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Letters to the Editor

Vinyl Chloride and Acroosteolysis

The excellent review of the article "Occupational Acroosteolysis" in the August issue (p 670) contains an error in the nonmedical field. The statement is made that cleaning of the polymerization reactors for vinyl chloride resins must be done by hand. This is in error, as solvent cleaning and steam cleaning, which obviate the necessity of the workers entering the kettle to carry out the cleaning is a technology that has existed for some time, and, of course, has been expanding since the advent of occupational acroosteolysis. It is of interest that in those installations where this method of cleaning has been carried out there is no acroosteolysis in their PVC workers.

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Hypersusceptibility and Genetic Problems

The recent article entitled, "Hypersusceptibility and Genetic Problems in Occupational Medicine—A Consensus Report," by Stokinger and Scheel¹ makes a number of assertions with regard to work published from our laboratory and which require clarification. While the authors state that they "... have tried to present a cross section ... without author bias," it is evident that their paper represents their personal opinion.

The authors make reference to our paper² and note that it is unique in that it is the only paper that examines serum alpha-1 antitrypsin levels in an industrial situation. They proceed to discredit the paper by quoting a letter to the editor of JAMA³ but omit to refer to our reply which followed on the same page.⁴ Furthermore, we should also like to point out that the very comments we made about methodology in our reply were recently raised by others in a recent symposium.⁵

Of further interest, is that about the time our study was completed, Fagerholm and Laurell⁶ reported on their crossed-immunoelectrophoresis phenotyping to detect genetic variants relative to alpha-1 antitrypsin deficiency. Subsequently, in a

paper by Talamo et al⁷ it was shown that with the exception of the homozygote deficient (PiZZ), no correlation between serum trypsin inhibitory capacity (TIC), or concentration, and the heterozygous phenotype was obtained whether or not obstructive pulmonary disease was present. Overlapping quantitative values were reported including those with variants PiMM, PiMS and PiMZ. In our study we also found it impossible to separate heterozygotes from normal by means of TIC determinations. Talamo et al⁷ go on to state that, "the clinical importance of intermediate serum alpha-1 antitrypsin deficiency remains uncertain." The recent studies by Galdston et al⁸ implicating leukocyte lysosomal proteases, as well as, the studies of Starkey⁹ and Werb¹⁰ on the inhibition of cathepsins and collagenase by the alpha-2 macroglobulin fraction may prove to be relevant; it is certainly too early to tell.

There is another matter raised by Stokinger and Scheel to which we should like to address ourselves. The authors make comment on the poor reception by industry of "genetic" testing. The reason for this may be that a "cause and effect" relationship between genetic predisposition and industrial disease has not been demonstrated. Indeed there is no biological phenomenon which is not in part a result of heredity; man is a "colossal variant." What is required in this important area of research is more quantitative studies and more facts rather than glib and facile explanations. An examination of the five (5) genetic tests and criteria suggested by Stokinger and Scheel suggests that their opinions are based on hypothesis rather than fact.

Serum alpha-1 antitrypsin deficiency. — With respect to the heterozygote state, no definite association between predisposition and occurrence of bronchopulmonary disorders has been established — especially in an industrially-oriented environment. The comments by Robin¹¹ are particularly relevant in this connection. Furthermore, with respect to prevalence, we should like to remind the authors that Eriksson¹² found only four (4) homozygote deficient after screening a random

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population of 6995; and only two (2) of the four had any history of emphysema. Would this be considered by the authors a relatively high prevalence in a working population? We hardly think so, although we still feel that the test should be performed. Furthermore, it should be stated that we know of no study indicating "respiratory irritants" in conjunction with alpha-1 antitrypsin deficiency may predispose to chronic obstructive pulmonary disease.

Glucose-6-Phosphate Dehydrogenase Deficiency. — The relatively high prevalence of heterozygotes for glucose-6-phosphate dehydrogenase deficiency appears to be the primary reason that this test should be performed rather than the "promise" of detecting chronic "pill-takers;" the individuals in the latter category are more in need of psychiatric counseling than genetic testing. Furthermore, the effects due to chemical exposure and those due to genetic variations should be delineated. While the drug induced anemias can compound the situation when a genetic deficiency is present, the nature of the effects of these compounds on the erythrocyte is varied and complex. This is especially true in a redox system where the integrity of the cell membrane is clearly dependent on the integrity of the thiol (-SH) groups. Thus urea, a common nitrogen-containing metabolite, which is freely diffusable through the erythrocyte cell membrane and a strong proton binder (pK in the neighborhood of 10-14) does not, to the best of our knowledge, have any potentiating effect on those with glucose-6-phosphate dehydrogenase deficiency disease.

CS₂ Genetic Testing. — The genetic risks in predisposition to CS₂ have never been clearly delineated; no genetic criteria relevant to CS₂ susceptibility have been determined. Furthermore, as the authors themselves noted, the available data (large spread in values) make the use of TETD for genetic testing highly questionable. The rate of formation of metabolic products from TETD may not be a consequence of a genetic "defect" per se.

Isocyanate Genetic Testing. — The immunologic testing for isocyanate allergic

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Toxic and Drug-Induced Hepatitis

GERALD KLATSKIN, M.D.

Hepatotoxins, a heterogeneous group of naturally occurring and synthetic chemical agents, produce a variety of lesions in the liver that are classified as forms of toxic hepatitis. Although they may differ in morphology and pathogenesis, all such lesions share a number of features in common. Characteristically, they (1) exhibit a distinctive histologic pattern for any given hepatotoxin, (2) vary in severity in direct relation to the dose, (3) can be elicited in all individuals, (4) are reproducible in experimental animals and (5) appear after a predictable and usually brief latent period following exposure. In many instances, hepatotoxins behave as general protoplasmic poisons and affect not only the liver but also other tissues. Carbon tetrachloride and phosphorus are typical examples in this group.

Many drugs can injure the liver, yet, paradoxically, few are true hepatotoxins. As is shown later, most drugs that produce hepatic damage appear to behave as sensitizing agents rather than hepatotoxins. Accordingly, a distinction must be drawn between drug-induced and toxic hepatitis. The features that characterize the lesions of *drug-induced hepatitis* and serve to distinguish them from those of toxic hepatitis may be summarized as follows: (1) they cannot be reproduced in animals; (2) only a small fraction of exposed individuals are susceptible to this type of hepatic injury; (3) neither the occurrence of such lesions nor their severity can be correlated with the amount of drug consumed; (4) the appearance of the lesions bears no constant temporal relationship to the institution of drug

therapy, the latent period being brief in some individuals and long in others; (5) the histologic pattern of the lesions is more variable, resembling that of extrahepatic biliary obstruction in some instances, and that of viral hepatitis in others; (6) often the lesions are accompanied by extrahepatic manifestations of hypersensitivity, such as fever, rash, arthralgia and eosinophilia.

A few drugs, such as chloroform, are true hepatotoxins and produce the typical lesions of toxic hepatitis. Others, like the organic arsenicals, may behave as sensitizing agents under some conditions and as hepatotoxins under others.

A number of drugs, including some C-17 alpha alkyl substituted steroids and certain agents used for cholecystography, interfere with bile secretion and may give rise to jaundice. However, the functional disorders they produce are not accompanied by hepatic necrosis or inflammation or by evidence of hypersensitivity, so that these drugs are neither true hepatotoxins nor sensitizing agents, and must be considered separately.

Transmission of the hepatitis virus by means of improperly sterilized syringes contaminated with blood constitutes one of the hazards of parenteral drug therapy and has been reported following the administration of a variety of therapeutic agents. This possibility must be borne in mind in evaluating the role of parenterally administered drugs in the etiology of hepatitis, especially when the latter develops during a long course of treatment, or after an extended latent period.

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TOXIC HEPATITIS

PATHOGENESIS

Several mechanisms have been proposed to account for the actions of hepatotoxins. These include: (1) disturbances in protein synthesis and energy production in the liver resulting from direct injury to hepatic cell membranes, or metabolic alterations in essential constituents of the hepatic cell; (2) impairment of hepatic blood flow, leading to ischemic necrosis, secondary to swelling of the hepatic parenchyma, or to stimulation of the sympathetic nervous system; and (3) alterations in lipid metabolism.

Considering that hepatotoxins differ markedly in chemical structure, it is highly improbable that they all attack the liver in the same way. The uniformity of the biochemical findings in the liver after exposure to hepatotoxins of diverse character suggests that, although these agents probably initiate cellular injury in different ways, the subsequent chain of biochemical events leading to necrosis follows a common pathway.

Several factors, including the nutritional state, alcoholism, pre-existent liver disease and infection, modify the effects of hepatotoxins and are of importance in the pathogenesis of toxic hepatitis (see below).

Some hepatotoxins attack the liver exclusively, though they enter cells elsewhere in the body. The reason for this is not clear. Since many of these agents are degraded or otherwise chemically altered in the liver, it has been proposed that their metabolites are responsible for their specific hepatic actions.⁴⁸⁰ Alternative possibilities that must be considered are that agents of this type are concentrated in the liver, or attack enzymes peculiar to the liver.

Direct Effects on Cell Membranes. More than 60 years ago Wells suggested that hepatotoxins produce cellular injury and death by inactivating essential oxidative enzyme systems, leading to cessation of anabolic processes and ultimate dissolution of cytoplasm by autolytic enzymes.⁷⁸⁰ The results of more recent studies support this view but attach special importance to enzyme systems concerned with energy production and protein synthesis.

Christie and Judah¹³⁵ and others^{111, 172}

have demonstrated that carbon tetrachloride alters the permeability of the mitochondria of the hepatic cells, resulting in loss of diphosphopyridine nucleotide (DPN) and a decrease in the activity of the DPN-linked dehydrogenases of the Krebs cycle. In addition, there is a concomitant fall in adenosine triphosphate (ATP)¹⁷³ and uncoupling of oxidative phosphorylation.^{111, 171} Biochemical¹³⁵ and electron microscopic¹⁷⁴ studies indicate that the mitochondria of the liver swell and fill with lipid under these conditions. Phosphorus¹⁷² and heliotrine¹³⁴ produce similar effects, but whether these occur in other forms of toxic hepatitis is not known.

That carbon tetrachloride can attack the mitochondria directly has been established in *in vitro* experiments.^{111, 135} However, anoxia produces similar effects, so that the *in vivo* changes in mitochondrial enzymatic activity observed following carbon tetrachloride poisoning have been attributed by some to ischemia.⁵¹⁶ The latter interpretation is open to question, but there can be little doubt that mitochondrial damage does not constitute the initial event that leads to necrosis, since other histologic,^{330, 631} biochemical⁵⁹⁸ and electron microscopic⁶⁰³ changes can be demonstrated much earlier.

Recent studies suggest that the primary site of action of carbon tetrachloride is in the endoplasmic reticulum,^{600, 606} a complex of cytoplasmic structures which are the source of the microsomes obtained on centrifugal fractionation of the cells. These play a role in protein synthesis¹¹³ and in certain conjugating systems³⁵⁵ and possibly in lipid metabolism.⁶⁰⁰ Marked dilatation of the cisternae of the endoplasmic reticulum on electron microscopy⁶⁰⁶ and inhibition of microsomal enzymatic activities⁵⁹⁸ are demonstrable early in the course of carbon tetrachloride poisoning, before morphologic or functional changes in the mitochondria are evident. Interestingly, carbon tetrachloride⁶⁰⁶ and other hepatotoxins, such as dimethylnitrosamine,³⁴⁵ inhibit the *in vitro* incorporation of labeled amino acids into protein by the microsomes of the liver. This supports the view that the inhibition of protein synthesis by hepatotoxins is responsible for the subsequent alterations in mitochondria.

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In both carbon tetrachloride⁷⁴⁴ and thioacetamide poisoning²⁵⁰ the calcium content of the hepatic cells increases rapidly. Since high concentrations of calcium produce swelling, loss of potassium and inhibition of respiration and oxidative phosphorylation in mitochondria,⁷⁴⁴ it is possible that agents of this type contribute to hepatic injury by altering the permeability of the cell membranes, permitting excess calcium to enter and attack the mitochondria.

Several investigators have suggested that carbon tetrachloride damages the endoplasmic reticulum by enhancing the peroxidation of its structural lipids.⁵⁹⁷

Indirect Metabolic Effects. Diets that are deficient in sulfur-containing amino acids produce massive hepatic necrosis in the rat.^{266, 323} According to Himsworth, this effect is dependent upon a specific deficiency of cystine.³²² Moreover, he suggests that lesions of this type are induced not only by dietary restriction but also by a relative deficiency of cystine as a consequence of excessive losses or increased demands. As examples, he cites the hepatic lesions of trinitrotoluene poisoning, which he attributes to the combination of cystine with free nitrous groups, and to the increased demand for cystine imposed by a raised metabolic rate, and the lesions of chronic selenium poisoning, which he believes are also dependent upon a relative deficiency of cystine, created in this instance by the substitution of selenium for sulfur.

The observation that protein deficiency enhances and that supplements of methionine or cysteine inhibit the hepatic necrosis induced by bromobenzene, and the fact that bromobenzene couples with cysteine before it is acetylated and excreted as mercapturic acid,³⁸⁸ lend support to the hypothesis that hepatotoxins injure the liver by inducing a relative deficiency of sulfur-containing amino acids. According to Drill, a deficiency of this type could lead to hepatic necrosis by interfering with intracellular enzymatic oxidation-reduction systems dependent upon an adequate supply of sulfhydryl groups.¹⁸⁵ However, direct measurements have failed to demonstrate a fall in

the glutathione content of the liver following carbon tetrachloride poisoning.²⁰² Moreover, it is difficult to reconcile this hypothesis with the observation that a dietary deficiency of sulfur-containing amino acids will not produce hepatic necrosis unless the diet is also deficient in vitamin E^{287, 288, 325} and factor 3,^{663, 664} a naturally occurring organically bound selenium compound found in many tissues and foods.⁶⁶⁵ Indeed, Schwarz has shown that the protective effects of methionine and cystine are dependent not upon their content of sulfhydryl groups but rather upon the presence of trace amounts of selenium.⁶⁶⁵

Ethionine, by trapping adenosine in S-adenosylethionine, depletes the liver of ATP, leading to inhibition of protein synthesis and accumulation of triglyceride.²²⁰ Since all of these effects can be prevented by intraperitoneal injection of ATP or its precursors, the inhibition of protein synthesis is related to the depletion of hepatic ATP. However, this is not the case in carbon tetrachloride poisoning, since ATP injection prevents the decline in hepatic ATP, but does not prevent inhibition of protein synthesis.³⁵¹

Vascular Factors. Alterations in the intralobular circulation may play a role in the pathogenesis of toxic hepatitis. Exposure to carbon tetrachloride, for example, produces an immediate but transient intralobular vasoconstriction, which, as exposure continues, is followed by a more sustained obliteration of the sinusoids, possibly as a consequence of hepatocellular swelling. This has been demonstrated both by the quartz-rod transillumination technique⁷⁶⁶ and by intrasplenic India ink injection.²⁶⁵ Calvert and Brody have attributed the vasoconstriction to stimulation of the central sympathetic areas resulting in a prolonged discharge of the peripheral sympathetic nervous system and increased secretion of epinephrine.¹¹²

Since the degenerative changes and necrosis produced by carbon tetrachloride and a number of other agents occur in the centrilobular areas where the circulation is most impaired, many investigators have attributed the lesions to ischemia.^{265, 766} Evidence in support of this hypothesis has been brought forward by Calvert and Brody.¹¹²

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They reported that cordotomy, a procedure that blocks sympathetic stimuli and prevents hepatic vasoconstriction, fully protects against hepatic necrosis and the alterations in mitochondrial enzymatic activity usually seen following carbon tetrachloride poisoning. However, Plaa and Larson have shown that the protective effect of cordotomy is due to the hypothermia it produces, and that it will not prevent carbon tetrachloride-induced hepatic necrosis if the body temperature is maintained at 36° C. ⁵⁷²

Interestingly, allyl formate, which causes dilatation of the sinusoids without impairment of circulation, produces peripheral rather than centrilobular necrosis. ⁶⁸³ In this instance the principal point of attack is in the area of maximal concentration of the agent, namely, where it enters the lobule via the portal tract at its periphery. However, the distribution of lesions produced by hepatotoxins may be determined by differences in the susceptibility of the cells in the various zones of the liver rather than by zonal differences in the concentration of hepatotoxin or by circulatory changes. This possibility is suggested by the variations in the biochemical activities of the cells found in different parts of the lobule. ⁶⁷⁵

According to Himsworth, ischemia produces hepatic necrosis by limiting the availability of circulating sulfur-containing amino acids. ³²⁴ If the hepatic necrosis produced by carbon tetrachloride is the result of ischemia, it is unlikely that a deficiency of sulfur-containing amino acids plays a role, since methionine supplements do not protect against this type of hepatic injury. ¹⁸⁴ A low oxygen tension would appear to be a more important factor, inasmuch as anoxemia *per se* can produce similar histologic ⁴⁹⁰ and biochemical ⁵¹⁸ lesions.

On the basis of hepatic blood flow measurements in the intact rat, using the Grayson method of internal thermal conductivity with an implanted thermocouple, Stoner has challenged the concept that ischemia plays a role in the development of central hepatic necrosis following exposure to carbon tetrachloride and other toxic agents. ⁷²⁶ According to this investigator, the impairment of blood flow previously observed by others, using the India ink injection method or the

technic of quartz-rod transillumination, can be attributed to the anesthesia and laparotomy required in such experiments. ⁷²⁶ It is difficult to reconcile Stoner's observations with other indirect evidence pointing to a circulatory disturbance. ¹¹²

A number of agents, including urethane, ¹⁸⁰ some senecio alkaloids ^{630, 670} and massive doses of arsphenamine, ³⁹⁴ appear to produce hepatic lesions by injuring the blood vessels of the liver, leading either to increased vascular permeability and extravasation of blood ¹⁸⁰ or to thromboses. ^{394, 630, 670}

Fatty Infiltration. One of the striking features of the hepatic lesions produced by carbon tetrachloride and a number of other toxic agents is an accumulation of fat within the parenchymal cells. This phenomenon has been variously attributed to (1) mobilization of nonesterified fatty acids from adipose tissue, as a consequence of sympathetic and adrenal medullary stimulation, ¹¹² (2) depression of fatty acid oxidation in the liver due to a reduction in available DPN ¹⁷² and ATP ¹⁷³ that follows mitochondrial damage, and (3) inhibition of the normal mechanism for the transport of triglyceride out of the liver, presumably because of injury to the endoplasmic reticulum. ⁶⁰⁰

The concept that carbon tetrachloride mobilizes lipid from the depots by stimulating the sympathetic nervous system and adrenal medulla, and thus produces fatty infiltration of the liver, stems from the observation of Calvert and Brody that adrenalectomy diminishes and cordotomy prevents this effect. ¹¹² More direct evidence indicative of fat mobilization has been obtained in animals whose depot fats were labeled with deuterium prior to carbon tetrachloride administration. ⁴⁴ The observation that the administration of epinephrine increases the release of nonesterified fatty acids from the isolated epididymal fat pad while carbon tetrachloride does not, ⁶⁸⁰ and the failure of adrenalectomy to protect against carbon tetrachloride-induced fatty infiltration in some experiments, ¹⁰ appear to be inconsistent with the theory that fat mobilization is mediated by sympathetic stimulation and increased epinephrine secretion. However, this does not exclude the possibility that carbon tetrachloride and other hepatotoxins

mobilize fatty acids by some other mechanism. Indeed, the elevated levels of free fatty acids found in the plasma following the administration of such agents³⁵¹ support this view.

Dianzani has reported that carbon tetrachloride uncouples oxidative phosphorylation and lowers the ATP content of the liver before it produces fatty infiltration.¹⁷³ Since ATP is essential in the activation of fatty acid oxidation, he postulates that the accumulation of fat is secondary to a reduction in its rate of oxidation. This view has been disputed by two groups of investigators who have shown that the fat content of the liver rises before there is any uncoupling of oxidative phosphorylation^{111, 690} or impairment of octoanate oxidation,⁵⁹⁹ and that this effect is not abolished by preventing mitochondrial damage with ethylenediaminetetraacetate.¹¹¹

Carbon tetrachloride, in addition to raising the concentration of lipid in the liver, lowers the plasma level of triglyceride and inhibits the hyperlipemia induced by intravenously injected Triton.⁶⁹⁰ From this, Recknagel and associates concluded that fat accumulates because of damage to the mechanism normally responsible for the transport of triglyceride out of the liver.⁶⁹⁰ Moreover, on the basis of indirect evidence, they have proposed that the most likely locus for this mechanism is the membranous component of the endoplasmic reticulum. Smuckler, Iseri and Benditt, who are in essential agreement with this view, attribute the block in triglyceride transport more specifically to the depressed synthesis of protein required for lipid conjugation.⁶⁹⁶ A number of observations support this concept. The most important of these are that on electron microscopy, the earliest findings in the liver following carbon tetrachloride administration are cystic dilatation of the rough endoplasmic reticulum and dislocation of the ribosomes from its membranes,⁶⁹⁷ and that these changes are accompanied by an inhibition of ribosomal protein⁶⁹⁷ and plasma lipoprotein⁶⁹⁷ synthesis.

Nutritional Factors. The susceptibility of animals to hepatotoxins is greatly influenced by their nutritional status. Clinical experi-

ence suggests that the same is true of man, but the evidence is not nearly as convincing. In general, starvation and high-fat diets enhance, whereas high-carbohydrate and high-protein diets protect against the hepatotoxic effects of these agents. However, in the case of many hepatotoxins the effects of diet are not known. Moreover, the results of changing a single dietary constituent are difficult to interpret, unless due consideration is given to concomitant changes in the other components and caloric value of the diet, and to their effect on net food intake—factors that frequently have been neglected in toxicity studies.

Even a relatively brief period of starvation increases the severity of the hepatic damage produced by carbon tetrachloride²³⁵ and chloroform.¹⁸⁷ High-fat diets enhance their toxicity to an even greater extent.^{80, 543} In contrast, carbohydrate appears to protect the liver against injury by these and other agents.^{80, 543}

The effects of protein are variable, depending not only on the nature of the hepatotoxin but also on other factors. Thus, protein deficiency increases the susceptibility of the liver to damage by chloroform⁵⁰⁶ but not by carbon tetrachloride.¹⁸⁷ Similarly, a surplus of protein protects against the hepatic effects of chloroform⁵⁰⁶ but not against those of carbon tetrachloride¹⁸⁷ or many other agents.¹⁹⁵ The protective action of protein also depends in part on the nutritional status. Thus, supplements are far more effective in preventing chloroform injury in the depleted animal than they are in the animal with normal protein stores.¹⁸⁷ The source of protein is another factor that may influence the results. Meat, for example, in contrast with other proteins, actually enhances the toxicity of some agents.⁸¹

Other dietary constituents are of interest in connection with toxic hepatitis, not only for their possible therapeutic value but also for the clues that they may provide to the mechanisms involved in the actions of hepatotoxins. Of these, choline, methionine, cysteine and tocopherol have received the greatest attention.

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bon tetrachloride⁴⁰ or phosphorus⁶⁹ poisoning but does not prevent hepatic necrosis under these conditions. Some investigators have reported that choline partially protects against the mitochondrial injury induced by carbon tetrachloride,¹³⁵ but this effect has not been confirmed by others.¹¹¹

Methionine protects against chloroform toxicity both in protein-depleted⁵⁰⁷ and stock-fed animals.¹⁰³ However, it is not certain that the site of its action is in the liver. At least in protein-depleted animals given carbon tetrachloride, methionine increases the survival time by preventing renal necrosis²³⁹ rather than by protecting against hepatic damage.¹⁸⁴ In conjunction with alpha-tocopherol supplements, methionine also prevents the development of cirrhosis following chronic selenium poisoning.⁶⁶⁹ Alpha-tocopherol alone protects against carbon tetrachloride toxicity in rats on low-casein diets. Prolongation of survival in this instance probably is not due to any hepatic effect, since liver damage is not prevented.³⁴¹

Cystine has not been studied as extensively as the other dietary constituents discussed. It affords some protection against the hepatotoxic effects of chloroform in the protein-depleted dog but is inferior to methionine in this respect⁵⁰⁶ and has no effect in other forms of toxic hepatitis.¹⁸⁵

The precise way in which dietary factors affect susceptibility to hepatotoxins is not known, but there is suggestive evidence that indicates that they may do so by altering either the fat content of the liver or the size of its protein stores. In general, susceptibility is enhanced by diets that lead to an increase in hepatic fat or depletion of protein and is reduced by those that produce the reverse changes.²⁷² The heightened susceptibility associated with fatty infiltration of the liver is thought to depend, in some instances at least, on the solubility of many hepatotoxins in fat.^{185, 272} Obviously, this cannot account for increased toxicity of agents that are relatively insoluble. As noted, it has been postulated that some hepatotoxins, and particularly the chlorinated hydrocarbons, produce hepatic necrosis by interacting with sulfur-containing amino acids, thereby in-

ducing a relative deficiency of sulfhydryl groups in essential enzyme systems of the liver.¹⁸⁵ Accordingly, it is believed that low protein diets potentiate the toxic effects of these agents by hastening such depletion. The failure to demonstrate a fall in hepatic glutathione following carbon tetrachloride²⁰² casts doubt on the validity of this interpretation. An alternative possibility that has received relatively little attention is that protein depletion increases the apparent toxicity of such agents by retarding the regeneration of injured hepatic cells.

At one time, the glycogen concentration of the liver was thought to be the major factor that determined its susceptibility to injury. This concept was responsible for the widespread adoption of high-carbohydrate diets in the therapy of hepatic disease. It is now known that the protective action of carbohydrate depends on its protein-sparing effect and its tendency to reduce hepatic lipids and not on an increase in hepatic glycogen.²⁷²

Contributory Factors. Ethyl alcohol potentiates the hepatotoxic effects of chloroform,⁶³¹ carbon tetrachloride,⁴⁰⁹ phosphorus²²⁸ and certain other chlorinated hydrocarbons.⁶⁰ Since all of these agents are highly soluble in lipid solvents, it has been suggested that ethanol, by serving as a vehicle, facilitates either their absorption from the intestinal tract or their penetration and storage in cells.⁶³⁷

In experimental animals, injection of relatively innocuous bacteria greatly enhances the hepatotoxic effects of chloroform and phosphorus and produces a type of mid-zonal or massive necrosis that is not seen in uncomplicated poisoning with these agents.³⁴² It has been proposed that under these conditions the hepatotoxins alter the permeability of the vessels in the liver and thus permit organisms to gain access to the parenchymal cells. Whether or not infection plays a similar role in man is not known.

Anoxia increases the hepatotoxic effects of certain anesthetic agents.⁶³² This would appear to be an additive rather than a synergistic effect, since anoxemia *per se* can produce serious liver injury.^{209, 490}

In experimental animals, antecedent he-

patic injury renders the liver more susceptible to further damage by other agents.⁶⁰ This may account, in part, for the apparent synergistic effects of chronic alcoholism, infection and anoxia in toxic hepatitis.

PATHOLOGY

The morphologic features of toxic hepatitis vary, depending on the agent, its dose and the route of administration. Usually, the acute hepatic lesions are distributed uniformly throughout the lobules, are arranged in a zonal pattern and show all stages of parenchymal degeneration from simple swelling to acute necrosis, with relatively little inflammatory reaction. Often fatty infiltration is a prominent feature. In the case of many hepatotoxins, the intralobular distribution of the lesions is distinctive. Thus, they characteristically occur in the centrilobular zones in carbon tetrachloride¹¹⁴ and chloroform⁷⁸⁴ intoxication and in the periportal zones in phosphorus poisoning.³²⁴ However, the distribution may vary in some forms of toxic hepatitis. Occasionally, the lesions extend beyond the confines of the individual lobules and give rise to areas of massive necrosis, as, for example, in poisoning with the *Amanita phalloides* toxin¹⁸⁰ and some of the chlorinated naphthalene and diphenyl compounds.²⁸¹ Curiously, agents that produce zonal lesions seldom give rise to massive hepatic necrosis, even when large doses are administered. In experimental animals, for example, even lethal doses of carbon tetrachloride or chloroform fail to produce this type of lesion unless they are injected directly into the portal circulation.¹¹⁶ Carbon tetrachloride poisoning in man may be an exception. The writer has seen two instances of acute poisoning—one by ingestion and the other by inhalation—that were associated with subacute hepatic necrosis and subsequent postnecrotic scarring.

As a rule, acute toxic hepatitis of the zonal type is a self-limited lesion that goes on to complete recovery without residuals. However, if the exposure to a hepatotoxin is continuous or is repeated at intervals that do not permit full recovery on each occasion, a diffuse fibrosis may ensue and terminate in a picture closely resembling Laennec's

cirrhosis.¹¹⁴ When necrosis is zonal, regeneration proceeds in an orderly fashion within the confines of an intact reticulum by proliferation of the remaining viable cells in the same lobule, thereby restoring the normal lobular architecture. However, this is not possible in massive hepatic necrosis, in which regeneration must proceed from distant lobules bordering the zones of necrosis. Large masses of parenchymal cells are formed which compress the intervening necrotic zones, containing intact reticulum, blood vessels and bile ducts, into broad bands. This produces the condition variously described as toxic cirrhosis, postnecrotic scarring with nodular hyperplasia and healed massive or subacute hepatic necrosis.

Prolonged exposure to hepatotoxins, including carbon tetrachloride,^{203, 215} selenium⁵³⁴ and others, induces hepatomas in experimental animals. Although cirrhosis usually precedes the appearance of these tumors, it is not known whether necrosis and regeneration of parenchymal cells are essential for their development.²¹⁵ Theoretically at least, hepatotoxins can induce hepatomas in man. However, no authenticated cases have been reported.

CLINICAL FEATURES

Characteristically, the clinical manifestations of hepatic injury do not become evident for a variable interval following exposure to hepatotoxins.

In acute poisoning with agents such as carbon tetrachloride and chloroform, the latent period is relatively brief, usually not exceeding a day or two, and is well correlated with the evolution of the lesion microscopically. Although histologic evidence of hepatocellular injury can be demonstrated within a few hours, necrosis does not reach its peak for a period of 48 hours.^{114, 784}

Following repeated exposure to relatively small doses of certain hepatotoxins, there may be a long interval before signs of cirrhosis become clinically evident.⁵⁷⁴ This does not constitute a period of true latency, since it is possible to demonstrate the presence of progressive lesions histologically at a very early stage.¹¹⁴ The delayed appearance of symptoms in this instance is probably related to the fact that the slowly progressive de-

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struction of the parenchyma is accompanied by compensatory hepatocellular regeneration.

SYMPTOMS

Not all of the clinical manifestations in acute toxic hepatitis are the consequence of liver injury, many being related to the extrahepatic pharmacologic and toxic effects of hepatotoxins. In many instances it is difficult to distinguish between the symptoms of hepatic and extrahepatic origin, and occasionally the latter predominate. Signs of renal damage and gastrointestinal irritation are especially common.

The usual clinical picture resembles that of viral hepatitis, except for the absence of preicteric fever and constitutional symptoms. Anorexia, nausea and vomiting are the principal symptoms, and jaundice and hepatomegaly are the major physical findings. In mild cases, jaundice may be absent. Usually, the icterus is accompanied by bilirubinuria, but acholic stools are rare.

In severely poisoned patients with massive or subacute hepatic necrosis, the clinical manifestations tend to be more severe and may include such unusual features as intense abdominal pain, coffee-ground vomitus, a rapid decrease in the size of the liver, ascites, edema, hemorrhagic phenomena, somnolence and coma.

As noted, repeated exposure to hepatotoxins may produce cirrhosis. The clinical course in such cases is variable. In some, there are repeated episodes of acute hepatitis before frank signs of cirrhosis become evident, whereas in others the onset is insidious without antecedent symptoms of acute hepatic injury. Unless the exposure to a hepatotoxin is recognized, the former may be mistaken for relapsing viral hepatitis with posthepatic cirrhosis, and the latter for Laennec's or some other type of cirrhosis.

Except in the most severely affected cases, recovery from acute toxic hepatitis tends to be more rapid and is less likely to be followed by sequelae than in viral hepatitis. However, the ultimate prognosis depends as much upon the accompanying extrahepatic lesions as upon the state of the liver. Thus, for example, in carbon tetrachloride poisoning, the hepatic lesions may be mild and

heal, while those in the kidney are extensive and lead to progressive renal failure and death.

LABORATORY FEATURES

The results of liver function tests are similar to those found in acute viral hepatitis, except that abnormalities of cephalin-cholesterol flocculation and thymol turbidity are less common.⁵⁸⁰ This difference may be related to the relative paucity of inflammatory cells in the lesions of toxic hepatitis.

Although liver function tests are of limited value in distinguishing between toxic and viral hepatitis, they can be of great assistance in detecting the early signs of liver injury following known or suspected exposure to hepatotoxins, and in evaluating the severity and the progress of the lesion once it is established. In this connection, the serum transaminase level, because of its sensitivity and the relative ease with which it can be determined, is the most useful single screening test available.

TREATMENT

If the patient is seen immediately after exposure, an attempt should be made to remove any remaining traces of hepatotoxin from the intestinal tract by lavage and catharsis, or by hyperventilation in the case of toxic vapors. However, such measures are seldom successful once signs of toxic hepatitis are evident, because of the relatively long period of latency between exposure and the appearance of clinical manifestations.

In the case of industrial hepatotoxins, it is important to keep all exposed personnel under close surveillance, preferably with periodic tests of hepatic function, and to remove such individuals from the contaminated environment at the first sign of functional impairment.

Antidotes. A number of chemical agents protect against the injurious effects of hepatotoxins in experimental animals.¹⁸⁸ Only a few have been tested in man, and these have proved to be of no value in the treatment of toxic hepatitis. This is not surprising, since in most experiments these agents have been used prophylactically rather than therapeutically.

BAL (2,3-dimercaptopropanol) would

appear to be an ideal antidote in the early management of toxic hepatitis due to compounds of gold and arsenic, since it combines both with free and tissue-bound metallic ions to form relatively innocuous, soluble thiometal complexes which are excreted readily by the kidneys. However, the results of treatment in man have been disappointing.¹⁹⁶ No doubt this is attributable to the fact that in most instances BAL has been tried in patients with hypersensitivity reactions induced by organic arsenical or gold compounds rather than in those with toxic hepatitis.

Since other chemical agents that protect against hepatotoxins in animals also contain sulfhydryl groups, their effectiveness has been attributed to a sulfhydryl-sparing action in essential enzyme systems. However, some of the nonsulfhydryl analogues of these agents are equally effective,¹⁰² so that their mode of action is unknown.

Reports indicating that antihistamines protect against the hepatotoxic effects of thioacetamide, possibly by preventing mitochondrial swelling,³⁶⁶ and that adrenergic blocking agents protect against carbon tetrachloride poisoning by preventing hepatic ischemia¹¹² suggest new approaches to the treatment of toxic hepatitis. Although these agents have not been tried in man, if they do prove to be effective, they will have to be used within a few hours of exposure to the hepatotoxin.

Diet. There are no well-controlled studies establishing the efficacy of dietotherapy in the management of toxic hepatitis in man, the rationale for such treatment being based almost exclusively on the results of animal experiments and on experience with other types of liver disease.

Most experimental studies of the interrelationships between dietary factors and the actions of hepatotoxins have been concerned with the influence of the *antecedent* nutritional status on the incidence and the severity of hepatic injury following intoxication, and not with the effects of diet on the regeneration and the repair of the injured liver—the major considerations in the treatment of toxic hepatitis. This is an important distinction, since it does not follow that a dietary constituent that protects against the hepato-

toxic effects of an agent necessarily facilitates recovery once such injury has occurred.

The effect of *protein* in chloroform poisoning is a case in point. Here there seems to be little doubt that protein depletion enhances toxicity and that protein supplements under these conditions are protective, even if given some hours after exposure.⁵⁰⁷ However, there is no evidence to show that such supplements hasten recovery when administered after overt signs of liver disease have appeared. Moreover, the protective action of most dietary constituents, including protein, have been demonstrated in depleted animals, so that no conclusions are warranted regarding their therapeutic value in well-nourished individuals with toxic hepatitis. Also, it cannot be assumed that because a dietary constituent protects against one hepatotoxin it will necessarily do so against all. This is well illustrated in the case of protein, which protects the depleted animal against chloroform⁵⁰⁸ but not against carbon tetrachloride¹⁸⁷ intoxication.

Finally, in assessing the results of animal experiments, care must be exercised in distinguishing between the effects of dietary measures on survival and their effects on the liver *per se*, since the former may be related to extrahepatic factors. Thus, in carbon tetrachloride poisoning, methionine increases survival by preventing renal injury but has no effect on liver damage.²⁸⁹

The impressive results of dietotherapy in Laennec's cirrhosis have encouraged its adoption in other forms of liver disease, including viral and toxic hepatitis. Although this practice is reasonable, there is no conclusive evidence to indicate that dietary measures are effective in any type of liver injury other than that associated with nutritional deficiency.

In the absence of more precise information regarding the most efficacious form of treatment in toxic hepatitis, it would seem logical to provide a diet rich in protein and carbohydrate on the principle that protein is required for tissue regeneration and is spared when adequate nonprotein calories are provided. Although there is no evidence to indicate that the addition of fat to a well-balanced protein-containing diet is in any way deleterious to the injured liver, fat may

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be poorly tolerated during the period of anorexia and indigestion in the early stages of hepatitis and has the disadvantage that it is difficult to administer parenterally. Later, however, when the appetite improves, liberal use of fat in the form of milk, cream, cheese and eggs should be encouraged, since it makes for a more palatable diet and facilitates the maintenance of a high caloric intake, thus preventing the weight loss and the debility that so often follow an attack of acute hepatitis.

Obviously, from what has been said, any statements regarding the precise protein and caloric requirements in toxic hepatitis are based on personal opinion and experience rather than on well-documented evidence. With this reservation in mind, it is suggested that 70 to 80 Gm. of protein and 3,000 calories constitute an adequate dietary intake. There is no evidence to indicate that a larger protein intake is more efficacious. Studies in cirrhosis⁵⁶⁷ suggest that excessive amounts may actually be harmful in the presence of advanced liver disease, by raising the level of blood ammonia.

In prescribing protein for the patient with toxic hepatitis, due consideration must be given to the status of the kidneys, since hepatotoxins not infrequently produce acute tubular necrosis. In such cases, measures designed to reduce nitrogen retention and to attain a normal internal environment take precedence over the less urgent needs of the liver. Usually this entails omission of dietary protein, provision of sufficient carbohydrate and fat calories to minimize endogenous protein breakdown, and careful regulation of fluid and electrolyte balance. Fortunately, the relatively brief period of protein deprivation usually required does not impede recovery from the associated liver injury. Similarly, individuals with severe anorexia and vomiting who require parenteral feedings do not appear to suffer any ill effects when protein is omitted for a number of days. Although parenterally administered amino acids can be utilized in the face of severe hepatic injury,¹⁹⁹ often they are poorly tolerated, so that their use is not recommended unless the situation demands long-term parenteral feeding.

From a practical standpoint, it is often

difficult to achieve an intake of 3,000 calories during the first few days of an acute hepatitis, even if the diet is supplemented with parenterally administered glucose. This need not cause concern, since the easily attainable level of 2,000 calories usually suffices to tide the patient over this acute phase without compromising his chances of recovery or leading to any significant degree of malnutrition.

When all or most of the calories must be administered by the parenteral route, there is an advantage in using relatively concentrated solutions of glucose. Provided that the infusion rate is slow, concentrations of 15 per cent can be infused over long periods of time without significant losses of glucose in the urine or the development of thrombophlebitis.

In experimental animals, vitamin B₁₂ given *prophylactically* protects the liver against carbon tetrachloride injury.⁵⁸¹ However, there is no evidence to indicate that vitamins administered *following* toxic injury to the liver facilitate recovery. Therefore, there would appear to be no rationale for supplementing the diet in the treatment of toxic hepatitis, except possibly in instances where the antecedent diet has been deficient, or where prolonged parenteral feedings of vitamin-free glucose may precipitate an acute deficiency state.

The effects of methionine and choline in experimental animals have encouraged the use of these agents in the treatment of toxic hepatitis.^{48, 201} However, there is no convincing clinical evidence to show that these dietary supplements have any therapeutic value in well-nourished individuals.

The principles governing the management of the cirrhosis that occasionally follows toxic hepatitis are essentially the same as those for Laennec's cirrhosis and therefore require no further discussion. However, the response to dietotherapy is likely to be far less impressive in the toxic type, since nutritional factors are either lacking or are of subsidiary importance in its pathogenesis.

Bed Rest. Although the importance of bed rest has not been established, it is recommended that the patient with acute toxic hepatitis be kept in bed until hepatic function returns to normal on the principle that

immobilization may facilitate repair of the injured liver by enhancing its blood flow and by reducing the metabolic demands made upon it.

DRUG-INDUCED HEPATITIS

CLASSIFICATION

Most drugs that injure the liver appear to do so by inducing a hypersensitivity reaction, but a few behave as true hepatotoxins. Methyltestosterone and a number of other substituted derivatives of testosterone comprise a special category whose actions are difficult to classify. The features that distinguish between these three groups of drugs are discussed at the beginning of this chapter.

The morphologic changes and the clinical manifestations in drug-induced hepatitis may be predominantly those of hepatocellular injury or those of cholestasis, but in many instances features of both types are evident. The synthetic androgens and anabolic agents also produce cholestasis, but the lesions differ in some respects from those seen in other forms of drug-induced hepatitis.

PATHOGENESIS

Surprisingly little is known about the mechanisms responsible for the development of drug-induced hepatitis, chiefly because the lesions are not reproducible in animals. Studies in man have been limited in scope, being largely concerned with the clinical, functional and morphologic features of the established lesion rather than with the fundamental disturbances that provoke hepatic injury.

Hepatocellular Injury. As pointed out, the few drugs that qualify as true hepatotoxins, such as chloroform, behave like other hepatotoxins in that they injure the liver in all individuals given sufficiently large doses, exhibit the same effects in experimental animals and produce a distinctive type of zonal hepatic necrosis following a predictable and usually brief latent period. Characteristically, the extent of the lesions varies with the dose. In contrast, most other drugs that affect the liver produce a type of hepatic

injury (1) that cannot be induced in all individuals, (2) that is not reproducible in animals, (3) whose morphologic features are more variable and less distinctive than in toxic hepatitis, (4) in which neither the occurrence nor the extent of the lesions can be correlated with the amount of drug consumed, and (5) in which the latent period is variable and unpredictable.

The sporadic nature of the susceptibility to drug-induced hepatitis and the frequency with which the hepatic lesions are accompanied by manifestations of hypersensitivity, such as fever, rash and eosinophilia, suggest that drug reactions of this type are allergic in nature. Longcope⁴⁵⁴ and Chase⁴⁵² have emphasized the similarities between drug reactions and serum sickness and have proposed that both represent forms of acquired hypersensitivity, a view that is supported by the observations of Landsteiner,^{411, 412, 413} Rich^{612, 614} and others.^{733, 777} Of particular interest in this connection is the fact that simple chemical compounds can serve as antigens and induce hypersensitivity,^{412, 733} and that the tissue changes in drug reactions closely resemble those of experimental anaphylaxis.^{311, 615}

Although the theory of acquired hypersensitivity is based on an impressive body of evidence, some aspects of drug reactions appear to be inconsistent. These include the rarity with which circulating antibodies and skin hypersensitivity can be demonstrated, the inconstancy of the interval between the first exposure to a drug and the development of a reaction, and the variable character of the clinical manifestations. In contrast, the anaphylactic type of hypersensitivity seen in serum sickness and under experimental conditions in animals is characterized by readily demonstrable circulating antibodies and skin sensitivity, an immediate reaction to the antigen in the sensitized host, and a response that is distinctive for the species.⁶¹³

Even in the delayed or tuberculin type of hypersensitivity, the interval between the injection of an antigen and the appearance of a reaction in a sensitive host is usually not longer than 24 to 48 hours, and skin hypersensitivity can be demonstrated with great regularity. At present, our knowledge of drug reaction is too fragmentary to ac-

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of the susceptibility and the frequency of lesions are accompaniments of hypersensitivity, eosinophilia, suggest this type are allergic and Chase¹³² have similarities between drug sickness and have prominent forms of acquired that is supported by Landsteiner,^{411, 412, 413, 433, 777} Of particular interest is the fact that conditions can serve as hypersensitivity,^{412, 733} changes in drug response of experimental

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count for these discrepancies, although several possibilities may be considered. Since simple chemical compounds require conjugation with protein before they can serve as antigens,^{411, 413, 777} it is conceivable that variations in the length of the latent period are related to differences in the speed with which such conjugates are formed, and that failure to demonstrate circulating antibodies and skin sensitivity may be due to the use of inappropriately conjugated antigens in testing.

Differences in the metabolic pathways followed by drugs may determine the readiness with which antigens are produced and hence account for variations in individual susceptibility. Although drug reactions occur more frequently in individuals with an allergic background, differences in susceptibility cannot be attributed to hereditary constitutional factors alone, since the vast majority of reactions occur in individuals with no such background.

The feature of drug hypersensitivity most difficult to explain is the extreme variability of its manifestations. Why such hypersensitivity is expressed as a fever and a rash in one individual, as hepatitis in another, and as a depression of myelopoiesis in a third, or why some drugs produce one or another of these manifestations more frequently than any of the others is completely unknown. Certainly, in experimental anaphylactic hypersensitivity, there is far less individual variation, and the nature of the sensitizing agent plays no significant role in determining the character of the reaction. Since the lesions are thought to be the consequence of an antigen-antibody reaction on or within cells,³¹¹ it has been suggested that the manifestations of hypersensitivity depend on the distribution of antibody within the tissues.

Closely related to this problem is the question of how the hepatic lesions are produced in drug reactions. Buckley¹⁰⁵ and Folliot²³³ have presented convincing evidence to show that the hepatic cells do not participate in experimental anaphylactic reactions, and that the focal necrosis and inflammation seen in the liver under such conditions^{308, 453} are the consequence of vascular injury. Although vascular lesions can be demonstrated in some cases of drug hypersensitivity,²⁴³

often the nature of the lesions suggests direct injury to the hepatic parenchymal cells. This raises the question of whether drug reactions may not be more closely related to the delayed tuberculin type of hypersensitivity, the type usually induced by infection, and characterized by sensitization of the tissues generally and by the absence of demonstrable circulating antibodies. Chase, who has studied this problem, believes that both the immediate anaphylactic and delayed tuberculin types of hypersensitivity may play a role in drug reactions.¹³² However, this has not been established, so that, for the present at least, drug reactions must be considered a unique form of hypersensitivity.

Some drugs, such as iproniazid, produce hepatic lesions that are indistinguishable from those of viral hepatitis.³⁷⁷ The possibility that agents of this type enhance the susceptibility to intercurrent infection with the hepatitis virus or light up latent infection in carriers has been considered but has not been investigated.

In differentiating between hepatotoxic and sensitizing drugs, and in evaluating the potential hazards of therapy with such agents, two generalizations are worth bearing in mind. First, if a drug produces hepatic injury in man but fails to do so in other species, it is likely to prove to be a sensitizing agent and may be expected to produce other manifestations of hypersensitivity. Second, if it gives rise to extrahepatic manifestations of hypersensitivity in some individuals, it can be predicted that sooner or later it will produce hepatitis in others.

Cholestasis. Many drugs, such as chlorpromazine, produce a type of hepatitis, generally classified as cholestatic, in which the clinical and the laboratory features resemble those of extrahepatic biliary obstruction. Characteristically, the liver shows evidence of bile stasis but few signs of hepatocellular injury. An inflammatory reaction in the portal triads is a constant feature, except in the type of cholestatic jaundice produced by methyltestosterone and other substituted derivatives of methyltestosterone.

Drug-induced cholestatic hepatitis has been variously attributed to (1) subtle toxic

injury to the hepatic parenchymal cells, leading to increased viscosity of the bile and occlusion of the canaliculi⁷¹² or to swelling of the parenchyma and compression of the canaliculi⁴⁴¹; (2) toxic injury to the canalicular membranes of the parenchymal cells, resulting in effacement or distortion of their microvilli, secondary stasis and inspissation of bile, and ultimate dilatation and rupture of the canaliculi into the spaces of Disse^{647, 649}; and (3) a hypersensitivity reaction with injury to both the parenchymal cells and small bile ducts.⁸⁰⁷ In support of the view that drugs of this type may be hepatotoxic, it has been demonstrated that in the rat chlorpromazine depresses Bromsulphalein excretion²⁵ and enhances the hepatotoxic effects of ethionine.⁵⁷⁹ However, direct measurements have failed to demonstrate any alterations in bile flow,⁶⁸⁸ and administration of massive doses of chlorpromazine for periods up to 6 months has not produced significant hepatic lesions or jaundice in such animals.⁵⁷⁹ These observations taken together with the fact that patients may recover from cholestatic hepatitis while still taking the offending drug,⁶⁸⁵ or may develop the disorder a week or two after discontinuing its use,³⁵⁴ appear to be inconsistent with the interpretation that these agents are hepatotoxic. As in hepatocellular type of drug-induced hepatitis, many features of the cholestatic type point to an underlying hypersensitivity reaction. These include its sporadic occurrence in patients receiving such drugs, the immunity of animals and the frequency of its association with fever,³⁷³ rash¹⁴¹ and eosinophilia.¹⁷⁶

The mode of action of methyltestosterone and other substituted derivatives of testosterone would appear to differ fundamentally from that of other drugs that produce cholestatic hepatitis. Although jaundice develops only sporadically following large doses of methyltestosterone⁷⁸¹ or norethandrolone,^{194, 649} the regular occurrence of Bromsulphalein retention in man^{313, 398} and of reduced bile flow²³ and alterations in the electron microscopic appearance of the canaliculi⁶⁵⁰ in the rat suggest that these compounds behave more like hepatotoxins than sensitizing agents. Consistent with this

interpretation is the fact that they do not provoke an inflammatory reaction in the liver or produce clinical manifestations of hypersensitivity, such as fever, rash or eosinophilia. However, they differ from most hepatotoxins in that they do not produce hepatic necrosis. Available evidence suggests that they interfere with bile excretion by some unknown mechanism.

Since the plasma levels of conjugated bilirubin and alkaline phosphatase are invariably elevated, it is generally agreed that regurgitation of bile is the major factor responsible for the development of jaundice in cholestatic hepatitis. Several mechanisms have been invoked to account for the reflux of bile under these conditions: (1) occlusion of the canaliculi by inspissated bile,⁷¹² (2) dilatation and ultimate rupture of the canaliculi into the spaces of Disse,⁶⁴⁷ (3) obstruction of the small bile radicles in the portal triads by inflammatory exudate⁷¹¹ and (4) increased permeability of the cholangioles.³²⁹ Since each parenchymal cell is drained by several canaliculi and all canaliculi are arranged in a complex network of intercommunicating channels, it is highly improbable that the scattered bile thrombi seen in cholestatic hepatitis obstruct the flow of bile significantly.

Although the possibility of rupture of the canaliculi into the spaces of Disse cannot be excluded with certainty, electron microscopic studies have failed to demonstrate such communications even under conditions of complete biliary obstruction.²⁹⁸

Occlusion of the cholangioles by inflammatory exudate is often cited as an important factor in the pathogenesis of drug-induced cholestasis. However, this has not been established histologically and appears unlikely, since the inflammatory reaction in the portal triads usually is less intense than in the hepatocellular type of drug-induced hepatitis and is totally absent in some cases.

Except in rare instances in which actual necrosis of the cholangioles has been demonstrated,⁸⁰⁷ there is no direct evidence that these structures are abnormally permeable under conditions of cholestasis.

One possibility that has received insufficient attention is that drugs may produce cholestasis by affecting the bilirubin trans-

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port system and permeability of the hepatic parenchymal cells, thus permitting the reflux of conjugated bilirubin from the cells and/or the canaliculi into the lymph spaces and the sinusoids. That cellular disturbances of this type can occur in the absence of histologic abnormalities is evident from the elegant *in vivo* studies of bile secretion carried out by Hanzon, using direct microscopy of the liver following the injection of uranin, a fluorescent dye that is excreted in the bile.³⁰² Similarly, reflux of bile from the canaliculi into the lymph spaces via the cytoplasm of the parenchymal cells has been confirmed by electron microscopy.²⁹⁸ More direct evidence suggestive of altered permeability of the hepatic cells in cholestatic hepatitis is the rise in the serum transaminase level that often occurs in the absence of overt hepatic necrosis.

Of interest are studies on the pathogenesis of "geel-dikkop," a naturally occurring form of cholestatic hepatitis seen in South African sheep that feed on the poisonous plant *Lippia rehmanni*.⁶²⁰ Rimington and associates have shown that in the rabbit, icterogenin, a triterpene acid derivative of this plant, suppresses bile secretion and blocks the excretion of intravenously injected conjugated and unconjugated bilirubin without producing histologic abnormalities in the liver.⁶¹³ They interpret these observations as evidence of a defect in the transport of bilirubin through the hepatic cells and suggest that icterogenin may alter cell permeability, permitting regurgitation of bile from the canaliculi.

PATHOLOGY

Drugs may give rise to a variety of lesions, depending on their mode of action. True hepatotoxins, such as chloroform, produce parenchymal necrosis, degeneration and fatty infiltration with a distinctive zonal pattern in the lobules, and little or no inflammatory reaction. In contrast, sensitizing drugs give rise to hepatocellular and/or cholestatic lesions that differ from those seen in toxic hepatitis.

In the hepatocellular type, produced by agents like the sulfonamides,²⁴³ the liver shows scattered foci of parenchymal necrosis and a diffuse inflammatory reaction that

usually is most intense in the portal triads. Bile stasis is an inconstant but common feature, whereas deposition of fat is rare. Occasionally, the portal triads contain granulomata, some of which may involve vessel walls.^{243, 517} Some drugs, such as iproniazid and cinchophen, cause lesions that are indistinguishable from those of viral hepatitis and occasionally involve large masses of parenchyma, producing the picture of subacute or massive hepatic necrosis.⁵⁷⁷ A fatal outcome is relatively common in this group; in survivors, healing of the liver may be accompanied by scarring and the development of postnecrotic cirrhosis.

Many sensitizing drugs, such as chlorpromazine, produce hepatic lesions in which bile stasis, particularly in the pericentral bile canaliculi, is the predominant feature. Usually, the portal triads are infiltrated to a variable degree with mononuclear, polymorphonuclear and eosinophilic leukocytes. The absence of hepatocellular necrosis and intralobular inflammation is generally emphasized as a characteristic feature of drug-induced cholestatic hepatitis. However, careful study of biopsy specimens frequently reveals such changes, although not to the same extent as in the hepatocellular type.^{383, 307} In the writer's experience no sharp distinction can be drawn between the lesions of cholestatic and hepatocellular hepatitis. Although cholestasis may predominate in the one and parenchymal damage in the other, most cases show evidence of both. The hepatitis produced by some drugs may be of the cholestatic type in some individuals and of the hepatocellular type in others.

Usually, recovery from cholestatic hepatitis is relatively prompt and without residuals. However, the disease may run a prolonged course with persistent jaundice and hepatomegaly, occasionally accompanied by splenomegaly, hypercholesterolemia³⁰¹ and xanthomatosis.^{70, 529, 724} This syndrome has been reported following hypersensitivity reactions to the arsphenamines^{301, 724} sulfanilamide,⁶² thiouracil,²⁵³ neocinchophen⁷⁰ and chlorpromazine.⁵²⁹ Although ultimate recovery without significant residuals occurs and is said by some⁵⁹⁴ to be the rule, there are well-documented instances of slowly progressive periportal inflammation and

fibrosis leading ultimately to the development of biliary cirrhosis.^{62, 70, 383, 529} Both the clinical and the histologic findings in such cases bear a remarkable resemblance to those described in primary biliary cirrhosis. This suggests the interesting possibility that, in some instances, unrecognized reactions to drugs are important in the pathogenesis of this otherwise obscure disease.

The hepatic lesions produced by methyltestosterone and other substituted derivatives of testosterone are characterized by pericentral canicular bile stasis and thus resemble those of drug-induced cholestatic hepatitis. However, they differ in that they show no significant hepatocellular damage or inflammatory reaction.^{649, 781} Rarely, drugs of this type produce peliosis hepatis,^{274, 378} an unusual disorder that may be fatal in which the parenchyma of the liver is studded with blood-filled cystic spaces lined by endothelial or hepatic parenchymal cells. Focal necrosis, vasculitis and agonal congestion have been invoked as possible factors in the pathogenesis of this lesion.

CLINICAL FEATURES

The interval between the first exposure to a drug and the onset of a reaction involving the liver tends to be longer and is less predictable than in toxic hepatitis. Reactions of this type are seen most commonly between the 2nd and 5th week, but may occur as early as the 1st day or only after many months of drug administration. Occasionally, the reaction appears as long as a week or two after cessation of therapy.³²⁹

Variations in the period of latency appear to be dependent on host factors rather than on the nature of the agent involved. In previously exposed individuals, readministration of a drug may provoke a reaction following the first dose, presumably because of antecedent sensitization. However, similar immediate reactions are seen occasionally in individuals with no history of previous exposure.⁴²⁶ It is difficult to account for such cases on the basis of hypersensitivity unless it is assumed that inadvertent contact with the drug or with some chemically related compound has occurred in the past.

SYMPTOMS

Not infrequently, the onset of drug-induced hepatitis is heralded by the abrupt appearance of constitutional manifestations of hypersensitivity, such as fever, chills, a morbilliform or urticarial rash, pruritus and arthralgia. Often these are accompanied by anorexia and nausea, and less commonly by vomiting and abdominal pain. Jaundice and dark urine become evident within a few days and usually are accompanied by enlargement and tenderness of the liver. Splenomegaly is seen occasionally but is less common than in viral hepatitis. Acholic stools and pruritus are frequent findings in cholestatic hepatitis but are inconstant features in the hepatocellular type.

In some cases the onset of jaundice is insidious without antecedent or accompanying constitutional symptoms. This is the rule in the type of cholestatic hepatitis produced by methyltestosterone and other substituted derivatives of testosterone and may be seen in other forms of drug-induced hepatic injury.

Liver damage may occur in the absence of jaundice. This is illustrated by the frequency with which Bromsulphalein retention,⁴¹⁹ rises in the serum levels of alkaline phosphatase³⁸³ and transaminase,⁶⁴⁹ and histologic changes in the liver³⁸³ can be demonstrated in the course of drug reactions unaccompanied by jaundice or other overt clinical signs of hepatic involvement.

Usually, prompt withdrawal of the offending drug is followed within a few days by subsidence of fever and other constitutional manifestations. However, the signs of hepatitis clear more slowly, usually requiring 2 to 3 weeks for full resolution. Occasionally, they persist for many weeks or even months.

Protracted cholestatic jaundice may be accompanied by progressive enlargement of the liver and the spleen, intractable pruritus and xanthomatosis,^{62, 70, 529} features indistinguishable from those of so-called primary biliary cirrhosis. In a few instances, cirrhosis has been demonstrated histologically,^{62, 70, 529} but in others the inflammatory reaction and fibrosis in the liver have been less extensive, and apparent clinical

recovery has come in the the histologic levels of cholesterol of the jaundice with documented tends to rule out other forms.

Drugs such as and cinchona that resemble sionally produced hepatic necrosis clinical manifestations are complicated include such as abdominal rapid decrease edema, hemolysis and course is difficult recovery taking of postnecrotic plasias. If the logically, then such cases signs of cirrhosis years later. more prolonged signs of liver may ensue usually is rhage from recent infection.

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recovery has occurred.⁵⁹⁴ The ultimate outcome in the latter group is uncertain, since the histologic abnormalities and the raised levels of serum alkaline phosphatase and cholesterol usually persist despite clearing of the jaundice and xanthomatosis. In cases with documented cirrhosis, the disease tends to run a more benign course than in other forms of biliary cirrhosis.

Drugs such as iproniazid, pyrazinamide and cinchophen, which give rise to lesions that resemble those of viral hepatitis, occasionally produce subacute or massive hepatic necrosis. As might be expected, the clinical manifestations under these circumstances are usually more severe than in uncomplicated acute hepatitis, and may include such unusual features as intense abdominal pain, coffee-ground vomitus, a rapid decrease in the size of the liver, ascites, edema, hemorrhagic phenomena, somnolence and coma. Occasionally, the clinical course is deceptively benign, apparent recovery taking place despite the occurrence of postnecrotic scarring and nodular hyperplasia. If the liver is not examined histologically, the true nature of the lesion in such cases may not become evident until signs of cirrhosis appear months or even years later. Usually, however, the course is more prolonged and is characterized by signs of hepatic decompensation. Death may ensue in a few weeks or months and usually is due to hepatic failure, hemorrhage from esophageal varices or intercurrent infection.

LABORATORY FEATURES

In the hepatocellular type of drug-induced hepatitis, the results of liver function tests are identical with those seen in acute viral hepatitis, with the exception that high levels of serum alkaline phosphatase are more common.

The typical biochemical pattern in the cholestatic type of hepatitis resembles that of extrahepatic biliary obstruction, except for the occurrence of high levels of serum transaminase early in the course of the disease. Characteristically, there is an increase in serum bilirubin involving the conjugated fraction predominantly, excretion of bilirubin in the urine, a decrease in the output

of urobilinogen in the feces, and a sharp rise in the serum levels of alkaline phosphatase and cholesterol. With few exceptions, thymol turbidity and cephalin-cholesterol flocculation remain normal. In the protracted form of cholestatic hepatitis, particularly in cases complicated by xanthomatosis, the concentration of cholesterol rises to high levels, often above those seen in extrahepatic biliary obstruction or primary biliary cirrhosis.⁵⁹⁴ Studies with acetate-1-¹⁴C indicate that the rate of cholesterol and phospholipid synthesis under these conditions is greatly increased.⁵²⁹ Both the serum alkaline phosphatase and cholesterol attain high levels relatively early in the disease, a point that may help to distinguish between drug-induced cholestasis and biliary obstruction.

Eosinophilia is an inconstant feature of drug reactions but, when present, may be an important clue to the etiology in drug-induced hepatitis. Usually, the leukocyte count is normal or moderately elevated, but leukopenia and agranulocytosis are seen occasionally.⁶³⁶

TREATMENT

Prompt withdrawal of the offending agent is of prime importance in the management of drug-induced hypersensitivity reactions, since this alone may abort the reaction and prevent serious injury to the liver and the bone marrow. However, once provoked, reactions of this type may run a fulminant and even fatal course despite the absence of further exposure to the drug.

Although ACTH and adrenal cortical steroids are useful in other allergic diseases, their efficacy in drug-induced hepatitis has not been established. Nevertheless, since favorable results have been reported in a few instances,^{159, 712} it would appear reasonable to employ these agents in severe drug-induced hepatitis that does not respond to drug withdrawal and simple supportive measures, or when continued administration of the offending drug is urgently needed.

Since a serious reaction may follow even a single small dose, it is unwise to readminister drugs that have previously provoked manifestations of hypersensitivity unless the

indications are urgent. Successful desensitization with graded doses has been reported,^{765, 772} but it is difficult to evaluate the efficacy of this procedure, since drug reactions may subside spontaneously despite continued administration of the offending agent^{354, 655, 689} or may fail to recur when drug therapy is resumed following recovery.⁷⁶⁵ If desensitization is attempted, concomitant steroid therapy early in the course may help prevent reactions.⁷⁶⁵

In general, the principles of treatment are the same as for toxic hepatitis and are discussed elsewhere.

In the protracted form of cholestatic hepatitis, special measures may be required to control intractable pruritus, diarrhea and the tendency to decalcification of the bones. Methyltestosterone and norethandrolone relieve the pruritus,⁵⁹⁴ but may intensify the jaundice. Although there is no conclusive evidence to indicate that this retards ultimate recovery, it is probably wiser to use cholestyramine, a resin that binds bile acids and prevents their reabsorption from the intestinal tract.¹²² Because of the malabsorption that usually accompanies the impairment of bile flow in prolonged cholestasis, vitamin D deficiency and decalcification of the bones may ensue. Accordingly, supplements of vitamin D and calcium should be prescribed to avoid this complication. Diarrhea related to malabsorption of fat may be partially alleviated by reducing the fat content of the diet, but this is done only if the diarrhea is troublesome, since it may lead to wasting.

PROPHYLAXIS

Since the potential hazard of sensitization cannot be evaluated in animals, all new drugs must be considered suspect until proved to be otherwise by prolonged trial in man. If a drug gives rise to any of the manifestations of hypersensitivity, one can be reasonably confident that sooner or later it will produce hepatitis.

Although it is not possible to predict the susceptibility to drug reactions, the hazard appears to be somewhat greater in individuals with an allergic background, particularly those with a history of a previous reaction to other drugs. Indeed, during a

reaction, patients may exhibit hypersensitivity to a wide variety of unrelated agents. For that reason it is best to stop all medications until the reaction subsides and then, if necessary, resume their use one at a time.

Patients receiving sensitizing drugs should be watched carefully for early signs of a reaction. If fever, rash or pruritus occur, the medication should be stopped immediately, at least until other possible causes can be excluded. In the case of patients given agents known to produce serious reactions involving the liver, the serum alkaline phosphatase and transaminase should be tested at weekly intervals during the first 2 months, the period of greatest risk.

SPECIAL FEATURES OF AGENTS CAPABLE OF PRODUCING LIVER INJURY

Hepatotoxins comprise such a heterogeneous group with respect to their chemical structure and mode of action that they are difficult to classify in any logical or orderly manner. For convenience, therefore, the following section is arranged alphabetically. The agents selected for discussion by no means constitute a complete inventory of substances that can injure the liver, but most of those known to produce toxic hepatitis in man are included.

ACCIDENTAL AND INDUSTRIAL POISONING

BERYLLIUM

Inhalation of beryllium compounds may provoke either an acute pneumonitis or a chronic granulomatous reaction in the lung. The former, which is more common, follows exposure to most of the beryllium dusts and fumes encountered in industry, appears after a relatively brief incubation period, is characterized pathologically by an exudation of mononuclear cells into the alveoli and usually resolves completely within 4 months.

In contrast, the chronic disease develops chiefly following exposure to beryllium oxide, appears after a relatively long latent period, ranging from a month to 15 years,³⁴³ is characterized pathologically by a diffuse

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extreme hypersensitivity to related agents. It is to stop all medication, the condition subsides and then, the use of one at a time. The sensitizing drugs should be given early signs of a re-pruritus occur, the condition is stopped immediately, the probable causes can be determined. For patients given these serious reactions, serum alkaline phosphatase should be tested during the first 2 months, if possible.

CLASSIFICATION OF AGENTS PRODUCING PULMONARY INJURY

Such a heterogeneous group with respect to their chemical nature and mode of action that they cannot be placed in any logical order of convenience, therefore, arranged alphabetically for discussion by the following inventory of agents: 1. Agents of the liver, but which produce toxic hepatitis.

2. INDUSTRIAL AND AGRICULTURAL

UNCOMMON

Many compounds may produce pneumonitis or a reaction in the lung. The reaction is common, follows beryllium dusts and fumes, appears after a latent period, is characterized by an exudation of fluid into the alveoli and usually develops within 4 months. The disease develops more sure to beryllium. Relatively long latent period, from 1 month to 15 years,³⁰³ is usually followed by a diffuse

granulomatous reaction that closely resembles sarcoidosis and runs a chronic progressive course that often terminates fatally.^{718, 759} Not infrequently, the disease is accompanied by hepatosplenomegaly, a raised level of serum gamma globulin, a negative tuberculin reaction, hypercalcaemia and renal stones,³⁰³ features that may make the differentiation from sarcoidosis exceedingly difficult.

Although acute and chronic berylliosis are considered distinct clinical and morphologic entities, it has been suggested, on the basis of autopsy studies, that the chronic granulomatous lesion represents a late development in the evolution of the acute pneumonic process.¹⁹⁵ This view is difficult to reconcile with the observation that, while the inhalation of beryllium compounds provokes an acute pneumonitis, neither inhalation⁷²² nor parenteral administration⁶⁶⁶ of such agents produces granulomas in the lungs of experimental animals.

Several features of the granulomatous reaction suggest that it results from sensitization to beryllium. These include its sporadic occurrence in exposed individuals, the long period of latency, the disparity between the amount of beryllium found in the lungs and the severity of the lesions⁷¹⁸ and the immunity of experimental animals. The fact that patch tests with beryllium salts provoke a granulomatous inflammatory reaction in the skin of affected individuals^{170, 701} lends support to the sensitization theory. However, the possibility that beryllium can provoke a granulomatous reaction in the lung by some direct action cannot be excluded with certainty, since subcutaneous injections of beryllium produce granulomas both locally^{251, 666} and in regional lymph nodes.²⁵¹

Berylliosis may be acquired in any occupation involving the handling of beryllium or its compounds. Metal workers who machine beryllium or alloys high in beryllium content, and manufacturers of ceramics, radio tubes and neon signs are the principal victims.⁷⁰² The use of beryllium phosphorus in fluorescent bulbs was discontinued in 1949, so that this no longer constitutes the hazard it once did.³⁰³ Individuals who live within a 3-mile radius of a beryllium plant

may acquire the disease as a consequence of prolonged exposure to low concentrations of beryllium-containing dust and fumes emitted from smoke stacks.^{133, 169} Inadvertent intoxication occurs also in individuals who come in contact with the contaminated clothing of beryllium workers.^{189, 303}

A variety of hepatic lesions are found in fatal cases of both forms of pulmonary berylliosis. These do not occur with any degree of regularity, nor do they give rise to overt signs of liver disease. In the acute pneumonic type, centrilobular necrosis is the principal finding.^{195, 759} Hepatic necrosis also occurs in animals after intravenous injections of beryllium compounds.⁶⁶⁶ However, the lesions produced tend to be midzonal in location and do not occur when the beryllium is administered by the respiratory route.⁷²² Therefore, the centrilobular necrosis in man may be due not to the local toxic action of beryllium but rather to the passive congestion and anoxia that occur terminally in acute beryllium pneumonitis.

In the delayed form of chronic beryllium intoxication, small granulomata, similar to those in the lung, are often found scattered throughout the liver.^{133, 169, 759} These are indistinguishable from the lesions seen in sarcoidosis and a number of other related diseases.³⁸⁵ Chronic passive congestion of the liver secondary to cor pulmonale and heart failure is another abnormality found with some frequency. In rare instances the liver may exhibit central and midzonal necrosis,¹⁶⁹ severe parenchymatous degeneration¹⁶⁹ and a diffuse fibrosis.¹⁰⁵ Whether or not these are directly related to the effects of beryllium is not known.

Both the clinical features and the histologic findings in berylliosis may be indistinguishable from those of sarcoidosis. Usually, a history of exposure to beryllium suffices for differentiation, but in doubtful cases a patch test may be required for confirmation. In this test a small gauze square moistened with a 1 or 2 per cent solution of beryllium sulfate or nitrate is applied to the skin for 48 hours. On removal of the patch, patients with berylliosis exhibit an area of erythema, induration and scaling which may persist for a number of weeks. Biopsy of the skin

late in the course of the reaction shows sarcoid-like granulomas with small zones of central necrosis.⁷⁰¹ From the evidence available, this test appears to be sensitive and specific.^{170, 701}

CARBON TETRACHLORIDE

Because of its widespread use as a solvent, fire-extinguisher and cleaning agent, carbon tetrachloride is an important cause of toxic hepatitis. Poisoning usually follows inhalation of the vapor in a poorly ventilated enclosed space but also occurs after its ingestion. It is not known whether it is absorbed significantly through the skin. It has been suggested on the basis of autopsy⁶⁹⁰ evidence that liver injury is more common after ingestion than after inhalation of carbon tetrachloride. However, this has not been borne out in all studies.⁵¹⁴

Susceptibility. In animals, as little as 0.02 ml. of carbon tetrachloride/kg. can produce histologically demonstrable hepatic lesions. On the basis of experiments carried out on criminals awaiting execution,¹⁷⁸ it would appear that only slightly larger doses (5 ml.), well within the antihelminthic therapeutic range, occasionally produce similar lesions in man. Although these are usually not detectable clinically, there are marked individual differences in susceptibility, so that even small doses of carbon tetrachloride occasionally inflict serious injury. Fatal intoxication has been reported after the ingestion of as little as 1.5 ml.,⁴³⁷ yet recovery has followed poisoning with amounts in excess of 100 ml.⁴²³

With respect to the toxic level of carbon tetrachloride in the atmosphere, it is obviously a function not only of the concentration but also of the duration of exposure. On the basis of animal experiments it has been estimated that a concentration in excess of 0.01 per cent in air is required to produce clinically detectable intoxication in individuals chronically exposed to carbon tetrachloride vapor in their work.⁶⁹⁸ The time-dose relationships under other conditions have not been worked out.

Alcohol Ingestion. Clinical and experimental evidence indicates that alcohol greatly increases the susceptibility to carbon tetrachloride. In one autopsy series,⁵¹⁴ for

example, 11 of 12 fatal cases of accidental poisoning occurred in alcoholics. Similarly, of 34 individuals being treated for hookworm infestation with small doses of carbon tetrachloride, the only 2 instances of toxicity were encountered in alcoholics.⁶⁹¹ Results of animal experiments confirm these clinical observations.⁴⁰⁹

The mechanism underlying this synergism is not known, but it has been suggested that alcohol, by virtue of its solvent properties, enhances the absorption of carbon tetrachloride from the intestinal tract⁴⁰⁹ and facilitates its penetration and storage in cells,⁶³¹ or it renders the liver more susceptible to injury by increasing its fat content.⁵¹⁴ Another possibility is that carbon tetrachloride is oxidized to phosgene and then undergoes condensation with ethanol to form ethylchloroformate, a compound allegedly more toxic than carbon tetrachloride.²⁸³

None of these theories alone, however, accounts for the fact that alcohol enhances the toxicity of both ingested and inhaled carbon tetrachloride, that it increases the severity of injury in both the liver and kidney, and that the increased susceptibility is seen in chronic alcoholics who have not been drinking immediately prior to poisoning.⁵¹⁴ Moreover, whereas alcohol enhances the acute toxic effects of carbon tetrachloride, it does not increase the severity of the hepatic lesions in chronic poisoning.⁴¹⁰

Nutritional Status. Susceptibility to carbon tetrachloride also appears to depend on the nutritional status. In animals, inanition²³⁵ and high-fat diets⁸⁰ increase the toxicity of carbon tetrachloride, whereas, surprisingly, low-protein diets do not.¹⁸⁷ The importance of these factors in man has not been investigated.

Pathologic changes in fatal cases of carbon tetrachloride poisoning⁵¹⁴ closely resemble those described in experimental animals.¹¹⁴

The *hepatic lesions* are characterized by diffuse fatty degeneration and necrosis of the centrilobular parenchyma, collapse of reticulum, hemorrhage and leukocytic infiltration. Regeneration occurs early and proceeds from intact cells at the periphery of the lobule. In animals cytologic changes

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alcoholics. Similarly, after treatment for hookworm, small doses of carbon tetrachloride produce 2 instances of toxicity in alcoholics.⁸⁹¹ Results confirm these clinical

regarding this synergism. It has been suggested that the solvent properties, the action of carbon tetrachloride on the gastrointestinal tract¹⁰⁹ and its storage in the liver more susceptible to increasing its fat content is that carbon tetrachloride added to phosgene and its combination with ethanol to form a compound, a carbon tetrachloride-

ethanol adduct, however, that alcohol enhances the toxicity of carbon tetrachloride. It is suggested and inhaled that it increases the toxicity of both the liver and the lungs. Increased susceptibility to carbon tetrachloride in individuals who have not been previously exposed to alcohol has been suggested. As alcohol enhances the severity of carbon tetrachloride poisoning, the susceptibility to carbon tetrachloride poisoning appears to depend on the individual. In animals, high protein diets⁸⁰ increase the toxicity of carbon tetrachloride, whereas, in humans, high protein diets do not.¹⁸⁷ The factors in man has

been studied in fatal cases of carbon tetrachloride poisoning⁵¹⁴ closely related to experimental animals.

The pathology is characterized by congestion and necrosis of the liver, collapse of the alveoli and leukocytic infiltration occurs early and is most marked at the periphery of the lobules. Cytologic changes

are evident within a few hours and reach a maximum in 24 to 48 hours; regeneration is active by the 3rd day, and histologic recovery is complete by the 14th day. However, the hepatic cells continue to exhibit an increased susceptibility to further injury long after their microscopic appearance has returned to normal.³³¹ Individuals who have succumbed to renal failure as long as 18 days following intoxication still show signs of liver injury,⁵¹⁴ which suggests that healing may occur more slowly in man.

Massive hepatic necrosis is rare. It will be recalled that the same is true in animals, unless the carbon tetrachloride is injected directly into the portal vein.¹¹⁶ The writer has seen two instances of subacute hepatic necrosis following a single exposure to carbon tetrachloride.³⁸³ Although these patients recovered clinically, residual postnecrotic scarring was evident on biopsy.

Renal lesions are invariably present in fatal cases and may be the cause of death. The principal findings include degenerative changes in the tubules, the presence of heme and cellular casts, cellular infiltration of the supporting connective tissue, and signs of active regeneration in the tubular epithelium.⁵¹⁴

The pulmonary findings in carbon tetrachloride poisoning are of considerable interest and are seen with great regularity in individuals who survive for longer than 8 days. Characteristically, the alveoli exhibit a fibrinous exudate with pseudomembrane formation, fibroblastic thickening of their walls, and proliferation of their epithelial lining cells.⁷⁵⁴ These appear to be related to renal insufficiency and are identical with those seen in other forms of acute renal failure. In addition, the lungs frequently show edema, hemorrhage, congestion and bronchopneumonia, features that are thought to be the result of shock, infection and other factors unrelated to the direct effects of carbon tetrachloride. Often, right-sided dilatation of the heart accompanies these pulmonary changes.

Areas of atypical focal pancreatitis may be seen.⁵¹⁴ These too appear to be related to the kidney damage, since they have been observed in other types of acute renal failure.²⁸ As a rule, the lesions are limited in

extent and severity and do not give rise to overt symptoms.

Clinical manifestations of acute carbon tetrachloride poisoning relate to (1) the general toxic and pharmacologic effects of the agent, (2) liver damage or (3) renal injury. Although any of these may predominate, careful examination usually discloses evidence of all three. Often the three groups of symptoms overlap, so that it may be impossible to specify their origin.

The general toxic and pharmacologic effects of the poison are the first to become evident. Usually, they appear within a few hours but may be delayed for as long as a day. With large oral doses and, more commonly following inhalation of toxic fumes, the onset may be immediate. The most frequent symptoms during this period include dizziness, headache, nausea and vomiting. In more severe cases, there may be confusion, abdominal cramps, diarrhea, generalized muscle pain and vasomotor collapse. Occasionally, exposure to a high concentration of fumes results in a deep but transient narcosis due to the anesthetic properties of the agent. Death seldom occurs during this initial period. Occasionally, even fatal doses of carbon tetrachloride do not produce immediate symptoms, so that the first signs of intoxication are delayed until hepatic or renal involvement becomes evident some days later.

Clinical signs of liver involvement appear 2 to 4 days after intoxication, or a day or two after the maximum injury demonstrable histologically. Jaundice and hepatomegaly are the principal clinical manifestations; however, it is evident from autopsy findings⁵¹⁴ that extensive hepatic necrosis may occur without producing either. Therefore, it is important to check the functional stasis of the liver in evaluating the severity of carbon tetrachloride intoxication. The gastrointestinal symptoms which appear shortly after exposure usually increase as the signs of liver damage become evident. In general, the severity of the poisoning is correlated with the depth of jaundice. However, death from renal failure may occur with little or no clinical evidence of hepatic injury.^{514, 890, 798}

Autopsy studies indicate that the kidneys

are involved about as frequently as the liver, and in many cases renal failure dominates the clinical picture.^{514, 680} It has been suggested that there is an inverse relationship between the severity of the lesions in the kidneys and the liver.⁵¹⁴ Most deaths attributable to hepatitis occur during the 1st week, whereas those due to renal failure occur in the 2nd and 3rd weeks.⁷⁵⁴ However, as indicated, usually there is evidence of both hepatic and renal injury in all cases. Even in mild intoxication, the urine usually contains albumin and casts during the first few days. In more severe cases, oliguria appears between the 2nd and 4th days and then may progress to complete anuria.

Azotemia is common and occasionally is accompanied by hypertension. During the period of oliguria the specific gravity tends to become fixed at a level of 1.010, and often the urine contains a significant number of red blood cells and polymorphonuclear leukocytes. In some cases, however, the urine shows little, other than a reduced volume and a low specific gravity, despite the presence of severe azotemia. The close resemblance of the clinical picture to that in other forms of acute tubular necrosis has been emphasized.⁷⁹⁶ However, dehydration due to fluid losses from the intestinal tract often plays an important role in the development of azotemia and must be taken into consideration in planning therapy.

Not infrequently peripheral and pulmonary *edema* supervene as the azotemia progresses. While cardiac failure may be responsible for this complication in some cases, often faulty regulation of fluid and electrolyte balance is the cause. The dyspnea, cyanosis and signs of consolidation that appear terminally are due usually to the pulmonary lesions associated with azotemia described previously. Occasionally, acute pulmonary edema is seen immediately following exposure to carbon tetrachloride. This is thought to be the result of the direct irritant effect of the agent on the alveoli.

Prognosis. It is difficult to predict the outcome in any given case of carbon tetrachloride poisoning. In general, the outlook is favorable if jaundice is mild and the signs of renal impairment are minimal or absent.

However, the prognosis should be guarded early in the course of mild hepatitis, since the appearance of renal failure may be delayed for a number of days and then terminate fatally. If the patient survives the 1st week he is not likely to die of hepatic failure. Similarly, if azotemia is not evident by the end of the 1st week it is unlikely to develop later, so that the outlook for recovery is excellent.

If the initial effects of acute carbon tetrachloride poisoning are survived, the signs of hepatitis usually subside in 2 to 4 weeks, a period slightly longer than that required for morphologic restitution of the liver in experimental animals.¹¹⁴ As a rule, there are no residuals, but in occasional cases healing of extensive lesions is followed by post-necrotic scarring.³⁸³ Recovery from renal injury is somewhat slower but is always complete. Occasionally, cirrhosis follows repeated exposure to subclinical toxic doses of carbon tetrachloride,⁵⁷⁴ as in experimental animals.¹¹⁴ The clinical picture in such cases does not differ significantly from that in other types of cirrhosis, so that the diagnosis depends almost entirely on the history of exposure. Early recognition of this condition is important, since the cirrhotic lesion may be reversible in its early stages if further exposure to the toxin is prevented.¹¹⁴

Treatment. The general principles of treatment are outlined on pages 505-508. As mentioned, there is no evidence to indicate that supplements of protein, methionine or choline exert any therapeutic effect in the well-nourished individual. However, it is possible that they may be of benefit in malnourished individuals if given immediately after intoxication.

A wide variety of chemically unrelated substances, including tocopherol,⁵⁴⁰ glutathione,¹⁰² sodium thiomalate,¹⁰² sodium malate,¹⁰² sodium thioglycollate,¹⁰² sodium glycocollate,¹⁰² vitamin B₁₂,⁵⁸¹ and adrenergic blocking agents¹¹² reportedly protect animals against the toxic effects of carbon tetrachloride when given *prophylactically*. However, they have not been tried as therapeutic agents, and their mode of action is not understood.

Hemodialysis is effective in the manage-

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Because of the ties, the diphenylsulation. However, that the dust. The most frequent consists thalenes tetrachloride it has been naphthalene directly is enhanced small amount of alcohol.⁶

Although may lead to inhalation agent due to the carbon tetrachloride hepatitis, often terminal necrosis. Characteristic of the development of anorexia and prolonged exposure it is hepatomegaly and acneiform eruptions. Recognition of the chloroform hepatitis and then the size of the disease usually death with

Occasionally and death of the liver sup abdominal in such cases patic necrosis pancreatitis is not

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should be guarded against hepatitis, since renal failure may be delayed and then the patient survives the attack to die of hepatic failure. If renal failure is not evident in the first week it is unlikely that the outlook for recovery is good.

In acute carbon tetrachloride poisoning, the signs of renal failure appear in 2 to 4 weeks, rather than the rapid deterioration of the liver in chronic poisoning. As a rule, there are occasional cases healing followed by post-recovery from renal injury, but it is always compensated cirrhosis follows renal toxic doses, as in experimental animals. The clinical picture in chronic poisoning is significantly different from cirrhosis, so that the onset is entirely on the basis of early recognition of the disease since the cirrhosis is in its early stage due to the toxin is

General principles of treatment are on pages 505-508. As evidence to indicate the use of methionine or penicillin in the treatment of carbon tetrachloride poisoning. However, it is of benefit in malnutrition given immediately

chemically unrelated to vitamin E, tocopherol,³⁴⁰ glutathione,¹⁰² sodium glycinate,¹⁰² sodium B₁₂³⁸¹ and adrenocortical hormones reportedly protect against the effects of carbon tetrachloride when given prophylactically. It has been tried as a therapeutic mode of action is not known. The use of these in the management

of severe renal failure due to carbon tetrachloride poisoning.²⁸³

CHLORINATED NAPHTHALENES AND DIPHENYLS

Because of their unique physical properties, the chlorinated naphthalenes and the diphenyls make ideal materials for the insulation of electrical wire and condensers. However, they are such potent hepatotoxins that they are no longer widely used in industry. The commercial product employed most frequently, and known as Halowax, consists of a mixture of chlorinated naphthalenes and at one time contained carbon tetrachloride as a solvent. Experimentally, it has been shown that the toxicity of the naphthalenes and the diphenyls is related directly to their degree of chlorination and is enhanced greatly by the presence of small amounts of carbon tetrachloride and alcohol.⁶⁰

Although ingestion of these compounds may lead to poisoning,⁶⁰ most cases follow inhalation of fumes given off by the molten agent during the soldering of condensers or the coating of wires.²⁷⁹ The type of hepatitis produced is unusually severe and often terminates fatally in subacute hepatic necrosis or postnecrotic cirrhosis.^{231, 279, 727} Characteristically, the onset is insidious with the development of general debility, anorexia and nausea and usually follows prolonged exposure to the toxin. Occasionally, it is heralded by the appearance of an acneiform rash (chloracne), one of the well-recognized signs of toxicity in handlers of the chlorinated naphthalenes. Jaundice and hepatomegaly appear a week or two later and then are followed by a decrease in the size of the liver, ascites and edema. The disease runs a chronic downhill course and usually terminates in hepatic coma and death within a few months.

Occasionally, the lesion is more fulminant, and death due to massive necrosis of the liver supervenes within 2 weeks. Severe abdominal pain is a characteristic feature in such cases. Whether this is due to hepatic necrosis or to the associated acute pancreatitis described by several authors^{231, 727} is not known.

Few cases of nonfatal hepatitis have been

reported, and no follow-up studies are available to indicate whether recovery without residuals is possible. The remarkable toxicity of the chlorinated naphthalenes and the diphenyls for the liver has also been observed in animals, who show the same tendency toward massive necrosis seen in man.⁶⁰

In contrast with carbon tetrachloride, the chlorinated naphthalenes do not produce renal lesions in animals.⁶⁰ However, nephrosis has been reported as an occasional complication in man.⁷²⁷

COPPER

Acute copper sulfate poisoning may follow its ingestion with suicidal intent,¹³⁶ or its application as a topical astringent and antiseptic agent in the treatment of wounds, dermatitis or burns.²³⁷ Doses of 10 or 15 mg. may produce signs of toxicity, and as little as 1 Gm. may be fatal, although the usual lethal dose is approximately 10 Gm. The principal lesions produced by copper sulfate include an erosive, hemorrhagic gastritis and enteritis, centrilobular hepatic necrosis with bile stasis, and renal tubular necrosis. In addition, it frequently produces severe intravascular hemolysis.

Soon after ingesting copper sulfate, patients note a metallic taste and experience epigastric pain, nausea, vomiting and diarrhea. In severe poisoning, hypotension and shock may ensue. Not infrequently, jaundice appears on the 2nd or the 3rd day, and may be due to either hepatocellular necrosis or hemolysis, or both. The hepatocellular type of jaundice tends to be severe, and usually is accompanied by enlargement and tenderness of the liver, and significant abnormalities of hepatic function. As a rule, hemolytic jaundice is mild, even when hemolysis is severe and associated with hemoglobinuria. Many patients exhibit transient oliguria, hemoglobinuria and microscopic hematuria, but in some, renal failure is severe and progressive.

In one large series, the mortality rate was approximately 15 per cent.¹³⁶ Deaths within the first 24 hours usually are attributable to shock, whereas those that occur later are due to hepatic or renal failure, or both.

As might be anticipated, the concentration of copper is increased in the serum,

but is even greater in whole blood, due to the unusual avidity of red cells for copper. In at least one case, the level of ceruloplasmin in the serum was greatly elevated.³³⁷ Penicillamine therapy in this case enhanced the urinary excretion of copper, reduced the concentrations of serum copper and ceruloplasmin, and appeared to alleviate the clinical manifestations of toxicity. Corticosteroids also are alleged to be effective in the management of acute copper sulfate poisoning.²⁸⁴

The possibility that chronic copper poisoning plays a role in the pathogenesis of the hepatic lesions in Wilson's disease is suggested by the high concentrations of copper found in the liver. However, with few exceptions,⁴⁸⁶ attempts to produce cirrhosis in animals by the chronic administration of copper salts have failed.²³²

DDT AND OTHER INSECTICIDES

DDT (2,2-bis[*p*-chlorophenyl]-1,1,1-trichloroethane) can produce central necrosis of the liver in animals,⁵³³ and is thus generally regarded as a potential hepatotoxin in man. However, despite its widespread use as an insecticide, it has rarely been reported as a cause of toxic hepatitis. In one instance, the accidental ingestion of 120 ml. of a 5 per cent solution in kerosene produced hepatomegaly, gastrointestinal bleeding, oliguria, coma and death.⁶⁹³ Autopsy revealed extensive central necrosis and periportal fatty infiltration of the liver and severe tubular degeneration and necrosis of the kidneys. Since DDT alone does not produce renal damage,⁵³³ it was suggested that the kerosene used as a solvent was an important factor in the pathogenesis of the lesions.

In another case, exposure to DDT used as an insecticide produced jaundice in an individual with an underlying cirrhosis.⁴³⁷

Rarely, DDT serves as a sensitizing agent. In one such case, it produced periarteritis nodosa.³²¹ At autopsy, the liver showed enlargement due to congestion, periportal fatty infiltration and a large, thrombosed vein.

A number of other chlorinated hydrocarbons used as insecticides, such as chlordane, dieldrin, lindane and toxaphene, produce characteristic alterations in the cytoplasm of

hepatic cells in the rat when administered at low-dose levels for long periods of time.⁵⁴⁷ However, overt hepatic injury has not been reported in man.

DIMETHYLNITROSAMINE

Severe toxic hepatitis can follow exposure to dimethylnitrosamine, an agent once used to inhibit corrosion. In the 2 cases reported by Freund, daily exposure to the fumes produced massive hepatic necrosis after 1 month and 12 days, respectively.²⁴⁵ The onset was abrupt with abdominal cramps, nausea, vomiting and jaundice and was followed within 2 weeks by the appearance of ascites. The less severely ill patient apparently recovered after a prolonged course, but jaundice recurred in 16 months, and the liver remained large and indurated, which suggests that postnecrotic cirrhosis developed. The other patient died in the 6th week following an acute illness characterized by deepening jaundice, intractable ascites and progressive enlargement of the liver and the spleen. Postmortem examination revealed extensive hepatocellular necrosis, a diffuse inflammatory reaction with a predominance of round cells and histiocytes, and periportal hemorrhages.

Dimethylnitrosamine exhibits the same propensity for producing massive hepatic necrosis and ascites in experimental animals, both when it is administered by inhalation^{245, 358} and when it is given orally³⁹ or intraperitoneally.^{30, 39} The lesions, which are characterized by extensive centrilobular and midzonal eosinophilic necrosis, resemble those of carbon tetrachloride poisoning but are more sharply circumscribed, show more hemorrhage and are devoid of hydropic or other slightly damaged cells.³⁹ Small doses given over a long period produce a fatal form of cirrhosis in the rat.³⁹ In addition, they may give rise to tumors in the liver, kidney and lung.⁴⁸¹

Although evidence indicates that following its administration dimethylnitrosamine is uniformly distributed through the body water and enters all cells freely, its toxic actions are limited to the liver exclusively.⁴⁸⁹ This, taken together with the fact that it exhibits no *in vitro* effects on the metabolic activities of the liver,^{30, 346} suggests that

the selective methylnitrosamine metabolite for

Accidental poisoning of iron is an old story, with children, who believe that the tablets of ferrous sulfate are con-

In fatal cases, the contents of the stomach and the periportal fatty infiltrations may be found.

Vomiting, accompanied by coma and death. Occasionally patients who have taken

Prompt lavage with sodium bicarbonate solution, deferoxamine, and intravenous resuscitation of acute

There are prolonged excessive hemosiderosis, a question of whether to hemochromatosis. Although produces hemochromatosis in rats, it does not on an adequate hemochromatosis in individuals who have iron therapy. The possibility of chronic anemia is an important factor in cirrhosis. Similar to hemochromatosis, Bantu,⁸⁷ who have excessive,⁷⁸⁹ and tumors as malignant as the principal brewed beer

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the selective hepatotoxic actions of dimethylnitrosamine may depend upon some metabolite formed in the liver.^{30, 345, 480, 482}

IRON

Accidental poisoning with compounds of iron is an important problem in young children, who not infrequently ingest coated tablets of ferrous sulfate in the mistaken belief that they are candies.^{338, 357, 415, 457}

In fatal cases, the principal autopsy findings are congestion and ulceration of the stomach and small intestine, and striking periportal parenchymal necrosis and mild fatty infiltration in the liver.⁴⁵⁷ Similar lesions may be produced in animals.⁴⁵⁷

Vomiting and diarrhea, occasionally accompanied by melena, occur soon after poisoning. In severe cases, shock, acidosis, coma and death follow in rapid succession. Occasionally, mild jaundice is observed in patients who survive.

Prompt lavage of the stomach with sodium bicarbonate and the administration of deferoxamine, by both the gastric and intravenous routes, are effective in the treatment of acute ferrous sulfate poisoning.³⁵⁷

There appears to be no doubt that a prolonged excessive intake of iron leads to hemosiderosis of the liver. However, the question of whether or not it can give rise to hemochromatosis remains unresolved. Although prolonged iron administration produces hemochromatosis in choline-deficient rats, it does not do so in animals maintained on an adequate diet.⁴⁶⁵ Several instances of hemochromatosis have been reported in individuals who have taken large amounts of iron therapeutically,⁵⁷³ but in such cases, the possibility cannot be excluded that chronic anemia and other factors play an important role in the development of cirrhosis. Similarly, the increased incidence of hemochromatosis in the South African Bantu,⁸⁷ whose dietary intake of iron is excessive,⁷⁸⁹ may be attributable to such factors as malnutrition and alcoholism, since the principal source of iron excess is home-brewed beer.⁸⁹

MANGANESE

Industrial workers exposed to manganese dioxide dust and fumes are subject to pneu-

monia²¹⁷ and a highly characteristic neurologic disorder that closely resembles the progressive lenticular degeneration of Wilson's disease.^{119, 131, 217} Because of the possible relationship of the neurologic changes in Wilson's disease to the associated cirrhosis, it has been suggested that a similar hepatic lesion may be responsible for the neurologic disorder in chronic manganese poisoning.¹³¹ The observation that repeated injections of soluble manganese salts produce cirrhosis in animals supports this hypothesis.^{226, 346} However, a complete review of all the reported cases of manganese poisoning in man^{217, 763} discloses only one instance in which a biliary cirrhosis is said to have been demonstrated.¹²⁵ Therefore, it is highly improbable that the type of chronic manganese poisoning encountered in industry produces liver injury.

PHOSPHORUS

With the legal prohibition of the use of elemental yellow phosphorus in the manufacture of matches in this country, acute phosphorus poisoning has become relatively rare. Currently, most cases are due to ingestion of roach paste^{408, 474} or rat poison.⁴⁰⁸ In the Orient, where yellow phosphorus matches are still in use, the incidence of poisoning is high. As might be expected, the victims are often children.

As little as 15 mg. of yellow phosphorus can produce signs of toxicity, and 60 mg. has caused death.²⁷³ Some roach pastes contain more than 1 Gm.% of phosphorus,⁴⁷⁴ so that the ingestion of as little as 5 Gm. may be fatal. The severity of the poisoning in the average case is well illustrated by the mortality rate of 75 per cent among 16 cases reported from the Charity Hospital in New Orleans.⁴⁰⁸

Red phosphorus, another form of the element, is relatively nontoxic apparently because it is insoluble and nonvolatile. Yellow phosphorus is also poorly soluble but is readily dispersed into an aqueous colloidal solution and is volatile.²⁷³

Although the hepatic manifestations of phosphorus poisoning are of special interest, phosphorus is a potent general protoplasmic poison and may be lethal within 10 hours,

even before characteristic tissue changes can be demonstrated histologically.⁴⁰⁸

Symptoms. The initial symptoms, including nausea, vomiting, epigastric burning, abdominal pain and diarrhea, usually occur immediately following the ingestion of phosphorus or within a few hours. These are due to the local action of the poison in the gastrointestinal tract. However, when symptoms do not appear for hours or days, they are related to the systemic effects of absorbed phosphorus.

Shortly after phosphorus is ingested, the breath has a garlic-like odor, and the feces are luminescent in the dark, features that may be of great diagnostic importance.

In severe poisoning, shock and coma follow the initial symptoms in rapid succession, and death may ensue within 48 hours. More commonly, however, the systemic effects are evident 1 to 3 days after phosphorus is ingested, and death occurs during the 1st week. Although it is highly probable that no tissue is wholly exempt, the liver and the kidneys suffer the most severe injury and manifest the most striking structural and functional changes. As in other severe intoxications, tissue damage is so widespread that often it is difficult to determine the site of origin of any given symptom.

The manifestations of systemic intoxication include intractable vomiting, often with blood-streaked material, diarrhea, abdominal cramps and severe prostration. Signs of severe liver injury can always be demonstrated, although hepatomegaly and jaundice may not develop. Jaundice seldom appears before the 4th day and may be delayed for over a week. The prognosis is somewhat better when jaundice appears late. As in other forms of severe hepatitis, the urine contains bilirubin, and the feces tend to become pale, which indicate that bile secretion is suppressed. Not infrequently, hemorrhages occur into the skin and the mucous membranes, presumably due to the associated fall in the prothrombin and fibrinogen levels of the plasma. Other features of severe hepatic failure can occasionally include edema, hypoglycemia, tyrosinuria and an increase in serum amino nitrogen. Usually the kidneys are affected equally severely. Oliguria and azotemia are

common, and the urine usually contains albumin, casts and red blood cells.

The latter part of the course is characterized by coma, delirium and vasomotor collapse and, as indicated, death occurs toward the end of the 1st week.

Occasionally, even severely poisoned individuals appear to recover completely. However, one such case, followed by serial biopsies of the liver over a period of 3 months, showed evidence of incomplete healing and progressive fibrosis, a lesion similar to that seen in animals with chronic phosphorus poisoning.⁴⁸⁵ How often this type of post-necrotic fibrosis and cirrhosis follows acute phosphorus poisoning in man is not known.

Pathology. At autopsy the liver is enlarged and exhibits extensive periportal fatty infiltration and degenerative changes in the parenchymal cells, occasionally accompanied by a mild inflammatory reaction in the portal triads. In one case seen by the writer, marked periportal bile stasis and pseudoduct formation were outstanding features late in the course of the disease. Massive necrosis of the parenchyma is said to occur⁴³⁷ but is exceedingly rare. The lesion in experimental phosphorus poisoning⁴⁸⁵ is similar, but cellular necrosis is a more prominent feature. The renal tubules and the myocardium also show degenerative changes and fatty infiltration.

Treatment. Gastric lavage with a dilute solution of copper sulfate (0.25 Gm. in a glass of water) and a magnesium sulfate purge are recommended to rid the intestinal tract of any remaining traces of phosphorus. Unfortunately, these are effective only if given within the first few hours.

Treatment is largely supportive, as outlined previously. Choline hastens the removal of fat from the liver in phosphorus poisoning.⁶⁹ However, its therapeutic value would appear to be negligible, since it does not prevent hepatic injury.

SELENIUM

In areas where the selenium content of the soil is high, livestock develop "alkali disease," a chronic illness characterized by emaciation, loss of hair, lameness and sloughing of the hoofs.⁵²³ At autopsy, the principal findings are cirrhosis of the liver

and myocardial renal hemorrhages and ulcers are also seen. This is due to ingested grain, forage produced in selenium-rich soil.

A more acute case, as the "blind" whose feed content. Myocardial testine and the principal congested arteries but frank cirrhosis.

In some cases, ingestion of selenium only hepatic adenomas and

Himsworth's study between selenium poisoning and tal dietetic suggested that the quence of a containing a placement of protein.³²² T and methionine would appear. However, the vent liver data doubt on this.

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A number genera *Senecio* contain pyrrolizidine alkaloids. In Asia and North America, disease are horses that die upon the de

usually contains alkaloids. The course is characterized by vasomotor collapse and death occurs to-day.

Severely poisoned individuals die completely. However, followed by serial biopsies, complete healing and return similar to that of iron phosphorus poisoning. This type of post-mortem follows acute poisoning in man is not known. In the liver is extensive periportal fatty acid changes in the normally accompanied reaction in the portal system by the writer, stasis and pseudo-standing features of disease. Massive thrombosis is said to be rare. The lesion of arsenic poisoning¹⁸⁵ is more prominent and the myogenic changes

age with a dilute solution (0.25 Gm. in a magnesium sulfate solution) to rid the intestine of traces of phosphorus are effective in a few hours. Supportive, as outstretches the reaction in phosphorus poisoning, therapeutic value is probable, since it does

and myocarditis. Glomerulonephritis, adrenal hemorrhages, erosion of the joint surfaces and ulceration of the intestinal tract are also seen in some instances. The disease is due to ingestion of selenium-containing grain, forage or vegetation, and can be reproduced in experimental animals by adding selenium salts to the diet.

A more acute form of poisoning, known as the "blind staggers," is seen in animals whose feed is unusually high in selenium content. Myocarditis, ulceration of the intestine and erosion of the long bones are the principal findings. Usually, the liver is congested and shows focal areas of necrosis, but frank cirrhosis is rare.

In some strains of rats, the chronic ingestion of seleniferous grain produces not only hepatic necrosis and fibrosis but also adenomas and low-grade carcinomas.⁵³⁴

Himsworth has emphasized the similarity between the hepatic lesions in chronic selenium poisoning and those of experimental dietetic massive necrosis and has suggested that the former may be the consequence of an induced deficiency of sulfur-containing amino acids related to the replacement of sulfur by selenium in plant protein.³²² The protective action of casein and methionine in animals fed selenium would appear to support this hypothesis. However, the fact that cystine does not prevent liver damage in such experiments casts doubt on this interpretation.

Of special interest to the clinician is the question of whether or not the ingestion of seleniferous grain leads to hepatic damage in man. Individuals living in seleniferous areas excrete appreciable amounts of selenium in the urine, which indicates that significant exposure has occurred. However, to date none of these has shown evidence of hepatic or other disease.⁶⁹²

SENECIO AND RELATED ALKALOIDS

A number of plants belonging to the genera *Senecio*, *Crotalaria* and *Heliotropium* contain pyrrolizidine alkaloids that are hepatotoxic. In South Africa, Australia, Central Asia and Norway outbreaks of severe liver disease are encountered in sheep, cattle and horses that feed on these plants. Depending upon the degree and the duration of expo-

sure, affected animals exhibit signs of either acute hepatic necrosis or cirrhosis. Similar lesions are reproducible in experimental animals.^{591, 658, 671} Occasionally, humans fall victim to this type of poisoning, but in man the senecio alkaloids produce an unusual form of liver disease in which the clinical and pathologic features resemble those of the Chjari syndrome.⁶⁷⁰ Both in animals⁶⁷¹ and in man,⁶⁷⁰ protein deficiency enhances the toxicity of these agents.

In South Africa, senecio poisoning has been reported in poorly nourished white Europeans who consume bread made of imperfectly winnowed wheat contaminated with the seeds of *Senecio ilicifolius* and *burchelli*, two weeds commonly known as ragwort.^{670, 792} A similar form of toxic hepatitis affects natives of Central Asia who eat cereal grains contaminated with the seeds of *Heliotropium lasiocarpine*.¹⁰⁶ Evidence suggests that the use of native "bush teas" containing extracts of *Senecio* and *Crotalaria retusia* for medicinal purposes may be responsible for the development of veno-occlusive disease of the liver in Jamaican children.⁷³⁰ A similar explanation has been invoked to account for the common occurrences of cirrhosis in the children of West Bengal and Madras, India.³⁶⁰ However, in this instance, there is contradictory evidence pointing to the hepatitis virus as the responsible agent.³

Pathologic Findings. In fatal cases of senecio poisoning, the principal findings are enlargement of the liver, widespread fibrous occlusion of the central and the sublobular veins, and intense congestion and destruction of the centrilobular parenchyma. Usually, the stroma is uninvolved, and there is little or no inflammatory reaction. Organized thrombi may be demonstrable in the larger hepatic veins. In more chronic cases, there is, in addition, fibrosis and round cell infiltration of the portal zones, giving rise to the picture of cirrhosis.^{670, 792} It is generally agreed that the primary lesion is in the vessels, and that the parenchymal changes are secondary to intense congestion. However, there is uncertainty whether the fibrous occlusion of the central and sublobular veins follows a proliferative endophlebitis or is the end-result of thrombosis

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and organization. Similar lesions have been described in the veno-occlusive disease of the liver seen in Jamaica.⁹³

The hepatic changes induced by senecio alkaloids in experimental animals are more variable than in man. Although some investigators have demonstrated alterations in the blood vessels with secondary congestion, atrophy and fibrosis of the parenchyma,^{318, 630, 792} others have shown that these agents may provoke acute centrilobular necrosis and cirrhosis by a direct action.^{108, 134, 658} In the more chronic lesion, there is striking enlargement of the hepatic cells, a feature thought to be characteristic of senecio poisoning, and indicative of a metabolic defect which prevents cellular division and thus leads to loss of cells and ultimate fibrosis.¹⁰⁸ Of particular interest is the fact that in the rat a single small dose of senecio alkaloid may, after a latent period of several weeks during which no necrosis is evident, give rise to a chronic progressive hepatic lesion terminating in a picture resembling postnecrotic cirrhosis.^{658, 659}

Clinical Features.^{670, 792} In acute senecio poisoning, the onset is sudden with gnawing and colicky epigastric pain, followed within a few days by a rapidly developing ascites. The liver enlarges and within a few weeks becomes firm. Jaundice is an inconstant feature and, in one series at least, occurred in only 2 of 12 cases.⁶⁷⁰ Vomiting and diarrhea are present in about a third of cases. Splenomegaly appears to be unusual despite the obvious development of portal hypertension. Occasionally, there is low-grade fever late in the disease. In severe poisoning, there may be early vasomotor collapse, followed later by hematemesis and melena.

Usually, the clinical course is prolonged and is characterized by rapid reaccumulation of ascites, recurrent attacks of abdominal pain, and cachexia. Hypoproteinemia is common, but edema is an inconstant finding. In approximately half the cases, death occurs within 1 to 3 months. Despite the apparent progressive downhill course in the remaining patients, clinical recovery ultimately takes place over a period of several months up to 2 years. Whether or not healing of the hepatic lesions is complete

in such cases is not known, since reports of long-term follow-up biopsy studies are not available.

Mild cases of intoxication probably occur, but have not been described in the literature.

The clinical picture of veno-occlusive disease in children resembles that of senecio poisoning.^{93, 730} However, an acute onset is not nearly as common, hepatosplenomegaly and other signs of cirrhosis appearing insidiously in many cases. Also splenomegaly and jaundice are seen more frequently. The mortality rate is high; hepatocellular failure and hematemesis account for most deaths.

Treatment. No specific therapy is available, so that treatment is supportive and directed at maintaining nutrition and controlling the ascites.

TETRACHLORETHANE

Of all the chlorinated hydrocarbons, tetrachlorethane is by far the most toxic. During World War I it was used widely as a solvent for cellulose acetate, chiefly in the "dope" used in varnishing the canvas surfaces of airplanes and, to a lesser extent, in the manufacture of rayon and lacquers. However, it proved to be so toxic that it was abandoned as soon as a suitable substitute (amyl acetate) was found. During World War II it was used again, since it was the only satisfactory solvent for impregnating clothing with materials that neutralized poisonous gases.²⁸⁶ Despite the imposition of stringent engineering and hygienic controls, signs of toxicity were encountered once again in a high proportion of workers exposed to the agent. However, the control measures prevented serious intoxication, so that no fatalities resulted.²⁸⁵

Intoxication usually follows inhalation of the agent but may occur also following its absorption from the skin or the intestinal tract. For reasons that are not entirely clear, females are more susceptible than males, and in both sexes intoxication is more common after the age of 30.²⁸⁶ The toxic level of tetrachlorethane in the atmosphere is estimated to be in excess of 10 parts per million for individuals exposed for long periods. The odor, which closely resembles that of carbon tetrachloride, is readily de-

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Pathologic Findings. The principal pathologic finding in fatal cases is a subacute or massive hepatic necrosis with preservation of the stroma, marked fatty infiltration of surviving parenchymal cells, absence of hepatocellular regeneration, and active proliferation of bile ducts.⁷⁰⁷ The early lesions in nonfatal cases have not been described. Fatty degenerative changes are also seen in the renal tubules and myocardium. Essentially the same lesions have been observed in rats exposed to tetrachlorethane vapor.^{707, 789}

Symptoms. The early symptoms of tetrachlorethane intoxication are of two types: gastrointestinal and neurologic.²⁸⁵ Following exposure to low concentrations of the vapor for a number of weeks, there is an insidious onset of anorexia, nausea and vomiting, or of headache, giddiness, drowsiness and paresthesias. These may occur singly or in combination and often are associated with hepatomegaly and impairment of liver function. Jaundice is also present in approximately 10 per cent of such individuals. Occasionally, jaundice appears before other symptoms develop. Prompt cessation of exposure to the contaminated environment at this stage results in rapid recovery, usually within a period of less than a month. Of possible diagnostic significance in early toxicity is the tendency for the absolute and relative number of large monocytes in the peripheral blood to increase.⁵⁰⁹

In more heavily exposed individuals, the onset is similarly delayed and gradual, but gastrointestinal symptoms, hepatomegaly and jaundice are constant findings and usually are associated with tenderness of the liver and weight loss. Not infrequently, the jaundice is intense and persists for weeks and even months following the last exposure to tetrachlorethane. Recovery is possible at this stage,⁵⁰⁹ but some individuals run a progressive downhill course, develop ascites and die of hepatic failure.⁷⁸⁹ These are the cases that, at autopsy, show subacute hepatic necrosis and postnecrotic scarring.

Prognosis. Before the toxicity of tetrachlorethane was fully understood and ap-

propriate protective measures instituted, the exposure tended to be heavy and often was continued long after signs of intoxication had appeared. As a result, the hepatitis produced was unusually severe. In one such series of 70 cases, for example, the mortality rate was 17 per cent.⁴²⁰ In contrast, no fatalities were seen in a more recently studied group of 55 cases encountered in a carefully supervised plant. Moreover, the disease was so mild that only 6 of the 55 developed jaundice.²⁸⁵

TOLUENE

This aromatic hydrocarbon derived from coal tar is widely used in industry, especially in the manufacture of paints and lacquers. Although it shares the excellent solvent properties of its homologue benzene, it is far less toxic. In individuals exposed to the high concentrations usually encountered during spray painting, toluene appears to exert no significant ill-effects. Hepatomegaly and mild macrocytic anemia are relatively frequent findings, but no instances of frank toxic hepatitis or aplastic anemia have been reported.²⁷⁸ The nature of the hepatic enlargement has not been investigated. However, in animals exposed to similar concentrations of toluene, both the liver and kidneys show mild degenerative changes.⁶⁹⁹

TRINITROTOLUENE (TNT)

Munition workers exposed to TNT are subject to a number of toxic manifestations of which hepatitis and aplastic anemia are the most important.^{448, 492, 551} Functional disturbances of the gastrointestinal, circulatory and central nervous systems, and local irritation of the respiratory tract and the skin are often troublesome but rarely give rise to serious difficulty. Absorption is chiefly from the skin and, to a lesser extent, from the mucous membranes.^{38, 420} The presence on the skin of oil and grease, in which TNT is soluble, enhances absorption and increases the chances of intoxication.^{38, 515} It is generally stated that inhalation of the fumes is without danger,⁵¹⁵ but this view is not shared by some authorities.⁴⁹²

Clinical Features. The hepatitis produced

by TNT has many unusual features, few of which have been adequately explained. Among these are the following: (1) Only a small proportion of individuals exposed to TNT develop hepatitis.⁴⁰² (2) Signs of hepatic damage usually appear only after many weeks of exposure⁴⁰² or, in some instances, not until several months after cessation of exposure.⁷⁸⁸ (3) The disease is almost always severe, being characterized by a prolonged course and a high fatality rate. (4) Massive and subacute necrosis of the liver occur far more frequently and resemble the lesions of idiopathic acute yellow atrophy far more closely than almost any other known type of toxic hepatitis.^{324, 719, 720} (5) It is difficult to reproduce the lesion in animals,³²² an unusual circumstance for an agent presumed to be a true hepatotoxin.

In many respects these unusual features are reminiscent of the hypersensitivity type of hepatitis produced by drugs such as cinchophen. However, the chemical structure of TNT and its failure to produce other manifestations of hypersensitivity make it highly improbable that it is a sensitizing agent.

Himsworth has suggested that the long latent period, the occurrence of massive hepatic necrosis, and the failure to reproduce the lesion in animals on normal diets may indicate that TNT injures the liver indirectly by inducing a relative deficiency of sulfur-containing amino acids.³²² In support of this hypothesis, he has pointed out that TNT raises the metabolic rate and thus increases the demand for protein, that at least 2 of its 3 isomers combine with amino acids and make them unavailable, and that by reducing the protein content of the diet it is possible to reproduce TNT hepatitis in experimental animals. However, the isomer of TNT that does not combine with amino acids also produces toxic hepatitis, and a low-protein intake favors the development of hepatic necrosis in experimental animals only when the diet is high in fat. The latter observation suggests the possibility that the peculiarities of TNT toxicity may be related to the fat solubility of the agent.

Possibly dietary fat enhances the absorption of TNT from the intestinal tract and

favors its retention in the liver at high concentrations by producing fatty infiltration. Similarly, the enhanced absorption of TNT from the skin in the presence of grease^{38, 515} may account for the sporadic occurrence of intoxication in groups of apparently equally exposed individuals. As for the long latent period, it does not necessarily point to an induced nutritional deficiency, as indicated, but may reflect a slow cumulative intoxication with an agent that is absorbed relatively slowly. In cases where the signs of liver disease appear weeks or months after the last exposure to TNT, it is possible that the initial injury incurred during exposure is asymptomatic, and that the lesion produced is progressive.

Symptoms. Usually, the onset of symptoms is insidious, with anorexia, nausea and vomiting. Jaundice appears within 2 weeks and often is followed by hepatomegaly. In severe cases, abdominal pain is a prominent feature, and the liver may be small. The course tends to be prolonged and often is complicated by the development of ascites and hemorrhagic phenomena. Occasionally, there is an associated disturbance of the hemopoietic system, as evidenced by severe leukopenia,⁷¹⁰ macrocytic anemia⁷¹⁹ or aplastic anemia.⁵⁵¹ Both hyperplastic⁷¹⁹ and aplastic⁴⁰² bone marrows have been described, suggesting that the changes in the peripheral blood may be due to a maturation arrest in some cases.

Prognosis. The outcome is unpredictable. In most cases reported in the literature death has occurred within a few weeks of acute massive necrosis of the liver^{324, 402} or after prolonged hepatic failure resulting from postnecrotic cirrhosis.^{720, 788} However, some individuals with TNT hepatitis recover. Unfortunately, little is known about the nature of the lesion in this group or its ultimate fate. In one 3-year follow-up study of 17 such cases,⁷²⁰ there were no clinical residuals, which suggests that the initial lesion was zonal rather than massive. However, reports of postnecrotic cirrhosis becoming evident as long as 10 years after apparent recovery from TNT hepatitis^{324, 788} illustrate that the scarred postnecrotic liver may be difficult to recognize clinically and

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may decompensate unexpectedly years after its inception. It is highly probable that such lesions can be recognized much earlier by the use of sensitive tests of hepatic function and especially by needle biopsy of the liver.

VOMITING SICKNESS OF JAMAICA

Native Jamaican children, usually from the age of 2 to 5 years are subject to an unusual disease characterized by a sudden onset of severe vomiting, followed soon thereafter by convulsions and coma. Death ensues within 2 or 3 days in 80 per cent of cases. The principal findings at autopsy include fatty infiltration of the liver and kidneys, hyperemia and petechial hemorrhages in the liver, spleen, heart, lungs and brain, and degenerative changes in the renal tubules. The etiology is unknown. However, Hill has reviewed evidence suggesting that malnutrition and the toxic effects of the ackee fruit, cassava and yams may play an important role in its pathogenesis.³¹⁷

This disease is of particular interest because of its striking resemblance to the Reye syndrome (encephalopathy with fatty degeneration of the viscera) first described in 1965.⁸⁰⁸ In the many reports, the possibility of intoxication has been considered, but in none has a specific hepatotoxin been implicated. A recent review suggests that the disease is of infectious origin, and possibly attributable to a variety of viruses, including those of chicken pox, measles and mumps.¹²⁷

ANESTHETIC AGENTS

In evaluating the role of an anesthetic agent in the pathogenesis of postoperative hepatitis, due consideration must be given to the nature of the underlying disease, the degree of anoxia attained during anesthesia and the presence of such complicating factors as shock and infection, since each of these alone can produce liver injury.

CHLOROFORM

Chloroform has the well-deserved reputation of being a dangerous hepatotoxin. Although largely supplanted by other less toxic anesthetic agents, it is still used to some extent in various parts of the world for

obstetric and minor surgical procedures. Most fatalities have followed prolonged anesthesia, especially during parturition, but deaths have occurred also after as little as ½ ounce of chloroform.²⁵⁸ Women undergoing prolonged labor appear to be peculiarly susceptible to this type of anesthetic death. This has been ascribed to the malnutrition and the infection which so frequently accompany such labors,⁸³⁷ a hypothesis consistent with the experimental observation in animals that malnutrition^{772, 507} and infection⁵⁴² enhance the hepatotoxic effects of chloroform.

From the paucity of reports dealing with nonfatal cases of chloroform hepatitis, it is easy to gain the erroneous impression that chloroform either injures the liver seriously or not at all. However, in animals even a 30-minute period of chloroform anesthesia causes significant impairment of hepatic function, which may persist for as long as 8 days.⁸³²

Clinical Features. The clinical manifestations of severe chloroform intoxication follow a uniform pattern.^{258, 637, 709} Characteristically, the onset of symptoms is delayed for 24 to 72 hours following recovery from anesthesia. Drowsiness and vomiting then appear and are soon followed by jaundice. Vomiting is copious and often becomes coffee-ground in nature. By the 4th day the drowsiness usually progresses to coma, and in approximately half the cases is followed by convulsions. Despite the regular occurrence of severe hepatic damage, jaundice fails to develop in some cases.⁷⁰⁹ Fever is unusual, except terminally. Azotemia and acidosis occur early and tend to increase in severity. Although these are usually associated with oliguria and albuminuria, in occasional cases the urinary volume and the urea content are high,²⁵⁸ suggesting that the azotemia is related in part to the rapid breakdown of protein, rather than to renal failure and dehydration alone.

Prognosis. Most severely intoxicated individuals die in 3 to 8 days, but an occasional patient survives and goes on to complete recovery. Residuals are unlikely in such cases, since the characteristic lesions seen at autopsy are zonal in type. Complete

recovery without scarring also occurs in animals exposed to nonfatal doses of chloroform.⁷⁸⁴

Individuals who are exposed to repeated doses of chloroform at frequent intervals occasionally develop cirrhosis. In one such case described by Wilcox, small amounts of chloroform were inhaled daily over a period of 6 months, at the end of which time jaundice and hepatomegaly developed.⁷⁸⁹ Subsequently, ascites and other signs of cirrhosis appeared, and death ensued in 18 months.

Pathology. At autopsy the liver is of normal size but may be small. Hepatocellular necrosis is invariably centrilobular in distribution and never massive. Varying fractions of the lobule are destroyed, but a small rim of intact cells is always present around the portal triads. The necrotic cells break up into hvalinized fragments and undergo lysis, while the intact cells peripherally show marked fatty infiltration. As in other types of toxic hepatitis, the reticulum is not destroyed and usually is infiltrated with a number of phagocytic mononuclear cells at the sites of necrosis. The remaining hepatic cells show little evidence of regeneration. Almost identical hepatic lesions have been described in the dog.⁷⁸⁴

The changes in the kidney are less conspicuous than in carbon tetrachloride poisoning and usually consist of fatty infiltration of the convoluted tubules.

Susceptibility. During the past decade considerable attention has been directed to the interrelationships between the hepatotoxic effects of chloroform and certain dietary factors. In brief, starvation,²⁷² protein-depletion⁵⁰⁷ and a high fat intake⁵⁴³ increase the susceptibility to hepatic damage by chloroform, and diets rich in protein²⁷² and carbohydrate²⁷² are protective when given prophylactically. Moreover, protein, methionine and, to a lesser extent, cystine protect protein-depleted animals against chloroform toxicity if given from 24 hours before to as late as 4 hours after anesthesia.^{508, 507} The theoretical implications of these observations are discussed elsewhere. None of these experimental observations is concerned with the therapeutic effects of these supplements when administered following

the development of toxic hepatitis, so that they do not provide a sound basis for treatment.

CYCLOPROPANE

Transient alterations in hepatic function have been observed following cyclopropane anesthesia. Usually, these are relatively minor, but in patients with liver disease they may be more severe.²⁴² Changes of similar magnitude are seen following anesthesia with ethyl ether. Since the degree of functional impairment bears little relation to the duration of anesthesia, it is highly probable that such hepatic injury is the result of circulatory changes and trauma incidental to surgery rather than of cyclopropane toxicity.

DIVINYL ETHER

Because divinyl ether can produce centrilobular necrosis in dogs,²⁷¹ it is generally regarded as a potential hepatotoxin in man. In the dog, the severity of the hepatic damage produced is closely correlated with the duration of anesthesia, the nutritional status and the degree of oxygenation.^{270, 271} Accordingly, certain precautions have been recommended. These include administration of carbohydrate preoperatively, limitation of the duration of anesthesia to 1 hour, use of oxygen whenever the period of anesthesia is to exceed ½ hour, and avoidance of divinyl ether in patients with liver disease.⁵⁹² Under these conditions, no instances of hepatic injury have been encountered in an extensive clinical experience with this agent.⁵⁹² Although it would be unwise to abandon this cautious attitude toward divinyl ether, it should be recognized that its hepatotoxicity for man has not been proved, and that the human liver may be as resistant to it as the monkey's.²⁷¹

ETHER (DIETHYL ETHER)

There are no clinical reports of toxic hepatitis following ether anesthesia. However, experimental evidence indicates that, in the dog at least, ether can produce mild liver injury²⁷⁰ and transient impairment of hepatic function.⁶³² Bromsulphalein retention¹⁴⁴ and other functional derangements²⁴² have been reported following ether anes-

thesia in man. These observations are difficult to interpret since circulatory changes and mechanical manipulations may affect hepatic function.

HALOGENATED HYDROCARBONS

In contrast to the hydrocarbons, the halogenated hydrocarbons, such as 1,1,1-trifluoro-2,2,2-trichloroethane, cannot be considered as anesthetics, since they are encountered only in the form of anesthetics. They are also known for their irritancy or hypoxia, and for their effect on the central nervous system.

In a review of the well-documented hepatic lesions caused by these agents, it is a sensitive subject, producing hepatic hypersensitivity in susceptible individuals. In some cases, the effect is attributed to sepsis,²⁷ or to a complete lack of fact that induced hepatitis is a recent³⁸² it of the National risk of ha proximately.

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themia in man also, but such observations are difficult to interpret in terms of toxicity, since circulatory disturbances and alterations in hepatic structure incidental to surgical manipulation may also affect hepatic function.

HALOTHANE (FLUOTHANE) AND METHOXYFLURANE (PENTHRANE)

In contrast to many other halogenated hydrocarbons, halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) does not produce hepatic necrosis in animals³⁶⁴ and, hence, cannot be considered an hepatotoxin. Nevertheless, cases of hepatic necrosis have been encountered in man following its use as an anesthetic.^{107, 108, 123, 440} Such lesions have been variously ascribed to halothane toxicity or hypersensitivity, to intercurrent infection with the hepatitis virus, or to coincidental factors unrelated to halothane.

In a review based on an analysis of 41 well-documented cases of halothane-associated hepatic necrosis, the writer has presented convincing evidence that halothane is a sensitizing agent, and is capable of producing hepatitis and other manifestations of hypersensitivity in a few uniquely susceptible individuals.³⁸² Judging from the number of cases of hepatic necrosis that could not be attributed to shock, cardiac failure or sepsis,²⁷ and making allowance for the incompleteness of the autopsy data and the fact that the mortality rate in halothane-induced hepatitis is approximately 50 per cent,³⁸² it may be estimated from the data of the National Halothane Study,⁷³⁴ that the risk of halothane-induced hepatitis is approximately 1 in 10,000.

As in the hepatocellular type of hepatitis induced by other sensitizing drugs, such as iproniazid, pyrazinamide and zoxazolamine,⁵⁸² the hepatic lesions seen following halothane anesthesia are indistinguishable from those of viral hepatitis, and cannot be reproduced in animals. Extensive hepatocellular necrosis, an intense inflammatory reaction and a high fatality rate are characteristic. That the hepatitis is attributable to a sensitization reaction rather than to intercurrent infection with the hepatitis virus is strongly suggested by the narrow limits of

the latent period between exposure to halothane and the onset of symptoms, the striking increase in the incidence of hepatitis following multiple exposures, the frequency with which the hepatitis is accompanied by other manifestations of hypersensitivity, such as chills, high fever, rash and eosinophilia, and, of particular significance, the regularity with which the hepatitis recurs following re-exposure to halothane.³⁸²

Characteristically, the onset of halothane-induced hepatitis is abrupt, with moderate to high fever, often accompanied by chills, and occasionally by rash, arthralgia and eosinophilia. In patients exposed to halothane for the first time, the average interval between anesthesia and the onset of symptoms is approximately 7 days, with a range of 1 to 12 days. Following multiple exposures, the latent period is shorter, averaging 3 days (1 to 10 days). Jaundice appears 3 or 4 days after the onset of fever, and usually deepens rapidly. Anorexia, nausea and vomiting are prominent features. Occasionally, there is severe abdominal pain. Coffee-ground vomitus, ascites, edema, somnolence and coma usually indicate a fatal outcome, which occurs in approximately half the cases.

In contrast to viral hepatitis, the leukocyte count tends to be high. Biochemical studies reveal abnormalities indicative of hepatocellular jaundice. However, significant elevations of serum alkaline phosphatase, negative cephalin-cholesterol flocculation reactions and normal thymol turbidity values are more common than in viral hepatitis.

In the writer's experience, prednisone therapy has appeared to be effective when instituted before the onset of hepatic coma, but has failed to prevent a fatal outcome in those with hepatic coma, even when used in massive doses in conjunction with exchange transfusions. However, the number of patients so treated is small, so that insufficient data are available to assess the therapeutic value of corticosteroids and exchange transfusions.

Halothane has a number of advantages over other anesthetic agents, not the least of which is that it is associated with a lower

overall postoperative mortality rate following middle- and high-risk surgical procedures.⁷³⁴ Since the degree to which halothane lowers the postoperative mortality from other causes is significantly greater than the estimated 0.005 per cent risk of fatal halothane-induced massive hepatic necrosis, continued use of halothane as an anesthetic for such procedures would appear to be both reasonable and desirable. However, every effort should be made to reduce the risk of this complication by avoiding, whenever possible, the use of halothane in low-risk surgical procedures, in planned serial operations and in individuals who have experienced an unexplained bout of fever or jaundice following a previous exposure to halothane. In this connection, it should be emphasized that the risk of halothane-induced hepatitis is twice as great following multiple exposures as it is following a single exposure.³⁸²

Methoxyflurane (Penthane, 2,2-dichloro-1,1-difluoroethyl methyl ether), a closely related halogenated ether, also may give rise to hepatic necrosis in susceptible individuals,^{385, 442} presumably by a similar mechanism, and may provoke a serious reaction in patients previously sensitized to halothane.⁴⁴⁰ Accordingly, one agent cannot be substituted for the other once sensitization has occurred.

Evidence suggests that halothane may constitute an occupational hazard for occasional, uniquely susceptible anesthetists or other operating-room personnel exposed to low concentrations of the agent in the course of their daily work. A recent report describes a young physician who experienced an attack of acute hepatitis after having served as an anesthetist for several months.⁵³ Following full recovery, he was anesthetized with halothane for a few minutes to test his reaction to the agent. Within 5 hours he had shaking chills and fever followed later by the appearance of eosinophilia and biochemical evidence of acute hepatitis. Another case seen by the writer involved an anesthetist who had had recurrent attacks of acute hepatitis that led to cirrhosis over a 5-year period.³⁸³ Almost all of the relapses had been ushered in by chills and fever that appeared within a few hours

of the patient's return to work following prolonged convalescence and ultimate recovery from a preceding attack. Challenge with a non-anesthetic dose of halothane for 5 minutes produced chills and fever within 5 hours, and, within 4 hours, evidence of acute hepatitis, which was documented both biochemically and histologically.

TRIBROMOETHANOL (AVERTIN)

As a member of the halogenated hydrocarbon group, Avertin might be expected to behave as a potent hepatotoxin. Actually, however, it produces only slight liver damage in dogs⁸⁹ and never has been implicated as a cause of toxic hepatitis in man. Nevertheless, it is generally assumed that liver disease contraindicates its use as an anesthetic agent, since the Bromsulphalein retention that usually follows Avertin anesthesia, both in man¹⁴⁴ and in experimental animals,⁸⁹ is significantly enhanced in the presence of hepatic damage. A more urgent reason for exercising caution in the patient with liver disease is the danger of delayed recovery from anesthesia related to a decrease in the rate of Avertin detoxification.⁸⁹

ANTIARTHRITIC AGENTS

CINCHOPHEN

Hepatitis is by far the most serious complication of cinchophen therapy and is largely responsible for the decline in the use of this agent over the past 3 decades. Although it occurs in less than 0.1 per cent of patients under treatment,⁷⁹³ the mortality rate is close to 50 per cent.³⁵⁰ This has encouraged a search for less toxic derivatives of cinchophen, but these have proved to be no safer than the parent substance. Included in this group are neocinchophen (the ethyl ester of methyl cinchophen), farastan (mono-iodo-cinchophen), biloptin (di-iodo-cinchophen), oxiliodide (cinchophen hydroiodide) and guphen (the guaiacol ester of cinchophen).

Clinical Features. A number of features strongly suggest that the hepatitis produced by cinchophen is a manifestation of drug hypersensitivity. These include the following:

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work following the ultimate re-attack. Challenge dose of halothane for 10 hours, evidence of vasodilation was documented both histologically.

OL (AVERTIN)

halogenated hydrocarbon is expected to be hepatotoxic. Actually, only slight liver damage has been implicated in hepatitis in man. Never-assumed that liver its use as an anesthetic. Bromsulphalein follows Avertin anesthesia and in experimental animals enhanced in the same. A more urgent situation in the patient is a danger of delayed de-toxification.⁵⁸

ICINCHOPHEN

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one of the most serious complications in therapy and is declining in the use of the past 3 decades. Although less than 0.1 per cent mortality, the mortality rate is 70%.⁵⁵⁰ This has been less toxic derivative than these have proved to be parent substance. These are neocinchophen (ethyl cinchophen), cinchophen, biloptin (oxilodide (cinchophen) and guphen (the phen)).

number of features of hepatitis produced by ingestion of drug include the follow-

1. Frequently, the hepatitis is associated with other symptoms suggestive of an allergic reaction, such as pruritus, rash, fever, arthralgia and edema.^{586, 682}

2. The ingestion of cinchophen sometimes is followed by sudden vasomotor collapse, respiratory distress and syncope, a syndrome closely resembling an anaphylactic reaction.^{42, 586, 682}

3. Usually, there is a long latent period between the onset of drug therapy and the appearance of symptoms.^{51, 778}

4. The reactions are particularly likely to occur in individuals previously exposed to the drug.¹⁶⁶

5. Neither the incidence nor the severity of the hepatitis can be correlated with the amount of cinchophen ingested.

6. There is a remarkable tendency for the lesion to progress after withdrawal of the drug.⁵⁵⁰

7. Even lethal doses of cinchophen fail to produce significant hepatic lesions in experimental animals.^{344, 421, 605}

Skin tests for hypersensitivity are positive only occasionally,^{586, 682} and the results of attempted passive transfer of antibody by the Prausnitz-Küstner technic and of precipitin tests are uniformly negative.^{586, 682} However, as indicated, these are seldom positive in other types of drug hypersensitivity.

Usually, hepatitis appears after prolonged cinchophen therapy, often weeks or months following its institution. In occasional instances, however, liver damage is not evident for as long as 6 months following cessation of drug ingestion.⁵⁵⁰ It is this long period of latency and the frequent occurrence of massive hepatic necrosis that have led to the suggestion that the injury to the liver may be based on an induced nutritional deficiency.³²⁴ No clinical evidence supports this hypothesis; indeed, the restriction of protein and methionine in the diet does not overcome the natural resistance of animals to hepatic injury by cinchophen.³⁴⁴ Other possible interpretations of the significance of prolonged latency are discussed elsewhere.

Attempts have been made to correlate the development of cinchophen hepatitis with antecedent liver disease⁴³⁶ or impaired he-

patic function,^{436, 593} on the theory that they may render the liver more susceptible to injury, or lead to the production of abnormal toxic metabolites. However, in animals, previous damage with toxic agents, such as chloroform and phosphorus, does predispose the liver to injury by cinchophen,^{421, 605} and as yet no toxic metabolites of cinchophen have been isolated.

Pathologic Findings. The high mortality rate in this form of hepatitis is related to the frequent development of acute and sub-acute massive necrosis of the liver. Almost invariably postmortem examination reveals a small liver without significant nodulation, even when the patient has survived for a number of months.^{51, 428, 450, 580, 604} This reflects the fact that usually the destruction is extensive, and unaccompanied by hepatocellular regeneration. Most of the parenchymal cells have either undergone lysis or show severe degenerative changes, including fatty infiltration, vacuolization and hyaline necrosis. The inflammatory reaction is variable, being minimal in some cases and intense in others. As in other types of acute massive hepatic necrosis, the reticulum framework is collapsed and condensed and the bile ducts show active regeneration. In older lesions, the areas of collapse are the site of connective tissue proliferation.

Except for the frequent occurrence of degenerative changes in the epithelium of the renal tubules, and certain alterations to be expected as secondary manifestations of severe hepatic failure, there are no other morphologic signs of cinchophen toxicity.

The nature of the hepatic lesions in non-fatal cases is not known, but there is no reason to believe that it differs fundamentally from that seen at autopsy, except possibly in extent. This raises the question of whether or not restoration of the normal architecture is possible following recovery. Of 3 such cases studied at the Mayo Clinic, 1 exhibited a nodular liver at operation, and 2 had relapses subsequently that proved to be fatal.⁷⁷⁸ Therefore, it is possible that postnecrotic scarring is more frequent than is generally recognized.

Symptoms. Usually, the onset is sudden, with anorexia, nausea and vomiting. These may be accompanied by chills and fever,

pruritus or urticaria. Jaundice usually follows within a few days but may be delayed for weeks or even months.⁷⁷⁸ Anicteric hepatitis has been described^{586, 778} but is rare. The jaundice increases in intensity, usually reaching its maximum in a few days and then persists.

As might be expected from the nature of the hepatic lesion, bilirubinuria and pale or clay-colored stools are seen early. Albuminuria, cylindruria and oliguria are common, but severe renal failure is rare. The subsequent course is variable.⁷⁷⁸

Prognosis. In fulminant cases, the patient lapses into coma and dies of hepatic failure within the first few weeks. This is by far the most common type of death. Other cases run a chronic course, occasionally interrupted by clinical remissions; ultimately ascites and edema develop and the patient dies within 6 months of hepatic failure or bleeding from esophageal varices. The most favorable cases improve slowly and go on to apparent recovery in 6 to 8 weeks. As indicated, the prognosis in this group must be guarded, since relapse and evidence of progression may appear at a later date.

In a recent report "cholangiolitic" cirrhosis with xanthomatosis, allegedly due to intrahepatic biliary obstruction, appeared 18 years following neocinchophen therapy.⁷⁰ There was no immediate reaction to the drug, but it was considered possible that an anicteric hepatitis had occurred and then progressed at a subclinical level for a number of years. This is a reasonable interpretation, in the light of experience with other drug reactions, although it is difficult to exclude alternative possibilities.

DESACETYL METHYL COLCHICINE (COLCEMIDE, DEMECOLCINE)

Desacetylmethylcolchicine, an alkaloid with antimitotic activity, is an effective therapeutic agent in acute gout and chronic myelogenous leukemia. It produces fewer gastrointestinal symptoms than colchicine. However, serious side reactions, including bone marrow depression, alopecia, fever, rash, stomatitis and jaundice, have been reported.¹⁷⁷

Hepatic involvement is relatively uncommon and usually is of the cholestatic type.⁷⁸¹

Although massive doses of desacetylmethylcolchicine can produce hepatic congestion and necrosis in rabbits,⁷⁸¹ the character of the hepatic lesions and the associated symptoms seen in man suggest that they are due to drug sensitization.

GOLD

The gold compounds used in rheumatoid arthritis frequently produce manifestations of toxicity. These fall into two groups: (1) anaphylactoid and febrile responses immediately following an injection and (2) delayed reactions involving the skin, mucous membranes, gastrointestinal tract, liver, kidneys and hemopoietic system.^{21, 157} It is not known whether these are due to drug intoxication or to sensitization, but the latter is generally considered more likely.

Hepatitis is one of the less common complications of gold therapy and is said to be clinically indistinguishable from the viral type.³⁰⁷ Since many of the cases reported have occurred in individuals undergoing group therapy in large outpatient clinics,³⁰⁷ it is possible that they represent instances of syringe-transmitted viral hepatitis. Unfortunately, no epidemiologic or histologic data are available to substantiate this. Massive hepatic necrosis is said to occur rarely,¹⁸⁶ but in no reported cases has the diagnosis been established by postmortem examination. In the few fatalities that have been investigated,²¹ the changes in the liver were nonspecific, and no lesions suggestive of a hypersensitivity reaction have been described.

BAL is of some value in the treatment of dermal reactions following gold therapy.⁴⁸⁸ Although it is worth a trial in all cases, it is not known whether it affects the course of more serious reactions involving the liver, kidney and hemopoietic system.

INDOMETHACIN (INDOCIN)

Indomethacin [1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid], rarely produces hepatitis. In one reported fatal case, that of a 12-year-old Negro boy, profuse rectal bleeding and deep jaundice appeared after 5 or 6 months of treatment with prednisone and indomethacin for severe juvenile arthritis.³⁷⁴ The liver was en-

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larged and tender, and laboratory studies revealed marked hyperbilirubinemia, increased levels of serum transaminase, a positive cephalin-cholesterol flocculation reaction, prolongation of the prothrombin time and marked leukocytosis. Jaundice deepened progressively, and the patient died 10 days later. Postmortem examination of the liver revealed extensive-centrilobular zonal necrosis with bile stasis, small-droplet fatty infiltration of the parenchyma and a minimal inflammatory reaction.

In a second, nonfatal case, jaundice, hepatomegaly and abdominal pain were noted 3 weeks after the onset of indomethacin therapy for chronic rheumatoid arthritis.²²⁴ An unusual feature was the presence in the serum and urine of biliverdin in sufficiently high concentrations to render them green in color. The skin too had a distinct greenish hue. The serum levels of bilirubin and transaminase were only moderately elevated, but those of alkaline phosphatase and cholesterol were high. Liver biopsy revealed centrilobular degeneration and swelling, mild fatty infiltration, bile stasis and an intense mononuclear and neutrophilic inflammatory reaction in both the parenchyma and the portal zones. Because the serum transaminase level continued to rise, prednisone therapy was begun in the 4th week of the disease. The patient was fully recovered 6 weeks later. There was no satisfactory explanation for the biliverdinemia in this case, although the authors suggested that indomethacin inhibited the activity of biliverdin reductase in the liver and spleen, or, alternatively, that a congenital partial deficiency of the enzyme was brought to light by the development of hepatitis.

It would appear from these two reports that indomethacin can give rise to either hepatocellular or cholestatic hepatitis. Although the mechanism has not been established, it is highly probable that hepatitis is attributable to a sensitization reaction, since indomethacin is known to produce other manifestations of hypersensitivity, such as rash, angioneurotic edema, asthma, leukopenia and thrombocytopenia.

PHENYLBUTAZONE (BUTAZOLIDIN)

The high incidence of untoward reactions

to phenylbutazone limits its usefulness as an antiarthritic agent.^{715, 717} Many of these, including rash, fever, agranulocytosis, thrombocytopenia, lymphadenopathy and swelling of the salivary glands, appear to be manifestations of drug hypersensitivity. However, others, such as edema and peptic ulcer,^{400, 680} are probably based on other mechanisms.

Hepatitis is a relatively uncommon complication of phenylbutazone therapy.^{213, 494, 713, 715, 721} When it occurs, it is almost always accompanied by other manifestations indicative of drug sensitization. It is seen most frequently during the first 6 weeks of therapy but may occur at long as 10 days after the drug is withdrawn.²¹³

Usually, the clinical and the laboratory features are those of acute hepatocellular disease with jaundice and hepatomegaly, but rare instances of anicteric hepatitis have been reported.⁷²¹ Histologically, the liver shows scattered parenchymal degeneration and necrosis and a polymorphonuclear and mononuclear inflammatory reaction in the portal triads.²¹³ Although most patients recover without residuals within 3 months, extensive hepatocellular necrosis with subsequent postnecrotic cirrhosis may be seen occasionally.²¹³ Rarely, the clinical and laboratory picture is that of cholestatic hepatitis, but even in cases of this type the liver shows evidence of significant hepatocellular involvement.²¹³ Several fatalities have been reported,^{213, 494, 713} but in only one of these was death clearly attributable to the hepatic lesion.²¹³

PROBENECID (BENEMID)

Fever, rash and other manifestations of drug sensitization occur in about 2 per cent of patients who receive probenecid and are seen almost exclusively in those given the drug intermittently.⁶¹⁰ Hepatic involvement is rare, but one fatal case has been reported.⁶¹⁰ In this instance, mild hepatitis followed a 2-year course of intermittent probenecid therapy in a patient with an allergic background. Recovery followed withdrawal of the drug, but when it was readministered a month later it promptly produced asthma and rash followed by progressive jaundice, clay-colored stools, hepatomegaly,

coma and ultimate death on the 27th day. Postmortem examination revealed massive hepatic necrosis involving the central and the midzonal areas predominantly, and a sparse portal inflammatory reaction without evidence of vasculitis.

ANTIBIOTICS

Some antibiotics can injure the liver, either directly by a toxic action or indirectly by inducing a hypersensitivity reaction. However, many of the infections for which they are used also produce hepatitis, so that often it is difficult to evaluate the role of antibiotics when this complication occurs. Moreover, in prolonged therapy the possibility of syringe-transmitted viral hepatitis must be considered. It has also become apparent that broad-spectrum antibiotics favor the development of disseminated mycotic infections and the emergence of resistant strains of staphylococci, both of which may produce an acute suppurative focal hepatitis.

CHLORAMPHENICOL (CHLOROMYCETIN)

A small proportion of individuals on chloramphenicol therapy develop severe blood dyscrasias related to toxic depression of the bone marrow.^{304, 423} In at least two instances, jaundice has been reported as a complication; in one of these it appeared after aplastic anemia developed and was due to an infection of the liver with staphylococci and candida, so that the drug was implicated only indirectly.⁸¹¹ In the other, an individual with a history of penicillin sensitivity in the past, nausea, vomiting and vertigo developed immediately following a second course of chloramphenicol.³⁰⁴ Jaundice appeared on the third day and then cleared promptly. Signs of aplastic anemia did not become evident for 2 months. At autopsy 2 weeks later the liver was normal. Possibly the jaundice in this case was the result of a hypersensitivity reaction involving the liver. This would be consistent with the observation that chloramphenicol does not injure the liver in animals⁶⁸⁴ or in patients with hepatitis.²⁹⁶ Routine biopsies in individuals without hepatic disease also have failed to demonstrate changes in the

liver following chloramphenicol therapy.⁸⁰²

Chloramphenicol should be used with caution in patients with severe liver disease, since they are unusually prone to bone marrow depression.⁷³¹ Their enhanced susceptibility to this complication appears to be related to the high levels of free chloramphenicol that occur in the serum as a result of impaired conjugation in the liver and the slow rate at which the unconjugated form of the drug is excreted by the kidneys.

ERYTHROMYCIN

Although erythromycin is relatively innocuous so far as the liver is concerned, one of its esters, propionyl erythromycin ester of lauryl sulfate (Ilosone), produces typical cholestatic hepatitis in a small proportion of exposed individuals.³⁸⁹ Since the hepatitis not infrequently is accompanied by eosinophilia and cannot be reproduced in experimental animals, it is reasonable to assume that it is due to drug sensitization. The occasional occurrence of urticaria and other rashes is consistent with this view.

In most cases, jaundice appears between the 2nd and the 21st days of medication and often is accompanied by abdominal distress, which may be colicky in nature.²²¹ Characteristically, thymol turbidity and cephalin-cholesterol flocculation are normal, while the serum bilirubin, alkaline phosphatase and transaminase levels rise. The signs and symptoms of liver disease promptly subside when the drug is withdrawn, but usually recur if it is administered a second time.

GRISEOFULVIN

In mice, chronic administration of large doses of griseofulvin leads to the development of hepatic and erythropoietic porphyria accompanied by enlargement of the liver, focal hepatocellular necrosis, ductular proliferation and deposition of pigment in Kupffer cells and bile ducts.¹⁸⁸ The hepatic lesions have been ascribed by some investigators to a direct toxic effect of griseofulvin,³⁷ and by others to overproduction and increased biliary excretion of protoporphyrin, leading to its deposition in parenchymal and Kupffer cells and its precipitation within the small intrahepatic bile

ph therapy.⁸⁰² It can be used with the severe liver disease usually prone to bone. Their enhanced suspension appears to levels of free chlorophyll in the serum as a reagent in the liver which the unconjugated is excreted by the kidneys.

ERYTHROMYCIN

It is relatively infrequently concerned, one of the erythromycin ester (erythromycin ester), produces typical of a small proportion of patients. Since the hepatitis is accompanied by eosinophilia produced in experiments, it is reasonable to assume sensitization. The occurrence of urticaria and other symptoms in this view.

It appears between the use of medication and abdominal distress, and is usually associated with the use of erythromycin.²²¹ Characteristically, the alkaline phosphatase is normal, while the signs and symptoms promptly subside when the drug is withdrawn, but usually return a second time.

ERYTHROMYCIN

Administration of large doses leads to the development of erythroid poikilocytosis, enlargement of the spleen, necrosis, ductular reaction, and deposition of pigment in the liver.¹⁶⁸ The hepatic effect of griseofulvin is thought to be due to overproduction and excretion of protoporphyrin in parallel with its precipitation in intrahepatic bile

radicles, resulting in biliary obstruction and secondary parenchymal changes.³⁴⁷ Rats, guinea pigs and rabbits are not susceptible to these effects of griseofulvin.

Many patients receiving therapeutic doses of griseofulvin for tinea infections also show increased protoporphyrin and coproporphyrin in their feces and red blood cells.⁸¹⁹ However, they do not exhibit other biochemical evidence of hepatic injury.^{444, 619} Several individuals with acute intermittent porphyria given therapeutic doses of griseofulvin during a remission have experienced a relapse.^{64, 601} In one of these, acute porphyria was accompanied by mild Bromsulphalein retention and an increase in serum transaminase.⁶⁰¹

Griseofulvin may serve as a sensitizing agent and give rise to reactions characterized by fever, rash, urticaria and angioneurotic edema.^{268, 710} In at least one instance, cholestatic hepatitis resulted.⁸⁵

NOVOBIOCIN

Therapeutic doses of novobiocin tend to raise the level of unconjugated bilirubin in the serum,⁵⁹ and occasionally give rise to overt jaundice,¹⁵⁴ especially in neonates.⁷³⁶ Since hemolysis does not appear to be the factor responsible for this effect, it is highly probable that the unconjugated hyperbilirubinemia is attributable, at least in part, to a defect in the hepatic uptake or conjugation of bilirubin. Attempts to establish the precise mechanism involved have been unsuccessful. In some strains of rats, novobiocin inhibits the uptake of bilirubin by the liver, but in others it does not.⁴ The fact that the hyperbilirubinemia seen in man usually is associated with abnormal retention of Bromsulphalein¹⁵⁴ suggests that there is a defect in bile secretion in addition to impairment of bilirubin uptake or conjugation. Since the hyperbilirubinemia occurs in the absence of detectable changes in hepatic morphology,⁷³⁶ it would appear to be related to a functional disorder of pigment metabolism rather than to toxic injury.

Not infrequently, novobiocin induces hypersensitivity reactions characterized by fever, rash, pruritus and eosinophilia.⁹⁸ Rarely, these may be accompanied by hepatitis. One such patient had massive hepatic

necrosis and died on the 13th day following the onset of symptoms.⁹⁸ The morphologic changes in the liver were indistinguishable from those seen in fulminant viral hepatitis.

OXACILLIN (PROSTAPHILIN)

The semisynthetic penicillin, sodium oxacillin, produces allergic reactions characterized by fever, rash, urticaria and eosinophilia in approximately 3 per cent of patients. In one such patient, the reaction was accompanied by typical cholestatic hepatitis that resolved in little over 3 months.⁷⁴²

Oxacillin therapy occasionally is accompanied by moderate elevation of serum glutamic oxalacetic transaminase.⁴⁹⁸ Since no details are available on the circumstances under which this occurs, it is not clear whether such alterations in serum transaminase are due to drug toxicity or sensitization, or to the underlying infection for which the drug is used.

PENICILLIN

In 1 or 2 per cent of individuals given penicillin, manifestations of hypersensitivity develop.⁴²⁷ Urticaria and other benign types of skin rash predominate, but fatal cases of anaphylactic shock,^{767, 791} exfoliative dermatitis³⁸⁷ and acute vasculitis⁸⁵ also have been reported.

Acute hepatitis is a relatively rare complication, usually seen in association with exfoliative dermatitis.^{387, 757} In one such nonfatal case, the serum bilirubin and alkaline phosphatase levels were moderately elevated, whereas cephalin-cholesterol flocculation and thymol turbidity remained normal.⁷⁵⁷ Biopsy of the liver revealed multiple foci of necrosis, diffuse infiltration of the parenchyma with histiocytes and neutrophils, proliferation of the reticuloendothelium, and portal exudates containing monocytes, eosinophils and neutrophils. Dubin has reported one instance of prolonged penicillin-induced cholestatic hepatitis in which recovery occurred in one and a half years.¹⁹¹ That the hepatitis provoked by penicillin is due to sensitization and not to hepatotoxicity is evident not only from the other manifestations of hypersensitivity with which

it is associated, but also by the fact that the lesions are not reproducible in animals.^{16, 299}

RIFAMYCIN SV

Large doses of rifamycin given intravenously produce a transient increase in serum bilirubin and interfere with the excretion of Bromsulphalein.⁶ Most of the bilirubin is in the unconjugated form, but at the peak of the rise 25 per cent may be conjugated.⁴ In rats, rifamycin reduces the Tm for both conjugated and unconjugated bilirubin, and increases their concentration in the liver, which suggests that rifamycin competes with bilirubin for excretion.⁵ However, since the bilirubin retained in the serum is predominantly unconjugated, it is highly probable that the drug also impairs the hepatic uptake of bilirubin.

STREPTOMYCIN

A variety of drug reactions may occur during streptomycin therapy.⁶⁰⁷ Some, such as disturbances of the 8th nerve and its nuclei, are clearly toxic in origin, whereas others, such as rash, fever and eosinophilia, are almost certainly manifestations of drug sensitization. The pathogenesis of the renal failure and the bone marrow depression that occur occasionally is not known.

Several instances of jaundice have been reported following streptomycin therapy.⁶⁰⁷ Unfortunately, insufficient data are available to state whether these were due to an incidental infection with the hepatitis virus, a toxic reaction or the development of hypersensitivity. However, animal experiments⁵¹² and studies of hepatic function⁶⁰⁷ and morphology⁸⁰² in man suggest that streptomycin is not a hepatotoxin, and that if jaundice occurs during treatment it is likely to be due to a hypersensitivity reaction, or to syringe-transmitted viral hepatitis.

TETRACYCLINES

Chlortetracycline (Aureomycin). Therapeutic doses of orally administered chlortetracycline frequently produce a fine fatty vacuolization of the hepatic parenchyma that is readily reversible on stopping the drug.^{643, 645, 802} However, the drug appears

to have little effect on hepatic function, even in patients with antecedent liver disease,^{143, 674} so that the lesion probably has no clinical importance.

Intravenous chlortetracycline, on the other hand, can produce significant liver damage, as evidenced by impairment of function, clinical jaundice and hepatomegaly.^{45, 428, 642} This is most likely to occur in individuals who have received excessively large doses intravenously in addition to oral medication,^{45, 428} but significant injury has been observed also after as little as 1 Gm. intravenously for 3 days.⁶⁴² Conceivably, hepatitis in such cases is due to the associated infection. However, the same type of injury has been produced experimentally in both man⁴⁵ and animals,⁴²⁹ so that there is little reason to doubt that intravenous chlortetracycline is potentially hepatotoxic. Histologically, the liver shows the same type of fine fatty vacuolization seen after the oral administration of chlortetracycline, but the centrilobular cells tend to undergo autolysis and fragmentation, and bile thrombi are common.^{45, 428}

In animals, inactivation of chlortetracycline by heat does not abolish its toxicity for the liver, which suggests that the hepatic lesions are due to a direct chemical effect and not to an indirect action related to chlortetracycline's antibiotic activity.

Of special interest is the observation that chlortetracycline protects animals against the massive hepatic necrosis produced by low-sulfhydryl, low-tocopherol diets, an effect thought to be related to inhibition of the intestinal flora and a reduction in the formation of hypothetical hepatotoxic bacterial metabolites.²⁹⁰ On the principle that similar bacterial factors may be of importance in the pathogenesis of hepatic coma, chlortetracycline has been recommended as a therapeutic agent in that condition.²²² On the whole, the results of this form of treatment have been disappointing.

Large doses of chlortetracycline also protect against the hepatic and the renal effects of choline deficiency in rats.⁴⁷ The mechanism of this action is not known but appears to be related to the antibacterial properties of the drug.

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Oxytetracycline (Terramycin). Fine fatty vacuolization of the hepatic parenchyma occurs with great regularity following therapeutic doses of oxytetracycline given either orally or parenterally over a period of several days.⁸⁴⁵ The lesion appears to have no clinical significance, since it is readily reversible following withdrawal of the drug and gives rise to neither symptoms nor significant impairment of hepatic function, even in patients with pre-existent liver disease.³⁸³ Similar lesions have been observed in mice and dogs⁴²⁹ but not in rats.³⁵⁰

Severe reactions resembling serum sickness are known to occur in individuals receiving oxytetracycline,³⁸¹ so that the occasional development of drug hypersensitivity hepatitis is to be anticipated. However, as yet no such cases have been reported.

Tetracycline (Achromycin). Orally administered tetracycline in doses up to 2 Gm. daily occasionally produces fatty infiltration of the liver, but has no adverse effect on hepatic function.²¹⁹

Large doses of tetracycline, especially when given *intravenously* to pregnant women with complicating pyelonephritis, may give rise to severe hepatic injury.^{405, 565, 661, 783} In such women, both the clinical and morphologic features mimic those of the acute fatty liver of pregnancy. Most cases occur 3 to 5 days after the onset of intravenous treatment with doses of tetracycline exceeding 2 Gm. daily. However, it has been reported after doses as small as 1 Gm. daily given either intravenously⁶⁶¹ or orally.⁷⁸³ Although women in the third trimester of pregnancy are the principal victims of this complication, it may occur in the postpartum period and is seen occasionally in nonpregnant women⁵⁶⁵ and children¹⁸¹ and rarely in adult males. The disease is fatal in approximately 80 per cent of cases.

At postmortem examination, most of the parenchymal cells of the liver are distended with fine vacuoles, giving them a foamy appearance. Although foci of necrosis and inflammation are not seen, the number of hepatocellular nuclei is reduced and the Kupffer cells contain large amounts of phagocytosed debris and pigment, indi-

cating antecedent necrosis and loss of parenchyma.⁴⁰⁵ In many cases, the kidneys show fatty vacuolization of the renal tubules and foci of cortical necrosis, unrelated to underlying pyelonephritis, and in a high proportion there is evidence of acute pancreatitis.¹⁰⁵

Inordinately high levels of tetracycline have been found in the serum of patients with tetracycline-induced toxic hepatitis.⁷⁸³ Accordingly, it has been suggested that impairment of renal function related to pyelonephritis and diminished extracellular fluid volume may be important factors in the pathogenesis of this complication. In addition, the possibility has been considered that pregnancy, by enhancing the uptake and diminishing the excretion of tetracycline by the liver, as it does in the case of Bromsulphalein, leads to an unusually high concentration of the drug in the liver and thus renders it susceptible to toxic injury.⁷⁸³

The principal clinical manifestations are nausea, vomiting, abdominal pain and jaundice. Not infrequently the vomitus is coffee-ground in character. Evidence of renal failure is common, and in some cases there are signs of acute pancreatitis. Remarkably, the recovery rate was 80 per cent in one series of 5 cases treated vigorously for acute pancreatitis. In fatal cases, the patient lapses into coma and dies within a few days. Fetal death occurs in 70 per cent of women who die, and in 40 per cent of those who survive.⁴⁰⁵

Laboratory studies reveal leukocytosis, azotemia, evidence of acidosis, and a moderate elevation of the serum levels of bilirubin, alkaline phosphatase and transaminase. Usually, thymol turbidity is normal, but the cephalin-cholesterol flocculation reaction tends to be strongly positive. In many cases, the serum levels of amylase and lipase are increased.

The occurrence of a Fanconi-like syndrome and features simulating disseminated lupus erythematosus have been reported following the use of degraded tetracycline.⁷³² These have not been accompanied by evidence of hepatic injury.

The hepatotoxic properties of tetracycline have been confirmed in the rat.⁵⁰⁸ However,

in this species pregnancy does not appear to increase the susceptibility to hepatic injury.

TRIACETYLOLEANDOMYCIN (CYCLAMYCIN)

A high proportion of individuals receiving triacetyloleandomycin in a dose of 1 Gm. daily for 2 to 4 weeks show variable alterations in hepatic function, including Bromsulphalein retention, cephalin-cholesterol flocculation, increased thymol turbidity or a raised serum level of transaminase, alkaline phosphatase or bilirubin.^{223, 748, 749} Occasionally, these are associated with clinically detectable jaundice, anorexia and mild discomfort in the epigastrium or right upper quadrant of the abdomen. Liver biopsy in patients with drug-induced jaundice reveals moderate cholestasis, foci of hepatocellular degeneration, acidophilic bodies and a portal mononuclear inflammatory reaction. Histologic changes in anicteric drug-induced hepatitis are similar but less striking. Functional abnormalities clear in a few weeks following withdrawal of the drug, but recovery from structural changes in the liver is much slower. Usually, there is a prompt relapse on subsequent challenge with the drug.

When given in doses of less than 1 Gm. daily and for periods of less than 2 weeks, triacetyloleandomycin appears to have no ill effects on the liver.

The pathogenesis of the hepatic lesions induced by this agent is unknown. The frequency with which functional abnormalities are produced, and their apparent dose dependence suggest that triacetyloleandomycin is a hepatotoxin. However, the morphologic features of the hepatic lesions and the promptness with which they recur following challenge are more consistent with drug sensitization. In this connection, it may be of significance that this drug is known to produce other types of allergic reaction.

ANTICONVULSANTS, MUSCLE RELAXANTS AND SEDATIVES

DILANTIN (Diphenylhydantoin Sodium)

Approximately 15 per cent of epileptics maintained on Dilantin therapy for prolonged periods develop drug reactions.

Those relating to the gums, the central nervous system and the gastrointestinal tract are almost certainly of toxic origin and usually can be controlled by adjusting the dose. On the other hand, skin reactions, which often are accompanied by fever and other constitutional symptoms, appear to be manifestations of drug hypersensitivity and are far more serious. Although they often subside despite continued drug administration, they occasionally give rise to exfoliative dermatitis^{129, 487, 760} or hemorrhagic erythema multiforme⁶²¹ and terminate fatally.

Several instances of Dilantin-induced hepatitis have been reported.^{129, 156, 193, 306} Without exception, these have occurred in association with other manifestations of hypersensitivity, such as rash, fever, lymphadenopathy and eosinophilia. Occasionally such reactions are accompanied by hepatosplenomegaly without jaundice.^{32, 487} In most cases, the clinical and biochemical features are those of hepatocellular jaundice with varying degrees of cholestasis. On biopsy, the liver shows evidence of diffuse injury, with foci of necrosis, acidophilic bodies, infiltration of both the parenchyma and portal triads with many mononuclear cells and eosinophils, and bile stasis.³⁰⁶ Occasionally, hepatic necrosis is submassive in character and leads to hepatic coma and death.¹⁵⁶ In one fatal case of Dilantin-induced exfoliative dermatitis, there was, in addition to hepatic necrosis, necrosis of arterioles and granuloma formation that involved many tissues, including the liver.⁷⁶⁰

MESANTOIN

(3 methyl-5.5-ethylphenylhydantoin)

Mesantoin, a compound closely related to Dilantin, may give rise to fever, rash, lymphadenopathy and aplastic anemia,²⁵⁵ features that are generally regarded as manifestations of drug hypersensitivity. Minor alterations in hepatic function may be observed under such conditions, but frank hepatitis has not been encountered.¹³ At least one instance of acquired hemolytic jaundice has been reported.⁷⁰⁰

NIRVANOL

(Phenylethylhydantoin)

Nirvanol, a compound closely related to

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Dilantin, was once widely used as a sedative and in the treatment of chorea.²¹¹ It regularly produces a typical sensitization reaction, characterized by fever, rash and eosinophilia, in 1 to 2 weeks. Occasionally, the reaction is severe and terminates fatally, so that the drug has been abandoned in this country. Agranulocytosis and autopsy evidence of liver injury have been described, but no instances of clinically detectable hepatitis have been reported.

PHENOBARBITAL

A review of the literature records only 17 fatalities as a result of reactions to therapeutic doses of phenobarbital.⁴⁸⁸ Since tons of the drug have been consumed since it was introduced into clinical medicine, the danger of serious reaction must be small. No doubt mild reactions are relatively common and attract little attention. The other barbiturates appear to produce reactions less frequently. However, none of them is used as widely as phenobarbital, so that the apparent difference in their toxicity may have no significance.

The principal clinical features of phenobarbital reactions are fever and rash. In more severe cases, there may be exfoliative dermatitis, renal failure, signs of hepatitis, and bleeding from the skin and the mucous membranes. It is highly probable that these are manifestations of drug hypersensitivity, although it is held by some that phenol derivatives, liberated during an abnormal type of metabolism in susceptible individuals, are responsible for tissue damage.

The cases of hepatitis reported have all occurred in association with dermal reactions.^{468, 776} In one of these,⁴⁸⁸ the liver showed extensive midzonal and periportal necrosis, with vacuolization of the remaining cells. However, the hepatocellular changes in other fatal cases⁷⁹⁰ have been less striking. In the one nonfatal case reported,⁷⁷⁶ moderately severe jaundice, clay-colored stools and dark urine occurred in association with a morbilliform and bullous eruption. Complete recovery followed within 3 weeks.

The writer has seen one instance of chronic hepatitis following a phenobarbital reaction in a 7-year-old child. The onset was

with rash, fever and splenomegaly. The rash subsided, except for residual pigmentation, but was followed by arthritis, lymphadenopathy, anemia and progressive hepatosplenomegaly. Biopsy of the liver at the end of 2 years revealed fibrosis of the portal tracts with an intense inflammatory exudate, composed of large reticulum cells, monocytes and plasma cells, and evidence of myeloid metaplasia. Death occurred 2½ years after onset. Unfortunately, permission for autopsy was not obtained.

PHENURONE (PHENACETYLUREA)

Of all the antiepileptic drugs, Phenurone is the one most likely to produce hepatitis.^{163, 259} One survey indicates that this complication occurs in approximately 2 per cent of patients under treatment, and that in approximately 10 per cent the disease is fatal.⁷⁵³ Bone-marrow depression⁷⁵³ and renal failure^{259, 432} are equally serious complications. Fever and rash occur somewhat more frequently but do not appear to be as lethal. Many clinical features suggest that these reactions are manifestations of drug hypersensitivity, which is consistent with the observation that Phenurone does not produce hepatic, renal or hemopoietic injury in animals.⁶¹⁷ As in the case of Dilantin, Phenurone may give rise to signs of true toxicity in the gastrointestinal tract and the central nervous system.^{259, 753}

Careful screening of patients may reveal alterations in liver function before clinical signs of hepatitis appear.¹ Therefore, it is probably wise to check the status of the liver with some simple test, such as the serum transaminase level, at frequent intervals, and to stop treatment if any abnormality is detected. As with other types of drug sensitivity, symptoms may appear as early as the first week of therapy, or not until many months have elapsed,¹²⁴ so that close supervision is essential for as long as treatment is continued.

The pathologic changes found in fatal cases of hepatitis are not constant.^{163, 432} In general, however, there is extensive nonzonal degeneration or necrosis of parenchymal cells with little inflammatory reaction. Occasionally, the renal tubules also show severe degenerative changes.⁴³²

TRIDIONE (TRIMETHADIONE)

A high proportion of individuals receiving Tridione develop rash, leukopenia, or a characteristic type of visual disturbance.⁴²⁵ Rarely, hepatitis,⁴¹⁷ nephrosis⁷⁸⁵ and fatal aplastic anemia⁴⁷⁷ may occur. In one patient with hepatitis,⁴¹⁷ jaundice and exfoliative dermatitis appeared 4 weeks after the onset of Tridione therapy and were associated with a leukemoid reaction in the bone marrow. Uneventful recovery took place in approximately 1 month.

Except for the visual disturbances, which may be of toxic origin, it is generally believed that the side-effects of Tridione are due to drug hypersensitivity, an opinion consistent with the observation that the drug does not produce visceral lesions in animals.⁶¹⁶

ZOXAZOLAMINE (FLEXIN)

Zoxazolamine (2-amino-5-chlorobenzoxazole) was introduced as a muscle relaxant and later found to be an effective uricosuric agent. Occasionally it produces a form of acute hepatocellular necrosis characterized by clinical and morphologic features indistinguishable from those of acute viral hepatitis.^{123, 330, 359} Of the cases reported, most have terminated fatally with signs of massive hepatic necrosis.^{123, 330, 436}

Usually, the hepatitis appears following a period of drug administration that may be as short as 1 week or as long as 2 months. The onset is abrupt, with anorexia, nausea, vomiting and abdominal pain, which are followed within a few days by jaundice, dark urine and light stools. Fever is uncommon. Enlargement and tenderness of the liver may be evident early in the course of the disease, but in severe cases, the liver soon shrinks in size and often is not palpable. The laboratory findings are those of severe hepatocellular disease, although high levels of serum alkaline phosphatase may be seen.³⁵⁹ In fatal cases, there is rapid deepening of the jaundice, fever and the development of hepatic coma with death in 2 or 3 weeks. Prednisone and cortisone have proved to be ineffective in such cases.^{123, 330} Full recovery within a period of 3 months has been reported in a patient with a less

severe form of zoxazolamine-induced hepatitis who was treated with ACTH.³⁵⁹

The pathogenesis of this type of hepatitis is not known. Since zoxazolamine occasionally produces a skin rash, the possibility of drug hypersensitivity must be considered. This is supported by the report that eosinophils predominated in the inflammatory exudate seen in the liver in one fatal case.¹²³ However, in none of the other reported cases have there been any clinical or morphologic features indicative of a sensitization reaction. A direct hepatotoxic action appears unlikely, since zoxazolamine does not produce hepatic lesions in animals.

CHEMOTHERAPEUTIC AGENTS
USED IN INFECTION

ANTIMONY

Although the inorganic compounds of antimony can injure the liver in animals,²⁷³ they do not appear to produce hepatitis in workers exposed to them in industry.²⁶⁷

Toxic doses of both the trivalent and the pentavalent organic antimonials induce fatty degeneration of the liver, kidneys and heart in patients undergoing treatment for kala-azar.⁷²⁸ However, frank hepatitis has been reported only in connection with the pentavalent group.^{531, 532} Almost without exception, the jaundice in such cases has appeared a month or two following completion of a course of intravenous injections. Therefore, these may represent instances of syringe-transmitted viral hepatitis. However, neither the clinical features nor the pathologic findings have been described in sufficient detail to permit definite conclusions regarding their etiology.

Antimony dimercaptosuccinate (Astiban), a trivalent antimonial used in the treatment of schistosomiasis, frequently raises the serum level of glutamic oxalacetic transaminase, and less commonly that of alkaline phosphatase.^{708, 775} Since the occurrence of these changes appears to be correlated with the total dose employed, it is assumed that they are manifestations of hepatotoxicity. However, biopsy studies of the liver in several patients undergoing treatment have failed to demonstrate sig-

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since zoxazolamine does
not cause lesions in animals.

CHEMOTHERAPEUTIC AGENTS USED IN INFECTION

ANTIMONY

inorganic compounds of
antimony are the liver in animals,²⁷³
and are known to produce hepatitis in
man in industry.²⁸⁷
Both the trivalent and the
pentavalent antimonials induce fatty
degeneration of the liver, kidneys and heart
in experimental animals.
For the treatment of kala-
azar, antimonial hepatitis has been
connected with the penta-
valent antimony.¹² Almost without excep-
tion in such cases has ap-
peared two following compli-
cations: intravenous injections.
They may represent instances
of untreated viral hepatitis. How-
ever, clinical features nor the
course have been described in
order to permit definite conclu-
sion as to its etiology.

Antimony (Asti-
mone) antimonial used in the
treatment of schistosomiasis, frequently
causes less commonly that of
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currence of changes appears to be
proportional to the total dose employed,
it is likely that they are manifestations
of toxicity. However, biopsy studies
in several patients undergoing
treatment failed to demonstrate sig-

nificant lesions.⁷⁰⁸ No cases of overt hep-
atitis have been encountered in patients re-
ceiving this drug.

It has been suggested that impairment
of hepatic function during the treatment of
schistosomiasis with antimonials is the re-
sult of an allergic reaction to products re-
leased from killed ova and worms, and that
this can be prevented by concomitant ad-
ministration of prednisone.⁸⁰⁴ Consistent
with this possibility is the observation that
antimonial treatment of schistosomiasis not
infrequently leads to an increase in eosino-
philia and the appearance of fever and
pruritus.⁷⁰⁸

ARSENIC

At one time it was thought that all types
of arsenical hepatitis had a common patho-
genesis. However, arsenic can produce liver
injury by: (1) a direct toxic action, (2)
inducing a hypersensitivity reaction or (3)
serving as a vehicle for the accidental trans-
mission of the hepatitis virus.

In animals, massive doses of arsenic, in
the form of either the organic compounds
once used in the therapy of syphilis^{304, 651}
or inorganic salts,⁷⁶² produce acute necrosis
of the liver. Depending on the circum-
stances, the lesions may be massive,³⁰⁴ cen-
trallobular⁶⁵¹ or focal⁷⁶² in distribution. The
counterpart of this type of liver injury is
not seen when intermittent therapy with
small doses of the arsphenamines is used in
the treatment of syphilis, but is common
after short-term massive arsenotherapy.²¹⁰
¹²⁴ Jaundice occurs in 1 to 4 per cent of pa-
tients on the latter regimen and, as might
be expected, frequently is associated with
other manifestations of acute arsenic tox-
icity, including fever, rash and cerebral
symptoms. Usually recovery is rapid and
complete.

In contrast, healing of the lesions pro-
duced by the inorganic arsenates in animals
often is followed by postnecrotic scarring
and the picture of cirrhosis.⁷⁶² A similar
sequence is seen occasionally in individuals
who have received potassium arsenite
(Fowler's solution) for prolonged periods.²³⁹
Usually, the signs of cirrhosis in such cases
develop insidiously without any recogniz-
able antecedent episode of acute hepatitis.

A small proportion of individuals who are
given small doses of the arsphenamines in-
termittently develop a reaction known as
"erythema of the 9th day," or Milian's syn-
drome.^{301, 624, 644} Usually, it appears several
hours after the 2nd or 3rd injection (8th
to 10th day of treatment) and is character-
ized by fever, rash, arthralgia and eosino-
philia and, in some instances, by hepatitis,
purpura and renal injury. The latter are par-
ticularly prone to occur if treatment is con-
tinued after the initial symptoms appear or
is resumed following their subsidence. Al-
though the reaction was once thought to be
of toxic origin,^{624, 704} it is now generally
agreed that it is due to drug sensitiza-
tion.^{301, 644}

The hepatitis associated with Milian's syn-
drome is of the classic cholestatic type.
Characteristically, jaundice appears on the
2nd or 3rd day of the reaction and usually
is associated with anorexia, nausea and vom-
iting. The liver tends to enlarge, the spleen
may be palpable, and itching is common.
As the jaundice deepens, the stools become
clay-colored, and the urine dark. The results
of liver function tests, especially if carried
out late in the disease, are more suggestive
of extrahepatic biliary obstruction than they
are of hepatocellular damage. Thus, the
serum alkaline phosphatase and the chole-
sterol levels tend to be high, while the cepha-
lin-cholesterol flocculation reaction usually
is negative. Liver biopsy at this stage reveals
pericholangitis and bile stasis, with little or
no evidence of parenchymal injury.

The course of Milian's syndrome is vari-
able. Although uneventful recovery may
occur within a few weeks, often it is delayed
for many months. Rarely, it is complicated
by the development of hepatic fibrosis and
xanthomatosis of the skin,⁷²⁴ a syndrome
difficult to distinguish from other types of
biliary cirrhosis.

By far the most common type of hepatitis
seen in individuals receiving any of the
arsphenamines occurs 3 to 18 months after
the onset of treatment.^{49, 704} There is now
unequivocal experimental,⁴⁶⁰ histologic¹⁷⁵
and epidemiologic⁶⁴⁴ evidence to show that
the liver injury in this instance is due not
to drug toxicity but rather to accidental
syndrome-transmission of the hepatitis virus.

No doubt most reported cases of massive hepatic necrosis²⁵⁶ and postnecrotic cirrhosis^{34, 175} following arsenotherapy also fall into this group.

In animals, high-protein and high-carbohydrate diets given *prophylactically* appear to protect against the hepatotoxic effects of arsenic.^{155, 503} However, claims for the therapeutic efficacy of cysteine and methionine supplements in postarsphenamine jaundice are based on unconvincing clinical evidence.⁵⁶⁴ Moreover, there would appear to be little logic in attempting to "detoxify" arsenic in this situation, since the jaundice is usually due to viral hepatitis or to a sensitization reaction.

The results of treatment with BAL have been equivocal.¹⁹⁶ Since BAL fixes and facilitates the removal of arsenic, it would appear to be a useful agent in the management of true arsenic intoxication, such as occurs after massive arsphenamine therapy, and conceivably may be of value in sensitization reactions when traces of the drug still remain. However, it obviously has no place in the treatment of postarsphenamine jaundice due to the hepatitis virus. No doubt the inclusion of many such cases in treated groups has made the evaluation of therapy difficult.

Inhalation of arsine (AsH_3 , arsenuretted hydrogen) usually is followed by the development of jaundice, an effect due to an acute hemolytic reaction.

Several instances of hepatitis following carbarsone therapy have been reported.^{535, 588} These have been attributed to the hepatotoxic effects of the drug itself or one of its hydrolytic products, arsanilic acid, presumably formed during its storage or manufacture.⁵⁸⁸ However, the hepatitis usually comes on abruptly following a relatively brief period of carbarsone administration at a low dose level, is typically cholestatic in type, almost always is accompanied by fever, and occasionally is associated with exfoliative dermatitis, features that strongly suggest that the drug is a sensitizing agent rather than an hepatotoxin.

ATABRINE

Prolonged administration of small doses of atabrine occasionally gives rise to skin

reactions. Rarely, these are accompanied by fulminant hepatitis, aplastic anemia or agranulocytosis.⁴⁴⁵ Similar reactions have been reported following intermittent therapeutic doses.¹¹ It is not known whether these are due to a toxic effect or to drug sensitization. Since patch tests may be positive,¹¹ and since large doses do not ordinarily impair hepatic function¹⁰⁹ a sensitization reaction is a distinct possibility. However, a direct toxic action cannot be excluded, since large doses of atabrine can produce hepatic necrosis in dogs.¹⁰⁹

BISMUTH

The only instances of hepatitis reported following exposure to bismuth compounds have occurred in syphilitics given repeated injections over a long period of time. Descriptions of the clinical features and certain epidemiologic data in these cases suggest syringe-transmission of the hepatitis virus.

ETHIONAMIDE

Ethionamide (α -ethyl-thioisonicotinamide), an effective agent in the treatment of tuberculosis, occasionally gives rise to acute hepatitis.^{147, 418, 520, 561, 569} The incidence of this complication is estimated to be 5 per cent.¹⁴⁷ Diabetics appear to be particularly susceptible.¹⁴⁷ Of the 18 cases reported up until 1964, 2 resulted in death from extensive hepatic necrosis.¹⁴⁷ Occasionally, this form of drug-induced hepatitis is unaccompanied by jaundice.¹⁴⁷ In addition, ethionamide therapy may lead to alterations in hepatic function without producing clinical signs of hepatitis.⁴¹⁸

The onset, which occurs 1 to 8 months after starting treatment with ethionamide, is characterized by anorexia, nausea and vomiting, followed within a few days by dark urine and jaundice. Occasionally, these are accompanied by fever and rash. Usually, the signs of hepatitis regress following withdrawal of the drug, and recur when it is administered at a later date.^{520, 561} However, hepatic functional abnormalities, in the absence of clinical signs of acute hepatitis, may subside despite continued drug administration.⁴¹⁸

In addition to hyperbilirubinemia, high

levels of SGOT are noted, and there is a marked increase in serum globulin, positive flocculation reactions, and elevated values of serum alkaline phosphatase. A less constant feature is the occurrence of eosinophilia.

The histologic picture of the liver biopsy¹⁴⁷ resembles that of viral hepatitis.

The occurrence of hepatitis in some patients with hepatic lesions and in those usually provoked by drugs, suggests that ethionine-induced hepatitis is a manifestation of a hypersensitivity reaction. This view is not shared by others who attribute this complication to infection with the hepatitis virus.

Isoniazid (isonicotinic acid hydrazide, Rimifon, Pyridin), a drug widely used in the treatment of tuberculosis, is a potential hepatotoxin. Prolonged administration, usually to 25.0 mg./kg. for 6 months, may lead to fatty degeneration of the liver and jaundice.⁵³⁹ The mortality in man (2 to 10 mg./kg. daily) may affect hepatic function, but, however, they induce fever, rash, and hepatitis.^{67, 142, 291, 540} Without exception, the jaundice reported in individuals receiving other sensitizing drugs, such as para-aminosalicylic acid, is due to isoniazid. Although sensitivity to isoniazid is not observed in such cases by provoking the hepatitis or following recovery, the condition is excluded that initiated by PAS. In those cases in which isoniazid alone causes hepatitis, there was no preceding reaction to PAS.

The clinical picture of the hepatitis produced by isoniazid is similar to those of viral hepatitis. Recovery follows withdrawal of the drug. However, at least two cases have been reported.^{142, 502} In

these are accompanied by aplastic anemia or similar reactions have been known whether these effects are due to drug sensitization or to drug sensitization tests may be positive,¹¹ but these do not ordinarily indicate a sensitization reaction.¹⁰⁹ It is a possibility. However, a reaction cannot be excluded, since ethionine can produce hepatic

ETHIONINE

Cases of hepatitis reported to be due to ethionine compounds in patients with syphilis given repeated treatment over a long period of time. Delayed clinical features and certain data in these cases suggest a reaction to the hepatitis

ETHIONAMIDE

2,4-Diethyl-thioisonicotinamide is an agent in the treatment of tuberculosis which usually gives rise to acute hepatitis.^{561, 569} The incidence of hepatitis is estimated to be 5 per cent, but it appears to be particularly high in the first 18 cases reported up to 1947. In addition, ethionamide has been reported to lead to alterations in hematological data without producing clinical

hepatitis occurs 1 to 8 months after treatment with ethionamide, with anorexia, nausea and vomiting within a few days by fever and rash. Usual hepatitis regresses following withdrawal of the drug, and recurs when it is resumed at a later date.^{520, 561} How- ever, occasional abnormalities, in- cluding signs of acute hepato- icity despite continued drug

levels of SGOT are the rule. Increased thy- mol turbidity, positive cephalin-cholesterol flocculation reactions and relatively high values of serum alkaline phosphatase are less constant features. In a few patients, eosinophilia occurs.

The histologic features found on liver biopsy¹⁴⁷ resemble those seen in viral hep- atitis.

The occurrence of fever, rash and eosino- philia in some patients, the character of the hepatic lesions and the prompt recurrence usually provoked by drug challenge suggest that ethionine-induced hepatitis is a mani- festation of a hypersensitivity reaction. This view is not shared by some authorities, who attribute this complication to intercurrent infection with the hepatitis virus.

ISONIAZID

Isoniazid (isonicotinic acid hydrazide, Rimifon, Pyrizidin, Nydrazid), an agent widely used in the treatment of tuberculosis, is a potential hepatotoxin. In animals, pro- longed administration of large doses (17.5 to 25.0 mg./kg. for 4 to 5 weeks) produces fatty degeneration of the liver and overt jaundice.⁶³⁹ The much smaller doses used in man (2 to 10 mg./kg.) do not appear to affect hepatic function.^{212, 625} Occasionally, however, they induce hypersensitivity and produce fever, rash and, less commonly, hepatitis.^{67, 142, 291, 302, 390, 609} Almost with- out exception, the hepatitis has been re- ported in individuals who have received other sensitizing drugs, and particularly para-aminosalicylic acid (PAS), in addition to isoniazid. Although evidence of sensi- tivity to isoniazid has been established in such cases by provoking an exacerbation of the hepatitis or fever with a test dose fol- lowing recovery, the possibility cannot be excluded that initial sensitization was in- duced by PAS. In several reported cases in which isoniazid alone appeared to produce hepatitis, there was a history of an ante- cedent reaction to PAS.^{67, 609}

The clinical and laboratory features of the hepatitis produced by isoniazid resem- ble those of viral hepatitis. As a rule, full recovery follows withdrawal of the drug. However, at least two fatal cases have been reported.^{142, 502} In one instance, drug ther-

apy was reinstituted 1 month after a reac- tion accompanied by jaundice. This pro- voked an exacerbation which was followed several months later by a fatal massive hem- orrhage from esophageal varices. Postmor- tem examination revealed postnecrotic cir- rhosis thought to be related to the ante- cedent drug reactions.⁵⁰²

In the second case, a patient being treated for sarcoidosis with prednisolone and isonicotinic acid, acute hepatitis with clinical, laboratory and histologic features undistinguishable from those of viral hep- atitis, appeared on the 30th day of treat- ment.¹⁴² Following withdrawal of the drug, full recovery occurred within 2 months. Isoniazid was restarted 10 days later, and the patient continued to take prednisolone. On the 45th day of treatment there was a recurrence of acute hepatitis with rapidly deepening jaundice followed by hepatic coma and death on the 21st day. Autopsy revealed a small liver (900 Gm.) and signs of submassive hepatic necrosis.

Although the hepatitis tends to recur when isoniazid therapy is resumed, oral de- sensitization has been successful in a num- ber of cases.⁶⁷

The closely related isopropyl derivative of isonicotinic acid, iproniazid (Marsilid), was abandoned as an antituberculosis agent soon after it was introduced, since it proved to be more toxic than isoniazid. However, its potential for producing serious hepato- cellular injury was not fully appreciated until it was reintroduced as an antidepressant. The features of this type of hepatitis are described in the section on Psycho- pharmacologic Agents.

NITROFURANTOIN (FURADANTIN)

Nitrofurantoin, when given in large doses, often produces gastric irritation with nau- sea and vomiting. Less commonly, it gives rise to sensitization reactions characterized by fever, rash, angioneurotic edema, hemo- lytic anemia or leukopenia. In at least one instance, such a reaction was accompanied by cholestatic hepatitis.²¹⁴ The patient, a female, experienced fever and rash during her second course of treatment with nitro- furantoin. On resuming treatment 2 months later, she had an exacerbation of fever,

maculopapular rash, pruritus and eosinophilia within 24 hours, and 4 days later was found to be jaundiced. The liver was enlarged and tender, and tests of hepatic function were typical of cholestasis with moderate elevation of serum bilirubin, high alkaline phosphatase and cholesterol, mild elevation of serum transaminase and negative flocculation reactions. Liver biopsy revealed severe centrilobular bile stasis, foci of parenchymal necrosis and inflammation, and enlargement of the portal tracts with ductular proliferation and an exudate containing numerous neutrophils, eosinophils and lymphocytes. Full recovery, except for mild residual Bromsulphalein retention, occurred within 7 weeks.

PARA-AMINOSALICYLIC ACID (PAS)

Both toxic and allergic reactions may complicate the course of PAS therapy. Toxic reactions, which are due to the local irritant action of the drug in the gastrointestinal tract, are common but seldom necessitate interruption of treatment. Allergic reactions, which are far more serious, occur in approximately 2 to 5 per cent of patients. Usually, such reactions appear between the 3rd and 6th weeks of medication and are characterized by fever, rash, eosinophilia and lymphadenopathy.^{435, 688, 772} Other less common manifestations of hypersensitivity include hepatitis,^{158, 435, 473, 688} Loeffler's syndrome,⁷⁷² neutropenia,⁴³⁵ atypical lymphocytosis⁴³⁵ and renal damage.¹⁵⁸ A history of antecedent allergy is relatively common.⁶⁸⁸

As a rule, the onset of hepatitis is preceded by other manifestations of PAS sensitivity, such as fever and rash. The principal clinical features include jaundice, dark urine and enlargement and tenderness of the liver. Occasionally, hepatosplenomegaly occurs without jaundice.⁴³⁵ Most cases show a marked increase in serum alkaline phosphatase and abnormalities in the cephalin-cholesterol flocculation and thymol turbidity reactions.⁴³⁵ Usually, recovery ensues in 4 to 5 weeks. Histologically, the liver shows scattered foci of hepatocellular necrosis, bile stasis and an inflammatory reaction that is most intense in the portal triads.⁶⁸⁸ A few fatal cases have been reported.^{54, 549, 688} In these, death has occurred in 2 to 7

weeks with clinical and morphologic signs of massive hepatic necrosis.

Occasionally, patch tests are positive,¹⁵⁸ which supports the view that PAS-induced hepatitis is due to hypersensitivity. Of interest in this connection, is the report of positive L.E. tests in the serum of a 32-year-old patient who had a severe reaction to PAS characterized by fever, urticaria, lymphadenitis, anicteric hepatitis and acute myocardial infarction.⁷¹

Although successful desensitization has been reported in a few instances,^{158, 548, 772} it is difficult to exclude the possibility of spontaneous desensitization in such cases.⁷⁷² Moreover, reinstitution of drug therapy often is followed by prompt recurrence of symptoms.

As pointed out, reactions to PAS not infrequently are associated with or followed by the development of sensitivity to other drugs.^{140, 688} It is not clear whether these are indicative of cross-sensitization or of multiple independent sensitizations.

PYRAZINAMIDE (ALDINAMIDE)

In combination with isoniazid, pyrazinamide is one of the most effective agents used in the treatment of tuberculosis. However, its usefulness is limited by its tendency to produce hepatitis when administered alone⁵⁸⁹ or in combination with other drugs.^{117, 464, 518, 662} A review of the literature indicates that jaundice occurs in approximately 3 per cent of patients receiving a daily dose of 40 mg./kg. of body weight. Evidence suggests that smaller doses are less likely to affect the liver.⁵¹⁸

Usually, the hepatitis occurs late in the course of treatment, most commonly during the 6th month, but occasionally as early as the 2nd. Its duration and severity are variable; some patients develop mild jaundice and recover within a week, whereas others run a severe and protracted course. Several fatalities have been reported.⁴⁶⁴

The clinical and laboratory features are those of acute hepatocellular disease. Rarely, in nonfatal cases of unusual severity, the jaundice is accompanied by ascites.⁴⁶⁴ Biopsy in such cases reveals a marked inflammatory reaction involving both the parenchyma and the portal triads, focal areas of

hepatocellular necrosis,³⁸⁸ stasis,³⁸⁸ and massive necrosis on portal tracts. Alterations demonstrate a zonal pattern of necrosis, rupture of the bile ducts, and dissemination of necrotic material. If treatment is continued, transaminase levels are avoided. It is produced or by infection, massive hepatic necrosis is not known. However, patic lesions and sensitization.

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hepatocellular necrosis and marked bile stasis.³⁸³ In a fatal case in which death occurred on the 8th day of illness,⁴⁶⁴ there was massive hemorrhagic necrosis of the liver on postmortem examination.³⁸³

Alterations in hepatic function may be demonstrable during the course of pyrazinamide therapy.^{464, 568} It is wise to interrupt therapy as soon as such abnormalities are discovered. Serum transaminase determinations are particularly useful in this connection. Indeed, it has been reported that if treatment is stopped as soon as the transaminase level rises, hepatitis can be avoided.⁵¹⁸

It is not known whether pyrazinamide produces hepatitis by a direct toxic action or by inducing a sensitization reaction. Since massive doses of the drug can produce hepatic necrosis in dogs,⁶²³ and since the drug is not known to produce other signs of hypersensitivity, a toxic action appears likely. However, the histologic features of the hepatic lesion are more consistent with a sensitization reaction.

STILBAMIDINE

The 4,4'-diamidino derivatives of stilbene (stilbamidine), diphenyl ether (phenamidine), diphenoxypropane (propamidine) and diphenoxypentane (pentamidine), agents once used exclusively in the treatment of trypanosomiasis²² and leishmaniasis,³⁷⁹ are of value in the management of multiple myeloma,²² actinomycosis,⁵⁰⁵ blastomycosis⁶⁵⁷ and tic douloureux. Because they produce lesions in the liver and the kidneys of animals,⁷⁸⁷ there has been concern over their possible toxic effects in man.

Transient vasomotor and gastrointestinal symptoms are common immediately following the first few injections of stilbamidine. Usually, these subside within a few minutes and may be avoided by injecting the drug slowly.^{390, 379} Of greater importance is the dissociated sensory disturbance over the distribution of the trigeminal nerve that frequently follows prolonged therapy.^{22, 379} The neuropathy appears from 2 to 3 months following cessation of the medication and is due to toxic degeneration of the principal sensory nucleus of the 5th cranial nerve.

Therapeutic doses of stilbamidine (2 to 3

mg./kg. daily or every other day in amounts up to 6.0 Gm.) do not ordinarily cause any significant depression of hepatic or renal function in man.²² However, in experimental animals, larger doses have produced severe fatty infiltration of the liver, degeneration of the convoluted tubules of the kidneys, and renal failure.⁷⁸⁷

Similar lesions were observed at autopsy in a 7-year-old girl with systemic blastomycosis who received 7.65 Gm. of 2-hydroxy-stilbamidine intravenously over a 36-day period.³³⁸ Each injection was followed by headache, nausea and fever. Twenty-four hours after her last dose of 450 mg., which in retrospect was considered excessive, she had a convulsion, followed by fever and enlargement of the liver. Death occurred on the 4th day. At the height of the reaction the serum bilirubin was 1.4 mg./100 ml.; cephalin-cholesterol flocculation, 4+; and thymol turbidity, 9 units.

A number of years ago a fulminant type of hepatitis was observed in patients undergoing stilbamidine therapy for kala-azar in the Sudan.³⁷⁹ Characteristically, the symptoms occurred from 1 to 3 months following cessation of therapy. At autopsy, the outstanding findings were extensive centrilobular necrosis and fatty infiltration of the liver. In some cases, the lesions closely resembled those of acute yellow atrophy. The hepatitis was attributed to an increase in the toxicity of the drug related to its storage and exposure to light.

Subsequently, the increase in the toxicity of stilbamidine on exposure to light was confirmed in animals.^{36, 247} However, in none of the experiments reported were the long latent period and centrilobular hepatic necrosis reproduced. In retrospect, these deaths were probably due to syringe-transmitted viral hepatitis, especially since the disease was prevalent in the Sudan at the time.

SULFONAMIDES

The sulfonamides fall into the category of drugs that can produce hepatic injury, both by direct toxic action and by the induction of a hypersensitivity reaction. From a clinical point of view, however, only the latter gives rise to serious consequences.

Prolonged administration of sulfonamides to animals leads to the development of focal inflammatory, degenerative and necrotic lesions in liver, kidneys, myocardium and lungs.^{164, 244} Similar lesions have been observed in a high proportion of individuals who have received sulfonamides shortly before death.^{244, 501} These are thought to be manifestations of true drug intoxication. The depression in hepatic function,^{18, 774} and the occasional occurrence of hepatitis in individuals without other signs of hypersensitivity⁷⁷³ have also been attributed to the toxic effects of the drug. However, the fact that these can seldom be correlated with the amount of drug ingested raises the question of whether they may not be related to some other factor, such as infection or sensitization.

A variable proportion of individuals, depending on the particular sulfonamide derivative employed, develop a reaction characterized by fever, rash, and signs of visceral and bone marrow injury. Although the clinical manifestations often suggest involvement of a single organ, postmortem examination usually reveals widespread inflammatory and necrotic lesions in many of the viscera and blood vessels.^{243, 517} Occasionally, identical lesions are found in individuals who have received sulfonamides but have not had clinical manifestations of a drug reaction.²⁴³ The clinical and morphologic features of such reactions resemble those of serum sickness so closely that it is difficult to escape the conclusion that they are allergic in nature,^{294, 454, 612} even though attempts to demonstrate specific antibodies have been unsuccessful.²⁹⁴

Acute hepatitis occurs in about 0.6 per cent of patients undergoing sulfanilamide therapy,^{62, 130, 138, 229, 254, 294, 452, 517, 641} and somewhat less frequently in individuals who receive sulfathiazole,¹³⁰ sulfadiazine,^{130, 314} sulfamethoxypyridine (Kynex),⁷⁵⁰ sulfamethoxazole (Gantanol),¹⁹² sulfadimethoxine (Madribon),²¹⁶ and other sulfonamide derivatives. The incidence and severity of the hepatitis cannot be correlated with the amount of drug administered. In most instances, the onset is within the first 2 weeks but may be delayed until the 6th week of

therapy, or even later.⁶⁴¹ Rarely, hepatitis and other manifestations of sensitization do not become evident until a number of weeks have elapsed following cessation of medication.²⁵⁴ Approximately one quarter of these reactions occur in individuals who have been exposed previously to the drug.

Usually, the onset of symptoms is sudden, with fever, anorexia, nausea and vomiting; they may be accompanied by a rash. Jaundice appears on the 3rd to 6th day but may be delayed for as long as 2 weeks. The liver enlarges and often is tender. Occasionally, there is splenomegaly. Dark urine and acholic stools are the rule, at least early in the course. The laboratory features, which are those of hepatocellular damage, are not distinctive, except that the serum alkaline phosphatase level may be very high.^{254, 750}

Most cases go on to slow recovery, but a few patients lapse into coma and die of hepatic failure.^{92, 138, 254, 314, 517, 641} Death may occur as early as the 5th day³¹⁴ or may be delayed for several months.⁶² Often, ascites is present when the course is chronic.

In mild cases of sulfonamide-induced hepatitis, a diffuse inflammatory reaction involves all portions of the liver, with scattered foci of hepatocellular necrosis⁷⁵⁰ and bile stasis. Occasionally, granulomata are seen.²¹⁶ In fatal cases, the liver is small and shows evidence of massive necrosis of the parenchyma, collapse of the stroma and an inflammatory reaction in the portal triads.^{62, 138, 314, 517} Individuals who die of more generalized reactions show scattered areas of hepatic necrosis, foci of inflammatory cells, and spotty necrosis of vessels. The exudate, which is composed of large mononuclear cells, is predominantly perivascular and periportal in location.^{243, 517} Similar lesions may be found in the myocardium, kidneys, bone marrow, skin and other tissues.

It has been suggested that pre-existent hepatic disease renders the liver more susceptible to further injury by the sulfonamides.^{130, 773} Autopsy experience does not bear this out. Moreover, there is no clinical evidence that sulfonamides increase hepatic dysfunction in such individuals.⁵⁶⁸ However, cirrhotics appear to be peculiarly susceptible to the other toxic effects of sulfonamides,

particularly in the case of acute hepatitis, it is probably wise to avoid their use in these patients.

Acute hemolytic anemia may follow the ingestion of sulfonamides and give rise to jaundice. It has been taken for a manifestation of hepatitis and occurs early in the course of the disease, especially after the administration of pyridine derivatives.

The etiology of the acute hemolytic anemia of sulfonamide therapy may be due to the direct toxic effect of the precipitated drug crystals on the red cells, or to the drug or to some other factor. The last type is most often associated with hepatitis.

(Amithiozone, *p*-Amino-4-thiozone)

Tibione, used in the treatment of leishmaniasis, is generally considered a potent hepatotoxin. Although it does not impair hepatic function⁷⁸⁸ the liver²¹⁸ has been found to be affected, there have been reports of hepatitis. The other effects, which include a rash¹⁴⁵ and agranulocytosis, the drug may be considered to be consistent with the effects of even massive doses of chymotrypsin or bone marrow transplants.^{595, 706}

Similar alterations in the liver may be observed following the administration of the zone (*p*-formylacetanilide zone), a component of Tibione.⁶⁸⁷

CYTOTOXIC SUPPRESSANTS

ANTIPURINES

Azathioprine (6-mercaptopurine) is a purine antagonist, which it is derived from, and an immunosuppressant.

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particularly in the kidney.^{106, 566} Therefore,
it is probably wise to avoid their use in liver
disease.

Acute hemolytic reactions occasionally
follow the ingestion of the sulfonamides and
give rise to jaundice, which may be mis-
taken for a manifestation of hepatitis. These
occur early in the course of treatment and
especially after sulfanilamide and sulfa-
pyridine administration.⁴⁵²

The etiology of the renal complications
of sulfonamide therapy is complex. Lesions
may be due to the mechanical effects of pre-
cipitated drug crystals, the toxic action of
the drug or to sensitization reactions. The
last type is most often associated with drug
hepatitis.

TIBIONE

(Amithiozone, *p*-Acetylaminobenzaldehyde
thiosemicarbazone)

Tibione, used in the treatment of tuber-
culosis, is generally regarded as a potential
hepatotoxin. Although minor alterations in
hepatic function¹⁸⁵ and fatty infiltration of
the liver²¹³ have been described as toxic
effects, there have been no reports of acute
hepatitis. The other manifestations of tox-
icity, which include nausea, vomiting,
rash¹⁸⁵ and agranulocytosis,⁵⁸⁵ suggest that
the drug may be a sensitizing agent. This
is consistent with the observation that
even massive doses fail to produce paren-
chymatous or bone marrow lesions in ani-
mals.^{585, 704}

Similar alterations in hepatic function and
symptoms of sensitization have been ob-
served following the administration of Myvi-
zone (*p*-formylacetanilide thiosemicarba-
zone), a compound closely related to
Tibione.⁶⁸⁷

CYTOTOXIC AND IMMUNO- SUPPRESSIVE AGENTS

ANTIMETABOLITES

Azathioprine (Imuran). Azathioprine, a
purine antagonist, has the same therapeutic
actions as 6-mercaptopurine (6-MP), from
which it is derived, but is more effective as
an immunosuppressive agent.⁵²⁶ Although

it is metabolized to 6-MP,²⁰⁶ it appears to
be less toxic.⁸⁴⁰ In dogs, doses of 3.5 to
5.0 mg./kg. daily for periods up to 60 days
raise the serum levels of alkaline phosphatase
and transaminase, and produce minor
degrees of focal hepatocellular necrosis and
degeneration, increased mitotic activity,
central congestion, bile stasis and, in some
cases, cholangitis, pericholangitis and peri-
portal fibrosis.⁷²⁹

Several instances of apparent hepatotox-
icity have been reported in man. In a series
of 46 patients given azathioprine for a va-
riety of "autoimmune" diseases, one case of
biopsy-documented cholestatic hepatitis was
encountered in a patient who had received
the drug for 178 days in doses up to 350 mg.
daily.¹⁵⁰ The relationship of the hepatitis
to azathioprine in this case was uncertain,
because the patient had also taken prochlor-
perazine, a known cholestatic agent. In an-
other group of 3 patients being treated with
azathioprine for active chronic hepatitis,
jaundice was encountered in one, a young
girl who had received 4 mg./kg.⁴⁷⁶ The hy-
perbilirubinemia in this case was unaccom-
panied by other biochemical evidence of
hepatocellular injury, and subsided despite
continued drug administration.

6-Mercaptopurine (6-MP, Purinethol). A
significant number of patients with leu-
kemia treated with 6-MP in doses exceed-
ing 2.5 mg./kg. daily exhibit manifestations
of hepatotoxicity.^{204, 469} These may appear
as early as 2 weeks or as late as 2 years after
treatment is begun.

Usually, signs of hepatic injury appear
abruptly, with jaundice, dark urine, light
stools and enlargement and tenderness of
the liver. Often these are associated with
other manifestations of drug toxicity, espe-
cially oral lesions and leukopenia. The
serum levels of bilirubin, alkaline phosphatase
and transaminase are elevated, and,
occasionally, thymol turbidity and cephalin-
cholesterol flocculation are abnormal. The
jaundice tends to clear rapidly when drug
administration is discontinued. Usually, re-
institution of 6-MP therapy provokes a re-
currence.²⁰⁴ Rarely, the hepatitis is progres-
sive and terminates fatally.

Patients with active chronic liver disease

appear to be peculiarly susceptible to the hepatotoxic effects of 6-MP. In one such case, a dose of only 1.5 mg./kg. given daily for 3 weeks produced fatal hepatic necrosis and marked cholestasis accompanied by hepatic coma, renal failure and terminal shock.¹⁰² Of 12 other patients with active chronic hepatitis, most of whom were given 1.5 to 2.5 mg./Kg. of 6-MP daily, half exhibited jaundice within 2 to 4 weeks.¹⁷⁶ An unusual feature in this group was the fact that the hyperbilirubinemia was unaccompanied by other biochemical evidence of hepatocellular injury, and cleared spontaneously despite continued administration of the drug.

In a nonfatal case seen by the writer, liver biopsy revealed enlargement of the portal triads with marked ductular proliferation, an intense neutrophilic and lymphocytic inflammatory reaction, marked bile stasis and many periportal acidophilic bodies. Post-mortem examination of the liver in a personally studied fatal case revealed extensive loss of parenchyma, marked pleomorphism of the remaining hepatocytes, gross distortion of the parenchymal plate pattern, pseudoduct formation and marked bile stasis.

Experiments in animals confirm that 6-MP is an hepatotoxin.¹³⁷ However, the doses required to produce hepatic lesions in the rat and the dog are considerably higher on a weight basis than those in man.

Methotrexate (Amethopterin). Methotrexate, an antagonist of folic acid metabolism widely used in the treatment of leukemia, lymphoma, ocular inflammatory disease and psoriasis, frequently produces biochemical evidence of hepatic injury,³¹⁶ and occasionally gives rise to overt clinical signs of liver disease.^{145, 345, 738, 741} The functional abnormalities, the severity of which appears to be dose related, are reversible if detected early.³¹⁶ However, drug treatment, if continued, may give rise to progressive hepatic injury leading to the development of cirrhosis.^{145, 738, 741} Formerly the hepatic fibrosis seen under such conditions was attributed to resolution of leukemic infiltrates in the portal triads with secondary collapse.¹⁴⁵ However, this is unlikely since similar lesions have been reported in a patient with psoriasis who had received methotrexate in-

termittently over a 2 year period.⁵⁴⁵ Children given the drug for acute leukemia appear to be more susceptible to severe hepatic injury than adults.

In a series of 10 patients with acute leukemia receiving intermittent intensive treatment with methotrexate, increased serum transaminase and Bromsulphalein retention were observed in 9, and hyperbilirubinemia in 2, functional abnormalities that were maximal following completion of each 5-day course of treatment, and tended to regress during drug-free periods.³¹⁶ There were no accompanying signs or symptoms of hepatic injury, but liver biopsy revealed infiltration of the portal and periportal zones with neutrophils and mononuclear cells, occasional binucleate hepatocytes, and, less commonly, bile stasis, fatty infiltration and portal fibrosis. Similar but less severe functional and histologic abnormalities were encountered in 8 of 12 patients with ocular inflammatory disease treated less intensively with methotrexate every 4th day for 6 weeks.³¹⁶

Of 7 children with acute leukemia treated with methotrexate by Colsky and associates,¹⁴⁵ all 5 who had a satisfactory remission and remained under treatment for 6 to 14 months developed hepatomegaly and ascites; at postmortem examination portal fibrosis was extensive, and in 3 instances it had progressed to cirrhosis. Jaundice was not a prominent feature, but hyperbilirubinemia was present in all cases.

In another group of 32 children given methotrexate for acute leukemia, 7 developed anorexia, vomiting, hepatosplenomegaly, ascites and edema after 3 to 10 months of treatment.⁷³⁸ Jaundice was observed in only one. Liver biopsy in 4 of the children revealed swelling and pleomorphism of the parenchymal cells, evidence of regeneration activity, acidophilic necrosis of some cells, and portal fibrosis with ductular proliferation and round cell infiltration. When cyclophosphamide was substituted for methotrexate, fluid retention and hepatosplenomegaly regressed.

ALKYLATING AGENTS

Chlorambucil (Leukeran). Evidence suggests that chlorambucil, a derivative of nitrogen mustard, is hepatotoxic in man. In

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ear period.⁵⁴⁵ Children with leukemia appear to have severe hepatic

lesions with acute leukemic intensive treatment, increased serum albumin retention, hyperbilirubinemia, and leukocytosis that were reversed after cessation of each 5-day treatment. There were no symptoms of hepatic disease revealed by infiltration of the liver with neutrophils, occasional eosinophils, and less commonly, lymphocytes and portal fibrosis. These changes were encountered in the inflammatory reaction to methotrexate.

Children with leukemia treated with methotrexate and associated with portal hypertension in some instances is. Jaundice was not hyperbilirubinemic.

In children given methotrexate, 7 developed hepatosplenomegaly 3 to 10 months after treatment. In 1 of the children, the morphism of the liver was regenerative necrosis of some type with ductular proliferation. When substituted for methotrexate and hepato-

one series of patients with chronic lymphatic leukemia and lymphoma, 6 exhibited jaundice after having received 6 to 15 mg. of the drug daily for periods of 18 to 75 days.¹⁷ At postmortem examination, the livers in this group showed varying degrees of hepatocellular necrosis, degenerative changes, bile stasis and portal fibrosis. In 2, the picture was that of postnecrotic cirrhosis.

Rarely, chlorambucil serves as a sensitizing agent and gives rise to an allergic type of hepatitis. In one such case, a young man with chronic lymphatic leukemia, a morbilliform rash appeared on the 15th day of treatment, and was followed by nausea, vomiting, abdominal pain and jaundice which lasted for 3 weeks.³⁹² When chlorambucil therapy was resumed 2 months later, the rash, abdominal pain and hepatomegaly recurred promptly, and subsided when the drug was withdrawn.

Nitrogen Mustard (Mechlorethamine). In the cat, nitrogen mustard produces focal areas of hepatic necrosis, but in most other animals the liver is not affected.²⁷⁶ There is some uncertainty regarding the possible hepatotoxic effects of the drug in man. In one study, 3 of 50 patients with Hodgkin's disease treated with nitrogen mustard showed miliary foci of hepatic necrosis at autopsy, and 2 of the 4 cases with jaundice appeared to get worse under treatment—effects that were attributed to drug toxicity.¹⁶⁰ However, in another investigation, tests of hepatic function and needle biopsy of the liver failed to show any evidence of injury that could be ascribed to chemotherapy.⁸⁰⁹ Moreover, the clinical and functional status of the liver appeared to improve in those cases with antecedent hepatic involvement.

Obviously, it is difficult to interpret the histologic and functional changes in a liver that is already the site of lymphomatous infiltration. Although the possibility of a hepatotoxic action cannot be excluded, the benefits to be derived from nitrogen mustard outweigh its possible dangers, so that the presence of hepatic lesions is not a contraindication to therapy.

A recent report of a hypersensitivity reaction to nitrogen mustard leading to appearance of erythema multiforme,⁹⁴ suggests

the possibility that, rarely, the drug gives rise to an allergic type hepatitis.

To date there have been no reports of hepatic injury following the use of *triethylenemelamine* (TEM).

URETHANE (ETHYL CARBAMATE)

Occasionally, patients undergoing prolonged therapy with urethane develop fatal massive hepatic necrosis, manifested clinically with jaundice, ascites and hepatomegaly.^{230, 312, 498, 541} Careful study of urethane toxicity in experimental animals suggests that the hepatocellular changes are secondary to vascular injury, with resultant extravasation of edema fluid and blood between the sinusoids and the parenchymal cells.¹⁸⁰

In one reported case, an elderly woman with suspected multiple myeloma, signs of decompensated cirrhosis appeared after 6 years of continuous daily treatment with urethane.³⁶⁵

FOOD POISONING

AFLATOXIN

A large number of deaths associated with hepatic lesions have been encountered in turkey poult and other farm animals fed peanut (groundnut) meal contaminated with the fungus *Aspergillus flavus*.¹⁸² The agent responsible for the hepatic lesions has been identified as aflatoxin, a product of the fungus. The lesions have been reproduced in a wide variety of experimental animals.^{479, 737} Protein deficiency enhances the hepatotoxic effects of aflatoxin. The hepatic lesions are characterized by focal hepatocellular necrosis, fatty infiltration, striking ductular proliferation and centrilobular endophlebitis. Prolonged administration of aflatoxin may give rise to cirrhosis or hepatoma.

As yet, aflatoxin has not been implicated in human disease, but on the basis of experience with animals, it has been suggested that contamination of food crops by *A. flavus*, and possibly other fungi, plays a role in the pathogenesis of cirrhosis and hepatoma, particularly in malnourished populations.¹⁸²

COMMENTS

1. Evidence suggestive of a toxic effect of nitrogen mustard in man. In

BOOK REVIEW

EPPING JAUNDICE

Occasionally, foodstuffs are contaminated during handling and shipment. A good example is the epidemic of jaundice reported from Epping, England, which was traced to the ingestion of bread baked with flour contaminated with 4,4'-diaminodiphenylmethane, an aromatic amine used as a hardener for epoxy resin.³⁹⁵ The flour had been contaminated during shipment in a van carrying a broken container of the amine.

In most of the 84 patients involved, the onset was sudden with intermittent, severe abdominal pain that resembled biliary colic. This was followed 2 or 3 days later by rigors and an obstructive-like jaundice, pruritus and hepatomegaly. Usually, jaundice cleared in 4 to 6 weeks; in several patients, it persisted for 3 or 4 months. The biochemical changes were variable, suggesting biliary obstruction in some, and hepatocellular disease in others. Moderate eosinophilia was present in half the cases, but the total leukocyte count remained normal.

The principal histologic features in the liver were portal inflammation with numerous eosinophils, cholangitis, cholestasis and minimal hepatocellular necrosis. In more prolonged jaundice, the picture resembled that of viral hepatitis. Minimal portal scarring was observed following recovery.

There were no deaths in the group.

MUSHROOM POISONING (MYCETISMUS)

Some 70 or 80 species of mushrooms are known to be toxic for man, but only one, *Amanita phalloides*, affects the liver. The others produce gastroenteritis, muscarinic effects, acute hemolysis and disorders of the central nervous system. The unusual toxicity of *A. phalloides* is attested by the 50 per cent mortality rate which follows its ingestion.²³⁷

Types of Toxin. Two types of toxin isolated from *A. phalloides* are: phallin, a thermolabile glucoside with hemolytic properties, and amanitotoxin, a thermostable agent which characteristically produces fatty degeneration and necrosis of the liver, kidneys and myocardium.²³⁶

Since phallin is destroyed readily by cooking and during ingestion, it probably plays

little role in human poisoning, although its effects can be easily demonstrated in animals when administered by the parenteral route.²³⁶ There is general agreement, therefore, that all of the manifestations of *A. phalloides* poisoning are due to amanitotoxin, which has been identified as a mixture of cyclic polypeptides.⁷⁸⁸

Phallin and amanitotoxin are antigenic and can produce specific antibodies in animals.²³⁶ However, the antigenicity of amanitotoxin is weak, so that it has not been possible to develop a potent antiserum for use in treatment.

Pathologic Changes. The principal pathologic changes in fatal cases are found in the liver, kidneys and central nervous system.^{190, 758} As a rule, the liver is small and exhibits massive hepatocellular necrosis, intralobular hemorrhage and an acute inflammatory exudate. The parenchymal cells are heavily infiltrated with fat droplets and do not undergo the type of rapid autolysis seen in many other forms of massive hepatic necrosis.

The kidneys show varying degrees of swelling, degeneration and fatty infiltration of the tubular epithelium and congestion of the glomeruli.

The principal findings in the central nervous system include widespread toxic swelling of the cerebral ganglion cells, scattered small punctate hemorrhages and perivascular lymphocytic exudates.

Not infrequently, the myocardium also shows fatty infiltration and degeneration.

Symptoms. Characteristically, the onset of symptoms following the ingestion of *A. phalloides* is delayed for 6 to 15 hours. In contrast, most other poisonous mushrooms produce symptoms within the first few hours. Nausea, vomiting, severe abdominal cramps and diarrhea appear in rapid succession and usually are followed within 24 hours by severe prostration, signs of dehydration and vasomotor collapse. In severe cases, coma supervenes, and death ensues in 3 to 8 days. Usually jaundice appears on the 3rd day⁷⁵⁸ but may be absent, even in individuals who survive for several days and then succumb to severe hepatic necrosis.¹⁹⁰

Enlargement and tenderness of the liver

and splenomegaly. Signs of renal failure. Early in the course, bUN, creatinine, oliguria and anuria are common. The central nervous system, postmortem, experiments show that coma is a fatal rhagic phenomenon common to all cases but does not

Prognosis. Patients with severe liver injury may not survive. It is difficult to predict the outcome. Nevertheless, azotemia and fever involve a poor prognosis. In some cases, recovery is complete, in some, it is partial. Few long-term survivors have been reported. The recovery is usually complete. It has been reported that in some cases, the recovery is complete. It has been reported that in some cases, the recovery is complete. It has been reported that in some cases, the recovery is complete.

Therapy. The treatment for mushroom poisoning is supportive. The importance of early diagnosis and initial critical care is emphasized. Vasomotor collapse and development of shock are common. These include hypotension and electrolyte imbalances. Blood and tissue levels of the toxin are not usually administered. Caloric requirements are high. Glycemia is usually normal. Gastric lavage is the mainstay of treatment. Procedures are not usually necessary. If there is a suspicion of poisoning, the patient should be treated. Phylloxylation is not recommended.

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and splenomegaly are inconstant findings. Signs of renal injury are always present. Early in the course, the urine contains albumin, casts and red blood cells; later, oliguria and azotemia supervene. Clonic spasms and convulsions may develop terminally. These are generally attributed to the central nervous system lesions found postmortem,¹⁹⁰ but evidence based on dog experiments suggests that severe hypoglycemia is a factor in some instances. Hemorrhagic phenomena and anemia are far less common than hepatorenal and neural symptoms but do occur occasionally.

Prognosis. Even the most gravely ill patients with signs of severe hepatic and renal injury may recover,⁷⁵⁸ so that it is difficult to predict the outcome in any given case. Nevertheless, vasomotor collapse, increasing azotemia and signs of central nervous system involvement usually denote an unfavorable prognosis. The recovery period is variable, in some instances being as short as 10 days, and in others as long as 6 weeks.⁷⁵⁸ Few long-term follow-up studies have been carried out, so that it is not known whether the recovery from hepatic injury is usually complete. However, hepatic fibrosis has been reported as a sequela in several instances,³²² so that residual damage may occur more frequently than is generally recognized.

Therapy. Although there is no specific treatment for *A. phalloides* poisoning, general supportive measures are of the greatest importance in tiding the patient over the initial critical period of dehydration and vasomotor collapse, and the subsequent development of hepatic and renal failure. These include careful regulation of fluid and electrolyte balance, transfusion of whole blood, and the provision of sufficient parenterally administered glucose to meet the caloric requirements and to prevent hypoglycemia. Gastric lavage and saline purges rid the gastrointestinal tract of possible remaining traces of mushroom; however, these procedures are of doubtful value, since usually there is a long interval between the ingestion of mushrooms and the onset of symptoms. However, they may be of value prophylactically in individuals who have

partaken of a bad lot of mushrooms, but are not yet ill.

HORMONAL AND METABOLIC AGENTS

ANDROGENS AND RELATED ANABOLIC AGENTS

Methyltestosterone, norethandrolone and a number of other C-17 alpha alkyl substituted steroids occasionally produce an unusual form of cholestatic jaundice. Characteristically, there are no accompanying clinical signs of hypersensitivity or histologic evidence of an inflammatory reaction in the liver, features usually seen in most other forms of drug-induced cholestatic hepatitis. Since Bromsulphalein retention can be demonstrated in a high proportion of individuals given large doses, it is generally believed that agents of this type interfere with the excretion of bile, probably as the result of a direct toxic action. Norethandrolone produces these effects more readily than any other steroid in this group.⁴⁸⁹ Neither testosterone and its esters, such as the phenylpropionate,³¹³ nor the closely related compound, norandrolone,⁷⁹⁹ exhibit any adverse effect on the liver.

Most of the substituted derivatives of testosterone stimulate the synthesis of creatine and increase the urinary excretion of creatinine.⁴⁸⁹ Although this effect parallels Bromsulphalein retention, the correlation in individual cases is not close. Neither the mechanism of increased creatine synthesis nor its relationship to altered hepatic function is known.

Methyltestosterone. Considering the frequency with which methyltestosterone is prescribed and the small number of cases of cholestatic jaundice reported,^{97, 238, 781} it is evident that the incidence of this complication is relatively low. However, when used as an antipruritic agent in obstructive jaundice, it invariably raises the level of serum bilirubin.⁴⁴⁹ Daily doses of 30 to 100 mg. for periods of 1 to 5 weeks produce significant Bromsulphalein retention without other signs of hepatic dysfunction in a high proportion of normal subjects and patients without evidence of antecedent liver disease.^{313, 489} Much of the Bromsulphalein re-

tained in the serum is in the conjugated form.¹²¹ This has been interpreted as evidence that methyltestosterone interferes with the excretion but not with the conjugation of the dye. However, studies of Bromsulphalein clearance in individuals receiving norethandrolone show that the uptake of dye by the liver also is impaired, so that the effects of steroids of this type may not be limited to impairment of dye transport out of the hepatic cells.⁴¹⁹

In patients who develop jaundice, the liver shows marked centrilobular bile stasis with little or no evidence of parenchymal damage or inflammatory reaction. In one reported case with prolonged jaundice, biopsy of the liver showed simple cholestasis at the end of 3 weeks, and signs of early biliary cirrhosis, confirmed by gross inspection of the liver, at 11 weeks.¹⁵

* Usually, symptoms appear between the 2nd and 5th months of medication but may be seen as early as the 8th day. The onset is characterized by malaise, nausea and other gastrointestinal disturbances. Jaundice follows within a few days to 4 weeks and is accompanied by dark urine, acholic stools and hepatomegaly. Splenomegaly and pruritus are seen in some cases. Usually, the serum alkaline phosphatase level is significantly elevated, but this is an inconstant finding. In contrast, the serum cholesterol level, the cephalin-cholesterol flocculation reaction and thymol turbidity tend to remain within normal limits.

Often, the jaundice is intense, but usually complete recovery ensues within 3 months. One fatality has been reported.³⁹⁹ In this case, jaundice appeared after 7 weeks of methyltestosterone therapy at a dose level of 30 mg. daily. The jaundice persisted and was complicated by progressive dehydration and metabolic acidosis which resulted in death at the end of 2 months. Postmortem examination revealed centrilobular hepatocellular degeneration with marked bile stasis.

Norethandrolone (17 α -ethyl-19-nortestosterone, Nilevar). The effects of norethandrolone on the liver are essentially the same as those produced by methyltestosterone but tend to be more intense. In a high proportion of individuals receiving this drug

in daily doses of 25 to 60 mg., impairment of Bromsulphalein excretion can be demonstrated in 1 to 3 weeks, depending on the dose.^{398, 649} Less commonly, there may be an increase in serum alkaline phosphatase³⁹⁸ and glutamic oxalacetic transaminase.⁶⁴⁹

Much of the Bromsulphalein retained in the serum is conjugated,¹²⁰ which has been cited as evidence in support of the concept that norethandrolone interferes with the excretion rather than with the conjugation of the dye.⁴⁸⁹ In the rat, a similar defect in bilirubin excretion can be demonstrated.²³

Since electromicroscopic studies of the liver in both man and the rat have shown that norethandrolone regularly produces dilatation of the canaliculi and effacement of their microvilli without any concomitant change in the appearance of the cytoplasm, it has been proposed that these anatomic alterations are responsible for the cholestasis and the impairment of Bromsulphalein excretion induced by this drug.⁶⁵⁰ However, clearance studies in man⁴¹⁹ indicate that norethandrolone interferes with both the excretion and uptake of Bromsulphalein by the liver. This suggests that the action of the drug is not limited to the canalicular membranes. The resulting functional derangement is selective and does not affect indocyanine-green clearance.⁴¹⁹

Only a few instances of overt cholestatic jaundice have been reported,^{194, 274, 649} but from the relatively high incidence observed in some series,^{194, 649} one may anticipate that many more cases will be encountered as norethandrolone is used more widely, and that they will be seen more frequently than in the case of methyltestosterone therapy. The interval between the onset of norethandrolone administration and the appearance of jaundice is unpredictable and may range from 2 weeks⁶⁴⁹ to 10 months.²⁷⁴ Usually, the jaundice is accompanied by an increase in serum alkaline phosphatase,^{194, 274, 649} and not infrequently there is a rise in the serum glutamic oxalacetic transaminase level⁶⁴⁹ and a positive cephalin-cholesterol flocculation reaction.^{274, 649} In some cases, the jaundice is intense and resolves relatively slowly.^{194, 649} Histologically, the liver shows centrilobular bile stasis with bile thrombi in the canaliculi, bile staining

of the Kupfer cells, and degeneration of the hepatocytes. Similar changes are also accompanied by portal triaditis and nuclear degeneration of the hepatocytes. In some cases, there is also evidence of icteric induration.³⁹⁸

At least one case has been reported. Both the clinical picture and the histologic picture following norethandrolone therapy are marked by cholestatic changes and hepatocellular damage. Because of the evidence of necrosis in some cases, complicating viral hepatitis was suggested, but this was not convincing.

Other Substances. Methyltestosterone. Bromsulphalein clearance studies in man⁴¹⁹ observed for methyltestosterone, methandrostenolone, methyldienolone, oxymesterone, methyltestosterone, progestational agents, ethinyl-19-nortestosterone, norethynodrel, (10)estren-3-one, methandrostenolone, the serum level of alkaline phosphatase.⁴⁸⁹ (C) the problem of the observation and synthetic glucuronide liver.³⁴²

Cholestatic jaundice after methyltestosterone has been reported in some cases.⁷⁵² and methyl-19-nortestosterone.

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impairment in bile secretion can be demonstrated depending on the dose, there may be a decrease in alkaline phosphatase³⁹⁸ and serum aminase.⁶⁴⁹ Bromsulphalein retained in the liver⁶⁵⁰ which has been part of the concept of cholestasis interferes with the excretion of bile following conjugation of similar defect in bile secretion has been demonstrated.²³ In studies of the rat have shown that bromsulphalein regularly produces bile and effacement of any concomitant of the cytoplasm, at these anatomic level for the cholestasis of Bromsulphalein drug.⁶⁵⁰ However, studies indicate that as with both the bromsulphalein by that the action of the drug is due to the canalicular obstruction of bile secretion does not affect bile secretion.⁴¹⁹ In overt cholestasis reported,^{194, 274, 649} but incidence observed may anticipate will be encountered used more widely, in more frequently methyltestosterone therapy in the onset of norethindrone and the unpredictable and⁶⁴⁹ to 10 months.²⁷⁴ accompanied by an alkaline phosphatase,¹⁹⁴ notably there is a rise in alkaline phosphatase and cephalin-cholesterol.^{274, 649} In some intense and resolves. Histologically, the bile stasis with dilated bile ducts, bile staining

of the Kupffer cells and secondary feathery degeneration of the parenchymal cells.⁶⁴⁹ Similar changes of lesser degree, occasionally accompanied by lymphocytosis of the portal triads, focal hepatocellular necrosis and nuclear changes indicative of regenerative activity, have been encountered in non-icteric individuals receiving norethandrolone.³⁹⁸

At least two fatalities have been reported. Both patients died of hepatic failure following a prolonged course of norethandrolone and at autopsy exhibited marked cholestasis, varying degrees of hepatocellular necrosis and peliosis hepatis. Because of the extensive character of the necrosis in one case, it was assumed that a complicating infection with the hepatitis virus was involved, but the evidence presented in support of this interpretation is not convincing.

Other Substituted Derivatives of Testosterone. Bromsulphalein retention has been observed following the administration of *methandrostenolone* (17 α -methyltestosterone, methandienone, Dianabol),⁷⁸⁹ *fluoxymesterone* (9 α -fluoro-11 β -hydroxy-17 α -methyltestosterone, Halotestin)³⁸⁹ and the progestational agents, *norethindrone* (17 α -ethynyl-19-nortestosterone, Norlutin), and *norethynodrel* (17 α -ethynyl-17 β -hydroxy-5(10)-estren-3-one norethisterone).⁵⁵³ In addition, methandrostenolone frequently raises the serum level of glutamic oxalacetic transaminase.⁴⁵⁹ Of interest in connection with the problem of jaundice in the newborn is the observation that most of the natural and synthetic progestational steroids inhibit glucuronide transferase activity in the liver.³⁴²

Cholestatic jaundice resembling that seen after methyltestosterone therapy has been reported in patients receiving *norethindrone*⁷⁵² and *methylestrenolone* (17 α -methyl-19-nortestosterone).⁵⁶³

ANTITHYROID DRUGS

Methimazole (1-methyl-2-mercaptoimidazole, Tapazole) produces rash and urticaria in approximately 5 per cent of patients,⁴³ and for that reason is thought to be a sensitizing agent. Less commonly, it gives

rise to agranulocytosis and cholestatic hepatitis^{628, 631} or cholestatic hepatitis alone.⁴⁹¹

Propylthiouracil. Rare instances of fatal generalized periarteritis with secondary involvement of the liver⁴⁸³ and transient hepatocellular jaundice in association with fever and neutropenia⁴⁴⁶ have been reported. Presumably, such reactions are due to hypersensitivity.

Thiouracil. Fever, rash, arthralgia, lymphadenopathy, agranulocytosis and swelling of the salivary glands—features suggestive of sensitization—have been observed in patients receiving thiouracil.^{248, 253, 336, 557} Less commonly, this drug produces hepatitis.^{253, 336, 557} The latter may be of the cholestatic type,²⁵³ but in at least one case which proved to be fatal the liver was greatly reduced in size and showed focal and central hepatocellular necrosis and bile stasis.³³⁶

Thiourea produces fever, rash, leukopenia and other manifestations of drug sensitization more frequently than does thiouracil.⁵⁵⁷ Rarely, it gives rise to periarteritis nodosa. In one such case, the manifestations of generalized vascular disease were accompanied by deep jaundice, which at autopsy appeared to be related to intrahepatic arteritis.²⁸⁰

CORTICOSTEROIDS

In experimental animals, large doses of cortisone produce scattered foci of hepatocellular necrosis, and enhance the hepatotoxic effects of carbon tetrachloride.⁷⁴³ In addition, they give rise to fatty infiltration of the liver, an effect attributable to increased mobilization of fatty acids from adipose tissue depots.³²⁰

Fatty infiltration of the liver has been observed following the administration of therapeutic doses of cortisone in man.⁷¹⁴ In a child given large doses of prednisone and hydrocortisone for 11 weeks, marked fatty infiltration of the liver was associated with massive fat embolism which resulted in sudden death.³¹⁹

DINITROPHENOL

Occasionally, small doses of dinitrophenol produce an acute cholestatic hepatitis.⁶⁸⁵ Although it has not been possible to demonstrate skin sensitivity or the presence of

circulatory antibodies in such cases,⁴⁹³ it is highly probable that the hepatitis is due to drug hypersensitivity. The reasons for believing so include the following: (1) hepatitis may be associated with an urticarial rash,⁶⁸⁵ (2) the clinical and laboratory features closely resemble those seen in the hypersensitivity type of arsenical hepatitis,⁶⁸⁵ (3) even fatal doses of dinitrophenol do not produce significant alterations in the liver, either in experimental animals⁷³⁹ or in man,^{576, 740} and (4) other common manifestations of drug hypersensitivity, including angioneurotic edema, neutropenia, renal injury and arthritis, have been reported.^{20, 459}

Large doses of dinitrophenol often stain the tissues yellow, due to the color of the drug itself. This must be distinguished from true icterus.

ESTROGENIC AND PROGESTATIONAL AGENTS

Natural Estrogens. Both estradiol and its metabolite estriol, when given in relatively large doses, produce abnormal Bromsulphalein retention, an effect attributable primarily to a defect in the transport of dye out of the hepatic cell.⁵²⁴ In addition, estradiol raises the serum level of alkaline phosphatase, but has no effect on serum bilirubin or other parameters of hepatic function, and does not alter the microscopic appearance of the liver.⁵²⁵

It has been suggested that the alterations in hepatic function that occur late in pregnancy are related to the accompanying marked increase in estrogen production.

Natural Progestins. In contrast to the natural estrogens, neither progesterone nor its metabolite pregnanediol impairs hepatic function, as judged by Bromsulphalein clearance in the rat.²⁵¹

Synthetic Estrogens, Progestins and Oral Contraceptives. As in the case of the synthetic androgens, a wide variety of synthetic estrogens and progestins impair the hepatic excretion of Bromsulphalein, possibly by interfering with the uptake and transport of the dye in the liver.²⁵¹ If given in sufficiently large doses, they may produce other biochemical and histologic evidence of hepatic injury and cholestasis.⁷²³ The 17-alpha alkyl 19-nor-steroids interfere most

with bile secretion,⁶⁴⁶ but other steroids in this group also affect the liver.

In animals, massive doses of stilbestrol (diethylstilbestrol), a nonsteroidal synthetic estrogen, produce hepatic necrosis,⁴⁹⁵ whereas small doses impair Bromsulphalein excretion,²⁵¹ as in the case of the steroidal estrogens. However, there is no evidence that the therapeutic doses used in man are hepatotoxic.^{247, 458, 495}

Most oral contraceptives contain a mixture of a synthetic progestin and a synthetic estrogen, usually in a ratio of approximately 10:1 or greater. Not infrequently, both components are C-17 alpha alkyl substituted 19-nor-steroids. The agents most commonly employed include the progestins, *norethindrone* (norethisterone, 17-alpha-ethinyl-19-nortestosterone, Norlutin), *norethynodrel* (17-alpha-ethinyl-5[10]-estraenolone), *ethynodiol diacetate* (17-alpha-ethinyl-4-estraenediol diacetate), or *lynestrenol* (ethinylestranol; 17-beta-hydroxy-17-alpha-ethinyl-estr-4-ene) in doses of 1 to 10 mg. and the estrogens, *ethinyl estradiol* or its 3-methyl ether, *mestranol*, in doses of 0.05 to 0.15 mg.

As might be anticipated from the behavior of their constituents in animals, oral contraceptives give rise to alterations in hepatic function in a significant number of healthy women, the principal abnormality, mild Bromsulphalein retention, occurring in 20 to 40 per cent of individuals tested.³³⁹ The serum alkaline phosphatase is elevated far less frequently. That the action of the oral contraceptives on the liver is not always limited to inhibition of bile secretion is evident from the fact that occasionally they raise the level of serum transaminase, an effect that suggests hepatocellular injury.⁴⁸ Menopausal women may be more susceptible to this type of reaction, although in most cases reported the dose employed has been larger than that used for contraception.^{205, 723} With large doses, the serum transaminase level rises with regularity, and may be accompanied by hyperbilirubinemia; liver biopsy in such individuals reveals centrilobular necrosis, either with or without cholestasis.⁷²³

Almost 100 cases of jaundice have been reported in women receiving oral contra-

ceptives.^{539, 544} However, considering the widespread use of these agents, the incidence of this complication must be exceedingly low. Genetic or other constitutional factors may be of importance in determining susceptibility to this form of jaundice. This is suggested by the observation that, in approximately 40 per cent of cases, previous pregnancies have been accompanied by manifestations of cholestasis,^{539, 544} a complication of pregnancy that may have a hereditary basis.⁵⁰³ In this connection, it is noteworthy that the largest number of cases of contraceptive-induced jaundice have been reported from Scandinavia^{416, 747} and Chile,⁵⁴⁴ areas where the incidence of the cholestasis of pregnancy also is relatively high.

The initial symptoms of contraceptive-induced cholestasis—malaise, anorexia and nausea—appear after 2 weeks to several months of medication. Jaundice, pruritus, dark urine and pale stools follow within a few days to 2 weeks. These are unaccompanied by fever, rash or adenopathy. In a few cases, the liver enlarges, but the spleen does not. Usually, the serum levels of bilirubin and transaminase are only moderately elevated, but deep jaundice and levels of transaminase in excess of 1,000 units have been reported.^{544, 747} Often, the serum alkaline phosphatase remains normal, but in some cases it rises significantly.⁵⁴⁴ On biopsy, the liver shows centrilobular canalicular and intracellular bile stasis, focal hepatocellular degeneration and necrosis, and a scanty parenchymal and portal inflammatory reaction.^{544, 747} Cessation of contraceptive therapy is followed by gradual recovery over a period of several weeks. Relapses have been reported following resumption of such therapy.⁷⁴⁷

Impairment of hepatic function and jaundice have been reported following the use of most oral contraceptives, including Enovid (norethynodrel 2.5–10 mg. + mestranol 0.075–0.15 mg.), Lyndiol (ethinylestronol 5 mg. + mestranol 0.15 mg.), Anovlar (norethindrone acetate 2.5 mg. + ethinylestradiol 0.05 mg.), Ortho-Novum (norethindrone 2 mg. + mestranol 0.1 mg.)

and Ovulen (ethynodiol diacetate 1 mg. + mestranol 0.1 mg.).

Available evidence suggests that the estrogenic component is responsible for the jaundice produced by oral contraceptives. Thus, following recovery from such jaundice, challenge with mestranol provokes a relapse, whereas administration of such progestational components as norethynodrel or lynestrenol does not.^{5, 756} In contrast to the synthetic estrogens, the natural estrogen estradiol does not induce jaundice in such cases, although it may raise the level of serum transaminase and cause bromsulphalein retention.⁷⁵⁶

The other manifestations of hepatic dysfunction encountered in women receiving oral contraceptives also appear to be due primarily to the synthetic estrogens contained in these agents.^{56, 295} However, at high dose levels, synthetic progestins may be even more injurious to the liver than the estrogens.⁷²³ Also, there is some evidence that the estrogens and progestins in oral contraceptives act synergistically in producing hepatic dysfunction.⁷²³

Since mestranol produces jaundice and other manifestations of hepatic dysfunction much more readily than norethynodrel, at least at the dose levels found in oral contraceptives, though both agents are C-17 alpha alkyl substituted steroids, alkylation at the C-17 position cannot be the only structural determinant of hepatotoxicity in this group of compounds. As further evidence of this, estradiol, a nonalkylated steroid, also impairs hepatic function.^{524, 756} In addition to alkylation at the C-17 position, the presence of a phenolic A ring appears to be a factor in determining the potential of C-18 steroids for blocking Bromsulphalein excretion, and may account for mestranol's unusual activity in this respect.²⁵¹ It has been suggested that hypersensitivity plays a role in the case of synthetic estrogens and progestins that produce signs of hepatocellular injury.⁶⁴⁶ This appears highly improbable, since large doses of lynestranol, particularly when fortified with mestranol, produce such injury with regularity.⁷²³

Although some estrogenic and progesta-

tional steroids inhibit hepatic glucuronyl transferase *in vitro*,³⁴³ there is no evidence that they play a role in the biliary excretory defects induced by oral contraceptives. However, pregnane-3(α),20-(β)-diol, an unusual metabolite of progesterone secreted only rarely in human breast milk, inhibits glucuronyl transferase *in vitro*, and gives rise to severe and prolonged unconjugated hyperbilirubinemia in young infants fed such milk.²⁴

Oral contraceptives appear to enhance the susceptibility to thromboembolic disease,^{499a} and several instances of the Budd-Chiari syndrome have been reported in young women who have used these agents for periods ranging from 2 weeks to 2 years.^{138a, 276a, 635a, 705a, 718a} Usually, the disease has proved fatal, but in one case recovery followed withdrawal of the drug.^{705a}

HYPOLYCEMIC AGENTS

Biguanides. Synthalin (decamethylene-diguanidine), one of the first oral hypoglycemic agents to be used in the treatment of diabetes mellitus, was abandoned soon after its introduction because it produces severe hepatic injury both in animals and in man.³³⁹ Other compounds of this type in current use do not appear to share this property and have not been implicated as etiologic factors in drug hepatitis.⁴⁰¹ These include phenethylformamidylinourea (phenformin, DBI), amylformamidylinourea (DBB) and isoamylformamidylinourea (DBC).

Carbutamide (1-butyl-3-sulfonylurea, BZ-55). Of the several sulfonylureas introduced as hypoglycemic agents in the treatment of diabetes mellitus, carbutamide is the least desirable because of the frequency with which it evokes reactions. These are of the same type produced by the closely related sulfonamides, and include fever, rash, agranulocytosis, hemolytic anemia and hepatitis, manifestations suggestive of drug sensitization.³⁶⁰

Several fatalities have been reported, death being due to acute myocarditis,²²⁵ hepatitis,¹¹³ exfoliative dermatitis³⁵⁰ and bone marrow depression.³⁶⁰ The most striking finding in these cases has been the presence of foci of necrosis with miliary

granulomata scattered through the viscera, of the type seen in patients with sulfonamide reactions.²⁴³ In one of these cases, the biochemical findings were those of cholestatic hepatitis, but hepatic failure ensued, and autopsy revealed a diffuse hepatitis with numerous areas of hepatocellular necrosis and bile stasis.¹¹³ Similar but less extensive changes have been observed in nonfatal cases.¹¹³

Chlorpropamide (1-propyl-3-([p-chlorobenzenesulfonyl])urea, Diabinese). One of the chief drawbacks to the use of chlorpropamide as a hypoglycemic agent is the frequency with which it produces cholestatic hepatitis.^{100, 292, 297, 603} The incidence of this complication has been estimated to be approximately 0.5 per cent.⁶⁰³ However, in some series, transient but significant elevations of the serum alkaline phosphatase level have been observed in as many as 25 per cent of patients under treatment with this drug.⁷⁵⁵

Usually, after 2 to 6 weeks of chlorpropamide therapy, the hepatitis is ushered in with anorexia, nausea and vomiting. Soon thereafter dark urine, jaundice and clay-colored stools appear. Fever, rash, pruritus, eosinophilia and hepatomegaly are common but inconstant findings. Although the regular occurrence of hyperbilirubinemia with high serum levels of alkaline phosphatase and cholesterol indicates a cholestatic form of jaundice, it is evident from the rise in SCOT⁶⁰³ and the positive cephalin-cholesterol flocculation reactions^{292, 603} seen in some cases that the cholestasis may be accompanied by significant hepatocellular injury, as in many other forms of cholestatic hepatitis. Histologic studies of the liver bear this out. Characteristically, there is centrilobular bile stasis with bile-staining of the hepatic and Kupffer cells, plus an inflammatory reaction in the portal triads with polymorphonuclear leukocytes, eosinophils and monocytes.^{199, 292, 297, 603} However, not infrequently the parenchyma shows feathery degeneration,⁶⁰³ small foci and necrosis⁶⁰³ and evidence of increased hepatocellular regenerative activity.²⁹⁷

Full recovery is to be anticipated in 1 to 3 months.

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in patients given the drug, the frequency with which the jaundice is accompanied by fever and eosinophilia, and the failure of the drug to produce hepatic lesions in animals^{387, 636} suggest that chlorpropamide is a sensitizing agent rather than a hepatotoxin. In some instances, readministration of the drug following recovery from an attack of chlorpropamide-induced hepatitis does not provoke a relapse.²⁹² This does not necessarily exclude a sensitization mechanism but may be indicative of spontaneous desensitization.

Of practical importance is the fact that diabetics who recover from chlorpropamide jaundice do not relapse when given tolbutamide.^{297, 603}

Metahexamide (N-[3-amino-4-methylbenzenesulfonyl]-N¹-cyclohexylurea, Euglycin), another of the sulfonureas, produces jaundice in approximately 1 per cent of patients,⁷⁵⁵ and at least 2 fatalities from progressive hepatic failure have been reported.³⁴⁰

The clinical features of the hepatitis are of the hepatocellular type in some cases^{175, 340, 755} and of the cholestatic type in others.^{179, 300} Histologically, the liver shows foci of hepatocellular necrosis, predominantly centrilobular in distribution, and, in some instances, an inflammatory reaction in the portal triads and evidence of bile stasis.^{179, 300, 340} This combination of hepatocellular injury and cholestasis is reflected in the results of laboratory tests which often show, in addition to hyperbilirubinemia, significantly elevated serum levels of transaminase^{300, 475} and alkaline phosphatase^{300, 475, 755} and a strongly positive cephalin-cholesterol flocculation reaction.

In fatal cases, the clinical and pathologic picture is that of subacute hepatic necrosis.³⁴⁰ One apparent recovery from this type of lesion has been reported.³⁴⁰ In another it was responsible for the development of postnecrotic cirrhosis.⁷⁵⁵

It is not clear whether metahexamide injures the liver by a direct toxic action or by the induction of a hypersensitivity reaction. The sporadic occurrence of the hepatitis and the occasional development of fever and rash in patients receiving the drug⁷⁵⁵ are consistent with the latter. However, the fact

that large doses produce hepatic lesions in experimental animals³⁶ suggests that, under some circumstances, metahexamide may behave as a hepatotoxin.

Tolbutamide (1-butyl-3-([p-tolylsulfonyl])-urea, Orinase). Of the sulfonylureas used as hypoglycemic agents tolbutamide appears to evoke drug reactions least frequently.

In an early report on 400,000 patients receiving this agent, no instances of drug-induced hepatitis or alterations in hepatic function are recorded.¹⁷⁹ However, since then, several cases have been encountered.

In one series of 1,500 patients given tolbutamide, 4 instances of liver injury were encountered.⁹¹ One of these, a patient with pre-existent cirrhosis, had a 2-week episode of jaundice following 3 months of drug therapy. In another, death from hepatic failure occurred after 12 months of treatment; postmortem examination revealed mild portal cirrhosis with superimposed acute hepatitis. In the 2 remaining cases, the outstanding features were fever, thrombocytopenic purpura, hepatosplenomegaly, Bromsulphalein retention and elevation of the serum alkaline phosphatase level. These appeared 1 and 6 months, respectively, after treatment was started. Biopsy of the liver in one of the cases revealed fatty infiltration. Recovery followed withdrawal of the drug in one case and administration of hydrocortisone in the other.

Several instances of typical cholestatic hepatitis have been encountered in individuals who have received tolbutamide for periods ranging from 1 to 24 months.^{31, 280} Prompt recovery has followed withdrawal of the drug. In one case, continued administration of tolbutamide for 2 months after jaundice appeared resulted in chronic cholestasis with the development of clinical and functional features and histologic changes in the liver that closely resembled those seen in primary biliary cirrhosis.²⁸⁰ On histologic examination, the liver showed cholestasis, destructive cholangitis and cholangiolitis, and disappearance of the interlobular ducts. Exploratory laparotomy, to exclude biliary obstruction, was followed by massive bleeding from gastric and esophageal microsal ulcerations, hepatic coma and death.

Since tolbutamide occasionally gives rise to allergic reactions, it is possible that the hepatitis it produces also is a manifestation of hypersensitivity. However, in none of the cases reported has the hepatitis been accompanied by fever, rash or eosinophilia.

METABOLIC DISTURBANCES

HYPERTHERMIA

Sustained elevation of the body temperature at a high level often produces severe liver damage. Approximately 20 per cent of individuals subjected to an artificially induced fever of 41.5° C. (106.7° F.) for 7 hours develop clinical jaundice,⁴⁶⁶ and an even higher proportion exhibit an increase in serum bilirubin.⁷⁷¹ Similar evidence of hepatic damage is seen also in association with the hyperpyrexia of heatstroke^{313, 798} and other febrile diseases.

Hyperpyrexia of sufficient severity and duration may be fatal.^{92, 273, 798} The principal findings at autopsy include hemorrhages into the skin, mucous membranes and serosal surfaces, and severe degenerative changes and necrosis in the liver, kidneys and adrenals.²⁷³ All patients who die later than the 2nd day exhibit jaundice and severe centrilobular hepatic necrosis. Superficially, the lesions resemble those in fulminant viral hepatitis. However, there is little or no inflammatory reaction, and the hepatic cells do not show the characteristic rapid and complete autolysis seen in that disease. Cases that run a more prolonged course may show evidence of hepatocellular and bile duct proliferation. Usually, the changes in the liver are the predominant lesion after the first 48 hours, so that they probably have an important bearing on the fatal outcome. In patients that die sooner, the hepatic parenchyma shows cloudy swelling, hydropic vacuolization and fatty infiltration and may be more seriously injured functionally than is evident histologically. This is suggested by the observation that the serum bilirubin invariably rises within 4 hours of the onset of hyperpyrexia.⁷⁷¹

Pathogenesis of the hepatic injury in hyperpyrexia is not well understood. It is generally believed that anoxia and alterations

in essential enzymatic reactions are the major factors responsible for tissue injury.²⁷³ The importance of anoxia has been disputed on the grounds that continuous oxygen administration does not prevent liver damage.⁴⁶⁶ However, this is not a valid objection, since oxygen therapy does not overcome the anoxemia of hyperpyrexia.⁷⁷¹ Shock and dehydration may be additional factors in some instances but are certainly not the essential ones.

Clinical manifestations of the hepatitis⁴⁶⁶ are difficult to distinguish from those due to the other effects of hyperthermia. Nausea and vomiting occur early and usually are followed on the 2nd or 3rd day by jaundice and hepatomegaly. There is an early increase in the urinary excretion of urobilinogen, and later the urine contains bile. Only occasionally, however, are the stools acholic. In severe cases, there may be central nervous system disturbances, vasomotor collapse and signs of renal failure. Purpuric manifestations have been emphasized, particularly in heatstroke,⁷⁹⁸ although they may occur in other types of hyperpyrexia.²⁷³ These appear to be related to the combined effects of a low prothrombin level, a reduction in platelets and an increase in capillary fragility.⁷⁹⁸ Pleural effusions, ascites and edema are not rare in fatal cases.^{92, 273}

Recovery without residual liver damage occurs in the vast majority of cases. The appearance of shock, anasarca, renal failure and neurologic disturbances are omens of a fatal outcome.

HYPERTHYROIDISM

A high proportion of individuals with hyperthyroidism show evidence of liver damage. In fatal cases, the incidence of significant hepatic lesions may be as high as 90 per cent,⁵⁰ and in those who survive the frequency of functional impairment is equally great. In both instances, the severity of the abnormalities correlates closely with the intensity and duration of the underlying thyroid disease. Nevertheless, it is by no means certain that the changes in the liver are due to the direct effects of the thyroid hormone; indeed, other possible interpretations are held to be more likely.

A variety of hepatic lesions occur in pa-

tients who die of complications.^{50, 118} (1) fatty metamorphosis, usually massive, (2) atrophy, (3) atrophy, (4) atrophy, (5) atrophy, (6) atrophy, (7) atrophy, (8) atrophy, (9) atrophy, (10) atrophy, (11) atrophy, (12) atrophy, (13) atrophy, (14) atrophy, (15) atrophy, (16) atrophy, (17) atrophy, (18) atrophy, (19) atrophy, (20) atrophy, (21) atrophy, (22) atrophy, (23) atrophy, (24) atrophy, (25) atrophy, (26) atrophy, (27) atrophy, (28) atrophy, (29) atrophy, (30) atrophy, (31) atrophy, (32) atrophy, (33) atrophy, (34) atrophy, (35) atrophy, (36) atrophy, (37) atrophy, (38) atrophy, (39) atrophy, (40) atrophy, (41) atrophy, (42) atrophy, (43) atrophy, (44) atrophy, (45) atrophy, (46) atrophy, (47) atrophy, (48) atrophy, (49) atrophy, (50) atrophy, (51) atrophy, (52) atrophy, (53) atrophy, (54) atrophy, (55) atrophy, (56) atrophy, (57) atrophy, (58) atrophy, (59) atrophy, (60) atrophy, (61) atrophy, (62) atrophy, (63) atrophy, (64) atrophy, (65) atrophy, (66) atrophy, (67) atrophy, 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tients who die of thyrotoxicosis and its complications.^{50, 115, 510, 673} These include: (1) fatty metamorphosis, (2) hepatocellular necrosis, usually focal or central, but occasionally massive, as in acute yellow atrophy, (3) atrophy of the parenchyma, as evidenced by a decrease in the weight of the liver, (4) venous congestion and (5) cirrhosis. Except for cirrhosis and atrophy, similar changes are seen in animals given massive doses of thyroid extract or thyroxine.^{257, 310} Nevertheless, some investigators maintain that most of the lesions are non-specific, and that only the cirrhosis can be attributed to the hyperthyroid state.

Weller describes the characteristic lesion as a patchy lymphocytic inflammatory reaction in the portal triads, which is followed by proliferation of connective tissue and the development of cirrhosis.⁷⁷⁹ Moschcowitz, on the other hand, believes that the primary lesion is venous congestion at the periphery of the lobules due to a disturbance in the normal pressure relationships between the branches of the hepatic artery and the portal vein.³¹⁹ Accordingly, the cirrhosis that follows resembles that seen in chronic congestive failure, except that the fibrosis is centered around the interlobular septa instead of the central veins. Few pathologists subscribe to either of these interpretations, and most regard the fibrosis as a consequence of fatty infiltration and necrosis of hepatic cells.¹¹⁵

Almost every test of liver function that has been investigated, including the concentration of serum bilirubin, the excretion of Bromsulphalein and hippuric acid, the tolerance for galactose and levulose, and the prothrombin level, is abnormal in a significant number of individuals with hyperthyroidism.^{295, 470, 478} Similar functional disturbances have been demonstrated in animals with experimentally induced hyperthyroidism.¹⁸⁸ The decrease in galactose and levulose tolerance may be due to alterations in carbohydrate metabolism or absorption, but there is little reason to doubt that the other abnormalities are indicative of liver damage.

The pathogenesis of the hepatic lesions found in hyperthyroidism is a controversial subject. The close relationship between the

severity of the hepatic damage and the intensity and the duration of the hyperthyroidism suggests that excessive amounts of thyroid hormone are hepatotoxic.⁵⁰ However, studies based on liver biopsy material indicate that, in the absence of complications, even severe hyperthyroidism may not produce significant alterations in hepatic structure or function.^{522, 571} This has led some to the conclusion that the lesions found at autopsy are either coincidental or the result of complications.

Although there is little doubt that infection, shock and cardiac failure are responsible for liver damage in many instances, the incidence of these factors in nonfatal cases appears to be too low to account for the frequency with which hepatic involvement can be demonstrated. For that reason many investigators regard liver injury as a manifestation of hyperthyroidism but attribute the deleterious effect of the thyroid hormone to some indirect action. Experimental evidence indicates that hyperthyroidism increases the susceptibility of the liver to injury by anoxia,⁴⁷¹ infection⁶⁶⁸ and toxic agents.⁴⁷² At one time these effects were thought to depend on a fall in liver glycogen.^{139, 303} However, more recent studies indicate that these effects cannot be attributed to changes in hepatic glycogen.⁴⁷²

Another interpretation is that hyperthyroidism induces a relative nutritional deficiency by increasing the demands for certain essential dietary constituents.^{183, 322} Although this might lead to fatty infiltration and cirrhosis, it would not account for the zonal and focal hepatic necrosis seen in hyperthyroidism. No one mechanism accounts satisfactorily for all the types of liver injury encountered in hyperthyroidism.

The clinical significance of these hepatic lesions is difficult to evaluate. Ordinarily, they give rise to no overt signs of liver disease, except for occasional hepatomegaly, but in approximately 20 per cent of fatal cases they produce jaundice.⁵⁰ Therefore, it would seem reasonable to assume that extensive lesions contribute to a fatal outcome. At one time, it was believed that they were responsible for thyrotoxic crises. However, this view has been abandoned for lack of supporting evidence.⁴⁷⁰

PSYCHOPHARMACOLOGIC AGENTS

A wide variety of drugs used as tranquilizers and antidepressants give rise to reactions, some of which affect the liver. The lesions produced may be either cholestatic or hepatocellular in type, depending on the nature of the agent, but in both instances the process appears to be due to drug sensitization rather than to any direct hepatotoxic effect. In dealing with agents of this type, the physician should recognize that, while alterations in chemical structure may reduce the frequency with which certain drugs produce hepatitis, they rarely, if ever eliminate this hazard completely. Accordingly, all newly introduced substituted derivatives of drugs known to provoke reactions involving the liver should be considered suspect, at least until prolonged experience proves them to be innocuous.

PHENOTHIAZINE DERIVATIVES

Cholestatic hepatitis has been reported more frequently after chlorpromazine (Thorazine) than any of the other phenothiazine derivatives used as tranquilizing agents. However, it is difficult to compare the hazards of the drugs in this group, since few of the newer phenothiazine derivatives have been used as extensively as chlorpromazine.

Chlorpromazine (Thorazine) Hydrochloride. Published statistics indicate that the incidence of cholestatic hepatitis in patients given chlorpromazine is 1 to 2 per cent.^{141, 354, 451} However, the findings on serial biopsy of the liver and the results of serial determinations of serum alkaline phosphatase and glutamic oxalacetic transaminase suggest that the incidence of anicteric reactions involving the liver is 20 to 50 per cent.^{176, 676, 785} Since the occurrence of such reactions is not dependent on the dose, and since the hepatic changes are not reproducible in animals,^{579, 695} chlorpromazine cannot be classified as a true hepatotoxin. Schnack has reported that chlorpromazine reduces the biliary excretion of BSP in rats, and interprets this as evidence of hepatotoxicity.⁶⁵⁴ However, others have not confirmed this observation.¹⁹⁸ Moreover, it has been found that, in the rat, chlorpromazine does not inhibit the biliary secretion of indo-

cyanine green or bilirubin,³⁰⁵ reduce the rate of bile flow,⁶⁸³ or raise the pressure within the common hepatic duct.⁶⁸³

Frequently, reactions are accompanied by fever, rash and eosinophilia^{141, 451} and less commonly by agranulocytosis⁴⁵¹ and a positive patch test.⁴³⁴ Taken together with the fact that the drug can produce contact dermatitis,⁴³⁴ these features strongly suggest that chlorpromazine is a sensitizing agent. However, as in many other drug reactions, attempts to demonstrate circulating antibody to chlorpromazine,⁸³ or to establish the presence of other immunologic abnormalities⁴³¹ have met with failure.

According to some reports antecedent liver disease predisposes to the development of cholestatic hepatitis.³⁷³ However, this has not been borne out in other studies.¹⁷⁸ As in the case of many other drug reactions, females appear to be more susceptible than males.

Usually, chlorpromazine jaundice appears between the 2nd and 4th week of therapy. Although it is uncommon in patients who have received the drug for less than a week, it has been reported following 1 day of therapy⁷⁹⁴ and even after a single dose.⁷³⁵ In such cases, and occasionally in others,^{207, 354} the onset of jaundice may be delayed for as long as 2 weeks following withdrawal of the drug. Only rarely are reactions of this type seen after the 5th week of drug administration.³⁷³ In patients who have recovered from chlorpromazine-induced hepatitis, re-administration of the drug produces a prompt relapse in some^{44, 407, 506} but not in others.^{44, 407} Moreover, recovery from chlorpromazine hepatitis may ensue despite continued administration of the drug,^{655, 689} a course of events generally attributed to spontaneous desensitization.

In most cases, the onset of chlorpromazine hepatitis is abrupt with fever and mild constitutional symptoms, which are followed in 1 to 4 days by jaundice, dark urine and clay-colored stools.^{354, 373, 451, 782} Occasionally, the fever is accompanied by a rash and by chilly sensations or frank shaking chills. Pruritus may precede the appearance of jaundice and often is a troublesome late manifestation. Anorexia, nausea, vomiting and abdominal pain are common but sel-

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bi jaundice³⁰⁵ reduce the pressure in the hepatic duct.⁶⁸³

Reactions are accompanied by eosinophilia^{141, 451} and less leukocytosis⁴⁵¹ and a positive skin test together with the reactions can produce contact dermatitis. These features strongly suggest that it is a sensitizing agent. In many other drug reactions, histamine circulating antihistamine, or to establish the immunologic abnormality failure.

Some reports antecedent to the development of jaundice.³⁷³ However, this has not been observed in other studies.¹⁷⁸ As with other drug reactions, the liver is more susceptible than

chlorpromazine jaundice appears within 4th week of therapy. Common in patients who use the drug for less than a week, following 1 day of therapy - single dose.⁷³⁵ In some cases, jaundice in others.^{207, 354} Jaundice may be delayed for 2 weeks following withdrawal of the drug. Reactions of this type within 2 weeks of drug administration in patients who have recovered from chlorpromazine-induced hepatitis, rechallenge with the drug produces a relapse.^{44, 407, 500} but not in others. Recovery from chlorpromazine may ensue despite continuation of the drug.^{655, 689} Jaundice is generally attributed to cholestasis.

Onset of chlorpromazine with fever and mild symptoms, which are followed by jaundice, dark urine, etc.^{354, 373, 451, 782} Occasional cases accompanied by a rash, skin eruptions or frank shaking. The appearance of jaundice is a troublesome late complication, nausea, vomiting are common but self-

limiting. Hepatic enlargement and tenderness are inconstant findings. Rarely, the spleen is enlarged.

Characteristically, the urine contains bile, and the serum shows a sharp rise in the levels of bilirubin, cholesterol, alkaline phosphatase and transaminase. In contrast, the thymol turbidity and cephalin-cholesterol flocculation reactions remain normal. Rarely, the latter are abnormal, and the serum globulins are increased.

The principal histologic findings in the liver are bile stasis with intra-canicular bile thrombi and bile-staining of the parenchymal and Kupffer cells in the centrilobular zones and a portal inflammatory exudate, consisting of polymorphonuclear leukocytes, monocytes and eosinophils.⁷⁸² Although the features of cholestasis have been emphasized, not infrequently the hepatic parenchyma shows scattered foci of necrosis and evidence of increased regenerative activity.

The intensity and duration of jaundice are variable. Often, jaundice is mild and clears without residuals in 2 to 8 weeks. However, a significant number of cases with intense and prolonged jaundice have been reported.^{33, 329, 348, 373, 391, 529, 594, 700} The duration of the disease in these individuals has ranged from 4 months to 5 years. Several have exhibited portal fibrosis histologically,^{348, 373, 529, 594} and have had clinical features suggestive of biliary cirrhosis, such as persistent pruritus and xanthomatosis.^{53, 348, 391, 529, 770} According to Read and associates,³⁹⁴ lesions of this type are reversible and never give rise to full-blown cirrhosis even though histologic abnormalities and raised levels of serum alkaline phosphatase and cholesterol may persist. However, this is not borne out by the course of events in the cases reported by Myers et al.⁵²⁹ and by Walker and Combes.⁷⁷⁰ In Myers' patient, portal hypertension and bleeding from esophageal varices developed 5 years after onset. At laparotomy for portacaval shunt, the liver was found to be cirrhotic.⁵²⁸ A similar case of chlorpromazine-induced biliary cirrhosis of 5-years' duration has been studied by Walker and Combes.⁷⁷⁰ The writer has had the privilege of examining serial biopsy sections of the liver from

both of these patients and can vouch for the development of unequivocal advanced biliary cirrhosis.

Several fatalities have been attributed to chlorpromazine hepatitis.^{77, 354, 626} However, in the 2 cases in which postmortem examination was carried out, unrelated complicating factors could have played an important role in the fatal outcome. The patient described by Boardman had mitral stenosis, severe congestive failure and a terminal purulent pericarditis.⁷⁷ Sections of liver, which the writer has had the privilege of examining, show marked passive congestion and bile stasis. In Rodin and Robertson's case, death occurred on the 40th day of jaundice, following an unexplained episode of shock.⁶²⁶ The liver showed extensive centrilobular parenchymal necrosis with some degree of bile stasis. Whether the necrosis was attributable to the chlorpromazine reaction or to the terminal episode of shock is not evident from the published protocol.

Because of the possible hazards involved, it is unwise to continue chlorpromazine therapy once the signs of a reaction appear or to resume such therapy following recovery from a reaction. Allegedly, cross-sensitization reactions between chlorpromazine and other phenothiazines are rare.³³⁴ However, promazine occasionally produces cholestatic hepatitis in patients previously sensitized to chlorpromazine. Accordingly, once a reaction has occurred, caution should be exercised in substituting one phenothiazine for another.

The effectiveness of cortisone in the management of chlorpromazine-induced hepatitis is in doubt. Favorable results have been reported in some cases^{159, 712} but not in others.⁷⁶⁵

Mepazine (Pacatal). Mild jaundice has been observed in a few patients receiving mepazine.³¹¹ Prompt recovery has followed withdrawal of the drug. Presumably, the underlying lesion in such cases is a cholestatic hepatitis of the type produced by chlorpromazine. However, neither the histopathology nor the clinical features have as yet been reported. Although the incidence of this complication appears to be low, in one series of 76 patients given mepazine,

jaundice developed in 2, an incidence of 5.4 per cent.⁵¹¹

Perphenazine (Trilifon). At least two instances of perphenazine-induced cholestatic hepatitis have been reported. In one, jaundice appeared after 56 days of drug administration, and cleared within 3 weeks.¹⁴⁸ In the other, the latent period was 60 days, and the duration of the hepatitis was longer, but full recovery occurred ultimately.⁶³

Prochlorperazine Maleate (Compazine). Cholestatic hepatitis with clinical and histologic features indistinguishable from those produced by chlorpromazine has been observed in patients receiving prochlorperazine.^{497, 705} In addition, several cases of fatal drug-induced massive hepatic necrosis have been reported,^{148, 467} illustrating the fact that sensitizing agents that produce cholestasis occasionally give rise to serious hepatocellular disease. The hepatitis in one of these cases was accompanied by agranulocytosis and thrombocytopenia.⁴⁶⁷

Promazine Hydrochloride (Sparine). This agent has no adverse effects on the liver in most individuals,³⁹⁷ but, rarely, it may give rise to cholestatic hepatitis. In 2 of the cases reported the patients had previously received chlorpromazine. In one, the latter drug had induced hepatitis,⁷⁶⁴ whereas in the other it had been well tolerated.³⁷⁵ Although cross-sensitization may have been a factor in both cases, there are instances in which promazine has failed to provoke a reaction in patients previously sensitized to chlorpromazine.⁷⁶⁴

Several fatalities have been attributed to promazine-induced agranulocytosis.^{284, 797} In one such case, the agranulocytosis was accompanied by jaundice.⁷⁹⁷ Death occurred on the 4th day, at which time the liver was infiltrated with fat. It is not clear from the published protocol whether the hepatic lesions were attributable to the promazine reaction or were produced by the antibiotics and cortisone used for several days prior to death.

Thioridazine Hydrochloride (Mellaril). At least one case of cholestatic hepatitis and two instances of pruritus accompanied by raised levels of serum transaminase and alkaline phosphatase have been reported in patients receiving thioridazine hydrochloride.

⁸⁰⁶ In two of these individuals there was evidence of an antecedent hepatic reaction to chlorpromazine. In the third patient, the serum transaminase and alkaline phosphatase levels returned to normal despite continued drug administration.

Trifluoperazine Hydrochloride (Stelazine). Although this agent has been administered to over a million patients, only 2 cases of cholestatic hepatitis have been reported.^{29, 390} One had a history of another drug reaction and chlorpromazine had been administered just prior to the use of trifluoperazine.²⁹ Cholestatic jaundice appeared after 3 days of therapy and persisted for more than 6 months. The other patient recovered in 3 weeks.³⁹⁰

The writer has seen a patient with the typical features of early "primary" biliary cirrhosis, in whom the onset with pruritus and jaundice followed several months of intermittent trifluoperazine therapy.³⁸³ Whether or not the drug was responsible for the liver disease in this case is unknown.

MONOAMINE OXIDASE INHIBITORS

A number of monoamine oxidase inhibitors, including iproniazid, isocarboxazid, nialamide, phenelzine and tranylcypromine (Parnate, Parstellazine) are widely used in the treatment of mental depression. All of these agents, with the exception of tranylcypromine, are hydrazine derivatives and produce a severe and often fatal form of hepatitis in a small number of uniquely susceptible individuals. Since tranylcypromine is not a hydrazine derivative and does not affect the liver, it has been suggested that the propensity of the other drugs in this group to produce hepatic injury may be related to their hydrazine content rather than to their capacity to inhibit monoamine oxidase activity. For reasons discussed below, it is highly probable that the hepatic lesions produced are attributable to drug sensitization rather than to a direct hepatotoxic action. In this connection, it is important to note that patients may react to several of the drugs in this group,³³³ so that it is hazardous to substitute one for the other once any of them has produced hepatitis.

Iproniazid (1-isonicotinoyl-2-isopropylhy-

drazine, Marsilid). Induced as a cholestatic hepatitis during treatment of depression, it was abandoned because of its toxicity, which was more toxic than the other drugs. It was effective compared with hydrazine, and was revived because of its potent antidepressive potential for its use in the treatment of depression. The jury fully apprised.

Characteristically, it is a form of hepatitis with morphological features that produced a cholestatic hepatitis. Moreover, it is associated with xanthomas and xanthosiderosis, and rises to massive hepatitis that often results in death.

The reported incidence of patients receiving iproniazid is 1.4 per cent.⁶²¹ The total sales of iproniazid are lower,⁶²⁹ serial increases in serum oxalacetic transaminase number of patients receiving therapy were reported. The incidence of hepatitis is considerably higher.

Since hepatitis is independently of the duration of the drug, and cannot be reproduced in animals,⁶¹ it is considered as an hepatotoxic effect of the hepatitis. It appears after several days to weeks of drug,⁶²⁹ and is associated with a rash,^{309, 308} and a sensitizing reaction with fever and eosinophilia. The reaction is contradictory. Because of the resemblance between induced hepatitis and considered the susceptibility of the patient lights up late in the day. A report of affected individuals hemagglutination and some support

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USE INHIBITORS

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drazine, Marsilid). Iproniazid was intro-
duced as a chemotherapeutic agent in the
treatment of tuberculosis but was soon
abandoned because it proved to be more
toxic than the closely related and equally
effective compound, isoniazid (isonicotinic
acid hydrazide). Some years later its use
was revived when it was found to be a
potent antidepressant. Only then was its
potential for producing serious hepatic in-
jury fully appreciated.

Characteristically, iproniazid gives rise to
a form of hepatitis that both clinically and
morphologically is indistinguishable from
that produced by the hepatitis virus.<sup>577, 578,
629</sup> Moreover, like pyrazinamide, cinchophen
and zoxazolamine, it not infrequently gives
rise to massive or subacute hepatic necro-
sis that often proves fatal.^{240, 577, 578, 629, 677}

The reported incidence of hepatitis in pa-
tients receiving iproniazid is approximately
1.4 per cent.⁶²⁹ Although estimates based on
total sales of the drug are considerably
lower,⁶²⁹ serial studies demonstrating minor
increases in serum bilirubin⁵⁷² and glutamic
oxalacetic transaminase⁵⁵² in a significant
number of patients suggest that if iproniazid
therapy were not controlled carefully, the
incidence of overt hepatitis would be con-
siderably higher.

Since hepatitis appears to occur inde-
pendently of either the dose of iproniazid
or the duration of its administration^{577, 629}
and cannot be reproduced in experimental
animals,⁶¹ it is difficult to classify iproniazid
as an hepatotoxin. The sporadic occurrence
of the hepatitis, the frequency with which
it appears after a latent period of several
days to weeks following withdrawal of the
drug,⁶²⁹ and its occasional association with
a rash^{389, 398} suggest that the drug may be
a sensitizing agent. However, the rarity of
fever and eosinophilia appears to be con-
tradictory. Because of the remarkable re-
semblance between viral- and iproniazid-
induced hepatitis, the possibility has been
considered that the drug either enhances
susceptibility to intercurrent infections or
lights up latent infections with the hepatitis
virus. A report indicating that a third of
affected individuals exhibited a positive
hemagglutination reaction³⁹⁸ appears to lend
some support to this hypothesis. However,

this observation has not been confirmed by
others.³⁸³

If hepatitis is to develop, it does so most
commonly after the 4th week of iproniazid
therapy, but the interval may be as short as
4 days or as long as 6 months.⁶²⁹ In almost
20 per cent of cases, it appears 1 to 4 weeks
after the cessation of drug administration.
The onset may be abrupt, but more often
it is insidious, with anorexia, weakness and
malaise, occasionally accompanied by pru-
ritus. In contrast with viral hepatitis, there
is no fever during the preicteric phase.
Darkening of the urine is noted within a
day or two and is followed by overt jaun-
dice which appears within 3 to 11 days of
the onset.³⁸⁹ The stools become clay-colored
in a high proportion of cases. Jaundice
deepens rapidly, reaching a peak in 2 to 4
weeks and usually is more intense than in
viral hepatitis. Early enlargement and ten-
derness of the liver are common and may
be accompanied by splenomegaly. In fatal
cases, the liver shrinks in size and can sel-
dom be palpated after the 1st week. Con-
comitantly, the jaundice deepens progres-
sively and often is associated with ascites,
gastrointestinal bleeding, fever and termi-
nal hepatic coma. Death may occur as early
as the 2nd week or not until several weeks
later.

In nonfatal cases, the course tends to be
prolonged, often exceeding 3 months. Al-
though no cases of postnecrotic cirrhosis
have been reported, subacute hepatic necro-
sis has been observed in a number of non-
fatal cases.⁵⁷⁷ On the basis of experience
with lesions of this type, it can be predicted
that some patients who apparently have re-
covered from an attack of iproniazid hepa-
titis will ultimately exhibit clinical or
morphologic evidence of postnecrotic cir-
rhosis.

Characteristically, the concentration of
serum bilirubin rises markedly, usually to
levels higher than those seen in most cases
of viral hepatitis. Although serum glutamic
oxalacetic transaminase activity is greatly
increased, levels over 500 units are less com-
mon than in viral hepatitis. A strongly posi-
tive cephalin-cholesterol flocculation reac-
tion and increased thymol turbidity are
common but inconstant findings. Raised

levels of serum alkaline phosphatase are seen more frequently than in viral hepatitis and in many cases reach the heights seen in cholestatic hepatitis. In fatal cases, the serum concentrations of albumin and cholesterol tend to fall, while that of globulin rises. Often prothrombin activity is greatly depressed in such cases.

As noted, the morphology of the liver in Marsilid-induced hepatitis is indistinguishable from that in viral hepatitis, except that subacute and massive hepatic necrosis are more common.

The mortality rate is approximately 20 per cent.⁶²⁹ Attempts to stem the downhill course in patients with massive hepatic necrosis by administering corticosteroids or ACTH have generally met with failure.^{677, 608} However, they appear to have been more successful in less seriously ill patients with subacute hepatic necrosis.^{58, 383} Whether or not cases of this type would have recovered spontaneously is unknown. Moreover, as pointed out, no data are available on the biopsy findings following recovery, so that the question of residual postnecrotic scarring in such patients is unsettled.

Isocarboxazid (Marplan). Although an analogue of iproniazid, this agent produces far fewer undesirable side reactions and thus far has caused only one case of hepatocellular jaundice.⁵⁷ In this instance, symptoms suggestive of an upper respiratory infection appeared 4 weeks after the institution of isocarboxazid administration. The preicteric phase was characterized by pruritus, a distaste for cigarettes and intermittent right flank pain. Although jaundice did not become clinically evident until the 3rd week, dark urine and light stools were noted as early as the 3rd day. The jaundice was moderate and cleared within 3 weeks. Serum bilirubin, alkaline phosphatase and transaminase showed modest increases, while the level of cholesterol was depressed. Thymol turbidity was increased, and the cephalin-cholesterol flocculation reaction was strongly positive.

Phenelzine (Nardil). Severe hepatitis has been encountered in patients given phenelzine for periods of 18 days to 5 months.^{148, 332, 362} As in hepatitis induced by iproniazid, the clinical features and the histologic find-

ings in the liver are indistinguishable from those of severe viral hepatitis. Death from massive hepatic necrosis within 3 weeks has occurred in 5 of 7 reported cases. Repeated exchange transfusions in one case,³⁶² begun 12 hours after onset of coma, failed to relieve the coma or to prevent death.

Pheniprazine (beta-phenylisopropyl-hydrazine, Catron, Cavodil). Several instances of severe hepatitis have been reported in patients receiving pheniprazine for periods of 2 weeks to 7 months.^{52, 63, 277, 333} In all respects, the clinical, laboratory, and morphologic features have resembled those of iproniazid-induced hepatitis. Two of 6 reported cases terminated fatally with massive hepatic necrosis.^{52, 333} One of the patients with nonfatal hepatitis had previously had a mild attack of jaundice while taking iproniazid.³³³ In another, following recovery from pheniprazine-induced hepatitis, administration of the monoamine oxidase inhibitor, nialamide (Niamid), provoked a relapse.³³³

Although the paucity of reports suggests that the incidence of hepatitis is low, in one series of 37 patients given pheniprazine for periods of 8 to 40 weeks, one developed severe hepatitis and 4 others showed a significant rise in SGOT.²⁷⁷

OTHER PSYCHOPHARMACOLOGIC DRUGS

Chlordiazepoxide Hydrochloride (Librium). Typical cholestatic hepatitis has been encountered in at least 2 patients receiving chlordiazepoxide for 5 and 35 days, respectively.^{2, 110} In addition, elevations of SGOT in the absence of jaundice have been observed.³³⁵

Another closely related benzodiazepine derivative, *diazepam* (Valium), has been implicated in at least one nonfatal case of severe hepatic necrosis.¹⁴⁸ However, since the patient involved has also received phenoxypazine, the role played by diazepam is uncertain.

Ectylurea (Nostyn). In the only reported case of hepatic injury induced by ectylurea, both the clinical and the histologic features were those of a mild cholestatic hepatitis.³²⁸ The onset was sudden, with anorexia, nausea and right upper abdominal pain, on the 14th day of therapy. Dark

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urine, pruritus and faint icterus were noted a few days later. There was a modest increase in serum bilirubin and glutamic oxalacetic transaminase and a marked rise in the alkaline phosphatase level. In contrast, the serum cholesterol concentration, thymol turbidity and cephalin-cholesterol flocculation reaction remained normal. All symptoms subsided within 5 days. When a single 300-mg. dose of ectylurea was given on 2 successive days approximately 3 weeks later there was an immediate relapse of jaundice, pruritus and anorexia, which cleared within a week.

Imipramine Hydrochloride (Tofranil). Jaundice is a relatively uncommon complication of imipramine therapy, and usually subsides promptly following withdrawal of the drug.^{19, 151, 327, 422, 484} In the few reported cases in which the clinical features are described, jaundice appeared between the 7th¹⁹ and 110th⁴⁸⁴ days of treatment, and was accompanied by fever^{19, 327} and biochemical changes suggestive of cholestasis.^{19, 327} The one available biopsy specimen of the liver is said to have shown slight, nonspecific inflammation in the parenchyma.¹⁹ In one series of 85 patients receiving imipramine, 19 exhibited a transient rise in serum transaminase unaccompanied by jaundice.¹⁹

The desmethyl analogue of imipramine, *desipramine hydrochloride* (*Norpramin*, *Pertofrane*), also may give rise to jaundice.¹⁵² Unfortunately, details of the illness in such cases are lacking.

From available data, it appears that both imipramine and desipramine usually produce a cholestatic type of hepatitis. However, in at least one instance, these agents produced massive hepatic necrosis that was fatal.⁵⁸⁴ The patient involved noted the onset of rash 2 weeks after starting treatment with imipramine. Substitution of desipramine at this point aggravated the dermatitis, so that drug treatment was discontinued 2 days later. Jaundice, fever and mild eosinophilia appeared 6 weeks after the onset of rash. The jaundice deepened rapidly, the rash became exfoliative in character, and ulcerations of the mucous membranes appeared. Death occurred 2 weeks after the onset of jaundice and approxi-

mately 8 weeks after the appearance of rash. Autopsy revealed massive destruction of the hepatic parenchyma, collapse of reticulin, numerous lipofuscin-filled macrophages and a mixed portal exudate of neutrophils, lymphocytes and histiocytes with occasional plasma cells and eosinophils, features seen in other forms of massive hepatic necrosis produced by reactions to drugs.

Considering the clinical features in this case, and the fact that imipramine and desipramine produce rash, fever, eosinophilia, thrombocytopenia and agranulocytosis, it is highly probable that the hepatic lesions they produce are attributable to drug sensitization.

Meprobamate (Miltown, Equanil). This agent, one of the most widely used tranquilizers, produces a variety of allergic reactions, including rash, fever, angioneurotic edema, arthralgia and thrombocytopenic purpura.^{46, 334} Although hepatic involvement in such reactions has not been reported, the writer has seen 2 instances of cholestatic jaundice in patients receiving meprobamate and has heard of 2 others.

MISCELLANEOUS

APIOL DERIVATIVES

Apiol, a camphoraceous material derived from parslev and an important constituent of many illegal proprietary abortifacients, produces hepatic injury in animals and occasionally has been implicated as a hepatotoxic agent in humans.⁴⁵³ However, in most such cases, complicating factors such as sepsis, hemolysis and shock have made it difficult to assess the role of apiol in the pathogenesis of the hepatic necrosis demonstrated at autopsy.

BURNS AND TANNIC ACID

A variety of hepatic lesions have been observed in individuals with extensive burns.^{58, 262, 795} Animal experiments show that most of these can be attributed to tannic acid therapy and possibly to infection.^{33, 234, 309} In dogs, extensive burns of the skin, if left untreated, are usually accompanied by central congestion and atrophy of the hepatic parenchyma. However, if infection super-

venous, or if tannic acid dressings are applied, central necrosis of the liver ensues.³⁰⁹ The presence of a burn is not essential for this effect for the same lesions occur when tannic acid is injected subcutaneously into normal animals.^{33, 284, 309}

It seems unlikely that burns give rise to hepatic necrosis by reducing blood flow through the liver, since in dogs hepatic oxygen uptake is not reduced following burns.²⁶³

Severe liver damage, occasionally accompanied by jaundice and ascites, is also seen in patients with fatal burns that have been treated with tannic acid. The midzonal necrosis and the Councilman bodies found in such cases closely resemble those of yellow fever.³⁶ In contrast, untreated cases show only minor alterations in the staining quality of the parenchymal cells, varying degrees of fatty infiltration and centrilobular atrophy without necrosis.²⁶² Impairment of hepatic function also has been reported following burns.⁷⁹⁵ However, the data do not indicate whether this occurs in the absence of infection and tannic acid therapy.

CARBAMAZEPINE (TEGRETOL)

Carbamazepine (5-carbamyl-5H-dibenzazepine) is chemically related to imipramine (Tofranil) and is used in the treatment of epilepsy and trigeminal neuralgia. It is a sensitizing agent, having produced rash, the Stevens-Johnson syndrome and fatal aplastic anemia in a number of cases.⁵⁸⁹ In addition, it has been responsible for at least 2 instances of cholestatic hepatitis on the 7th and 20th day of drug administration.⁵⁸⁹

CHLOROTHIAZIDE

Rarely, chlorothiazide gives rise to cholestatic hepatitis.^{182, 349} In one case, itching was noted after only three 0.5 Gm. doses given at daily intervals.¹⁸² The drug was taken intermittently for an additional 2 weeks, at the end of which time jaundice appeared. Except for pruritus, there were no associated symptoms. The histologic and laboratory features were consistent with cholestatic hepatitis; but, because of uncertainty about the diagnosis, exploratory laparotomy was carried out, revealing

a normal biliary tree. Full recovery occurred by the end of 2 months.

In a second case, the jaundice was protracted, and was associated with a lesion resembling biliary cirrhosis.³⁴⁹ The patient involved took chlorothiazide daily for more than 2 years without ill effects. Two and one-half months after resuming therapy with chlorothiazide she noted the onset of low grade fever, pruritus, anorexia and jaundice. She continued taking the drug for 5 weeks. Liver function studies suggested obstructive jaundice, so that exploratory laparotomy was carried out in the 8th week. The biliary tract proved to be normal. Wedge biopsy of the liver revealed expanded portal tracts with numerous neutrophils and eosinophils, granulomata, atypical ductular proliferation and periportal parenchymal necrosis, bile stasis and early fibrosis. Jaundice and pruritus persisted for several months and then cleared. However, the serum alkaline phosphatase level remained high. The patient died of a cerebrovascular accident 16 months after the onset of jaundice, and, at autopsy, the liver was nodular with portal fibrosis, nodular regeneration and a mononuclear reaction in the triads and septa.

CHOLECYSTOGRAPHY DYES

Bunamiodyl (Orabilix). In a high proportion of individuals given bunamiodyl, a tri-iodophenyl compound, there is a transient increase in the indirect-reacting (unconjugated) fraction of serum bilirubin by the next morning.⁸² The rise in total serum bilirubin, which at its peak reaches levels of 1.5 to 2.0 mg./100 ml, returns to normal within 24 hours. Concomitantly, there is a transient increase in Bromsulphalein retention.⁶⁸⁴

Although bunamiodyl inhibits bilirubin conjugation by rat liver *in vitro*, other experimental evidence suggests that the retention of unconjugated bilirubin in the serum is due primarily to competitive inhibition of bilirubin excretion in bile,⁷² or impairment of bilirubin uptake by the liver.⁶⁸ With respect to Bromsulphalein retention, animal studies suggest that bunamiodyl impairs the hepatic uptake of dye.⁶⁸

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**Iopanoic Acid (Telepaque) and Iodi-
pamide (Cholografín)**, two other iodinated
compounds used for cholecystography, also
produce transient mild hyperbilirubinemia⁷²
and Bromsulphalein retention,^{72, 504} pre-
sumably by the same mechanisms involved
in the case of bunamiodyl. In addition, *in*
vitro studies with iopanoic acid suggest that
inhibition of the Bromsulphalein-glutathione
conjugating system is a factor in the dye
retention produced by this agent.⁵¹³

Rarely, orally administered cholecystogra-
phy dyes produce reactions that appear to
be allergic in nature. In one such case seen
by the writer, the temperature rose sharply
several hours after 3 Gm. of iopanoic acid
was administered. Chills and fever con-
tinued for 6 days. A morbilliform rash and
eosinophilia were noted in the 3rd day. At
the height of the jaundice the liver was en-
larged but not tender, serum bilirubin rose
to 4.8 mg.%, serum alkaline phosphatase
was 26 Bodansky units, thymol turbidity
was 7 units, and the SGOT level was 60
units. The cephalin-cholesterol flocculation
reaction remained normal. Biopsy at this
time revealed a diffuse mononuclear inflam-
matory reaction involving all portions of the
lobules and some of the central veins, and
extensive centrilobular and periportal ne-
crosis. Repeat biopsy 2 months after the
reaction revealed normal liver tissue. How-
ever, full clinical and functional recovery
did not occur for another 3 months.

ETHYL ALCOHOL

As pointed out, alcohol enhances the
hepatotoxic effects of agents such as carbon
tetrachloride, chloroform and phosphorus.
In addition, it appears to play a role in the
pathogenesis of Laennec's cirrhosis. This
raises the question of whether or not alco-
hol is a hepatotoxin. According to many au-
thorities, alcohol has no direct effect on the
liver, but, when imbibed in excessive
amounts, encourages a reduction in food
consumption that leads to malnutrition,
hepatic injury and, ultimately, to Laennec's
cirrhosis.

However, experimental studies in animals
indicate that, apart from its effects on food
consumption, alcohol raises the choline re-
quirement,³⁸⁴ increases fatty acid synthe-

sis,⁴³⁸ mobilizes fat from the depots to the
liver⁵⁹⁵ and potentiates the development of
nutritional cirrhosis.³⁸⁴ Moreover, even in
healthy nonalcoholic individuals maintained
on a high protein diet, alcohol administra-
tion leads to fatty infiltration of the liver,
raises the serum transaminase level and
produces ultrastructural changes suggestive
of toxic injury.⁶³⁸ Whether or not these
effects are implicated in the pathogenesis
of Laennec's cirrhosis remains to be estab-
lished.²⁹² For a more complete review of
this subject see References 356 and 381.

MALE FERN

Male fern extract, widely used in the
treatment of tapeworm infestation, regu-
larly raises the level of the indirect-reacting
(unconjugated) fraction of bilirubin in the
serum and increases Bromsulphalein reten-
tion.⁵³⁷ These changes, which appear within
24 hours, are unaccompanied by alterations
in serum alkaline phosphatase or transami-
nase, and subside within a few days. Usua-
lly, the alterations in serum bilirubin and
Bromsulphalein are slight, but, occasion-
ally, overt jaundice or a high degree of
Bromsulphalein retention may be produced.

It has been suggested that male fern in-
terferes with the hepatic uptake of bili-
rubin and Bromsulphalein. However, the
mechanism involved has not been ade-
quately investigated.

METHYLDOPA (ALDOMET)

Abnormalities of hepatic function, includ-
ing Bromsulphalein retention, and raised
levels of serum transaminase and alkaline
phosphatase, occur in a small but significant
number of patients receiving methyldopa
in the treatment of hypertension.¹⁵³ Those
that appear within the first 10 days may be
accompanied by fever and malaise, but
more often they occur insidiously and with-
out symptoms during the first few months
of therapy. As a rule, such functional ab-
normalities promptly revert to normal when
the drug is withdrawn. Liver biopsy in sev-
eral patients has revealed foci of necrosis
considered compatible with drug hyper-
sensitivity.

In a few instances, the hepatic functional
abnormalities produced by methyldopa have

been accompanied by mild jaundice that has cleared promptly on discontinuing medication.⁴⁹⁹ However, one instance of severe hepatitis has been reported.⁵⁰⁵ In this case, the clinical features and the histologic findings in the liver were indistinguishable from those of viral hepatitis or those produced by drugs like iproniazid. The serum levels of bilirubin, glutamic oxalacetic transaminase and alkaline phosphatase reached peak values of 30 mg./100 ml., 1120 units and 25 K-A units, respectively. On withdrawal of the drug, the hepatitis subsided, but the serum bilirubin level was still elevated on the 45th day.

Considering that methyl dopa can give rise to drug fever, agranulocytosis, thrombocytopenia¹⁵³ and Coombs' positive hemolytic anemia,⁵⁵ and that such reactions may be accompanied by a positive L.E. test and the appearance of rheumatoid factor in the serum,⁵⁷⁹ it is highly probable that the hepatic lesions produced by this agent are due to drug hypersensitivity.

NICOTINIC ACID

A significant number of patients on prolonged nicotinic acid therapy for hypercholesteremia show minor degrees of Bromsulphalein retention and slight elevations of serum transaminase, lactic dehydrogenase, and alkaline phosphatase.⁵⁵⁵ Raised levels of serum bilirubin are less common.⁵⁵⁴ Withdrawal of the drug is followed by prompt recovery. Evidence suggests that preparations designed to provide slow release of the drug may produce hepatic dysfunction more frequently than pure nicotinic acid.⁵⁵⁴ Liver biopsy studies in patients maintained on the drug for at least a year have revealed no abnormalities.⁵⁵⁶ Although several patients with altered hepatic function have shown a variety of histologic changes in the liver, their relationship to nicotinic acid therapy is uncertain since other etiologic factors have been involved.⁵⁵⁵

At least two instances of apparent nicotinic acid-induced cholestatic hepatitis have been reported. In one, pruritus was noted after 13 months of drug therapy.⁶²² Treatment was interrupted for a month and then was resumed. Three months later there was

a relapse of pruritus, accompanied this time by jaundice. There were no associated gastrointestinal or constitutional symptoms. The liver was enlarged but nontender, and serum bilirubin was increased to a level of 7.4 mg./100 ml., only 1.0 mg. of which was of the direct-reacting type. There were elevations of serum alkaline phosphatase to 45 K-A units and SGOT to 91 units; thymol turbidity and cephalin-cholesterol flocculation were normal. The drug was stopped, and jaundice cleared in 3 weeks.

In the second case, pruritus appeared several weeks after a 15 month course of nicotinic acid had been discontinued.⁵⁵⁴ Jaundice followed 8 days later, but there was no associated anorexia, nausea, vomiting, or hepatomegaly. Serum bilirubin rose to 7.0 mg./100 ml., with a direct-reacting fraction of 5.4 mg., SGOT to 200 units, and serum alkaline phosphatase to 50 K-A units; thymol turbidity remained normal. Drug therapy was discontinued and jaundice cleared in 4 days.

The pathogenesis of the hepatic dysfunction produced by nicotinic acid is not clear. Considering the absence of features suggestive of an allergic reaction, it is unlikely that drug hypersensitivity is involved. Although the occurrence of Bromsulphalein retention, the occasional development of pruritus and jaundice, and the absence of histologic changes in the liver suggest the type of functional cholestasis produced by agents like methyltestosterone, the frequency of raised levels of serum transaminase is atypical and suggests a mild hepatotoxic action.

PHENINDIONE (PHENYLINDANDIONE, HEDULIN, DANILONE)

Phenindione, a widely used anticoagulant, occasionally gives rise to reactions that appear to be allergic in nature. These are characterized by fever, rash, granulocytopenia and/or eosinophilia and may be accompanied by a cholestatic type of hepatitis.^{99, 197, 363, 483, 583} and rarely by nephritis.⁹⁹ As a rule, the onset is abrupt during the 3rd or 4th week of drug administration, but may occur as early as the 10th day and as late as the 9th week. Rarely, the reaction appears

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used anticoagulant, o reactions that appear. These are characterized by granulocytopenia and may be accompanied by hepatitis.⁹⁹ by nephritis.⁹⁹ As it during the 3rd or 4th administration, but may 1 day and as late as 10 days reaction appears

a few days after withdrawal of the drug.⁴⁸³ Usually, resumption of therapy following recovery provokes a prompt relapse.^{99, 483}

Usually, hepatitis subsides following withdrawal of the drug. In some cases, ACTH and corticosteroids have appeared to hasten recovery.^{99, 197, 483}

Although some patients with allergic reactions to phenindione can tolerate other anticoagulants, such as ethyl biscoumacetate,⁷³ relapses or exacerbations have been reported following resumption of treatment with acenocoumarin (nicoumalone, Sintrom).³⁵³ It is probably unwise, therefore, to use any agent in this group once a reaction has occurred.

PHENYLHYDRAZINE

The jaundice seen during phenylhydrazine therapy for polycythemia vera is due primarily to the rapid hemolysis of erythrocytes. It has been suggested that prolonged or excessive treatment also results in liver injury. This is based on the observation that massive doses produce fatty degeneration and centrilobular necrosis of the liver in rabbits,⁷⁹ and that following repeated courses of treatment occasional patients develop cirrhosis.⁴³⁰ However, even prolonged administration of therapeutic doses does not impair hepatic function, either in man¹⁰¹ or in animals,²⁶¹ and following such treatment the liver shows no change other than mild hemosiderosis.¹⁴ There is no reason to implicate phenylhydrazine as the etiologic factor in cirrhosis, since the lesion occurs spontaneously in untreated cases of polycythemia vera.

POLYVINYL PYRROLIDONE (PVP)

The intravenous administration of PVP, a synthetic plasma expander, is followed within a few months by the appearance in the Kupffer cells of globular basophilic deposits thought to be macromolecules of PVP.²⁴⁹ At least up to a year, the amount of phagocytized material appears to increase with time. Occasionally, a mild inflammatory reaction is associated with the deposition of PVP, but there is no fibrosis or evidence of hepatocellular dysfunction. In animals given repeated injections of PVP, ag-

gregates of PVP-filled histiocytes accumulate in the parenchyma and then extend into the triads.²⁴⁶

PRESSOR AGENTS

Although shock alone²⁰⁸ or shock associated with cardiac failure³⁷⁸ may produce centrilobular necrosis, the lesions are seldom massive.¹⁰⁴ However, in patients given pressor amines for the control of shock that ultimately proves to be fatal, the liver not infrequently shows large areas of infarction or extensive zones of hemorrhagic necrosis.¹⁰⁴ It has been suggested that the pressor amines are responsible for such lesions by producing ischemia.¹⁰⁴ Consistent with this view is the observation that in healthy dogs infusions of epinephrine, levarterenol, metaraminol, methoxamine, phenylephrine or mephentermine give rise to diffuse hepatic necrosis.³⁷⁷ However, hemodynamic studies in the dog indicate that, under conditions of hemorrhagic shock, vasopressor drugs like levarterenol increase hepatic arterial blood flow.¹⁴⁹

Although further study of the problem in man is needed, the latter observations suggest that, under such conditions, pressor amines do not produce hepatic ischemia. However, it is possible that they lead to massive hepatic necrosis indirectly by prolonging survival under conditions of shock and thus permit lesions to develop that otherwise would not become manifest.¹⁰⁴

PYRIDINE

At one time, pyridine was used in the treatment of convulsive seizures and asthma and still is employed widely in industry as a solvent and as a reagent in the synthesis of certain organic compounds. It can produce severe hepatic and renal injury in man,⁵⁷⁵ but the lesions have not been described. In the rat, pyridine produces both fatty infiltration and acute hepatic necrosis and, following prolonged administration, may give rise to cirrhosis.⁴⁶ Methionine and choline partially protect against the fatty infiltration and fibrosis but do not prevent the necrosis. Therefore, it has been suggested that pyridine injures the liver, both by a direct toxic action and by producing

an intrinsic nutritional deficiency, possibly by diverting methyl groups during its methylation.

QUINETHAZONE (HYDROMOX)

Jaundice has been reported in a patient receiving quinethazone, a nonmercurial diuretic, unrelated to the benzothiadiazines, used in the treatment of hypertension.^{350a} In the case involved, asymptomatic mild scleral icterus, slight hepatomegaly and elevation of the serum bilirubin to 3.3 mg./100 ml., with a direct-reacting fraction of 1.5 mg., were noted after 7 weeks of drug therapy. Other tests of hepatic function are said to have been normal. Liver biopsy revealed intracellular bile pigment granules in the centrilobular parenchyma, evidence of increased regenerative activity and infiltration of the portal triads with mononuclear cells and eosinophils. A direct Coombs' test was positive on two occasions. The jaundice cleared rapidly when the drug was withdrawn, but recurred within a week when treatment with quinethazone was resumed.

Since the direct Coombs' test was positive in the case described, and reports indicate that quinethazone occasionally produces rash, it may be a sensitizing agent.

RADIATION

X-ray irradiation of the liver provokes more intense radiation sickness than irradiation over any other area of the body. Although it is clear from both experimental and clinical observations that irradiation can damage the liver, the symptoms of radiation sickness do not appear to be dependent upon hepatic injury, which suggests that they may be due to the indirect effects of irradiation.

In some cases, intensive irradiation over the liver produces severe degeneration and necrosis of the intrahepatic bile ducts while sparing the parenchyma.¹²⁶ Thus, the hepatic parenchyma is thought to be relatively resistant to irradiation damage. However, in experimental animals, the parenchymal cells appear to be far more sensitive than the biliary epithelium when massive doses of x-ray are employed, the principal effects being degeneration and necrosis of hepatocytes by a direct action, and varying degrees

of edema, hyperemia and leukocytic infiltration attributable to vascular damage.²⁶ Smaller doses also affect the hepatic parenchyma, but the changes are more subtle.^{447, 793} Similarly, in man, intensive irradiation (3,000 to 6,000 rads) over the liver produces severe damage, giving rise to a syndrome called "radiation hepatitis."^{98, 353, 414} Characteristically, ascites and hepatosplenomegaly, occasionally accompanied by abdominal pain and jaundice, appear 2 to 6 weeks following completion of a course of irradiation. The hepatic lesion may heal without residuals, lead to fibrosis of the liver or result in death.

Histologically, the lesion is characterized by progressive fibrosis and obliteration of the central veins, and centrilobular congestion, hemorrhage and atrophy of the parenchyma, features that closely resemble those of the veno-occlusive disease seen in Jamaica and produced by senecio alkaloids.⁶⁰² The concept that the vascular lesions precede and are responsible for the congestion and loss of hepatic parenchyma is open to question, since in some studies the parenchymal changes have been observed prior to the appearance of hepatic venous occlusion.³⁵³ There is evidence that, in some cases, the lesions regress or heal without residuals after a period of 4 months.^{353, 602} However, marked fibrosis may persist and often is accompanied by terminal jaundice.⁹⁸ Rarely, such hepatic lesions may be complicated by stricture of the common duct or fibrosis of the pancreas.⁹⁸

Surprisingly few changes in the liver were observed in *atom bomb casualties*.⁴³⁹ In individuals who survived for less than 6 weeks, the principal findings were central congestion with atrophy of the hepatic parenchyma, and edema of the central veins. In those who survived longer, the liver exhibited fatty infiltration.

At least two radioactive materials used as therapeutic or diagnostic agents can produce liver injury: *radioactive colloidal gold* and *thorium dioxide (Thorotrast)*.

Although there are no clinical reports of liver injury following the use of radioactive colloidal gold, it produces severe midzonal hepatic necrosis in rats.³⁹³ The architecture

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and leukocytic infiltrative vascular damage.²⁶ The hepatic parenchyma is more subtle.⁴⁴⁷ Intensive irradiation over the liver giving rise to a synovial hepatitis.^{396, 333, 414} Lesions and hepatosplenomegaly accompanied by jaundice, appear 2 to 6 months after the completion of a course of radiation therapy. The lesion may heal to fibrosis of the liver.

Jaundice is characterized by a yellow discoloration of the skin and sclera and obliteration of the portal venous system. The portal venous system at closely resemble the disease seen in the liver. It is characterized by senescent atrophy of the portal venous system and the vascular lesions responsible for the hepatic parenchyma. In some studies, jaundice has been observed in the course of hepatic irradiation. There is evidence that the lesions regress or disappear after a period of 4 to 6 weeks. Marked fibrosis is accompanied by jaundice. Rarely, such hepatic lesions are complicated by stricture of the portal veins or fibrosis of the pancreas.

Changes in the liver were observed in casualties.⁴³⁹ In irradiated livers for less than 6 weeks, the lesions were central congestion of the hepatic parenchyma and the central veins. In longer, the liver exhibited extensive materials used as contrast agents can produce radioactive colloidal gold (Thorotrast). No clinical reports of the use of radioactive contrast agents severe midzonal lesions.³⁹³ The architecture

of the liver is grossly distorted, both by necrosis and by the transformation of the parenchyma to masses of bizarre giant cells. Although the lesion may resemble cirrhosis, there is no fibrosis. Clinically, jaundice and ascites are evident prior to death. Survival varies from a few days to 7 months.

Despite claims to the contrary,^{800, 801} there is convincing evidence to show that Thorotrast can produce hepatic injury and give rise to malignancy and certain hemopoietic disorders.

Hepatosplenomegaly with varying degrees of fibrosis and cirrhosis of the liver occurs in a significant number of individuals who have received large doses of colloidal thorium dioxide in the course of hepatosplenography or angiography.^{12, 161, 252} Usually, the signs of hepatic disease appear after a latent period of at least 15 years. In animals, large doses of Thorotrast produce foci of hepatic necrosis and fibrosis in a much shorter period of time.⁵⁴⁶ A significant number of patients with the disease die of hepatic failure.

A wide variety of malignant tumors have been encountered following Thorotrast administration, usually after a latent period of approximately 20 years.^{161, 536, 562} Most often these have involved the liver, and have been of varying histologic types, including hepatoma, cholangiocarcinoma, sarcoma and hemangioendothelioma. Hemangioendotheliomas are particularly frequent.¹⁶¹ In addition to those found in the liver, carcinomas have been encountered in many other tissues, although their relationship to antecedent Thorotrast administration has been less well defined.¹⁶¹ Also, instances of both acute and chronic leukemia, lymphoma, aplastic anemia and thrombocytopenic purpura have been reported as late complications of Thorotrast deposits.¹⁶¹

All of the injected thorium dioxide is retained in the reticuloendothelium, and especially in the liver and spleen. Over a period of years, some may shift from the liver and the spleen to adjacent lymph nodes, but none is excreted. Although large particles can be demonstrated in the Kupffer cells of the liver and in the reticuloendothelium of the spleen, it is generally believed that the fibrosis that occurs in these organs is

due to radioactivity and not to a foreign-body reaction. The 75 ml. dose of 25 per cent thorium dioxide solution required for hepatosplenography has been estimated to possess an alpha ray activity equivalent to that of 1.5 to 3.0 micrograms of radium.⁸⁰¹ In the course of its degradation, a series of other radioactive elements are produced, some of which emit beta and gamma rays in small quantity. Several of these have been identified in the excreta and the expired air many years after the injection of Thorotrast.⁷¹⁶ The carcinogenic potentiality of Thorotrast is also presumed to be related to its radioactivity.

TRANSFUSION REACTIONS

Not infrequently, severe reactions to transfusions of incompatible blood are accompanied by jaundice, a manifestation almost certainly due to acute hemolysis. However, evidence suggests that hepatic injury plays a contributory role. In most fatal cases, the liver shows areas of central necrosis,^{85, 269} and similar lesions have been produced in dogs by injecting heterologous hemagglutinins.⁵⁵⁹ Healing is followed by diffuse fibrosis in animals that survive, but a similar sequence has not been described in man.

The pathogenesis of the hepatic lesions in transfusion reactions is not well understood. Possibly they are related to shock, which is often present. It has also been suggested that hepatic necrosis results from impaction of the sinusoids with agglutinated erythrocytes.

Jaundice may also follow the transfusion of well-matched blood. This complication, designated by some as "benign postoperative intrahepatic cholestasis,"⁸⁵² is seen most commonly during the postoperative course of patients who have been transfused with bank blood.^{570, 570, 652, 672} However, it may also occur after transfusions administered to patients with severe trauma or burns.⁶⁷² The writer has seen one instance following multiple transfusions in a patient with chronic renal failure who was undergoing periodic hemodialysis. Characteristically, the jaundice appears on the 1st to the 6th postoperative day, increases over the next few days and then clears within a week or two. Both the direct-reacting (conjugated)

and indirect-reacting (unconjugated) fractions of serum bilirubin are increased, and are associated with bilirubinuria, but acholic stools and pruritus do not occur. Raised levels of serum alkaline phosphatase and transaminase are common but inconstant findings. Usually, peak values of serum bilirubin are under 10 mg./100 ml., but concentrations of 25 to 40 mg./100 ml. have been reported.^{370, 652} Histologically, the liver shows centrilobular bile stasis which, occasionally, is accompanied by focal hepatic necrosis and degenerative changes.^{370, 652} In cases with elevated levels of serum alkaline phosphatase, the clinical features may suggest obstructive jaundice. As a rule, the jaundice is asymptomatic and appears to have no adverse effect on the clinical course. Fatalities have been reported in cases of severe postoperative jaundice, but, in these, death has been due primarily to other factors.³⁷⁰ The possibility that the cholestasis in such cases has played a contributory role cannot be excluded.

The jaundice seen following the transfusion of matched blood is clearly not due primarily to hemolysis. Although not proved, the mechanism involved appears to be related to two factors: first, a disturbance in hepatic secretory function (cholestasis) secondary to impairment of hepatic blood flow related to the effect of surgery, anesthesia, congestive heart failure, shock, trauma or sepsis, and second, a large increase in the load of bilirubin presented to the liver as a result of hemolysis of transfused blood.

TRIMETHOBENZAMIDE HYDROCHLORIDE (TIGAN)

Thus far, only one instance of hepatitis has been attributed to trimethobenzamide hydrochloride, an agent widely used as an antiemetic and for the control of motion sickness.⁸⁴ The patient involved noted the onset of jaundice and dark urine, accompanied by epigastric discomfort, anorexia and nausea, on the 5th day of drug administration. The jaundice deepened over the next few days and then began to fade. The results of hepatic function tests were consistent with hepatocellular jaundice, peak values being: serum bilirubin 14.9 mg./100 ml., glutamic oxalacetic transaminase 660

units, glutamic pyruvic transaminase 375 units, alkaline phosphatase 15.3 Sigma units, thymol turbidity 9 units and cephalin-cholesterol flocculation 3+. Biopsy of the liver revealed centrilobular bile stasis, foci of parenchymal necrosis, proliferation of Kupffer cells, enlargement and inflammation of the portal triads and rare acidophilic bodies.

Jaundice cleared rapidly following cessation of drug therapy, but the serum bilirubin was still slightly elevated when last studied at the end of 3 weeks.

Considering that this agent occasionally gives rise to allergic manifestations, such as rash, it is highly probable that the hepatitis described was another manifestation of drug hypersensitivity.

TRIPLENNAMINE (PYRIBENZAMINE) HYDROCHLORIDE

A brief report implicates Pyribenzamine as a cause of cholestatic hepatitis.⁷⁴ In the patient involved, an obstructive-like jaundice appeared during the course of treatment with the drug. Exploratory laparotomy failed to demonstrate any evidence of extrahepatic biliary obstruction. On biopsy, the liver showed centrilobular bile thrombi, foci of hepatocellular degeneration and necrosis and an inflammatory reaction. The jaundice persisted for 5 months, but then cleared. Follow-up clinical and biochemical studies several months later revealed no residuals.

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