after having been placed for exhibition in Zenker's solution.

The tumor had the same pinkish color as the mucous membrane of the trachea. There seemed to be no ulceration, the right half of the tumor, consisting of two fairly good-sized nodes, must have considerably obstructed the lumen of the tube during life. The borders of the growth were, therefore, slightly elevated and differentiated from the normal tissue. When a section of the tumor and tracheal wall was made, it was found that its extension into the substance of the trachea was accompanied by loss of substance, that the cartilage rings of the organ had disappeared and that its wall had been reduced to the layer of connective tissue. The lymphatic nodes about the bifurcation of the tumor were slightly enlarged, and one at least presented small nodes as if from secondary invasion by the tumor, and on microscopic examination this was found to be correct. The nodes thus invaded were immediately beyond the tumor and were adherent to the trachea wall. A portion of the esophagus, fortunately that part underlying the tumor, had been removed together with the trachea, and when opened showed no abnormality. There seemed to be no connection whatever between the neoplasm of the trachea and the tissues of the esophagus.

Microscopic Examination.—Examination of the microscopic section with the hand lens showed that the cartilaginous rings of the trachea were not completely destroyed beneath the tumor, but that the tumor invaded the trachea wall between the cartilaginous rings and partly surrounded them. Under the microscope the entire structure of the mucous membrane was disturbed by the neoplasm. In the lower layers of the mass were found mucous glands not showing any marked departure from the normal, but these glands seemed to extend upwards into the tumor mass, and as one followed them in this direction their cells became more and more degenerated until rounded openings devoid of cells were occasionally observed.

From the connective tissue of the tracheal wall prolongations extended inward, branching so as to have a dendritic appearance. These were covered by layers of epithelial cells of a peculiar flattened spindle shape, the superficial layers of which were in process of active desquamation. In the depths of the tumor this desquamation caused the spaces between the dendritic outgrowths to be filled with a seminecrotic mass of desquamated cells. The interspaces between closely approximated villi not infrequently contained cells massed together in a manner suggestive of the epithelial pearls of the common forms of squamous epithelioma. In these cells various peculiar inclusions may be observed. The cells on the terminal branches of the villi desquamate singly and in masses, so that the surface of the tumor presents a very much frayed appearance.

As has already been suggested, the invasive nature of the tumor was shown by the metastatic growths in the adjacent lymph nodes, in one of which there was a nodule ½ c. in diameter, distinctly circumscribed and corresponding in all its histologic details with the primary growth. The situation of the tumor, the peculiarity of the cells of which it was composed, the partial cornification of the cells, suggest that the tumor had developed from an inclusion of esophageal epithelium in the wall of the trachea during embryonal life, and we are lead to believe that this is the true explanation of the origin of the growth.

The Word Neurasthenia.—The *Lancet*, April 30, begins an editorial article as follows: "Invented by Beard, of America, in the 'sixties' to describe and to include a class of nervous affections more common in America than elsewhere, the term 'neurasthenia' has been used with great elasticity," etc. It is true that we owe much of our knowledge of neurasthenia to the late Dr. Beard, but he did not invent the word, says the (N. Y.) *Medical Record.* Old Ludwig Kraus defined it in his "Kritisch-etymologisches medicinisches Lexikon," the third edition of which was published in Göttingen in 1844, long before Beard dealt with the subject.

REGENERATIVE CHANGES IN CIRRHOSIS OF THE LIVER.*

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In the literature and in the text-books of pathology little reference is made to the evidences of regeneration in cirrhosis of the liver. It is true that it is stated that regenerative changes are evident in certain cases leading to the production of adenoma-like nodular masses of liver tissue, and there is in general a tendency to regard the bile duct-like structures which occur in the fibrous bands as newly formed and as representing an effort toward the restitution of the liver to its original bulk. Especial stress is, however, usually laid on the degenerative changes in the liver cells and the anatomic picture presented by a cirrhotic liver is commonly looked on as the expression of a steadily progressive destructive process.

Kretz[1] only, so far as I can see in the literature at my command, has especially emphasized the importance of the regenerative changes in the ordinary type of cirrhosis and the fact that the anatomic condition as found at autopsy is probably the product of numerous attacks of some destructive affection from which the liver has more or less completely recovered. He discusses these changes briefly in a variety of conditions in an earlier paper, and in his later communication speaks particularly of the disturbed anatomic arrangement of the liver tissues in cases of advanced cirrhosis and of the consequent obstruction to the circulation. His attention is particularly attracted to the masses of liver tissue which he thinks are no longer to be regarded as acini since they have lost the typical architecture of the acini and the typical relation to the blood vessels. He states that many of these nodules are without central veins—others have central veins at their edges, while within the nodule the capillaries are so distorted that injections through the portal vein pass more readily to the hepatic veins by way of the fibrous tissue than through their substance, and even that the blood from these masses reaches the central vein by way of the fibrous strands. He regards these isolated masses of liver tissue as largely new formed and defines cirrhosis as essentially a combination of focal or localized recurring chronic degenerative processes with regeneration.

All of the studies of regeneration in cirrhosis are based on the experimental work of Ponfick, Podwyssozki, von Meister and others, and the anatomic observations of Marchand, Meder, Stroebe, Barbacci and others who have investigated the late results of those destructive processes loosely classed under the name "Acute Yellow Atrophy of the Liver," in which conditions for the study of regeneration almost identical with those produced experimentally are presented.

It is well established, as I have also pointed out in a previous paper,[2] that in those cases in which, after extensive destruction of the liver substance, the individual survives for a considerable time, not only is the débris of the necrotic liver substance removed and scar tissue

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1. Kretz: Ueber Lebercirrhose, Wiener klin. Woch., 1900, vol. xiii, p. 271.

2. W. G. MacCallum: Regenerative Changes in the Liver After Acute Yellow Atrophy, Johns Hopkins Hospital Reports, 1903, vol. x.

formed throughout the skeleton of the liver thus left without cells, but the specific elements which remain evince an extraordinary power of reproducing themselves, tending by this hyperplasia to replace the lost tissue. This repair takes place according to Marchand in three ways:

1. By hyperplastic proliferation of the larger intact remains of the gland parenchyma.

2. By proliferation of isolated liver cell clumps or remains in the region of the most intense destruction.

3. By proliferation of the interacinous gall ducts which, in conjunction with the latter, form new liver cell strands.

Of the cell tubules making up the last group he says elsewhere that they are by no means to be considered as atrophic rows of liver cells, but are doubtless new formed. In their production not only the small interacinous ducts, but also those liver cells which have escaped destruction in the acinus, take part. While the first grow from the periphery into the loose meshwork of the acinus, the isolated liver cells in proliferating provide them with new formative material.

In the case reported by me it was possible to support these views in their entirety, with perhaps the exception of the last point. That this process of the combination of sprouting bile ducts with proliferating isolated liver cells could not be seen, was doubtless due to the fact that in that particular case in the area of most intense cell destruction all the cells of the acini were destroyed or so far degenerated that they were incapable of any participation in the regenerative process, and regeneration necessarily resulted from a proliferation of the bile ducts alone. I regret, therefore, that my statement should have been regarded by Professor Marchand as an opposition to his views,[3] since it was merely intended to describe the conditions in a special case.

I have there expressed the view that whenever the highly differentiated liver cells remain, the regeneration is simply enough effected by their proliferation. Where, however, they are all destroyed the less highly differentiated but genetically identical cells of the bile ducts proliferate and subsequently become specialized in form and function until they are indistinguishable from liver cells. To what extent, then, can these principles be shown to be active in cases of cirrhosis?

The material at my disposal consists of those cases of cirrhosis of the liver which were found in the series of 2,300 autopsies which were performed at the Johns Hopkins Hospital, together with a few miscellaneous cases from other sources, in all sixty cases. For the present, instances of cirrhotic changes in connection with chronic passive congestion, tuberculosis, syphilis, tumors, abscesses, etc., have been left out of consideration.

The general anatomy of the cirrhotic liver is so universally well known that I need not dwell on it here. The difficulty of making a sharp distinction on purely anatomic and histologic grounds between the generally established classes of atrophic cirrhosis, hypertrophic cirrhosis, etc., is also well recognized, and the clearing up of the processes under discussion may throw some light on it.

Kretz claims that a source of confusion in the study of cirrhosis of the liver lies in the tendency to explain the nodular masses which occur there on the basis of the normal acinus, whereas they are very different, the difference being largely in the loss of their central veins, a process for which he offers no satisfactory explanation.

3. Perzina: Inaug. Diss., Leipsic, 1903.

These nodules vary greatly in size, sometimes forming masses which project above the surface of the liver or stand out sharply on the cut surface, distinct in color and consistence from the surrounding tissue. It is to these very large nodules that reference is especially often made in connection with hyperplastic and regenerative changes in cirrhosis. Often they are composed of very large masses of liver tissue with central vein and radially arranged cell strands in every way like a magnified liver lobule. In other cases, however, they are masses of numerous lobules or portions of lobules, no one of which very greatly exceeds the normal lobule in size. As we proceed to the smaller and smaller nodules there are fewer masses which resemble a complete acinus. Many consist of masses of somewhat atypically arranged cells in which no central vein can be seen. Of course these may be explained as lobules cut tangentially. Others have the central vein situated near to one side or even at the extreme margin, or sometimes one may recognize the central vein embedded in loose connective tissue at a slight distance from the edge of the nodule.

Here the question arises as to what we are to consider the true normal form of the lobule or acinus. Obviously on embryologic grounds the lobule should be the mass of tissue which is drained by the ultimate branch of the bile duct, but mainly on account of the peculiar abundance of connective tissue in the liver of the pig which outlines lobular masses, the highly irrational plan of adopting the efferent vein as the center and index of the position of the lobule has become firmly established. This, however, is justified by the very distinct demarcation of such masses of tissue and by the fact that these masses do behave more or less as individual structures under the stress of circulatory disturbances, etc. If now we inject the hepatic vein with colored celloidin and then clear up or corrode the preparation, it will be found that the vein branches very profusely and at the periphery of the liver there are even found anastomoses between the adjacent branches. Reconstructions of such a liver now show that the lobules are by no means isolated, rounded, cylindrical or polyhedral masses with a single central vein, but that the liver tissue really forms a sort of thick mantle for the hepatic vein and its branches interrupted when the vein becomes too large by the approach of another similar mass (Mall). Thus a lobule has a very complicated outline and the areas of tissue which are usually regarded as cross-sections of the acinus are in reality cross-sections of a branch only of the coherent mass which in its entirety answers to the definition of the lobule in this somewhat broader conception. This, as is readily seen, is not fundamentally different from the current idea, but it is of interest in explaining some of the relations seen in cirrhosis. It is also true that in many of the acini there are side branches of the central veins, about which the liver cells are radially arranged, but which do not thereby produce much disturbance of the general outline of the lobule; with the increase of their surrounding liver cells such a system would probably constitute a branch of the lobule.

One may readily convince oneself of the truth of the statement which has been repeatedly made, that in cirrhosis of the liver there may be masses of liver cells as large in cross-section as the branches of the normal acini, which have no central vein and the cells of which are arranged in more or less parallel rows, but not radially, about such a point. Other such masses are found in which a central vein is visible eccentrically placed, sometimes even at the very margin of the mass. Some-

times one can see what appears to be a central vein in the connective tissue adjacent to the mass of liver cells. Unfortunately I have had no opportunity as yet to inject the hepatic vein in an advanced case of cirrhosis of the liver; by such a method one would be able to recognize easily all the relations of such branches as had not been obliterated.

In the study of the changes after acute yellow atrophy or other destruction of a large part of the liver tissue referred to above, it was easy to reach an obvious explanation of these relations. In some instances the lobules were intact, and then after the hyperplastic process has run its course large symmetrical lobules resulted with the central vein in its normal relations. Of other lobules half of the tissue was destroyed, only the skeleton of the connective tissue remaining from the other half. From such, large masses were produced with the central vein at one margin. In case only a sector of the lobule remained there ensued the formation of a larger wedge-shaped mass with the central vein at the point of the wedge. Finally, at any given level, all the cells of the lobule might be destroyed except a group originally situated toward the periphery. Then there would arise the enlargement of this mass into a mass of irregular form, the original central vein of which might be situated at some distance in the connective tissue skeleton. Now, as this skeleton usually collapses to a great extent and becomes overgrown with scar tissue, the central vein may become very inconspicuous or even completely obliterated, and hence the appearance of lobules or nodular masses without any central vein.

Precisely this process can be demonstrated in most instances of cirrhosis of the liver, more easily and plainly in the coarsely nodular forms than in the finely granular or smooth cirrhotic livers.

To form a clear idea of the conditions which result from such a process, single sections of the liver will not suffice. The nodules, which appear to be entirely isolated masses of liver cells in a single section, usually prove in serial sections to be merely the outlying spurs of other ramifying, irregular conglomerates. Really isolated groups of cells do occur, but are relatively rare.

From the study of serial sections one gains the idea that instead of the normal, smoothly outlined, branching acini, we have here acinoid masses with extremely irregular gnawed-out outlines, the erosions being often so deep as to expose on many sides the branching central vein or even so deep as to completely cut off portions of the lobule.

Were the process to stop there this explanation would be much more evident than it is; on the contrary, regenerative hyperplastic changes occur in these injured lobules so as to restore to a great extent their rounded outlines and to bring them back to their original bulk or even to a bulk greater than that of the original lobule. This occurs expansively in the remains of the liver tissue, and although if one were to model such a mass it might in outline roughly resemble the model of a normal acinus, the introduction into the model of the central vein would at once show what an extremely irregular eccentric structure such a rehabilitated lobule really is. Instead of the branching central vein with its uniform mantle of liver cells we would find the vein quite exposed in places, surrounded by cells in other places, and in still other places large, irregular clumps of cells might be applied to one side of it or throughout some distance be separated from it entirely.

Reconstructions from hardened livers without any injection of the hepatic veins are, therefore, of relatively little value, but when a suitable case presents itself it will be possible to illustrate this point very graphically by means of a proper wax model.

The radial measurement of these nodules must also afford an indication of the increase in size over the normal. This could be effected best by the measurement of such a model as mentioned above in which one could be sure of measuring the line at right angles to the central vein where the lobule has its greatest radius. Only the extreme measurements would be of value, for elsewhere one could not be sure whether he were dealing with the original thickness of the lobule or with the thickness resulting from primary atrophy and secondary hypertrophy. The extreme measurements found in serial sections, however, where one is careful to measure the real radius (not an oblique radius) at its greatest length, will practically correspond with this, and while it must vary greatly in different cases (being often greatest in the cirrhosis of children, which is notoriously coarsely granular owing to the active power of regeneration in children), it will at least prove that enlargement has occurred. So, for example, while the average radius of the lobule (i. e., thickness of the mantle of cells about the central vein) in a number of normal livers was found to be about .66 mm., acini were found in advanced cases of cirrhosis which measured from central vein to periphery, 1.00 mm. or more.

Positive evidence of hyperplasia are abundantly present in these acini. Cirrhosis is, of course, a chronic process of long duration, so that it is not surprising that in most cases mitoses are seldom seen. From the study of the early stages, however, it is seen that mitosis is then extraordinarily abundant in the liver cells and that it occurs as an almost immediate sequence of the destruction of the rest of the liver cells. Such necroses destroying a portion of lobule occur, as is well known, and as Dr. Opie has recently emphasized, as the result of a great variety of infections and toxic processes, and in one such case at least which Dr. Opie has brought to my notice I was able to find numerous karyokinetic figures in the peripheral parts of the lobule, while the cells of the central part, although necrotic and devoid of nuclei, were still present in almost their normal position and arrangement.

Similarly, in another case, which I must regard as an early stage in the production of cirrhosis of the liver, the cells throughout the remnant of the lobule, even after a certain amount of scar tissue had been formed in the periphery, were in a state of active division.

Ponfick showed, as has been mentioned in the previous paper referred to, that although mitoses were abundant in the early stages after the extirpation of portions of the liver, they were represented in the later stages only by such conditions as are almost constantly seen in cirrhosis and in the regenerating liver after acute yellow atrophy, i. e., the presence of two or more nuclei in a single swollen cell, the occurrence of large, clear cells with convex outline, etc. Further, one may frequently observe side by side in such a mass, cells which retain the usual form and sometimes deep pigmentation, and cells which are much larger and plumper and are relatively free from pigment. These latter may even form masses of thick columns so arranged in a rounded form as to compress by their expansile growth the neighboring nonproliferating liver cells. One can scarcely escape the conclusion that these are new formed cells.

If now we turn from the recognizable liver tissue to

the remaining tissue we find conditions about which there is perhaps more ground for controversy. As to the significance of the fibrous tissue there has been much discussion, but the weight of opinion is now against the idea that it constitutes a primary new growth of connective tissue which by its contraction compresses the liver tissue and causes the destruction of that tissue, which is apparent in any advanced cirrhosis. Briefly, examination of a section of almost any advanced coarsely granular cirrhosis will show at once that part of the connective tissue is the pre-existing fibrous skeleton of the liver, for it is frequently easy to make out the collapsed framework of the lobule from which the liver cells have been destroyed and eliminated; part of it is the tissue which originally surrounded the vessels and bile ducts and part of it is new formed in the sense that a scar appears to take the place of more highly specialized tissue which has been destroyed. That this scar may by its later contraction constrict the highly specialized elements that are enclosed within it can not be denied. Beside these things which we have described there are the bile ducts and bile duct-like structures whose rôle in cirrhosis has given rise to the most active discussion. The literature on this question has been so well reviewed by Meder and others who have considered the similar or identical structures in connection with the regenerative processes following acute yellow atrophy, that it is not necessary to repeat it here. It may be well, however, to review briefly the anatomic conditions as exhibited by our series of cases.

It has been shown that the disturbance in the structure of the liver indicates that a destructive process, affecting chiefly the peripheries of the lobules, but sometimes extending so deep as to involve the whole diameter, leaves behind it a collapsed skeleton which soon becomes almost indistinguishable from the pre-existing connective tissue about the portal spaces and which, with the coincident growth of new scar tissue, is quite merged into the wide bands of fibrous tissue which run through the liver. This in itself would bring about a concentration of the pre-existent bile ducts on the disappearance or collapse of the liver lobules. The bile duct-like structures sometimes present only in small numbers, sometimes very abundant, lie for the most part in this tissue, and it is naturally of interest to us to know whether they lie in the skeleton of the old lobule or not. Since, however, the greater part of the fibrous tissue coincides with this, or is new formed, we may regard this relation as very close. The point of dispute is, therefore, whether the structures are to be interpreted as compressed or otherwise modified liver cells undergoing a retrogressive process, i. e., the remains of the injured constituents of the lobule, or as newly-formed strands arising from the bile ducts, or possibly as a combination.

Now the condition actually found is about as follows: Where the lobule is relatively intact there are relatively few bile duct-like structures at its margin communicating with the liver cell strands, as in the normal liver. Where the erosion or dismantling of the lobule has been extensive there is a wider strand of fibrous tissue and the bile duct-like channels are numerous; and one may distinguish the main bile ducts, which are unmistakable, and are lined with cylindrical epithelium. Many of these are obviously elongated and even spirally twisted and branched. Beside these there are smaller channels with narrow lumen and a lining of cubical or flattened cells. These, too, branch and sometimes anastomose and many of them are continuous with the liver cells of the adjacent side of the lobule. When the destruction of the lobules has been very widespread and the fibrous band is very wide, it is frequently found that no such connection takes place, but another change is substituted, which will be described later.

It is perfectly conceivable, therefore, that the portions of these strands in connection with the liver cells for such a distance as would correspond with the remainder of the radius of the old lobule, may represent compressed or modified liver cells, and it is not possible to bring absolute proof in all cases that this is not so. Frequently, however, the ducts are very much longer than could be accounted for in this way, and it will be decisive in this regard to search for evidence as to whether their cells are in a stage of degeneration or retrogression, or in a condition of progression or proliferation. Sometimes the strands of fibrous tissue are so narrow and the ducts so short that this latter point alone could yield a decision.

In a case which presented itself recently at the Johns Hopkins Hospital the state of the liver seems to throw some light on the process.

CASE 1.—Autopsy, 1829. This was the case of a man who died after a brief illness, in which icterus, delirium, etc., were prominent symptoms. The liver was pale greenish-yellow in color, quite smooth, and on section showed the lobules very distinctly as slightly prominent, rather opaque, greenish-yellow masses. The consistence of the liver was slightly increased, but there was, macroscopically, no distortion of its structure. Microscopically, there was found to be a slight irregularity in the form of the lobules, with a moderate increase in the periportal connective tissue. The liver cells in the lobules were not homogeneous in appearance, but some, chiefly the more peripheral, were greatly enlarged and so loaded with fat that the protoplasm appeared as a delicate web. The nuclei were all well preserved. The remaining cells were small and flattened, and frequently arranged in double rows so as to present a rather wide lumen. Their protoplasm stained rather deeply and was not granular to the degree seen in the normal liver. In both of these types of cells abundant mitotic figures could be seen. In the connective tissue strands, but continuous with the liver cells, there were numerous ducts, readily distinguishable from the duct-like strands of liver cells in the lobule. In these, numerous mitotic figures were found. The bile ducts proper were not especially altered, but occasionally mitoses were found in their cylindrical cells.

In this case, with the typical formation of bile duct-like strands in the connective tissue, it is clearly seen that these structures are by no means degenerative in character, but are due to an active production of new cells by an intercalated mitosis. In the advanced cases of cirrhosis such distinct evidence of proliferation of the cells of the ducts is usually not to be found, but the great length and tortuous branching which often characterizes them, and the good state of preservation of their cells makes it practically certain, in the light of this case and of the cases of regeneration after acute yellow atrophy, that they are due to a proliferative process. Their lack of resemblance to the elongated red staining cells so familiar as the result of compression of the liver by tumors or abscesses need scarcely be mentioned.

While these strands must be regarded as progressive in character we can not be sure that they are exclusively derived from the bile ducts. Where the case can be observed in the early stage, as in the one described, the continuity of the duct with the liver cells is often to be made out, and even when this continuity is broken through, as it must be in most instances, no greater difficulty in the reinstatement of the continuity need be anticipated than in the fusion of the edges of proliferat-

ing epithelium which approach one another to heal over an ulcer in the intestine or a wound in the skin.

In the case described above there was, further, the modification in the liver cell strands, which produce an appearance something like that of the bile ducts, but since these cells were in active mitosis they could not be compressed or degenerating. On the contrary, it seems probable that they should be regarded as a reversion to a less highly specialized and temporarily nonfunctional form for purposes of reproduction, and in all probability in a later stage such cells would have regained the ordinary appearance of liver cells. A similar modification in the liver cells was pointed out to me by Dr. Opie in another case, in which, as a result of appendicitis with generalized acute peritonitis, there was widespread necrosis of the central portions of the lobules. In this case, in which death occurred so soon that the necrotic cells were all in their original position, many strands of the intact liver cells within the lobule had assumed the form described in the other case, although there was nowhere any proliferation of connective tissue and I was able to find abundant mitotic figures among these intact cells of the lobule.

Thus, while we can not say absolutely that the injured liver cells in a compressed state do not constitute some part of the duct-like strands found so abundantly in the wider bands of fibrous tissue, the weight of evidence is entirely in favor of the idea that these are the result of intercalary proliferation by mitosis in the bile ducts or, perhaps, in peripheral portions of the liver cell strands which remain in continuity with the pre-existing bile duct. Where the liver cell strands are interrupted or destroyed, partial or complete collapse of that portion of the lobule results, but whatever cells are left in the direction of the large bile duct proliferate and reinstate, if possible, the connection with whatever cells remain in the lobule. If liver cells are left in connection with the duct they proliferate with the same end in view.

This brings us to another point, perhaps the most important, in showing this proliferative power of the bile ducts in the older cases of cirrhosis. Often the connection with the liver cells is not reinstated and the bile ducts are left ending blindly in the connective tissue. Such ducts may often be shown to give rise to isolated bulbous masses of cells which gradually acquire the characteristics of highly specialized liver cells. That they are newly formed is shown by their form, their fresh appearance, and by the lack of pigment frequently found in the adjacent old liver cells. Further, it is interesting to note that one may be certain that they are actually formed from the bile duct epithelium and not merely isolated from the neighboring lobule by the fact that specialized pink-staining liver cells may be found not only in the bulbous extremity, but also intercalated singly among the ordinary cells of the ducts. These are, therefore, in every way like the bulbous sprouts which are described in the case of regeneration after acute yellow atrophy, and indicate very clearly not only that the so-called newly formed bile ducts really are newly formed bile ducts and not compressed liver cells, but that they possess a very considerable power of producing new liver tissue.

All of these processes taken together show that we must regard the cells of the bile ducts and the liver cells as identical and equivalent as far as regeneration is concerned, and that while the liver cells are specialized for functional purposes, they are perhaps a little more ready but no more potent in the reproduction of new liver cells than the epithelium of the bile ducts. It is, therefore, of little moment to determine whether doubtful cells are liver cells or bile duct cells, the essential point in this study is the proof that these cells are proliferating and not degenerating.

Of the degenerative changes which are in progress throughout the cells of the lobules and of the inflammatory reaction so frequently seen in the intervening tissues I shall not speak. Nor of the somewhat unsatisfactory classification of the forms of cirrhosis on anatomic grounds, although the idea is of interest that the difference between the hypertrophic or intralobular form of cirrhosis and the annular atrophic or portal cirrhosis lies in the distribution of the necrotizing process which affects the liver cells and which, as Dr. Opie has recently emphasized, depends so largely on the circulation of the lobule.

CONCLUSIONS.

In conclusion we may state that in the ordinary type of interlobular cirrhosis there is a primary destructive process leading to the disappearance of portions of the cell mantle surrounding the central vein of each lobule. The framework of the lobule persists but usually collapses, and there is produced an irregular lobular mass in which the central vein is in places left more thinly covered by the radial strands of liver cells, or even completely exposed and surrounded only by the connective tissue framework. The remaining liver cells proliferate rapidly by mitosis and generally increase the size of the portion of the lobule which is left. In this process they sometimes assume temporarily almost the form of bile duct cells. The connective tissue bands which run through the liver and separate these irregular hypertrophied remains of lobules consist of pre-existing connective tissue together with some which is newly formed. Numerous bile duct-like canals course through these bands and it is thought that these are produced by proliferation from the pre-existing bile ducts. The degeneration of compression of liver cells in the production of this appearance is not thought to be of importance. That the canals are composed of proliferating cells is shown by reference to a fresh case in which mitoses were abundant in their walls and by the fact that they frequently sprout out to form isolated bulbous masses of new liver cells. The bile duct epithelium and the liver cells are shown throughout these processes to be equivalent so far as the regeneration of the liver tissue is concerned.

The anatomic picture presented by a cirrhotic liver is, therefore, usually one in which the regenerative processes are the most striking, the destructive process being sometimes evident, sometimes entirely past and represented only by the widespread scars.

Cirrhosis of the liver may be defined as a chronic disease in which destructive processes, probably often repeated, result in a loss of the functional liver tissue immediately followed by the formation of a scar, the healing process, and later by an attempt at the restitution of the liver to normal by regenerative processes.

DISCUSSION.

DR. FELIX ADLER, New York City—At a very early stage in the experimental cirrhosis of the liver is seen the proliferation going on in the interior of the bile ducts—larger bile ducts, common smaller bile ducts down to the very minute ones—where no liver cells could possibly go. The proliferation of epithelium is followed by the widening out and distortion of the basilar membrane and finally the sprouting into branches. This occurs at a very early stage, for in-

stance, in that form of experimental cirrhosis which can be induced by the feeding of tobacco, and it bears out Dr. MacCallum's theory very thoroughly that at so early a time, when the cirrhotic condition—when the affection of the interstitial tissue—is progressing and is at a very early stage, the bile ducts begin to sprout and proliferate.

DR. E. LIBMAN, New York City—Some years ago I saw the liver of a child supposed to be suffering either from sepsis or hypertrophic cirrhosis, with fever; the entire period of observation only extended (so far as could be determined) over four or five weeks; and it turned out, at the postmortem, to be a case of sepsis, with abscesses of the kidneys. It was interesting to know that in that liver there were in five weeks an increase in connective tissue, and many of the changes which Dr. MacCallum has pointed out; it is particularly interesting because Dr. MacCallum mentions that the changes can come early.

DR. JOSEPH MCFARLAND, Philadelphia—Did I understand Dr. MacCallum to say that he thought the changes in cirrhosis of the liver were primarily necrotic and secondarily productive, or the reverse?

DR. WALTER L. BIERRING, Iowa City—It would seem to me that we might include in these regenerative changes, referred to in connection with cirrhosis, also that condition known as cirrhosis carcinomatosis, which is a sort of adenomatous hyperplasia taking place in a cirrhotic liver. There is a definite new growth of cells which resemble hepatic glandular cells, and frequently take on an atypical growth, subsequently undergoing a certain necrosis or fatty degenerative change and presenting to the naked eye yellowish-white or softened areas in the cirrhotic tissue. The term "carcinoma in cirrhosis" or cirrhosis carcinomatosis is usually applied to this regenerative process.

DR. W. G. MACCALLUM—Although I have not paid special attention to the forms of cirrhosis resulting from biliary obstruction, the anatomic conditions in those cases which occurred in our series have been practically the same, with the exception of the addition of the continued inflammation about the bile ducts. The hypertrophic or intralobular cirrhosis may perhaps be explained in the same way, excepting that there the cell's destruction has occurred diffusely throughout the lobule, leaving scattered cells from which regeneration occurs. In answer to Dr. McFarland's question I feel quite convinced that cirrhosis of the liver is not due to a primary growth of connective issue; we must, with Ackermann, regard the cirrhotic liver as a condition in which a primary destruction of the liver cells has been followed by scar formation. Dr. Adler's observations seem to me to correspond very closely with what I was able to observe in the case of which I have spoken as an early stage of cirrhosis, and in which in the delicate bands of fibrous tissue new bile ducts in the form that Dr. Adler has described, were found. With reference to Dr. Bierring's remarks I may refer to the paper of one of our students[1] wherein was expressed the idea, really suggested at first by Weigert, that in all probability the cirrhosis of the liver had been the result of destructive and degenerative changes, of healing, and of a subsequent regenerative process, which in Weigert's phrase had overstepped the mark and had gone on to the formation of a true tumor which could produce metastases. I have been particularly interested in the early appearance of these regenerative changes to which Dr. Libman refers. The necrotic liver cells may still be present where abundant mitoses in the intact cells are visible. Quite the same thing I think must be familiar to you all in the cases of acute nephritis in which the destruction of many epithelial cells stimulates the production of mitotic figures in those that are left, while, although regenerative changes are certainly present in the chronic nephritis, one is no longer able to find mitotic figures in such kidneys.

1. Catherine Travis: Johns Hopkins Hospital Bulletin, vol. xiii, 1902, p. 108.

Bartholin's glands are named for Thomas Bartholin, a Danish physician, who was born at Copenhagen in 1619 and who died in 1680.

HEART DISEASE AS AN OBSTETRIC COMPLICATION.*

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For many years heart disease has been recognized as an important disturbing complication of pregnancy, labor and the puerperium, while on the other hand, careful attention has been directed to the deleterious influences of pregnancy, labor, etc., in the causation of heart disease. This subject has furnished several interesting pathologic questions that are not yet solved, and some questions of management are not yet agreed on. I do not hope to add new facts, but especially to direct attention to a few points in the management of this complication that are somewhat frequently overlooked.

The term heart disease is a broad one, and of course embraces many different pathologic conditions. It might be of advantage to separately consider some of these different conditions, and especially to distinguish between diseases of the myocardium and those of the endocardium. However, in a general paper, we may adopt the usual custom of considering together all these conditions.

Heart disease may arise and develop during the pregnant or puerperal state, and be due to it, or it may have existed previous to pregnancy, and influence the course of pregnancy or labor, or be itself influenced by them. An example long recognized of heart disease arising during the puerperium is furnished by cases of endocarditis resulting from puerperal infection. Another condition less known is that of myocarditis resulting from the toxemia of pregnancy. A parenchymatous degeneration of the myocardium is a common and characteristic finding in postmortem examinations of women dying of gravidal or puerperal eclampsia. Careful study of the heart and circulation during an attack of eclampsia confirms the belief that myocardial degeneration is a common condition in eclampsia, and also probably in the large number of cases of eclamptogenic intoxication when convulsions do not supervene. The lesion is of all degrees of severity from a slight cloudy swelling to a very serious fatty degeneration. Corresponding to the anatomic changes the symptoms are from those of a slight disturbance of the pulse on exertion to the most serious circulatory disturbances consisting of general edema, and especially edema of the lungs, coughing and spitting blood, nausea and vomiting, dyspnea and palpitation. The frequency of this condition, if it corresponds to the frequency of the disease, is several times as great as that of eclampsia, being found, perhaps, in 1 per cent. of all pregnancies.

Fritsch and Loehlein have also called attention to the fact that a systolic murmur heard over the base of the heart and propagated along the vessels is found very frequently in the puerperium and occasionally during pregnancy. It resembles in some ways the murmurs of anemia and chlorosis, but its mode of production and its significance are not determined.

In this connection a word may be said concerning the much-debated question of hypertrophy and dilatation of the heart during normal pregnancy. First Larcher and some others found, in postmortem examinations of women dying in labor, that the weight of the heart is greater than in case of the non-pregnant women. These

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