XXIV. *On the Secretory Apparatus of the Liver.*

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THE general arrangement of the structures composing the liver, especially of the vascular portion of the organ, has been well understood since the time when Mr. Kiernan's researches were published; the chief points which since then have engaged further inquiry, are the exact mode in which the minute biliary ducts take their origin, and the disposition and function of the epithelial cellular element, which physiologists now justly consider as an agent of primary importance in the elaboration of the biliary, as well as of every other secretion. Mr. Kiernan described the biliary ducts occupying the interlobular fissures, as anastomosing and giving off branches, which entering the tissue of the lobule, formed there a "reticulated plexus;" this account has been very recently confirmed by German anatomists of celebrity, viz. Muller, Weber, and Kronenberg, and their view is adopted and further confirmed by Mr. Paget in the last Report of the progress of Anatomy and Physiology, January 1845. Mr. Bowman's view of the arrangement is different; he denies the existence of any lobular biliary plexus, and states that the basement membrane terminates at the surface of the lobules; he confesses however that we possess no accurate account of the mode of termination of the biliary ducts, and seems to agree with Henle that it has not yet been determined in what manner the contents of the epithelial cells find their way into the ducts: these two points I hope to elucidate in some degree satisfactorily in the account which follows.

If a thin section of the liver be examined under moderate compression with a linear power of 70 to 100 diameter, a number of lobules are observed of an irregular form, which on the whole approaches the circular; in or near the centre of each of these is a large foramen indicating the position of the intralobular vein, the lining membrane of which can be clearly distinguished; from this to the circumference of the lobule, lines of dark or mottled appearance about $\frac{1}{1000}$th of an inch in width are seen radiating on every side; these radii can seldom be traced in a continuous line to the margin of the lobule, but either pass into others so as to form a long meshed network, or else dip down and become lost to view; those, however, which reach to the margin can often be followed for some distance towards the centre. The appearance now described is best observed in the liver of the Rabbit or the Sheep, but can be seen also more or less perfectly in the human liver, and in that of the common domestic animals. If in a broken lobule one of these radii be examined with a power of 200

linear, it is seen to be formed by the apposition of numerous epithelial cells in a linear series; these series are not constituted by a single file of cells, but they are to a certain extent superposed, so that one cell may be overlapped by one or more adjacent. No enveloping membrane can be discovered containing the lines of cells; they evidently lie free, side by side, in the interstices of the blood capillaries, and are surrounded and imbedded in a structureless substance of indistinct granular appearance, which probably constitutes their "blastema" or formative material. Each lobule is separated from the adjacent ones by narrow spaces, the interlobular fissures of Mr. KIERNAN; and where three of these unite there is a triangular interval, the interlobular space. Now if the margin of an entire lobule be examined, it is found to be invested by a delicate membrane, through which the outline of the last epithelial cells of the several linear series may be clearly discerned; this corresponds to the basement membrane of Mr. BOWMAN; and the perfectly defined and smooth margin of a lobule invested by it, is strongly contrasted with the irregular jagged appearance of a broken edge. Traced laterally, this membrane is found to line the side of one lobule, to form the floor of the intervening duct, and then to ascend along the side of the opposite lobule, thus investing by a continuous surface the opposite sides of two adjacent lobules. Again, if we follow it along the margin of the lobule, we may often assure ourselves of its existence for one-half or more of the periphery; but it is rarely possible to trace it completely round, inasmuch as the plane of the section scarcely ever coincides perfectly with that of the duct; I have however in three or four instances *succeeded* in doing so; and in many others, where after tracing it along a great part of the circumference it has for a short distance been lost to view, I have obtained assurance of the presence of the duct by appearances of the following kinds, viz. the lighter colour and evident depression of the interlobular fissure, the existence of an opake deposit occupying the course of the duct, and which had been observed in other ducts whose cavities had been laid open; or lastly, by a dark line extending from one interlobular space to another, which was formed by the concurrence of the radiating linear series of two opposite lobules, which appear to meet and terminate above their common duct. But though the real arrangement be as I have now described it, yet in by far the greater number of instances the lobules appear to be continuous with each other at one or more points, so that although at one level the outline of the lobule be well-defined by the zone of the portal vessel and the accompanying duct, yet in all others there is a continuity of tissue, both of the capillary and of the epithelial element; this view, which differs from that of Mr. KIERNAN, seems to be admitted at present by most observers*.

It might be objected to the above description, which regards the lobules as embraced by interlobular ducts on every side, that those lobules which form the walls of portal canals must be without ducts on the side looking toward the canal, since

* I have since ascertained that the livers of different animals vary in this respect; the lobules of the organ in the Pig are separated by fissures exactly in the manner Mr. KIERNAN describes.

there exist no lobules there with which they can be in relation; the arrangement, however, appears to be quite in harmony with the description I have given. Those lobules which adjoin the portal canal on the side of the branch of the hepatic duct contained in it, have a collateral canal running along their sides from which interlobular ducts pass in at each corresponding fissure; the floor and sides of this canal are beset on their outer surface with epithelial cells; the remaining lobules, by far the greater number, which adjoin the branch of the portal vein, have a similar collateral canal from which interlobular ducts proceed, but it differs from the preceding one in not having a layer of cells on its outer surface; from both these canals branches pass off, which probably directly proceed to enter the main duct*.

The most important point in the foregoing description relates to the absence of real tubular ducts from the interior of the lobules, a view which, proposed some time ago by Mr. Bowman, has lately been contradicted by the German anatomists before mentioned, who in this respect coincide with Mr. Kiernan; I will therefore shortly state the proofs which appear to me satisfactory on this point. These are, first, the non-existence of basement membrane in the interior of the lobules, which in common with Mr. Bowman I have been unable to detect; yet were this simplest constituent of a duct present it could hardly escape notice, especially as in other glands it admits of being readily demonstrated; at the broken margin of a lobule it may be well seen that the projecting extremities of the linear series are quite free, and exhibit no trace of any containing membrane. Secondly, if the margin of a lobule be carefully examined, where it forms the side of a fissure, the basement membrane may often be clearly seen, and through its transparent texture the terminal cells of the linear series are easily distinguished, resting against and contained by it. Now were the membrane inflected to form lobular ducts, surely some indentation or irregularity would be visible at the margin of the lobule, but I have often traced the outline carefully without observing any such. A third proof is supplied by the result of some experiments which I made on rabbits. I tied the duct. com. choled., and shortly after death, which took place at periods varying from one to four days, I examined their livers: these organs were found to be beset on the surface and throughout their substance with numerous spots of deep yellow colour, evidently produced by accumulation of bile; a section of these spots, examined under the microscope, showed that they were very partial, never extending throughout the whole of a lobule, but frequently situated in two or more adjacent; their outline was always well-defined, and not the slightest appearance of a distended plexus of ducts could be observed: this last evidence appears to me conclusive. I can hardly conceive that if any plexus of anastomosing ducts existed, the accumulation of bile should take place in definite spots, and those not always situated in a single lobule, but in two or three adjacent. With regard to the proofs from injection which may be adduced in

* The description above given has been taken from examination of the larger portal canals; with regard to the smaller ones I cannot speak so decidedly, but it seems fair to infer that the arrangement is similar.

support of the contrary view, the suggestion of Mr. Bowman appears to me most probable, that the injection urged along the ducts had made its way into the interstices of the capillaries, and thus given rise to the appearance of a plexus; and in a subsequent part of this paper it will be shown that a condition of the lobules temporarily exists, in which such an occurrence might easily be conceived to take place.

Supposing it then conceded that the above account is correct, we may next inquire in what manner the structure described subserves the process of secretion as carried on in this organ. Now one peculiar circumstance at once arrests our attention, viz. that whereas in most other glands the epithelial cells are situated on the free surface of the basement membrane, and therefore in the cavity of the duct, they are here found on its deep or attached surface; in explanation of this it may be remarked, as Mr. Bowman observes, that the epithelial cells are, in point of function, the real continuations of the ducts, and the remarkable linear arrangement which so generally prevails, appears to me to suggest the idea that the rows of cells represent an intermediate stage of the development of primary duct tubules, the cells being apposed to each other, as in the formation of an ultimate nerve tube or muscular fibre. That the epithelium is the essential agent in the process of secretion, is now I think acknowledged by the great majority of those who have examined the subject. Mr. Goodsir, in his lately published work, has brought together a great number of examples, chiefly from the lower animals, in which it is distinctly shown that secretions of various kinds are formed during the growth of nucleated cells; and similar particles, especially under certain morbid conditions, may, in the very organ we are now examining, even in the human subject, be proved to fulfill the same office. Now where the epithelial cells are found on the free surface of the basement membrane, it is easy to conceive that the materials assimilated during their growth, are by the dehiscence of the cell, or its being cast off during the formation of fresh cells, set free in the cavity of the duct; but in the case of the liver the arrangement is very different, the greater proportion by far of the secreting cells being remote from any free surface on which their contained products might be poured out: the question then presents itself, in what manner does the secreted material of the cells find its way into the cavity of the surrounding duct? I will now detail the observations I have made which bear on this point.

The ductus communis choledochus of a rabbit was tied, death ensued in about twenty hours, apparently from gradual sinking, no traces of inflammation being visible; the gall-bladder was found tolerably full of healthy bile, the liver healthy, with the exception of some masses of morbid deposit which I have elsewhere described*; these were however quite local. On examining thin sections near the surface, where a good view of the lobules and their intervening ducts was obtained, it was manifest, in almost every instance, that accumulation of bile had taken place in the centre of the lobules, as indicated by a yellow zone of some width surrounding the intralobular

* Medical Gazette, October 24.

vein; no other change from the usual appearance was observed. Now this case presents, I think, the earliest effect of interruption to the flow of the secretion, and the appearance noticed seems to point out the exact point where the secreting process has its first origin, viz. in the commencement of the rows of cells surrounding the central axis of the lobule; here, though in so remote a situation, bile is formed, and from hence it is doubtless transmitted.

In many livers I have observed a remarkable difference between the condition of the peripheral cells adjoining the duct and those situated more centrally, while those in the interior appeared of their usual pale or light yellow colour; the terminal zone was of a much darker and more opake aspect; and often, where the cavity of the duct in the fissure was not exposed, its course was manifestly indicated by this dark tract, extending from one interlobular space to another; on more particular examination this dark aspect was found to depend on the presence of very numerous oil-globules in the cells which intercepted the light. Now as we find one or two minute oil-globules in almost every cell, the conclusion seems quite legitimate, that where these are found greatly multiplied, the cell which has produced them must be in a much more advanced state than those which contain but a few. In a human liver which appeared perfectly healthy I made an observation of similar import; the section had laid open the cavity of a duct for some distance, the margin of which on each side presented a perfect fringe of cells containing bile, while for a short space further on the course of the unopened duct was indicated by a yellow tract of cells extending above it, whose deep biliary tinge contrasted strongly with the pale tint of the surrounding substance; in several other ducts of the same liver a similar condition was observed. These observations render it nearly certain that the secreting process reaches its termination at the margin of the lobule, and I shall now endeavour to show in what manner the secretion is discharged into the cavity of the duct. The appearance which the margin of a lobule presents when the process of secretion has been proceeding actively, differs much from that which is observed when the lobule, so to speak, is quiescent; in the latter case, as I have described it, the margin is well-defined, and bounded by a distinct basement membrane, while the terminal cells of the linear series contain few and minute oil-globules, and do not appear to project outwards in any degree; in the other case the margin of the lobule has an opake cloudy appearance from the multitude of oil-globules; several cells are seen projecting into the cavity of the duct, giving the wall occasionally a tuberculated appearance; these cells contain oil-globules, and their wall is sometimes so extremely delicate as to be barely perceptible, even under a high power. Very many oil-globules are also seen, which lie evenly in contact with the sides and floor of the duct; it is difficult to determine whether these have escaped from their cells or not; it seems probable, however, that they are for the most part free, having recently been liberated by the solution of their cell-wall. The margin of a lobule in the condition now described presents no trace of basement membrane, the cells themselves form

the wall of the ducts, preserving still the general outline; it seems therefore certain that the basement membrane is only a temporary structure, which disappears when the cells are actively discharging their contents. A forcible and instructive contrast to the above condition was exhibited by a liver which I examined, which was in an advanced stage of fatty degeneration; in this the linear arrangement of the cells was lost; they lay confusedly together, and were gorged with their fatty contents; the margin of the lobule, far from exhibiting any tendency to discharge the retained secretion, was invested, and, as it were, closely bound by a membrane, not of the delicate transparent texture of the basement tissue, but much more opake, and closely resembling the semi-fibrous aspect of thin layers of false membrane*. I may here observe that I have not been able to find any epithelium lining the interlobular ducts; the basement membrane, where it exists, appears quite bare, and through its transparent texture the terminal cells can be plainly discerned with their granular or oily contents; this is not in accordance with Mr. BOWMAN's opinion, who considers "the epithelium of the lobules to be continuous with that of the ducts;" from this however I am led, both by observation and the bearing of the facts now related, to dissent: it then becomes a question, in what manner does the epithelium of the larger ducts terminate? This is difficult to determine, but I am inclined to think that it serves only as a lining to those ducts which have no secreting parietes, and that in these it supplies the mucous secretion, with which we know they are lubricated. In the gall-bladder of a sheep examined immediately after death, the basement membrane of the plicæ was found to be beset with particles which had not the usual finely mottled aspect of columnar epithelium, but seemed to be composed of very minute globules; in a short time these dissolved away into an amorphous matter. In the hepatic duct the epithelial particles were very small, about $\frac{1}{7000}$th of an inch in diameter; these also disappeared very soon; the general surface was covered by a great number of globules considerably larger, but of very various size, which closely resembled the mucous globules in the secretion of the nose or pharynx. A similar appearance was observed in the hepatic duct of a dog, where after a very short time, the epithelial particles covering the surface became converted into groups of minute globules; according to this view, the *excretory* part of the duct would have its own peculiar protecting epithelium, preparing the surface for the passage of the bile furnished by the *secretory* portion†.

From all the facts which have been now related, it may, I think, be concluded, that the cells forming the margin of the lobule are those in which the elaboration of the secretion is perfected, and that as this is effected, they burst and discharge

* In cases of this kind the primary cell membrane is often seen to be manifestly altered, appearing striated and of a coarser texture.

† I have ascertained subsequently, by examination of perfectly recent specimens, that there is occasionally a layer of epithelium on the free surface of the basement membrane, but it is extremely delicate when it exists, is often absent, and does not appear to be in any way continuous with the secreting epithelium of the lobules.

their contents into the cavity of the duct; this view accords with that of M. HENLE, as to the arrangement of the ultimate secreting elements of the mammary, lachrymal and salivary glands, which he believes to consist of vesicles filled with nucleated particles, seated on the closed extremity of a terminal branch of the duct.

It has now been shown that the secreting process commences in the centre of the lobule, and terminates at its margin along the line of the surrounding duct; but we have yet to consider the mode in which its progress is conducted, how the secreted material makes its way from cell to cell. This is a subject of which we have but little knowledge; the existence and nature of organic forces are as yet declared to us by their effects only; we can however refer to several examples, which exhibit a process similar to the one we are now considering; in cartilage, we believe the nutrition of the greater part of its substance to be performed by the nucleated cells which lie scattered throughout it, and attract from each other the nutrient fluid originally received from the blood; in the less perfect varieties of bone, crusta petrosa, the process is nearly the same. Mr. GOODSIR, in his description of the human placenta, has stated that a double layer of cells is interposed between the maternal uterine sinuses and the umbilical capillaries of the fœtus, which are probably concerned in the transmission of fluids from one to the other; and lastly in plants, we know that there are several parts of their structure through which fluids are transmitted, which consist of nothing else but a congeries of cells. Some observations may now be mentioned which elucidate in some measure this function of transmission as performed in the liver. Having examined a considerable number of these organs, I have generally noticed that those which had been secreting most actively, which presented the least appearance of retained bile or oil, exhibited the linear arrangement of the cells most perfectly; while in cases of disease, where the secretion has been more or less retained or suppressed, the disposition of the cells has been much more irregular. It would therefore seem that the linear arrangement bears a relation to the integrity of the secreting process*. In examining isolated portions of rows of cells, where their outlines could be clearly distinguished, it has been very evident that they were differently disposed with regard to each other; some were seen to overlap the next in order, and the cell-wall could be clearly traced all round; others were flattened at their apposed edges, and simply united without overlapping; in others again the septum formed by their apposed walls was so indistinct that it could only just be discerned; and in a few instances it has appeared to be wholly or in part wanting, so that the cavities of the cells were fused together. Occasionally a globule of the secretion has been observed in the act of passing from one cell to the next, but in the greater number of instances there has not been any marked difference in the contents

* In the case of a patient who died from the effects of dilatation of the heart, the liver was found to present the "nutmeg" appearance in a very marked manner, the cells mostly containing particles of bile of a bright yellow colour; their arrangement was remarkably plexiform, so as to give the appearance of a close network with small light interspaces.

of cells constituting a linear series. Finally, I have several times noticed that the formation of young cells takes place chiefly at the extremities of the rows; I do not mean at the margin of the lobule, but in those which were seen projecting from a broken edge; in one instance a young cell had formed at the extremity of a row of four, it was distinguished by its smaller size, more distinct nucleus, and the absence of granular or oily contents; in front of it was a large and very distinct nucleus, with only a trace of cell-wall on one side. This would seem to indicate that the organic force which determines the formation as well as the growth of the cells is exerted chiefly in the longitudinal direction, *i. e.* in the axis of the row. The observations now related have an interesting correspondence with those recorded with respect to the behaviour of the cells at the margin of the lobule; in both instances the mature cell appears to dehisce in order to give exit to its elaborated contents; but in the one case this takes place into the cavity of the next cell; in the other, into the cavity of the surrounding duct. From all these observations, strengthened by the analogy to be mentioned, the following theory may perhaps be considered probable:—The mode of development of the Haversian canals in bone, of the primitive nerve tube and muscular fibre, presents us with examples of cells arranging themselves in linear series, very similar to those which we have described in the lobules of the liver; these cells thus arranged coalesce, and form the elementary parts of their respective tissues. In the liver the same type of arrangement seems to prevail; each linear series may be conceived to represent a primary duct tubule, the cavity of which remains divided by septa formed by the walls of contiguous cells; these septa at intervals give way, and by some unknown force (perhaps a *vis a tergo*, from accumulated secretion) the elaborated material is passed on to the next in order; a similar process being repeated in each cell of the series, till, by the dehiscence of the terminal one, the secretion is set free in the cavity of the duct.

Appendix.

The condition of the cells with regard to their coalescence is very various; in livers of sheep examined during the winter, a section, however thin, has been so opake that no satisfactory view could be obtained of it; in such the cells are found gorged with particles of secretion, and seldom, if at all, communicating; the basement membrane of the ducts has also a semi-fibrous aspect, and it is rare to observe the margin in an active condition. These facts, and the circumstance that the fusion of the cells is not so frequent in any case, as we should expect if it were essential, have led me subsequently to believe that a process of transmission *may* go on *through* the septa of the rows of cells and basement membrane, though there can be no doubt that it must proceed much more rapidly when the cells have coalesced and the basement membrane disappeared.

Explanation of the Plate.

PLATE XXII.

Fig. 1. Seven cells forming a linear series. None of them communicate with each other; they contain many oil-globules; no distinct nuclei. (From the liver of Sheep.)

Fig. 2. Four cells united together by their flattened and apposed margins.

Fig. 3. Three cells and part of a fourth. The septa between the 2nd and 3rd and between the 3rd and 4th have disappeared, and oil-globules are seen *in transitu*.

Fig. 4. Five cells of a linear series. The last is recently formed, as indicated by its smaller size and absence of granular contents; in front of it is a very large and distinct nucleus, round which a cell-wall has begun to form on one side.

Fig. 5. An interlobular duct partially exposed. Its margins are formed by cells containing bile, which also extend above it, in the direction of its course.

Fig. 6. View of a lobule completely surrounded by interlobular ducts. The basement membrane existed in each except where the dotted line is drawn. (From the Rabbit.)

a. Intralobular vein.

b.b.b. Interlobular ducts.

Fig. 7. Portions of five lobules, showing some interlobular ducts fairly exposed; the course of others is indicated by a dark tract of cells extending over them; in other parts adjacent lobules appear to blend with each other.

a.a.a. Interlobular ducts laid open by the section.

b.b.b.b. Interlobular ducts not laid open; a dark line indicates their course.

c.c.c. Margins of lobules indistinctly seen.

d.d.d.d. Intralobular veins cut across.

e. Branch of a portal vein cut across.

Fig. 8. The contiguous margins of three lobules, with the intervening ducts and the opening of an efferent trunk *c*.

a. Basement membrane distinctly seen limiting the dark peripheral tract of cells; secretion not proceeding.

b. No basement membrane existing; the extreme cells of the rows form the wall of the duct; the whole side of the lobule is covered with oil-globules which appear to be escaping from *open* cells.

c. An opening of communication with another duct; the basement membrane is seen lining the floor of the exposed duct, and is represented by fine striæ.

d. Sections of intralobular veins.

The above diagrams have been taken in all essential particulars from actual observation.