THE DISTRIBUTION OF FAT IN THE LIVER.[1]

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We have endeavored in the work upon which this paper is based to obtain some information relative to the fat which appears in the liver at death, as well as its nature and distribution. Fat which can be stained and recognized as such appears in a large percentage of all cases irrespective of age; in the one hundred cases comprised in this series, ninety-eight showed a recognizable amount of it; of twenty successive cases taken from our autopsy series, all showed it. In one hundred cases, fourteen times fat was present in extreme amount, a condition certainly pathological, for in thirteen of these where mention was made of the point, the macroscopic appearance was abnormal; thirty-two times it was considerable in quantity, which condition is probably pathological, for it is attended by an undue friability of the organ; often, too, the lobules are much less distinct than in the normal liver. In fifty-two cases, the fat was slight in amount, and twice it could not be demonstrated. These fifty-four cases are open to the interpretation that the fat is merely the expression of low vitality of the cell which is in some way prevented from carrying out completely its metabolism.

The cell may be likened to a mill which, with the usual number of workers, can handle a certain quantity of raw material, transform it into the finished product, without storing any of it on the premises. Let the mill be only half efficient by reason of half its employees being idle, and half its raw material is stored up on the premises. Or if the mill is suddenly supplied by one and a half times its usual raw material, one half of its daily income in raw material will be stored up. Thus the cell appears encumbered by fat when its working efficiency is lowered or when its fat supply is abnormally increased. We do not know whether the fat is the real raw material,

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or is an imperfectly finished product, but we assume that fat microscopically shown as such in the cell is material which in the normal liver cell would not appear; in other words, the normal cell-processes are accomplished with soluble materials, and these are ordinarily not to be demonstrated.

For the demonstration of the various types of fatty deposit in the liver, we have found Sudan III to be the most serviceable stain. Other methods, including staining by Nile blue sulphate, were also used, but we experienced some difficulty in interpreting our results from these sections. Although one of us (Klotz) has shown that *in vitro* the neutral fats, the fatty acids and the fatty acid soaps do give certain differences of color, yet by the use of Sudan III here no differentiation can be made with certainty between the neutral fats, fatty acids or oleic acid soaps, more particularly as these substances occur in mixtures.

From our observations we have been able to distinguish four types of fatty deposits in the lobules of the liver. Although these four types are readily distinguished, and are quite characteristic in themselves, we are by no means convinced that they differ as definitely in origin. These four types of fat deposit in the liver are as follows: (1) fat deposits in which globules alone are present in the lobule; (2) fat deposits in which granules alone are present; (3) fat deposits in which globules and granules are found in the same lobule; (4) fat deposits in which granules and globules are found in the same cell.

In the above classification we are laying considerable stress upon the *appearance* of the fat deposit in the liver. We are fully aware that a classification determined upon the physical characters of a substance is insecure, yet, as we shall point out later, these physical differences are associated with fairly definite differential staining properties.

Globules of fat may be of various sizes, ranging from minute spherical bodies to large masses occupying almost the entire liver cell. In some cells fat droplets of the smallest size are seen. These droplets are commonly aggregated towards one side of the cell, leaving the rest of the cytoplasm fairly free from fat droplets. As they increase in size, the droplets become fewer in number and the nucleus becomes slightly shifted to the cell wall, away from the fat deposit. This eccentric position of the nucleus is increased as the fatty materials accumulate until eventually the nucleus becomes flattened and elongated along one border of the cell. When smaller globules are present, the nucleus occupies a central position and shows no evidence of distortion. Gradually, however, when the fat droplets in the protoplasm coalesce, the nucleus is shifted eccentrically, and eventually occupies a position on the outer border of the large fat drop. The ectoplasm of the cell forms the boundary of the fat drop, while the protoplasm of the cell is reduced to a small area lying about the eccentric nucleus. Both the nucleus and the reduced protoplasm form a crescentic mass over the fat drop. It is, however, to be noted that the nucleus never becomes so compressed as to simulate that of the true fat cell. When thick sections are made, and the nucleus of the liver cell is observed in a vertical position, it has a round contour, and gives the impression that it is lying in the centre of the cell. When seen laterally, however, the nucleus appears oval with blunt and rounded ends.

Occasionally liver cells are completely distended with fat; the fat, however, is separated into several globules which have not coalesced. These globules seem to have between them a thin dividing membrane, which prevents their coalescence. When such cells are ruptured, the fatty contents flow together to form a single mass.

Granules, on the other hand, are readily distinguished from globules of the smallest size. In the case of globules, the intensity of the Sudan absorption increases with the size of the globule, the smallest globules appearing the lightest in color. Granules are uniformly of a brownish color, not unlike that seen in the granules of brown atrophy. The contour of the granules is moreover irregular, and commonly one can make out sharp corners and edges in their structure. Cells are frequently packed with these irregular granules, in which there appears to be no tendency to coalesce. The granules frequently take a concentric arrangement about the nucleus, but in other cases they are distributed diffusely, or in the periphery of the cell protoplasm. These granules we think to be evidence of degeneration.

In staining with Sudan III and hematoxylin, one can readily pick out the areas occupied by fat and distinguish the zone in the lobule which is affected. In the cases in which there is diffuse globular infiltration of fat in the lobule, it is difficult to make out the individual liver cells, as the knife drags a considerable amount of fat which blurs the section. In these cases of diffuse infiltration each liver cell is distended with the semifluid fat. In the older specimens crystals sometimes appear in these fat globules, probably crystals of neutral fats.

To sum up this question, we admit at the outset that we have no power of differentiating with certainty neutral fats from fatty acids or soaps. It is notable that fat appears in two forms, granular and globular, differing in appearance and perhaps in nature. We are not able to say whether one kind of fat can take two forms, although we are disposed to think that it does not, and that the globular and granular forms of fat may well be different forms, for example, the globular being perhaps neutral fat and the granular being soaps or yet other combinations.

In the fourteen cases which are definitely pathological, large globules of fat were always present, small globules frequently (eight), and granules rarely (three). If our supposition that the granules are quasi-pathological, be a correct one, it is likely that a liver so damaged as to be loaded with fat globules, would be perverted in function so that many of its cells would show fat granules; but the absence of these granules in eleven of fourteen cases seems to indicate that the two conditions do not necessarily arise from the same cause, or under similar circumstances; or else that the liver cell degeneration has advanced so far that it has passed the stage in which granules are to be seen.

The Globular Form.—There is no reason to suppose that small and large globules are different, for every gradation of size can be found, and globules appear to have the power of fusing just as they do in fluid; nor is there any reason to suppose that they exist outside of the cells, until such time as having distended the cells, they appear to have burst these and to have fused with other globules in inter-cellular spaces. In the light of the views held to-day as to the nature of the cell wall, namely, that it is a colloidal concentration of protoplasm rather than a real membrane, we find it hard to see why this so-called membrane should be resistant long after the cell protoplasm has been replaced: we incline to think that the signet-ring cell may gradually merge into a mere mass of globular fat, the nucleus disappearing. The most potent argument for this view is the huge size of fat globules in the liver. A digression may be made here to remark that in the case of globules of fat, large but not larger than the normal cell, the existence of this fat is consistent with the life and usefulness of liver cells. Whether the signet-ring cells functionate as liver cells we cannot say, but liver function can apparently be performed when no normal liver protoplasm other than nuclear can be made out in the section. It is well to make a mental correction of the apparent functional power of fatty liver tissue, because the tissue probably always seems more injured than it really is.

The fourteen cases of intense fatty change in this series do not arrange themselves naturally: twice they are alcoholic (a condition in which intense fattiness is well known to be almost, if not quite universal), seven times septic, five times toxic as the result of chemical poisons (compare the well-known effect of phosphorus), and once uremic. The last named was in no sense septic, and suggests that sepsis is not a necessary cause of this state: yet the fourteen cases uniformly exhibit a metabolic disturbance caused by a chemical or otherwise toxic agent. This observation does little more than support our previous supposition that fat is an evidence of the inability of the liver to perform satisfactorily one of its perhaps lesser functions, viz., the metabolism of fat. Carrying this statement further, we would expect to find that the mere process of disease-produced death, would, in itself, be attended by a lowering of metabolic power, so that all livers, save those found after instant death by accident, might be expected to show some fat; and so it appears to be.

Distribution of Large Globules.—Large globules occur most frequently in all parts of the lobules (twenty-seven): when one part only of the whole lobule is affected it is oftenest the peripheral (twelve), next oftenest the central (six), the middle zone never being the only part affected. If we count all combinations, globules are peripheral in forty-six, central in forty, middle in thirty-one. No generalization from this statement is possible, unless it may be said that the part which has the best double blood supply, viz., the mid-zone, is least often affected, and the change is not definitely connected with an over-supply of fat from the portal blood, otherwise the mid-zone would be more liable than the central. More likely does it seem that the mid-zone, which has, in addition to its portal supply, a supply of oxygenated blood from the hepatic artery, is by reason of its better supply of oxygen able to use up any excess of fat. Further, the central zone being next in order to receive oxygenated blood, is freer from this form of fat than the peripheral zone, which has only its portal supply.

Granular fat, on the other hand, we suppose indicates degeneration of the protoplasm, a condition that is not bettered by an increased oxygen-supply. Nor was the chronic passive congestion of the nutmeg liver a predisposing factor in those cases where the central zone was much affected; this observation at first sight appears to conflict with what we have just stated, because stagnated venous blood is the least oxygenated of all, but our supposition is not that lack of oxygen caused the defect, but that plentiful oxygen remedies it.

Irregular Areas of Large Globules.—In one case, groups of large globules appeared quite at random. It must be kept in mind that the knife may carry isolated globules across the section into different parts of the tissues, but this is generally readily recognizable. Twice, however, we have found a remarkable state of affairs: a definitely bounded macroscopically yellow area has proved to be made up of huge globules, the mass looking microscopically like a lipoma; however, in the liver tissue nearby globules of various size in the cells have indicated that the condition was one of gradual cellular acquirement, although we have no idea of the nature of the process which permits such a complete metamorphosis of localized pieces of tissue. These masses comprised many lobules, and their boundaries were those of lobules, a part of a lobule not entering into this state while the rest remained healthy.

Granular Fat.—Granular fat occurred more often than the globular, in the proportion of eighty-seven to fifty-eight. Granular fat alone occurred in forty, globular alone in eleven, while both were combined in forty-seven instances. The usual form is a slight distribution of granular fat throughout the lobules, while with this change are often united various distributions of globules. This universally distributed granular fat we suppose to be the true fatty degeneration of the liver (the word being used to designate a condition comparable to that found in the heart, and without prejudice to the question whether it is ultimately true infiltration or protoplasmic transformation). Whether these granules are a special form of fat, or whether they can coalesce and form globules we cannot say, but we think that they cannot coalesce. The occurrence of such universal granular fat appears to be consistent with otherwise perfectly healthy liver tissue, judged by the microscopic appearance, with ordinary stains.

When the granules are not diffuse but are limited to one or more zones of the lobule, they are most often central (ten), less often peripheral (two), and never median. If these granules have to do with ill nutrition or slight intoxication, as we suppose, it is to be expected that the part of the lobule doubly supplied with blood should be most free from them.

The appearance of fat when it occurs in the granular form is so distinct from the globular type that there is no difficulty in recognizing the condition. The character of the granules, whether in the peripheral or central zone, is the same. The granules first appear as very minute points distributed in the protoplasm of the liver cell without affecting the position of the nucleus. The granules later increase in size and also in number, until the cytoplasm is loaded with these discrete bodies, which have little if any tendency to coalesce. In no instance was it found that the quantity of fatty granules altered the central position of the nucleus, nor was the degeneration associated with any nuclear change.

Fat Globules and Granules in the Same Lobule.—In a fair number of cases it was noted that in the same liver lobule there appeared a deposit of fat, both of the granular and globular type. When these deposits were thus associated, the granular deposit was present in a diffuse form, while the fat globules were most commonly found in the peripheral zone. Such cases we describe as fat distributed diffusely in the lobule. The deposit of granular fat in the periphery was similar to the deposits in which globules alone were present in the lobule, and we could make out no direct association between the deposit of the globular and granular forms.

In other instances it was found that the granular deposit was predominant in the lobule, and only here and there was a cell or a small collection of cells containing fat globules. In these cases the globular deposit appeared to select no particular zone, but occurred sporadically in the lobule. These globular deposits were often very few, only one cell in a lobule, which was otherwise crowded with granular fat showing this deposit.

It is probable that, where there is a considerable deposit of fat in one or other zone of the liver along with the granular deposit in the other zones, we have to do with two separate pathological conditions, the one being superadded upon the other.

Granules and Globules of Fat Appearing in the Same Cell.—As we have noted above, fat may appear in the granular and globular type in the same lobule, and in some instances it appeared as if some of the granular deposit had coalesced to form globules. In only a few instances was it noted that definite small globules were present in a cell, while granules were also to be noted in the protoplasm of the same cell. This appearance was found the least frequently. It was sometimes noted that the globules in these cells had the same dark staining characters as were seen in the granular fat deposit. These cells containing both granules and globules had no fixed situation in the liver lobule, but were to be found in any of the three zones.

Fat in the Central Zone.—Our sections show that when we are considering the central zone alone, the fat found here is oftener granular (thirty-two), less often globular (sixteen). If our supposition that globular fat is a "physiological" phenomenon be a correct one, the difficulty is not to see why globular fat should be the rarer form in the central zone, but why it should be there at all, especially when the mid-zone is repeatedly free from it; yet we found this condition in six cases.

Is there a deposition of fat characteristic of uremia? In thirteen cases of uremia the fat was extreme once, considerable nine times, slight three times; it was diffuse four times, and the single areas affected were central (nine), peripheral (seven), middle (six); five times granular, four times granular and globular, and three times globular. From this observation, we are compelled to think that there is not a characteristic distribution of fat in cases of uremia.

It is of interest to note that of the sixteen cases in which the fat appeared in the central zone alone, thirteen were in females. Five of these were associated with recent pregnancies, three with uremia, one with pus tubes, and four with various infections.

CONCLUSIONS.

1. Nearly all livers at autopsy contain fat which is histologically demonstrable.

2. Fatty substances in the liver appear chiefly in two forms, as small granules and as globules of various sizes.

3. We suppose that granules indicate the (protoplasmic) change commonly spoken of as fatty degeneration, and that globules of small size are excess of fat, stored up by reason of some pathological change which may be merely temporary.

4. Fat is oftenest central, least often in the mid-zone.

5. A heavy deposit of fat is compatible with a competent liver.

6. Intense fattiness, generally globular, occurs with intoxications of bacterial and chemical nature, as well as in cases where a complex toxin is manufactured by the body-cells.

7. Granular fat occurs oftener than globular: it affects most often the central zone; globular affects most often the peripheral.

8. "Accidental" masses of globular fat are found at times, and appear to follow no rule of position: these are comparable to lipomata, which are evidently the result of a pathological process.

9. We found no deposit of fat characteristic of uremia.

10. We know of no analysis of the liver fats in the granular and globular states respectively: it seems to have been taken for granted that the deposits were one and the same. To determine the relationship, if any, between these two forms should be the basis of investigation.