ON PROLIFERATION OF THE CELLS OF THE LIVER.[1]

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(Plates XXXII.–XXXIV.)

Within the last few years I have had an opportunity of studying proliferation of the cells of the liver under various conditions, and the present paper contains the results of the observations made. If we exclude the case of new growths we may say that proliferation in the liver, in common with other tissues, is met with under two chief conditions, namely, (*a*) in repair following breach of continuity of structure, and (*b*) in compensatory hypertrophy and hyperplasia. The distinction between these two conditions is an important one, both as regards the mechanism by which the proliferation is brought about and as regards the structural changes which follow. Breach of continuity means disturbance of the normal equilibrium or tissue tension, and is followed by proliferation of all the cells whose normal relationships are interfered with; the result is that there is a growth of connective tissue elements in addition to proliferation of the more specialised cells, and the former exceeds the latter both in rapidity and in extent. Thus the epithelial elements are overgrown, as it were, by young connective tissue, and as the latter contracts the former undergo atrophic change rather than full development. It follows that under these circumstances, while there may be a considerable amount of epithelial proliferation, the amount of efficient repair may be comparatively slight. In compensatory hyperplasia the stimulus to proliferation apparently comes from increased metabolism, the result of abnormal functional activity; it may be considered, as Weigert puts it, to be due to molecular damage (*Schädigung*) in the widest sense. It is well seen in the surviving liver tissue when a considerable proportion of the liver has been destroyed by disease or artificially removed. In this case the liver cells alone are affected, and thus a proliferation of them occurs without any participation on the part of the connective

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tissue. The results of the proliferation under the two conditions are well exemplified in the later stages of subacute yellow atrophy.

In another section I have considered the origin of tumours from the liver cells, and its relation to the process of compensatory hyperplasia. The question concerning the relationship of chronic irritation to proliferation of cells is one of great difficulty, and I have omitted it in the present communication.

I. Proliferation in Repair following Breach of Continuity.

(*a*) *Repair following Rupture.*

I have had an opportunity of studying this in three cases where death occurred on the fifth, seventeenth, and thirty-seventh days respectively after the injury. The changes observed in the second case are the most important, and may be described first. In this case the patient was a man, æt. 48, who had received a severe injury; death occurred from empyema on the seventeenth day after the injury. In the liver there was an antero-posterior rupture about three inches from the right margin, along with several secondary tears. The various fissures were filled with firm blood-clot, and the distal portion of the liver had a dull brownish-yellow tint, as if it were necrosed. Along the margins of the tears, between the healthy liver tissue and the clotted blood in the lacerations, one could see a thin greyish band, apparently of newly formed tissue, and in this the important reparative changes were found.

The histological appearances need not be given in detail; it is sufficient to mention those bearing on the present subject. It can be seen that the distal portion of the liver has undergone complete necrosis, the cells having completely lost their nuclei, though the structural outlines of the tissue can be made out; this dead liver tissue is separated from the living by coagulated blood, as already stated. In the blood itself are only a few fibroblasts and young capillaries, but next to the surviving liver substance there is a comparatively broad band of fairly compact fibro-cellular tissue, and it is in this band that the important newly formed epithelial structures are to be seen. These are in the form of irregular masses of fairly large cells, which are in some places arranged around a lumen, in others massed together (Plate XXXII. Fig. 1). They are seen to be extending from the liver tissue in spaces in the connective tissue, and in their mode of growth are not unlike what is seen in adeno-carcinoma. A comparatively common appearance is that of an acinus-like arrangement of cells with others irregularly arranged alongside. Some of the cells have a somewhat columnar form, but most are rounded, oval, or irregular in shape. The protoplasm is finely granular, and has an eosinophile reaction; this varies in degree, but, as a rule, it is less marked than in the case of the

liver cells. Where there are larger spaces in the young connective tissue such cells may form masses measuring as much as 0·2 mm. across (Plate XXXII. Fig. 6). The nuclei of the newly formed cells are on the whole rather larger than those of the liver cells; they are round or oval, with well-marked nuclear membrane, and the chromatin is arranged in somewhat coarse fragments with comparatively clear karyoplasm between. Accordingly in this case we have extensive proliferative changes both on the part of connective tissue and epithelial elements. The growth of the latter, though not quite able to keep pace with the former, is still of considerable degree, and indicates great proliferative activity on the part of the cells concerned. What is the source of the new epithelium? My first impression was that the epithelial outshoots were derived from the bile-duct epithelium, the lumen-like space in many of them at once suggesting such an origin. On more careful examination, however, I became convinced that this was not the case; in fact, I obtained clear evidence of the origin of most of them from liver cells. Direct continuity with columns of liver cells can in many places be seen (Plate XXXII. Figs. 4 and 5), and all transitions as regards cell characters can be traced between the pre-existing and the new columns. Where the offshoots are seen growing out, the liver cells always show changes both in the protoplasm and in the nucleus. The former becomes less granular, and in preparations faintly stained is seen to be rather less eosinophile; it also sometimes shows a streaked appearance as if drawn out. The nucleus becomes increased in size, the nuclear membrane more distinct, and the chromatin reticulum opener and coarser. It is also of importance to note that these changes may be observed in part of a column of liver cells, while at either end of such a portion the liver cells have a normal appearance (Plate XXXII. Fig. 3); here there seems no possibility of the cells in question being derived from the bile ducts. Furthermore, the changes in the liver cells which are undergoing proliferation are closely similar to those noted when cancer is originating from liver cells (*vide infra*). In one or two instances I found mitotic figures in the liver cells in close proximity to the new offshoots (Plate XXXII. Fig. 2). The proliferation of the liver cells in relation to the injury is accordingly beyond question. It is difficult to say whether or not any of the larger epithelial masses have come from the bile ducts. In places one can find distinct offshoots from the latter, but in these the epithelium is much more distinctly of the cubical or short columnar form and much more regularly arranged. Such offshoots may, however, possibly come to show more exuberant and irregular growth, and produce some of the structures in question. But from what I have seen of direct transition from liver cells, and also from the fact that continuity with these can be traced at several places in a comparatively small mass of liver tissue, I believe that most of the newly formed epithelial structures have taken origin from the latter.

Opportunities for examining the process of repair at such a stage in the human liver must be exceedingly rare, and Marchand, in his monograph on regeneration of the tissues in *Deutsche Chirurgie* (1901), makes no reference to the subject. A case somewhat similar to that just described is, however, recorded by Hess (1890), death of the patient having occurred on the fifteenth day. In his paper he describes newly formed epithelial structures of the same nature as the above, and concludes that they have a double origin, namely, from the liver cells and from the bile-duct epithelium, though he considers that the latter origin is the commoner. He found glycogen in many of the cells, though in less amount than in the liver cells. The cell columns and groups as figured and described by him appear to have been of smaller size than in my case, and he compares them to the bile-duct-like structures seen in cirrhosis and other conditions. Certainly in the present case, as will be seen from the photographs, they have a different appearance, and there are none of the thin columns and processes such as are seen in cases of cirrhosis and acute yellow atrophy (cf. Plate XXXII. Fig. 1 and Plate XXXIII. Fig. 9). The question may be asked, Why should there be this difference in the epithelial outgrowths in the two conditions? One answer which suggests itself is that in acute yellow atrophy the breach of epithelial continuity will always be at the same point, namely, at the junction of the smallest bile ducts with the liver cells, and accordingly the new structures will conform in their type of epithelium with the former; whereas in a case of rupture the chances of the breach being at this point are exceedingly small, while columns of liver cells will be ruptured at many places. Furthermore, in acute yellow atrophy the surviving liver cells will be more or less damaged, and thus have their proliferative capacity impaired, though it is not abolished. The large size of the epithelial outgrowths in the case of rupture as well of the individual cells may in part be due to their lying in a young connective tissue of comparatively loose texture; but whatever may be the explanation, I have never seen similar large epithelial masses in the liver in any condition other than that described.

In the case of rupture of the liver where death occurred on the fifth day after the injury there are practically no epithelial outgrowths, but on examining carefully the liver cells along the margin of the breach one can see commencing changes both in the protoplasm and in the nucleus similar to those described above as associated with proliferation. These, though at an early stage, are confirmatory of what has been stated as to the part played by the liver cells. There is in this case an absence also of any distinct outgrowths from the bile ducts. The want of proliferation may be due in part to the fact that the patient was in a condition of collapse after the injury.

In the *third* case, where death occurred more than *five weeks* after the injury (there was also fracture of the spine, which led to the fatal result), the microscopic appearances do not give much additional

information in relation to the present subject. The ruptures have been of the nature of narrow fissures, and these are completely healed by well-formed connective tissue. In this there are a few bile-duct structures and a few collections of epithelial cells of indeterminate character in a more or less atrophic condition. The connective tissue extends for some distance into the adjacent liver lobules, and some of the columns of liver cells are considerably atrophied. There is, however, no evidence of newly formed liver tissue, but the breaches of continuity have been slight and healing has occurred rapidly.

As regards the ultimate fate of the large epithelial outgrowths above described, I accordingly cannot speak definitely, as I have not had an opportunity of following the subsequent changes in detail. Some regeneration of fully functioning liver tissue may result, but it seems extremely probable that in the course of the condensation and contraction of the newly formed connective tissue many of the epithelial structures will suffer atrophic change and may disappear. An essential condition for the hepatic cells carrying on their function is an intimate relation to the capillaries, and it is difficult to see how this will be attained in the newly formed connective tissue. We have here, just as in acute yellow atrophy (*vide infra*), abundant epithelial proliferation as the result of breach of continuity, but regeneration in the strict sense will occur to an unimportant degree owing to the more rapid growth of connective-tissue elements.

(*b*) *Repair following the Destruction of Liver Cells.*

This is seen especially in acute yellow atrophy and allied conditions. In this group of affections portions of the liver undergo necrosis to a varying degree, and the dead liver cells afterwards become absorbed. As the bile ducts escape the toxic action their extremities are left free at the sites of union with the columns of the pre-existing liver cells; in other words, a breach of continuity is formed at these points, and the bile-duct epithelium accordingly undergoes proliferation, and grows into the empty framework of the lobules. The extent to which this takes place will depend in great part on the duration of life of the patient after the initial lesion of the liver. The formation of new bile ducts in acute yellow atrophy has long been recognised, but it is only within the last dozen years or so that attention has been specially directed to the later proliferative changes in cases where life has been prolonged; the interpretation of such changes having been aided by important facts established by experiment. For a considerable period the naked-eye characters of the liver in what may be called "subacute yellow atrophy" resemble the appearances in more acute cases, but later the surviving liver tissue undergoes marked compensatory hypertrophy, while the areas where the original destruction occurred come to have the appearance of a comparatively vascular tissue in process of contraction. This later stage, to which

further reference is made below, is generally known by the name of "multiple nodular hyperplasia" (multiple knotige Hyperplasie). Furthermore, the facts obtained by comparative observations at different periods of such destructive lesions are of high importance in interpreting the histological changes in the various cirrhoses, as has been pointed out by MacCallum.

I have had opportunities of examining livers at various stages of such affections, but the most important changes were found in a case of subacute yellow atrophy on which I made the post-mortem examination some years ago, and which may be conveniently used for purposes of description. All the important facts have, however, been confirmed by observations on other cases. I am indebted to Dr. Bramwell, under whose charge the patient was, for furnishing me with some of the clinical facts.

CASE.—The patient was an unmarried woman, æt. 43, and the chief symptoms were jaundice, pain over the right hypochondrium, symptoms of general toxæmia, drowsiness, and, before death, much hæmatemesis. The jaundice appeared about four weeks before death, but the illness seemed to start about two months previously, after the patient had received a wound of the hand from a hatchet, this wound suppurating and never properly healing.

Post-mortem.—The liver was found to be small, with wrinkled capsule (the weight was 2 lb. 6 oz.), and it showed the appearances seen in acute yellow atrophy, both "yellow" and "red" areas being present; the latter were, however, less deep in colour, and firmer in consistence than usual. The histological appearances may be briefly summarised as follows: The yellow areas may be said to be constituted by necrosed liver tissue, though at places there are surviving portions which still show nucleus staining. In places the delicate supporting framework also is necrosed, and there is some necrosis even of the connective tissue of the portal spaces. The yellow areas are practically free from the proliferative changes seen in the reddish areas. In many parts of the latter the liver cells have entirely disappeared, and the lobules are occupied by a somewhat cellular connective tissue in which are numerous newly formed bile ducts, for the most part arranged in a more or less radiate manner. In many of the lobules these structures extend inwards almost to the centre of the lobule (Plate XXXIII. Fig. 8), running with a somewhat sinuous course. The epithelium varies in character: in some it is constituted by small rounded or cubical cells like those in the smaller interlobular ducts, but in most the cells are elongated and form cord-like processes in which a lumen is visible only at places. Here and there, however, in these latter the cells have more of the cubical shape. In the connective tissue occupying the place of the former lobules are a considerable number of capillaries, which may be said to have an irregularly radiate arrangement, leucocytes chiefly of the small mononuclear type are also fairly abundant. The primary significance of these changes seems a matter of easy interpretation,—we have before us what is essentially allied to a process of organisation. After the destruction and absorption of the liver cells there occurs a proliferation of interlobular connective tissue, and this takes place along the lines of the interlobular capillaries. Along with the connective tissue there grow offshoots from the extremities of the bile ducts where the ends are left free by the destruction of the liver cells. These changes go on until the collapsed remains of the lobules are practically occupied by the newly formed elements. I may mention that the continuity of the epithelial processes with the bile ducts in the portal spaces can be traced in many places.

Before considering these changes in relation to regeneration we may first refer to one or two other points. Although in many parts of the red areas there are no liver cells to be seen, in others there are islets of liver tissue the cells of which show the nuclei well preserved. Between such columns of liver cells there is, as a rule, no increased amount of connective tissue. There is, in my opinion, no doubt that these are portions of liver tissue which have escaped the destructive process. Around them can be seen the young connective tissue and bile ducts, but in places there is a zone in which no bile ducts are present. This is well illustrated in Plate XXXIII. Fig. 9. It is evident that the bile ducts are growing towards the liver tissue, and that the ultimate result will be the establishment of a continuity between the bile-duct epithelium that has grown in and the liver cells which have escaped necrosis. The latter may thus be enabled to continue their function in a normal manner. The surviving liver cells occur in groups of varying size, and are in great part normal in appearance. Some, however, are distinctly enlarged and contain more than one nucleus, or the nucleus may be somewhat convoluted. These changes are commonly seen in liver cells undergoing compensatory hypertrophy, though in the present instance they are not of marked degree. Mitoses in the liver cells which have escaped destruction in acute yellow atrophy have been observed by M'Phedran and Macallum (1894), and by Meder (1895). I have not been able to find any in this case, and from the negative results of various other observers it is evident that they are rarely to be seen. Nevertheless, their occurrence must be accepted as a fact. In places I have observed slender offshoots from groups of surviving liver cells—offshoots in which the cells are thin and elongated, and which are not unlike the newly formed bile ducts. I have seen these in places where there are none of the latter in the neighbourhood, and they appear to me to be really outgrowths from the liver cells. We may thus summarise by saying that beyond a certain amount of compensatory hypertrophy and some tendency to send out their offshoots there is no noteworthy active change in the liver cells; whilst, on the other hand, there is extensive growth of the bile-duct epithelium.

The question as to the relation of the proliferative changes in the bile ducts to regeneration of the liver cells is one of high importance, and has received a considerable amount of attention. Podwyssozki (1886), from experiments on animals, found that there were two chief types of regeneration, one in which there was an active proliferation of liver cells in relation to the injury, and another in which there took place a great outgrowth of bile-duct epithelium in the form of slender duct-like processes, the cells of which afterwards became transformed into liver cells. The extent to which these types predominated varied in different species of animals. Thus in rats and cats the proliferation of liver cells was the chief method of re-

generation, whilst in guinea-pigs and rabbits the bile-duct epithelium supplied the chief source of new liver cells. It has further been shown experimentally by Ponfick (1892) and v. Meister (1894), that in addition to regeneration in the proper sense a great amount of compensatory hypertrophy and hyperplasia occurs in the surviving liver tissue when a part of the liver has been removed by operation (*vide infra*).

The subject of regeneration after acute yellow atrophy has been considered in relation to these facts by Meder (1895), Marchand (1895), Stroebe (1897), Ibrahim (1901), MacCallum (1902), and others. They all agree that the cells of the newly formed bile ducts may come to assume the characters of liver cells, and thus regeneration of liver tissue may be brought about. In the case under consideration I have found evidence of such an occurrence, though it is not present to any great extent. Here and there the cells in the new bile ducts can be seen to be becoming broader (Plate XXXIII. Fig. 10), their protoplasm more granular and eosinophile—coming, in short, to acquire the characters of liver cells. Moreover, some of these cells contain brownish granules of bile pigment, and between them may be seen larger fragments of inspissated bile. As such an appearance may be seen in areas from which the liver cells have completely disappeared, it seems justifiable to conclude that the bile has been formed by the newly formed cells. It may also be noted that at places along the course of the duct-like structures one can find the degenerated remains of old liver cells. These may be more or less necrotic, and often contain fatty droplets, and are quite different in appearance from the cells of the new bile ducts. Their relation to the latter is a clear evidence that the bile-duct epithelium has grown along the spaces formerly occupied by the columns of liver cells. While, therefore, the sections show undoubted evidence that this transformation may occur, it is by no means a prominent feature in the sections, and in large areas the epithelium of the new bile ducts retains its primitive characters, without showing any tendency to form liver cells. The change seems to have been more extensive in cases described by others.

Another point which remains to be discussed is to what extent this transformation of bile-duct epithelium is *efficient* as a means of regeneration of liver tissue. In the first place, it is to be noted that where a continuity is present between liver cells and the new bile-duct epithelium it does not follow that the former are derived from the latter. For, as pointed out above, there are often islets of surviving liver tissue, and the new bile ducts certainly grow towards them and, if there be sufficient time, form a continuity with them. Such an appearance as Stroebe figures, for example, may quite possibly be capable of such an interpretation. Only careful observation in suitable cases will determine the matter definitely. Moreover, along with the new bile ducts there is always a growth of young connective tissue, often in

considerable amount, and from what we know of the subsequent changes in such conditions it is, to say the least, unlikely that this tissue becomes absorbed, whilst the capillaries once more become widened and the epithelial cells acquire in full the characters of liver cells. Meder apparently believes that much regeneration of liver tissue takes place, and in fact supposes that a *restitutio ad integrum* is possible. From what I have seen I do not consider that the fibro-cellular tissue permeated by the bile-duct-like structures ever acquires the full characters of normal liver. It seems to me that, on the contrary, the tendency will be towards increasing density of the connective tissue; in fact, to a cirrhotic condition. The parts from which the original liver cells have been absorbed will tend to contract more and more, whilst the surviving liver tissue will undergo great compensatory hypertrophy. A condition will result like that described by Marchand (1895), and more recently by Barbacci (1901), under the name of multiple nodular hyperplasia. In Marchand's case there were rounded masses of liver tissue of reddish-yellow colour in a groundwork of dark red tissue, which he describes as being like spleen in appearance.[1] This latter was a vascular fibro-cellular tissue permeated by bile ducts, the cells of which were in places acquiring the characters of liver cells. He regards the changes as the result of the lesions of yellow atrophy, the occurrence of which dated back six months previously, and rightly remarks, in my opinion, that the final outcome would have been a coarse form of cirrhosis. The red parts of such livers as those referred to represent the imperfect process of direct repair, whilst the yellow parts are the result of a very efficient formation of new liver tissue by compensatory hyperplasia. As the epithelial ingrowths are derived from the bile-duct cells next to the liver columns it is only natural that these cells should have the power of forming liver cells; they are probably cells of intermediate character. It must not be assumed, however, as some have done that bile-duct epithelium in general has this regenerative faculty.

SUMMARY.—In breach of continuity following trauma and destruction of liver cells alike, extensive epithelial proliferation is to be found. In the former case it is chiefly on the part of the liver cells, owing to the multiple ruptures of the columns. On the other hand, following the destructive lesions in acute yellow atrophy and allied conditions, the proliferation is chiefly seen on the part of the bile-duct epithelium. This grows into the lobules in the spaces formerly occupied by the liver-cell columns, and may come to effect continuity with cells which have escaped the destructive process. A certain amount of transformation of bile-duct epithelium into young liver cells may be observed, but little effective regeneration of the liver tissue is brought

[1] A liver in a closely similar condition was demonstrated by Dr. Stuart Macdonald at the meeting of the Pathological Society to which this communication was made.

about in this way, owing to the concomitant growth of connective tissue which afterwards undergoes contraction. The bile-duct structures may be found in broad areas of connective tissue for a long time afterwards, and apparently undergo little change. A certain amount of proliferation in surviving liver cells may be met with, and they may also produce duct-like offshoots; compensatory hyperplasia occurs in the larger areas.

II. Proliferation in Compensatory Hypertrophy and Hyperplasia.

As already stated, it is by compensatory hypertrophy and hyperplasia that the chief restoration of liver tissue takes place after a large portion has been lost. The experiments of Ponfick and von Meister referred to above show in a striking manner how great such restoration may be, as in many instances as much as three-fourths of the liver was removed, and in the course of from four to eight weeks the organ had almost regained its original weight, though of course its configuration was much altered. The latter observer found that the newly formed tissue might reach, in some cases, as much as four-fifths of the original weight of the liver. In such experiments mitotic figures appear about the third day, and thereafter the process of multiplication becomes very active. The proliferation appears to be most abundant at the periphery of the lobules, and the young cells are distinguishable by their larger size and clearer protoplasm. The liver columns become broader than normal, sometimes containing several cells abreast, and many of the cells are large and contain more than one nucleus. The restoration of tissue accordingly occurs by an enlargement of the surviving lobules, the diameter of these becoming much increased. The proliferative change does not always occur uniformally, however, and accordingly the lobules may become altered in form. Confirmatory results to these are found in human pathology. Ponfick (1891) showed that a similar change followed destruction of portions of the liver by hydatids, and it has also been observed and described in various other destructive and atrophic lesions. It is well seen in the hypertrophic nodules of multiple nodular hyperplasia already referred to, and it is also to be found in practically every case of coarse cirrhosis. In the latter condition, as pointed out by Kretz (1900) and by MacCallum (1902), while destruction of one part of the nodule is going on, enlargement of another part may be taking place, so that in the latter the distance from the central vein to periphery of the nodule may actually be increased. Thus the two processes, destruction of liver tissue and restoration, go on side by side, the latter, however, being strictly more compensatory in nature than reparative. The bile-duct structures in cirrhosis are probably in great part produced by a similar process as has been described in the later stages of

acute yellow atrophy, and the larger the size of liver tissue destroyed at one time the longer and more distinct are likely to be these structures. In addition, however, the formation of similar structures by atrophic changes in columns of liver cells must in my opinion be admitted. In all the cirrhotic livers referred to below, in which cancer became super-added, well-marked hypertrophy is present in the liver cells. The change chiefly occurs in foci, in the centre of which the cells are much enlarged, and may contain more than one nucleus or a somewhat convoluted nucleus; whilst at the margins the cells may be stretched out and somewhat flattened. There is no doubt that the latter change is produced by the hypertrophic changes, and not in any way by the growth of the connective tissue. These hypertrophic areas may sometimes become specially distinct and even recognisable to the naked eye by their pale colour. In other words, the process is not a uniform one, but is much more distinct in some parts than in others. It is in these livers that a transition to true tumour growth is apt to occur, as will now be described.

III. Proliferation of Liver Cells in New Growths.

The origin of tumours, both simple and malignant, from liver cells, has now been recognised for a considerable time, and the frequent association of new growth with cirrhosis has attracted the attention of numerous observers. Hanot and Gilbert (1887) in their important work describe as varieties of primary cancer of the liver, *cancer massif*, *cancer nodulaire*, and *cancer avec cirrhose*. As regards the minute structure, they distinguish an *alveolar* form, the cells in which may be polyhedral, cylindrical, or of the giant-cell type, and a *trabecular* form with an arrangement on the plan of the normal liver. They trace the origin of all varieties to the liver cells, and note that the histological features do not correspond with the general anatomical characters mentioned, a statement which my own cases confirm. In their opinion the trabecular type is specially associated with cirrhosis, its occurrence, in fact, being rare apart from the latter. As will be shown below, however, we may have a tumour in connection with cirrhosis growing from the liver cells, and still showing great diversity in structure in different parts. My own observations on tumours whose origin can clearly be traced to liver cells refer to adeno-carcinoma arising in connection with cirrhosis and the simple solitary adenoma. These correspond with the varieties described by Engelhardt (1898), and they afford an interesting study, as in the first we have an example of a distinct relationship of cancer to pre-existing lesions, and in the other an example of a condition which is to be referred to congenital abnormalities. Tumours arising from the bile ducts will not be considered.

(*a*) *Adeno-Carcinoma.*

I have had an opportunity of examining *post-mortem* six cases of carcinoma following on cirrhosis, the chief facts of which may be briefly summarised.

Case 1.—W. G., a man, æt. 65. Symptoms present for only about a month before death; much ascites with rapid accumulation of the fluid after tapping. History of alcoholism and syphilis. Purulent peritonitis as a terminal phenomenon. No jaundice. Liver considerably enlarged = 5 lb. 8 oz. Multilobular cirrhosis throughout; extensive malignant growth in the right lobe in multiple foci almost completely replacing the liver tissue in the lower part, also scattered nodules of varying size but mostly small; in the left lobe a few scattered islets of growth. The colour of the tumour is pale grey or yellowish, owing to degenerative change. The portal veins in the right lobe are distended with cylindrical masses of growth, in great part undergoing necrotic softening. Microscopically the tumour is found to be an adeno-carcinoma, or cancer of the trabecular type, but showing considerable variations in structure, to be described below. Its origin from liver cells can be clearly traced in many places.

Case 2.—F. R., a man, æt. 60. Illness of about three months; ascites and rapid emaciation. One attack of jaundice, which passed off; no jaundice present at post-mortem. Liver small = 2 lb. 6 oz. Coarse cirrhosis present throughout; in right lobe a mass of new growth about 3 in. in diameter and numerous smaller islets scattered throughout the lobe. These have a whitish yellow colour, and are often necrotic in central parts. Portal vein and branches occluded by tumour, as in Case 1. Microscopically an adeno-carcinoma with broad bands of liver cells; a direct continuity with the latter can be clearly traced.

Case 3.—C. M., a man, æt. 53. Considerable emaciation, marked ascites, no jaundice. Liver somewhat enlarged = 4 lb. 12 oz. It showed throughout a coarse cirrhosis, moderately advanced. In left lobe there are, in addition, numerous nodules of new growth. These replace the liver tissue, and are surrounded by the cirrhotic bands; they form larger masses by their confluence, the liver tissue in the posterior part of the lobe having almost entirely disappeared. The portal vein and branches in the liver are distended with new growth, and the vein below the liver is filled with recent thrombus. The tumour was of the trabecular type, and its cells closely resembled liver cells, with which they were in direct continuity.

Case 4.—A man, æt. 60. This was a case of cirrhosis with "massive cancer." The cirrhosis was of rather fine type, and the liver was distinctly atrophied. In the upper part of the right lobe was a large oval mass measuring 7 in. across and 5 in. in the other two axes. The tissue was to a large extent necrotic and hæmorrhagic. The rest of the liver was free from new growth; no growth in the portal vein. A few small secondary growths present in both lungs. No jaundice. The mass in the liver had the structure of a soft and rapidly growing cancer, with great aberration in the type of its cells, many being giant cells. The appearance corresponded with that seen in parts of the liver in Case 1; direct continuity with the liver cells could not be traced in this case, as the tumour mass was distinctly encapsulated. In the secondary growths in the lung the cells were arranged in broad cell masses, and closely resembled liver cells in appearance.

Case 5.—A man well up in years (exact age not known) was admitted to hospital in a moribund condition after profuse hæmatemesis. There was marked ascites. The hæmorrhage had occurred from ulceration of veins at lower end of œsophagus. The liver was about normal size, and showed an extreme cirrhosis of the hobnail type. It contained also numerous nodules of

new growth. Three of these were fully 2 in. in diameter, composed of necrotic tissue, and well encapsulated. Numerous other nodules were present, chiefly of a small size.

The tumour microscopically was found to be a liver-cell carcinoma of the trabecular type, the trabeculæ being broad and containing several rows of cells abreast; the cells at the periphery somewhat intermediate in character between liver cells and columnar epithelium. The direct continuity with and origin from liver cells could be traced in many places.

CASE 6.—A man, æt. 52. For several years he had suffered from gastric symptoms, and latterly from hæmatemesis. There was marked ascites. The liver was considerably enlarged, weighing 5 lb. 13 oz.; marked cirrhosis of a coarse character was present throughout. The left lobe was studded with numerous pale nodules, mostly of small size, replacing the liver tissue almost completely, these being separated by the cirrhotic bands. In right lobe similar nodules were also present, but a large proportion is free. There were also a large spherical mass of about $3\frac{1}{2}$ in. diameter, and a smaller one $1\frac{1}{2}$ in. in diameter surrounded by a dense capsule of connective tissue; the tissue in these was largely necrotic, and in the smaller one growth appeared effete. Numerous secondary growths were present in the lymphatic glands (Plate XXXIII. Fig. 12), in the vicinity, and in the great omentum. There was malignant infiltration of the portal vein, and all its branches were filled with a mixture of blood and tumour cells.

Microscopically the growth is a liver-cell carcinoma of the trabecular type. The cells in many places are closely similar to liver cells, and their origin from the latter can be easily traced. Transitional forms to large giant cells are seen in various parts (Plate XXXIV. Figs. 14–17). There was a large chronic gastric ulcer which had opened into an arterial branch. No tumour in the stomach.

With regard to the general facts, the following summary may be made: In all six cases there was marked cirrhosis throughout the liver, this being of the multilobular type, though the islets of liver tissue varied considerably in size. The cancer occurred in five cases in multiple foci; the tumour tissue in many places merely replacing the liver tissue, without producing any marked increase in size of the part. In two cases there were larger nodules of older standing, and in one there was a single huge mass. The tumours were of a yellowish white and pinkish colour, markedly anæmic as compared with the liver tissue, and of softer consistence; necrosis was common in the larger tumours. In four cases there was extensive invasion of the branches of the portal veins, both larger and smaller veins being filled with rapidly growing and more or less necrotic growth. In two cases secondary growths were present in other parts. Cloin (1901) describes the production of bile pigment by the cells of the secondary growths, but I have not been able to find any evidence of this. In none was jaundice present at the time of death; in one case it had occurred, but had passed off. In all six instances the patient was a man and was aged 50 years or over.

In these six cases the origin of the tumour from liver cells is undoubted. In all of them the cells of the growth are in places closely similar to liver cells, and in five of them direct continuity with the liver columns can be traced at places, the appearances indicating multiple foci of origin. In five of them the cells may be said to be

arranged on the plan of trabeculæ, though the structure may show great deviations in parts; whilst in the sixth case the secondary growths in the liver also show the trabecular type. In three of the cases great aberration in the characters of the cells are present, there being many giant cells. It is unnecessary to describe in detail the histological features in the different cases; it will be sufficient to refer specially to those in Case 1, as here the transitions from one type of growth to another can be readily followed. The histological appearances in this case are of especial interest, on account of the great variety in the form of cells and in their arrangement. As in the others the origin from liver cells can be easily followed in many parts. The cells undergoing the change show enlargement of nuclei, with assumption of the vesicular type, as described above in the case of trauma; the nuclei also show considerable varieties in size. The cells become larger, their protoplasm less eosinophile, and the trabeculæ wider, though it is a noteworthy feature that the general configuration of the original trabeculæ is continued into the lines of cells which are clearly part of the tumour. As regards the types of growth in the fully developed parts of the tumour, the following may be mentioned as the chief varieties:—(*a*) Masses of cells which resemble liver cells more or less closely. They are arranged in broad trabeculæ, or form masses lying in alveoli. In other parts cells of this class are loosely arranged, and are often of considerable size. (*b*) Irregular masses of cells arranged in alveoli, but showing a more or less adenomatous arrangement; the protoplasm of these cells is almost free from eosinophile reaction. This is the type when the tumour is growing in dense tissue, though larger masses of the same character also occur. (*c*) Tissue composed of aberrant type of cells, giant cells in many parts constituting a striking feature. These latter reach a great size, are irregular in form, and possess either a huge highly convoluted nucleus showing great variety in disposition of chromatin, or they contain a large number of nuclei which in certain instances appear to be formed by the division of a large nucleus. Such cells are derived from cells of the liver-cell type, and occur where the tumour is growing most actively in large masses. Mitotic figures are very numerous in these parts, and multiple mitoses also are frequent. Although, of course, the figures are imperfectly preserved, some of them appear to be heterotypical, and are not infrequently in the neighbourhood of multiple mitoses.

The variations in structural characters are therefore very great, and the examination of some sections from different parts would give the impression that we were dealing with distinct and independent growths. In certain portions, however, transitions between the types can be made out, and from the appearances found in these I think the following statements can be made: In its earliest form the tumour is of the trabecular type, though the cells show the deviations from the

characters of normal liver cells mentioned above. The tumour may grow to a considerable extent in this form, and larger masses may result in which all the cells are more or less of the same character. On the other hand, the cells may take on a more aberrant type of growth, and give rise to great varieties in size and form of cell, the extreme example being the giant cells described. Further, when the tumour is infiltrating the denser connective tissue the cells become smaller and somewhat columnar in shape; in fact, assume what I have called the duct type.

These facts are brought out in a striking manner where the tumour has invaded the portal vein. The infiltration of the vessel wall is all of the bile-duct or acinus type, whilst the cells, growing freshly within the vein, are of the liver-cell type, and often show the large aberrant forms. The passage from one type of cell into another can thus be readily traced. The origin of the tumour from liver cells and the transitional stages to the giant-cell type are followed with great ease in Case 6, and are illustrated in Plate XXXIII. Figs. 11, 12, and Plate XXXIV. Figs. 14–17.

The relationship between cirrhosis and new growth originating from liver cells has been variously interpreted by different observers. According to some, the two processes are not related to each other as cause and effect. Hanot and Gilbert take such a view, though they regard them as dominated by the same etiological factors—the same agents, acting on different tissues, producing the widely different results. They recognise the frequent association of the two conditions, stating that in about a third of the cases of primary cancer of the liver cirrhosis is present. Frohman (1894) also holds that the cirrhosis and "adenoma formation" are independent of each other, and v. Heukelom (1895), although stating that the cirrhosis precedes the cancer, and that the latter starts in multiple foci, hesitates to draw any definite conclusion as to the relationship. One or two observers, amongst whom Marckwald (1896) may be mentioned, hold that the cirrhosis is secondary to the tumour formation. As, however, he found cirrhosis present only where there was tumour, his cases are manifestly different from those before us. So far as I know, Orth ("Lehrbuch d. path. Anat.," 1887) was the first to suggest that the tumour was associated with the vicarious hypertrophy occurring in cirrhosis, the hypertrophic process overstepping its goal, as it were, and leading to atypical growth and tumour formation. Von Schmieden (1900), who worked in Orth's laboratory, has adopted and elaborated this view; and Eggel (1901), who gives an extensive review of the whole subject, Travis (1902), and Rolleston (1905) express themselves in much the same terms. Some writers speak of cirrhosis with multiple adenoma formation, but I believe that a line cannot be drawn between simple and malignant varieties; we are dealing with a true neoplasm, which appears potentially malignant from the outset.

SUMMARY.—From a careful consideration of the above six cases I have reached the following conclusions:—(1) In all of them the cirrhosis, which is uniformly distributed in the liver, has preceded the origin of the cancer. The association of the two conditions is also much too frequent to be a mere coincidence, as is admitted by practically all writers on the subject. (2) The origin of the growth in all cases is from the liver cells. The original type of growth is in the form of trabeculæ of cells closely similar to, and continuous with, liver cells; the resemblance to liver cells may be maintained throughout the growths in the liver, and also in the metastases; but considerable deviations may occur, as has been described above. I may also repeat that the changes in the liver cells where the tumour is starting are closely similar to those seen in the early stages of proliferation following rupture. (3) The cancer takes origin in multiple independent foci. In many of the small nodules in the same case direct continuity of the tumour with the liver columns can be seen; and further, the general configuration of the latter is often maintained into the tumour, as is well shown in Plate XXXIII. Fig. 12. As these appearances are seen when multiple nodules of considerable area are already present, the conclusion seems inevitable that these young nodules are not secondary, but are fresh foci of growth. I may also add that I have never seen corresponding appearances in secondary carcinoma of the liver. It is also worthy of note that in two cases there were present in the liver much older nodules, which were necrotic and surrounded by a dense capsule of connective tissue. One or two examples seemed to be practically effete, and their appearances suggested the possibility of spontaneous cure. Some young foci of growth are related to the islets of hypertrophic liver cells, but this is not invariably the case. Even where the cells are not hypertrophied, however, a compensatory proliferative process may have previously been taking place. We can at least say that the origin of the tumours in these cases is preceded by a progressive destruction of liver cells, followed by a progressive compensatory hypertrophy and hyperplasia, and the most reasonable explanation seems to be that of Orth, namely, that the vicarious proliferative process, for some unknown reason, oversteps the normal, and takes on the autonomous character of a new growth. If we read the history of the above cases in the light of the various lesions found we may say that the cancerous process may in some cases start in a single focus, or in one or two foci; that the growths may progress slowly, reach a considerable size, and be comparatively localised by encapsulation. At a certain period, however, there may follow an active outgrowth of tumour in multiple independent foci, or secondary growths may occur before this has taken place (Case 4). In other cases, however, the cancer appears to originate almost contemporaneously at many different points. In view of the fact that the various parts of the liver have been passing through similar pathological changes, which

lead in some way to cancer, this occurrence can scarcely be considered as surprising. The origin of cancer from the liver cells as a sequel to cirrhosis, it is scarcely necessary to point out, is of great importance in connection with the general pathology of new growths, as it is one of the best examples of its occurrence after long-continued irritation or stimulation to growth, and of its starting in multiple independent foci.

(*b*) *Simple Adenoma.*

Another striking example of tumour originating from liver cells is afforded in the case of the simple adenoma, usually occurring singly, though sometimes as one or two independent nodules. Many cases of this kind have been recorded, and the literature on the subject is extensive. I shall, however, merely give a short account of one case, which is of interest as affording a contrast to what has been described above. The patient was a young girl, aged 9 years, and death occurred from broncho-pneumonia. The presence of a large tumour in the liver had been detected during life, and on post-mortem examination the following condition was found. The tumour was a large oval mass, which was situated in the anterior margin of the left lobe, and projected downwards. Its measurement in the long axis was 4 inches, and in each of the other two, 3 inches. On section it was seen to be well marked off from the liver tissue, and its substance had a pinkish-grey appearance, with numerous areas of marked vascularity and hæmorrhage. On microscopic examination it was found to be composed of masses of liver cells, fairly normal in appearance, but somewhat irregular in arrangement. There is no evidence of distinct lobules, but the masses of cells are separated by fairly abundant blood vessels with thin walls. One striking fact is that throughout the whole growth no bile ducts are found. The close similarity of the tumour to liver cells is shown in Plate XXXIV. Fig. 18. In this and similar cases we have probably to do with a tumour arising from some abnormality in the process of development. Its origin may perhaps best be explained by supposing that a distal portion of the epithelial outgrowths which form the liver had become cut off, and had grown independently to form the tumour in question. The displaced cells were evidently representatives of liver cells already differentiated, seeing that no bile-duct epithelium is present.

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DESCRIPTION OF PLATES XXXII.-XXXIV.

Plate XXXII.

Fig. 1.—Proliferative changes at margin of rupture of liver, of sixteen days' standing. The epithelial outgrowth are seen throughout the greater part of the field. Surviving liver tissue is present at left margin. (× 60.)

Fig. 2.—Early proliferative changes seen in rupture of liver. (*a*) Mitotic figure in liver cells; (*b*) small group of proliferated liver cells, showing alterations in their appearance as described.
From the same case. (× 300.)

Fig. 3.—Proliferative changes following rupture of liver. In the centre of the field a portion of a cell column shows the result of more advanced proliferation. Note the direct continuity of the cells in question with the unaltered liver cells, which have a more deeply stained and more granular protoplasm.
From the same case. (× 300.)

Fig. 4.—Proliferation at margin of rupture. On the left side is seen a column of proliferated cells, continuous with unaltered liver cells at the upper part.
From the same case. (× 300.)

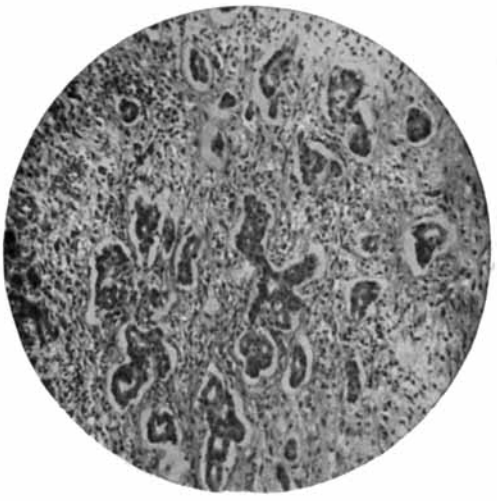


Fig. 1.

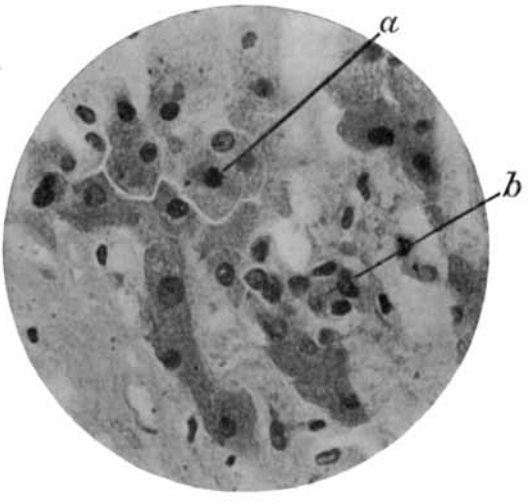
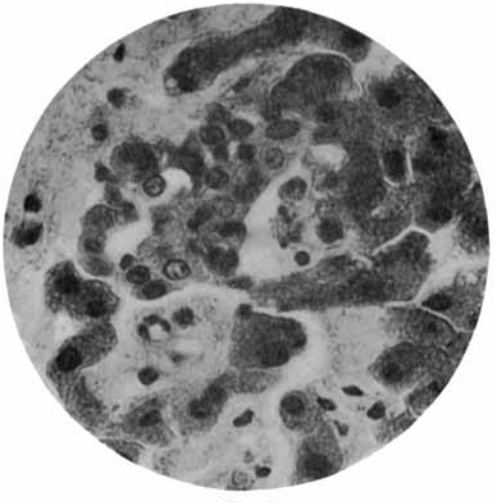


Fig. 2.



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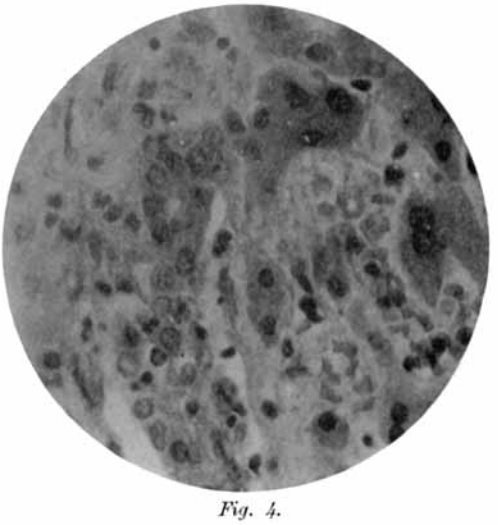

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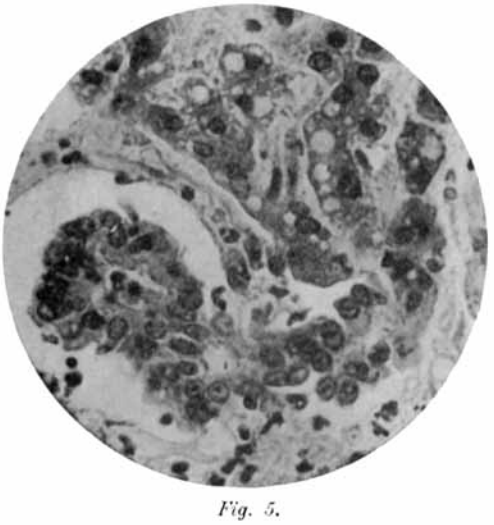

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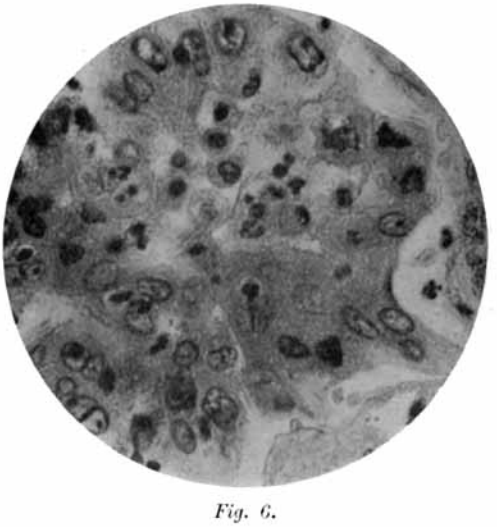

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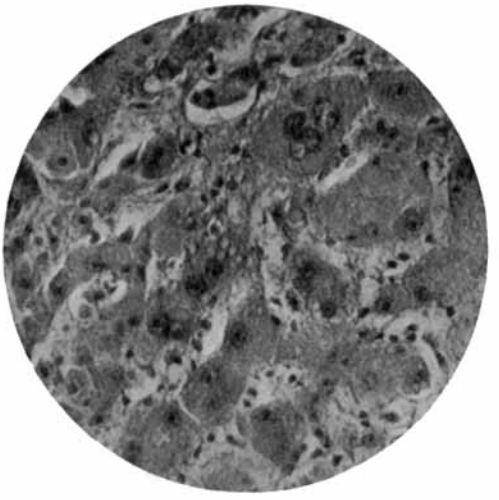
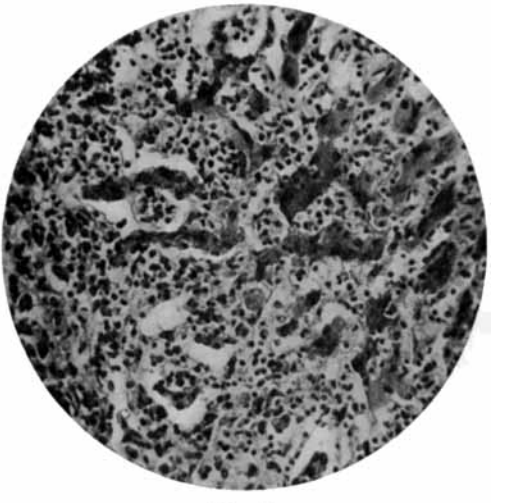


Fig. 7.

Fig. 8.

Fig. 9.



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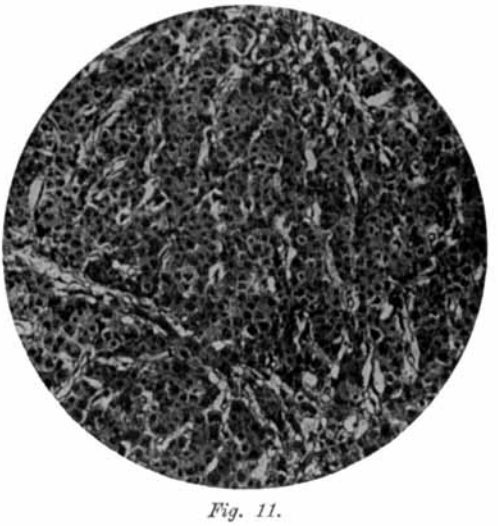

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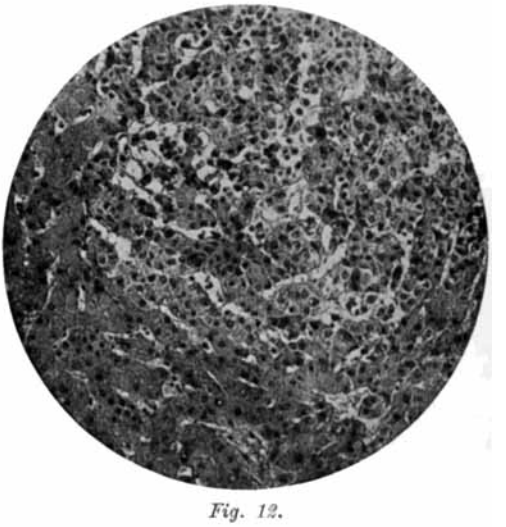


Fig. 12.

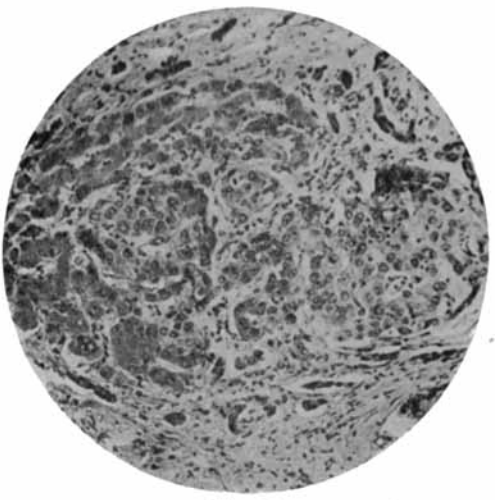
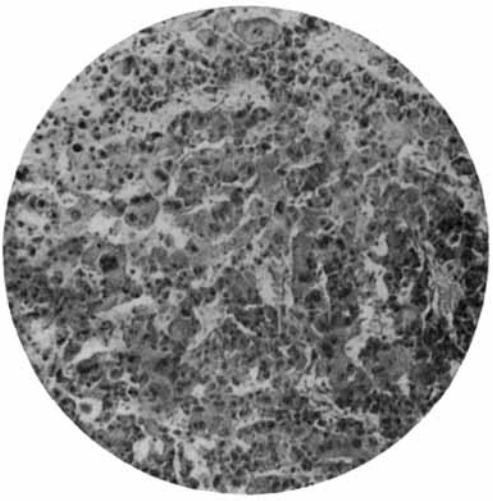


Fig. 13.



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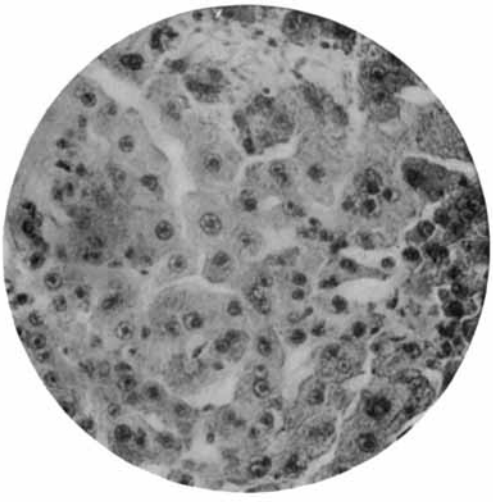

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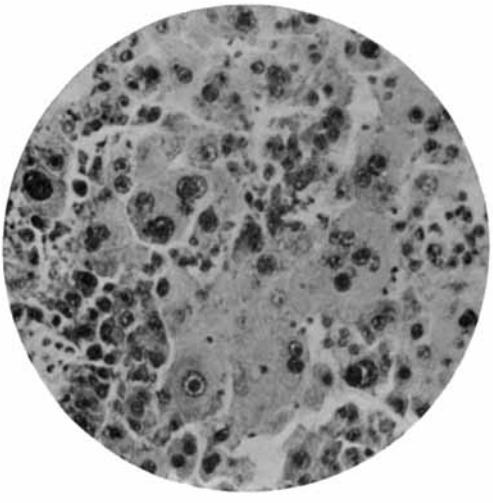

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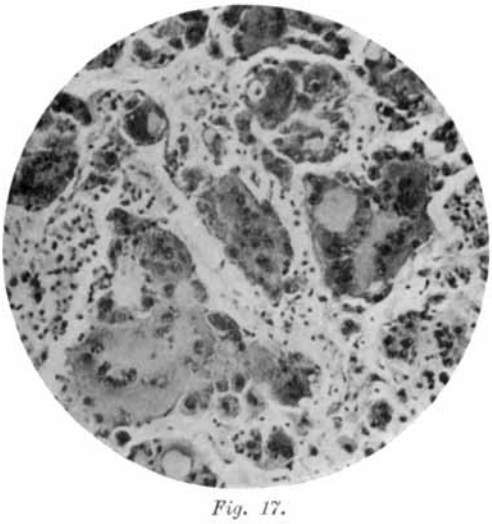

Fig. 17.

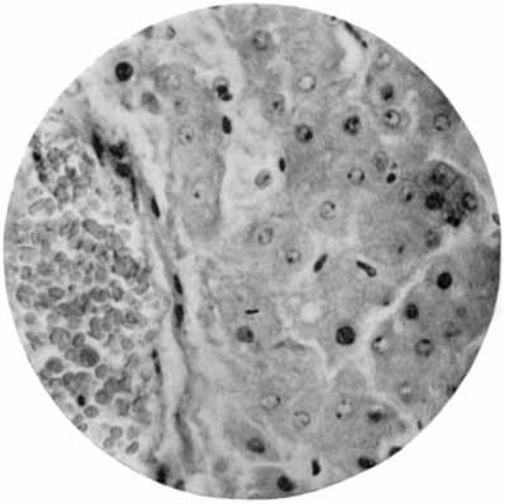

Fig. 18.

FIG. 5.—Rupture of liver; bulbous outgrowth of cells from the surviving liver tissue. From the same case. (× 300.)

FIG. 6.—Large mass of proliferated liver cells, lying in a space in the newly formed connective tissue at margin of rupture. From the same case. (× 300.)

PLATE XXXIII.

FIG. 7.—Hypertrophied liver cells in a case of cirrhosis of the liver with cancer. Some of the cells are multinucleated. From the same case as Fig. 13. (× 250.)

FIG. 8.—Portion of a "red area" in a case of subacute yellow atrophy of the liver. The liver tissue has been replaced by a fibro-cellular connective tissue, in which numerous bile ducts are present. (× 50.)

FIG. 9.—Another portion of a similar area. In the upper part of the field is seen a group of surviving liver tissue. The bile ducts are seen growing towards it on every side, and have almost effected continuity with it. (× 50.)

FIG. 10.—Subacute yellow atrophy of the liver, showing the gradual transition between bile-duct epithelium and columns of young liver cells. (× 250.)

FIG. 11.—Primary carcinoma, following cirrhosis of the liver. Section of secondary nodule in lymphatic gland, showing the characteristic trabecular arrangement of the cells. (× 100.)

FIG. 12.—Section of one of the nodules in the liver, from the same case as the previous. The cancer occupies the upper part of the field, and the direct continuity of its cells with, and origin from, the liver cells can be seen all around the margin. (× 100.)

PLATE XXXIV.

FIG. 13.—Shows the origin of cancer from the liver cells in another case of cirrhosis. The surviving liver cells are seen around the left margin. The rest of the nodule consists chiefly of cancer cells. (× 100.)

FIG. 14.—Section of primary liver cell cancer from another case of cirrhosis, showing the trabecular arrangement of the growth. (× 100.)

FIG. 15.—Another portion of the same growth, showing the similarity of some of the cells to liver cells. (× 250.)

FIG. 16.—Another portion of the same tumour, showing the tendency to aberrant growth. (× 250.)

FIG. 17.—Still another portion of the same tumour, showing large multinucleated cells. (× 200.)

FIG. 18.—Section of primary simple adenoma of the liver (from the case described), showing the similarity of its cells to liver cells. At the right margin is a large vascular space. (× 250.)