glands.	-	-
5	M	43	Pyloric end of Stomach.	Liver enlarged. Several large.	Upper Abdominal.	-	-	Pr. + Pl. +
9	M	69	Head of Pancreas	R.lobe - one large	Periportal. Upper Abdominal. Mediastinal. Cervical.	R. Kidney.	+	L.Pl. + (bile stained)
10	F	62	Right Breast	Liver greatly enlarged.	Right dorsal.	-	-	-
13	F	66	Right Kidney.	Liver enlarged. numerous.	Retro-peritoneal. Coeliac.	L.Adrenal Gland.	-	-
14	F	67	Cardiac end of Stomach.	A few small.	Retro-peritoneal. Peritoneal.	Tail of Pancreas.	-	Pl. +
18	M	42	Prostate Gland.	Diffuse 1-3 cms. diameter.	Retro-peritoneal.	Wall of Urinary Bladder (direct spread).	+	Pr. + Pl - + (bile stained)

No.	Sex	Age	Primary Source	Liver Involvement (Metastases)	Lymphatic Involvement	Metastases in other Organs.	Jaundice	Effusion into Body Cavities
19	F	55	Right Breast.	Several of varying size.	Pleural. Substernal. Upper Abdominal. Peritoneal. Diaphragmatic.	Ribs. Sternum.	-	R.Pl.
24	F	32	Pelvic Colon.	Numerous 1-4 cms. in diam.	Pelvic. Lower Abdominal.	Ovaries.	-	Pr. ++
29	M	62	Lower end of Oesophagus.	A few small.	Oesophageal. Mediastinal. Pleural. Coeliac.	-	-	Pd. ++
33	F	64	Pyloric end of Stomach.	Liver enlarged. Numerous 0.2-1.5cms. in diam.	Coeliac. Retroperitoneal. Peritoneal. Pleural.	-	-	Pr. - + R.Pl. +
36	M	40	Right Kidney.	Liver enlarged. Several large.	R. paraaortic. Mediastinal.	R.Adrenal Gland.	+	Pr. + +-
39	M	64	Rectum.	Liver enlarged. Numerous 1-3 cms. in diam.	Lower Abdominal. Coeliac. Peritoneal. L.Pleural. Chest Wall.	Spleen.	-	Pr. ++ (Purulent) R.Pl. ++
42	M	51	Trachea.	R. lobe - one, 1 cm. in diam. (subcapsular).	Mediastinal.	-	-	Pd. + -
46	M	57	Left Bronchus.	Liver enlarged. Numerous 1-1.5 cms. in diam.	Mediastinal. R.Pleural. Upper Abdominal.	L. Lung.	-	R.Pl. +
50	M	69	Head of Pancreas.	Liver Greatly enlarged. Numerous 0.1-2cms. in diam.	Coeliac	-	-	Pr. + (blood-stained).

No.	Sex	Age	Primary Source	Liver Involvement (Metastases)	Lymphatic Involvement	Metastases in other Organs.	Jaundice	Effusion into Body Cavities
52	F	78	Breast.	A few small.	Pleural. Chest Wall.	-	-	L.Pl. +++ R.Pl. +++
54	F	36	Head of Pancreas.	Direct Spread to R. lobe (adherent).	Peritoneal. Mesenteric.	Gall Bladder. Duodenum. (Direct Spread).	+++	-
57	M	48	Prostate Gland.	R. lobe - one 3 cms. in diam.	Para-aortic. Coeliac. R.mediastinal.	Adrenal Glands. Kidneys. Brain.	-	Pd. +
58	M	48	Gall Bladder.	Direct Spread; Also numerous small metastases.	Liver Hilar.	-	+++	-
61	M	72	Prostate Gland.	Two in anterior surface. R.lobe,1 cm. in diam.	Pelvic. R. para-aortic.	-	-	Pl. ++
65	M	60	Prostate Gland.	Numerous. 0.5-2 cms. in diam.	Retro-peritoneal. Mesenteric.	-	-	Pr. +
67	F	60	Head of Pancreas.	Liver enlarged. Numerous small.	Coeliac. Pancreatico-Duodenal.	-	++	Pr. ++ (bile-stained). Pl. +
70	M	73	Prostate Gland.	Numerous. 1-2 cms. in diam.	Pelvic.	-	+++	Pl. + Pd. +
71	M	53	Left Bronchus.	Liver greatly enlarged. Numerous varying in size.	Mediastinal. L.Pleural. Upper Abdominal. Liver Hilar.	L.Lung.	-	Pr. + L.Pl. + (blood-stained).

No.	Sex	Age	Primary Source	Liver Involvement (Metastases)	Lymphatic Involvement	Metastases in other Organs.	Jaundice	Effusion into Body Cavities.
73	F	38	Pyloric end of Stomach.	Liver greatly enlarged. Numerous 1-4 cms. in diam.	Regional. Coeliac.	-	-	Pr. ± Pl. ±
74	M	70	Left Kidney.	R. lobe - two small.	R.para-aortic. R.bronchial. Pleural.	Lungs.	-	Pr. ± Pl. ± Pd. ±
75	M	70	Gall Bladder.	Direct and one in R. lobe - 6 cms. in diam.	Retro-peritoneal. Coeliac. Mesenteric.	Adjacent Omentum.	+++	Pd. + (bile-stained).
76	M	71	Head of Pancreas.	A few 0.5-1.5 cms. in diam.	Coeliac. Pancreatico-duodenal.	-	+++	Pl. ± Pd. - ±
77	M	73	Gall Bladder.	Direct spread to R. lobe - Numerous small.	Liver Hilar.	-	++	Pl. ± Pd. - ±
78	M	69	Lower end of oesophagus.	Liver enlarged. Numerous 0.5-1.5cms. in diam.	Upper Abdominal.	-	-	Pr. ±
80	M	63	Descending Colon.	Liver enlarged. Numerous 0.5-1 cm. in diam.	Peritoneal. Mesenteric. Para-aortic.		± -	Pr. ++ Pd. ++
82	M	52	Left Lung.	Posterior inferior Surface Large. Anterior Surface several small.	Mediastinal. Coeliac. Para-aortic.	Adrenal Glands. Right Kidney.	-	R.Pl. ±

No.	Sex	Age	Primary Source	Liver Involvement (Metastases)	Lymphatic Involvement	Metastases in other Organs.	Jaundice.	Effusion into Body Cavities.
83	M	42	Left Bronchus.	Several small.	Mediastinal. Pleural. Pericardial. Diaphragmatic. Retro-peritoneal. Gall bladder surface.	Pancreas. Spleen.	-	-
84.	M	65	Common Bile Duct.	R.lobe - one 3 cms. in diam.	Liver Hilar.	-	+	-
85	M	65	Gall Bladder.	Liver greatly enlarged. Direct spread to R.lobe and numerous small in both lobes.	Liver Hilar.	-	-	-
88	M	56	Pyloric end of Stomach.	Three small.	Gastric - lesser curvature.	-	-	Pd. +
89	M	47	Pyloric end of Stomach.	Liver greatly enlarged. Numerous large.	Gastric - lesser curvature. Coeliac.	-		Pr. ++ (blood-stained). L.Pl. + Pd. +
90	F	62	Pelvic Colon.	Liver greatly enlarged. Numerous large.	Mesenteric. Para-aortic.	-	++	Pr. +++ (bile-stained).
91	M	69	Sigmoid Colon.	Liver enlarged. Numerous.	Mesenteric. Retro-peritoneal. Coeliac. Gastric.	-	-	Pr. ++ Pl. +

No.	Sex	Age	Primary Source	Liver Involvement (Metastases)	Lymphatic Involvement	Metastases in other Organs.	Jaundice	Effusion into Body Cavities.
96	M	49	Left Lung.	Liver greatly enlarged. Numerous 1-3 cms. in diam.	Mediastinal. Pleural. Retro-peritoneal.	-	-	Pr. ± - L.Pl. ± - (purulent)
98	M	53	Prostate Gland.	Several 0.5-2 cms. in diam.	Para-aortic. Peritoneal. Diaphragmatic.	Left Lung.	-	Pr. ++
99	M	86	Pelvic Colon.	Liver enlarged. Numerous 0.1-10 cms. in diam.	Mesenteric. Retro-peritoneal.	-	-	Pr. ++
100	F	31	Left Breast.	Liver enlarged. Numerous 0.5-2 cms. in diam.	Pleural. Upper Abdominal. Peritoneal.	Ovaries. Skin.	-	L.Pl. ++ R.Pl. ± -
101	M	57	Pyloric end of Stomach.	Several large.	Gastric - Lesser Curvature. Coeliac.	-	+	Pr. ++ Pl. ±
105	M	64	Head of Pancreas.	Liver greatly enlarged. Numerous small.	Pancreatico-duodenal. Liver Hilar and Cystic Lymphatic Glands. Coeliac. Para-aortic. Peritoneal. Mediastinal. Diaphragmatic. Pleural. Left Internal Mammary.	-	+++	Pr. ±

No.	Sex	Age	Primary Source	Liver Involvement (Metastases)	Lymphatic Involvement	Metastases in other Organs.	Jaundice	Effusion into Body Cavities.
107	M	58	Cardiac end of Stomach.	Numerous 1-3 cms. in diam.	Gastric - Lesser Curvature. Superior Mesenteric. Coeliac. Mediastinal.	Kidneys. Pancreas. Lungs.	-	Pr. ++ Pl. ++ Pd. ++
111	M	47	Pelvic Colon.	Liver greatly enlarged. Numerous 0.5-6 cms. in diam.	Mesenteric. Retro-peritoneal.	-	-	Pr. ++ Pd. + -
114	M	51	Prostate Gland.	A few 0.5-2 cms. in diam.	Para-aortic. Mesenteric. Mediastinal.	Adrenal Glands. Kidneys. Lungs. Skull Bones.	-	R.Pl. +
116	M	68	Pyloric end of Stomach.	Several small.	Upper Abdominal. Gastric - Greater Curvature. Coeliac. Para-aortic.	L.Adrenal Gland. Pancreas.	-	Pl. + Pd. +
117	F	75	Gall Bladder.	Direct spread to R. lobe.	-	-	-	-
119	M	57	Right Bronchus.	Postero-inferior substance, Numerous large.	Cervical. Mediastinal. Coeliac.	R.Adrenal Gland. Brain.	-	Pr. + Pd. + +
121	F	47	Pyloric end of Stomach.	Several, 1-3 cms. in diam.	Gastric - Lesser Curvature.	Cervical. Vertebrae.	-	Pd. - +

No.	Sex.	Age	Primary Source	Liver Involvement (Metastases)	Lymphatic Involvement	Metastases in other Organs.	Jaundice	Effusion into Body Cavities.
125	M	63	Pyloric end of Stomach.	Liver greatly enlarged. Numerous large.	Gastric - Lesser Curvature. Coeliac.	-	-	Pl. + - Pd. + -
127	M	71	Right Bronchus.	Subdiaphragmatic substance. Several 0.5-1.5 cms. in diam.	Pleural. Chest wall. Diaphragmatic.	R. Lung.	-	-
128	M	47	Cardiac end of Stomach.	Liver enlarged. Several large.	Gastric - Lesser Curvature (Cardiac end). Liver Hilar. Peritoneal.	Spleen (direct extension).	+	-
129	M	23	Head of Pancreas.	Direct spread to R. lobe.	R.Mediastinal.	-	++	Pr. ++ (bile stained). L.Pl. +
132	F	39	Pyloric end of Stomach.	Liver greatly enlarges. Very numerous 0.5-1.5 cms. in diam.	Coeliac. Liver Hilar.	-	-	-
134	F	61	Pyloric end of Stomach.	Numerous large.	Gastric - Lesser Curvature. Coeliac. Mesenteric.	-	-	Pr. ++ Pl. - + Pd. - +
136	F	49	Left Breast.	A few small in subdiaphragmatic substance.	Thoracic wall. Pleural. Upper Abdominal.	Lungs. Pancreas. R.Adrenal Gland. Kidneys.	-	Pl. ++ Pd. +

No.	Sex	Age	Primary Source	Liver Involvement (Metastases)	Lymphatic Involvement	Metastases in other Organs.	Jaundice	Effusion into Body Cavities
137	F	79	Lesser Curvature of Stomach.	Numerous large.	Upper Abdominal.	-	-	Pl. + - Pd. + -
139	F	34	Right Ovary.	Liver greatly enlarged. R. lobe - one large 10 cm. in diam.	Pelvic. Para-aortic. Pancreatico-duodenal. Liver Hilar.	Kidneys. Cranial Bones.	++	Pr. + Pl. + -
143	M	68	Pyloric end of Stomach.	Liver enlarged. Large.	Gastric - Lesser Curvature. Coeliac.	-	-	-
145	F	78	Left Bronchus.	Numerous small.	Mediastinal. Pleural. Upper Abdominal.	L.Lung.	-	L.Pl. -
146	M	23	Head of Pancreas.	Several, 0.2-1.5 cms. in diam. especially in L.lobe.	Coeliac. Para-aortic. Mediastinal.	R.Adrenal. R. Lung.	++	Pr. ++ (bile stained). L.Pl. + -
147	F	74	Head of Pancreas.	A few small in substance of R.lobe in hilum of Liver.	Pancreatico-duodenal. Liver Hilar.	-	+++	Pr. + Pd. - + Pl. - +
154	M	57	Prostate Gland.	One in sub-capsular substance of Anterior Surface R. lobe.	Para-aortic. Coeliac. Mediastinal.	Kidneys. Adrenal Glands. Spleen. Brain.	-	-
156	M	55	Left Bronchus.	A few small in R. lobe.	L.Mediastinal. Upper Abdominal.	L. lung. Adrenal Glands.	-	Pr. + - R.Pl. + - Pd. + -

No.	Sex	Age	Primary Source	Liver Involvement (Metastases)	Lymphatic Involvement	Metastases in other Organs.	Jaundice	Effusion into Body Cavities
166	M	54	Right Bronchus.	R. lobe - Two, 1 cm. in diam.	Mediastinal.	-	-	R.Pl. ++ Pd. ++
170	M	60	Right Adrenal Gland.	Liver greatly enlarged. Numerous small.	Retro-peritoneal. Mesenteric. Peritoneal.	Lungs.	-	Pr. +++ (blood stained). Pd. - +
172	M	45	Right Lung.	Numerous in subcapsular substance, pinhead to 5 cms. in diam.	Mediastinal. Upper Abdominal. Para-aortic. Iliac. Inguinal.	-	-	L.Pl. + Pd. + -
174	F	32	Sigmoid Colon.	Liver enlarged; several large and small.	Mesenteric. Retro-peritoneal.	-	-	Pr. + (Purulent). Pd. + -
177	F	56	Head of Pancreas.	R. lobe - one small in subcapsular substance.	Retro-peritoneal. Peritoneal. Mediastinal. Pleural.	Ovaries.	-	Pr. +++ R.Pl. ++
179	M	52	Right Bronchus.	Several 0.5-1.5 cms. in diam.	Mediastinal. Pleural. Diaphragmatic. Upper Abdominal.	Lungs. Skin.	-	R.Pl. +
180	M	56	Right Lung.	Liver greatly enlarged. Numerous 0.5-1.5 cms. in diam.	Mediastinal.	-	-	R.Pl. + (Purulent). Pd. +
181	F	58	Gall Bladder	R.lobe - Direct spread; numerous and small.	Pancreatico-duodenal. Liver Hilar.	-	++	Pr. ++ (bile stained); Pl. + -

No.	Sex	Age	Primary Source	Liver Involvement (Metastases)	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
182	M	53	Pyloric end of Stomach.	Several, 1-2 cms. in diam.	Upper Abdominal.	L.Lung (lower lobe).	-	R.Pl. (blood stained).
183	F	65	Left Lung.	Liver enlarged. Several small.	Pleural. Diaphragmatic.	Spleen.	-	R.Pl.
184	M	55	Right Lung.	Liver enlarged. Numerous small.	R.mediastinal.	R. Lung.	-	Pl. + -
186	M	63	Pyloric end of Stomach.	Liver greatly enlarged. Numerous large and small.	Gastric - lesser Curvature. Pancreatico-duodenal. Liver Hilar. Retro-peritoneal. Peritoneal.	-	++	Pr. +++ (bile stained). Pl. +
187	M	57	Pyloric end of Stomach.	Liver enlarged. Numerous large and small.	Gastric. Coeliac. Pancreatico-duodenal.	-	-	Pd. - +
188	F	54	Left Bronchus.	Numerous, 0.5-2 cms. in diam.	L. Mediastinal. Upper Abdominal. Liver Hilar.	L.Lung.	-	R.Pl. - + Pd. - +
190	M	58	Pyloric end of Stomach.	Direct spread to L. lobe.	Coeliac. Gastric - Lesser Curvature.	-	-	-
192	F	32	Undetermined ? Pelvic.	R.lobe- one in substance of antero-inferior surface, 1-5 cms. in diam.	Mesenteric. Retro-peritoneal. L.para-aortic.	Kidneys. Spleen.	-	Pr. + Pl. + Pd. +

No.	Sex	Age	Primary Source	Liver Involvement (Metastases)	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
193	M	74	Head of Pancreas.	Numerous small.	Pancreatico-duodenal.	-	+++	Pr. +++ (bile stained).
195	F	55	Pyloric end of Stomach.	Liver enlarged. Numerous varying in size.	Pancreatico-duodenal. Upper Abdominal. Gastric - Lesser Curvature. Coeliac.	L. Lung.	-	Pl. + - (blood stained).
200	M	57	Left Bronchus.	L.lobe - one in subcapsular substance, 2.5 cms. in diam.	L.Medias-tinal. L.Pleural.	Lungs. Pelvic Bone.	-	Pl. + Pd. + -
208	M	50	Left Lung.	Numerous 0.5-1.5 cms. in diam.	Mediastinal.	-	-	-
209	M	63	Cardiac end of Stomach.	Liver enlarged. Numerous 1-5 cms. in diam.	Lower Medias-tinal. Gastric - Lesser Curvature.	-	-	Pd. - +
210	M	35	Undeter-mined.	Liver enlarged. Numerous large and small.	Coeliac. Para-aortic.	Kidneys. Skull.	-	-
215	F	67	Right Bronchus.	Liver enlarged. Numerous varying in size.	Mediastinal. Coeliac.	R.Lung. Adrenal Glands. Spleen. Kidneys.	-	L.Pl. + Pd + -
218	F	68	Head of Pancreas.	Several 0.5-1 cm. in diam.	Retro-peritoneal.	Duodenum (direct).	+++	-

No.	Sex	Age	Primary Source	Liver Involvement (Metastases)	Lymphatic Involvement	Metastases in other Organs.	Jaundice	Effusion into Body Cavities
219	M	56	Right Bronchus.	R.lobe - two small.	Mediastinal. R.Pleural. Coeliac. Pericardial.	R.Lung. R.Adrenal Gland.	-	Pd. + (blood stained). Pl. + -
221	F	54	Tail of Pancreas.	Liver enlarged. Numerous small.	Retro-peritoneal. Diaphragmatic. Pleural. Mediastinal.	R.Adrenal Gland. L.Lung. Skull Bones.	-	Pl. +
224	M	57	Right Bronchus.	Several 0.5-1.5 cms. in diam.	Right Mediastinal. Pericardial. Upper Abdominal.	R.Lung. Kidneys.	-	L.Pl. + - Pd. + -
225	M	67	Left Kidney.	Liver enlarged. Several.	L. para-aortic. L. ureteric.	-	-	Pl. +
226	M	58	Left Bronchus.	Liver enlarged. Several 0.5-1.5 cms. in diam.	Mediastinal. Liver Hilar.	L.Lung.	-	L.Pl. ++ R.Pl. + Pd. +
231	M	76	Pyloric end of Stomach.	Liver enlarged. Numerous large and small.	Gastric. Mesenteric. Coeliac.	Spleen. Lungs.	-	-
236	M	25	Head of Pancreas.	Numerous small.	Pancreatico-duodenal. Retro-peritoneal.	Jejunum (direct spread).	-	Pr. ++ Pl. ++ Pd. + -
238	M	60	Sigmoid Colon.	Liver greatly enlarged. Numerous large and small.	Mesenteric. Coeliac.	R.Lung (lower lobe).	-	-

No.	Sex	Age	Primary Source	Liver Involvement (Metastases)	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
239	M	68	Right Bronchus.	Liver enlarged. Numerous small.	Mediastinal.	R.Lung. L.Lung (lower lobe). L.Kidney.	-	Pl. ++
241	F	56	Head of Pancreas.	Several small.	Pancreatico-duodenal. Coeliac. Mesenteric.	-	+++	-
242	M	43	Left Bronchus.	Liver enlarged. Numerous 0.5-2 cms. in diam.	Mediastinal. Upper Abdominal. Para-aortic.	L.Lung. L.Adrenal Gland. Kidneys. Lumbar Vertebrae.	-	-
244	M	55	Left Pleura.	R.lobe - one, 0.5 cms. in diam.	Parietal. Pleural. Coeliac.	-	-	-
245	F	69	Head of Pancreas.	Numerous small.	Coeliac. Pancreatico-duodenal. Liver Hilar.	Stomach (direct spread).	+	Pr. +
246	F	41	Left Bronchus.	Liver greatly enlarged. Several large.	Left Medias-tinal. Coeliac.	L.Adrenal Gland. R.Kidney.	-	-
247	M	38	Right Bronchus.	Several 0.25-2 cms. in diam.	Mediastinal. Upper Abdominal.	-	-	L.Pl. + - Pd. +
249	F	43	Right Bronchus.	Liver enlarged. Several large.	Mediastinal. R.Pleural. Pericardial.	Skin. Adrenal Glands.	-	Pd. + - (blood stained).

No.	Sex	Age	Primary Source	Liver Involvement (Metastases)	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
250	M	68	Head of Pancreas.	Liver enlarged. Numerous varying in size.	Retro-peritoneal. Pancreatico-duodenal. Liver Hilar.	-	-	Pr. + -
253	F	60	Common Bile Duct.	Liver enlarged. Numerous small.	Coeliac. Liver Hilar.	-	+++	Pl. +
254	M	35	Left Bronchus.	Several small.	Mediastinal. L.Cervical. Pleural. Gastric - Lesser Curvature. Para-aortic. Liver Hilar.	R.Lung.	-	L.Pl. ++ Pd. +
256	F	47	Left Bronchus.	R. lobe - Two small.	Mediastinal. Pericardial. L.Axillary. Upper Abdominal. Para-aortic.	L.Lung.	-	L.Pl. ++ (blood stained). Pd. + (blood stained).
257	M	60	Head of Pancreas.	Liver enlarged. Numerous small.	Coeliac. Mesenteric. Peritoneal.	Lungs.	-	Pr. +
259	F	51	Head of Pancreas.	Liver enlarged. Direct spread to L. lobe.	Retro-peritoneal. Gastric - Greater Curvature. Liver Hilar.	-	+++	-
263	M	73	Right Pleura.	Several small in superficial substance.	Pleural. Pericardial. R.Mediastinal. Diaphragmatic. Suspensory Ligaments of Liver. Peritoneal.	-	-	R.Pl. ++ L.Pl. + Pd. ++ (blood stained).

No.	Sex	Age	Primary Source	Liver Involvement (Metastases)	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
266	M	44	Undetermined.	Numerous small.	Liver Hilar.	-	+++	-
268	M	60	Pyloric end of Stomach.	Liver enlarged. Numerous small.	Gastric on Lesser Curvature. Coeliac. Liver Hilar.	-	-	-
271	F	77	Cardiac end of Stomach.	Liver enlarged. R. lobe - large. L. Lobe - numerous small.	Upper Abdominal.	-	++	Pr. + / - Pl. + / - Pd. + / -
272	M	50	Pelvic Colon.	Liver enlarged. Numerous large and small.	Pelvic. Para-aortic. Coeliac. Peritoneal. Pleural.	Spleen (Hilar portion).	-	Pr. +++ Pl. ++
273	F	80	Descending Colon.	Liver enlarged. Numerous 1-2 cms. in diam.	Mesenteric. Para-aortic. Liver Hilar. Peritoneal. Mediastinal.	Lungs.	+	Pr. ++ Pl. + Pd. - / +
274	M	47	Head of Pancreas.	Liver enlarged. Numerous C.2-2 cms. in diam.	Pancreatico-duodenal. Liver Hilar. Peritoneal.	-	+	Pr. + / - Pd. - / +
276	F	57	Left Breast.	R. lobe - One in substance of Anterior Surface.	Parietal. Pleural. Mediastinal. Coeliac. Para-aortic.	-	-	-

No.	Sex	Age	Primary Source	Liver Involvement (Metastases)	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
277	M	67	Urinary Bladder.	Liver enlarged. Numerous up to 1.5 cms. in diam.	Pelvic. Deep Inguinal. Para-aortic. Coeliac. Liver Hilar. Right Diaphragmatic.	-	-	-
278	M	56	Pyloric end of Stomach.	R. lobe - One small in diaphragmatic substance.	Gastric - Lesser Curvature. Coeliac.	Duodenum. Pancreas (Direct spread).	-	Pr. +++ L.Pl. +
280	M	75	Gall Bladder.	Liver enlarged. Numerous small.	Liver Hilar. Diaphragmatic. Pleural. Peritoneal.	-	++	-
286	M	65	Pyloric end of Stomach.	Liver enlarged. Numerous large and small.	Gastric in Lesser Curvature. Coeliac. Para-aortic. Liver Hilar.	L.Adrenal Gland.	-	Pr. + (Purulent) Pl. +
287	F	77	Gall Bladder.	R. lobe - Direct spread.	-	Duodenum. Transverse Colon (Direct spread).	-	L.Pl. - +
288	M	64	Right Kidney.	Liver enlarged. Numerous large (also direct spread).	R.Renal. Para-aortic. Coeliac. Liver Hilar. Diaphragmatic. Mediastinal.	L.Adrenal Gland. Lungs - subpleural substance.	-	Pd. + -
289	M	55	Left Bronchus.	Liver enlarged. R. lobe - One large in subcapsular substance.	Mediastinal. Coeliac. Upper Abdominal. Liver Hilar. Para-aortic. Diaphragmatic. Pleural. Pericardial.	R.Adrenal Gland.	-	-

No.	Sex	Age	Primary Source	Liver Involvement (Metastases)	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
290	F	63	Head of Pancreas.	Liver enlarged. Numerous large and small.	Coeliac. Pancreatico-duodenal.	-	+++	-
291	F	75	Transverse Colon.	Several in sub-capsular substance.	Retro-peritoneal. Peritoneal.	-	-	Pr. + Pl. +
292	M	70	Right Bronchus.	Several small in subcap-sular substance.	R.Pleural. Para-aortic. Peritoneal.	L.Adrenal Gland.	-	R.Pl. ++

(II) Cases of Primary Intrahepatic Carcinoma.

Pr. =Peritoneal; Pl. =Pleural; Pd. =Pericardial; R =right; L =left.

No.	Sex	Age	Primary Source	Spread Within the Liver	Lymphatic Involvement	Metastases in other Organs	Jaundice	Diffusion Into Body Cavities
120	M	75	Intra-hepatic Bile Ducts.	L. lobe - diffuse. R. lobe - numerous but discrete.	-	-	-	Pr. + (blood stained). Pl. - + Pd. - +
155	F	60	Liver cell.	Liver enlarged. Numerous.	Upper Abdominal. Para-aortic.	Adrenal Glands.	-	Pr. ++
162	F	29	Intra-hepatic Bile Ducts.	Liver enlarged. Diffuse (Necrosis and haemorrhage).	-	-	++	Pr. + (purulent) Pl. + - Pd. + -
163	F	60	Liver cell.	Liver enlarged. Numerous.	Liver Hilar.	-	++	Pr. +
189	M	71	Liver cell.	R. lobe - large and numerous small.	Coeliac.	Gall Bladder. (Direct). Lungs.	-	-
227	M	72	Liver cell.	Liver enlarged.	-	-	++	Pr. +++ R.Pl. +
279	M	69	Liver cell.	Liver much enlarged. R. lobe - numerous diffuse; L. lobe - numerous discrete, 0.2-1.5 cms. in diam.	Liver Hilar. Diaphragmatic. Peritoneal. Pleural.	Lumen of Portal Vein. (Permeation).	+++	Pr. +++ (bile stained). Pl. + (bile stained).
285	F	72	Intra-hepatic Bile Ducts.	Liver enlarged. Numerous small.	Liver Hilar. Pancreatico-duodenal. Coeliac.	Lumen of Portal Vein (Permeation).	-	Pr. ++

(III) Cases showing no Involvement of the Hepatic Substance by Carcinoma.

Pr. =Peritoneal; Pl. =Pleural; Pd. =Pericardial; R =right; L =left.

No.	Sex	Age	Primary Source	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
1	M	64	Mouth Alveolar Margin.	Left Cervical.	-	-	-
3	M	70	Descending Colon.	-	-	-	-
6	F	65	Left Breast.	Left Axillary. Mediastinal. Left Pleural. Pericardial.	Lungs.	-	Pl. ++ Pd. ++
7	F	74	Thyroid Gland.	Left Cervical. Mediastinal.	R. Kidney. Adrenal Glands.	-	Pl. - +
8	M	59	Oesophagus.	Mediastinal.	Bronchus (direct).	-	-
11	M	29	Right Tonsil.	Right Cervical.	Bone.	-	Pd. + -
12	M	39	Bronchus.	Mediastinal.	Brain. Adrenal Glands.	-	Pd. ++
15	M	62	Head of Pancreas.	Coeliac. Pancreatico-duodenal.	-	-	Pl. + -
16	M	72	Head of Pancreas.	Retro-peritoneal. Mediastinal. Cervical.	L.Adrenal Gland.	-	-
17	M	56	Left Bronchus.	Left Mediastinal.	-	-	Pr. - +
20	F	48	Left Bronchus.	Mediastinal.	-	-	L.Pl.
21	M	69	Head of Pancreas.	Gastro-hepatic. Mesenteric. Peritoneal.	-	-	-

No.	Sex	Age	Primary Source	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
22	M	53	Right Bronchus.	Cervical. Mediastinal. Pleural. Diaphragmatic. Upper Abdominal.	Right Lung.	-	Pl. +
23	M	54	Right Bronchus.	Mediastinal.	-	-	-
25	F	39	Left Ovary.	Pelvic. Retro-peritoneal. Peritoneal.	-	-	Pr. ++ Pl. ++ Pd. +
26	F	62	Left Pleura.	Pleural.	-	-	L.Pl. + -
27	M	69	Sigmoid Colon.	Peritoneal.	-	-	Pr. +++
28	F	39	Urinary Bladder.	Pelvic.	-	-	Pd. +
30	F	48	Head of Pancreas.	Coeliac. Pancreatico-duodenal. Lymphatics of Chest wall.	Adrenal Glands.	-	-
31	M	58	Larynx.	Cervical.	-	-	-
32	M	52	Head of Pancreas.	Retro-peritoneal. Mediastinal.	L.Adrenal Gland. Kidneys. R.Lung.	-	Pl. - +
34	M	63	Pelvic Colon.	Pelvic.	-	-	-
35	M	59	Head of Pancreas.	Retro-peritoneal. Peritoneal.	-	-	Pr. ++

No.	Sex	Age	Primary Source	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
37	M	65	Head of Pancreas.	Pancreatico-duodenal. Coeliac.	Lungs.	++	Pr. + (bile stained).
38	M	68	Prostate Gland.	Pelvic. Retro-peritoneal. Peritoneal.	-	-	Pr. ++ Pl. +
40	M	57	Head of Pancreas.	Retro-peritoneal. Peritoneal.	Adrenal Glands. Skin.	+	Pr. + (bile stained).
41	M	54	Left Bronchus.	Mediastinal. Pericardial.	-	-	Pd. +
43	F	42	Head of Pancreas.	Pancreatico-duodenal. Retro-peritoneal. Mediastinal.	Adrenal Glands. R.Lung.	-	Pr. + - Pd. + -
44	M	79	Head of Pancreas.	-	-	+++	Pr. + - Pl. + - (bile stained). Pd. + -
45	F	33	Left Bronchus.	Mediastinal. Pleural. Chest Wall. Left Upper Abdominal.	L.Lung.	-	R.Pl. + -
47	M	53	Left Bronchus.	Mediastinal.	L.Lung. Cerebrum.	-	Pl. - +
48	M	29	Left Bronchus.	Posterior Mediastinal.	-	-	-
49	M	49	Head of Pancreas.	Retro-peritoneal. Pancreatico-duodenal.	L.Adrenal Gland. R.Lung.	-	R.Pl. + -
51	F	43	Vagina	-	-	-	Pl. - + Pd. - +

No.	Sex	Age	Primary Source	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
53	M	57	Head of Pancreas.	Retro-peritoneal. Mediastinal. Inguinal.	Skin. R.Lung.	-	-
55	M	42	Rectum.	-	-	-	-
56	M	73	Head of Pancreas.	Retro-peritoneal. Pancreatico-duodenal.	Duodenum (direct spread).	+++	Pr. +++ (bile stained).
59	M	51	Oesophagus.	Mediastinal. Pericardial.	-	-	-
60	M	70	Sigmoid Colon.	-	-	-	Pr. + Pd. + -
62	F	38	Right Bronchus.	Mediastinal.	R.Adrenal Gland.	-	Pd. +
63	M	58	Undetermined Mediastinal.	R.para-aortic.	L.Adrenal Gland.	-	-
64	M	47	Right Bronchus.	Mediastinal.	-	-	-
66	M	72	Transverse Colon.	-	-	-	-
68	M	71	Prostate Gland.	Retro-peritoneal. Peritoneal. Pleural.	L.Kidney. Spleen. Ribs.	-	Pl. + Pd. + -
69	M	61	Right Bronchus.	Mediastinal.	-	-	Pl. ++
72	M	74	Oesophagus.	Upper Abdominal.	-	-	Pr. (purulent).
79	M	27	Head of Pancreas.	Retro-peritoneal. Peritoneal. Mediastinal.	Lungs.	-	Pr. - + Pd. +

No.	Sex	Age	Primary Source	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
81	M	66	Common Bile Ducts.	-	-	+++	-
86	M	54	Left Bronchus.	Mediastinal. L.Pleural.	L.Lung.	-	-
87	F	44	Pelvic, Undetermined.	Pelvic. Retro-peritoneal. Peritoneal.	-	-	Pr. + Pl. +
92	F	46	Pyloric end of Stomach.	Gastric - Lesser Curvature.	-	-	Pl. ± Pd. ±
93	F	64	Pyloric end of Stomach.	Gastric - Greater Curvature.	-	-	-
94	M	59	Left Bronchus.	Mediastinal.	-	-	L.Pl. +
95	M	35	Cardiac end of Stomach.	-	-	-	Pd. +
97	M	44	Head of Pancreas.	Retro-peritoneal. Mediastinal.	-	-	Pd. +
102	F	31	Cervix.	Pelvic.	Skull Bones.	-	L.Pl. +
103	M	43	L.Bronchus.	Mediastinal.	L.Adrenal Gland.	-	Pd. +
104	F	55	Urinary Bladder.	-	-	-	-
106	M	38	Head of Pancreas.	Coeliac.	-	+++	Pr. ++ (blood stained). Pl. ± Pd. ±

No.	Sex	Age	Primary Source	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
108	F	37	R.Lung	Mediastinal.	Adrenal Glands.	-	L.Pl. ++ Pd. + -
109	M	65	Prostate Gland.	L. Iliac.	-	-	-
110	M	42	L.Bronchus.	Mediastinal.	L.Lung. Adrenal Glands.	-	Pr. + R.Pl. ++ Pd. + -
112	M	60	R.Lung.	R.Mediastinal.	Brain.	-	R.Pl. +
113	F	52	Cervix.	-	-	-	Pr. +++ Pl. + - Pd. + -
115	M	81	Caecum.	-	-	-	Pl. - + Pd. - +
118	M	68	L.Breast.	Pleural.	R.Lung. Skin.	-	Pr. ++ Pl. ++
122	M	41	L.Bronchus.	Mediastinal.	L.Lung.	-	Pr. + Pl. + Pd. ++
123	F	51	R.Breast.	Pleural. Mediastinal. Peritoneal (Liver surface).	-	-	-
124	F	59	L.Bronchus.	Mediastinal. Retro-peritoneal.	-	-	-
126	M	75	Transverse Colon.	-	-	-	Pr. ++ (Purulent). Pd. + -

No.	Sex	Age	Primary Source	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
130	M	49	L.Bronchus.	Mediastinal.	R.Adrenal Gland. Brain.	-	Pl. ++ Pd. + -
131	M	55	Larynx.	-	-	-	R.Pl. + -
133	M	62	Pyloric end of Stomach.	Mesenteric. Peritoneal.	-	-	Pr. ++ (blood stained). Pd.
135	M	68	R.Kidney.	Para-aortic.	L.Kidney. Adrenal Glands. Lungs.	-	Pr. + R.Pl. + Pd. + -
138	F	50	L.Lung.	Diaphragmatic. Pleural.	-	-	L.Pl. ++ (blood stained).
140	F	40	Head of Pancreas.	-	R.Lung.	-	L.Pl. + - Pd. + -
141	M	55	Head of Pancreas.	Coeliac. Mesenteric. Mediastinal.	Adrenal Glands. R.Lung.	-	L.Pl. Pd. + -
142	M	58	R.Lung.	Mediastinal.	Adrenal Glands.	-	Pr. + Pl. + - Pd. + -
144	M	41	L.Bronchus.	Mediastinal. Pleural.	L.Lung.	-	Pr. + - Pl. + Pd. ++
148	M	70	Oesophagus.	Mediastinal.	R.Lung.	-	R.Pl. +
149	F	33	Descending Colon.	Mesenteric.	-	-	Pr. + -
150	F	54	R.Bronchus.	Mediastinal. Para-aortic.	R.Lung.	-	R.Pl.

No.	Sex	Age	Primary Source	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
151	F	47	L.Lung.	Mediastinal.	Brain.	-	Pr. ± Pl. ± Pd. ±
152	M	74	Cardiac end of Stomach.	-	-	-	L.Pl. +
153	M	78	Oesophagus.	Cervical.	-	-	-
157	M	58	Oesophagus.	Mediastinal.	-	-	Pd. +
158	M	52	L.Bronchus.	Mediastinal. Intercostal.	-	-	L.Pl. ++
159	F	28	Cervix.	Pelvic.	Rectum. Urinary Bladder. (direct spread).	-	-
160	F	50	Pelvic Organs.	Pelvic.	-	-	Pr. ++ Pl. ± Pd. ±
161	M	34	Pyloric end of Stomach.	Upper Abdominal. Mediastinal.	Lungs.	-	Pd. ±
164	F	65	Parotid Gland.	Cervical.	-	-	-
165	M	42	R.Bronchus.	Mediastinal. Cervical.	-	-	R.Pl. ++ L.Pl. +- Pd. +
167	M	49	Larynx.	-	-	-	-

No.	Sex	Age	Primary Source	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
168	M	42	R.Bronchus.	Mediastinal. Sterno-clavicular. Para-aortic. Peritoneal. Inguinal.	Pancreas. R.Adrenal Gland.	+	Pl. + Pd. + (bile stained).
169	M	52	Parotid Gland.	-	-	-	-
171	M	36	Duodenum.	-	-	-	-
173	F	37	R.Bronchus.	R.Mediastinal.	-	-	R.Pl. + (purulent).
175	F	33	Cervix.	Pelvic.	Bladder. Rectum (direct spread).	-	-
176	M	63	Pyloric end of Stomach.	-	-	-	Pr. +
178	F	54	R.Breast.	-	Adrenal Glands. Dura Mater.	-	Pd. +
185	M	42	Testicle.	Pelvic. Lower Para-aortic. Ureteric.	-	-	-
191	F	75	R.Lung.	-	Brain.	-	-
194	F	63	R.Bronchus.	R.Mediastinal.	-	-	R.Pl. + (purulent).
196	M	42	Tail of Pancreas.	Coeliac. Pancreatico-duodenal.	-	-	Pl. + -

No.	Sex	Age	Primary Source	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
197	M	70	Cardiac end of Stomach.	Diaphragmatic.	Spleen. L.Kidney (direct).	-	Pr. ++ L.Pl. ++ (purulent).
198	M	60	R.Bronchus.	Mediastinal.	-	-	Pr. ± Pl. + Pd. ++
199	M	48	R.Bronchus.	Mediastinal.	-	-	L.Pl. ++
201	F	48	R.Lung.	Mediastinal.	-	-	R.Pl. ±
202	M	67	R.Bronchus.	Mediastinal.	Lungs. L.Adrenal Gland.	-	R.Pl. + + L.Pl. + Pd. +
203	M	31	R.Bronchus.	Mediastinal.	R.Lung. R.Kidney.	-	Pd. +
204	M	53	R.Bronchus.	Mediastinal. Pericardial.	R.Lung.	-	Pr. ± R.Pl. ++ Pd. (blood stained).
205	M	67	Sigmoid Colon.	Mesenteric. Para-aortic. Peritoneal.	Urinary Bladder (direct spread).	-	-
206	F	47	R.Brest.	Mediastinal. Retro-peritoneal.	Adrenal Glands. Dura mater. Brain.	-	-
207	M	77	Pyloric end of Stomach.	Mesenteric. Coeliac.	-	-	-
211	M	44	R.Bronchus.	Mediastinal. Pericardial.	R.Lung. Heart (direct spread).	-	Pd. ++ (blood stained).
212	M	37	R.Bronchus.	Mediastinal. Upper Abdominal.	R.Adrenal. Gland. Kidneys. Brain.		

No.	Sex	Age	Primary Source	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
213	F	10	Thymus.	Mediastinal. Para-aortic.	Sternum (direct spread).	-	-
214	M	59	R.Lung.	Mediastinal.	L.Lung.	-	-
216	M	53	Oesophagus.	Mediastinal.	L.Lung. L.Kidney.	-	-
217	M	52	R.Bronchus.	R.Mediastinal.	-	-	-
220	M	56	R.Bronchus.	Mediastinal. Pleural.	R.Lung.	-	R.Pl. + (blood stained).
222	M	13	? Mediastinal.	Mediastinal. Retro-peritoneal. Pleural.	R.Lung. Kidneys. Adrenal Glands. ? Spleen.	-	Pl. +
223	F	64	L.Breast.	Cervical. Axillary. Upper Mediastinal.	-	-	Pl. ++
228	M	47	R.Bronchus.	Mediastinal.	R.Lung. Brain.	-	-
229	M	71	Head of Pancreas.	Coeliac. Mesenteric.	Stomach (direct spread).	+	-
230	M	52	R.Lung.	Pleural.	-	-	L.Pl. + - Pd. + -
232	F	65	Pelvic Colon.	-	-	-	Pd. + -
233	M	50	R.Bronchus.	R.Mediastinal.	R.Lung. Heart (direct spread).	-	Pr. + - L.Pl. ++ Pd. + (blood stained).

No.	Sex	Age	Primary Source	Lymphatic Involvement	Metastases in other Organs	Jaundice	Effusion into Body Cavities
234	F	62	R.Bronchus.	Mediastinal.	-	-	-
235	M	45	R.Bronchus.	Mediastinal.	L.Kidney.	-	-
237	M	51	L.Bronchus.	-	Brain.	-	-
240	M	73	Tail of Pancreas.	Retro-peritoneal. Peritoneal. Mediastinal. Pleural.	-	-	Pr. ++ Pl. +- Pd. -+
243	M	64	Pyloric end of Stomach.	Coeliac. Mesenteric.	Pancreas.	-	-
248	M	77	Sigmoid Colon.	-	-	-	-
251	F	47	Pelvic Colon.	-	-	-	-
252	F	77	Pyloric end of Stomach.	-	10th Dorsal Vertebra.	+	Pd. + -
255	F	46	L.Breast.	Intercostal. Mediastinal.	Lungs. Adrenal Glands. Kidneys. Brain.	-	-
258	F	70	Head of Pancreas.	Coeliac.	-	+++	-
260	F	70	Uterus.	Pelvic.	Urinary Bladder (direct spread).	-	Pr. + Pl. ++
261	F	62	Undetermined.	R.Pelvic. R.Inguinal. Para-aortic.	-	-	-
262	M	54	Pyloric end of Stomach.	Coeliac.	R.Lung.	-	-
264	M	66	Transverse colon.	Mesenteric. Peritoneal.	-	-	Pr. +++

No.	Sex	Age	Primary Source	Lymphatic Involvement	Metastases in other Organs.	Jaundice	Effusion into Body Cavities.
265	M	68	L.Kidney.	Retro-peritoneal. Mediastinal.	Lungs.	-	-
267	F	59	Pelvic Colon.	Pelvic. Retro-peritoneal.	-	-	-
269	M	70	Sigmoid Colon.	-	-	-	-
270	F	54	R.Ovary.	Pelvic.	-	-	Pr. ++ Pl. ++
275	F	24	L.Bronchus.	Mediastinal. Pericardial.	-	-	L.Pl. + Pd. ++
281	M	64	Pelvic Colon.	Mesenteric. Retro-peritoneal.	-	-	Pr. +++ (purulent). Pd. +
282	F	56	Pyloric end of Stomach.	Coeliac. Gastro-Hepatic. Liver Hilar. Para-aortic.	-	-	Pd. +
283	F	70	Caecum.	Mesenteric. Retro-peritoneal.	-	-	Pr. ++ (blood stained).
284	F	59	Pyloric end of Stomach.	Coeliac. Peritoneal.	-	-	Pr. ++ (blood stained).

710-1945

CONCERNING THE MODE OF SPREAD OF CARCINOMA

A Pathological Study of a Series of Cases with Special Reference to the Route of Spread to the Liver and to the Factors that Determine the Mode of Spread within that Organ.

- by -

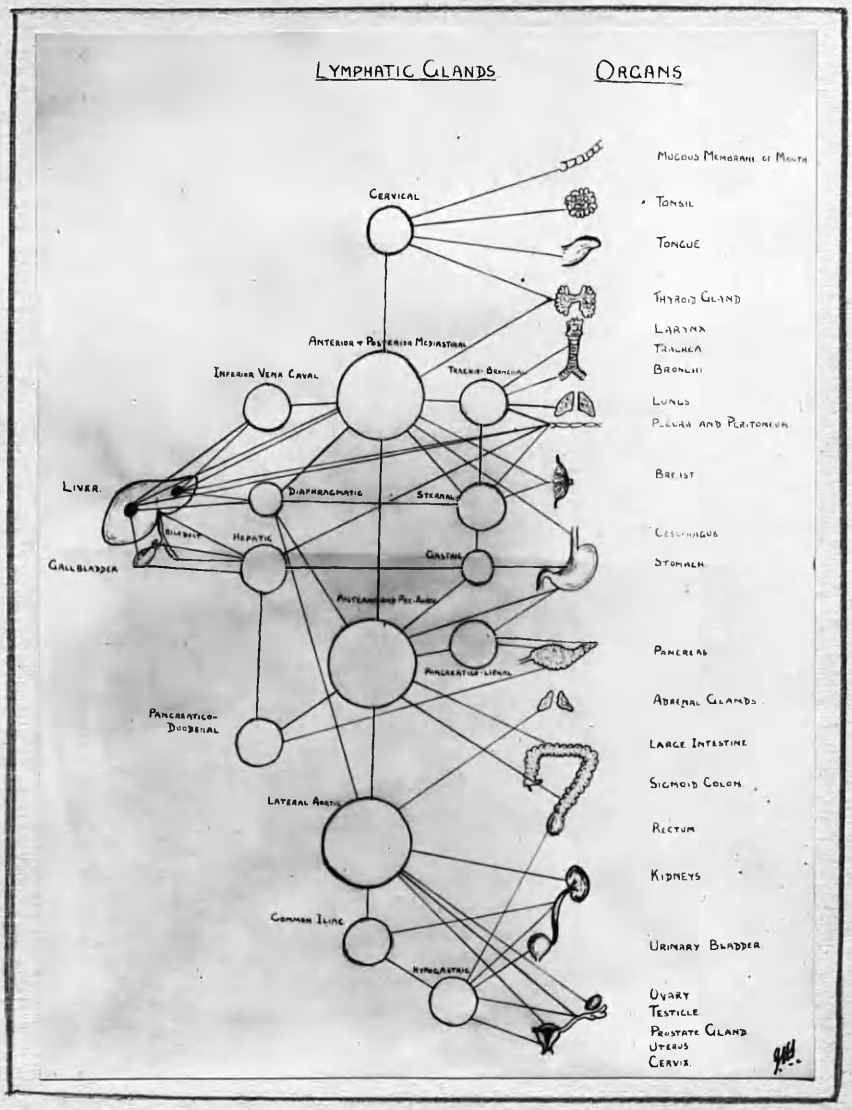
JAMES HILL STIRRAT

B.Sc., M.B., Ch.B.

Fifty One Illustrations.

Fig. 1	Diagrammatic Representation of the Lymphatic System.
Fig. 2	Diagrammatic Representation of the Anatomy of the Liver.
Fig. 3	Massive Permeation by Carcinoma along the Lumen of the Portal Vein in the Hilum of the Liver.
Figs. 4 to 7	The Fibrous Reticulum of the Liver Lobule.
Figs. 8 to 14	Invasion of the Liver by the Capsular Route.
Figs. 15 to 20	Spread by Lymphatic Channels.
Fig. 21	Invasion of a lymph node.
Figs. 22 to 24	Invasion of the Liver by the Hilar Route.
Figs. 25 & 26	Pseudo-capsule Formation.
Figs. 27 to 30	Invasion of the Blood Vessels within the Liver.
Figs. 31 to 38	Spread Within the Liver by Lymphatic Channels.
Fig. 39	Invasion of the Liver Lobule.
Fig. 40	Spread within the Liver by Lymphatic Channels.
Figs. 41 to 51	Spread within the Liver Lobule.

Fig. 1 - Diagrammatic representation of the lymphatic system with especial reference to the chief communications between the liver and the other organs of the body.


LYMPHATIC GLANDS
ORGANS
CERVICAL
ANTERIOR & POSTERIOR MEDIASTINAL
INFERIOR VENA CAVAL
TRACHEO-BRONCHIAL
LIVER
DIAPHRAGMATIC
STERNAL
BILIARY
HEPATIC
GALL BLADDER
GASTRIC
PANCREATICO-LIENAL
PANCREATICO-DUODENAL
LATERAL AORTIC
COMMON ILIAC
HYPOGASTRIC
MUCOUS MEMBRANE OF MOUTH
TONSIL
TONGUE
THYROID GLAND
LARYNX
TRACHEA
BRONCHI
LUNGS
PLEURA AND PERITONEUM
BREAST
OESOPHAGUS
STOMACH
PANCREAS
ADRENAL GLANDS
LARGE INTESTINE
SIGMOID COLON
RECTUM
KIDNEYS
URINARY BLADDER
OVARY
TESTICLE
PROSTATE GLAND
UTERUS
CERVIX

l.c.
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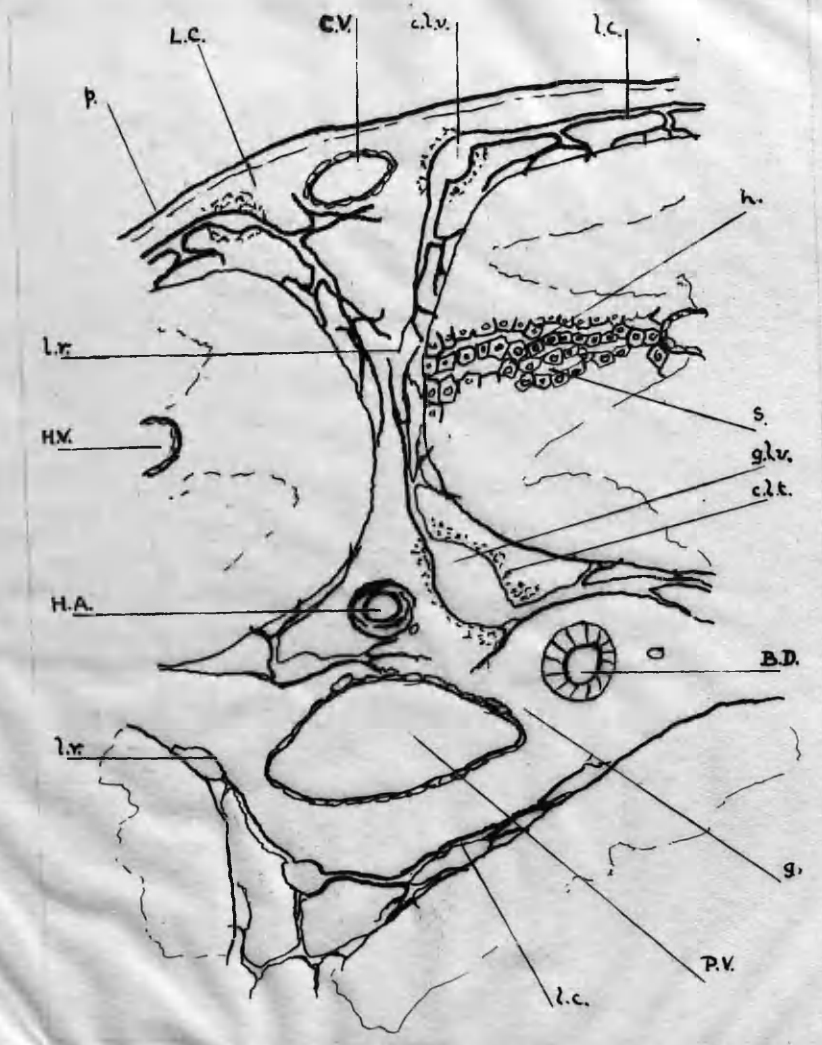
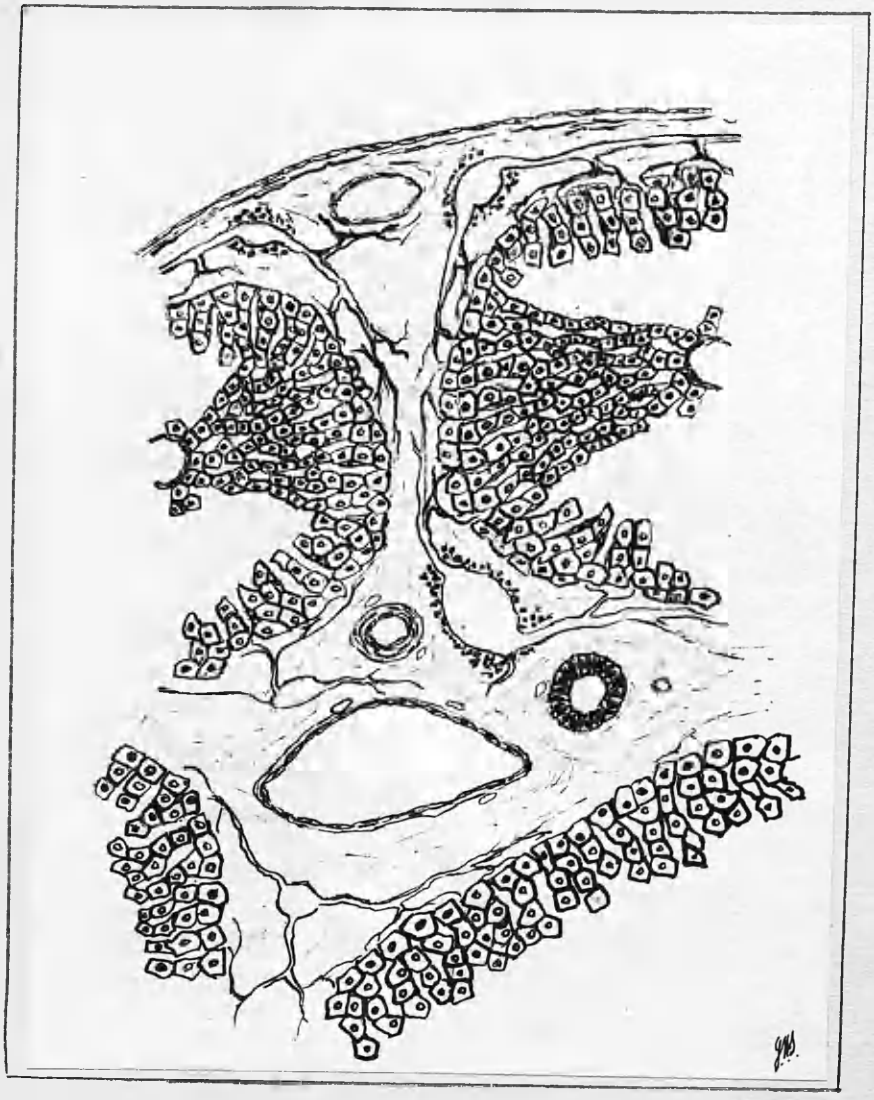
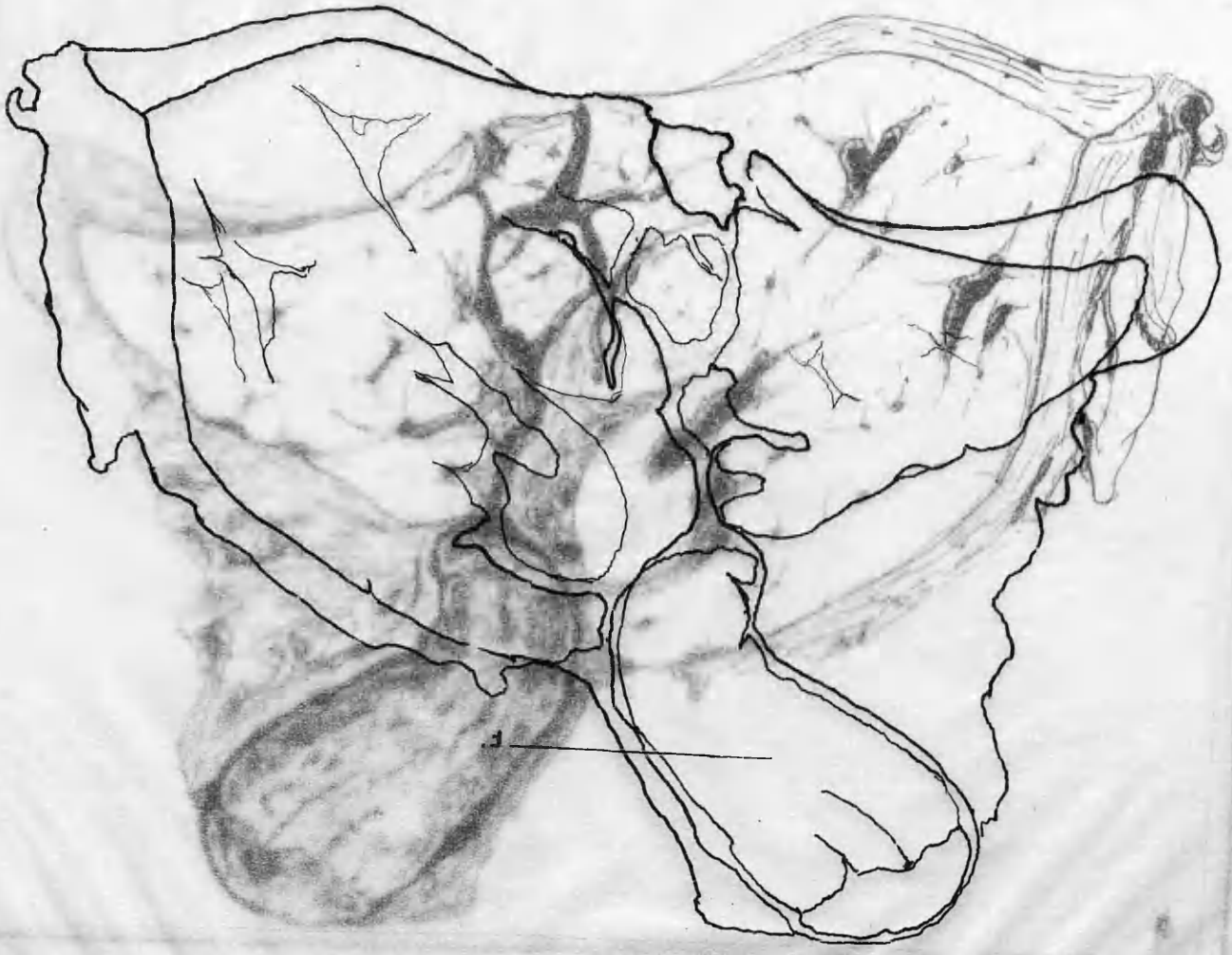


Fig. 2 - A diagrammatic representation of the anatomy of the liver, showing the relationship of the lymphatic vessels in Glisson's capsule to those of the hepatic capsule, and the relationship of each of these to the liver lobule.

P.V. - branch of portal vein; H.A. - branch of hepatic artery; B.D. - small bile duct; H.V. - central vein of hepatic lobule; C.V. - capsular vein; L.C. - Liver capsule; p. - peritoneum covering liver; g. - Glisson's capsule; h. - hepatic cells; s. - blood sinusoids.

c.l.v. - capsular lymphatic vessel; g.l.v. - lymphatic vessel in Glisson's capsule; c.l.t. - collection of lymphoid tissue surrounding lymph vessel; l.c. - lymphatic capillary; l.r. - lymphatic radicle.





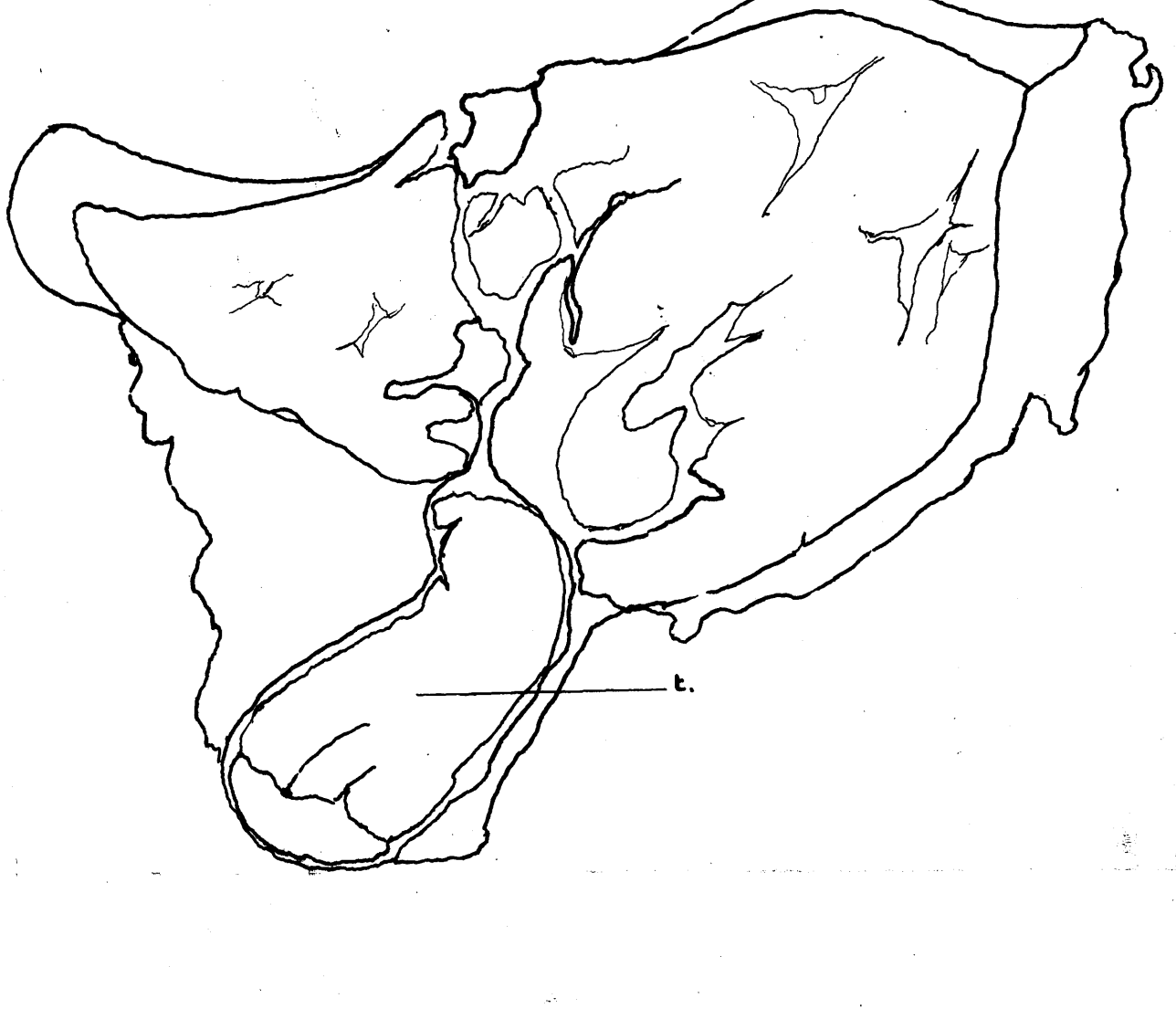
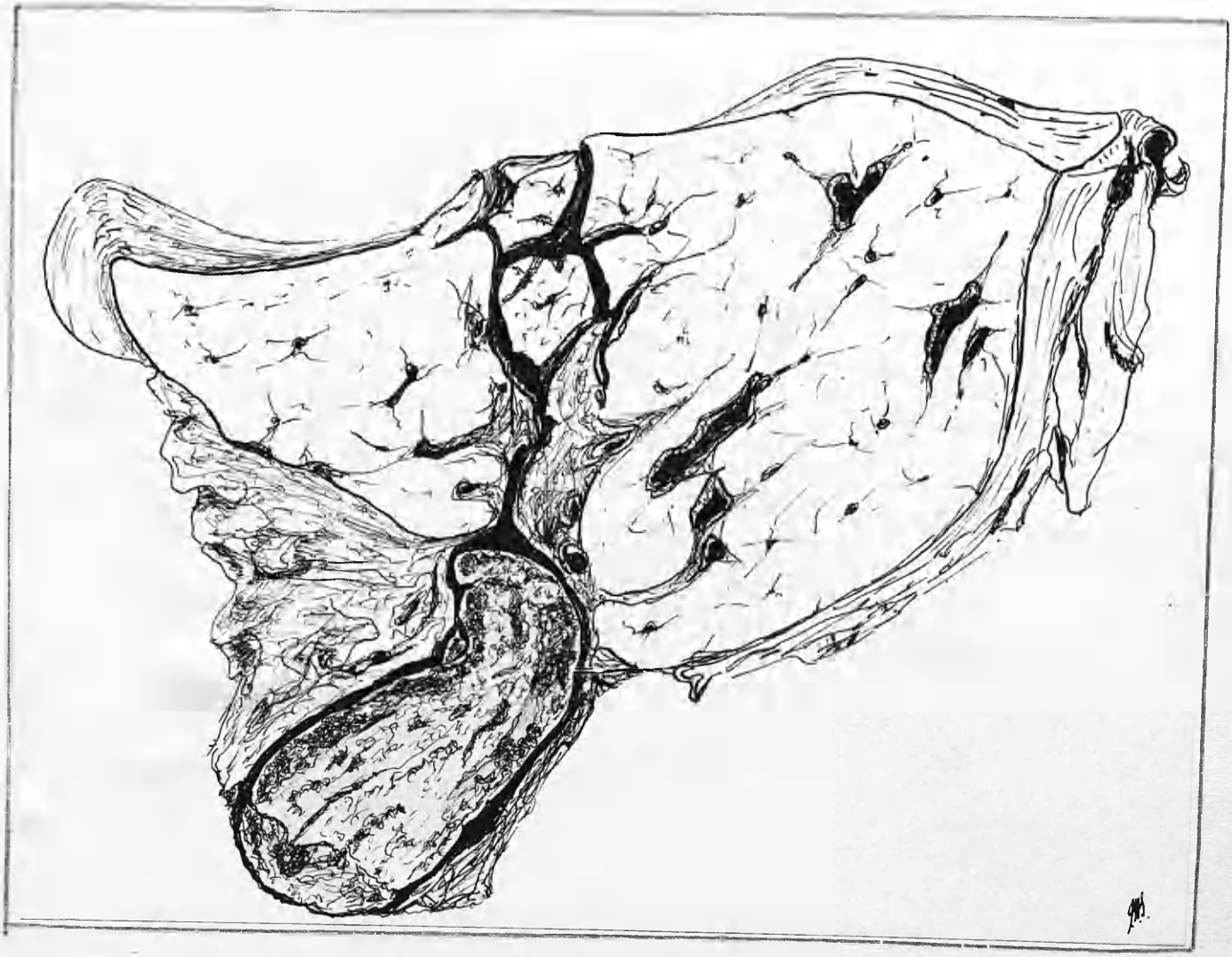
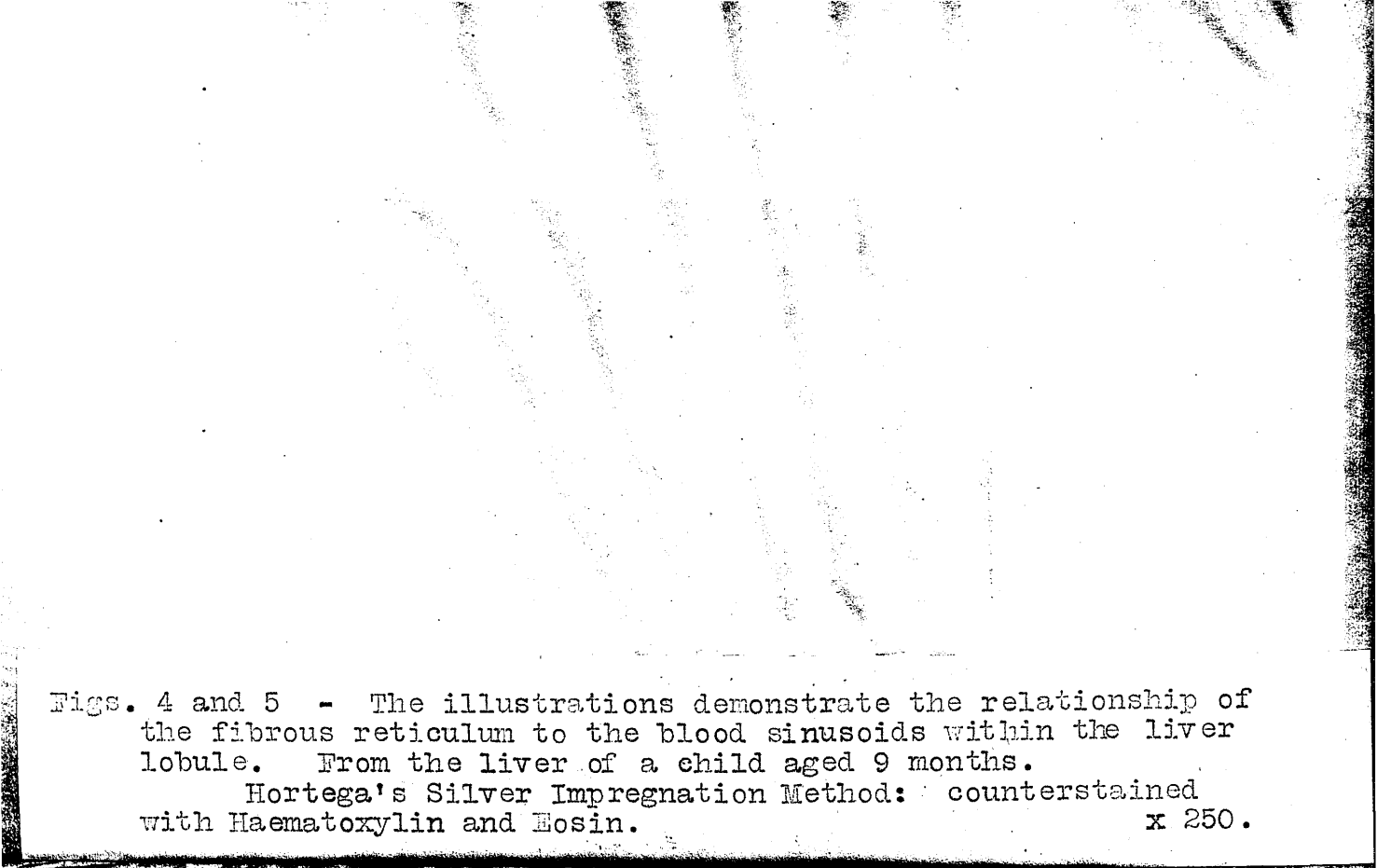


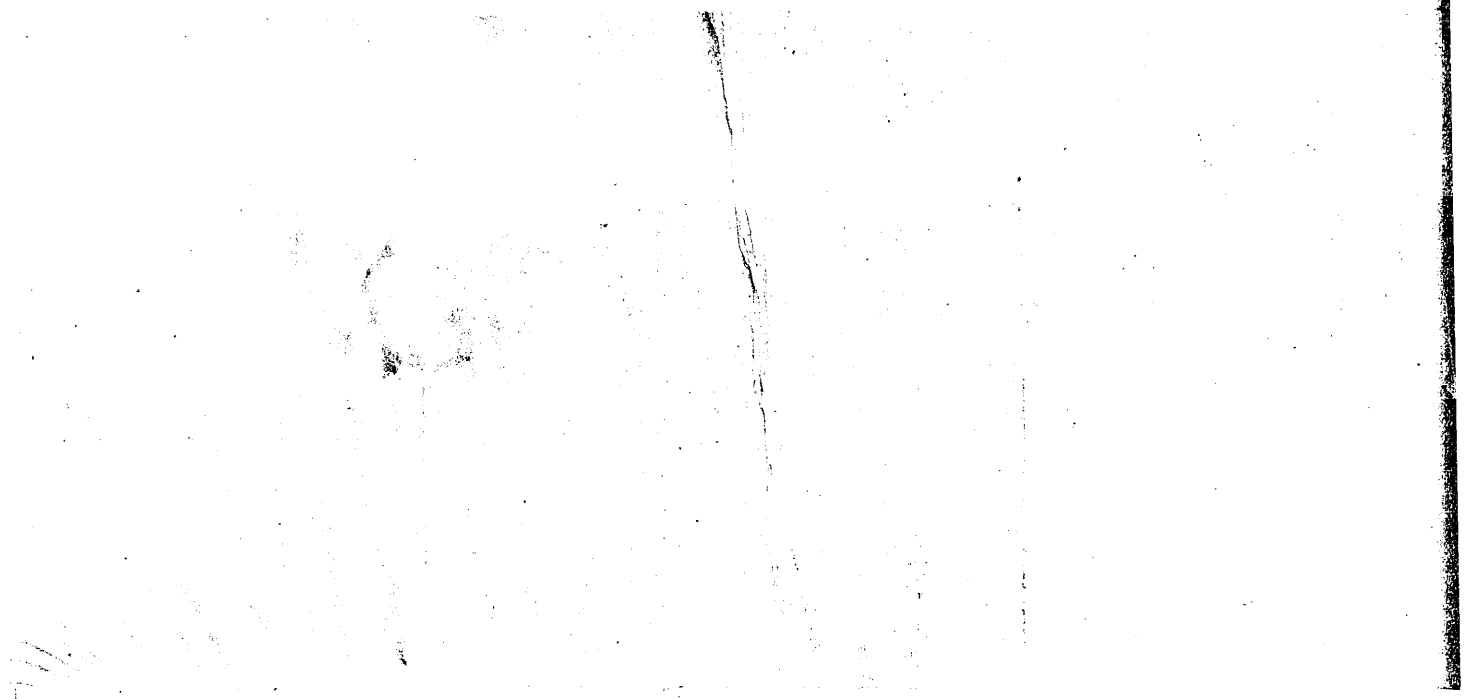
Fig. 3 - The illustration shows massive permeation by carcinomatous tissue along the lumen of the portal vein in the hilum of the liver. This had resulted from invasion of the portal vein from the primary growth.

Only one small subcapsular secondary tumour nodule was found in the liver. (Primary Carcinoma of the Pyloric end of Stomach).
t - tumour tissue in lumen of portal vein.





Figs. 4 and 5 - The illustrations demonstrate the relationship of the fibrous reticulum to the blood sinusoids within the liver lobule. From the liver of a child aged 9 months.
Hortega's Silver Impregnation Method: counterstained with Haematoxylin and Eosin. x 250.



Figs. 6 and 7 - Enlargements from Figs. 4 and 5. These show the denser reticular fibres running parallel to the endothelial lining of the blood sinusoids while the finer reticular fibres form an interlacing network around the sinusoids. Fine fibres extend for a short distance over the surface of the liver cell columns.

Hortega's Silver Impregnation Method: counterstained with Haematoxylin and Eosin. x 350.

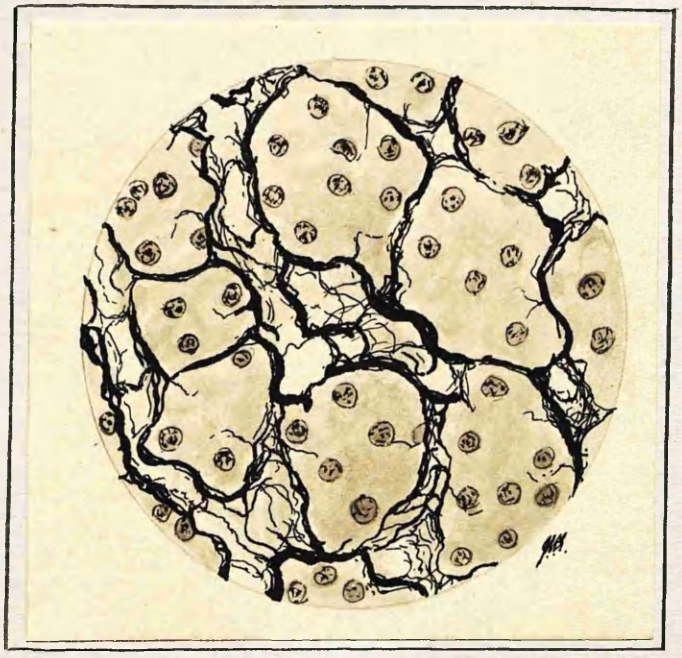
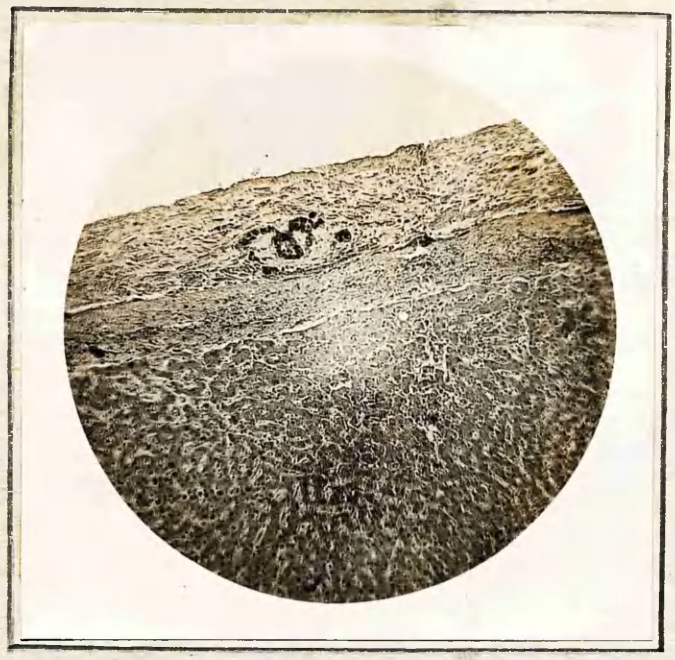


Fig. 8 - Invasion of the Liver by the Capsular Route.
Tumour cells are seen in the capsular lymphatic vessels.
(Primary Carcinoma of Bronchus).

H. and E. x 75.

Fig. 9 - Invasion of the Liver by the Capsular Route.
The illustration is from the same case as Fig. 8. A further stage in the invasion of the liver is shown. Indentation of the hepatic substance has resulted from the proliferation of the neoplastic cells in a capsular lymphatic space. The capsular blood vessel is not involved in the carcinomatous process. (Primary Carcinoma of Bronchus).

H. and E. x 75.



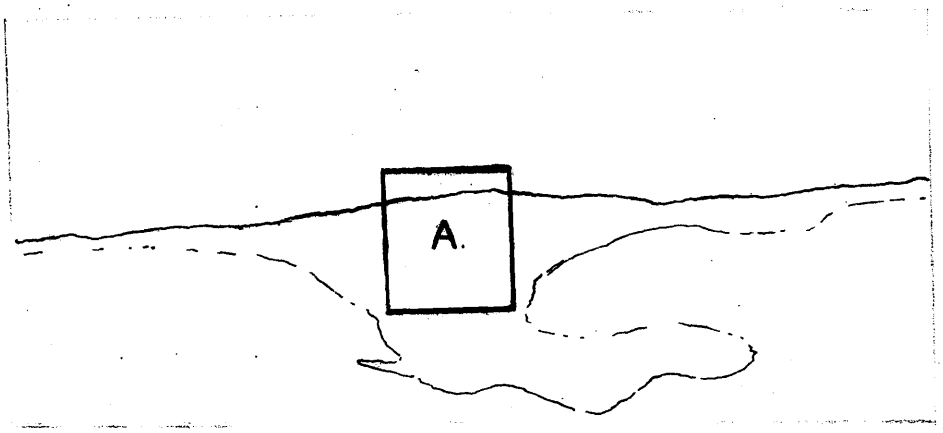
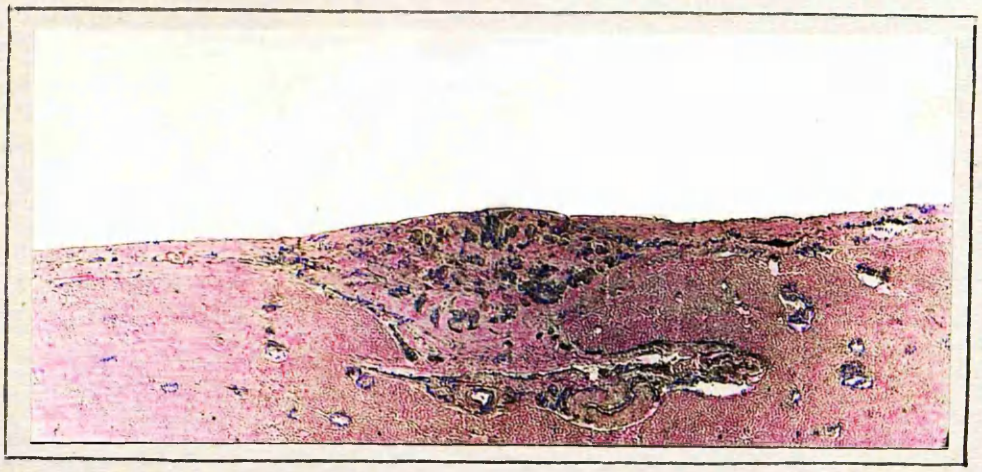


Fig. 10 - Invasion of the Liver by the Capsular Route.
The illustration is from the same case as Figs. 8 and 9 and shows an early secondary carcinomatous nodule. Here extension has occurred along the lymphatic channels of Glisson's Capsule to an adjacent portal tract. (Primary Carcinoma of Bronchus).
H. and E. x 10.

Fig. 11 - Invasion of the Liver by the Capsular Route.
Enlargement of the portion of the tumour nodule marked A in Fig.10. In the upper part of the field the neoplastic cells are in the capsular lymphatic channels. (Primary Carcinoma of Bronchus).
H. and E. x 80.



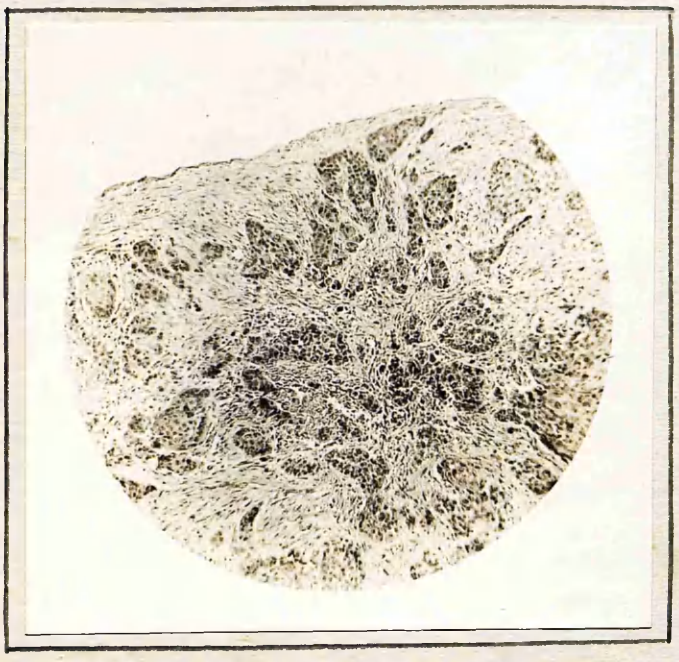


Fig. 12 - Invasion of the Liver by the Capsular Route.
The capsular lymphatic vessels and lymphatic spaces contain neoplastic cells. Carcinomatous infiltration of the lymphatic channels in Glisson's Capsule is illustrated in the lower part of the field. (Primary Carcinoma of the Gall bladder).
H. and E. x 75.

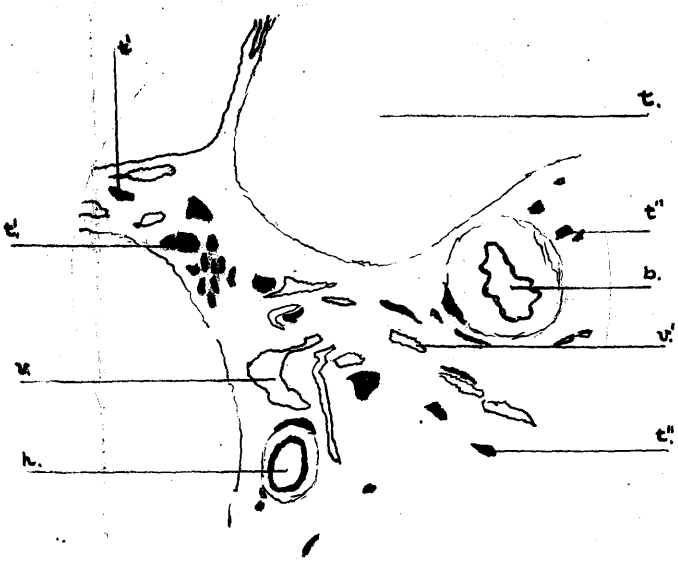


Fig. 13 - Invasion of the Liver by the Capsular Route.
In the upper part of the field is a subcapsular tumour nodule. The capsular lymphatic channels and those in relation to the bile duct, hepatic artery, and portal vein are invaded by carcinoma cells. (Primary Carcinoma of the Head of the Pancreas).
t, t', t" - tumour tissue; b - bile duct; h - hepatic artery; v, v' - portal vein.
H. and E. x 75.

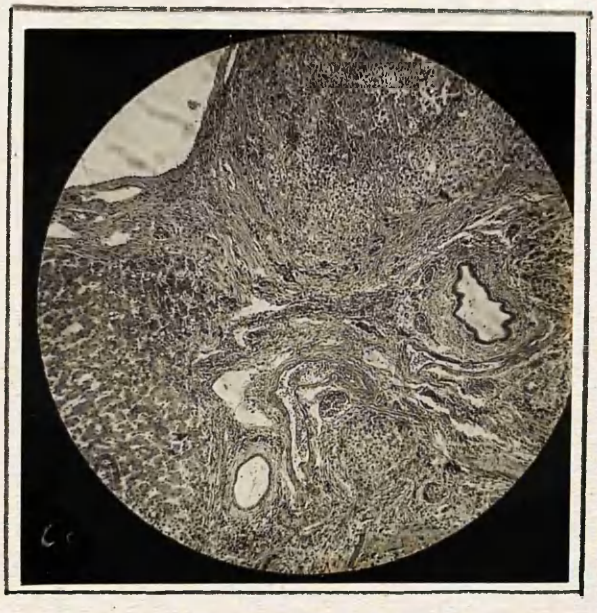


Fig. 14 - Invasion of the Liver by the Capsular Route.
In the upper part of the field neoplastic cells are seen in the lymphatic channels and tissue spaces of the fatty areolar tissues in the hilum of the liver; in the middle part of the field the lymphatic channels in the liver capsule contain tumour cells; in the lower left part are seen the first stage in the process of invasion of the actual hepatic substance, cf. Fig. 9. (Primary Carcinoma of Bronchus).

H. and E. x 80.

Fig. 15 - Spread by Lymphatic Channels.
Carcinomatous infiltration of the hilar tissues of the liver. In the upper part of the field the lymphatic channels have been invaded by tumour cells. Between them and the hepatic substance are several small bile ducts. The epithelial lining cells of the latter are less deeply stained than those of the carcinoma. (Primary "Pleural Endothelioma").

H. and E. x 100.

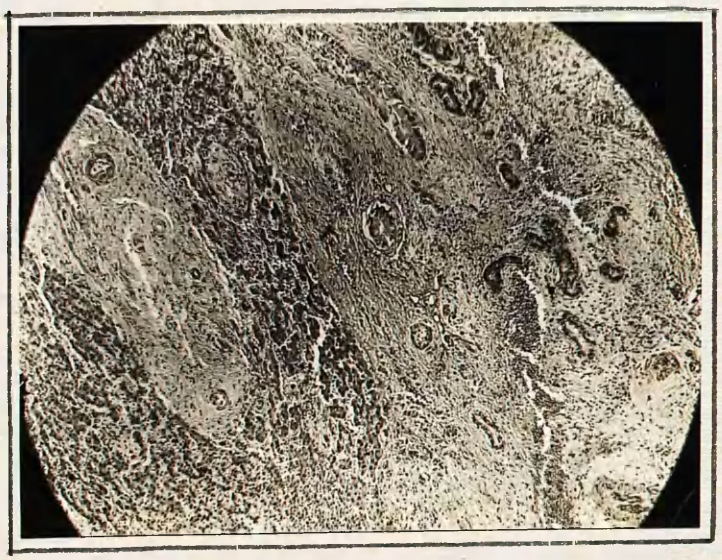


Fig. 16 - Spread by Lymphatic Channels.
Carcinomatous infiltration of the lymphatic channels and tissue spaces in the suspensory ligaments of the liver is demonstrated. (Primary "Pleural Endothelioma").

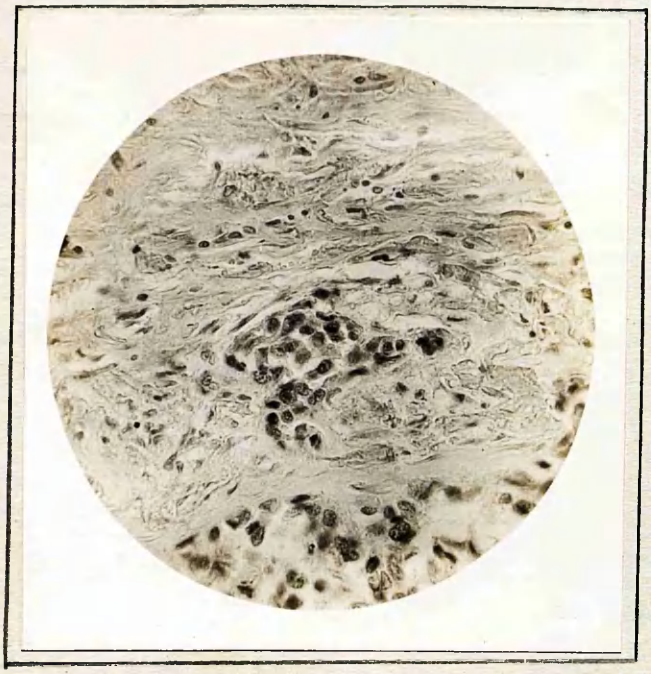
H. and E. x 80.

Fig. 17 - Spread by Lymphatic Channels.
Enlargement from Fig. 16. Invasion of the perineural sheath of a small nerve trunk in the suspensory ligaments of the liver. (Primary "Pleural Endothelioma").

H. and E. x 350.

Fig. 18 - Spread by Lymphatic Channels.
Neoplastic cells have infiltrated along the perivascular and perineural sheaths in the hilum of the liver. The wall of the blood vessel in the upper part of the field and the small nerve trunk in the lower part of the field have been cut in longitudinal section. (Primary Carcinoma of the Gall Bladder).
H. and E. x 50.

Fig. 19 - Spread by Lymphatic Channels.
A small group of neoplastic cells is seen in a connective tissue space in the hilum of the liver. (Primary Carcinoma of bronchus).
H. and E. x 250.



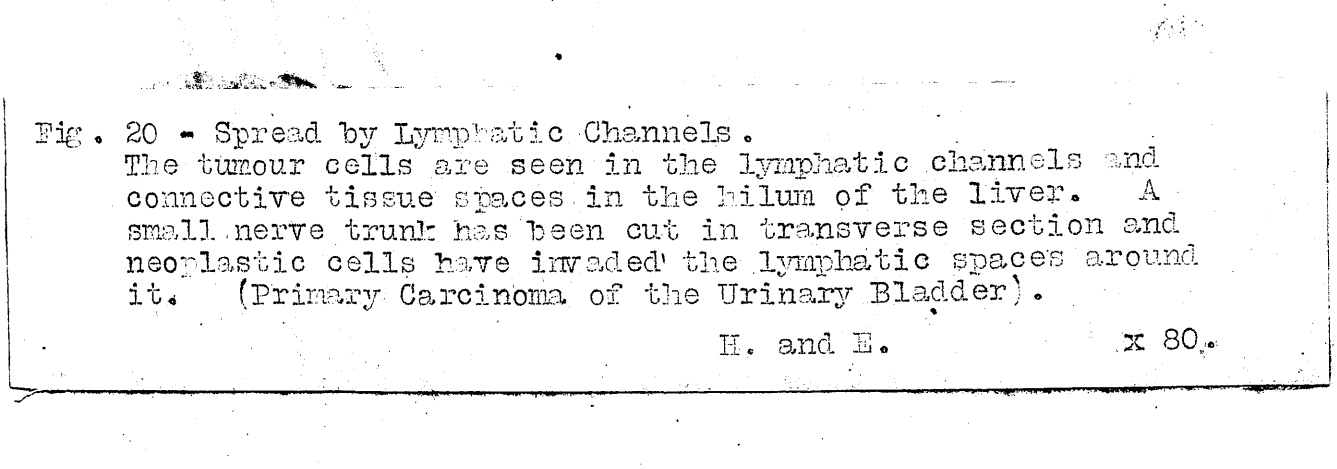


Fig. 20 - Spread by Lymphatic Channels.
The tumour cells are seen in the lymphatic channels and connective tissue spaces in the hilum of the liver. A small nerve trunk has been cut in transverse section and neoplastic cells have invaded the lymphatic spaces around it. (Primary Carcinoma of the Urinary Bladder).

H. and E. x 80.

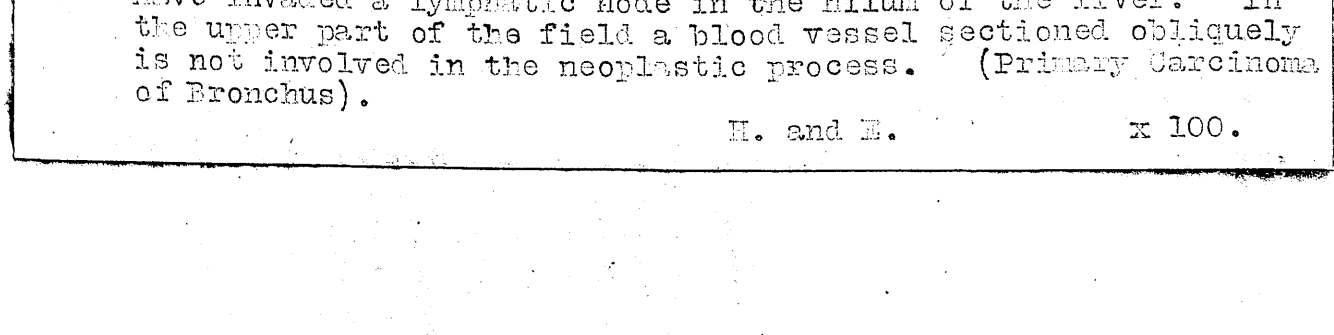
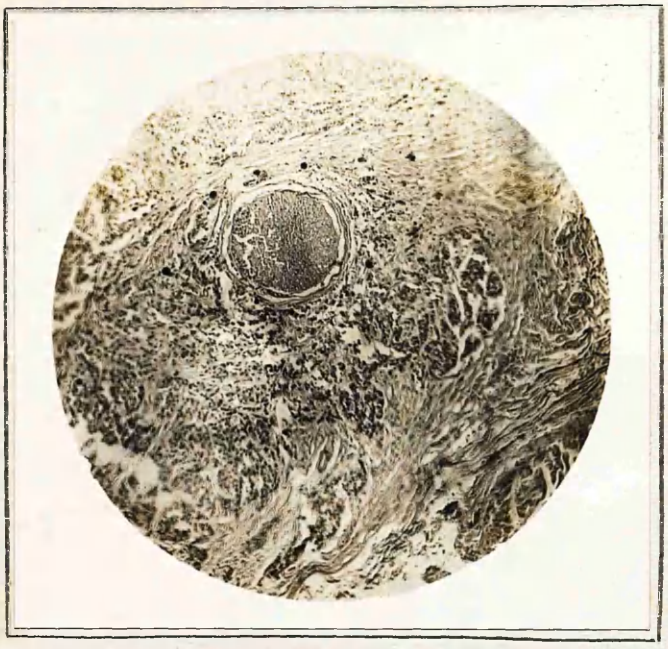


Fig. 21 - Invasion of a Lymphatic Node.
The tumour cells, which show little structural differentiation, have invaded a lymphatic node in the hilum of the liver. In the upper part of the field a blood vessel sectioned obliquely is not involved in the neoplastic process. (Primary Carcinoma of Bronchus).

H. and E. x 100.



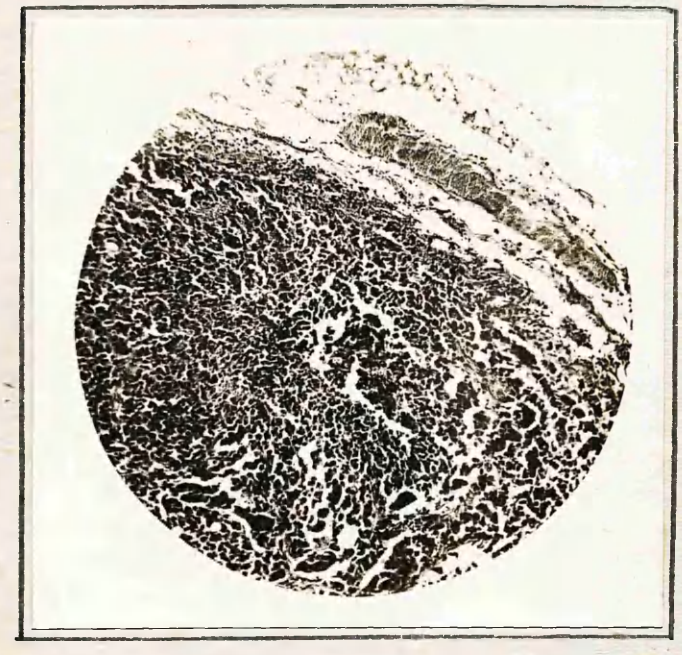
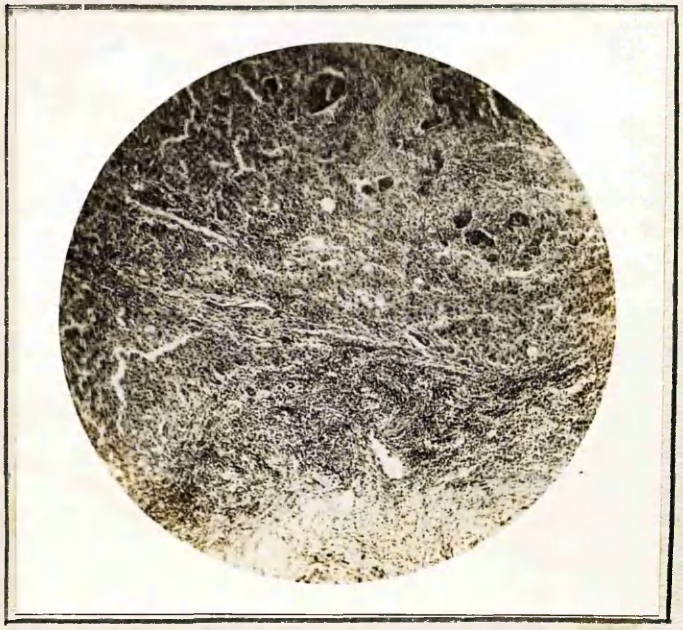


Fig. 22 - Invasion of the Liver by the Hilar Route.
The illustration shows diffuse carcinomatous infiltration of the lymphatic channels in the hilar connective tissues. The liver cells in the upper part of the field are vacuolated. (Primary Carcinoma of the Extra-Hepatic Bile Ducts).
H. and E. x 50.

Fig. 23 - Invasion of the Liver by the Hilar Route.
Neoplastic cells from the hilum of the liver have invaded the lymphatic channels of Glisson's capsule. (Primary Carcinoma of the Head of Pancreas).
t, t' - tumour cells in the lymphatic channels of Glisson's capsule; c - liver hilar connective tissues; h - liver cells.
H. and E. x 50



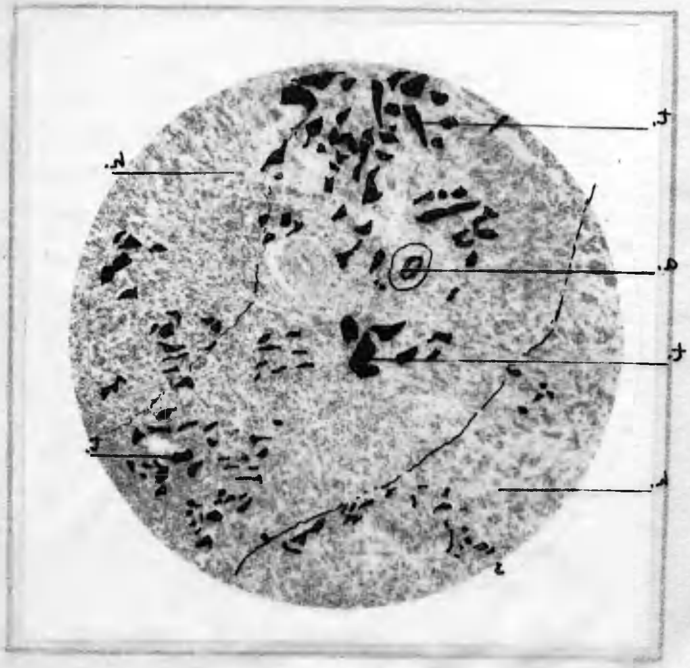
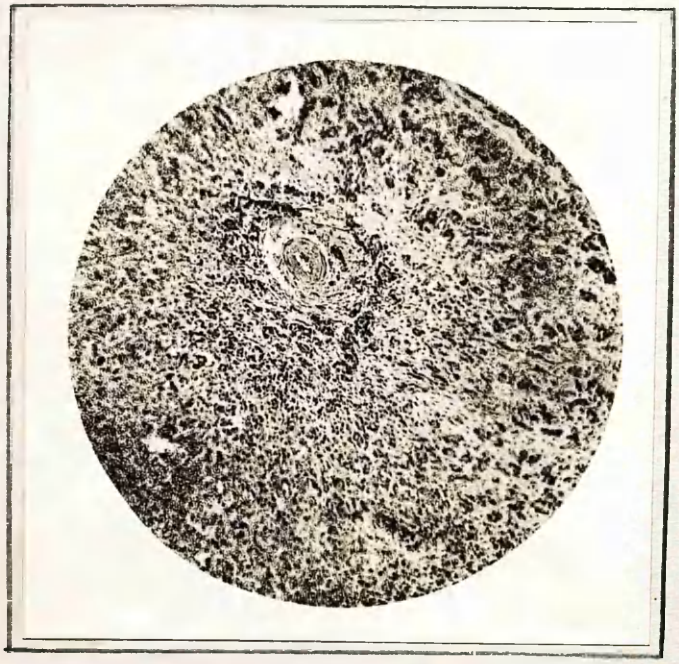


Fig. 24 - Invasion of the Liver by the Hilar Route.
The liver substance has been diffusely invaded from the lymphatic channels in the hilar connective tissues. The small round mononucleated cell reaction is conspicuous. The small artery in the upper part of the field is not involved in the carcinomatous process. (Primary Carcinoma of the Gall Bladder).
t, t' - tumour tissue; h - liver tissue; a - artery.
H. and E. x 80.



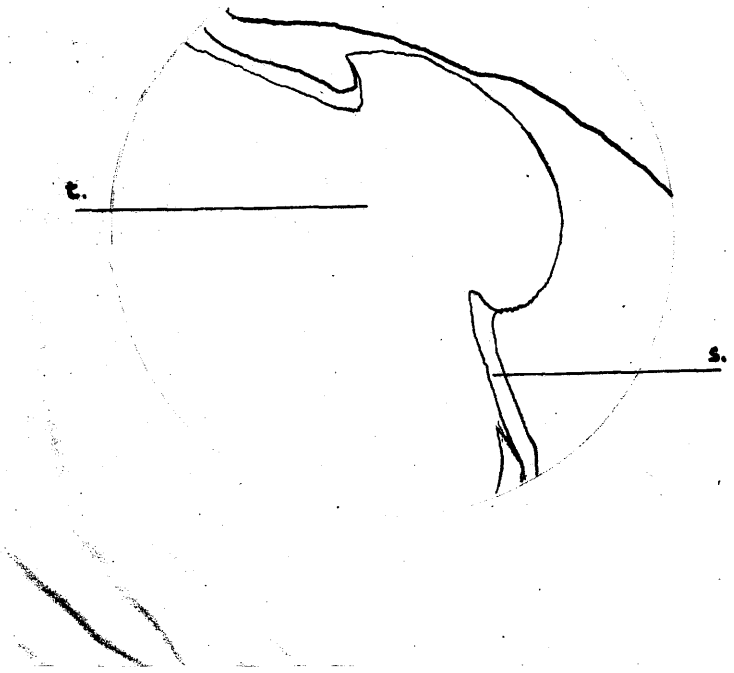


Fig. 25 - Pseudo-capsule Formation.
Around the periphery of the tumour nodule the liver cells are compressed forming a pseudo-capsule. In the upper left part of the field, beyond the pseudo-capsule, the blood sinusoids are dilated. In this illustration extension of the tumour is by expansive growth. (Primary Carcinoma of the Prostate Gland).
t - tumour tissue; s - pseudo-capsule.
H. and E. x 75.

Fig. 26 - Pseudo-capsule Formation.
The same process is shown as in Fig. 25. (Primary Liver Cell Carcinoma).
H. and E. x 75.

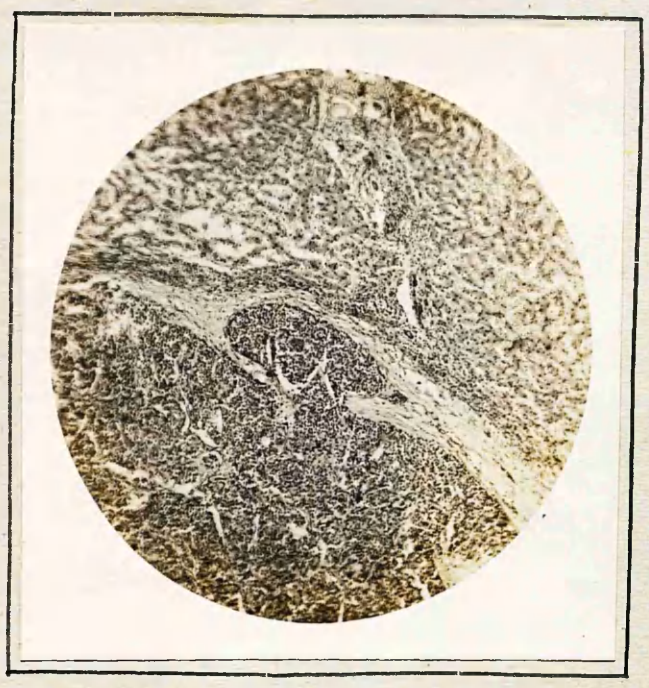


Fig. 27 - Invasion of Blood Vessels within the Liver.
The wall of a relatively large branch of the portal vein has been invaded. The neoplastic cells have proliferated within the muscular coat of the blood vessel and a small thrombus has formed on its endothelial surface. (Primary Carcinoma of the Urinary Bladder).

H. and E. x 80.

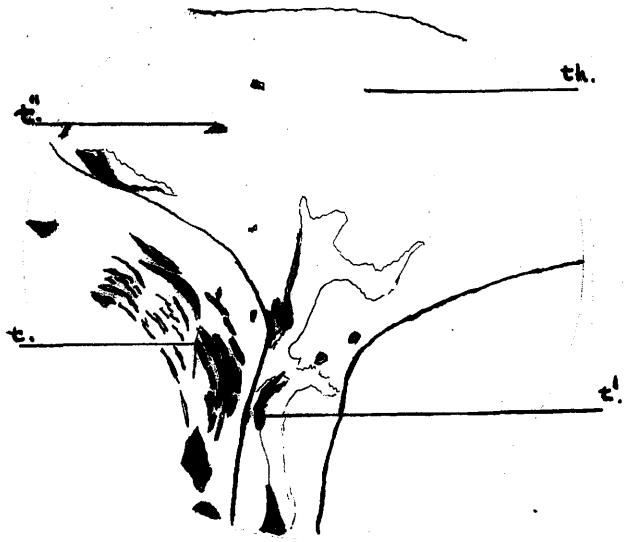
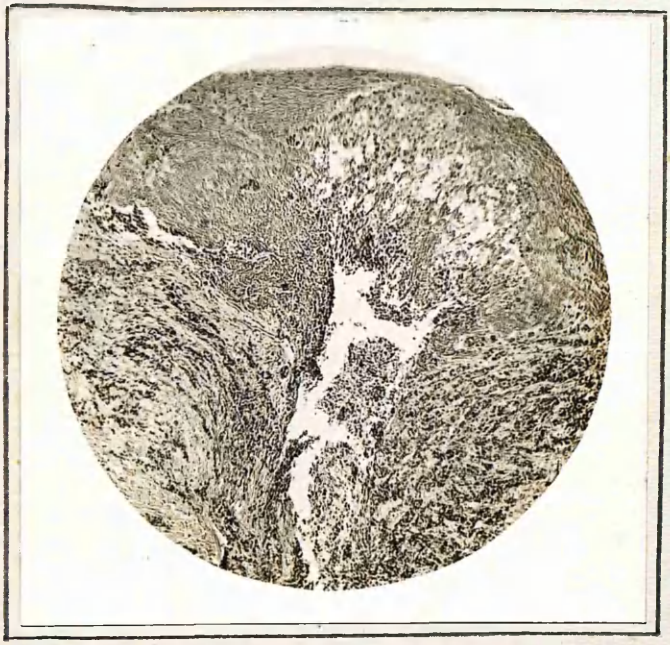


Fig. 28 - Invasion of Blood Vessels within the Liver.
A thrombus has formed over the mouth of a branch of the portal vein. Tumour cells, having infiltrated through the wall of the blood vessel, are seen in its lumen and are invading the thrombus. (Primary Carcinoma of the Urinary Bladder).
t - tumour cells in the blood vessel wall; t' - in the lumen of the vessel and t" - invading the thrombus; th - thrombus.

H. and E. x 80.



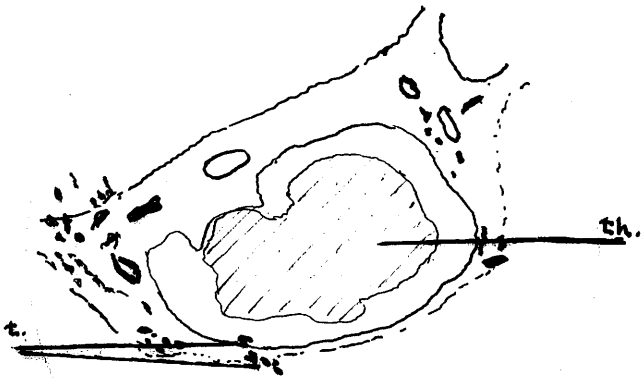


Fig. 29 - Invasion of Blood Vessels within the Liver.
A similar process is shown to that illustrated in Fig. 28. The neoplastic cells have invaded the wall of a portal vein and a thrombus has formed within the blood vessel. The hepatic artery and bile duct are not invqlved in the neoplastic process. (Primary Carcinoma of the Urinary Bladder).
t - invading tumour cells; th - thrombus.
H. and E. x 80.

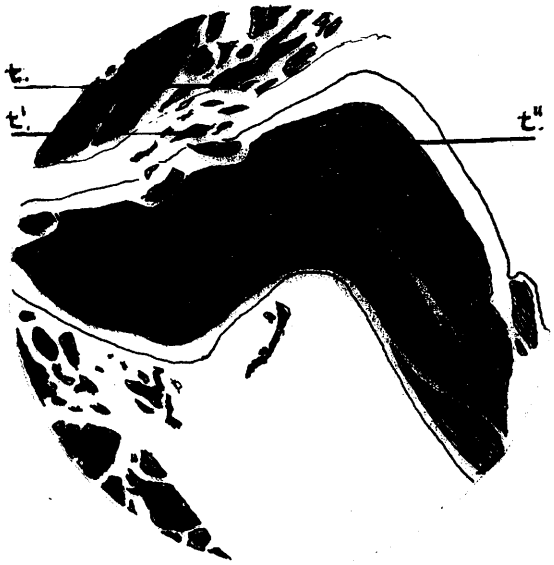


Fig. 30 - Invasion of Blood Vessels within the Liver.
Tumour cells from an adjacent neoplastic nodule have invaded the wall of a branch of the portal vein and have proliferated within its lumen. (Primary Liver Cell Carcinoma).
t - tumour nodule, t' - tumour cells in the blood vessel wall, t" - tumour cells within lumen of the portal vein.
H. and E. x 75.

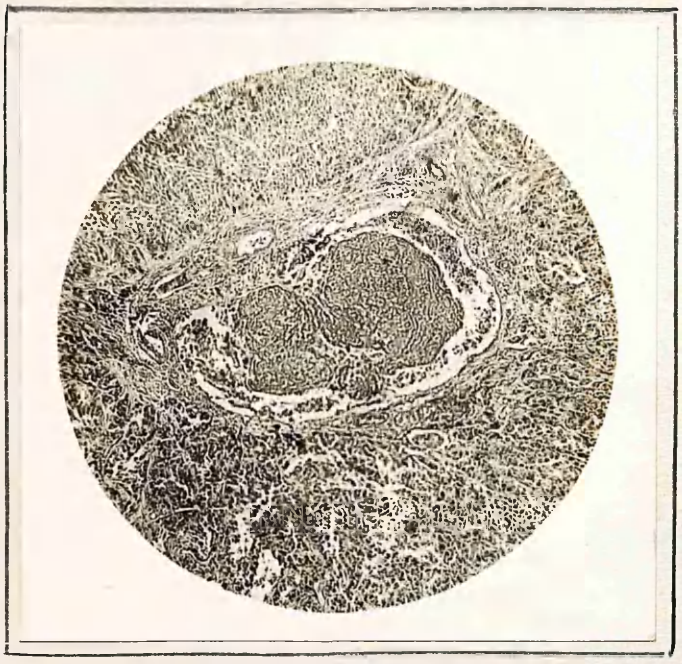


Fig.31 - Spread within the Liver by Lymphatic Channels.
The periportal lymphatic channels contain neoplastic cells.
(Primary Carcinoma of the Head of the Pancreas).
t - tumour tissue; a - hepatic artery; p - portal vein.
H. and E. x 50.

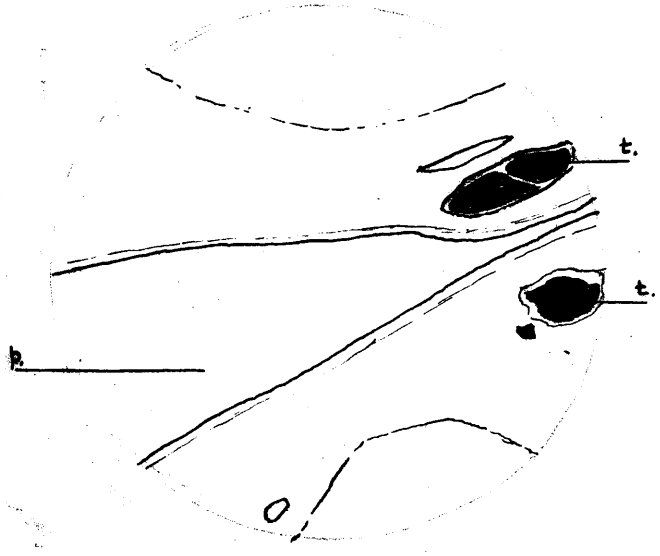


Fig. 32 - Spread within the Liver by Lymphatic Channels.
The periportal lymphatic vessels are invaded by neoplastic cells.
(Primary Carcinoma of the Head of the Pancreas).
t - tumour tissue; p - portal vein.
H. and E. x 50.

Fig. 33 - Spread within the Liver by Lymphatic Channels.
The lymphatic channels around the bile duct have been invaded by tumour cells. (Primary Carcinoma of the Pancreas).
t - tumour cells; b - bile duct.
H. and E. x 80.

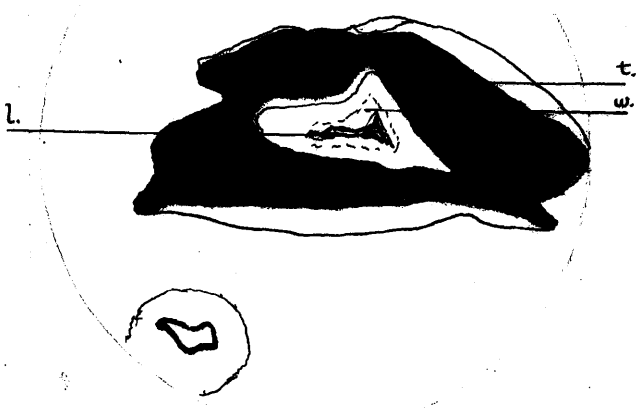


Fig. 34 - Spread within the Liver by Lymphatic Channels.
Tumour cells have invaded the perivascular sheath of a portal vein in Glisson's Capsule. The wall of the vein is almost completely collapsed. A hepatic artery is seen in the lower left part of the field. (Primary Carcinoma of the Oesophagus).
t - mass of tumour cells; l - lumen of portal vein;
w - wall of vein.
H. and E. x 200.

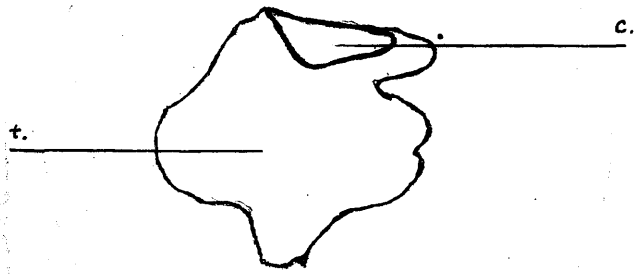
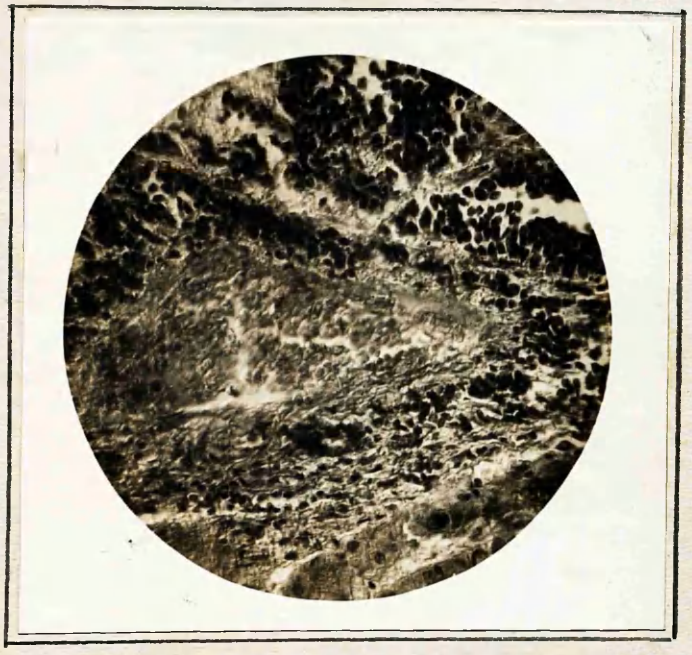


Fig. 35 - Spread within the Liver by Lymphatic Vessels.
The small tumour nodule has arisen in relation to a branch of the hepatic vein. The lumen of the blood vessel has not been invaded by neoplastic cells. (Primary Carcinoma of Bronchus).
c - hepatic vein; t - tumour tissue.
H. and E. x 50.

Fig. 36 - Spread within the Liver by Lymphatic Vessels.
Enlargement from Fig. 35. The perivascular lymphatic vessels are invaded. Extension has occurred into and has replaced the hepatic substance in the upper part of the field. (Primary Carcinoma of Bronchus).
H. and E. x 200.



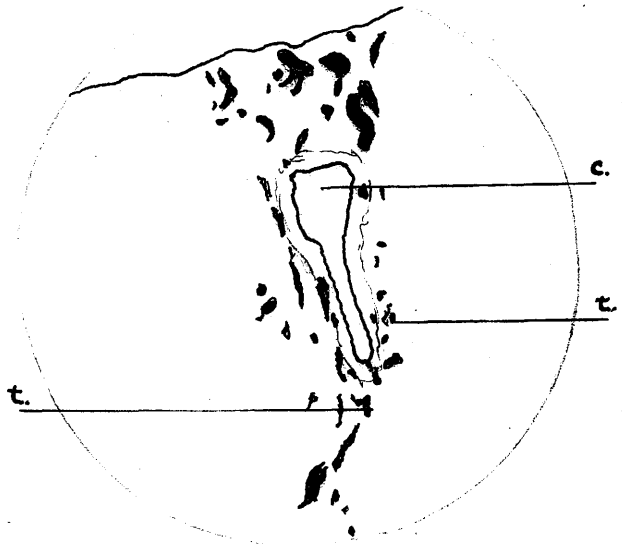


Fig. 37 - Spread within the Liver by Lymphatic Vessels.
Tumour cells are present in the perivascular lymphatic channels around a branch of a hepatic vein. (Primary Liver Cell Carcinoma).
t - tumour tissue; c - hepatic vein.
H. and E. x 80.

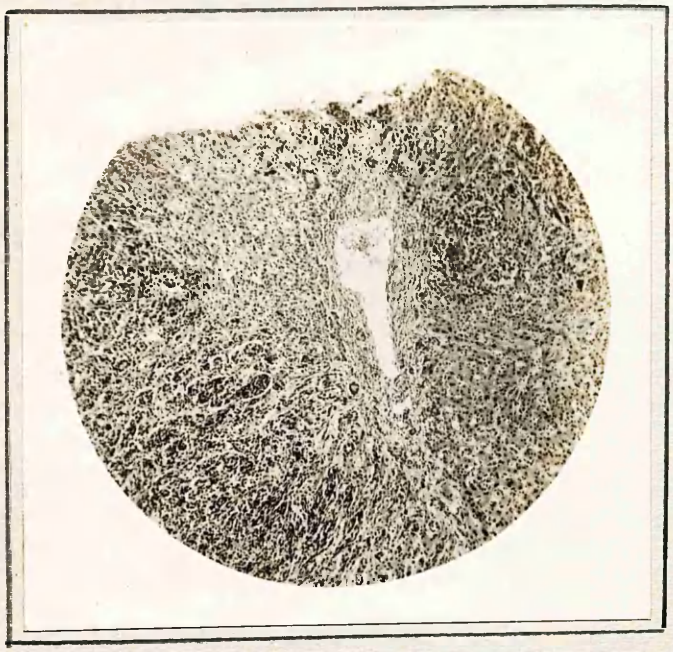
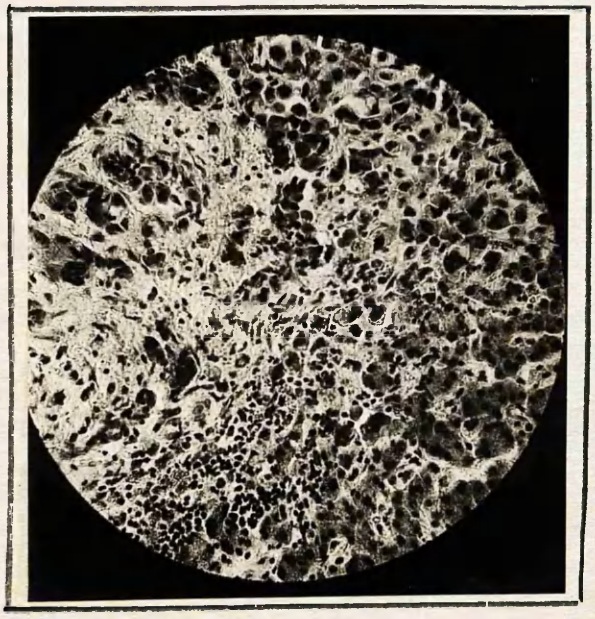


Fig. 38 - Spread within the Liver by Lymphatic Channels.
The perilobular lymphatic vessels are invaded by tumour cells. The lumina of the portal vein, hepatic artery and bile duct do not contain neoplastic tissue. (Primary Carcinoma of the Head of the Pancreas).

H. and E. x 50.

Fig. 39 - Invasion of the Liver Lobule.
The tumour cells invading the periphery of the hepatic lobule are seen on the left of the field. A marked small round mononucleated cell reaction is present. (Primary Carcinoma of the Gall Bladder).
t - tumour tissue; h - hepatic tissue.

H. and E. x 250.



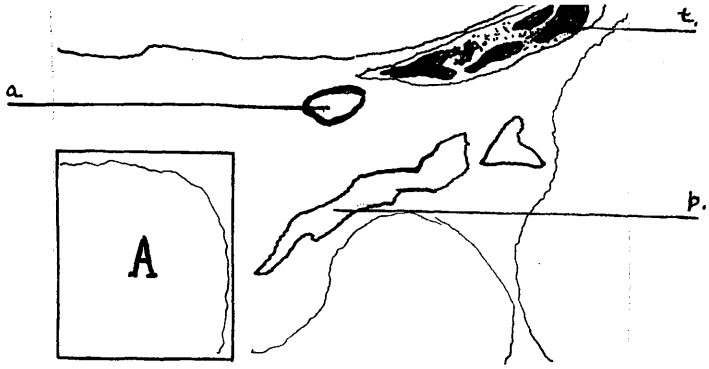
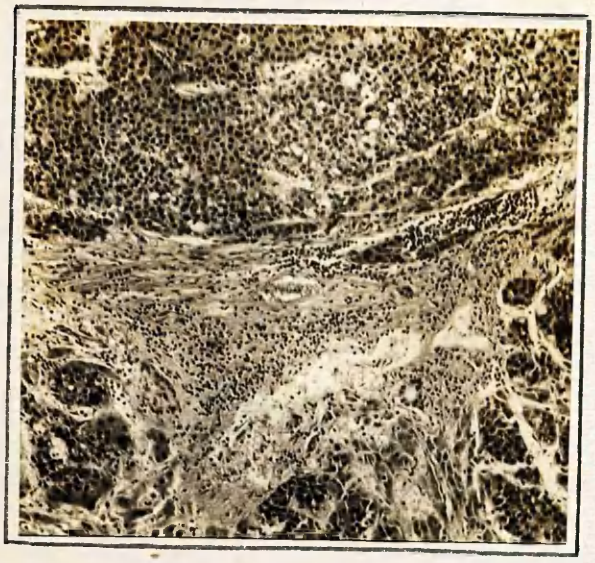


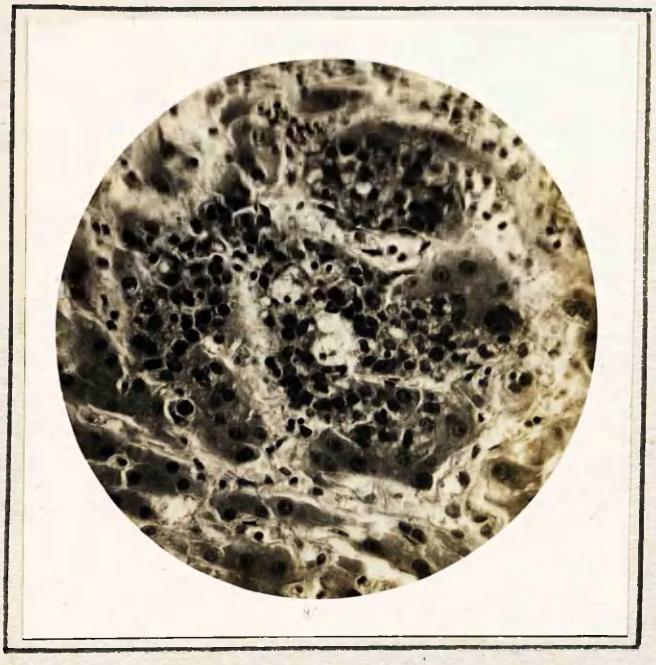
Fig. 40 - Spread within the Liver by Lymphatic Channels.
Tumour cells are demonstrated in a lymphatic sinus in Glisson's Capsule. The main tumour mass is in the upper part of the field. The hepatic artery and portal vein are not invaded in the neoplastic process. There is a small round mononucleated cell reaction and an increase in fibrous tissue in Glisson's Capsule. (Primary Carcinoma of Bronchus).
t' - tumour cells in lymphatic sinus; a - hepatic artery;
p - portal vein.

H. and E. x 100.

Fig. 41 - Spread within the Liver Lobule.
Enlargement of section A in Fig. 40. The neoplastic cells have infiltrated between the liver cells and the endothelial lining of the blood sinusoids but have not invaded the lumina of the blood sinusoids; several Küpffer cells can be seen between the masses of neoplastic cells and the lumina of the blood sinusoids. (Primary Carcinoma of Bronchus).
t - tumour cells; h - liver cells; k - Küpffer cells;
s - lumina of blood sinusoids.

H. and E. x 280.





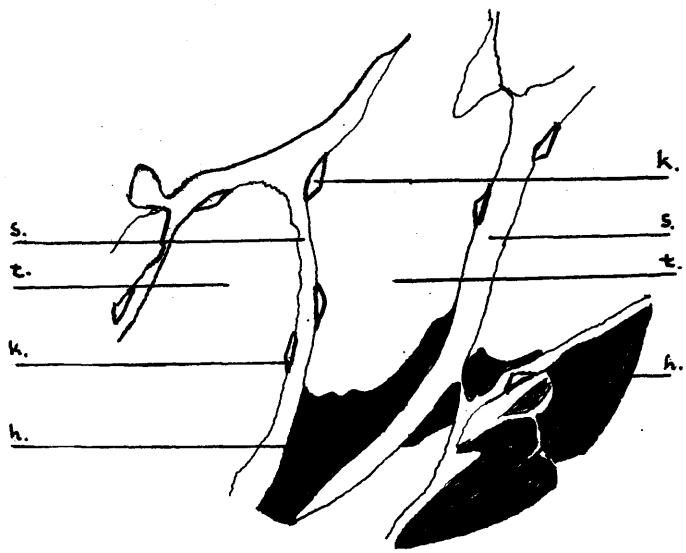


Fig. 42 - Spread within the Liver Lobule.
From the same case as Figs. 40 and 41. The carcinomatous cells have infiltrated between a column of liver cells and the endothelial lining of a blood sinusoid. (Primary Carcinoma of Bronchus).
t - tumour cells; h - liver cells; k - Küpffer cells; s - blood sinusoids.

H. and E. x 300.

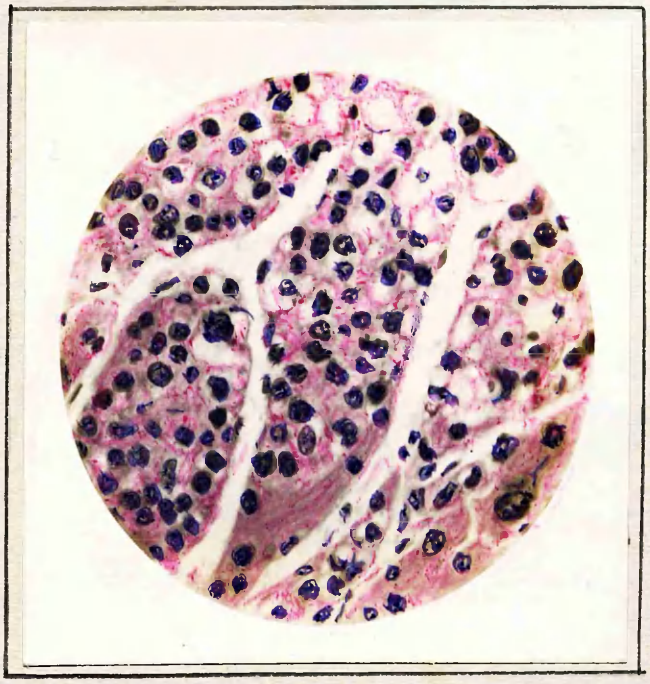


Fig. 43 - Spread within the Liver Lobule.
A further demonstration of the replacement of liver cell columns by carcinomatous cells. The blood sinusoids are patent and have not been involved in the neoplastic process. (Primary Carcinoma of the Head of the Pancreas).
t - tumour cells; h - liver cells; s - blood sinusoids;
k - Küpffer cells.

H. and E. x 300.

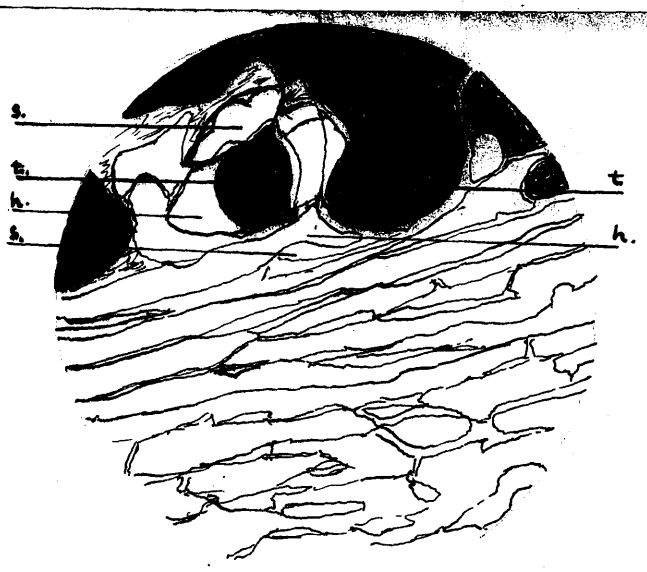
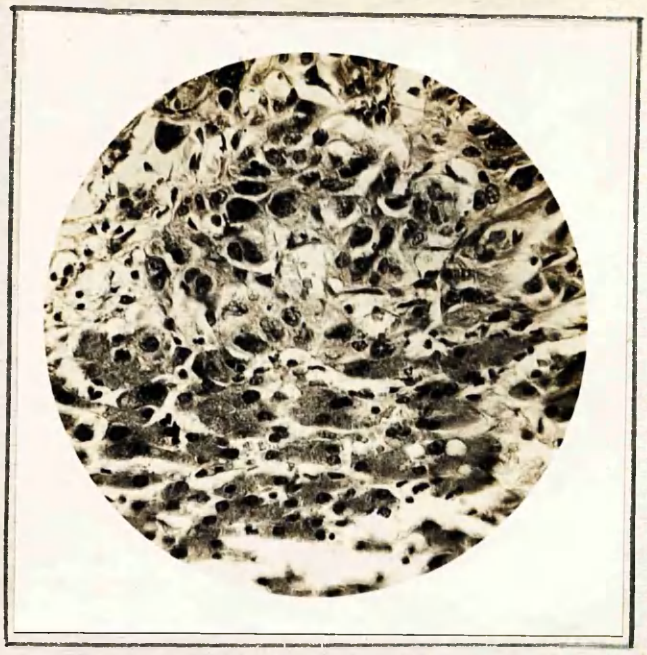
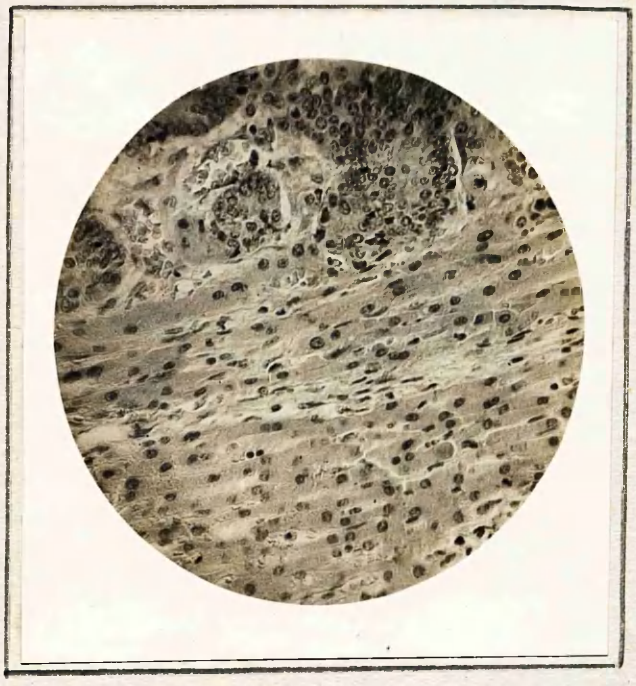


Fig. 44 - Spread within the Liver Lobule.
As in Fig. 41 and Fig. 43, the carcinomatous cells have infiltrated along the liver cell columns. In this instance the blood sinusoids have become partially collapsed and the compression of the hepatic cells has caused them to become elongated around the margin of the neoplastic nodule.
(Primary Carcinoma of the Sigmoid Colon).
t - tumour cells; h - liver cells; s - blood sinusoids.

H. and E. x 150.





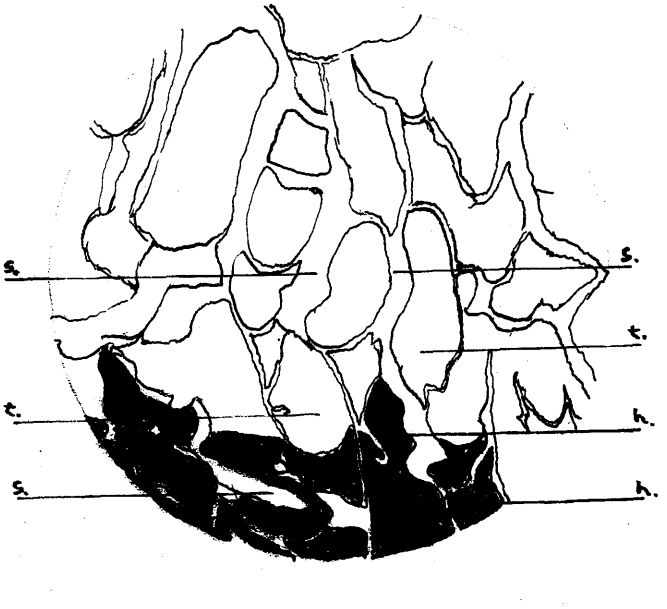
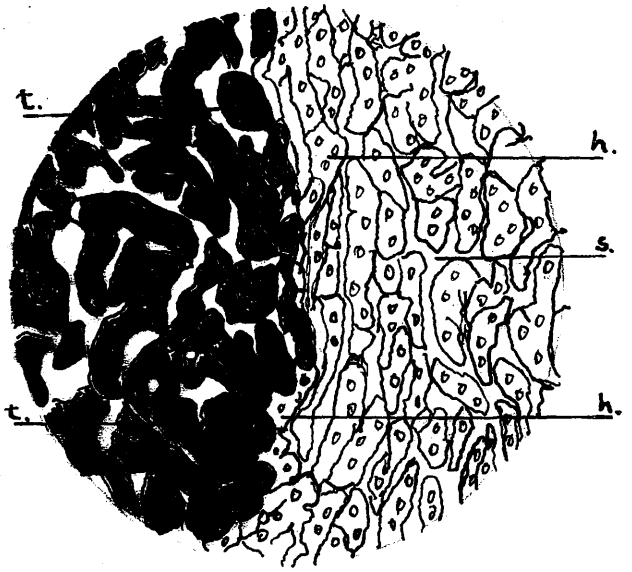
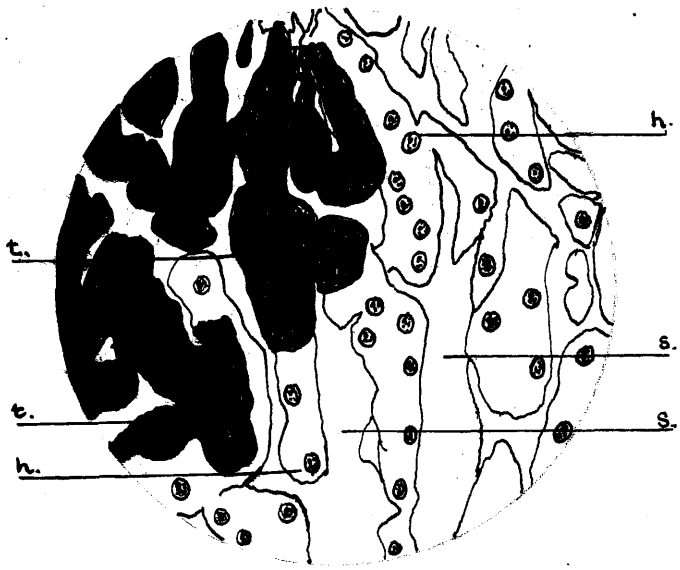


Fig. 45 - Spread within the Liver Lobule.
Replacement of the liver cell columns is shown, cf. Figs. 41 to 44. (Primary Carcinoma of Bronchus).
t - tumour cells; h - liver cells; s - blood sinusoids.
H. and E. x 150.

Fig. 46 - Spread within the Liver Lobule.
As in Fig. 44, the hepatic cells around the periphery of the neoplastic nodule have been compressed. The blood sinusoids are partially collapsed and the neoplastic cells have replaced the columns of liver cells, but they have not invaded the lumina of the blood sinusoids. (Primary Carcinoma of Bronchus).
H. and E. x 250.



Figs. 47 and 48 - Spread within the Liver Lobule.
The illustrations demonstrate the relationship of the intra-lobular fibrous reticulum to the blood sinusoids in a case of secondary carcinomatous invasion of the liver. (Primary Carcinoma of Bronchus).
t - tumour cells; h - liver cells; s - blood sinusoids.
Hortega's Silver Impregnation Method; counterstained with Haematoxylin and Eosin. x 250.



Figs. 49 and 50 - Spread within the Liver Lobule.
Enlargements from Figs. 47 and 48. The relationship of the fibrous reticulum to the blood sinusoids and the hepatic cells, and to the cells of the neoplasm is demonstrated in these illustrations. (Primary Carcinoma of Bronchus).
t - tumour cells; h - liver cells; s - blood sinusoids.
Hortega's Silver Impregnation Method; counterstained with Haematoxylin and Eosin. x 350.

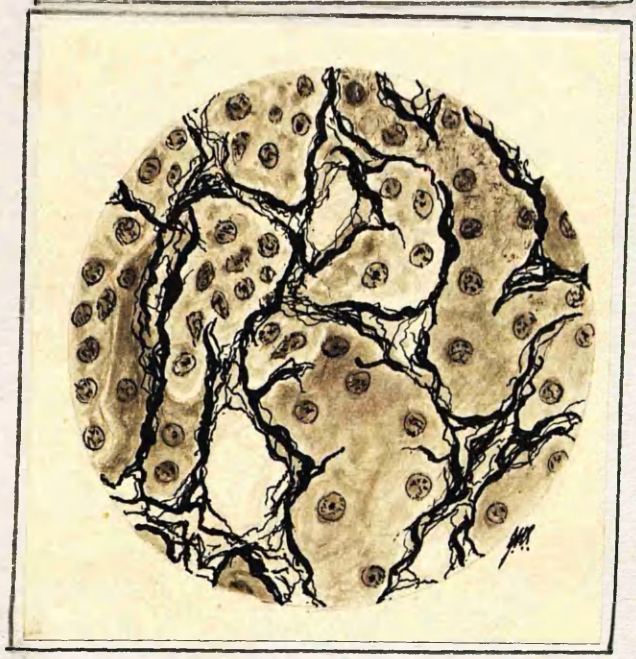


Fig. 51 - Spread within the Liver Lobule.

As in Figs. 41 - 46, the carcinomatous cells have infiltrated between the columns of liver cells and the endothelial lining of the blood sinusoids. (Primary Liver Cell Carcinoma).
H. and E. x 300.