In assessing the value of this therapy, one factor to be weighed is the patient's reaction. Some have become seriously depressed and two have committed suicide by cutting the exteriorised arteriovenous fistula.[15] The patient's relatives may also become depressed when they are told how impermanent the success of these new techniques must be.[18] But the efficacy of the method may yet be increased—for instance, by improving the efficiency of the dialyser and administering anabolic steroids (particularly to males) to improve nitrogen balance.[19] It is doubtful whether this form of therapy should be generally practised, at least in this country where many artificial-kidney units are inadequately staffed, and one specially designed unit cannot be opened owing to shortage of nurses. Our limited resources should not be squandered on " mass-dialysis " for all suitable patients with irreversible renal failure if this involves curtailing treatment of frankly reversible lesions.

Hepatotoxicity of Drugs

THE liver is the first organ which a drug reaches after its absorption from the gastrointestinal tract and is also the main site of the mechanisms of detoxication. It is therefore not surprising that reports are accumulating of toxic liver injury associated with a bewildering variety of new and highly potent drugs.

Carbon tetrachloride is a well-known direct hepatocellular poison in animals and man. The liver is large and tender, and jaundice becomes progressively deeper. The centrizonal hepatic cells are necrotic and hydropic, and contain brown lipofuscin. Electron microscopy reveals swelling of the liver-cell mitochondria, and increased permeability of the mitochondrial membrane leads to the escape of enzymes and cofactors.[20 21] This state is reflected in very high serum-transaminase levels.[22] In severe cases acute renal tubular necrosis overshadows hepatic destruction. This description of carbon-tetrachloride poisoning serves as a prototype; an essentially similar picture may be produced by chloroform, tetrachlorethane, tetrachlorethylene, ethyl chloride, methyl chloride, dichloro - diphenyl - trichlorethane (dicophane, D.D.T.), muscarine, naphthalene, benzene derivatives, and certain metallic poisons.

The condition can be easily reproduced in animals. With the older drugs the severity of the liver damage depends chiefly on the dose of drug; but, with some of the newer drugs in clinical use there is apparently no such close relationship. In many instances hepatotoxicity was not observed in preliminary animal trials but has become evident only after long-continued clinical use; the development of jaundice seems to be unrelated to dosage or duration of therapy. The clinical picture is very like that of acute virus hepatitis; and, since the biochemical findings and the microscopic appearance of the liver in the two conditions are identical, it was at first not unreasonable to consider that the drug and the hepatitis-like illness were coincidental. Cincophen has long been incriminated as a cause of such a syndrome in a small proportion of patients receiving this drug. A similar hepatitis-like jaundice after the administration of iproniazid renewed interest in this type of liver injury.[23] Other hydrazine monoamine-oxidase inhibitors which are believed to cause this serious type of hepatocellular jaundice include pheniprazine,[24] isocarboxazid,[25] and phenelzine.[26] It has also been reported with isonicotinic acid, hydrazide,[27] pyrazinamide,[28] the oral hypoglycæmic agent metahexamide,[29] and the uricosuric and muscle relaxant zoxazolamine.[30] Jaundice may recur when a second different, monoamine-oxidase inhibitor is given.[26] This type of drug jaundice is grave; in about 20% of those affected the liver shrinks, signs of hepatic failure ensue, and death in coma results. This fulminant course can be halted neither by corticosteroids nor by any other means. How this drug hepatitis is produced is ill understood. Its predominant association with hydrazines and monoamine-oxidase inhibitors (most of which are again hydrazines) points to a possible intracellular biochemical upset.

In contrast to this sinister, potentially fatal type of drug jaundice is the more benign intrahepatic cholestasis due to drugs. The clinical and biochemical picture is of painless, afebrile, obstructive jaundice with troublesome pruritus. The liver is of normal size (or just slightly enlarged) and not tender. If the diagnosis is in doubt, aspiration liver-biopsy may be undertaken; but it is often unhelpful. Even the most experienced pathologist has difficulty in deciding whether the histological picture is that produced by intrahepatic or by extrahepatic cholestasis. Confusion may be increased if methyl testosterone or norethandrolone is given to relieve the intolerable itching; this it does effectively, but, with the symptomatic relief, the serum-bilirubin level rises still further in response to this fresh icterogenic drug. At this stage surgical advice is often sought, and laparotomy may follow; but the surgeon finds, to his chagrin, that the main bileducts are patent. Faced with this situation, the surgeon should now undertake cholangiography on the operating-table, to exclude any biliary block beyond his reach. Needless laparotomy may be avoided if a history of recent drug-taking is elicited and attention is paid to the normal size of the liver and to the absence of fever, rigors, leucocytosis, and pain. In the difficult case, percutaneous transhepatic cholangiography may be helpful; a bileduct is readily punctured in patients with extrahepatic obstruction, but not in those with intrahepatic cholestasis.[31] It should, however, be emphasised that this helpful procedure carries a risk of biliary peritonitis and should only be

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resorted to after careful clinical and biochemical observation and aspiration liver-biopsy, and when the procedure can be followed by operation within three hours.

Two types of such cholestatic drug jaundice are recognised, the one attributable to hypersensitivity and the other not. Chlorpromazine jaundice [32] is an example of the hypersensitivity group, and an essentially similar picture is produced by some other phenothiazine derivatives.[33 34] Frank jaundice may be anticipated in about 1% of those taking the drug; it usually develops during the first month, and may be heralded by leucopenia, eosinophilia, drug fever, and drug rash. Hypersensitivity is also suggested when the jaundice follows a single dose or one day's treatment; it may recur when the drug is taken on a subsequent occasion. Chlorpromazine-type jaundice has been noted, too, in association with arsphenamine, *p*-aminosalicylic acid, thiouracil, chlorpropamide, cetylurea, and carbasone.[33] Unlike the hepatitis of the monoamine-oxidase inhibitors, clinical recovery can be confidently anticipated in time, although this may take up to three years.[35] Thus the patient can be reassured with confidence—an important point in managing those with the types of personality which originally needed the phenothiazine drugs.

Acute cholestatic drug jaundice also complicates treatment with methyltestosterone and related derivatives [33]; but this differs from chlorpromazine jaundice in two respects. There is no evidence that the toxic effects are due to hypersensitivity, which would confine such effects to the 1% of susceptible individuals; instead, most of those receiving enough of the drug for long enough will develop bromsulphthalein retention,[36–38] if not frank cholestatic jaundice. Secondly, although the clinical picture is essentially the same, there are histological differences: the liver lesion is that of simple cholestasis, with slight hepatocellular changes; there is neither the portal-zone cellular reaction nor the eosinophilia which point to an allergic reaction.[39] Besides methyltestosterone, steroids reported to cause this type of jaundice have alkyl substitution at the carbon-17 position of the steroid nucleus. Such substitution also provides a group of compounds which are active when taken by mouth. The importance of C17α-alkyl substitution, both in the pathogenesis of cholestasis and in conferring oral activity, sheds light on the old problem of why methyltestosterone is, and testosterone propionate is not, icterogenic. The latter, which is given by injection, does not carry this steroidal configuration. Likewise, nandrolone, which differs from most of the other commonly used nonvirilising anabolic steroids, is given by injection, does not seem to cause cholestasis, and does not have the C17 alkyl substitution. As these orally active anabolic nor-steroids with reduced virilising action or with potent progestational properties become increasingly popular, it is as well to remember their peculiar effect on the excretory capacity of the liver, and in particular on bromsulphthalein excretion. Otherwise the finding of this biochemical evidence of hepatic dysfunction in the absence of clinical evidence of liver disease may lead to the unfortunate patient being warned about his health and placed on a rigid " liver regimen ".

Unlike chlorpromazine toxicity, which seems to be an allergic reaction to a small dose in the hypersensitive host, steroidal toxicity is a straightforward consequence of dosage and duration of administration. Perhaps the agent which will be used for the longest periods—namely, over the childbearing years of life—is the new oral contraceptive, norethynodrel, a C17-alkylated C19 steroid. This has already been reported to cause bromsulphthalein retention,[40] and time will show whether it can produce cholestatic jaundice. Any organisation responsible for the widespread dissemination of " the pill " would be wise to include tests of bromsulphthalein excretion in its surveys, certainly until all doubt on this point has been dispelled. Meanwhile, " the pill " should not be overlooked when the medicine-chest is scrutinised for potentially icterogenic drugs.

Preparation for Retirement

RETIREMENT from work is a 20th-century institution. More older people, mechanisation, pensions and superannuation, and a new philosophy of leisure are all reasons why the number of retired men and women has risen steadily. If current trends continue, by 1980 more than 3 out of every 4 people over sixty-five will be retired.

Is retirement " the roleless period " that some writers have described? Do many retired people find acceptable substitutes for work, and what kind of guidance is offered to those who do not? Questions of this kind are being asked more and more by men and women who have begun to realise that some advance thinking is a better approach to retirement than blind refusal to prepare for the break from work. Of course, many people make a success of retirement and adjust themselves happily to their new leisure. The reasons for this are sometimes obvious: release from an uninteresting job and an absorbing hobby; a move to pleasanter surroundings or nearer to kin; freedom to stroll, observe, read, or help in the home. But what about the others who find they have retired *to* nothing, whose thoughts dwell often and nostalgically on what they have retired *from*—the wage or salary, the companionship of work, the status? These are the people who enter retirement unprepared either to cut its losses or exploit its gains. To help them to acquire well in advance a realistic understanding of its true meaning schemes of preparation have been started in this country and America, and Dr. ALASTAIR HERON has lately reviewed their origins, development, and programmes.[41]

The first in this country was started four years ago in an engineering firm in Birmingham. Six weekly discussion

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