battle colours of the defeated and disbanded French regiments. In the sad-faced crowd of watching Frenchmen, there was an old man . . . weeping.

An old man wept, his happiness gone, as they carried the colours away:
So the apple was rotten, with maggots inside (understanding of death and decay).
They bore of his honour; they trampled his pride—as they carried the colours away.
Franz took the red greys of Rouen; Hans the green blues of Calais
Banners of silk that dripped like a wound; and a dying old man turned away.

Modecate, Depixol, Moditen, and fluphenazine inhibit the imagination and, whereas once I lived in a fascinating ocean of imagination, I now exist in a mere puddle of it. I used to write poetry and prose because it released and satisfied something deep inside myself; now I find reading and writing an effort and my world inside is a desert.

I am blessed in having a friendly GP, who is prepared to listen sympathetically to my schizophrenic problems, do everything he can, speak the correct kind words, and then leave me feeling better with seemingly profound wisdom or with an outrageously funny joke. One GP like this is worth an infinite number of social workers, and much much more than those oh-so-objective registrars. These doctors, as well as psychiatrists

and the occasional consultant, may learn something from what I have to say.

A manic-depressive friend of mine complained that the Priadel to which she owes her health is packed in such enormous pills that she is sick when she takes them. For this reason she doesn't always take them—and her illness returns. My own experience of chlorpromazine is that the 100 mg pills are likely to stick in the thorax and cause hours of acute pain. May I suggest that drug manufacturers reduce the size of their large pills (and, if necessary, increase the cost). Some research, too, should be done to make it possible to administer Depixol in slimmer hypodermic needles—the average 40 mg injection is similar to a twin thrust with bayonets in the buttocks. I have found that Tryptizol and similar antidepressants are effective in treating many types of depression but don't work with schizophrenics—not with me, anyway.

Most people who see a psychiatrist seek a certain amount of humanity. Unfortunately, this panacea for many clients' needs has been trained out of psychiatrists in the name of the god "objectivity." If someone without feeling is what is wanted in the psychiatrist's room, then I suggest that it would be cheaper to install computers instead of a psychiatrist. Occasionally, a patient meets a psychiatrist who is willing to become emotionally involved with him; the patient frequently makes a speedy return to health. No psychiatrist should philosophise: "You may commit suicide; you may not commit suicide; there is nothing I can do about it." This happened once, and somebody died.

Today's Treatment

Drug-induced diseases

Drug-induced liver disease

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In about 8% of reports of adverse drug reactions the liver is affected, although deaths are unusual. The liver is central in the metabolism and excretion of many drugs. Metabolism inactivates them, but some, such as cyclophosphamide and paracetamol, are converted in the liver into powerful intermediate metabolites. In general, drug metabolism proceeds in two phases, both catalysed by enzymes in the membranes of the endoplasmic reticulum in the cell.¹ The first is of oxidation, reduction, or hydrolysis, the second of conjugation with glucuronic acid, amino-acids, or sulphate. Larger, more water-soluble (polar) compounds are the end result, the larger being excreted into bile, the smaller into urine. Although there are differences between the activities of metabolising enzymes in cells in different parts of the hepatic lobule, it is not generally

possible to relate these to the site of damage in the hepatic lobule produced by drugs.

Predictable (direct) hepatotoxins

LIVER CELL NECROSIS

A few drugs and chemicals, such as ferrous sulphate excess, tannic acid, paracetamol excess, tetrachloroethylene, aspirin, cytotoxic drugs, and tetracycline excess, predictably produce necrosis of liver cells—namely a hepatitis—when given in sufficient dosage to man and many animals. Young animals are often more resistant.

Tannic acid caused liver damage when applied to burns from the surface of which it was absorbed, and mild liver damage has been reported after barium enemas to which tannic acid had been added to improve coating of the mucosa. The drug is itself hepatotoxic, without undergoing metabolic transformation to an active molecule.

Tetracyclines—Large doses of tetracyclines have produced in animals and man a strange, often fatal liver disease, in which there is infiltration of the liver with fat but little necrosis of liver cells. The liver damage occurs chiefly in pregnant women, particularly those with renal failure. Tetracyclines have wide-

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spread poisonous effects on cellular metabolism, and this presumably underlies this toxicity.

Paracetamol is transformed into a toxic metabolite.² It is rapidly removed from the blood into liver cells, where chiefly glucuronic acid and sulphate conjugates are formed that pass into urine. Minor amounts are oxidised to metabolites that combine with the sulphur-containing glutathione. Although therapeutic doses are therefore harmless, overdoses (25 g or more) cause severe liver damage, since the huge load of drug saturates these normal detoxification pathways. There is then intracellular accumulation of toxic metabolites, and they bind to membranes and irreversibly damage them and their enzymes. This knowledge has led to a rational treatment of paracetamol poisoning with sulphur compounds, such as cysteamine, acetylcysteine, and methionine. The degree of liver cell damage depends on the dose of paracetamol and also the rate of its absorption, since this determines the rate at which it is presented to the liver.

Tetrachloroethylene can damage the liver by a similar mechanism.

Recently mild hepatotoxicity has been reported in patients with rheumatological diseases taking large doses of aspirin, and the high frequency of this reaction suggests that it is a direct toxic effect.

Cytotoxic drugs, such as azathioprine and mercaptopurine, have caused liver damage in a few patients, even though these drugs are sometimes given to treat chronic liver disease. Cholestasis also occasionally occurs in patients with renal disease treated with azathioprine.

CHOLESTASIS

Careful studies have shown that oestrogens administered to women in amounts no larger than those secreted during pregnancy regularly produce impairment of the secretion of bile and of excretion of the dye sulphobromophthalein sodium into bile; that is, they cause cholestasis.³ In a few women the contraceptive pill invariably produces itching, and less often reversible jaundice, and in a minority of these women a similar cholestasis always develops during the last trimester of pregnancy. This hepatic reaction is thought to be an exaggerated response to the oestrogen component.

Some other groups of patients are also abnormally sensitive to oestrogens—namely, those with primary biliary cirrhosis (chronic, destructive, non-suppurative cholangitis) or with the rare congenital Dubin-Johnson and benign recurrent cholestatic syndromes. They develop jaundice.

Large doses of anabolic steroids and some androgens also invariably produce a mild cholestasis and, in a few patients, jaundice. Patients with primary biliary cirrhosis are again more susceptible, and most of them when given norethandrolone to relieve itching become more jaundiced.

So far the molecular structure of all these cholestatic drugs has included a 17 α -alkyl-substituted group. The mechanism of the effect is unknown, although oestrogens may increase the permeability of the wall of the bile canaliculi so that water leaks out of bile, concentrating it, and leading to stagnation in these tiny intercellular channels.

Unpredictable hepatic reactions

A large and increasing number of drugs have caused liver damage varying from mild hepatitis, cholestasis, or granuloma formation to fatal hepatic necrosis.⁴ Generalised signs of hypersensitivity, such as rashes, arthralgia, and eosinophilia are also sometimes seen. The reactions are unpredictable, and occur in only a few patients taking the drug, usually within the first weeks of treatment. These unusually susceptible patients may have some underlying immunological defect, or they may have an inherited abnormality of the hepatic enzymes metabolising the

drug. The hepatic damage is often classified into hepatitis or cholestasis, but these may be difficult to separate.

HEPATITIS (see table)

Widespread necrosis of liver cells and release from them of aminotransferase (transaminase) enzymes into blood has been seen with several psychiatric drugs, among which iproniazid caused the highest frequency of deaths relative to the amount that was prescribed.

Drugs causing unpredictable hepatitis

Monoamine oxidase inhibitors Antituberculosis drugs Anaesthetic agents Phenytoin Penicillin Chlordiazepoxide Phenindione
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Antituberculosis drugs^{4 5}

The mechanism of the hepatic reactions antituberculosis drugs may cause is complex. Firstly, serious liver damage after taking isoniazid, para-aminosalicylic acid, rifampicin, ethambutol, and pyrazinamide is rare. Many more patients develop mildly raised levels of aminotransferases during the first few weeks of treatment with isoniazid and rifampicin, but spontaneously improve if treatment is continued.

Secondly, these abnormalities seem to be more frequent in patients who are fast acetylators—that is, those who carry the genetic trait of relatively fast hepatic acetylation of drugs, such as isoniazid. Acetylation is the rate-limiting step in isoniazid metabolism, so hepatotoxicity may be due to an abnormal accumulation and binding to cellular membranes of one of its metabolites in the liver (that is, a direct toxic effect). Abnormal results of liver function tests seem to be more common when both rifampicin and isoniazid are given together to older patients, and possibly to those with pre-existing chronic liver disease.

Thirdly, rifampicin reversibly impairs bilirubin metabolism and in some patients raises blood levels of unconjugated bilirubin; this may falsely suggest to the doctor that serious liver damage is developing.

Finally, rifampicin induces drug-metabolising enzymes in the liver, and probably therefore increases the rate of its own metabolism and that of isoniazid. This may explain why results of liver function tests are usually most abnormal in the first weeks of treatment, and later improve, and why rifampicin may increase the frequency of isoniazid hepatitis.

Postanaesthetic hepatitis

Abnormal results of liver function tests, and occasionally jaundice and fatal liver failure mimicking viral hepatitis, can follow anaesthesia and surgery, but controversy surrounds the role in this of anaesthesia in general versus halothane in particular. Transient impairment of liver function is more common after halothane than other anaesthetics, but it is important to balance this against the knowledge that halothane is a safe anaesthetic and the most used. Abnormal results of liver function tests and raised levels of serum enzymes have long been known to follow any anaesthetic, however brief, but there is more concern about the infrequent occurrence of severe liver failure that may develop about a week after anaesthesia. There is now plausible evidence that this hepatic reaction is more common in the obese, and when halothane anaesthetics are given repeatedly at intervals of less than a month.

The reaction was thought to be a hypersensitive one, but there is increasing evidence that halothane can be metabolised,

especially by the hypoxic liver, to hepatotoxic metabolites. Immunological sensitivity to halothane has also been found in patients tested after an episode of postanaesthetic jaundice.

GRANULOMATOUS HEPATITIS

Localised areas of liver cell damage and collections of histiocytes (granulomas) have been found within the hepatic lobules of a few patients taking various drugs, such as phenylbutazone, halothane, sulphonamides, and allopurinol, of which phenylbutazone is the best recorded. This reaction is seldom severe, although deaths have been reported.

UNPREDICTABLE CHOLESTASIS

Some drugs, such as phenothiazines, iprindole, chlorpropamide, thiouracil, erythromycin estolate, and gold, produce a selective cholestasis in a few patients taking them.

Phenothiazines, especially chlorpromazine, have a particularly bad reputation, and some abnormalities of liver function occur in a large minority of patients taking them, although jaundice is rare. The mechanism is not known, but in animal experiments chlorpromazine has various effects on the liver, including an impairment of excretion of sulphobromophthalein sodium, so it may prove to be a direct hepatotoxin.

In occasional patients jaundice is prolonged for months, and the development of cirrhosis and death have been reported. The jaundice usually develops within a few weeks of starting the drug, but we are sceptical of suggestions that a single tablet can induce it.

Erythromycin—One, and only one, ester of erythromycin, the estolate, produces cholestasis, and so the reaction must be linked to the side chain rather than to the antibiotic itself.

CHRONIC HEPATITIS AND CIRRHOSIS^{2 4}

Until recently it was believed that chronic hepatitis, in which chronic inflammatory cells infiltrate the portal tracts of the liver and raised levels of hepatic enzymes are found in blood, did not occur from drug-induced liver damage, even though prolonged intake of alcohol, for instance, readily causes the disease. It is now clear, however, that a few drugs such as oxyphenisatin, methyl dopa, nitrofurantoin, methotrexate, and vitamin A excess may be implicated. The liver recovers when they are withdrawn.

Oxyphenisatin—This laxative was fortunately not much used in Britain, but it has been associated with chronic hepatitis in other European countries and in North America and Australia. Such an association is easily overlooked, and was for a long time, so that there may be other drugs and environmental toxins that can cause non-virus-associated chronic liver damage.

Methyl dopa and *nitrofurantoin* are also implicated.

Methotrexate—Chronic fibrosis of the liver follows prolonged administration of methotrexate, usually given for severe psoriasis, but the frequency of this is uncertain since many patients have also admitted heavy alcohol intake. The concomitant portal hypertension is not always reversible on withdrawing the drug.

Other hepatic reactions

HEPATIC VEIN THROMBOSIS

Obstruction of the large hepatic veins draining the liver causes rapid enlargement of the liver, ascites, and often liver failure—the Budd-Chiari syndrome. The incidence of this rare syndrome is greater than expected in women taking the contraceptive pill,⁵ as are thromboses elsewhere in the body.

PELIOSIS HEPATIS

Lately there have been reports of this unusual lesion, which consists of dilated sinusoidal vessels and multiple blood cysts in the liver, developing in patients who have been receiving either anabolic steroids or the contraceptive pill.³ It regresses on stopping treatment, but may present as an acute abdominal emergency from rupture of the liver.

HEPATIC TUMOURS⁶

Benign liver cell tumours have been reported in a few patients taking oral contraceptives or androgens, and these may also rupture. There is also suspicion that malignant hepatomas occur more often in these patients. Hepatomas and haemangioendotheliomas developed in patients 15-20 years after receiving the x-ray contrast medium thorium dioxide (Thorotrast), but new cases are now rare.

PORPHYRIA

Many drugs precipitate crises in patients with the rare disease acute intermittent porphyria. Barbiturates seem particularly dangerous, but also anticonvulsants, sedatives, and griseofulvin. The mechanism appears to be induction in liver cells of the rate-limiting enzyme of the porphyrin pathway, aminolaevulinic acid (ALA) synthetase. Great excesses of the toxic porphyrin precursors ALA and porphobilinogen are then synthesised, and accumulate in the body because of a defect in the further conversion of porphobilinogen to uroporphyrin.

GALL STONES

A clear association between the prevalence of gall stones and the administration of clofibrate has emerged⁷ in recent trials of this agent in the prevention of coronary artery thrombosis. This may be because, as well as lowering blood cholesterol, clofibrate increases cholesterol and decreases bile acid excretion into bile.

In recent animal experiments oestrogens decreased the synthesis of bile acids in the liver; this would tend to reduce the solubility of cholesterol in bile, and may help to explain the association of gall stones with the female sex and the contraceptive pill.

Management of hepatic drug reactions

There are now few drugs that have not at some time been incriminated in the development of abnormal results of liver function tests, particularly in the correspondence columns of medical journals. So what does the doctor do when faced with a patient with increasingly abnormal test results and whom he finds has taken one or more potentially hepatotoxic drugs?

The patterns of liver function tests are too variable to help unless the aminotransferases are greatly raised. The histological appearance of liver biopsy specimens have lately been clearly reviewed.⁸ Features favouring a drug lesion included a severe histological lesion relative to the clinical state of the patient, granulomas, and infiltration with eosinophils. These appearances, however, are not diagnostic, though they should exclude some other causes of jaundice, such as gall stones.

The doctor also has to balance the possible benefits of treatment against the real, if small, risk of fatal liver failure. If an equal, alternative treatment is available, such as for a hypotensive drug, this should be given. Indeed, there is seldom any place for a trial re-exposure of the drug. With antituberculosis treatment it seems wise to investigate liver function in patients not rapidly improving with treatment, or who develop nausea or increasing fever. Treatment can be continued if transaminase

levels remain below an arbitrary level of three times raised and if one's nerves hold out, but if more than this treatment may have to be changed, even though the options for effective drugs are then so much reduced.

The diagnosis of postanaesthetic jaundice is difficult, although if severe it includes considerably raised aminotransferase levels, abnormal clotting, and liver failure with encephalopathy. If a patient has developed abnormal liver function or jaundice after a previous anaesthetic a non-halothane anaesthetic should probably be given if the interval between anaesthetics is less than a month. If halothane is required a senior anaesthetist should administer it knowing the small risk that is entailed.

Attempts have been made to differentiate the total clinical picture of drug-induced hepatitis from viral hepatitis by entering the clinical and biochemical data into a computer model. Diagnosis is improved, but the model is not yet reliable enough to relieve the doctor of often difficult decisions.

This article has strictly adhered to the title and has therefore not discussed the effects of toxins, such as alcohol, on the liver, nor physiological defects of bilirubin metabolism produced by drugs, nor the general effects of induction of hepatic enzymes by drugs.

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MATERIA NON MEDICA

A colourful assemblage

During the latter part of the eighteenth century London hostesses eschewed such inane activities as the prevailing recreation of card playing and promoted their salons to the "central point of union" for intellectual, literary, and artistic concourses. Mrs Elizabeth Montagu, who combined beauty, wit, and learning, attained supremacy in this sphere, her evening assemblies attracting people such as Garrick, Burke, Reynolds, Horace Walpole, and Dr Johnson. Benjamin Stillingfleet, a habitué, contravened social conventions by wearing blue worsted instead of black silk stockings; accordingly Admiral Boscawen, scoffing at his wife's similar social ambitions, dubbed the coterie "the Blue Stocking Society." However, the sobriquet dates from earlier times. In the "Little Parliament" of 1653 "blue stocking" referred to the puritanically plain attire of the members. A society, which included both sexes, was formed in Venice in 1400, under the name della calza, its members being distinguished by the colour of their stockings, and a similar society in Paris in 1590 became the rage of female savants.

Other examples of colour being used to imply features other than pigmentary qualities are equally diverting. Blue is commonly accepted as signifying constancy and unchangingness: hence "true blue." This term was applied to members of the Scottish Presbyterian Party because of the exhortation in Numbers that fringes should be worn at the borders of garments, and that a ribbon of blue be placed on the fringe.

Dickens is credited with the introduction of "red tape" and Carlyle popularised this expression of the evil of officialdom. One who wishes to divert the course of an argument may introduce a "red herring." A red herring was one made red by curing with smoke and was notorious for its strong flavour: when drawn across the path of a hunted fox it was believed to destroy the scent and so forestall further pursuit by the hounds. In old liturgical calendars, saints' days and festivals were marked in red—hence "a red letter day" signified an important and memorable one, whereas the Romans marked dates of misfortune with black charcoal.

An Act passed in 1722 imposed the death penalty for contravening the games laws. This became known as the Black Act, since it was directed particularly against the Waltham deerstalkers, who blackened their faces for their activities in Epping forest. Dick Turpin was a member of the gang at the outset of his career.

The term "yellow press," applied to sensational journalism, has two possible origins. When William Randolph Hearst bought the *Journal* he competed with Joseph Pulitzer's *World*. A cartoonist, the producer of a successful comic picture series—"The Yellow Kid"—was persuaded by Hearst to leave the Pulitzer camp, but his replacement continued the strip. The competing attempts of the two "Yellow Kids" to gain precedence resulted in banner headlines, behind-the-scene reporting, and other forms of publicity, leading to what became described as "yellow journalism." An alternative claim interprets the expression as a reference to the alarmist campaigns in the American press about the alleged fearful consequences of the rapidly increasing

populations of China and Japan.—J SHAFAR (retired consultant physician, Burnley).

Problems with wantoks

The Chimbu is a region of the lush Central Highlands of Papua New Guinea. It is densely populated, with houses clinging to steep green hillsides amid splendid mountains and spectacular gorges. The people, who have a reputation for roguishness, are known loosely as Chimbis but in fact include many different tribes with separate languages. In Pidgin (the main national language) a fellow tribesman is known as a "wantok," literally "one talk," meaning that he speaks the same language. Looking after one's wantoks is an integral part of the tribal system, while avenging the death of a wantok is something of a communal obsession.

My wife and I visited the Chimbu primarily to climb Papua New Guinea's highest mountain, the 14 800-ft Mount Wilhelm. We accomplished this aim without any difficulty, and our chief excitement came not on the mountain itself but while hitch-hiking back along the very rough access road.

Our driver looked worried as we left Keglsugl. He was delivering timber from the sawmill there to the town of Goroka on the Highlands highway. A week earlier in Goroka he had knocked down and killed a man from a neighbouring tribe and he was expecting some reprisal as we passed through the dead man's village. His fears were well founded, for, as we turned a corner, the road was barred by about fifty of the deceased's wantoks armed with bows and arrows, axes, and spears. The lorry screeched to a halt and the driver leapt out and ran for his life, happily managing to outpace his pursuers. Some of his wantoks were less fortunate and had to be admitted to hospital later in the day with axe and arrow wounds. Back at the vehicle about thirty tribesmen had gathered around us but seemed to recognise our independent wantok status and did us no harm. After a couple of hours the police arrived and confiscated the weapons of tribesmen who had not had the foresight to hide them in the long grass. Passions were temporarily cooled and the sawmill owner was able to pick up the driver and escort us safely through the troubled zone.

The drama we had observed was a serious one in that the driver would certainly have been killed if he had been caught. Yet at the same time there was an incongruous air of playfulness about the whole episode and the warriors were quite willing to pose for photographs. As we drove down the valley news of the conflict was passed on rather like the test score in a match for the Ashes. Although full-scale tribal war is now rare in Papua New Guinea through the efforts of government and missionaries, minor incidents are still quite common, particularly in the Chimbu region. Many village people find it difficult to grasp the concept of accidental death on the roads and feel honour-bound to perpetuate the pay-back system. Indeed one of the first pieces of advice the experienced expatriot will give you is never to stop after a road accident—just keep driving to the nearest police station.—PETER STANDING (general practitioner, Bury).