CHLOROFORM NECROSIS OF THE LIVER.*

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The occurrence of serious, frequently fatal, poisoning as a sequel of chloroform anesthesia, manifesting itself first several hours or even a few days after the use of the drug, has been brought into prominence through the articles of Ballin, Bevan and Favill, Brewer, Brackett and others in this country, and of Guthrie in England; therefore, it is unnecessary for me to discuss the literature at length, as this will be found fully abstracted to 1905 in the article of Bevan and Favill,¹ and subsequent articles are indexed in the foot notes to this article.

REPORT OF THE CASE.

I desire merely to report a study of both the pathologic anatomy and the chemistry of a typical case, which I had the opportunity of examining at autopsy, through the courtesy of Dr. F. S. Tufts, and to consider certain features illustrated by this case and those so far recorded in the literature. Dr. Tufts has kindly furnished me the clinical history, which follows:

Clinical History.—"The patient, a vigorous young man, was born in Wisconsin in 1878. The family history is negative. He came to Chicago in 1899, and has been employed as a foreman in the hog-casing department of a packing house. In 1900 he married a first cousin, who gave birth to a healthy boy in 1904. His childhood history was negative, and up to 1902 he was strong, robust, and of very good color. In 1902 he lost weight and color, and began to complain of an occasional stomach trouble. He had no acute attacks or colic, but occasionally there was acute distress from gas after meals, with a sensation of fullness. The first acute attack of colic and cramps occurred on Jan. 1, 1907, and was brought on by a hearty packing-house restaurant dinner. I saw him two hours after the attack and found slight tenderness in the umbilical region, but nothing around or near the gall bladder; he returned to work the next day and was free from trouble until March 17. This second attack was apparently caused by fruit salad which he had eaten the day before. At this time I found no fever, some rigidity in the right rectus, but not much tenderness; he had had colic and cramps all night but not severe enough to call me. On the next day, March 18, he went to work, although still a little lame, and the following day visited me at my office, when the gall bladder was found markedly distended; it extended 10 cm. below the costal arch, was freely movable and slightly tender. At this time there was no fever, no icterus, nor even bile in the urine (Gmelin's test). On the next day his condition was about the same, although the temperature was 99.2, pulse 78. The following day (March 21) the temperature was normal and the tenderness was

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1. Bevan and Favill, Jour. Am. Med. Ass'n., 1905, xiv, 691-696.

subsiding, but he was quite pale and complained of feeling very weak; in the evening he was taken to the Englewood Hospital." Here his pulse, temperature and respiration were recorded as normal, and he was prepared for operation, which was performed at 4 p. m. on March 22.

Anesthesia.—The anesthetic was chloroform and it was "given with a free hand" by the anesthetizer, and cyanosis was very marked. The duration of anesthesia, however, was not long, as it is recorded that the patient left the ward for the operating room at 4 p. m., returned at 5 p. m., and was again conscious at 5:30 p. m.

Operation.—When the abdomen was opened the upper surface of the liver was found freshly adherent to the parietal peritoneum, while the lower surface, gall bladder and intestines were bathed with lymph and fresh adhesions everywhere. The gall bladder was thickened, but neither it nor the ducts were distended, and no stones could be palpated. On account of the evidently acute nature of the infection it was deemed wiser not to open the gall bladder, and the bad way in which the patient was taking the anesthetic impelled haste, so the abdomen was closed again without draining the gall bladder.

Postoperative History.—Following the operation the patient slept fairly well and the next day at noon the temperature rose to 99.7, but subsided on the following morning, March 24, although at this time there was a leucocytosis of 17,000. All this day the patient was in good condition, sleeping much of the time, until 11 p. m., fifty-five hours after the operation, when he began to be restless. By 3 a. m., March 25, he began to be delirious, acutely maniacal, and was unconscious from that time on, although he could be roused somewhat by calling. On the morning of this day the temperature at 10:30 was 99.3, pulse 82, respiration 22. The patient was very thirsty, icterus began to appear, and the urine, which before the operation had been normal, now showed much bile, albumin and hyalin and granular casts, but no crystals of leucin or tyrosin could be found. Under the influence of chloral and bromids the patient became more quiet at about 4 p. m., laughter and crying taking the place of the wild delirium previously exhibited. The jaundice had increased during the day. By 3 p. m. the temperature had risen to 103; at 5 p. m. it was 104; at 7 p. m., 106; and at 8 p. m., 107. Death occurred at 9:30 p. m., 100 hours after the operation.

Autopsy.—This was performed at 9 o'clock the next morning, in the undertaker's room, to which the body had been removed. An attempt at embalming with an arsenical solution had been made just before our arrival, but fortunately this was so ineffectually done that practically none of the fluid penetrated the viscera and they were almost unaffected; however, there had been some fluid introduced directly into the peritoneal cavity, which interfered with cultures being made from the peritoneal exudate and gall bladder; while of course blood cultures were made valueless by the intravascular injection.

Autopsy Report.—This is summarized below.

Anatomic Diagnosis: Acute hepatic degeneration and atrophy. Cholelithiasis with chronic suppurative and proliferative cholecystitis. Acute fibrinous pericholecystitis. Suppurative cholangitis with fibrous pericholangitis. Partial occlusion of cystic duct near juncture with hepatic duct. Recent operative incision in right hypochondrium. General icterus. Multiple ecchymoses in serosa of thoracic and abdominal cavities. Hypostatic pulmonary congestion. Right inguinal hernia.

External Appearance: Young man, slenderly built; fairly nourished; very icteric all over the body, especially the face; sclera bright yellow. Scar of old trauma over right tibia. Recent operative incision three inches long in right hypochondrium; also embalmer's incision in right arm. Discolored skin areas from saline transfusion over both pectorals. Right inguinal canal open a short distance.

Abdominal Cavity: Distended by clear embalming fluid (arsenic and bichlorid of mercury). (Clinically it was flaccid up to death.) Omentum free. Numerous small blood extravasations throughout omentum. Many hemorrhagic foci, size of pea and smaller, scattered throughout mesentery and retroperitoneal tissue. Several larger suggillations more sparsely distributed. Appendix free; three inches long, no mesoappendix; no changes.

Gall Bladder: Adherent to colon and pylorus by fresh, easily torn, fibrinous adhesions. Surface of gall bladder covered by fibrin, beneath which are numerous hemorrhagic extravasations into the subperitoneal tissues. Gall bladder wall greatly thickened, about 5 to 8 mm. thick. On palpation the bladder apparently semi-solid; cystic duct thickened and distended. Lesser peritoneal cavity free. Diaphragm at fourth rib on both sides. Slight adhesions about spleen.

Chest: The entire mediastinal tissue riddled by ecchymoses, averaging about the size of a pinhead. Pericardium studded with the same. Pericardial cavity normal. Both pleural sacs free from adhesions. Pleura everywhere studded with small ecchymoses.

Heart and Great Vessels: Normal. Portal system free from thrombi.

Lungs: Posterior parts of each lung congested and darker than the anterior and contain much fluid. (Probably part is embalmer's fluid; no clinical indication of edema before death.)

Liver: This is small; weight 1,050 g. The margin is two fingers' breadth above costal margin. The right lobe has been superficially hardened by embalming fluid. The left lobe is not hardened to any extent. The latter is very flabby, pinkish gray in color and looks almost as if decomposed. The anterior margin is very sharp. Surface discolored to a dirty pinkish-gray color and somewhat wrinkled. The right lobe shows the lobular marks with unusual distinctness on the external surface, as a fine network of lighter gray lines with reddish hexagonal areas between. The cut surface of the right lobe shows the same mottling as seen externally, and is of a light yellow tinge. The left lobe is very distinctly yellow; the lobular markings are difficult to distinguish. The consistence is very flabby so that the liver can be folded upon itself. The bile ducts and large vessels show no evident changes. On pressure on ductus choledochus, a purulent yellow fluid exudes into the duodenum from the ampulla of Vater. On incision of gall bladder a yellow muco-pus escapes. In the bladder are over 100 stones, black, hard, varying in size from 3 mm. in diameter down to that of the finest sand. The gall bladder wall is 6 mm. thick. There is nearly total obstruction of cystic duct near its junction with the hepatic duct by a fibrous occlusion (scar tissue) and pressure of a mass of recent fibrous tissue about the duct. The hepatic duct seems to be normal. A few stones occur in the ductus choledochus. The latter shows an inflammation and swelling of the mucosa.

Spleen: Apparently normal. Very much hardened by embalming fluid.

Pancreas: No evidence of fat necrosis, and no other change observed.

Kidneys: Somewhat hardened by embalming fluid. Normal size. Capsule strips normally; no evident pathologic alterations.

Adrenals: Normal.

Histologic Findings.—**Liver:** There is not a normal liver cell to be found, and very few, indeed, that are not totally necrotic. At first glance the liver resembles an organ that has undergone extensive postmortem decomposition, but it is soon seen that only the parenchyma cells have been affected, and that there are quantitative differences between the conditions in the center and periphery of the lobules. The lobules are somewhat reduced in size and only at the very periphery of the lobules can there be found parenchyma cells that show any approach

to the normal structure; these cells are never more than one or two layers deep from the periportal tissue, and the best of them show cloudy swelling and fine granules of fat. Immediately next to these cells is a narrow zone, representing a width equal to two to ten liver cells, in which the cells consist of a mere mesh-work of fat droplets with no cytoplasm remaining and only exceptionally a nucleus. In all the rest of the lobule, which part constitutes from two-thirds to four-fifths of the entire radius of each lobule, is total necrosis of the liver cells; nothing remains of them but the dead bodies of the cells, deeply stained by eosin and evidently greatly reduced both in size and number. There is no thrombosis in the hepatic capillaries, no acute or chronic inflammation, and no evidence of alteration in the bile ducts. By sudan III the necrotic central cells are found rarely to contain small fat droplets, although between them can be found Kupfer cells that are quite fatty. The vacuolated zone near the periphery is composed of cells containing large amounts of fat, and the most normal peripheral cells show numerous fat droplets.

Kidney: Epithelium of convoluted tubules is granular and many of the tubules are swollen shut, and some contain occasional fat droplets; these are especially numerous in the straight collecting tubules. Some of the epithelial cells seem to be necrotic. The glomeruli contain a considerable amount of granular debris, but otherwise no changes. There is no hemorrhage, acute inflammation or connective tissue increase.

Spleen, Myocardium and Pancreas: No changes found, except a small amount of fat in some of the muscle cells of the heart.

Gall Bladder: Diffuse infiltration of the wall with lymphoid cells, plasma cells and some polymorphonuclear leucocytes.

Chemical Examination of Liver.—Immediately after the autopsy the liver was cut into thin slices, and 850 grams of the fresh tissue were placed in a large volume of 95 per cent. alcohol until thoroughly hardened, and then subjected to chemical analysis, the details of which will be published elsewhere.² The chief results of this study may be summarized as follows: Among the water-soluble substances obtained by extraction of the liver tissue were considerable quantities of free aminoacids, presumably derived from the proteins of the liver cells through autodigestion; of these aminoacids there were obtained in pure enough condition for identification 0.34 gram of histidin, 0.26 gram of tyrosin; 1.50 grams of leucin, 1.57 grams of glycocoll and 0.58 grams of glutamic acid. The presence of arginin, lysin, and pyrrolidin-carbonic acid could not be definitely established, although there was obtained evidence which indicated that these substances were in the extracts. A further indication of the autolytic destruction of the liver proteins that was going on in this case was the finding of considerable quantities of proteoses, peptones, and probably of polypeptids. Free xanthin and hypoxanthin were also found in the extracts, undoubtedly derived through autolytic disintegration of the nucleoproteins of the liver cells. There was no increase in the gelatigenous substance of the liver, such as has been observed in acute yellow atrophy, since this is the result of regenerative proliferation of connective tissue, which had not begun to take place in the chloroform necrosis liver. The composition of the insoluble coagulated proteins left after thorough extraction of the liver with alcohol, ether, and cold and hot water, was found to be quite the same in this liver as in two normal livers, at least so far as the form in which the nitrogen is bound; whereas a liver from a typical case of advanced acute yellow atrophy showed some loss of diamino-nitrogen. This is shown in the following table giving the results of analyses of these four cases by Hausmann's method:

2. Wells, H. G.: Jour. Biol. Chem., 1908, vol. v.

COMPARISON BETWEEN ACUTE ATROPHY, NORMAL AND CHLOROFORM NECROSIS LIVERS.

	Acute Atrophy.	Normal (anemic)	Normal (congested)	Chloroform Necrosis.
Amid nitrogen.....	5.5	3.7	4.8	3.9
Humus nitrogen.....	3.6	3.4	4.9	5.7
Diamino nitrogen.....	26.2	32.8	30.0	30.0
Monamino nitrogen.....	64.8	60.3	60.2	60.3

This same insoluble residue, which consisted chiefly of proteins, contained the same amount of sulphur as normal liver extracted under the same conditions. The amount of iron was slightly increased, presumably because the hemolysis that always occurs in jaundice sets free iron-containing pigment which the liver stores up. Phosphorus was found increased by three or four times the amount found in normal livers, and this in spite of the great destruction of nuclei that had taken place. No satisfactory explanation for this increased amount of phosphorus has been found.

There was found 72.4 per cent. of water in this liver, 8 per cent. of fats and lipoids and 18.8 per cent. of dry, fat-free solids, which is somewhat different from the proportions found in typical acute yellow atrophy, as shown by the following table:

	Water.	Fat.	Fat-free Dried Substance.
Normal liver (Quinke).....	76.1	3.0	20.9
Normal liver (Wells).....	77.6	5.0	17.4
Acute atrophy (Perls).....	81.6	8.7	9.7
Acute atrophy (Perls).....	76.9	7.6	15.5
Acute atrophy (v. Starck).....	80.5	4.2	15.5
Acute atrophy (Taylor).....	85.8	2.0	12.2
Acute atrophy (Wakeman).....	79.3	...	...
Acute atrophy (Wells).....	83.8	2.5	13.7
Acute atrophy (Voegtlin).....	78.0	6.6	15.4
Phosphorus poisoning (v. Starck).....	60.0	29.8	10.0
Fatty degeneration (v. Starck).....	64.0	25.0	11.0
Chloroform necrosis (Wells).....	72.4	8.8	18.8

In respect to the amount of water, this chloroform necrosis liver stands between the typical acute yellow atrophy liver and the ordinary fatty liver, just as it does in its histology; that is, there has been some replacement of water by fat, as in the fatty livers, but not so much replacement of protein by water as in typical acute yellow atrophy. These figures emphasize the fact that in chloroform necrosis the amount of fat is distinctly increased, although not so much is found on analysis as might be expected from the microscopic findings. Taylor states that, in the chloroform necrosis liver which he examined, there were 200 grams of fat, which would be about twice the proportion that was found in my case; unfortunately he has not published sufficient details of the analysis to furnish the accurate information desired.

The amount of lecithin and cholesterin in this case was found to be not greatly different from that present in normal livers, and thus again in marked contrast to the liver in acute yellow atrophy, as seen by the accompanying table.

While the total amount of lecithin has decreased, this is only in proportion to the decrease in the total size and weight of the liver; this proportional decrease has gone on in spite of a relative increase in the amount of simple fat, showing the same lack of correlation between the lecithin and the neutral fat which has been observed by others who have determined the lecithin content of organs showing fatty degeneration. Evidently, therefore, the increase in the fat content of the liver in chloroform necrosis is due entirely to neutral fats. The cholesterin, on

the other hand, has apparently remained in about the normal amount, and has not decreased with the lecithin and proteins; this is quite what might be expected from what we know of the tendency of cholesterin, when liberated by degenerating cells, to remain at the place where it is formed.

	Lecithin.				Cholesterin.			
	Normal. (Anemic)	Normal. (Congestion)	Chloroform Necrosis.	Ac. Atr.	Normal. (Anemic)	Normal. (Congestion)	Chloroform Necrosis.	Ac. Atr.
Fresh weight, per cent.....	1.6	1.4	1.5	0.45	0.26	0.37	0.52	0.3
Total dry weight, per cent.....	6.3	6.25	6.2	2.9	1.0	1.7	1.9	1.8
Dry, fat-free material, per cent.	7.7	8.0	8.1	3.2	1.25	2.1	2.9	2.1
Ether-soluble substances, per cent	35.3	28.0	17.3	17.6	5.7	7.4	5.9	11.1
Grams in entire liver.....	23.7	22.4	16.0	4.4	3.8	5.95	5.4	3.38

GENERAL CONSIDERATIONS.

If we examine carefully the cases of "delayed chloroform poisoning," as reported in the literature under various titles, it becomes apparent that there are included two fairly distinct types of cases resulting from the same cause, and that these types differ both clinically and anatomically. In one set the patient is usually a child; the clinical manifestations are vomiting, restlessness or extreme excitement, terminating in coma, frequently more or less cyanosis, and sometimes definite air hunger, a sweetish odor of the breath and acetone bodies present in the urine in most of the cases in which they were sought for; in other words, the symptoms resemble in many respects "acidemia" or "acetonemia," under which titles many of these cases have been described. The liver in these cases generally shows more or less fatty change; usually when described carefully the fat is said to have been chiefly in the periphery of the lobules, and there is no mention of necrosis of the hepatic cells in the published accounts of these cases. Generally, fatty degeneration and more or less acute parenchymatous degeneration, sometimes even severe necrosis, are found to have taken place in the kidney. In practically none of these cases has jaundice been observed, and the liver changes have not usually been very severe. To this group belong all but perhaps one or two of the cases described by Guthrie, and the cases of Brackett, Brewer, and Telford and Falconer.

Quite different from this group are the cases of Stocker, Bandler, Erlach, Marthen, Mintz, Ballin, Campbell-Horsfall, Guleke, Cushing, Taylor, Holmes and the one described in this report. Here the clinical picture at first is rather similar to the first group, in that the onset is usually with restlessness, excitation, and delirium, which passes into coma. However, in place of those symptoms which are usually considered as manifestations of acetonemia, there appears a rapidly developing

jaundice, which toward the end is generally very severe. Associated with this jaundice are frequently observed cutaneous hemorrhages. The manifestations resemble in every respect a severe cholemia, associated in some cases with the finding of leucin and tyrosin crystals in the urine. Consequently several of these cases have been reported under the title of "acute yellow atrophy of the liver," which diagnosis is supported in the main by the anatomic findings at autopsy. The liver is usually decreased greatly in size, with wrinkled capsule, friable consistence, and yellowish or red and yellow discoloration; often the organ is so severely disorganized, as in the cases of Taylor and the one here reported, that it may be best described as "putty-like." While there is always more or less fatty increase, this is usually more apparent than real, much of the yellow color commonly described as "fatty degeneration" being due to bile pigments; necrosis is the predominant change, beginning in the center of the lobules, as in typical "idiopathic" acute yellow atrophy.

I have had the opportunity to study the histologic appearance of three typical cases of this kind, including one that was reported by Dr. Bayard Holmes³ and, through the kindness of Dr. Hektoen, the case reported by Drs. Bevan and Favill, and the resemblance of the findings in all three is very striking. As compared with the histologic picture described above in connection with the case which is the subject of this report, the differences are but slight. The Holmes case differs only in having a slightly wider zone of well-preserved cells in the periphery and in the presence of more leucocytes, especially at the junction of the fatty and the necrotic zones. In the case of Bevan and Favill, which clinically was without jaundice or other evidence of hepatic involvement, the fatty zone is very much wider, and the necrotic central cells contain more numerous and larger fat droplets; the size of each lobule is, if anything, increased rather than shrunken. But, taken all together, the histologic picture is strikingly similar in all three livers, practically identical in fact, and indicates the specificity of the effects of chloroform on the liver.

This necrosis is associated with rapid autolysis of the dead cells, so that in my case the weight of the liver had fallen in four days to 1,050 grams, presumably from a normal weight of from 1,600 to 1,800 grams. As a result of this autolysis, leucin and tyrosin may appear in the urine, and free amino-acids may be found in extracts from the liver itself. Of particular interest is the fact that in all the reported cases of this type, as far as I can find, the patients were adults, varying from 20 to 42 years of age; whereas, in the acetonemia type, the patients were nearly all young children. The Bevan and Favill case, in "a girl, aged 12½ years,

3. Holmes, Bayard: Appendicitis, 1904, p. 214.

with the stature of a woman," seems to lie at the border line between the two groups, for clinically there was no jaundice and the manifestations were of the "acetonemia" type, but histologically the liver, which was enlarged rather than shrunken, showed a considerable amount of central necrosis, although the fatty changes were more marked than in either of the other two cases that I have studied, and the necrosis and autolysis a little less extensive.

Both sexes are represented in each type, with perhaps a slight preponderance of females. Why there should be this difference in the results of delayed chloroform poisoning in children and in adults I do not know, but the number of cases reported is too large to make it seem purely a matter of coincidence. Nearly all reported cases of fatal delayed chloroform poisoning seem to have occurred in the young, only two or three patients having reached the forties. Consequently there appears to be some difference in the liver or in the entire organism between youth and later life that determines this susceptibility to chloroform. In young adults the susceptibility of the liver seems to be particularly great, so that severe necrosis of this organ, with symptoms of hepatic insufficiency, dominates the anatomic and clinical picture.

The changes in the liver, in this second type of delayed chloroform poisoning, are not essentially different from the changes in the early stages of acute yellow atrophy, except that there seems to be a more extensive fatty degeneration and infiltration. In true acute yellow atrophy there is no distinct increase in the proportion of fatty matter in the liver, while the total amount of fat is decreased more or less from the normal, along with the general loss of hepatic substance. In chloroform necrosis there is always more or less fatty metamorphosis noticed microscopically, and in the two cases in which the fat was extracted and weighed, Taylor's and my own, the amount of fat was distinctly increased above normal. It is possible that if one were to secure a liver in chloroform necrosis as long after the onset of the hepatic injury as is the case with acute yellow atrophy, where death occurs usually only after weeks rather than days, the changes might be found still more similar, for I have found that it is possible for a fatty liver to lose much of its fat and to have the fat replaced by fluid during the healing stages of the hepatic lesions produced by hydrazine poisoning.⁴ However, even with this disparity of time, the results of analysis of a liver in idiopathic acute yellow atrophy of several weeks' duration are, on the whole, very similar to those obtained with this chloroform necrosis liver,⁵ and

4. Wells, H. G.: Pathologic Anatomy of Hydrazine Poisoning, *Jour. Exper. Med.*, 1908, x, No. 4.

5. Wells, H. G.: Chemistry of the Liver in Acute Yellow Atrophy, *Jour. Exper. Med.*, 1907, ix, 627.

I can not take issue with those who have diagnosed their cases of delayed chloroform necrosis as acute yellow atrophy. Nevertheless, I believe that it would be well to reserve this term for those cases of hepatic atrophy which occur without evident cause, and which are characterized by a widespread necrosis of the liver cells without fatty metamorphosis, followed by rapid autolysis and removal of the necrotic cells, and early proliferative activity of the interstitial tissues and the bile duct epithelium. As a particular characteristic of this disease should be mentioned the fact that the organs other than the liver seem scarcely to suffer at all or only secondarily to the hepatic insufficiency. Chloroform necrosis, puerperal eclampsia, and certain violent septicemias, produce changes in the liver that are more or less similar to those described above, but never quite the same, especially in the relatively great injury of other organs and the extent of fatty changes in the liver; therefore, I believe that we would do best to refer to these several forms of hepatic necrosis by the names of the condition causing them, considering the typical "idiopathic acute yellow atrophy" as a pathologic entity, which perhaps may be found to have a specific cause.

As to the reason for the severe effects that chloroform sometimes produces on the liver, some time ago I advanced a hypothesis somewhat as follows:⁶

Chloroform is a protoplasmic poison for cells of all kinds, stopping their synthetic activities but not seriously impairing their autolytic enzymes. This we see if we add chloroform to a culture or emulsion of bacteria, the cells at once die and begin to undergo autolysis. In view of the nature of the changes that occur in the liver in chloroform necrosis it seems probable that a similar effect has been produced by the chloroform upon the liver cells, that is, their synthetic activities are checked, and autolysis goes on unbalanced by constructive processes. Presumably it is the oxidative enzymes that are chiefly affected by chloroform, for, if these were destroyed, the resulting changes would be exactly what we observe taking place in chloroform necrosis; that is, the lipase would act unbalanced by the normal oxidative destruction of fatty acid and glycerin and so fat would accumulate in the cell, while at the same time synthetic changes, which seem to depend upon oxidative processes and the correlated reductions, would be stopped, and autolysis would assume the upper hand. While at the present time we have no means of determining the correctness of this hypothesis, still it can be said that nothing that is not in harmony with this theorization has yet been learned concerning the processes that take place in chloroform necrosis. Chemical analysis has merely corroborated the anatomic evidence of autolysis and fat increase in the liver cells.

Just why the liver should only occasionally suffer this serious injury from chloroform is still unexplained. Although in my own case it is probable that excessively free administration of chloroform may have been of influence, in many of the recorded cases this explanation has not been available, for often it is stated specifically that only a small amount

6. Wells, H. G.: Delayed Chloroform Poisoning and Allied Conditions, *Jour. Am. Med. Ass'n.*, Feb. 3, 1906, xlv, 341.

of chloroform has been used. There is abundant evidence that anything that impairs oxidation favors the occurrence of chloroform poisoning, and diseases that are prone to affect the liver, especially those that of themselves frequently cause fatty changes in the liver, are said, by all who have studied delayed chloroform poisoning, to be important predisposing factors. As a possible explanation of this apparent relation of pre-existing fatty changes in the liver to chloroform necrosis of the same organ, I would make the following suggestion:

Chloroform, like other anesthetics, seems to owe its effect on the nervous system to the fact that it is a strong fat solvent, and hence is taken up by the lipoids of the nervous tissues. This fact was first brought out by Overton and Meyer. The amount of chloroform that a tissue will take up, therefore, depends on the amount of fatty material in it which can dissolve the chloroform out of the blood; this is on the same principle as the method used in the laboratory for separating substances of different solubility in water and ether, water and chloroform, or other immiscible liquids, for the substance in solution distributes itself between the two solvents according to its solubility in each. This phenomenon is manifested when anesthetics are administered to obese persons, whose fatty tissue absorbs so much of the anesthetic that it requires a correspondingly larger amount to affect the nervous system. It would seem probable, therefore, that a fatty liver would abstract much more chloroform from the blood than a normal liver, and that this chloroform would thus act more strongly and for a longer time on the protoplasm of the fatty liver cells than it would in a normal liver.

As to the fact that the necrosis observed in these livers is in the center of the lobules, and that the fatty changes are sometimes central and sometimes peripheral, it would be hazardous to offer an explanation. This distribution of the hepatic lesions in the lobule is always a puzzling question, for, although we can construct explanations on the basis of the fact that poisons first reach the lobule at its periphery and that the oxygen supply is poorest at the center, yet we always find that exceptions are so abundant for any rule we may attempt to formulate that our attempted explanations of the observed facts have no value. For example, in phosphorus poisoning in most of the lower animals we find the fatty changes beginning at the periphery of the lobule; yet in monkeys and apes the changes are said to be central; furthermore, another steatogenetic poison, hydrazine, always produces the fatty changes in the center of the lobule in the same animals in which phosphorus attacks the periphery.

The necrosis of the liver in puerperal eclampsia is ordinarily periph-

eral, and is ascribed to capillary thrombosis. Mulzer⁷ found that chloroform administered to rabbits rapidly produces fibrinous thrombi in the capillaries, especially of the lungs, but also in the liver and kidneys. These thrombi are probably initiated by the clumping of injured red corpuscles, and their development is favored by the increased coagulability of the blood, which develops during the anesthesia. It is well known that injection of substances that cause agglutination of the red corpuscles produces extensive necrosis of the liver tissue, but the distribution and appearance of the lesions produced by agglutination thrombi are quite dissimilar to the lesions of chloroform necrosis. In my own specimens, from two cases, I was unable to demonstrate capillary thrombi by Weigert's fibrin stain, and in other cases in the literature the report of the pathologic anatomy is far too incomplete to permit one to judge as to the presence or absence of such thrombi. Of course, it might be possible to explain the anatomic and clinical findings on the basis of capillary thrombosis, if this existed to a sufficient extent, but so far there is no evidence of the occurrence of such a process. It has been suggested that chloroform lowers the normal power of the blood to inhibit autolysis, and if this were extensive enough it might account for the sudden autolysis of the liver that appears in chloroform poisoning. Studies of the inhibiting power of the serum of animals during chloroform anesthesia might throw some light on this.

Two therapeutic hints that have recently appeared seem to be well enough supported by the pathologic and clinical observations to be referred to in closing. J. H. Lyons, of Seattle, in discussing the treatment of puerperal eclampsia,⁸ objects to the prevalent custom of suppressing the convulsions by the use of chloroform, often for long periods of time. The similarity of the effects of chloroform and puerperal eclampsia on the liver, and the well-established fact that pre-existing injury to the liver predisposes to delayed chloroform necrosis, are certainly weighty reasons for this caution. It is also quite probable that chloral is not altogether a safe sedative in cases of this kind, since it is known to produce changes in the liver similar to those caused by chloroform. Beddard⁹ suggests that in the treatment of chloroform necrosis, and more especially for its prevention in cases where it is deemed necessary to use chloroform in spite of possible existing disease of the liver,

7. Mulzer: Die Auftreten intravitaler Gernnungen und Thrombosen in der Gefässen innerer Organe nach Aether-und Chloroformnarkosen. München med. Wehnschr., 1907, liv, 408.

8. Lyons, J. H.: Northwest Med., December, 1906.

9. Beddard, A. P.: A Suggestion for Treatment in Delayed Chloroform Poisoning, Lancet, March 14, 1908, p. 782.

the administration of glucose may be of value. This suggestion is based on Rosenfeld's view that poisoned hepatic cells can utilize carbohydrates well, but proteins and fats only poorly, and that consequently when the cells have used up their meager store of carbohydrate they are unable to utilize the proteins and fats that are available, and hence undergo starvation and death. Experiments have shown that feeding of dextrose to animals lessens the amount of fatty degeneration which results from phosphorus poisoning, and presumably it should have some similar effect in chloroform poisoning.

SUMMARY.

The cases of delayed chloroform poisoning described in the literature apparently tend to group themselves into two classes. In one, which affects chiefly children, the symptoms are those of "acidemia" or "acetonemia," without jaundice, and in these cases the changes of the liver are not so very marked, consisting, according to the published descriptions, chiefly of fatty degenerations about the periphery of the liver lobules. The other type is observed chiefly in young adults, and clinically is marked by profound jaundice, cholemia, hemorrhages, and the usual symptom-complex of a rapidly fatal acute yellow atrophy of the liver; anatomically the liver appears much as it does in acute yellow atrophy, being reduced in size, flabby, yellow and showing microscopically an extreme degree of necrosis, beginning in the center of the lobule, with more or less peripheral fatty degeneration. Intermediate cases occur that do not fall distinctly into one or the other of the two types. Histologic study of these cases of the second type, to which the name "chloroform necrosis of the liver" may be appropriately applied, shows a striking constancy of structural changes; these consist of total necrosis of all the liver cells, except those at the periphery of the lobule, with autolytic disintegration of the necrotic cells, and fatty degeneration of those cells that are not necrotic. The capillaries and bile vessels do not seem to be affected; there is no thrombosis and no inflammation or proliferative reaction. Chemical analysis corroborates the histologic evidence of fatty changes and autolysis, there being found a slightly increased amount of fat, and the presence of considerable quantities of free amino-acids, purins, proteoses, peptones and polypeptids, derived from the autolysis of the cells.

The condition in the second set of cases resembles very closely that of typical acute yellow atrophy of the liver, except in the greater tendency to fatty changes. Nevertheless, it seems best for the present to reserve the term acute yellow atrophy to that form of liver necrosis and autolysis

which occurs "idiopathically," and which presents certain features different from chloroform necrosis, puerperal eclampsia and phosphorus poisoning, and which is possibly due to some specific cause. The fact that chloroform seems particularly to affect livers in which fatty degeneration has been previously produced by some other disorder, may possibly be due to the known absorption of chloroform by intracellular fats, which in this case would increase the concentration and duration of action of the chloroform in the degenerated liver cells. Chloroform is a violent protoplasmic poison and, if it were to inhibit or destroy the oxidizing enzymes of the liver cells, the results would presumably be quite the same as those characteristic of chloroform necrosis; hence it seems probable that chloroform produces its effects by acting on the oxidizing enzymes, without corresponding inhibition of the autolytic enzymes and the lipase of the cells.

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BIBLIOGRAPHY.

In addition to the articles cited in the text, the following may be consulted on the subject:

Buckmaster, G. A., and Gardner, J. A.: The Anesthetic and Lethal Quantity of Chloroform in the Blood of Animals, *Proc. Roy. Soc., London Series B*, 1906, lxxviii, 410.

Cushing, H. E.: Acute Atrophy of the Liver from Chloroform Poisoning, *Jour. Am. Med. Assn.*, 1906, xlvii, 1191.

Campbell-Horsfall, C. E.: Acute Yellow Atrophy of the Liver, Following Operation for Intestinal Obstruction. *Lancet*, Sept. 7, 1907.

Doyon: Conditions dans lesquelles le chloroforme provoque l' incoagulabilité du sang, *Compt. rend. Soc. de biol.*, Paris, 1905, lviii, 704.

Fiessinger, N.: Action précoce du chloroforme sur le foie, *Compt. rend. Soc. de biol.*, Paris, 1906, lx, 870.

Guleke, N.: Acute gelbe Atrophie im Gefolge der Chloroformnarkose, *Arch. f. klin. Chir.*, 1907, lxxxiii, 602.

Günter, E.: Der Chloroformgehalt von Blut, Leber und Niere während der Narkose, *Dissertation*, Giessen, 1906.

Guthrie: Delayed Chloroform Poisoning, *Lancet*, Dec. 1, 1906, p. 1542.

Herter, C. A., and Williams, W. R.: Experimental Hepatic Cirrhosis in Dogs from Repeated Inhalations of Chloroform, *Proc. Soc. Exper. Biol. and Med.*, 1905, iii, 23.

Madison, J. D.: Delayed Chloroform Poisoning, with Report of Three Cases, *Wisconsin Med. Jour.*, March, 1906.

McArthur, A. N.: Acidosis (Delayed Chloroform Poisoning), *Intercolonial Med. Jour.*, Aug. 20, 1907.

Renton, J. C.: Delayed Chloroform Poisoning, *Brit. Med. Jour.*, March 16, 1907, p. 617.

Taylor, A. E.: The Occurrence of Amido-acids in Degenerated Tissues, *Univ. Calif. Pub. Path.*, 1904, i, 43.

Telford, E. D., and Falconer, J. L.: Delayed Chloroform Poisoning, *Lancet*, Nov. 17, 1906, p. 1341.

Tissot, J.: Détermination du chloroforme dans le cerveau, le sang, etc., dans la mort par la chloroforme, au début de l' anesthésie, *Compt. rend. Soc. de biol.*, Paris, 1906, lx, 195, 198, 200, 203.