LIVER INJURY IN THE SURGICAL PATIENT: A CRITICAL REVIEW

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SUMMARY

This is a critical review of the reports of postoperative jaundice and liver necrosis that have been published during the past twenty-five years. Postoperative liver damage has the following causes: transmitted, provoked, or coincidental viral infections; acute sepsis and septicemia states; blood transfusion; widespread vasoconstriction with hypotension lasting more than twenty-four hours; allergic reactions to antigenic substances; alleged "hypersensitivity" to drugs to which antibodies cannot be identified; the direct effects of certain therapeutic agents on the liver; surgical trauma to the liver and its appendages; and postoperative pancreatitis. Several of these factors may operate simultaneously in the patient recovering from a surgical operation and in these circumstances it is impossible to dissociate one particular cause from the others. The syndromes of viral hepatitis and drug "hypersensitivity" are indistinguishable. Both are associated with fever, skin rashes, leucopenia, arthralgia, cholestatic jaundice, and liver necrosis with a mononuclear infiltration of the liver. Both are peculiar to man and the time interval between the exposure to risk and the appearance of jaundice varies from less than seven days to more than three months. The development of immunity to the one or desensitization from the other is not universal. There is no inhalational anaesthetic agent in common use which comes within the definitions of directly or indirectly hepatotoxic substances. The pharmacological methods of screening inhalational anaesthetic agents for hepatotoxicity have always been reliable and there is no reason to doubt their efficacy at the present time.

During the past two years several attempts have been made to impute liver necrosis to anaesthesia. Much of the information on which the attempts were based was put forward by persons without responsibility for either the anaesthesia or the surgical treatment of the patients involved and who gave no indication of their right to publish clinical data obtained in this manner. A typical example is to be found in the report of Lindenbaum and Leifer (1963). These physicians, with no apparent connection with anaesthesia or surgery, collected nine cases of transient postoperative liver dysfunction and suggested that halothane was the cause. In their attempt to implicate the anaesthesia they not only ignored the fact that similar hepatic reactions have been reported not infrequently for the past thirty years but they also failed to acknowledge the permission of the anaesthetists and surgeons to publish the case records. This is a disturbing departure from the accepted procedure of medical journalism and practice. Those responsible do not appear to have realized that the nature of clinical anaesthesia—and of surgery—places its practitioners in a situation which is unlikely to be improved by the irresponsible spon- taneity of clinical naivété. It would seem desirable, therefore, in the interests of anaesthesia, to review briefly some of the more informative reports concerning the liver and its reactions to drugs, disease, and trauma, with particular reference to the liver dysfunction which may follow surgical operations.

It is axiomatic that a substance which is directly hepatotoxic in man will readily cause liver necrosis in most, if not all species of animal; chloroform...
and carbon tetrachloride are notable examples (Himsworth, 1950). At the present time there is no anaesthetic drug in common use which will cause liver necrosis in both man and the experimental animal.

Investigations of the liver function of patients before and after major operations performed under modern anaesthetic methods have failed to reveal any deterioration beyond that normally expected after major surgery (Sadove and Wallace, 1962). The degree of postoperative liver dysfunction appears to be unal influenced by the type of anaesthesia used (Little and Given, 1964; Joseph, 1964). Retrospective studies of the incidence of postoperative liver failure have shown it to be relatively unaltered irrespective of the changes which have occurred in anaesthetic methods (Dawson et al., 1963; Mazzia, 1963; Keéri-Szántó and Laffeur, 1963; Wilson, Tarrow and Garvin, 1964; Allen and Metcalf, 1964; Slater et al., 1964; Mushin et al., 1964; Reichmann and Wohlgemuth, 1964; Collins and Fabian, 1964; Henderson and Gordon, 1964).

Every case of postoperative jaundice that has been published during the past twenty-five years has described, in addition to the anaesthesia, the simultaneous use of agents and procedures that are known to cause liver damage from time to time. In most instances the significance of the non-anaesthetic factors was appreciated.

The incidence of postoperative liver failure is low, but there is reason to believe that it may be on the increase. Viral hepatitis is spreading rapidly during recent years according to a symposium on the subject (McCullum, 1962). The chance of coincidental, provoked, or transmitted, postoperative hepatitis is therefore increased. If the hepatic hazards of chemotherapy, as described by Ticktin (1963) in another symposium, are to be accepted, the incidence of postoperative liver damage must increase inevitably as the number of drugs administered to patients before and after operations becomes increasingly large. The causes of postoperative liver failure may therefore be conveniently divided into four groups:

Viral hepatitis.
Blood transfusion.
The direct and indirect effects of trauma.
The direct and indirect effects of drugs.

VIRAL HEPATITIS

Viral hepatitis may develop in surgical patients from infection acquired before, during or after the surgical operations. The disease is increasing at what is authoritatively described as a "tremendous" rate (Havens, 1962; McNeel, 1952). Several reports of unusually severe epidemics have appeared simultaneously with those ascribing hepatotoxicity to anaesthesia (Bothwell et al., 1963; Schreier and Khodabakhsh, 1963; Dougherty and Alman, 1962; Gabinus and Jonsson, 1962). The growing importance of viral hepatitis in relation to public morbidity and mortality has been emphasized, particularly as the incubation period may be as low as fifteen days (McCollum, 1962). In a recent outbreak, due to the ingestion of infected food, it was stated that the symptoms often appear within a week or ten days after infection (Hunter, 1964).

It has been estimated that about 100 patients per million of those anaesthetized may develop coincidental viral hepatitis at any time from one week to several weeks after the anaesthesia (Bunker and Blumenfeld, 1963; Mungavin, personal communication, 1963). Mungavin's report was based on the incidence of infective hepatitis in Australia where the disease is notifiable, the Morbidity Statistics from General Practice in Britain, and on the distribution by age of patients having operations under general anaesthesia at the Royal Infirmary, Cardiff. The estimate of Bunker and Blumenfeld was based on the new cases of viral hepatitis reported to the U.S. Public Health Service during 1961 and covers the whole of the U.S.A. A sub-acute or chronic form of the disease may occur in postmenopausal women, the aged, the infirm (Tisdale, 1963; Schaffner and Popper, 1959), in those previously exposed to major surgery (McDonald and Mallory, 1958), and may simulate disease of the gall bladder and bile ducts (Stauber, 1962). Surgical operations and intercurrent illnesses may precipitate acute exacerbations of chronic viral hepatitis (Tisdale, 1963). The earlier symptoms may simulate those of an acute surgical condition in the abdomen (Gowan, 1964). Operations on patients in the acute phases of the infection carry a high mortality rate from liver failure (Harville and Summerskill, 1963). Deaths from what appear to be viral hepatitis have
occurred shortly after operations under cyclopropane anaesthesia (Bennike and Hagelsten, 1964). The drinking of orange juice prepared by a cook with sub-clinical hepatitis recently caused an epidemic of viral hepatitis in a general hospital (Eisenstein et al., 1963). The incubation period varied from 20 to 42 days and the clinical signs included fever, anorexia, abdominal pain, jaundice, myalgia, skin rash, rigors, hepatomegaly, splenomegaly, leucopenia with atypical lymphocytes and cervical lymphadenopathy. It was noted that hepatitis developed in patients without the obvious manifestation of the disease as well as in those with jaundice, the ratio of sub-clinical to overt cases being 12 to 1. Skin rashes of the allergic or sensitivity type have often been reported during the acute phases of viral hepatitis (Goldgraber and Kirsner, 1961; Ballance, 1950). It has been estimated that the carrier rate among the healthy population may be at least 6 per cent (Capps, Sborov and Scheiffley, 1948).

The disease is equally prevalent in children and neonates and the development of immunity is not universal (Schreier and Khodabakhsh, 1963). The suggested measures for preventing its spread in hospitals include the dry-heat sterilization of equipment, the use of sterile disposable syringes and needles, the serving of food on paper plates and containers and individual allocation of toilet paper.

It has been suggested that there may be a connection between the virus of infective hepatitis and the occurrence of neoplastic changes in the genital epithelium of women (Ferguson and Arias, 1963). One-third of thirty-six women suffering from acute viral hepatitis were found to have cytological changes indicative of uterine neoplasm, an incidence which is far in excess of that occurring in patients with presumably normal livers. This suggestion may have a bearing on the occasional occurrence of liver necrosis after radiotherapy under anaesthesia for carcinoma of the uterus, though irradiation per se may impair the liver function (Snively, Bullington and Schlosser, 1953).

Twenty-five years ago it was generally believed that arsphenamine caused liver damage in man, though the pharmacological evidence for this was not convincing. In some anti-syphilitic clinics the incidence of jaundice during or following therapy was as high as 68 per cent of all patients treated (Salaman et al., 1944). Similar hepatotoxic reactions were also observed after the parenteral injection of substances such as insulin, gold, bis-muth, penicillin, thiopentone, tetanus toxoid, typhoid, yellow fever vaccines, and other preparations derived from human serum (Hawley, McFarlan and Steigmen, 1944). The interval between the injection and appearance of the jaundice varied from 16 to 200 days and deaths from massive necrosis of the liver followed occasionally (Sherwood, 1950; Lucké and Mallory, 1946).

During World War II it was convincingly shown that the inadequate sterilization of needles and syringes and the use of multi-dose containers for the drugs permitted the transmission of an hepatotropic virus which frequently caused jaundice and occasionally fatal liver necrosis. The aetiology was confirmed by the experimental inoculation of volunteers. The disease was virtually eliminated in some places by the more stringent application of aseptic methods. However, the preventive measures were not adopted universally as the disease was later described as “hospital hepatitis” (Rosenthal, 1948) when it was realized that a skin puncture for any therapeutic or diagnostic reason might transmit the virus. The problem was surveyed by Sherwood (1950) who suggested that the only reliable way to avoid the transmission of the virus during parenteral injections was to use sterile disposable syringes and needles and to issue all drugs in sterile, pyrogen-free, single-dose ampoules.

Sherwood’s recommendations have still not been universally adopted. Some drugs are still issued in multi-dose containers, including several of those used regularly in clinical anaesthesia. The most lethal outbreak of viral hepatitis, with a 37 per cent mortality rate, was traced to the intravenous injections from multi-dose containers of short-acting barbiturates similar to those used for the induction of surgical anaesthesia (Dougherty and Altman, 1962).

Other occasionally hepatotropic viral and viral-type infections to which surgical and obstetric patients are not immune include infective mononucleosis (Stevens, Bayrd and Heck, 1951; Ross, 1964), the Coxsackie viral infections (O’Shaug-
nessey and Buechner, 1962), and benign lympho-cytic choriomeningitis (Rivers and Horsfel, 1959; Smadel et al., 1942). One of the symptoms which is regarded as characteristic of these infections, including viral hepatitis, is generalized aches and pains—arthralgia and myalgia—associated with fever and rigors. Septicaemias, bacteraemias and other incidental infections may still complicate surgery and affect the liver; the consequences are usually obvious (Popper and Schaffner, 1957; Weil, Shubin and Biddle, 1964).

**BLOOD TRANSFUSION**

During the Korean War it was estimated that 3.6 per cent of the patients treated by blood trans-fusions and 31.9 per cent of those given the blood plus plasma transfusions developed viral hepatitis; ultra-violet irradiation of the blood prior to trans-fusion had no effect on the incidence of the trans-mitted hepatitis (Sborov, Giges and Mann, 1953). Japanese workers (Shimizu and Kitamoto, 1963) performed bi-weekly liver function tests for three months on 175 patients who received blood transfusions during major surgical operations. In all cases the serum transaminases and icteric indices were normal pre-operatively. From the postopera-tive changes observed in the sera transaminases, icteric indices and liver biopsies, it was concluded that 64.5 per cent of the patients developed viral hepatitis after blood transfusion, the incubation period varying from less than 14 days to more than 11 weeks. Their results confirmed the belief that most patients with viral hepatitis remain an-icteric, as only 1 in 10 of their patients became obviously jaundiced despite the usual changes in the other parameters.

The death in hospital of a patient from chronic post-hepatitic cirrhosis of seventeen years dura-tion has been reported (Greutzfeldt et al., 1963). It was subsequently discovered that the deceased had been a professional blood-donor to the hospi-tal for ten years. A retrospective study of the hos-pital records revealed that postoperative jaundice had occurred in at least nine patients who had received blood from this donor and one of them died from postoperative liver necrosis on the twenty-fifth day after the operation. The incidence of viral hepatitis after blood transfusions in the United States is about 3 per cent with a 1 per cent mortality rate mainly affecting patients over the age of 40 years (Allen and Sayman, 1962). The collection of blood from voluntary donors under the most careful conditions carries a 1.86 per cent incidence of transmitted hepatitis with an incubation period varying from 22 to 145 days (Adashek and Adashek, 1963).

Blood transfusion occasionally causes jaundice from causes other than hepatitis, incompatibility and intravascular haemolysis (James, 1954). Sevitt (1958) reported transient jaundice in sixteen in-jured patients shortly after blood transfusion. The jaundice was partly of hepatic origin and partly due to the overloading of the circulation with bilirubin from the transfused blood when the hepatic function was impaired by traumatic shock. In one of his cases the jaundice appeared within 6 hours of transfusion and was not related to haemolysis or incompatibility.

Pichlmayr and Stich (1963) have reported simi-lar reactions in patients after major operations performed under general anaesthesia. The anaes-thetic methods included halothane-oxygen, nitrous oxide-relaxant, and neuroleptanalgesia. The jaundice usually appeared within 24 hours of the operations and occurred most frequently after operations lasting more than 4 or 5 hours. They considered the icterus to be bilirubinostatic caused primarily by the transfusion of blood more than 10 days old at a time when the recipient's hepatic function was impaired by surgical trauma. They made the interesting suggestion that the bilirubinostasis might be an acquired form of the hereditary Rotor syndrome.* Similar postoperative hepatic reactions have also been reported after major gynaecological operations performed under spinal or ether anaesthesia (Chakravorty, 1962).

**THE EFFECTS OF DIRECT AND INDIRECT TRAUMA**

**Direct trauma.**

Surgical operations in the upper abdomen in-volving prolonged retraction on the liver and its appendages continue to cause postoperative jaun-dice and liver damage from time to time (Braasch and Preble, 1963; Glenn and Hays, 1952; Zam-check, Chalmers and Davidson, 1949). Hepato-renal failure or the so-called hyperpyrexial "liver-

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*Familial non-haemolytic jaundice with conjugated bile in the serum (Schiff, Billing and Oikawa, 1959).
"death" syndrome has been described as an important cause of death in surgery of the biliary tract as well as in thyroid disease and an occasional cause of death after other operations (Sutton, 1943; Boyce, 1941; Wilensky, 1939). A recent investigation by Reichmann and Wohlgemuth (1964) indicates that advances in anaesthetic and surgical techniques have not eliminated this syndrome. Jaundice which appears after a cholecystectomy is a grave omen and may be due to biliary calculi, cholangitis, a blocked T-tube, blood clot, oedema of the ampulla of Vater, pancreatitis, or damage to any portion of the extrahepatic biliary passages (Maingot, 1963) or to the hepatic artery and its branches (Pass, 1935). Prolonged or heavy retraction on the liver or on the gastro-hepatic omentum may be followed by the signs of liver necrosis (Ravdin and Vars, 1950; Edlund and Zettergren, 1957). Infarction of the liver from disease or during operations such as mitral valvotomy may precipitate acute liver failure (Pass, 1935; Robertshaw, personal communication, 1964).

At the Mayo Clinic during the years 1958–59 acute postoperative pancreatitis was responsible for 12 per cent of the deaths following surgery of the biliary tract and pancreas (Ferris et al., 1961). It is an occasional cause of death after other operations (Saidi and Donaldson, 1963; Ponka, Landrum and Chaikof, 1961). Acute pancreatitis may cause either cholestatic or hepato-cellular jaundice as the result of oedematous obstruction of the bile duct or ischaemic necrosis of the liver respectively (Weinstein, Korn and Zimmerman, 1963; Reis, 1963; Roberts, Baggenstoss and Comfort, 1950).

Indirect trauma.
Necrosis of the liver, kidneys, and myocardium are common pathological findings when death is preceded by acute shock or acute circulatory collapse lasting more than 24 hours prior to death (Ellenberg and Osserman, 1951; Bywaters, 1946). A high proportion of severely injured patients show central and midzone necrosis of the liver sometimes within 24 hours of the injury. Shock due to haemorrhage, coronary occlusion, burns, narcotic or chemical poisons, sepsis, the hypoxia of low atmospheric pressure or high altitude, heatstroke, abdominal surgery and anaphylaxis, may cause parenchymatous degeneration and necrosis of the liver, kidneys and heart (Moon, 1948). Pulmonary embolism may also cause the sudden appearance of jaundice, particularly in patients with myocardial insufficiency (Keefer and Resnick, 1926). The aetiological factor which is common to all these conditions appears to be ischaemia of the liver from blood loss, hypotension and vasoconstriction. The mode of onset and the pathological appearance of the liver in these circumstances are indistinguishable from those caused by chloroform both in man and the experimental animal (Ellenberg and Osserman, 1951). It is therefore believed that centrilobular necrosis of the liver is a non-specific change which is simply a manifestation of anoxaemia, vasoconstriction, or acute circulatory insufficiency lasting more than 24 hours.

A precipitous increase in the incidence of hepatic necrosis during the years 1950 to 1955 was attributed by Brunson, Eckman and Campbell (1957) to the excessive use of pressor amines in the treatment of surgical and other forms of shock. This figure was based on the records of 3,229 autopsies performed at the University of Minnesota Hospitals, Minneapolis. They observed in dogs, that a single dose of any one of the sympathomimetic amines including methoxamine, mephentermine, phenylephrine, adrenaline and noradrenaline may cause diffuse necrosis of the liver. An interesting corollary is the observation that adrenolytic drugs and sympathetic blockade appear to protect the liver from the toxic effects of carbon tetrachloride (Brody, 1963).

THE DIRECT AND INDIRECT EFFECTS OF DRUGS

The direct effects of drugs.
A drug which is directly hepatotoxic has the following characteristics (Klatskin, 1960):

(1) It invariably causes hepatic injury when administered in sufficient doses.
(2) The severity of the lesion produced is directly related to the dose.
(3) Identical lesions are reproducible in most if not all experimental animals.
(4) The morphology of the lesion is characteristic for any given agent and is identical in all species.
The latent period between the acute exposure and the appearance of the hepatic damage is constant and almost always brief. None of the drugs used in clinical anaesthesia, with the exception of chloroform and possibly divinyl ether, has these characteristics.

The indirect effects of drugs.

Many of the drugs used today in the treatment of medical and surgical diseases are associated with an increasing incidence of jaundice and liver necrosis which are thought to be due to a process of sensitization. Comprehensive treatises by Ticktin (1963) and by Goldgraber and Kirsner (1961) provide much useful information and over 900 references on the hepatotoxicity of therapeutic agents. Many of the drugs are commonly used on patients either before, during or after surgical operations. They include several in the antibiotic, antidepressant, anticonvulsant, antihypertensive, oral hypoglycaemic, tranquilizer, sedative, diuretic, antineoplastic, analgesic and steroid groups. The relaxant zoxazolamine (Flexin) has also been implicated (Zimmerman, 1963).

The circumstances in which jaundice appears during treatment with some of these agents make it reasonable to suspect that the drugs may be indirectly responsible. The incidence of the complication with others is no greater, however, than one would expect from coincidental viral hepatitis, a disease which the drug-reaction simulates to a remarkable degree (Kline, 1964; Popper et al., 1963; Griffith and Oblath, 1962). The mode of action of these drugs in causing liver damage is obscure as the lesion cannot be reproduced in animals and specific antibodies to them cannot always be detected. The recent application of the electron-microscope to the study of the problem in animals has produced evidence that some of the drugs, including the steroids and chlorpromazine, may damage the bile-secreting apparatus of the hepatocytes (Schaffner and Kniffen, 1963). Autoimmunity and genetic differences have also been invoked to explain the hepatic reactions to some drugs (Kalow, 1963; Havens, 1963).

The liver injury alleged to be due to the development of an "allergic" or "hypersensitive" reaction to a drug has the following features (Klatskin, 1960).

(1) Only a small fraction of exposed persons are affected, neither the appearance nor the extent of the lesion having any relation to the dose.

(2) Similar lesions cannot be reproduced in animals even when the drugs are given in fatal doses.

(3) The morphology of the lesion is less constant than is the case of that caused by hepatotoxins.

(4) The interval between the start of the drug therapy and the appearance of the liver injury is highly variable, being as short as a few hours in some instances and as long as many months in others.

(5) The hepatic lesions are often accompanied or preceded by other signs such as fever, skin rashes, arthralgia, lymphadenopathy, eosinophilia and the disturbances of renal and haemopoietic functions generally regarded as part of the hypersensitivity syndrome.

Drug sensitivity with liver damage in man began to appear shortly after the introduction of the sulphonamides and penicillin (Menten and Andersch, 1943; French, 1946; More, McMillan and Duff, 1946; Waugh, 1952; Kern and Wimberley, 1953; Jamar, 1959). Other antibiotics have since been implicated, including aureomycin (Lepper et al., 1951), erythromycin (Herrold, Robson and Smith, 1958; Ticktin and Robinson, 1963), chloramphenicol (Cable and Reid, 1957; Foot and Thompson, 1963), novobiocin (Haubrich, 1959; Lokietz, Doroben and Hsia, 1963), tetracyclines (Schultz et al., 1963), and triacyctyleandomycin (Montes, Middleton and Fisher, 1962; Robinson, 1962). The liver reactions are sometimes severe and fatal, and have occurred in patients recovering from surgical operations. Rutenberg and Pinkes (1952) reported fifteen cases of transient postoperative jaundice due to aureomycin. Deaths from postoperative hepatorenal failure related to penicillin or sulphonamide sensitivity have also been recorded (Lichenstein and Fox, 1946; French, 1946; More, McMillan and Duff, 1946; Murphy and Mirales, 1962; Corrin, 1964).

It has been stated that a drug which causes any of the commoner manifestations of sensitivity—
skin rashes, fever and eosinophilia—will sooner or later cause jaundice in some patients (Klatskin, 1960). Sabesin (1963) has shown conclusively that the antigen-antibody reaction in the livers of animals sensitized to a specific antigen will rapidly cause widespread liver necrosis. He used the protein antigen ferritin to sensitize guineapigs and confirmed the presence of allergy by the appropriate tests. Liver necrosis followed the injection of small amounts of antigen into the portal circulation. The latter route of injection avoids death of the animal from anaphylaxis. The initial changes in the liver parenchyma appear within 15 minutes after exposure to the antigen and are rapidly followed by coagulative necrosis and total destruction of the parenchyma. The damaged tissue is infiltrated with acute inflammatory cells, extravasated erythrocytes and lipochrome pigment. Electron microscopy revealed the cause of the necrosis to be infarction of the liver from the occlusion of the sinusoidal system with antigen-antibody thrombi.

It would appear that a substance which produces circulating antibodies may cause liver necrosis if the subject survives the initial anaphylaxis and sufficient numbers of the antigen-antibody complexes reach the liver. Penicillin and its analogues are the commonest antigens in use and circulating antibodies to them have been recognized (Wagelie, Dukes and McGovern, 1963; Schwartz and Vaughan, 1963; Levy et al., 1958). Hepato-renal failure has occurred in patients who survived the initial anaphylaxis, some of them whilst recovering from surgical operations (Valdivia-Barriga, Feldman and Orellana, 1963; Murphy and Miraes, 1962; Baker, 1951; Felder and Felder, 1950). It has been estimated that at least 10 per cent of the patient population of the United States has been sensitized to penicillin (Shelley, 1963).

Cholestatic and hepatocellular jaundice are commonly attributed to treatment with phenothiazine drugs (Zimmerman, 1963), which include chlorpromazine (Goldgraber and Kirschner, 1961), promazine (Herron and Bourdo, 1960), and prochlorperazine (McFarland, 1963; Weinstein, Alper and Dade, 1959). The cause is presumed to be the development of sensitivity because of the associated fever, skin rash, rigors and eosinophilia. Readministration of small doses of the drugs results in the prompt recurrence of hepatitis in approximately 70 per cent of patients who have had chlorpromazine jaundice (Hollister, 1957). Circulating antibodies have not been demonstrated, however, and the syndrome cannot be reproduced in animals.

Prochlorperazine (Compazine) therapy has been associated with the appearance of jaundice in patients recovering from surgical operations (Mechanic and Meyers, 1958; Soloman and Campagna, 1959; Lindenbaum and Leifer, 1963). Other drugs which may be used in conjunction with surgical therapy and which have been held responsible for causing liver damage include phenylbutazone (MacCarthy and Jackson, 1955), para-aminosalicylic acid (Smetana, 1963), isoniazid, iproniazid, thiouracil (Trucco, Argonz and Gambin, 1948), propylthiouracil (Eisen, 1953; Walzer and Einbinder, 1963), barbiturates (Welton, 1950; Young, 1957), the anticoagulants (Perkins, 1962; Baker and Williams, 1963), the anabolic steroids (Yanoff and Rawson, 1964) and others. Most of these compounds have been dealt with in detail in the reviews of Ticktin (1963), Goldgraber and Kirschner (1961) and Carr (1954). Other substances which occasionally cause severe sensitivity reactions are the organic iodides which are used as contrast media in radiography and other diagnostic procedures (Crocker and Vandam, 1963; Hansen and Crampton, 1963; Schimmel, 1964; Fisher and Fisher, 1963; Margolis and Yeasimides, 1962; Malt, Olken and Goade, 1963), and dextran (Getzen and Speiggle, 1963); these substances are not infrequently administered to anaesthetized patients.

It seems unlikely that the commonly used inhalational anaesthetic drugs will provoke the sensitivity reaction. The exposure time is relatively short and their excretion is rapid and complete. They do not combine with protein and they are not, as far as can be ascertained, subject to metabolic degradation processes. Anaphylaxis and the common manifestations of allergy have not been observed in persons constantly exposed to small doses—anaesthetists, nurses and laboratory workers. It has been suggested that the exposure of patients to repeated anaesthesias with halothane may precipitate sensitivity reactions to halothane.
LIVER INJURY IN THE SURGICAL PATIENT: A CRITICAL REVIEW

It should not be forgotten that "repeated anaesthesias" in the modern idiom implies the repeated parenteral injections of several other drugs over a period of time which exceeds the minimum incubation period of viral hepatitis. Sensitivity to atropine, particularly in the form of urticarial and erythematous skin rashes, is not uncommon and may appear during anaesthesia if the atropine is administered shortly before or during induction (Schroeder, 1963). Suxamethonium has also produced what appears to be a mild anaphylactic type of reaction (Fellini, Bernstein and Zauder, 1963).

CONCLUSION

The liver is a pharmacological and immunological enigma and will remain so until a specific diagnostic test for viral hepatitis is discovered. The syndromes of viral hepatitis and drug sensitivity are indistinguishable. Both are associated with fever, skin rashes, leucopenia, arthralgia, cholestatic jaundice and liver necrosis with a mononuclear infiltration of the liver. Both are peculiar to man and the time interval between the exposure to risk and the development of lesions is variable, being less than 7 days in some instances and more than 7 months in others. The development of immunity to the one or desensitization from the other is not universal.

It is clear from the evidence available in many published reports that postoperative jaundice may be caused by trauma, shock, hypoxia, blood transfusion, sensitivity to antigenic drugs, vaccines, antisera and viral hepatitis. Several of these factors may operate simultaneously in the patient recovering from a surgical operation; in these circumstances it is impossible to dissociate one particular cause from the others.

At the present time there is no inhalational anaesthetic agent in common use which comes within Klatskin's definitions of directly and indirectly hepatotoxic substances. The pharmacological methods of screening inhalational anaesthetic agents for hepatotoxicity have always been reliable and there is no reason to doubt their efficacy at the present time. Nevertheless, it cannot be denied that postoperative liver failure is still a threat, albeit a small one, to the surgical patient. It is suggested, therefore, that the following recommendations may help towards a better understanding of the situation:

(1) In the event of hepatitis appearing unexpectedly in a patient recovering from a surgical operation the various possibilities of exposure to a viral infection should be explored in the patient's hospital and home environments. Serological tests for hepatotropic viruses should be applied as far as possible. Viral hepatitis should be made a notifiable disease.

(2) The use of sterile disposable syringes and needles and the issuing of drugs in single-dose ampoules are among the prerequisites for safety in anaesthesia and in all forms of parenteral therapy, as is the use of disposable equipment for blood transfusion.

(3) All patients prior to anaesthesia should be carefully questioned as to previous treatment with, and reactions to, all forms of therapy likely to be associated with the development of sensitivity or allergy. All such treatment should be withheld until declared safe after the appropriate clinical evaluation.

(4) Skin sensitivity or the serological tests for allergy should be applied to patients showing signs of unexpected liver damage after surgical operations, using as antigens all drugs, vaccines, and antisera administered before, during, or after the operations.

(5) Sabesin's (1963) method for producing allergic liver necrosis in animals should be extended as far as possible to include all drugs known or suspected to cause allergy in man.

(6) Editors and others responsible for the publication of reports on adverse reactions during or following anaesthesia should ensure that the full data are presented in their proper perspective and that the professional propriety is preserved.

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LIVER INJURY IN THE SURGICAL PATIENT: A CRITICAL REVIEW


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LESIONS DU FOIE CHEZ LE MALADE CHIRURGICAL: UNE REVUE CRITIQUE

SOMMAIRE
Voici une revue critique des rapports d’ictère et de nécrose hépatique post-opératoire qui ont été publiés au cours de ces dernières vingt-cinq années. Les lésions hépatiques post-opératoires ont les causes suivantes: infections virales transmises, provoquées et coïncidentes; septicémie aiguë et états septique-miques; transfusion sanguine; vasoconstriction étendue avec hypotension durant plus de vingt-quatre heures; réactions allergiques à des substances antigéniques; "hypersensibilité" confirmée à des drogues pour lesquelles on ne peut pas identifier des anticorps; effets directs de certains produits thérapeutiques sur le foie; lésion chirurgicale du foie et de ses annexes; pancréatite post-opératoire. Plusieurs de ces facteurs peuvent agir simultanément chez un malade qui se remet d’une opération chirurgicale et dans ces circonstances il n’est pas possible de dissocier un facteur particulier des autres facteurs. Le syndrome d’hépatite virale et "l’hypersensibilité" medicamenteuse ne peuvent être dissociées: toutes les deux accompagnent de fièvre, de rashes cutanés, de leucopénie, d’arthralgies, d’ictère cholostatique et de nécrose hépatique avec infiltration mononucléaire du foie. Toutes les deux sont particulières à l’homme et l’intervalle qui sépare l’exposition au risque et l’apparition de l’ictère varie de moins de sept jours à plus de trois mois. Le développement d’une immunité envers l’une et d’une désensibilisation envers l’autre n’est pas universel. Il n’existe aucun agent anesthésique d’inhalation et d’usage courant qui soit suspect d’avoir un effet hépatotoxique direct ou indirect. Les méthodes pharmacologiques utilisées pour détecter une action hépatotoxique chez les anesthésiques inhalatoires ont toujours été fidèles et dans l’état actuel des choses il n’y a aucune raison de mettre en doute leur efficacité.

LEBERSCHÄDIGUNG BEI CHIRURGISCHEN PATIENTEN: EINE KRITISCHE LITERATURDURSICHT

ZUSAMMENFASSUNG