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HEPATIC DRUG REACTIONS

MEDICAL GRAND ROUNDS

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INTRODUCTION

It is an essential truth that any medication has the potential to cause hepatic injury. Some agents are much more likely to do so than others and indeed, certain drugs are associated with rather characteristic patterns of injury. These are not too difficult to recognize once thought of. The larger and more difficult problem is the presence of some minor abnormalities of liver tests in an asymptomatic patient who is taking a number of therapeutic agents none of which has a reputation for hepatotoxicity. To establish that such a phenomenon is a drug reaction and to identify the specific culprit may be very difficult and at times not possible. In many such instances the drugs in fact are not responsible and even when they are, the lesion they cause may be unimportant. The lessons provided by oxyphenisitan must be kept in mind, however. This constituent of many over-the-counter laxative preparations was in use for 50 years before it was finally recognized to be the cause of a reasonably common and often serious form of chronic hepatitis. When in doubt, it is safer to assume a drug-induced cause for liver injury and seek alternative forms of therapy.

This survey of drug-induced hepatic reactions is not meant to be comprehensive but rather to provide a framework within which such disorders can be understood.

CLASSIFICATION:

No entirely satisfactory classification of drug-induced liver lesions is available. It is helpful to consider them in 2 frames of reference; one determined by the pathogenesis of the drug-liver interaction and the other by a description of the clinical (and histologic) features that result.

1. PATHOGENETIC TYPES:

There are 2 broad categories to consider:

a) Predictable Reactions:

These are manifestations of injury which are dose-related both in terms of occurrence and of severity; are universal and occur in all persons exposed to a "toxic" dose; can be reproduced in animal models and develop within a very brief (and fixed) interval from exposure. The injury may be induced by the unchanged drug itself or depend upon the development of excess amounts of a normal metabolite.

b) Unpredictable Reactions:

These are injuries which develop in only a small minority of persons exposed. Neither the occurrence nor the severity of the lesion is determined by the dose of the agent and the injury cannot be reproduced in animals. There is a quite variable interval from first exposure to the declaration of damage but re-exposure to the drug results in a prompt recurrence. There are probably a number of different ways in which such unpredictable reactions are mediated. Hypersensitivity to haptens formed by the drug itself or by a metabolite is the most time honored mechanism. The idiosyncratic production of an abnormal metabolite which is toxic to cells is another postulated pathway.

2. *CLINICAL TYPES:*

Predictable and unpredictable reactions may present clinically and histologically in an indistinguishable fashion. Drugs of either type may produce a clinical picture which is identical to that seen in patients with acute or chronic viral hepatitis. On the other hand, cholestasis may be the predominant characteristic of injuries mediated by both mechanisms. Some drug reactions (e.g. vascular lesions, oncogenetic lesions) are mediated by mechanisms which are very poorly understood and which are not clearly explicable by this classification. The clinical forms of drug-induced injury then are:

Hepatitis - acute and/or chronic

Cholestasis

A *mixture* of the above

Vascular lesions - Budd-Chiari syndrome

- peliosis hepatitis

Tumors - adenoma, hepatoma

An attempt to classify the most common hepatic drug reactions using both frames of reference is presented on the following page.

The hepatotoxicity incited by virtually any therapeutic agent can be fitted into this schema. The ultimate mechanism by which the various xenobiotics cause hepatic cell damage is usually not known but it is generally possible to distinguish predictable from unpredictable reactions and to define the clinical characteristics of the reaction.

PATHOGENESIS:

Most *predictable reactions* are mediated directly by a "toxic" consequence of the agent itself or one of its normal metabolites. There is usually a minimal dose which is necessary to produce the effect. There is often individual variation in the dose required to produce toxicity, however, and the dose necessary in a given individual may be modified by other drugs or environmental factors which influence the absorption, metabolism or excretion of the drug.

Unpredictable reactions may be the result of a hypersensitivity reaction to haptens formed between cellular macromolecules and the drug itself or one of its metabolites. On the other hand, these idiosyncratic reactions might represent the production of an abnormal metabolite which has toxic potential. In most circumstances the distinction between hypersensitivity reactions and "toxic metabolite" reactions is dependent upon the presence of associated features (e.g. skin rashes, arthralgias, arthritis, fever, eosinophilia, eosinophilic portal infiltrates or serologic markers of altered immunity such as ANA, Coomb's test, etc.) of hypersensitivity. This is probably an inadequate means of defining the pathogenetic mechanisms involved but in most instances it is all that is available. In short, we do not know the precise mechanisms involved in most unpredictable drug reactions.

PREDICTABLE DRUG REACTIONS

HEPATOTOXIC	a) acute	e.g.	Acetaminophen Tetracycline Aspirin
	b) chronic	e.g.	Methotrexate
CHOLESTATIC		e.g.	Methyl testosterone Estrogens Azathioprine

UNPREDICTABLE DRUG REACTIONS

HEPATOTOXIC	a) acute	e.g.	Halothane Propyl Thiouracil Isoniazid
	b) chronic	e.g.	Aldomet Oxyphenisitan Nitrofurantoin
CHOLESTATIC		e.g.	Phenothiazines Gold Salts Chlorpropamide
MIXED		e.g.	Phenytoin Erythromycin Estolate Sulphonamides Phenylbutazone

OTHER FORMS OF DRUG REACTIONS

BUDD-CHIARY SYNDROME	e.g.	Oral Contraceptives
PELIOSIS HEPATITIS	e.g.	Androgens Azathioprine
TUMORS	e.g.	Oral Contraceptives Androgens Thorotrast

CLINICAL MANIFESTATIONS:

Hepatotoxic or hepatitic reactions are characterized by a lesion which is indistinguishable in most respects from that produced by viral hepatitis. Acute episodes therefore are often associated with generalized constitutional symptoms, predominant G.I. symptoms and evidence of tender hepatomegally. Jaundice is variable depending on the severity of the disorder. The SGOT is frequently very high (>1000 u/ml) and the alkaline phosphatase is elevated to a variable extent. If the lesion is very severe, the prothrombin time may become prolonged and the patient may develop hepatic encephalopathy and ultimately ascites and edema. Histologically the lesion is characterized by cell injury with eosinophilic or balloon necrosis and areas of cell drop-out. More severe instances will show bridging necrosis, panlobular necrosis or massive hepatic necrosis. A moderately intense inflammatory reaction will be seen in the portal tract and in the areas of cell necrosis. Characteristically the severity of the cell injury found on biopsy appears to be greater than that anticipated on clinical grounds. If the drug is continued and the lesion becomes chronic, fibrous tissue will be laid down in the portal areas, in areas of cell necrosis and collapse. All of the histologic patterns seen with chronic hepatitis (chronic persistent, chronic active, chronic active with bridging, and cirrhosis) may be present.

There are some hepatotoxic reactions (e.g. those caused by phosphorus, tetracycline, methotrexate) where these clinical and histologic characteristics are not found. Evidence of cell necrosis is minimal and there is either a profound functional failure of liver cells or a progressive fibrogenesis. Both patterns are associated with fat accumulation in the liver cells.

Cholestatic reactions reach clinical awareness because of pruritus or of jaundice. There are usually few other clinical manifestations. The pruritus is often intense and is believed to be consequence of bile salt accumulation in the skin. The serum bilirubin may be normal or variably elevated, depending on the severity of the excretory defect. The alkaline phosphatase activity in serum is characteristically very high but may be normal, especially in patients exposed to estrogens or azathioprine. The SGOT and SGPT are usually elevated but to minor degrees. Hepatic function remains otherwise intact and serum albumin levels and the prothrombin time are generally normal. On biopsy, there is usually a minimal degree of cell necrosis (which may be the consequence of retained bile salts rather than the cause) and a minimal inflammatory response. Bile stasis is prominant as bile plugs in canaliculi or as bile stained parenchymal cells. It is distinctly unusual for evidence of chronic disease to develop.

Mixed reactions combine features of both cholestasis and hepatitis. Sometimes a drug will produce a predominantly hepatitic reaction in one person and a predominantly cholestatic reaction in another. Other agents produce hepatitic reactions with marked cholestatic features in the one patient. This, of course, is not an unusual phenomenon with acute viral hepatitis as well.

SPECIFIC DRUG-INDUCED REACTIONS

I have chosen a few particular drugs and will summarize the major characteristics of the liver disorders with which they are associated. I have chosen them for their frequency, their usefulness in illustrating a mechanism or their value

as representatives of this classification system. As a reference source to find what is known about the hepatic consequences of any specific drug, I refer you to Hy Zimmerman's recent textbook HEPATOTOXICITY published in 1978 by Appleton-Century-Crofts of New York.

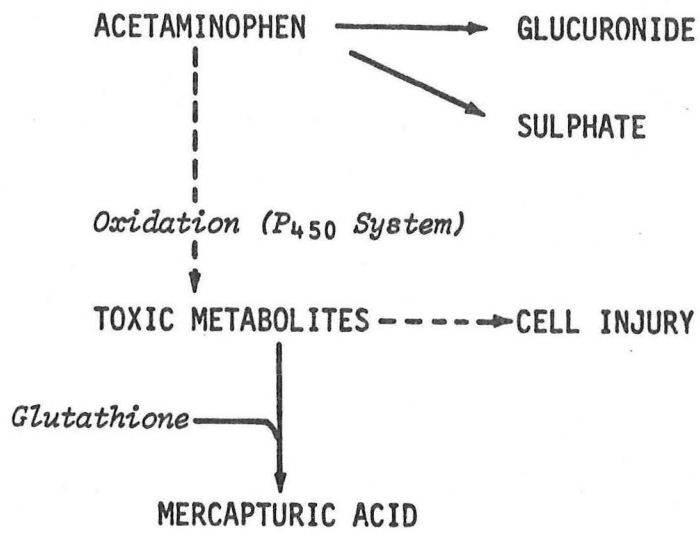
PREDICTABLE DRUG REACTIONS

ACUTE HEPATOTOXIC:

Acetaminophen

Pathogenesis:

MECHANISM OF ACETAMINOPHEN INJURY



A therapeutic dose of acetaminophen is metabolized principally in the liver by sulfation and glucuronidation processes which render non-toxic metabolites. A small part of such a dose is metabolized by the mixed function oxidase system (P_{450} system) and yields a very active metabolite. Under normal circumstances these unstable molecules are rendered harmless by the anti-oxidant glutathione (glycylglutamylcysteine). If more of the active metabolite is formed than can be dealt with by the available glutathione (GSH), the metabolite will covalently bind to cellular macromolecules and initiate cellular injury and ultimately cell death. This situation can result from any one or a combination of the following circumstances:

a) *Overdosage.* The capacity for glucuronidation and sulfation is quite finite. As the dose of the drug delivered to the liver is increased, the amount which is metabolized by the P_{450} system increases exponentially.

b) *Stimulation of the P_{450} system.* A number of therapeutic agents (notably phenobarbital, phenytoin and chronic alcohol consumption) will induce the P_{450} such that a greater proportion of any given dose will be metabolized via this system.

d) *Depletion of glutathione stores.* This can be achieved by a number of chemical means (e.g. chronic use of acetaminophen) and by short-term deficiency of the essential amino acid cysteine. In animal models fasting for as short a time as 24 hours will reduce hepatic glutathione levels. The most dramatic depletion occurs, however, if protein-free diets are supplemented with some carbohydrate calories. This prevents the breakdown of endogenous protein and markedly aggravates the essential amino acid deficiency.

It is quite common to find two or all three of these factors operating when patients present with evidence of acetaminophen toxicity.

Pathology:

The liver lobule has a certain functional heterogeneity and the pericentral cells contain a greater concentration of P_{450} than do the periportal cells. The toxic metabolite which is formed by oxidation in this system is extremely reactive and is not transported from its site of origin. It immediately reacts with either GSH or cellular organelles. The cell that produces the toxin is the cell that is affected by it. The injury that follows acetaminophen hepatotoxicity is typically zonal and involves the pericentral cells first. There is an all-or-nothing quality to the injury. For the most part, cells are either necrotic or normal. In more severe episodes, virtually all of the parenchymal cells are destroyed although usually a small rim of periportal cells persists. There may be a small amount of fatty change in the cells at the border of the necrotic zone and the inflammatory response is mixed with both mononuclear cells and polymorphs. Eosinophils are lacking. This injury usually can be distinguished from that caused by viral hepatitis. If the patient survivies, the liver architecture is restored completely to normal. Occasionally there will be some residual fibrosis, but cirrhosis and chronic liver disease are not seen.

Clinical Manifestation:

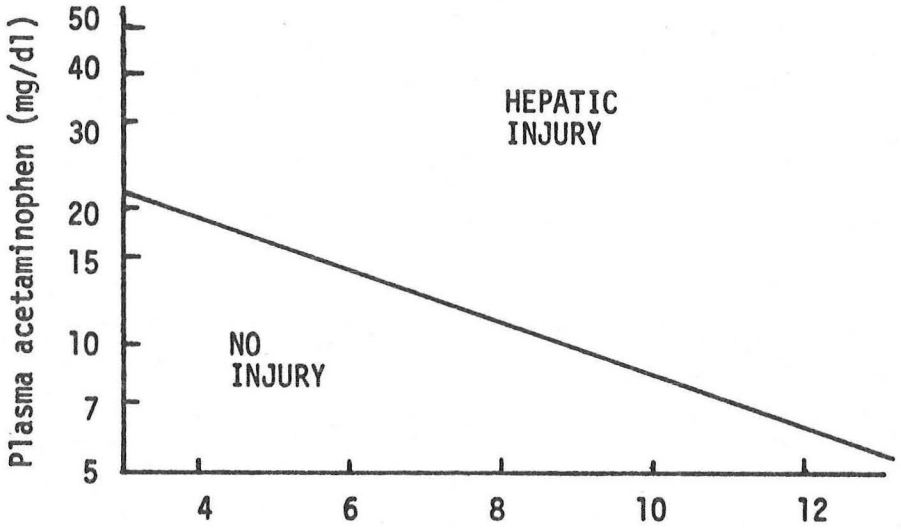
Clinical manifestations developing within the first few hours of ingesting toxic quantities of acetaminophen are confined to a variable degree of nausea and vomiting or are the consequence of other agents taken as part of a mixed overdose. The patient usually remains quite well for the next few days. If significant hepatotoxicity does occur, its manifestations are deferred for 4 or 5 days. The patient may then have recurrence of GI symptoms with fever, malaise, icterus, and, too frequently, signs of hepatic encephalopathy and fulminant hepatitis supervene. Many patients have chemical evidence of a milder liver injury without any clinical accompaniments. If no chemical evidence of hepatic injury has been documented 5 days after the ingestion, it is unlikely that any will develop. Evidence of other organ damage is usually subordinate to liver injury. Acute renal failure from ATN is a common accompaniment of severe liver injury. Its genesis lies in the local production of toxic acetaminophen metabolites from P_{450} present in renal tubular cells. Occasionally the renal failure will prove to be the major clinical problem. Pancreatitis is also common in patients with massive hepatic necrosis. It is not clear whether this lesion derives from pancreatic metabolism of the drug itself or whether it is of the same idiopathic origin as pancreatitis seen in many other forms of fulminant hepatitis. There are some scattered autopsy reports that indicate there may be a specific focal myocardial lesion in these patients as well, but this remains questionable.

Prediction of Outcome:

The use of acetaminophen as a means for suicide attempts and suicide gestures continues to increase. The number of patients who present to emergency rooms with a history of having taken excess amounts of acetaminophen is sufficiently large to require some means of identifying those patients at risk to develop serious liver injury. Experience from England has allowed the development of the following prognostic guidelines in untreated patients.

- A serum acetaminophen level of >300μg/ml (30 mg/dl)
- A serum half-life of >4 hours
  Both indicate a high probability that severe injury will follow.
- A nomogram which correlates serum acetaminophen with time during the first 12 hours following ingestion has been developed. Values falling above the line indicate a high probability that significant liver injury will ensue.

ACETAMINOPHEN TOXICITY



- The presence of a serum bilirubin >4 mg% or a prothrombin time >20 seconds by the 3rd to 5th day indicated a high likelihood of death in untreated patients. Such individuals usually have had abnormal bilirubin and prothrombin time values by the second day.

Treatment:

Specific therapy for acetaminophen toxicity can be applied to

- *prevent absorption of ingested drug* - e.g. gastric lavage, activated charcoal
- *prevent the production of the active metabolite* - by P_{450} inhibitors (e.g. Cimetidine)
- *prevent the toxicity of the metabolite* by providing sulfhydryl groups, e.g. acetylcysteine (mucomyst).

To be effective, therapy must be initiated within 24 hours of ingestion. Death from liver failure is very uncommon in patients treated within this time interval. If liver dysfunction is already present (i.e. delayed diagnosis), the NH_3 load provided by mucomyst therapy may compound the hepatic problem rather than help it. Nor is it likely that any of the other modalities will be of use if applied late. Therapy then becomes the support of a patient with acute liver failure.

Clark, R., Thompson, R. P. H., et al. Hepatic damage and death from overdose of paracetamol. Lancet (i):66-70, 1973.

Mitchell, J. R., Tollow, D. J., Potter, W. Z., et al. Acetaminophen-induced hepatic necrosis. IV. Protective role of glutathione. J. Pharm. Exp. Ther. 187:211-217, 1973.

Black, M. Acetaminophen hepatotoxicity. Gastroenterology 78:382-392, 1980.

Mitchell, M. C., Schenker, S., Avant, G. R., et al. Cimetidine protects against acetaminophen hepatotoxicity in rats. Gastroenterology 81:1052-1060, 1981.

Tetracycline

Tetracycline is an inhibitor of protein synthesis and will produce functional liver failure in a predictable dose dependent manner. This may arise from the receipt of excessive doses or follow the administration of therapeutic doses to individuals with a decreased GFR. Renal excretion of unchanged drug is the major means of tetracycline disposition. Most reported episodes of hepatotoxicity have occurred in patients receiving 2 grams or more of TCN intravenously to treat acute pyelonephritis in the face of an associated impairment of renal function. Most of these reports have concerned pregnant women and indeed, the resultant syndrome is indistinguishable from steatosis of pregnancy. Tetracycline-induced disease has been described, however, in men and in non-pregnant women and its apparent predilection for pregnant women probably reflects prescribing habits rather than any predisposition in the pregnant woman for TCN hepatotoxicity.

The critical point to make about TCN induced liver disease is that it represents a state of functional failure of hepatic cells without cell necrosis. The major site of injury appears to be mitochondrial. There appears to be a shutdown of energy production in the cell. All energy requiring processes are impaired and the consequence is an illness marked initially by hypoglycemia, prolongation of the prothrombin time and hyper-ammoniacal encephalopathy. Only later do more traditional signs of liver disease such as jaundice become prominant. Clinically the patient develops G.I. symptoms and then encephalopathy before or soon after jaundice is noted. Pathologically the liver looks normal apart from the presence of microvesicular (i.e. small droplet) fat in the parenchymal cells. This pattern of fat accumulation is quite different from that seen in conditions such as alcoholic liver disease, diabetes, obesity or following corticosteroid therapy. In these latter circumstances, the parenchymal cell contains a single large (macrovesicular) droplet of fat which displaces the cell

nucleus and other intracellular organelles to the very periphery of the cell. There is very little functional impairment of the cell despite the apparent complete replacement of its substance with this one fat droplet. The parenchymal cell in patients with TCN toxicity retains a centrally placed nucleus. There are a number (5 to 8 usually) of small droplets of fat arranged concentrically around the nucleus and this gives the cell a foamy appearance. The cells suffer severe functional impairment. There is, however, no cellular necrosis, no inflammatory response and no fibrogenesis. If the patient survives, there will be complete restitution of normal hepatic histology and function.

The clinical syndrome of TCN toxicity is associated frequently with acute pancreatitis and acute renal failure. Fatty metamorphosis of renal tubular cells has been described along with evidence of acute tubular necrosis. The pathogenesis of the pancreatic and renal lesions has not been established but the renal failure especially is likely to be multifactorial in its origins. There is a substantial mortality rate. The essentials of management in these patients include the prompt recognition and discontinuation of the drug and then the general measures which are applicable to the care of a patient with acute liver failure.

Whalley, P. J., Adams, R. H. and Combes, B. Tetracycline toxicity in pregnancy. J.A.M.A. 189:357-362, 1964.

Breen, K., Schenker, S. and Heimberg, M. The effect of tetracycline on the hepatic secretion of triglyceride. Biochim. Biophys. Acta 270:74-80, 1972.

Combes, B., Whalley, P. J. and Adams, R. H. Tetracycline and the liver. In: Progress in Liver Disease, edited by Popper, H. and Schaffner, F. Grune and Stratton, Vol. IV, pp. 589-596, 1972.

Aspirin

The association of hepatic dysfunction and aspirin use has been recognized only since the introduction of the serum transaminase assays as a sensitive indicator of liver injury. The following points can be made about this association.

- All salicylates (not just aspirin) can produce the effects.
- The hepatic disorder is almost always without clinical consequence.
- There is an asymptomatic increase in SGOT and SGPT in many patients receiving therapeutic doses of aspirin. These enzyme elevations are usually between 100 and 500 but may be even higher.
- The elevation of the transaminases is produced by aspirin in a dose-dependent manner and is seen usually when the salicylate level exceeds 25 mg%.
- Only about 50% of individuals with these salicylate levels will have abnormal transaminases.
- There appears to be a predisposition to the occurrence of salicylate hepatotoxicity in adults and children with SLE and rheumatoid arthritis.

- The disorder is benign and reversible with discontinuation of the drug or a decrease in the dose.
- The lesion is associated with histologic evidence of focal cell necrosis and mononuclear infiltration.
- There is no convincing evidence that either serious acute hepatitis or chronic hepatitis are consequences of therapy with this agent.

Rich, R. R. and Johnson, J. S. Salicylate hepatotoxicity in patients with juvenile rheumatoid arthritis. Arth. Rheum. 16:1-9, 1973.

Seaman, W. E., Ishak, K. G. and Plotz, P. H. Aspirin-induced hepatotoxicity in patients with systemic lupus erythematosus. Ann. Int. Med. 80:1-8, 1974.

Zimmerman, H. J. Aspirin-induced hepatic injury. Ann. Int. Med. 80:103-105, 1974.

Miller, J. J. and Weissman, D. B. Correlations between transaminase concentrations and serum salicylate concentration in juvenile rheumatoid arthritis. Arth. Rheum. 19:115-118, 1976.

Seaman, W. E. and Plotz, P. H. Effect of aspirin on liver tests in patients with RA or SLE and in normal volunteers. Arth. Rheum. 19:155-160, 1976.

Methotrexate

This folic acid antagonist is unique as a hepatotoxin in that it is capable of producing a chronic form of liver disease without there being either clinical or chemical evidence of an acute injury. The original reports of methotrexate-associated hepatotoxicity were weakened by being retrospective, uncontrolled and beset by a high frequency of associated alcoholism in the psoriatic patients studied. A prospective study was completed in 1976 in Scandinavia and the following points emerge as being probably true.

- There is a high frequency (approximately 50%) of abnormal liver biopsy findings in patients with psoriasis severe enough to warrant methotrexate therapy.
- These are usually mild and can be reasonably explained by co-existing diabetes, obesity and alcoholism.
- A proportion of patients treated with methotrexate (perhaps 10 to 15% over 2 years) will develop significant hepatic fibrosis or frank cirrhosis.
- The injury appears to be related to total cumulative dose and duration of therapy.
- This usually occurs despite persistently normal results of routine liver tests.
- The lesion may only be determined by serial liver biopsies.
- The mechanism of the injury is not known but there is a concentration and a persistence of methotrexate in liver cells for as long as 3 months after exposure.
- Methotrexate as therapy for psoriasis should be reserved for "last resort" situations.

- Patients who are so treated should have a pre-treatment liver biopsy and the biopsy should be repeated at perhaps 12 to 18 month intervals during therapy.

Weinstein, G. et al. Psoriasis-Liver-Methotrexate intoxication. Arch. Derm. 108:36-42, 1973.

Warin, A. P., Landells, J. W., Levene, G. M. et al. A prospective study of the effects of weekly oral methotrexate on liver biopsy. Findings in severe psoriasis. Brit. J. Derm. 93:321-327, 1975.

Nyfors, A. and Poulsen, H. Liver biopsies from psoriatics related to methotrexate therapy. Acta Path. Microbiol. Scand. 84:253-270, 1976.

CHOLESTATIC:

Estrogens

Estrogens consistently promote cholestasis in man and other animals. This is demonstrable in all people by sophisticated methods for measuring organic anion transport but reaches clinical and chemical expression in only a minority of persons exposed. These persons (both men and women) appear to have an exaggerated response to the universal cholestatic effect of estrogens. This hyperresponsiveness is under genetic control and accounts for the racial predilection for cholestasis of pregnancy and oral contraceptive-induced cholestasis among Scandinavian and Chilean people.

The clinical manifestations, when they occur, usually begin within the first 6 cycles of oral contraceptive therapy and often during the first cycle. Pruritus is usually the first and most important symptom. There is seldom a significant G.I. disturbance and fever, arthralgias and skin rashes do not occur. Jaundice, if it developes, is usually mild. The liver and spleen size remain normal and are usually non-tender. Serum bilirubin levels are often normal and are rarely greater than 10 mg/dl. Serum alkaline phosphatase levels may remain normal despite the intense cholestasis or may be variably increased. Transaminase elevations tend to be minor. The histologic findings are largely confined to the presence of canalicular bile plugs. Cell necrosis, fibrosis and inflammatory cells are trivial or absent. The disorder remits usually within a month of discontinuing the estrogen therapy and there are no chronic sequelae. Recurrence is to be expected if the patient is exposed to the same dose of the agent.

This syndrome is also likely to recur if the patient is exposed to high endogenous levels such as occur late in pregnancy. The condition, then called pruritus gravidarum or cholestasis of pregnancy, is similar in all respects to the OCP induced disease except that the serum alkaline phosphatase is always elevated (in part from the placental contribution) and the disorder persists, sometimes intolerably, until delivery. It then remits over the next 4 weeks. There is no associated maternal morbidity but the syndrome has been associated with an increased incidence of premature birth with all of its accompanying problems.

Holzback, R. T. Jaundice in pregnancy - 1976. Am. J. Med. 61:367-376, 1976.

Metreau, J. M., Dhumgaux, D., and Berthelot, P. Oral contraceptives and the liver. Digestion 7:318, 1972.

Ockner, R. K. and Davidson, C. S. Hepatic effects of oral contraceptives. N. Engl. J. Med. 276:331, 1967.

Azathioprine

This analogue of 6- mercaptopurine has been used most extensively to treat patients with organ transplantations but has had use as well in patients with chronic active hepatitis, polymyosites, Crohn's disease and hematologic malignancies. Patients with these conditions are subject to numerous causes for the development of abnormal results of liver tests. It is often difficult in such patients to define a specific cause for hepatic dysfunction. It now seems clear, however, that azathioprine (or 6MP) predictably will cause a dose-dependent cholestatic syndrome in people and dogs. There is, however, quite a variation from person to person in the dose required to provoke cholestasis. Many patients do not ever reach a cholestasis-inducing dose because this is either greater than their therapeutic requirements or because they develop marrow suppression first. The likelihood of clinically apparent cholestasis is enhanced if there is underlying liver disease (e.g. in patients being treated for chronic active hepatitis or in renal transplant recipients who have chronic viral hepatitis) or if the patient is exposed to another cholestatogenic process (e.g. during pregnancy or oral contraceptive therapy).

The clinical manifestations are those of rather pure cholestasis. The patient complains of generalized pruritus and may be variably jaundiced. Fever, skin rash or G.I. symptoms are not usually present and the patient usually feels well otherwise. In renal transplant recipients the serum alkaline phosphatase activity may remain normal or be elevated appropriately. The SGOT activity is only mildly increased. Histologically there is cholestasis with only a little evidence of cell injury (?the consequence of retained bile salts). There is a scanty inflammatory infiltrate and usually some evidence of regeneration. The liver disease remits over a period of weeks after the drug is discontinued. It recurs if therapy is resumed at the same dosage but lower doses of azathioprine can be tolerated without clinical or chemical signs of recurrence. There is no evidence that this lesion has any chronic sequelae.

There is evidence that azathioprine does not exert a subclinical effect on organic anion transport in patients who manifest no clinical or chemical sign of cholestasis (cf. estrogens). The storage capacity (S) and the transport maximum (Tm) for BSP (a measure of excretion of the organic anion) was normal in a group of unaffected transplant recipients receiving azathioprine in routine doses of 2 mg/kg/day. Nonetheless, the most likely mechanism for the production of cholestasis with this agent is that the drug itself or one of its metabolites interferes directly with the process of bile secretion at the canaliculus. There is nothing to support the notion that this is a hypersensitivity reaction.

The acute cholestatic lesion induced by azathioprine is benign. Two renal transplant recipients have been described, however, who developed a cholestatic syndrome which progressed and led to their demise in liver failure. Both patients were taking azathioprine but were not exposed to any known hepatotoxic agent. In both instances the liver biopsies were remarkable in that besides severe choles-

tasis and evidence of some cell necrosis, many of the parenchymal cells contained large inclusions reminiscent of "ground glass cells". On electron microscopy these inclusions were found to be aggregates of what seems to be polyglucose polymers (akin to glycogen). Their appearance was reminiscent of Lafora bodies which have been described in the neurons of the cerebral cortex in patients with progressive myoclonic epilepsy (Lafora's disease). In one instance similar bodies were described in the liver cells of an afflicted individual. Similar structures have been described in the liver cells of 3 alcoholics treated with disulfiram. The liver disorder in these patients was asymptomatic and apparently benign.

It is not certain that the 2 transplant recipients had a disease initiated by azathioprine. The disorder certainly did not resolve with interruption of therapy. On the other hand, the predominantly cholestatic nature of the disorder and the absence of any other apparent cause makes a reaction to this drug a real possibility and should encourage us not to take lightly cholestatic episodes that develop in patients receiving such therapy.

Sparberg, M., Simon, N. and del Greco, E. Intrahepatic cholestasis due to azathioprine. Gastroenterology 57:439-441, 1969.

Shorey, J., Schenker, S., Suki, W. N., et al. Hepatotoxicity of mercaptopurine. Arch. Int. Med. 122:54-58, 1968.

Haxhe, J. J., Alexandre, G. P. J. and Kestens, P. J. The effect of imuran and azathioprine on liver function tests in the dog. Arch. Int. Pharmacodyn. 168:366-371, 1967.

Worth, W. S. Azathioprine effect on normal canine liver and kidney function. Toxicol. Appl. Pharmacol. 12:1-6, 1968.

Rosman, M., Bertino, J. R. Azathioprine. Ann. Int. Med. 79:694-700, 1973.

UNPREDICTABLE DRUG REACTIONS

ACUTE HEPATOTOXIC:

Halothane

Incidence:

Reported rates are approximately 1:10,000 exposures but this is probably an underestimation. It is very rarely seen in children, is most commonly reported in patients of middle age and has a predilection for obese women. There is no relationship between the development of halothane hepatitis and the duration of anesthesia or the seriousness of the operative procedure. The majority of events are in people with a history of previous halothane exposure. This previous exposute has been followed often by an episode of unexplained postoperative fever, or documented abnormal LFT's.

Clinical Features:

Fever characteristically is the first sign of illness. This occurs from the 8th to the 14th day postoperatively in patients exposed to halothane for the first time and more quickly (1 to 8 days) after multiple exposures. Fever and generalized constitutional symptoms are followed by the onset of jaundice in a few days. The liver tests reflect a pattern of acute hepatitis with transaminase levels >1000 u/ml. This lesion has a very high mortality (>50%) and evidence of encephalopathy and coagulopathy are very common often quite early in the course of the disease. There is generally a leukocytosis in company with the fever. Eosinophilia and a generalized rash are described in only a minority of the patients.

Pathology:

No convincing differences between the liver biopsy findings in this disease and those seen in equally severe episodes of acute viral hepatitis have been found.

Mechanism:

Clearly there have been described true hepatic hypersensitivity reactions to halothane, but the majority of affected patients do not reflect these features. The decreasing frequency of hepatic reactions with decreasing hepatic biotransformation of related halogenated hydrocarbon anesthetics speaks to the importance of a derived metabolite in the genesis of the observed liver disease. Whether this metabolite acts directly as a hepatotoxin or by forming a hapten with cellular macromolecules and thus inducing a necrotizing immunologic response remains to be answered.

Management:

The management of patients with halothane-induced hepatitis is the management of patients with acute liver failure. Despite the convincing evidence that corticosteroids offer no benefit to patients with fulminant viral hepatitis, such therapy continues to be recommended for patients with halothane-induced disease. This recommendation is based on the possibility that the lesion is mediated by a hypersensitivity mechanism. It is extremely unlikely that the value of steroid therapy in these patients will ever be determined because of the rarity of the problem.

Inman, W. H. W. and Mushin, W. W. Jaundice after repeated exposure to halothane: An analysis of reports to the Committee on Safety of Medicines. B.M.J. 1:1-10, 1974.

Carney, F. M. T., Van Dyke, R. A. Halothane hepatitis: A critical review. Anesthes. Analges. ..Current Researches 5-1:135-160, 1972.

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Isoniazid

There are two patterns of hepatic dysfunction associated with the use of INH.

a) Asymptomatic Transaminasemia:

This is very common and is described in from 10 to 22% of people who take the drug. In most series the abnormality described has been an elevation of the SGOT without mention of the SGPT. The following points emerge with respect to the elvated transaminase activity:

- It is usually low grade and seldom is >200 u/ml.
- It frequently returns to normal even if the isoniazid is continued.
- It frequently does not recur if INH is re-instituted.
- It is not a methodologic artefact caused by INH.
- A small number of liver biopsies performed in patients with this syndrome have shown focal areas of cell necrosis and inflammation.
- It appears to develop at any time after the institution of therapy and may be a late phenomenon.
- A substantial number (10 to 15%) of normal people on no medication will develop an elevated SGOT if they have serial LFT's tested over a 12 month period.
- It is not clear whether this benign event has any relationship to the second syndrome.

b) True Hepatotoxicity:

This is much less common but much more serious.

Incidence:

The frequency of important liver injury from INH therapy is dependent on the patient's age. It is very uncommon in children and becomes increasingly common with increasing age. In patients older than 50 years, the incidence of real liver injury is approximately 3%. The incidence in the population at large is approximately 1%. Other factors which may increase the risk of developing INH hepatotoxicity include:

- daily alcohol ingestion
- co-administration of rifampicin

- the isoniazid (and other drugs) acetylator status of the patient. The rate at which these drugs are acetylated in the liver is variable from person to person and this rate appears to be under genetic control. The evidence suggests that rapid acetylators are at particular risk for the development of hepatotoxicity. This suggestion has been denied recently.

Clinical Characteristics:

The hepatic lesion is essentially a hepatitic one. Submassive hepatic necrosis and massive hepatic necrosis are rather frequent. If drug administration is continued despite the presence of liver disease, a histological picture of chronic active hepatitis progressing to cirrhosis may be seen in those patients who do not die of fulminant disease.

The onset of hepatic dysfunction is very variable. Less than half of the events begin within the first 2 months of INH therapy. The mean interval from initiation of therapy to onset of disease is approximately 3 months. The hepatic illness may be delayed for as long as 12 months after the initiation of therapy. The first evidence of disease may be an isolated elevation of SGOT. In contrast to the first syndrome, however, this usually is (or rapidly becomes) greater than 200 u/ml and is soon associated with the onset of symptoms and the development of abnormalities of other liver tests (alkaline phosphatase, bilirubin, prothrombin time).

The symptoms are usually confined to general systemic complaints, G.I. disturbances and evidence of liver disease (e.g. dark urine and jaundice). Clinical evidence of a hypersensitivity reaction is unusual and fever is uncommon except when the disease has become fulminant. Skin lesions and lymphadenopathy do not occur. Cholestasis is not a common feature of the disorder.

The lesion is variably severe. The mortality rate is approximately 10% of those recognized as having a real liver lesion. The severity and mortality are enhanced by

- increasing age
- co-administration of rifampicin
- continued administration of INH after the onset of liver injury
- underlying chronic liver disease.

Mechanism:

This is not at all clear. There is no evidence to incriminate hypersensitivity reactions in this lesion. Eosinophilia and hepatic eosinophilic infiltrates are rare and the clinical and temporal characteristics of the illness do not suggest this mechanism. The apparent dependence on acetylator status argues for the genesis of a toxic metabolite in such patients. The best candidate for such a role is acetylhydrazine which is a known hepatotoxin and is also the end product of INH metabolism by acetylation. While this notion is a very attractive one, there is serious doubt about its likelihood. The most damaging evidence has been more recent data disavowing the relationship between hepatotoxicity and acetylator status. At present it is probably enough to say that the lesion is initiated by an idiosyncratically derived metabolite which is toxic to the parenchymal cells. Which metabolite and how it is generated remains unresolved.

Implications:

These considerations lead to 2 different levels of concern with respect to isoniazid therapy.

1. *The decision to use INH.* Isoniazid remains the single most useful agent with which to treat TB and should be used in all patients with active TB except those who previously have manifested untoward reactions to the drug. The use of this drug as prophylaxis, however, should be considered on a case-by-case basis. In young patients, the cost-benefit ratio seems to be in favor of the drug but in patients more than 50 years of age, the frequency of serious liver disease (3%) and the mortality rate (>10%) argue that the indication for its use has to be substantial and the risk of death from TB has to be greater than 5 per 1000 before prophylaxis is warranted. In many instances, careful follow-up without therapy is preferable.

2. *Monitoring patients receiving INH.* Most of the abnormal results of liver tests seen in patients receiving INH will prove to be a) vagaries of the test or b) manifestations of the benign transaminasemia syndrome. Nonetheless, all patients should have monthly transaminase values checked. The evidence that early recognition of real liver injury and the early interruption of therapy in such patients can modify the severity of the ensuing lesion is substantial. A reasonable approach to the problem is to check the SGOT activity (or perhaps SGPT) each month in all patients receiving the drug but to interrupt therapy only if

   - SGOT exceeds 200 u/ml in an asymptomatic patient.
   - Abnormalities of SAP or bilirubin also develop.
   - The patient develops symptoms in company with the abnormal test result.

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CHRONIC HEPATOTOXIC:

Alpha Methyl Dopa (Aldomet)

This drug is representative of a small number of agents that are capable of causing a chronic form of hepatitis that is indistinguishable from that idiopathic form of chronic active hepatitis called "lupoid" hepatitis. Other drugs that cause a similar syndrome are oxyphenisitan (a component of many laxative preparations no longer in use) and nitrofurantoin (furadantin).

The most common hepatic reaction induced by aldomet is an acute "hepatitic" reaction. There appears to be a particular prediliction for a severe degree of cell necrosis, manifest histologically by submassive necrosis and clinically by overt symptoms and a finite risk of death from acute hepatic failure. There are reports in the literature of asymptomatic mild abnormalities of liver function occurring in as many as 35% of patients receiving aldomet. Interpretation of these data is difficult. The most likely explanation is that these abnormalities do not represent instances of true liver disease. The acute hepatitis pattern of aldomet hepatotoxicity resembles acute viral hepatitis by clinical, chemical and histologic criteria. Serologic abnormalities (Coombs' test, LE prep and ANA) may be positive transiently in this setting as well. The onset is usually within 2 months of initiation of therapy although 10% of instances occur after a longer period of therapy and reactions have developed as long as 12 months after the drug was started.

Some patients, however, do not have dramatic symptoms acutely and liver disease is not recognized until subacute injury has been occurring for many months. This is the population whose disease mimics "lupoid" hepatitis. The presentation may be insidious with clinical manifestations of fatigue, malaise and finally symptoms and signs of established chronic liver disease. Some patients have experienced a prolonged polyarthritis while others have developed skin rashes. The similarity to "lupoid" hepatitis is enhanced by the frequent findings of polyclonal gammopathy, positive ANA and LE preparations, positive Coombs' test and positive antismooth muscle antibodies. The histological features are those of chronic active hepatitis. The portal tracts are expanded with productive fibrosis, there is piecemeal necrosis with a mononuclear infiltrate, and a variable degree of intralobular cell necrosis. Bridging necrosis is common and the lesion tends to progress quite rapidly to an established cirrhosis. When the specific etiology has not been recognized, such patients have been treated with corticosteroids, often with amelioration. Discontinuation of the drug leads to resolution of disease activity but not reversal of established fibrosis. The serologic abnormalities may also reverse. Rechallenge with aldomet will excite a rather prompt relapse of biochemical abnormalities. Occasionally such rechallenges have led to very severe (even fatal) acute exacerbations.

The mechanism of aldomet-induced liver injury has not been established. It is clearly unpredictable and idiosyncratic. Eosinophilia, fever and skin rashes are not the rule but the frequent serologic abnormalities strongly suggest there is an immunologic basis to the lesions. Whether these are mediated directly by the drug itself or demand the presence of an abnormal metabolite is unresolved. Aldomet-induced liver disease has the potential of being a very grave disorder and any suspicion that links this agent with liver disease should lead to prompt withdrawal of therapy and the avoidance of any further exposure to the drug.

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CHOLESTATIC:

Phenothiazines

These drugs are generally regarded as representing the prototype of hypersensitivity mediated cholestasis. The association between chlorpromazine and acute cholestasis was recognized very soon after the drug was introduced. Several studies have assessed the risk of overt jaundice from using chlorpromazine at between 1 to 2%. Prospective studies have shown that as many as 50% of recipients will develop an impairment of BSP clearance after taking this drug. The onset of jaundice is characteristically within 4 weeks of initiation of therapy. There is often a prodrome of fever with malaise and GI symptoms and pruritus is common. There is sometimes an associated rash and often eosinophilia is present. Liver tests show a variable degree of hyperbilirubinemia, a high SAP and a mildly elevated SGOT. Liver biopsies demonstrate cholestasis, often an eosinophilic portal infiltrate, minor evidence of individual cell necrosis and not much else. No specific therapy is required and the lesion has usually completely resolved within 3 months of cessation of the drug. An occasional patient has been described who appears to progress to a chronic cholestatic syndrome even after stopping the agent. A clinical and histological picture akin to biliary cirrhosis has been observed in such patients.

The nature of the pathogenesis of this drug-induced lesion is called into question by the experimental evidence that in animals chlorpromazine, in a dose-dependent universal manner, interferes with bile secretion. The effect is predominantly on the bile salt independent fraction of bile and is believed to be linked to the demonstrable inhibition of Na^+, K^+ ATPase by this drug. Chlorpromazine is also an ampipathic molecule which allows it to intercalate into lipid bilayers (e.g. membranes). Thus, it may also alter membrane function by virtue of its physical presence in the membrane. Correlating these direct effects of the drug to the clinical circumstances which suggest a hypersensitivity reaction is not easy. In truth, the clinically apparent episodes of cholestasis may indeed be mediated by hypersensitivity reactions and be quite independent of this universal dose-dependent subclinical phenomenon.

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MIXED:

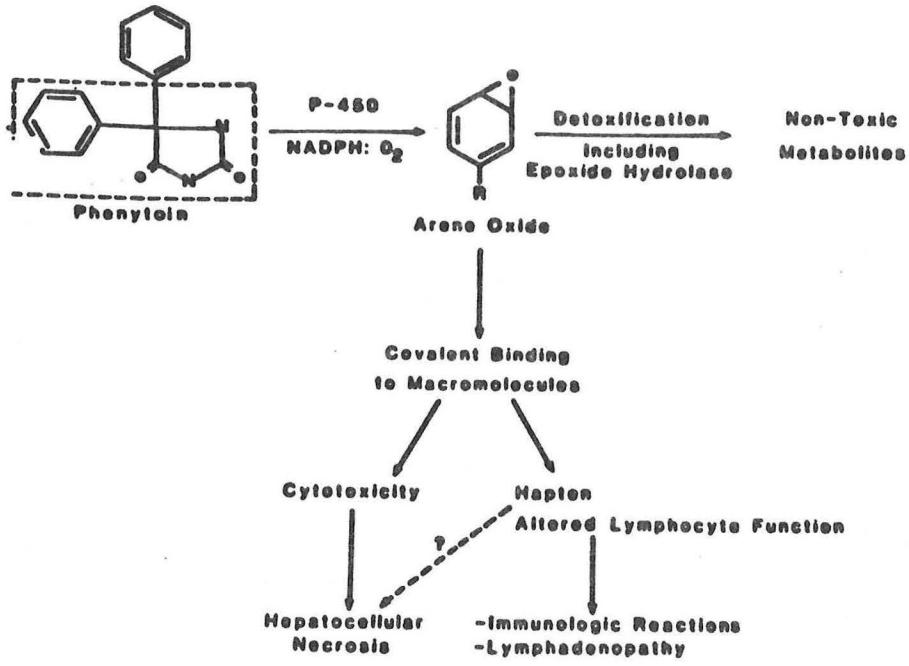
Phenytoin

Clinical Features:

This is the prototypic "hypersensitivity" drug reaction involving the liver. When present, liver disease is almost always seen in association with other classical manifestations of a hypersensitivity reaction. These most commonly consist of fever, a morbilliform erythematous rash that often progresses to an exfoliative dermatitis, generalized RE hyperplasia (lymphadenopathy and splenomegaly), leukocytosis with a left shift, atypical lymphocytosis and eosinophilia. Occasionally a Coombs' positive hemolytic anemia will be seen. The less florid syndrome may resemble mononucleosis. Skin rashes with or without fever are described in as many as 5% of patients exposed to phenytoin. Liver disease is quite uncommon but may be very serious. The onset is usually within six weeks of initiation of therapy. The clinical presentation is either hepatitic or a mixture of hepatitis with cholestasis. The severity of the hepatitis is very variable. A number of patients have developed massive hepatic necrosis and died in hepatic coma while others present primarily with features of cholestasis and have a fundamentally benign course. The pattern of liver function abnormalities is also variable. The level of serum bilirubin and the prothrombin time vary with the severity of the episode. The serum transaminases may be very high (>1000 u/ml) or may be lower in the more cholestatic forms. The serum alkaline phosphatase is usually quite high.

Mechanism:

The pathogenesis for this injury is presumed to be hypersensitivity because of the associated clinical features and because the drug has been shown to stimulate lymphoblast transformation in affected individuals. Circulating anti-phenytoin antibodies have also been described in survivors of this reaction. Recently, Spielberg et al have demonstrated that metabolites of phenytoin but not phenytoin itself are cytotoxic in a dose-dependent manner to lymphocytes derived from patients who have recovered from phenytoin-induced liver disease. This reaction was not seen in normal controls or in persons taking the drug without side effects. Family studies suggested that this predisposition may be transmitted as an autosomal recessive characteristic. A similar pattern of lymphocyte toxicity could be produced in control cells by the addition of a compound which selectively blocked the subsequent metabolism of arene oxides, the putative toxic intermediates of phenytoin degradation.



Pathway of Phenytoin Metabolism and Proposed Role of the Arene Oxide Metabolites in the Pathogenesis of Hepatotoxicity.

from Spielberg, S. P., et al, N.E.J.M. 1981.

The accumulation of these electrophilic intermediates would lead to their covalent bonding with intracellular macromolecules. In order to link these observations to the evidence for hypersensitivity in the pathogenesis of these reactions, it would be necessary for these complexes to serve as haptens and incite the immunologic consequences seen clinically in the reactions associated with this drug.

Pathology:

The pathology of this hepatic lesion is a variable combination of cholestasis with hepatic cell necrosis. The inflammatory infiltrate is generally mononuclear and there is almost always an increased number of eosinophils in the portal triads. On rare occasions a granulomatous reaction has been noted to accompany these changes.

Therapy:

Steroid therapy has been effective in dealing with the associated features (fever, skin rash, etc.) of phenytoin reactions. The value of such therapy for the liver disease is less clear although occasional patients seem to respond dramatically to these agents and to relapse if they are withdrawn too precipitously. It is recommended that patients with phenytoin-induced liver disease be treated with high dose steroid therapy and that the drug be withdrawn gradually over 3-4 months, even if the patient's clinical response is complete in a couple of weeks.

Other Effects:

It is important to distinguish phenytoin-induced liver disease from phenytoin-induced alterations in liver tests. A number (perhaps 30%) of patients receiving this drug long term will develop an increase in the serum activity of alkaline phosphatase. This has two potential origins. One is the interference phenytoin is known to have on the metabolism of vitamin D. The consequence is a decrease in 25-hydroxyvitamin D, metabolic bone disease, a tendency to hypocalcemia and an increase in SAP from skeletal sources. Phenytoin is, as well, a powerful enzyme inducer and in some chronic users it will cause a dramatic increase in the smooth endoplasmic reticulum of hepatic parenchymal cells. This may be profound enough to be visible under light microscopy as "ground glass" cells. These cells in contradistinction to those seen with the HBsAg carrier state do not stain with orcein or aldehyde fuchsin. This generalized enzyme induction may also account for an elevation in the hepatic isoenzyme of serum alkaline phosphatase.

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OTHER FORMS OF LIVER INJURY

VASCULAR LESIONS

Budd-Chiari Syndrome:

This syndrome is the consequence of occlusion of the normal hepatic venous blood flow. The site of the obstruction to flow may be anywhere from the terminal hepatic venules to the right atrium. Most commonly there is thrombosis of the major hepatic veins near their entry into the inferior vena cava. Clinically this syndrome is characterized by the abrupt onset of right upper abdominal pain, marked hepatomegally and the development of a high protein transudative ascites. Chemically, the serum bilirubin elevation is quite mild but there is a disproportionate prolongation of the prothrombin time. The SGOT may be transiently very high but this peak may be missed and only low grade elevations may be documented. The alkaline phosphatase is variably increased. If the occlusion is complete, the patient progresses to acute hepatic failure and there is an extremely high mortality rate. Less complete occlusion is compatible with a state of chronic disease in which the consequences of portal hypertension become more important. The patient develops splenomegally and varices and, as the serum albumin drops, there is peripheral edema. A protracted but still nasty illness is the consequence. Histologically there is ischemic necrosis with hemorrhage

involving the pericentral cells of the hepatic lobules. These zones of necrosis may link once with another and ultimately fibrous tissue is deposited in the necrotic areas. A picture equivalent to cardiac cirrhosis is the end result.

Oral contraceptive agents have been associated with the development of the Budd-Chiari syndrome in at least 30 instances. Other episodes have occurred during pregnancy. It is not entirely certain which progestational hormone is responsible but the venous thrombosis found in the major hepatic veins has been ascribed to the known thrombogenic effects of the estrogen component of these preparations.

A similar clinical syndrome has been described in patients receiving 6-thioguanine for leukemia, in patients following bone marrow transplantation and in some patients receiving azathioprine for renal transplantation. In these patients the occlusion has been in the small hepatic venules. The condition is called *veno-occlusive disease* and was originally described in children in Jamaica and South Africa exposed to pyrrolizidine alkaloids from plants of the Senecio species.

Peliosis Hepatis

The histologic hallmark of this disorder is the presence of blood-filled lacunae in the liver. These are of variable size and may become very large and clearly visible microscopically. The earliest manifestation of the disorder is the random dilatation and congestion of hepatic sinusoids with sequestration of red blood cells and atrophy of the adjacent parenchymal cells. Original descriptions of this lesion linked it to chronic wasting disorders (malignancies and granulomatous diseases). More recently the important association of this lesion and a number of different drugs has been made. Both contraceptive and anabolic steroids have been shown to be associated with peliosis hepatis. Usually there is an associated tumor (adenoma or hepatoma) but peliosis may be the sole lesion with either agent. An association between azathioprine therapy and peliosis in renal transplant recipients has been established recently. These patients often have a cholestatic injury as well.

The clinical consequence of peliosis may be none, or the patient may present with hemoperitoneum from rupture of the liver, or with evidence of portal hypertension or with signs of acute liver failure.

Tumors:

Estrogens have been directly linked with the development of hepatic adenomas. These lesions may be quite estrogen-dependent although this is not always true. Androgens have been associated with hepatoma development. Occasionally, the reverse associations have been described (i.e. hepatoma with estrogens and benign tumors with androgens). Other tumors such as the hemangioentotheliomas (and hepatomas) associated with thorotrast exposure have been described as being the consequence of drug therapy.

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