Report of the Pathology Panel

National Halothane Study

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THE NATIONAL HALOTHANE STUDY, sponsored by the Committee on Anesthesia of the National Research Council, was instituted to investigate the relationship, if any, between the administration of halothane as an anesthetic and the occurrence of hepatic damage. Massive hepatic necrosis was selected as the basis for analysis as a hallmark of halothane toxicity. The occurrence of this catastrophe in individuals receiving the agent precipitated the survey. It seemed reasonable to assume that this condition could be related to universally acceptable criteria and that, when present, it would constitute a lesion sufficiently important to find its way into a necropsy summary or a list of diagnoses. Thus, in each of 34 participating general hospitals of varied types, a physician ("local selector") reviewed the files of the cases necropsied at his institution during a four-year period (1959–1962) and selected for more detailed investigation all those cases thought to reflect massive hepatic necrosis that occurred within six weeks of the administration of a general anesthetic. This survey yielded a total of 184 cases from all institutions; these were gathered from an over-all total of 10,171 complete necropsies.

Later, abstracts of all necropsy reports were resurveyed by another person in a central institution (a nurse-medical librarian), to be certain that no cases of hepatic necrosis had been missed by the local selector. To ensure the inclusion of all possible cases, the reviewer selected all additional cases that were thought to represent massive or even lesser degrees of necrosis or those in which hepatitis was mentioned. This survey yielded 42 additional cases. The aggregate from the two surveys therefore was 226 cases.

To establish the fact of massive necrosis with reasonable consistency and assurance, a Pathology Panel was convened, consisting of six members with special interest and experience in hepatic disorders. For each of the 226 cases, a complete abstract (lacking only an indication of the anesthetic used), a summary of the necropsy findings, and representative sections or blocks of liver were supplied to the Panel.

Method of Pathology Review

Initially, each member of the Pathology Panel received sections of all 226 livers stemming from this portion of the survey, but with no knowledge of the source or the clinical manifestations. The Panel developed a simple tally form on which were indicated the various histologic features to be evaluated (Pathology Form 1). This tally had two purposes: 1) to determine the nature and extent (or absence) of necrosis, and 2) to permit tabulation of the histologic features that, in aggregate, might constitute a complex with specific implications for halothane or other agents. Thus, parenchymal cellular alteration, autolysis, fatty change, inflammatory exudate, cholestasis, and ductal and ductular peculiarities, and their

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degree and distribution, were listed and directed the attention of all panelists to common features. It must be emphasized that throughout this and later steps the pathologists did not know which anesthetic had been used in any patient.

Extent of Necrosis

In examining the liver for necrosis, each Panel member substantiated its existence (or absence) and indicated its degree. The latter was arbitrarily classified as: 1+, minor, not affecting more than 25 per cent of the lobular parenchyma; 2+, affecting 25 to 50 per cent of the parenchyma; 3+, destruction of approximately 75 per cent of the parenchyma; or 4+, massive, affecting all or almost all the parenchyma. No effort was made to delineate the nature or cause of the necrosis during this phase of the study. In a later survey, however, those cases that exhibited histologic features attributable to coincidental intrahepatic disorders, such as infarction, abscess, necrotic neoplasm, and alterations related to biliary obstruction, were deleted from further consideration, as were those with autolysis of a degree sufficient to preclude interpretation.

Regarding the cases retained as acceptable examples of hepatic necrosis, there was reasonably close agreement among the evaluators. Variations in scores were usually minor, but it was necessary for the members of the Panel to resolve differences in the relatively few cases at issue. This was accomplished readily, inasmuch as the discrepancies were almost wholly related to a failure, in the course of the preliminary planning, to consider the obscuring factors cited above and those related to pre-existing hepatic disease. When the differences had been reconciled, the scores were averaged and three categories of necrosis were established: minimal, with an average score of 1.5+ or less (fig. 1); intermediate, with a score of 1.6 to 2.5+ (fig. 5); and massive, with a score of 2.6+ or more (fig. 6).

At the outset of the study, in the course of determining the terminology to be used, it was difficult to select phrases that would alert nonpathologist screeners at each participating hospital to cases of hepatic necrosis that might be classified in other diagnostic categories. These selectors therefore, were urged to be lenient in their interpretation of terminology, so that borderline cases would not be missed. Undoubtedly as the result of this, the Panel found it necessary to eliminate 29 of the 226 cases initially received; of these, three were thought to exhibit no evidence of necrosis, seven to be associated with neoplasm, and 19 to be the seat of marked uninterpretable autolysis. Moreover, among the 197 cases retained, 131 were judged to represent minimal necrosis, occasionally barely detectable. Lesions of this type are common in any necropsy population; they constitute a nonspecific reflection of the agonal state and are considered to have negligible significance. These cases, obviously not properly included among *bona fide* cases as examples of hepatic necrosis, were deleted. There remained, however, 66 cases: 35 with necrosis of intermediate degrees and 31 with massive necrosis (2.6+ or more). This relatively small yield (29 per cent) among the cases originally selected for consideration will be discussed further.

Supplementary Selection

Experience with selection on the basis of necropsy abstracts suggested that some examples of massive necrosis might have been overlooked by local selectors. It seemed desirable, therefore, to make another effort at screening cases of necrosis that might conceivably have been missed in the first search. This was accomplished by another survey of necropsy protocols. A pathologist [*] was selected by the Panel and was requested to gather all conceivable examples of hepatic necrosis for final study. In reviewing the 10,171 necropsy reports, it was found that the liver was mentioned in the list of final diagnoses in 5,967. The pathologist was asked to consider these carefully and, as in the case of the local selector, to cull those cases whose necropsy reports contained any indication of primary hepatic injury, including hepatitis. Cases of necrosis in proximity to metastatic neoplasm; those in which there was fatty metamorphosis without necrosis, and others in which there was an obvious independent condition (*e.g.*, infarction, abscess, pylephlebitis, obstructive jaundice, alcoholic

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hepatitis, or other pre-existing disease) were not to be included.

On the basis of this survey, 746 additional cases were selected for more detailed evaluation. Histologic preparations were obtained from 720 of these; neither tissue nor sections were available from the remainder. Two pathologists ** at the Armed Forces Institute of Pathology, Washington, D. C., with considerable experience in hepatic disorders, reviewed the 720 preparations. They were familiar with the needs of the Study and selected all examples of necrosis, regardless of degree, that were not obscured by autolysis or readily attributable to obvious intrahepatic cause.

An additional 146 cases of hepatic necrosis were brought to light. Representative sections of these were circulated among members of the Pathology for review, as in the original group of cases submitted. The Panel agreed on the existence of necrosis in all instances. As in the initial survey, the scores rendered were averaged; in 80 there was intermediate necrosis, and in 51 massive necrosis. The remainder represented minimal necrosis and were excluded. The final tally, therefore, combining both the initial screening and the supplementary selection, was 82 cases of massive hepatic necrosis and 115 cases of intermediate hepatic necrosis.

Causes of Hepatic Necrosis

At this stage another method of study was carried out with the 226 cases submitted originally by local selectors. Members of the Pathology Panel, who already had reviewed and evaluated the histologic sections, now received abstracts of the clinical course with details of the operative procedure(s), laboratory tests, postoperative course, and findings at necropsy. Again, knowledge of the anesthetic(s) was withheld. From this information and with appreciation of the histologic features in the liver, another form was completed (Pathology Form 2). This permitted the panelists to indicate their impressions of the causative basis for the hepatic necrosis (i.e., halothane, any hepatotoxin, any drug sensitization, or hepatitis virus; shock, anoxia, or sepsis; any other factor; autolysis; etc.). Unfortunately, in this phase of the study, opin-

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ions were greatly individualized and thus showed little uniformity. No pertinent criteria for designating the various etiologic categories had been agreed on in advance by members of the Panel. Each pathologist, therefore, used his own criteria and often found it necessary to designate more than one possible cause. Indeed, it is well recognized that a number of different agents may cause identical hepatic alterations.[1-3] In one category, nonetheless, there was a remarkable degree of conformity: in the group attributed to "shock, anoxia, or sepsis." This group did not, of course, constitute a pathologic entity, but included many overlapping patterns. Moreover, the clinical record made it fairly obvious that one or more of these conditions had prevailed and undoubtedly influenced the pathologist in his conclusion.

Pathologic Features

Hepatic necrosis has no consistent pattern; all forms and variations may be observed.[4] These range from minor focal lesions, with either random or regular zonal distribution, to total parenchymal destruction. Thus, among the cases excluded there were those with small collections of neutrophils intermingled with clusters of necrotic liver cells, scattered irregularly, and with no uniform lobular orientation. These occurred frequently, affected considerably less than 25 per cent of parenchymal substance, and were deemed of minor import (fig. 1). They represented the hepatic counterpart of terminal infection or the disintegrative effects of the agonal state.

Another reflection of the metabolic derangements of terminal illnesses and of the postoperative state was the occurrence of fatty vacuolization, which in various degrees might accompany any form of necrosis or indeed appear in marked degree without any necrosis at all (fig. 2). Such cases were excluded because in most instances they represented coincidental concomitants and, although they may have attained considerable prominence, in themselves appeared to have no bearing on the maintenance of hepatic integrity. In a few instances, however, the lesion constituted a significant widespread alteration reflecting severe parenchymal injury (fig. 3). In these the appearance of the lipid differed somewhat
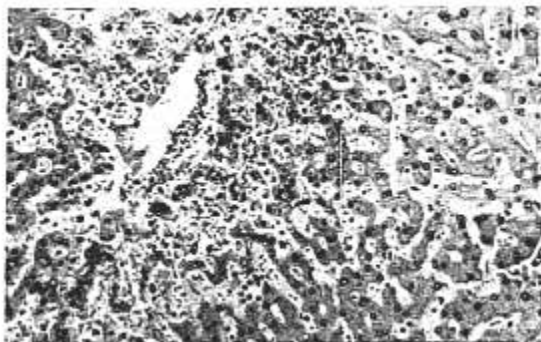
FIG. 1. Minimal centrilobular necrosis (Case 7). Necrosis affects less than 25 per cent of the lobular parenchyma. Cells bordering on the centrilobular vein have undergone disintegration and there is dilatation of related sinusoids with a scant intermixture of neutrophils. The remainder of the lobule is intact. Postmortem change affects sharpness of detail. H. and e. ×150.
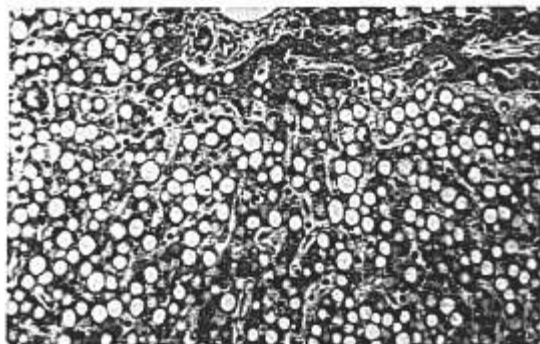

FIG. 2. Fatty liver (Case 105). Liver cells are the seat of severe coarse vacuolization. There is, however, no disarrangement of parenchymal plates and no evidence of accompanying necrosis. A portal area included is quiescent, exhibiting no inflammation. H. and e. ×150.
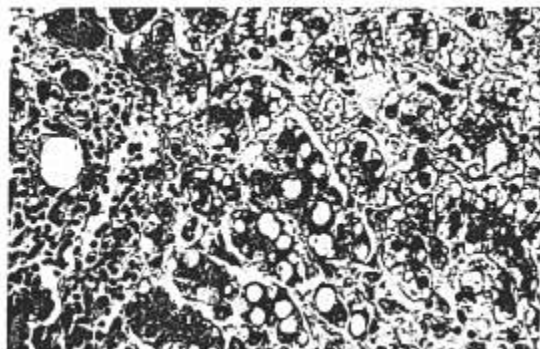

FIG. 3. Toxic hepatitis (Case 206). Severe fatty vacuolization is here characterized by a prevalence of fine foamy cytoplasmic vacuolization with irregularly swollen epithelium. Liver plates are two or more cells thick and elsewhere in this lobule are minute areas of acute necrosis with neutrophil reaction. The portal area included also exhibits a significant inflammatory (lymphocytic) exudate. H. and e. ×200 (see fig. 6).

FIG. 4. Alcoholic hepatitis (Case 33). Liver cells are markedly swollen and irregularly disposed and exhibit foci of individual cell necrosis surrounded by a narrow halo of inflammatory cells. Some of the swollen cells appear vacuolated, and others exhibit condensation of cytoplasm to form a refractile eosinophilic coagulum (alcoholic hyalin). H. and e. ×250.
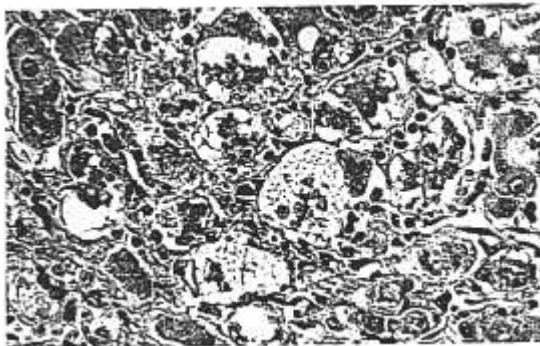

FIG. 5. Intermediate necrosis (Case 200). The central portion of all lobules has undergone necrosis and disintegration. H. and e. ×100.
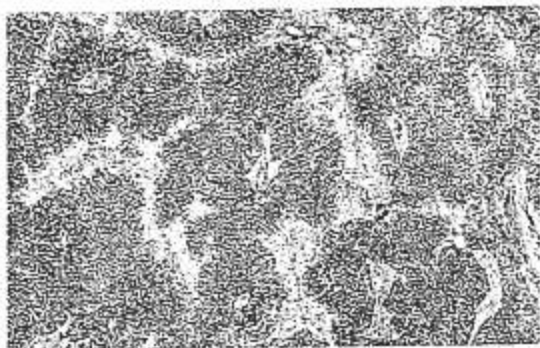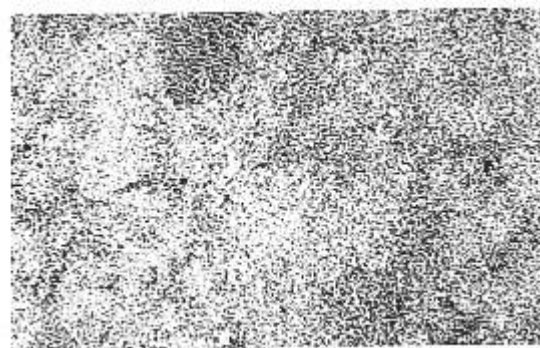

FIG. 6. Massive necrosis (Case 91). Most of the parenchyma has undergone necrosis, with only a few small islands of viable cells remaining. In the main, the necrosis centers about central veins, one of which may be seen in the center of the photograph. H. and e. ×100 (see fig. 3).

from that unaccompanied by recognizable hepatic cell injury. It exhibited a microvacuolar form causing marked enlargement and irregularity of cells and much architectural disarrangement. Nuclei variously exhibited swelling and pyknosis. Cells underwent cytoplasmic coagulation and necrosis, usually focal; in some this had a rather widespread distribution. Paralleling these changes were canalicular bile stasis, neutrophil aggregation, pigment deposit in and undue prominence of Kupffer cells, and occasionally inflammatory exudate in portal areas. In two cases this pattern had the added feature of "alcoholic hyalin" formation (fig. 4); both patients were flagrant overusers of alcohol.

In most instances the necrosis was oriented about the centrilobular vein with the extent varying from minimal, or less than 25 per cent of the lobule (fig. 1), to maximal, or more than 75 per cent of the lobule (figs. 5, 6). Total loss of parenchyma (fig. 7) was rare; the lesions of major degree often showed a thin periportal row of disturbed but viable parenchymal epithelium (fig. 8).

Two basic patterns were recognized, but on occasion they appeared to overlap, particularly if of some duration or obscured by postmortem changes. In one pattern, constituting the result of vascular disturbance and thus characterized by passive congestion, there was dilatation and engorgement of centrilobular veins and the central reaches of hepatic sinusoids (fig. 9). Seepage of red cells or plasma into the spaces of Disse resulted in attenuation of parenchymal cell plates and ultimately in their necrosis. Cells underwent direct disintegration or exhibited cytoplasmic eosinophilia and nuclear pyknosis. It is probable that these cytologic features merely represented variations of the same process. In those with terminal accentuation of congestion or the later superimposition of another clinical complication (e.g., hemorrhage, shock, or sepsis), cytoplasmic coagulation resulted; in the others, parenchymal attenuation or frank necrosis followed a longer and perhaps more gradual process. Inflammatory cells appeared in moderate numbers, neutrophils predominating in the acute lesion and macrophages in those of longer standing. In cases with sudden and fatal shock, a central pooling of blood and loss

of parenchyma were manifest. In this circumstance the linear division between viable and nonviable parenchyma was usually irregular and ill-defined, with contiguous viable cells containing small amounts of lipid. Occasional cells were swollen but exhibited few features of regeneration. The portal areas in these cases were essentially normal.

The other pattern lacked significant evidence of congestion. Here also, however, various components of the lesion exhibited features that appeared to depend in large part on duration. In its most striking form, acute coagulation necrosis of part or all of the lobular parenchyma appeared (fig. 10). All cells were in an identical state of recent death, characterized by a granular, coagulative shrinkage of cytoplasm with loss or pyknosis of nuclei. A sharp line of separation existed at the juncture with viable elements. Neutrophils were intermingled with the necrotic cells and were aggregated at the zonal margins; various numbers, usually few, were evident in the peripheral viable zone. A rare necrotic cell, sequestered from its neighbors, assumed a hyaline appearance reminiscent of the acidophilic body observed in viral hepatitis.[5–7] Usually little fatty change accompanied this lesion and the portal areas were unaffected, except in cases of total parenchymal destruction. In the instances of total or subtotal destruction, the peripheral residuum of parenchyma was the seat of some regenerative activity with swelling and multinuclearity of the parenchymal cells. This was often accompanied by early "ductular" proliferation.

In still other examples, presumably representing the same lesions but probably with more prolonged courses (or perhaps with long postmortem intervals), cytoplasmic disintegration had occurred, with "fallout" of cells (fig. 11). The zone of necrosis in these was characterized by a content of granular detritus, fewer or no neutrophils, and an intermingling of macrophages (or Kupffer cells) filled with bile and hemosiderin pigment. The line of juncture here was not sharp. The residual viable cells now exhibited irregularity, loss of polarity, multinuclearity, and even mitotic activity. At this stage few neutrophils remained. In the more extreme lesions in which the periphery of the lobule

FIG. 7. Massive necrosis (Case 46). Massive necrosis is characterized by complete loss of parenchyma with replacement by detritus, Kupffer cells, and a mixed inflammatory exudate. At the left is the remnant of a portal area containing interlobular bile ducts and inflammatory cells. H. and e. ×200.
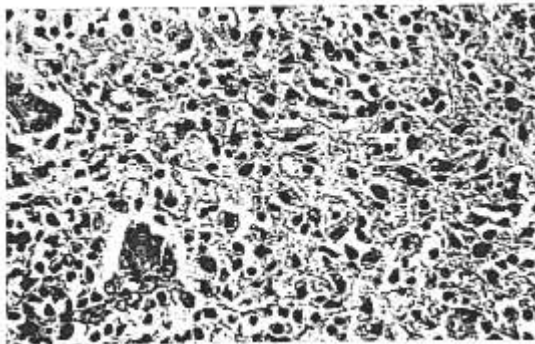

FIG. 8. Massive necrosis, periportal area (Case 36). Almost all the lobular parenchyma has undergone coagulation necrosis and distintegration. A thin rim of viable but abnormal and irregular cells remains, fringing the portal tract. H. and e. ×150 (see fig. 18).
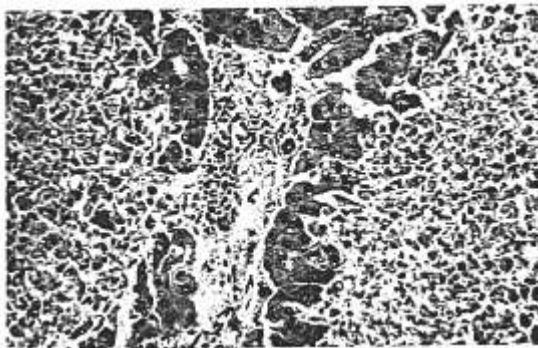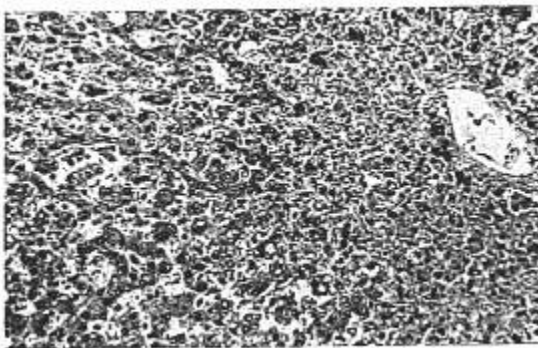

FIG. 9. Intermediate necrosis with centrilobular congestion Case 82). Centering about the central vein, sinusoids are widely distended by packed red cells, which, because of destruction of approximately one-third of the parenchyma, appear to be pooled. A scant inflammatory reaction appears in the area of destruction. H. and e. ×150.
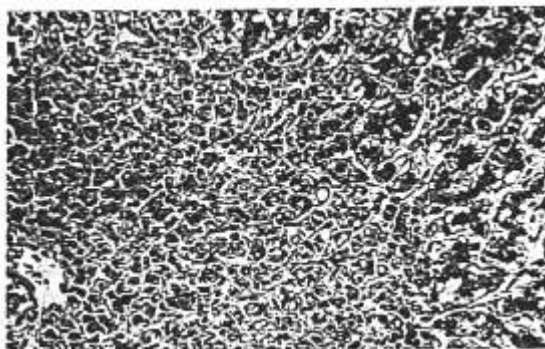
FIG. 10. Centrilobular necrosis (Case 98). Parenchymal cells in the central half of this lobule have undergone coagulation necrosis. Shadowy outlines of the affected cells persist but the cytoplasm has become granular, refractile, and eosinophilic. A few pyknotic nuclei remain but nuclear staining is generally absent. Only a mild early inflammatory reaction is evident at the margin of the necrotic zone. The more peripheral viable parenchyma exhibits cytoplasmic swelling and fatty vacuolization. H. and e. ×150.
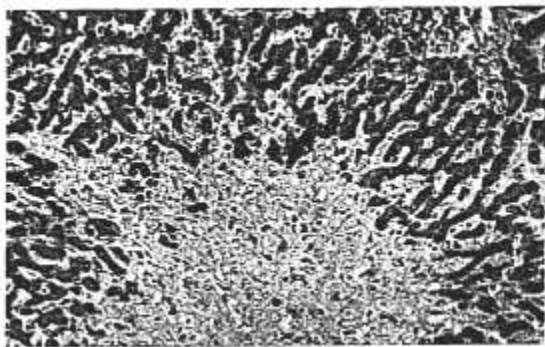

FIG. 11. Intermediate centrilobular necrosis with "fallout," probably reflecting duration and, perhaps, postmortem interval (Case 86). Necrotic cells have disappeared, leaving behind only an amorphous stromal matrix in which are fragments of nuclear debris and pigment-laden phagocytes. The radial pattern of residual viable cells is undisturbed. H. and e. ×150.

was affected, periportal ductular proliferation was striking (fig. 12). In some of these the portal areas were edematous and contained moderate lymphocytic infiltration. In a few, in both acute coagulative and "fallout" lesions, a very heavy lymphocytic exudate prevailed in the portal areas and was, on occasion, universal in its distribution (fig. 13).

Discussion

The incidence of postoperative hepatic necrosis was relatively modest. The massive lesion appeared in approximately 0.7 per cent of necropsy cases, and intermediate necrosis in 1 per cent. The minimal lesion was ignored because, as indicated, it is considered to be commonplace in the process of dying and is universally accepted as such. For this reason, its existence might or might not be listed among anatomic diagnoses and its selection by the screener would be unpredictable. This minor degree of alteration, moreover, would not be expected to have significant clinical manifestations or to bear on the outcome of a case. Intermediate necrosis, however, could well contribute to a lethal outcome. Although the Study was not designed to collect cases of this nature, some actually appeared in the first group gathered by local selectors, and others came under consideration in the later collections. Such cases would not, however, be expected to cause death unless associated with another potentially fatal disorder. On the other hand, massive

FIG. 12. Massive necrosis (Case 93). Coagulated necrosis cells border on an inflamed portal tract. The few remaining viable elements are swollen, their nuclei are vesicular and bizarre, and there is a ductule-like proliferation. This is thought to represent an abortive effort at regeneration. H. and e. ×200.
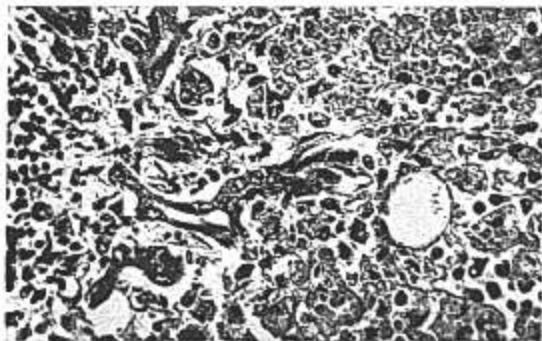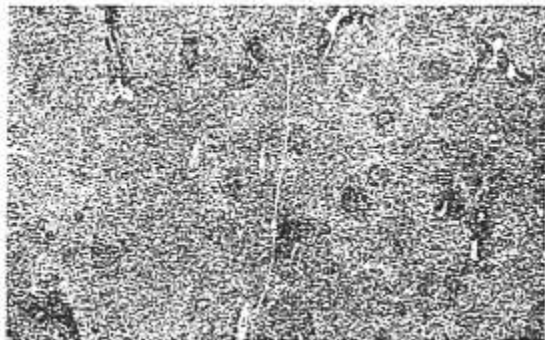

FIG. 13. Massive necrosis (Case 44). Only a few small islands of viable parenchyma remain; the bulk of the liver is necrotic. Each portal area stands out as darkly stained, because of heavy lymphocytic infiltration. There is little inflammation in the parenchymal region. H. and e. ×100 (see fig. 19).

hepatic necrosis as defined by the Panel (figs. 6, 7, 8, and 12), is with very rare exceptions incompatible with life; it is in itself fatal.[5, 9]

It seems most unlikely that instances of truly massive hepatic necrosis would escape the screening methods used among the necropsy cases. It would have been unusual, indeed, for massive lesions to fail to come to the attention of the local selector, the nurse-medical librarian, and the pathologist examining the necropsy abstracts. It was with this in mind that wide latitude was given the case finders in determining those cases to be subjected to pathologic scrutiny. Such categories as "hepatitis" and "liver degeneration," for example, were included initially, inasmuch as

it was intended from the outset to submit sections from all cases to scrutiny by the Pathology Panel. Although some of these did prove to be hepatic necrosis, many were of necessity excluded, and only 31 of the originally collected cases found their way into the final group with massive necrosis.

Nonethless, in the face of the obvious difficulties in case finding, one may well raise the question of how many examples of hepatic necrosis observed pathologically may have failed to emerge in the diagnostic listings and thus may never have come to the attention of the various screeners. As an additional precaution, the necropsy cases were sampled to detect hepatic abnormality that was not recorded in the final diagnosis (Full Report,
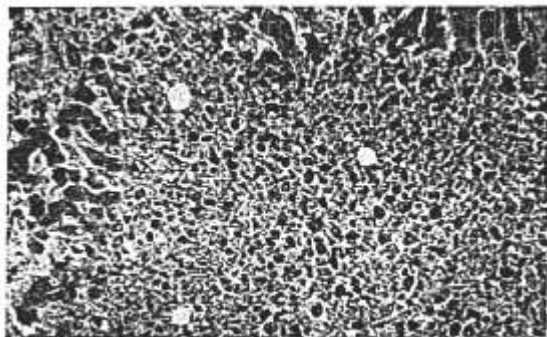
Fig. 14. Autolysis (Case 27). Staining capacity is lost, cytologic detail is obscured, and inflammatory cells cannot be identified. It is still possible, however, to distinguish the centrilobular zone of necrosis from the peripheral fringe of quasi-preservation. H. and e. ×150.

National Halothane Study). There were no instances of massive necrosis which had failed to be included in the lists of diagnoses in the necropsy protocols examined, although there were several cases of intermediate necrosis which had been missed.

It is reasonable to conclude that almost all examples of massive necrosis in the necropsy population were recognized and examined by the Panel. There is no doubt that there were additional fatal cases with similar lesions among those not necropsied. There is no feasible way of detecting these at present.

RELIABILITY OF CODED DIAGNOSIS

A more disturbing matter, however, was the apparent lack of uniformity among pathologists at large in recognizing or designating hepatic necrosis in such a way that it could be appreciated by nonpathologist readers of the pathology reports. The need of the Pathology Panel to reject out of hand 29 of the original 226 cases and to consider 131 others to have only negligible necrosis may be attributed in some measure to typographical errors, the submission of poor or improper sections for review, the manner of performance of necropsies, or the coding of diagnoses by inadequately trained personnel, as well as to the policy adopted of encouraging the local selector to submit questionable cases for evaluation. A review of the abstracts, unfortunately, also indicated a distressing variation in nomenclature and a significant range of pathologic criteria for the diagnosis of necrosis.

Among the 226 cases submitted initially, 108 were stated by the local pathologists to have some form of hepatic necrosis and 66 were classified as hepatitis. The submission of the remaining 52 may have represented bias or error, but in most cases undoubtedly reflected an arbitrary choice by the local selector in an effort to avoid missing possible cases of necrosis. They had been listed as fatty infiltration, biliary obstruction, hepatic neoplasm, putrefaction (? autolysis), or pre-existing cirrhosis. Even among the 108 in which the pathologist's opinion clearly stated that necrosis or hepatitis existed, however, the Panel found that the lesion could be established as massive necrosis in only 31 cases, and as intermediate necrosis in 35. There was no necrosis in two, necrotic neoplasm in five, and sufficient autolysis to preclude interpretation in 10; in the remaining 25 cases, the necrosis was minimal.

INTERPRETATION OF AUTOLYSIS

Because it was known that the presence of autolysis could neither exclude nor substantiate the existence of necrosis, the sections and clinical abstracts in 19 cases were evaluated more critically (the ten originally listed as necrosis by the submitting pathologist and 9 considered to represent autolysis but with other features contributing to the selection). In order to determine whether necrosis might have been masked by autolysis, the appraisal consisted of a correlation of clinical phenomena and detectable evidence of hepatic necrosis in

FIG. 15. Normal liver (Case 288). Radiating from the central vein are clearly outlined liver cells with uniform nuclear content. The preservation of the sharp cell membrane is a feature of the liver in sudden death. H. and e. ×200.
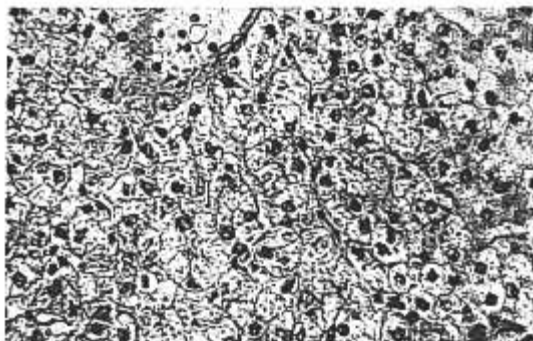
the poorly-stained section (fig. 14). It appeared reasonable to make this distinction, and in three of the 19 cases hepatic necrosis undoubtedly existed before death. One. of these was a patient with choledocholithiasis and biliary obstruction, and another was considered to have had homologous serum hepatitis. The third case, however, could not be explained by the clinical data. The remaining livers, ten of which had been claimed by the local pathologist to show necrosis, were considered to have been undamaged in life.

PATHOLOGIC ALTERATIONS MISTAKEN FOR NECROSIS

A number of cases were listed in necropsy reports as examples of hepatic necrosis but were not so considered by the Panel. The reasons for their exclusion are given below.

In instances of sudden death in healthy persons whose livers were unaffected by degradation before death, the preservation of hepatic parenchymal glycogen, the clarity of cytoplasmic staining, and the sharpness of cell outline contrasted with the usual somewhat blurred "normal" postmortem appearance (fig. 15). This was, in at least one case, misinterpreted as an abnormality and bears comment only because it was taken as an indication of intrinsic hepatic injury.

The accumulation of parenchymal fat also was considered by some to be evidence of hepatic damage. Actually, it is common during a terminal period of illness with re-

stricted caloric and protein intake, and in the postoperative state as well. Such fatty "degeneration," reflecting reduced protein synthesis (fig. 2), may be mistaken for toxic hepatitis, which is also characterized by lipid accumulation (fig. 3).[10, 11] Examples of the former complicated by minor evidences of agonal hepatic cellular necrosis, passive congestion, or postmortem parenchymal-cell "fallout" seemingly had been misinterpreted as hepatic necrosis, particularly when the accumulation of fat was considerable.

A distinction between this form of fatty degeneration and that more commonly associated with toxic injury to the liver, whether following the ingestion of noxious agents (as in carbon tetrachloride toxicity) or in the case of acute alcoholism, should be possible in most instances.[12] The latter condition was encountered occasionally among the cases with intermediate necrosis. The fuzzy microvacuolar appearance of the lipid (fig. 3) and its accompanying focal necrosis, bile stasis, neutrophil exudate, and (in the patients with alcoholism) alcoholic hyalin (fig. 4) constituted clearly distinguishing features. No example of sudden death with simple fatty metamorphosis was encountered.

In a few cases, pre-existing hepatic disorders were improperly. related to the postoperative state. Although in some there was evidence of terminal necrosis, most fell into the pattern of chronic hepatitis with portal area inflammation and ductular proliferation but little current parenchymal alteration. Obviously, these

FIG. 16. Hepatic abscess (Case 214). Case of obstructive jaundice with suppurative cholangitis. H. and e. ×100.

had been vulnerable livers and could have been unduly susceptible to vasomotor disturbances. As examples of necrosis induced by anesthetics, however, such cases would have little validity.

Extrahepatic biliary obstruction appeared with the usual manifestations of cholestasis[5] but were often overlain by suppurative complications as well. Whether for this reason or other causes, autolysis was a frequent concomitant, leading in some instances to inclusion in the hepatic necrosis group. In like manner, cases with inflammatory reaction reflecting systemic infection, some with abscess formation (fig. 16) or advanced autolysis (in gas bacillus infection), were included unjustifiably. Other conditions encountered were arterial or venous vascular occlusions (some with pylephlebitis), infarction (fig. 17), and metastatic carcinoma with necrosis of contiguous parenchyma.

Each of these conditions exhibited distinguishing features, and the Pathology Panel felt justified in their exclusion from consideration. Indeed, in almost every instance the manner of death was unrelated to hepatic failure and reflected, instead, another primary disorder.

The Panel thus accepted only those cases in which cell death in vivo was recognizable and in which none of the factors indicated above could be incriminated. This constituted the basis for the ultimate selection of the 222 cases.

HEPATIC NECROSIS ATTRIBUTABLE
TO ANESTHETIC AGENTS

Any organ as susceptible to injury by such a wide variety of influences as the liver poses a problem in determining the immediate cause of its malfunction. It is relatively easy (and many have followed this course) to indict an adventitious circumstance in a given instance of hepatic necrosis. But experience has shown that easy assumptions are not particularly fruitful. All attendant conditions require critical evaluation before any single factor can be implicated. This was essentially the situation in patients receiving an anesthetic; they suffered from ailments, serious or not, that required operation, and thereafter they were subjected to the surgical procedure and a host of adjuvant treatments. Each of these provides inherent risks. Moreover, the population at large carries adventitious illness at a certain rate, whether or not manifestations are overt (e.g., viral hepatitis).[13, 14, 15] Finally, potential risks exist in the anesthetics themselves. Thus, in determining the causal relationships between anesthetics and a group of cases with hepatic necrosis, each case requires individual probing.

In the complete report of the National Halothane Study the results of a survey carried out by four members of the sub-committee, representing different medical specialties (anesthesiology, medicine, surgery, and pathology) are recorded in Chapter III-1. That group attempted to determine, on the

basis of the clinical data available, whether the hepatic necrosis could be attributed to factors other than the anesthetic. The group found itself in agreement that the cause of the lesion was apparent in the patient's record in 90 per cent of the 197 cases of massive and intermediate necrosis. It would follow that the anesthetic, whatever it proved to be, could well be exonerated in those cases. But there were 19 cases in which all or most of the group did not determine an apparent cause for the necrosis. These were considered "unexplained," as distinct from the "explained" cases in which a clinical basis for the liver destruction was apparent. In these 19 cases, neither the clinical course, the operative procedure, nor the existence of complicating illness appeared to have had the capacity to contribute to the hepatic process.

In nine of the 19 cases the lesion was massive, and in ten it was intermediate (see complete report). When decoded as to the anesthetic exposure, it was found that halothane was the agent used in 14 cases (seven massive and seven intermediate), nitrous oxide-barbiturate once (intermediate), ether twice (both intermediate), cyclopropane once (massive), and "other" (ethylene) once (massive).

The occurrence of 19 instances of "unexplained" hepatic necrosis in a necropsy population of 10,171 persons (with abdominal necropsy examination) exposed to anesthesia may be taken to indicate that the liver is

FIG. 17. Hepatic infarct (Case 4). A sharply circumscribed zone of necrosis is brightly eosinophilic and set off from the surviving viable hepatic substance. In the higher-power (lower) view, the contrast between the cells in the infarct and the viable survivors is well shown. A narrow zone of inflammatory cells encircles the necrotic elements. H. and e. ×100; ×150.
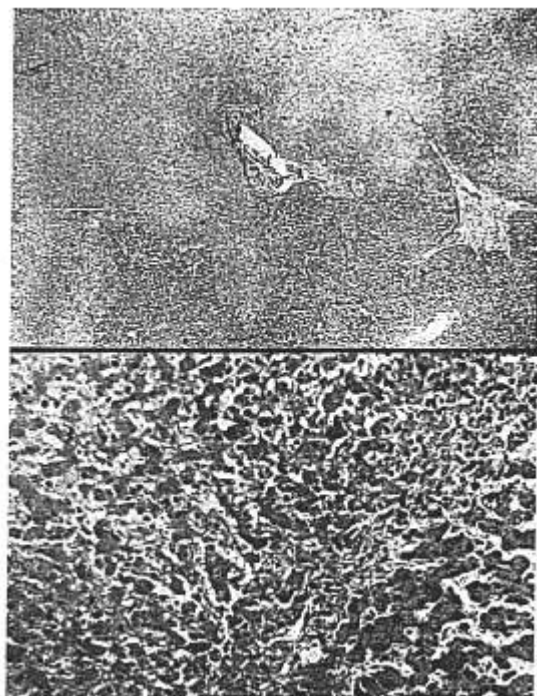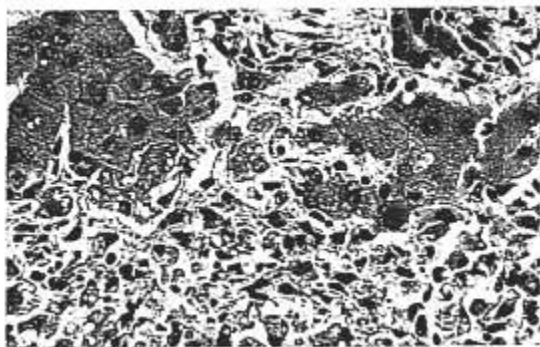
FIG. 18. Massive necrosis (Case 36). A residual peripheral island of viable parenchyma borders the necrotic lobules in which coagulated and disintegrating cells have not yet lost individuality. Contrast with fig. 10. H. and e. ×200 (see fig. 8).

only rarely vulnerable to an anesthetic agent. The question at issue, however, is: "Does halothane have a greater role in this respect than other agents?" In this small group halothane appeared to be a more common offender.

It is obviously possible that anesthetic-induced hepatic disorder also occurred among those cases ascribed to definable causes in the "explained" category. It is equally plausible to argue that an undetected factor, other than an anesthetic, may have prevailed in the "unexplained" group. If one deals only with the results of the methodology used, whatever its crudities, one may conclude that, among the 10,171 necropsied persons subjected to anesthesia (and among the 197 patients with massive and intermediate hepatic necrosis), there were 19 in whom the hepatic process might reasonably have been attributed in some way to the anesthetic used. Of these, 14 patients had received halothane and 5 had received other anesthetics.

SPECIFIC LESION CAUSED BY HALOTHANE

Once the category of "unexplained" hepatic necrosis had been established, an effort was made to distinguish a histologic pattern that might reflect the specific effects of halothane and aid in the distinction of the lesion from that appearing after the administration of other agents. As indicated above, members of the Pathology Panel were unable to find a common meeting ground to derive such a conclusion.

In a further effort, sections from the 19

cases were intermixed with those from 19 "explained" cases selected at random and examined by one member of the Panel * without recourse to clinical information until the analyses were completed. Of the 19 "explained" cases, 17 fell among the group ascribed to "shock, anoxia, or sepsis"; six of the 19 "unexplained" cases exhibited such lesions.

As in the original survey, many variations appeared related to the duration of the lesion. Thus, a necrotic zone might exhibit cytoplasmic coagulation (fig. 18) and disintegration in some sections, and "fallout" in others (fig. 11); the one would reflect a recent lesion, and the other, one of longer standing. This was also the case with intralobular inflammatory reaction; cases of recent origin exhibited little or no exudate; those of longer duration exhibited a neutrophil reaction reaching from the margin of necrosis and ultimately intermingling with the nonviable cells. Cases characterized by "fallout" exhibited little neutrophil reaction; here, macrophages prevailed, but with varied prominence. Except in one instance (case 98, fig. 10), parenchymal fat was purely adventitious. Regeneration was evidenced by irregular swelling of residual liver cells, multinuclearity, and, rarely, mitoses (fig. 12). These changes were paralleled by periportal ductular proliferation, which, however, was not striking. Such bile stasis (cast formation) as occurred was limited to these ductules and was rarely marked.

* E. A. Gall.

FIG. 19. Massive necrosis with portal area exudate (Case 44). Coagulation necrosis has destroyed all but two- or three-cell-layered periportal lamina. The portal area itself is heavily infiltrated with lymphocytes; this was a feature of all portal areas in this liver. H. and e. ×200 (see fig. 13).
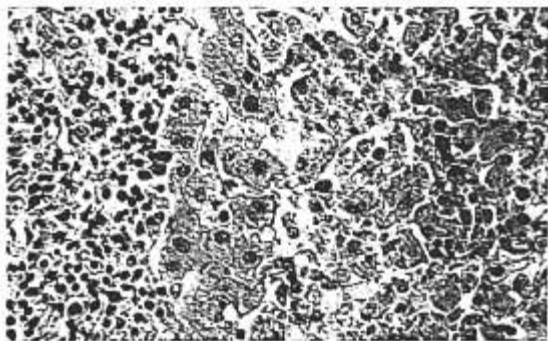
In 15 cases (13 "unexplained" and two "explained"), the portal areas exhibited enlargement, edema, and inflammatory (mononuclear) reaction of rather marked degree. In 12, the distribution of this process was universal, affecting all portal areas (figs. 13 and 19).[2] Of the "unexplained" cases, 11 were patients who had received halothane; one was given nitrous oxide-barbiturate and one, cyclopropane. In neither of the two cases of "explained" necrosis was halothane involved.

Although there was no unique or consistent lesion reflecting the effects of halothane administration, the feature of severe and universal portal-area inflammation occurred with significantly greater frequency in the small group of "unexplained" cases in which halothane was the agent used. None of the other histologic changes (distribution, type or degree of necrosis, type of intralobular exudate, etc.) appeared to have any pertinence. It is noteworthy that neither canalicular bile stasis nor a prevalence of eosinophils appeared in any of the cases. The pattern of portal-area inflammation, however, is not unfamiliar to the pathologist; it has been observed also in cases of fatal hepatic disease of other causation, notably in fatal viral hepatitis [16] and in some drug intoxications.[16, 17, 18, 19]

Summary

A pathologic survey concerned with the incidence and nature of postoperative hepatic necrosis was carried out in 10,171 necropsy cases. These were all the cases in which there had been complete necropsy, including examination of the abdomen. Variations in diagnostic criteria and nomenclature in the different participating hospitals, in methods of classification, and in screening techniques interfered with proper case selection. Despite this, it is believed that all examples of massive hepatic necrosis and almost all those with intermediate necrosis among cases necropsied were brought to light.

A scrutiny of necropsy diagnoses by varied means led to the accumulation of 972 cases of possible hepatic necrosis; microscopic sections of 946 of the livers were procured for review.

A panel of six pathologists, experienced in hepatic disorders, reviewed the sections obtained, independently and with no knowledge of the clinical histories or anesthetics used. Hepatic necrosis of various degrees was found in 222 cases: 82 massive, 115 intermediate, and 25 minor and deemed negligible.

The Pathology Panel next attempted to assign a cause for the hepatic necrosis, combining a knowledge of the clinical data (except the anesthetic used) and the histologic pattern of the liver. Except for recognition of the effects of anoxia, shock, or sepsis, the Panel was not able to determine an etiologic basis for the lesions with any degree of uniformity or consistency.

The histologic appearances of sections from 19 cases with necrosis, considered by a multi-specialty committee to be "unexplained" by factors detectable in the clinical record, were studied critically and compared with 19 cases

in which the hepatic necrosis was deemed to be the result of overt factors. No consistent histologic pattern could be attributed to halothane. It appeared, however, that cases associated with halothane, more often than cases associated with other anesthetics, exhibited a lesion simulating that encountered in fatal viral hepatitis and some drug-induced forms of hepatitis.

In respect to the apparent relationship, three questions may be posed:

(1) Had the patient harbored a clinically inapparent viral hepatitis that had progressed by spontaneous exacerbation to a fatal outcome?

(2) Had an occult and seemingly innocuous viral hepatitis been provoked into violent progression under the stress of a complicating disease, the surgical procedure required for its correction, or the anesthetic used?

(3) Had the hepatic disorder been induced *de novo* by the anesthetic, either as a direct toxic effect or by reason of idiosyncrasy?

Unfortunately, the evidence gathered does not permit unequivocal affirmation of any of the assumptions implicit in these questions. One may suspect that in a rare person exposed to halothane a special sensitization constitutes a triggering mechanism, but there is no indication that this was regularly the case or that one or the other mechanism may not have existed equally as well.

Conclusion

The incidence of massive hepatic necrosis in a large postoperative necropsy population was exceedingly low. Moreover, in the bulk of such cases the hepatic lesions were readily attributable to such factors as shock, infection, anoxia, pre-existing disease, and even extensive surgical manipulation. Only rarely did the anesthetic appear to be involved: in 19 cases of massive and intermediate necrosis among the 10,171 necropsied cases investigated. Of these, 14 cases involved halothane, and 5 did not. No clear-cut or universally acceptable histologic lesion was found regularly in the cases attributed to halothane.

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