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Progress report

Hepatic reactions to drugs*

The liver is particularly concerned with drug metabolism and especially with drugs given orally (Fig. 1). These must be lipid soluble to have passed the membrane of the intestinal cell and must be converted to water soluble (more polar) compounds for excretion *via* the urine or bile.

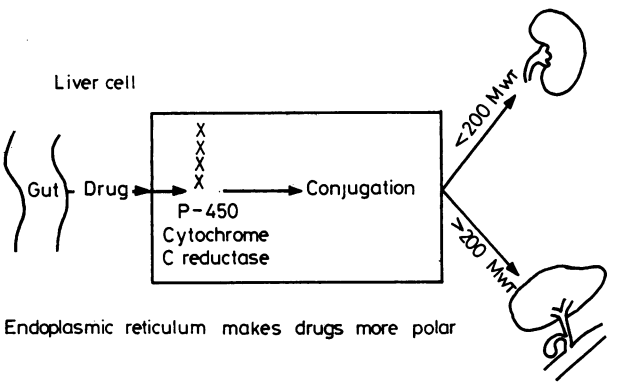

Fig. 1 *Hepatic drug metabolism.*

The main drug metabolising system resides in the microsomal fraction of the liver cell (smooth endoplasmic reticulum). The enzymes concerned are cytochrome C reductase and cytochrome P450, reduced NADPH in the cell sap being a co-factor. The drug is rendered more polar by hydroxylation or oxidation and is additionally made more polar by conjugation with such substances as glucuronic acid or sulphuric acid[1].

The drug metabolising enzyme system may be increased (induced), so increasing drug oxidation, by many lipid soluble substances. These include barbiturates, alcohol, anaesthetics, hypoglycaemic and anticonvulsant agents, griseofulvin, rifampicin, glutethimide, phenylbutazone, and meprobamate. At least 200 different substances may be enzyme inducers[2]; enlargement of the liver after the introduction of drug therapy can be related to enzyme induction. Inhibitors of the enzyme system include para-aminosalicylic acid. Two active drugs competing for the enzyme-binding site may lead to the drug with a lower affinity being metabolised more slowly, so that it thus has a more prolonged action.

Factors determining whether the metabolised drug will be excreted ultimately in bile or urine are multiple and many are unclear. High polar

*Based on the Sir Arthur Hurst Memorial Lecture delivered to the British Society of Gastroenterology, Edinburgh, 22 September 1978.

substances are excreted unaltered in the bile and also those which become more polar after conjugation. Those with a molecular weight exceeding 200 are excreted in the bile, while, as the molecular weight gets smaller, the urinary route becomes more important.

Factors determining the effect of drugs include age[3], parenchymal liver disease[4], biliary excretion, previous drug administration[5], the enterohepatic circulation, and the gut flora.

Mechanisms of drug hepatotoxicity

Drugs rarely seem to cause damage by a direct action on the liver cell, and two other mechanisms are probably concerned. The first is mediated by metabolite-related substances which combine covalently with cell proteins (Fig. 2). The second is by the development of an immunological reaction to the drug which renders a constituent of the liver cell antigenic (Fig. 3). In the case of some drugs—for instance, paracetamol (acetaminophen)—the metabolite-related injury seems particularly important. In others—for instance, halothane—the immunological reaction may be predominant. With many drugs the mechanism of the drug-liver reaction remains poorly understood.

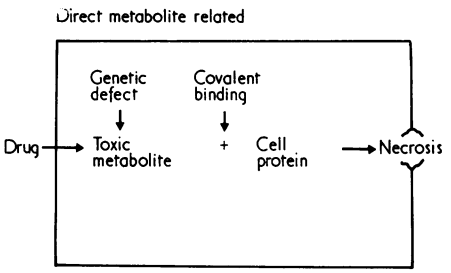

Fig. 2 *The pattern of direct metabolite related liver-cell necrosis.*

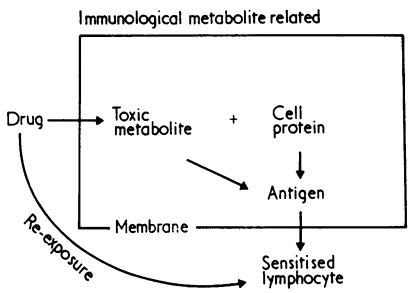

Fig. 3 *The pattern of immunologically related liver-cell necrosis.*

DIRECT (METABOLITE-RELATED) FACTORS

The hepatic drug metabolising enzymes activate chemically stable drugs to potent alkylating, arylating or acylating agents. These bind covalently to liver macromolecules essential to the life of the liver cell and necrosis ensues[6]. The liver usually contains substances, such as glutathione, which are capable of preferentially conjugating with a toxic metabolite. It is only when the stores of these substances are exhausted that necrosis results.

The extent of the necrosis is increased by pre-treatment with enzyme inducers such as phenobarbital and reduced by enzyme inhibitors.

The reaction is dose dependent and animal models exist. Organs other than the liver also suffer and renal damage is often the most important.

In mild cases, jaundice may be mild, slight, and transient. Serum biochemical tests show marked rises in transaminases and prothrombin time increases rapidly.

Light microscopy shows clear-cut centrizonal necrosis with scattered fatty change and little inflammatory reaction[7]. Periportal fibrosis may sometimes be marked.

The problem, if this concept is correct, is to relate the extent of the liver injury to the small amounts of active metabolite that are released. Another factor that also needs explaining is the relative rarity of the reaction compared with the many patients who receive the drug.

IMMUNOLOGICAL FACTORS

Liver injury is unrelated to dose and only a small proportion, usually about 1%, of those receiving the drug suffer liver injury, children usually being unaffected. Associated phenomena may include fever, skin rashes, and eosinophilia. Animal models do not exist and the diagnosis can be confirmed only by drug challenge; this is ethically unjustified if the original reaction has been a serious one. Familial reactions suggest hereditary factors which may influence the rate and form of metabolism of a drug. Microsomal enzyme activity is genetically determined. No relationship to HLA phenotypes has been shown.

The drug concerned is usually too small a molecule to become antigenic and the drug or its metabolite may act as a hapten combining with a normal membrane antigen. Alternatively, the drug or its metabolite may bind covalently to a liver macromolecule, so rendering it antigenic. Lymphocytes are sensitised and, on re-exposure, a delayed hypersensitivity reaction to the antigen is mounted and liver cell necrosis ensues. The reaction is unlikely to be self-perpetuating once the drug is removed.

The prodromal symptoms resemble those of acute viral hepatitis. Biochemical tests indicate hepatocellular damage, while hepatic histology shows a picture virtually indistinguishable from that of acute virus hepatitis[7]. Milder cases show spotty necrosis becoming more extensive and reaching a stage of diffuse liver injury and collapse; inflammatory infiltration is marked. Chronic active hepatitis and macronodular cirrhosis may be sequels.

Hepatotoxic substances

CARBON TETRACHLORIDE

Overdose with this agent can be the result of an attempt at suicide or be accidental. Jaundice develops within 48 hours with very high serum transaminase values and markedly increased prothrombin time. The effects are also seen on the kidney, renal failure being more important than hepatic. Liver biopsy shows centrizonal hydropic degeneration and variable amounts of fat. Portal zones are spared and portal tracts normal. Chronicity does not develop.

The liver injury is induced by a toxic metabolite of microsomal origin[8] which combines covalently with cell proteins and induces necrosis (Fig. 4).

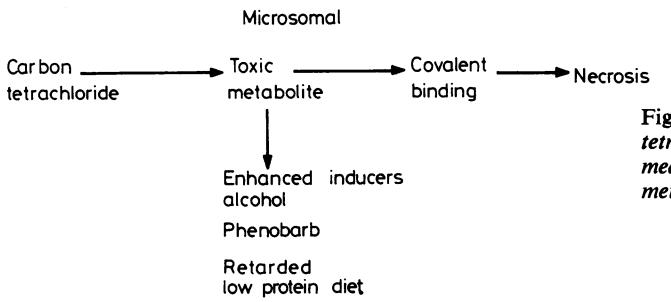

Fig. 4 *Carbon tetrachloride liver injury mediated by a toxic metabolite.*

The effect is enhanced by enzyme inducers such as alcohol and barbiturates, and reduced by protein malnutrition, which depresses drug metabolising enzymes. This may explain the apparent resistance of those in underdeveloped countries to the hepatotoxic effects of carbon tetrachloride and similar compounds when used as vermifuges.

Related substances

Other chlorinated hydrocarbons and benzol derivatives may act similarly. Teenagers sniffing cleaning fluid which contains trichlorethylene[9] or glue containing toluene[10] may develop jaundice with centrizonal liver necrosis and renal failure.

Chlorophenothane (DDT) in large doses causes fatty change and hepatocellular necrosis. It is a potent enzyme inducer when it is consumed as a food additive.

Hycanthone, used in the treatment of schistosomiasis, is hepatotoxic. Fatalities are seen particularly with overdose or in those with underlying liver disease[11].

PARACETAMOL (ACETAMINOPHEN)

Paracetamol is being increasingly used as a suicidal agent[12]. About 10 g produces hepatic necrosis but the dose actually ingested is difficult to assess because of the early onset of vomiting and the difficulty in obtaining a reliable history.

The electrophilic metabolite of paracetamol preferentially conjugates with hepatic glutathione. When the glutathione is exhausted the paracetamol metabolite arylates essential nucleophilic macromolecules so producing hepatic necrosis[13] (Fig. 5).

Shortly after ingestion the patient becomes nauseated and vomits; consciousness is preserved. After about 48 hours recovery seems in progress when

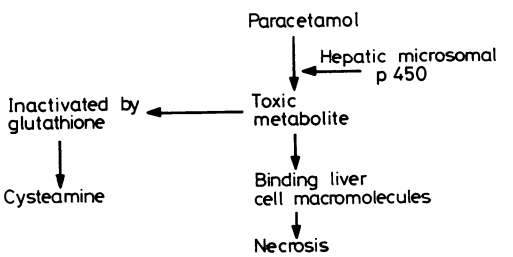

Fig. 5 *The mechanism of paracetamol liver injury and of cysteamine treatment.*

the patient's condition deteriorates and jaundice appears on the third or fourth day. Serum transaminase levels and prothrombin times are extremely high, and acute liver failure supervenes. Myocardial and renal damage and hypoglycaemia are prominent. The overall mortality for 201 patients admitted to a district general hospital was 3·5%[14]. A prothrombin ratio of 20% and hepatic coma are unfavourable prognostic signs. The severity of the patient's condition can also be assessed by the paracetamol blood level, which should always be determined. The normal plasma half life is two hours; if it exceeds four hours hepatic toxicity is likely and if greater than 12 hours severe hepatic damage is probable. If the plasma level four hours after the overdose exceeds 300 μg/ml there is 100% incidence of hepatic toxicity and if less than 120 μg/ml there is no danger. If the paracetamol level exceeds 50 μg/ml 12 hours after administration hepatic toxicity is likely and if less than 50 μg/ml there is no danger[15,16].

Hepatic histology shows centrizonal necrosis, some fatty change and very little inflammation[17]. Reticulin collapse may be confluent and massive, but cirrhosis is not a sequel.

Treatment is aimed at replenishing the glutathione reserves of the liver cell. Unfortunately, the penetration of glutathione itself into liver cells is poor. Precursors of glutathione and glutathione-like substances have therefore been used. They are necessary only when hepatic damage is likely. This is assessed by blood levels. Cysteamine was the first drug used[18]. Two grams are infused over 10 minutes, then three 400 mg doses, each in 500 ml 5% dextrose in water, are infused over periods of four, eight, and eight hours. The infusion causes marked anorexia, drowsiness, malaise, and flushing. Methionine (2·5 g orally over four hours to a total dose of 10 g) given within 10 hours of the overdose may be effective in reducing the frequency and severity of liver damage[19]. It must not be given later when hepatic encephalopathy can be induced. N-acetyl cysteine, which is rapidly hydrolysed to cysteine *in vivo*, is better tolerated than cysteamine and is now the treatment of choice[20]. It is given as a 20% solution diluted with three parts unsweetened fruit juice. One hundred and forty milligrams per kilogram orally is the loading dose and this is followed by 70 mg/kg every four hours. Treatment depends on plasma paracetamol levels: the patient's value is plotted against a line joining 200 μg/ml at four hours, and 60 μg/ml at 12 hours on a semi-log graph of concentration versus time[17]. If the concentration is below this line, liver damage will be clinically insignificant and treatment can be stopped.

Chronic hepatitis

Long-term (about one year) exposure to paracetamol (within the therapeutic upper limit of 4 g daily) may lead to chronic hepatitis[21,22]. Underlying liver disease may potentiate the effect[23].

Salicylates

Patients on salicylate therapy for acute rhematic fever, juvenile and adult rheumatoid arthritis, and systemic lupus erythematosus may develop acute hepatic injury and even chronic active hepatitis[24]. This may develop even with serum salicylate levels below 1·81 mmol/l (25 mg/100 ml)[25].

METHOTREXATE

Methotrexate is first metabolised to 6-mercaptopurine. Hepatotoxicity results

from a toxic metabolite of microsomal origin which induces fibrosis and ultimately cirrhosis[26]. Electron microscopy shows membrane whorls, lipid droplets, and autophagic vacuoles[27].

This complication is likely to follow long-term therapy, usually for psoriasis[28] or leukaemia. A cumulative dose exceeding 2 g is especially dangerous[29]. Increased alcohol intake adds to the risk. Serum transaminases and, if possible, needle biopsy should be performed before starting and at regular intervals during treatment; any abnormality is a contraindication to starting the drug and an indication to stop it. Repeated biopsies are helpful in following the patient's condition.

OTHER CYTOTOXIC DRUGS

These drugs cause rises in serum transaminases and phosphatases if large amounts are given. Hepatic histology shows centrizonal necrosis, and the pattern is of metabolite-related liver injury. This complication applies to such drugs as mithramycin, mitomycin, and actinomycin.

More long-term use of cytotoxic agents such as azathioprine, 6-mercaptopurine, and cyclophosphamide in recipients of renal transplants or in children with acute leukaemia leads to chronic hepatitis, fibrosis, and portal hypertension.

Azathioprine may lead to cholestasis and in recipients of liver transplants this may be confused with impending rejection. Such cholestatic reactions should not be treated with azathioprine, as this demands good hepatocellular function for its metabolism to the active 6-mercaptopurine.

ISONIAZID

This hydrazine weak amine-oxidase inhibitor has recently been associated with severe hepatotoxicity. This followed its use alone for asymptomatic persons with positive tuberculin skin tests. In one serious outbreak, 19 of 2231 government employees in Washington developed clinical signs of liver disease within six months of starting isoniazid[30]. Thirteen were jaundiced and two died.

The liver injury is metabolite related (Fig. 6). After acetylation the isoniazid is converted to a hydrazine which is changed by drug metabolising enzymes to a potent acylating agent that produces liver necrosis[13]. Rapid acetylators are probably at particular risk of developing liver damage and this applies particularly to Orientals, 90% of whom are fast acetylators[31]. Combination of the isoniazid with an enzyme inducer such as rifampicin increases the risk[32]. The combination of isoniazid and rifampicin can be particularly serious, and may lead to fulminant hepatitis[33]. Jaundice develops six to 10 days after starting the drugs, and the liver shows centrizonal necrosis; hypersensitivity phenomena are absent. Anaesthetic drugs may also enhance

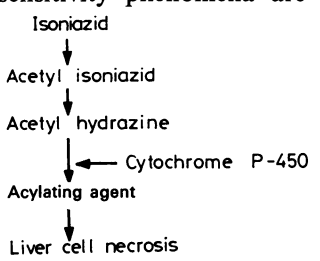

Fig. 6 *The mechanism of isoniazid liver injury.*

isoniazid toxicity. Para-amino salicylate on the other hand is an enzyme retarder, and this may account for the relative safety of the para-amino salicylate-isoniazid combination formerly used in the treatment of tuberculosis.

The possibility of immunological liver injury cannot be excluded. However, 'allergic' manifestations are not seen and the incidence of 12-20% developing subclinical liver injury is very high.

Patients are usually more than 35 years old and females are affected three times more often than males. The reaction is seen within three months of starting therapy. The condition may be clinically silent and marked only by rises in serum transaminases. Liver biopsy shows spotty necrosis. Resolution usually follows stopping the drug. Prodromata resemble virus hepatitis and last one to four weeks with anorexia and weight loss. Severity is greatly increased if the drug is continued after symptoms develop or serum transaminases rise. The mortality is 12% if overt liver damage develops[34]. The reactions are more serious if the patient presents after more than two months on the drug[34].

The liver biopsy may show extensive bridging necrosis and fibrosis. Continued administration leads to the picture of chronic active hepatitis and even cirrhosis[35]. This probably does not progress if the drug is withdrawn.

RIFAMPICIN

In the majority of patients reporting with rifampicin hepatotoxicity, isoniazid has also been given[36]. Rifampicin on its own may cause a mild hepatitis but this is unlikely to be serious or to have permanent effects on the liver. In some patients the drug has been continued and liver function and structure have returned to normal[37].

METHYL DOPA

Asymptomatic increases in serum transaminases, which generally subside despite continued drug administration, are reported in 5% of those taking methyl dopa. This may be metabolite related, for human microsomes can convert methyl dopa to a potent arylating agent[13]. An immunological mechanism is also possible, for methyl dopa is known to induce such reactions as direct Coombs' positivity and a positive LE cell test.

The patient is often post-menopausal and has been on the methyl dopa for one to four weeks. The reaction usually appears within the first three months, and prodromata include pyrexia and are short. The reaction is much more severe in those continuing the drug[38]. Liver biopsy shows bridging and multilobular necrosis. Deaths may occur in the acute state, but clinical improvement after drug withdrawal is usual[39]. Chronic active liver disease has been reported[35,39]; this is probably not progressive.

HALOTHANE

There seems little doubt that, rarely, this anaesthetic causes hepatitis. Convincing evidence has come from challenge experiments such as that in an anaesthetist who developed clinical, biochemical, and hepatic histological deterioration when re-challenged with halothane[40]. Two controlled perspective clinical trials have been reported. The first from Oxford[41] reported liver function tests in women receiving multiple anaesthetics for the treatment of cancer of the uterine cervix. The second from Southampton[42] in addition

studied men receiving multiple anaesthetics during the treatment of cancer of the bladder. In both there was an increased incidence of raised transaminase values in those receiving halothane. In the Oxford trial, four of 18 halothane-treated patients showed serum transaminase values exceeding 100 before the third radium treatment, compared with none of the 21 in the control group who received a non-halothane anaesthetic. The delay between halothane anaesthesia and the diagnosis of the hepatic reaction, usually pyrexia, is at least seven days after a first exposure to halothane. Jaundice appears two to three days later. The patient may therefore have been discharged home from the hospital before the hepatic reaction appears. The anaesthetist has lost contact with the patient who is expecting to be unwell after a hospital admission. Many hepatic reactions to halothane are thus overlooked. Three liver biopsies were performed in the Oxford and Southampton trials on patients with increased serum transaminase values. These showed definite and sometimes severe acute hepatitis which would have been overlooked if the transaminases were not being monitored. The danger of such patients receiving further halothane anaesthetics is obvious[43].

The mortality is high if deep jaundice develops. Those who recover probably show no late chronic effects despite marked bridging necrosis in the acute stage[44].

The mechanisms of the hepatotoxicity remain obscure. Halothane is metabolised to trifluoroacetic acid, bromide, and chloride. The first product of reductive metabolism is theoretically toxic and unstable. It could bind covalently with hepatic metalloenzymes of cellular protein and so lead to direct liver injury. In an animal model and in man, the three such reductive metabolities have been demonstrated[45]. In a rat with liver enzymes induced and receiving halothane plus 14% oxygen, the metabolites were increased at least fourfold, while transaminases increased 10 times and the liver showed centrizonal necrosis. This would explain the potentiation of halothane hepatotoxicity by postoperative hypoxaemia. The metabolites are stored in adipose tissue and may be released later. Obesity is frequently associated with halothane hepatitis[46]. The hepatic histology in some patients is very suggestive of direct liver injury, the centrizonal necrotic area being particularly well demarcated and the liver cells sometimes containing fat.

It is also possible that the liver injury is mediated immunologically. The association with multiple exposures, the pattern of fever, and the occasional eosinophila and skin rash would support this view. Smooth muscle antibodies may be present in low titre and a liver-kidney microsomal antibody is sometimes found[47]. Lymphocyte transformation with halothane has been described in subjects with halothane hepatitis[48] but this has not been confirmed[46]. Halothane macrophage migration inhibition factor tests have given positive results in patients with halothane hepatitis[49]. The sensitisation to a halothane altered rabbit liver cell component has been shown by the leucocyte migration tests in eight of 12 patients with halothane-associated hepatitis[50]. Halothane is a small molecule which binds poorly, if at all, with protein. Binding to a carrier protein is necessary before a small molecule can become immunogenic. In the case of halothane, covalent binding to protein has been considered obligatory before a hypersensitivity reaction can develop. It seems more likely that a metabolite of halothane binds to the carrier protein and so acts as an antigen. Idiosyncrasy might be expressed by the formation of excessive amounts of toxic metabolites or normal amounts of abnormally toxic ones.

CHLORPROMAZINE

Chlorpromazine jaundice has a strong immunological association. Only 1-2% of those taking the drug develop cholestasis; the reaction is unrelated to dose; and in 80-90% the onset is in the first four weeks. There may be associated hypersensitivity. Excess eosinophils may be found in the liver. The liver biopsy shows not only cholestasis but also a cellular reaction within the portal zones.

Evidence is accumulating that chlorpromazine is also directly hepatotoxic. Histologically, damage to liver cells may be noted in almost every patient. Chlorpromazine produces a dose-related enzyme release from Chang liver cells and liver slices[51]. It inhibits bile salt independent biliary flow in the monkey[52] and in the isolated perfused rat liver[53]. The drug is an amphilic cationic detergent, and can insert itself into the lipid bilayer of cell membranes. The drug forms free radicles which can bind covalently to cellular components and so could induce liver injury. The liver cell has two inbuilt safeguards: firstly, the production of a more stable chlorpromazine sulphoxide, and, secondly, the protective action of hepatic glutathione (Fig. 7).

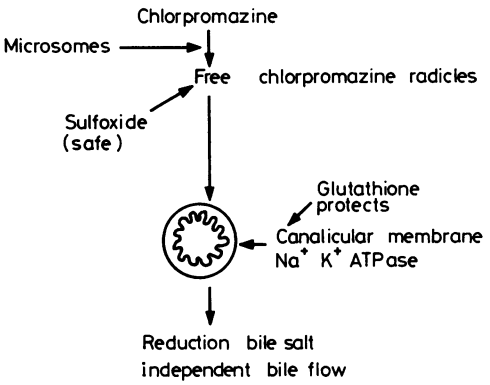

Fig. 7 *The possible mechanism of chlorpromazine cholestasis (after Samuels and Carey[54]).*

If isolated liver membranes enriched with bile canaliculi are used, chlorpromazine-free radicles markedly inhibit Na^+K^+-APTase at much lower concentrations than chlorpromazine itself[54]. Such an inhibition would account for the reduction of bile salt independent biliary flow which depends on Na^+K^+-ATPase. This might, in part, account for cholestasis. It would not entirely explain it, for the histological and electron microscopical picture of the liver is not simply that of canalicular membrane injury.

Other effects of chlorpromazine, such as the delay in onset of jaundice, the extrahepatic manifestations, and the lack of a dose relationship, remain unexplained. There may be an individual idiosyncrasy in the production of free chlorpromazine radicles or in chlorpromazine sulphoxide formation or even in glutathione metabolism. It is also possible that chlorpromazine, or one of its metabolites, may induce alterations in the liver cell membrane so that it becomes antigenic.

OTHER DRUGS

A large number of drugs cause hepatic reactions of 'hypersensitivity' type and of variable severity, with or without jaundice. The reaction usually appears within four weeks of starting therapy and is most frequent with multiple

exposures. Liver histology shows focal spotty necrosis of liver cells, and a mononuclear and sometimes eosinophilic reaction in the portal zones. Granulomas are sometimes found.

Sulphonamides, particularly those that are long acting, can cause hepatitis, and widespread granulomas may be found. Sulphasalazine has also been incriminated[55]. Erythromycin estolate[56], penicillin, and oxacillin[57] can cause a similar type of reaction.

Allopurinol may cause a granulomatous hepatitis[58] as may also indomethacin and phenylbutazone[59].

Hepatotoxic effects have been associated with anticonvulsants including diphenyl dyantoin[60] and the muscle relaxant dantrolene[61,62].

Hepatotoxicity has been associated with most of the anti-thyroid drugs including methimazole[63] and the oral hypoglycaemic agents such as chlorpropamide or carbutamide.

SEX HORMONES

Cholestasis

This is a well-recognised complication of the use of sex hormones particularly in oral contraceptive pills. It is usually associated with a history of cholestasis (pruritus) in the last trimester of pregnancy. Cholestasis is rare in relation to the millions of women taking these pills. The continual reduction of the dose of active hormone is further lessening this complication.

The drugs are usually C^{17} substituted testosterones. They include norethandrolone, methylestrenolone, norethindrone, methandrenone, and norethisterone, mestranol, and norethyndrol. The reaction has, however, been reported with methylandrostenolone, which lacks a C^{17} substitution. Moreover, the sufferers tend also to exhibit cholestasis during pregnancy where the natural oestrogens and progestens are not C^{17} substituted. The cause is unlikely to be abnormal metabolism of the hormone but is probably an exaggeration of the mild cholestatic effect seen in normal late pregnancy or in normal women given sex hormones.

Cholestasis is probably related to the effect of oestrogen on the permeability of the canalicular membrane[64,65]. A block in biliary micelle formation has also been suggested[66]. Sex hormones may also affect the cytoskeleton of the liver cell with failure of the pericanalicular microfilaments to contract[67].

The cholestatic effects of oestrogens are enhanced in those with biliary excretory failure. Patients with the Dubin-Johnson syndrome show an accentuation of bilirubinaemia without change in serum alkaline phosphatase levels[68]. Patients with pre-symptomatic primary biliary cirrhosis may develop pruritus. The sex hormones are usually contraindicated in patients with chronic liver disease.

Theoretically patients with acute viral hepatitis who take oral contraceptives should develop a cholestatic attack with very deep jaundice and pruritus. However, this is not always so. Fifty-four women took oral contraceptives during acute viral hepatitis and there was no difference in the severity of acute illness or frequency of complications compared with 34 matched control women[69]. A woman convalescent from viral hepatitis may resume the use of the pill as soon as she wishes.

Gall stones

Women, whether on long-term oral contraceptives or post-menopausal replacement oestrogens, show a 2-2½-fold increased incidence of surgically confirmed gall stones[70,71]. This might be related to chemical changes in the bile secondary to the cholestatic effect of oestrogens. The bile of women taking oestrogens shows a significant rise in cholesterol concentration and a decrease in the concentration, size, and synthesis rates of bile acids[72]. The cholesterol saturation of bile increases as women start oral contraceptives[73].

Hepatic venous obstruction

This is a rare but often fatal complication of oral contraceptives[74]. The clots are usually multiple involving veins of various sizes. Endophlebitis of small veins is frequent, the picture being that of veno-occlusive disease. The prognosis is poor.

SEX HORMONE TUMOURS

Oral contraceptives

The association of hepatic adenoma, a hitherto very rare benign tumour, with oral contraceptives was first suggested by Janet Baum and co-workers in 1973[75]. By 1977, 237 published cases were reviewed[76]. The adenoma consists of sheets of normal or near normal liver cells. Bile duct and central veins are absent. The tumour is usually solitary. It may or may not have a capsule. Focal nodular hyperplasia consists of a central focal scar containing proliferating bile ducts and from which radiate fibrous septa. It is not so closely linked to sex hormone therapy as is adenoma. Hepatocellular carcinoma is a very rare association[77,78].

Vascular lesions may accompany adenoma or focal nodular hyperplasia or may be seen alone. Large arteries and veins are present in excess. Sinusoids are focally dilated. Sometimes the blood spaces are particularly large and without endothelial linings. This is termed peliosis hepatis. Peliosis has been described in the absence of nodular lesions in patients taking oral contraceptives[79] and in men having androgenic and anabolic steroids. Peliosis has been reported in the recipients of renal transplants, perhaps due to azathioprine blocking blood flow from the sinusoids[80].

The mechanism of tumour formation is complex (Fig. 8). The oestrogens might be directly carcinogenic, which is unlikely. Oral contraceptives, as enzyme inducers, might potentiate the carcinogenesis of certain compounds by increasing their rate of conversion to toxic (? carcinogenic) metabolites. Cholestatic properties of steroids might enhance the potentially carcinogenic

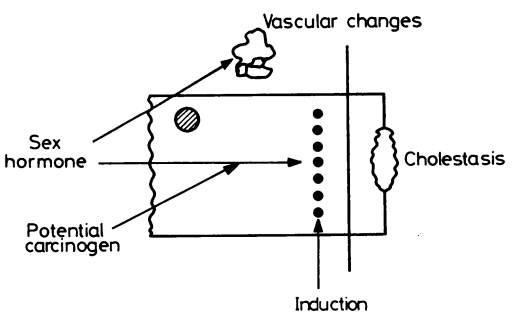

Fig. 8 *Possible mechanisms of tumour production by sex hormones.*

action of substances normally excreted in the bile. Concomitant drugs might act as additional enzyme inducers; in a Swedish series of 28 patients with focal nodular hyperplasia, two patients were epileptics and three diabetic[81]. The vascular changes probably represent part of the general vasodilatation associated with sex hormones and are analogous both to the vascular spiders developing in the skin and to the endometrial arterial hypertrophy found in pregnancy.

Prolonged use seems important in determining the risk of developing adenoma. A study was done comparing the contraceptive history of women with hepatic adenoma and those without[82]. Mean months of use in the 29 patients with adenoma was 79·7 compared with 27·8 months in 26 age matched controls (P less than 0·001). The risk increases dramatically with duration of use, particularly after 48 months. Presentation is as pain in the abdomen caused by haemorrhage either into the tumour or into the peritoneal cavity. The presence of an abdominal lump may lead to the diagnosis.

Combined angiography and liver scan may be helpful in distinguishing between focal nodular hyperplasia, which is hypervascular and exhibits normal uptake on the scan, and liver cell adenoma, which is hypovascular and cold on a scan[83]. Liver biopsy is contraindicated in vascular cases because of the risk of haemorrhage.

The temptation to operate on space-filling lesions in the liver is almost overwhelming to some surgeons. However, in most uncomplicated cases it is advisable to be conservative. If when operating for intraperitoneal haemorrhage multiple tumours are found, all cannot be removed. If the tumour is diagnosed but there are no complications, it should be left *in situ* and sex hormones stopped. Tumours may regress[84,85]. Women must be warned of the possibility of rupture and the significance of any unexplained right upper quadrant pain or swelling in the abdomen. Rupture becomes more likely in pregnancy. Liver ultrasound or scan should be repeated every six months.

Surgery may be needed for complications, particularly intraperitoneal or intratumour bleeding with severe abdominal pain and anaemia. Hepatic arteriography is particularly valuable in planning surgery. Local resection of the tumour is advised in amounts sufficient to control haemorrhage[86]. In some instances hepatic lobectomy may be needed.

ANDROGENIC HORMONES

Adenoma, peliosis, and particularly hepatocellular carcinoma may complicate long-term use of C^{17} substituted testosterones. These may be given for the treatment of aplastic anaemia[87], hypopituitarism, eunochoidism[88], impotency, or in female trans-sexuals[89].

Hepatocellular cancer of a rather benign type is much more frequent with male than with female hormone therapy, perhaps due to the much larger doses needed. The incidence of hepatic abnormality is particularly high: in one series 19 of 60 patients given methyltestosterone showed abnormal liver function tests.

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