tained by percutaneous liver biopsy it is often impossible to be certain about the absence of cirrhosis.

Since cirrhosis, then, is one of the most consistent features of this condition, both the clinical label of active chronic hepatitis and the term chronic aggressive hepatitis—as used by the pathologist in describing the pathological appearances—are as inappropriate as they are confusing. Furthermore, in active chronic hepatitis different areas of the liver may vary greatly in appearance. Indeed, this was why Cook and colleagues did not attempt to analyse the serial biopsies in their patients for the effects of the corticosteroid therapy, though the histological appearances of chronic aggressive hepatitis were considered to be of importance in deciding on the inclusion of patients in their trial.

In most series of patients with active chronic hepatitis there are some with few or no clinical signs and with minimal changes in liver function tests, though the histological appearances indicate considerable activity of the underlying process. Other cases like these may pass unrecognized until the cirrhosis has become gross. By that time the histological appearances of activity may have lessened, and if the presentation of the patient at that stage is with variceal bleeding, encephalopathy, or ascites the diagnosis usually made is one of cryptogenic cirrhosis. The term cryptogenic cirrhosis is not particularly satisfactory, for in many cases liver biopsy shows some evidence of inflammatory activity, and the same autoantibodies may be present in the serum (though at a lower frequency) as in patients with active chronic hepatitis. Indeed, Deborah Doniach and J. G. Walker[5] have proposed that active chronic hepatitis and cryptogenic cirrhosis as well as primary biliary cirrhosis are all part of the spectrum of autoimmune liver disease. Though some of the clinical and histological features of primary biliary cirrhosis are distinct, recent studies have indicated some overlap with active chronic hepatitis. Certain patients with the latter condition, for instance, have some of the features of biliary cirrhosis in the liver biopsy and a considerably raised serum alkaline phosphatase level, which is more characteristic of primary biliary cirrhosis.

Disease in several systems is also found in cryptogenic cirrhosis, though less frequently than in active chronic hepatitis or primary biliary cirrhosis. Histological examination of the organs affected, including salivary gland, kidney, or lung in all three diagnostic groups, discloses varying degrees of lymphocytic infiltration like that seen in the liver. Such infiltration is suggestive of a cell-mediated immune response, and recently M. G. M. Smith and colleagues[6] have shown with the leucocyte migration test (a known measure of cellular hypersensitivity) that abnormal responses can be detected in some patients with active chronic hepatitis, primary biliary cirrhosis, or cryptogenic cirrhosis. Furthermore, in those patients who had developed renal tubular acidosis or Sjögren's syndrome abnormal responses to kidney and salivary antigens could also be detected. These workers suggested that damage to the liver initially from virus, drug, toxin, or unknown agent led to release or alteration of a cell antigen, which in patients with an abnormal central immune system is followed by a cell-mediated response directed against the liver and other organs with common antigens. If the cell-mediated response were directed mainly against cell surface antigens in active chronic hepatitis and cryptogenic cirrhosis, and against bile ductule antigens in primary biliary cirrhosis, this could account for the differences in clinical picture usually observed.

Since corticosteroid therapy is effective in prolonging survival in active chronic hepatitis, and since asymptomatic cases have had florid histological changes progressing to cirrhosis, it may be unwise to stop treatment as soon as the clinical and biochemical features return to normal. For even though the disease may appear to be inactive when assessed by all possible methods (including immunological) no controlled trial has yet shown whether further treatment, perhaps by preventing a relapse, is beneficial or harmful.

The value of azathioprine, both initially in the control of the disease and as maintenance therapy, is also uncertain at present. The preliminary reports of the Mayo Clinic controlled trial indicate that it is less effective than corticosteroids.[2] Perhaps this is not surprising, for the immunosuppressive activity of azathioprine is thought to be dependent on its metabolic transformation, probably in the liver, and it has been shown that the level of immunosuppressive activity attained in the serum is reduced when liver function is impaired.[7] There are also some reports suggesting that patients with liver disease are unduly susceptible to the hepatotoxic effects of azathioprine and that the use of doses of more than 100 mg per day may be followed by an increase in jaundice and the development of hepatic coma.[8] Though it is possible that a combination of azathioprine and corticosteroid, each in a smaller dose, is better than either singly, this too remains to be established.

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[2] *Immunology of the Liver*, ed. Smith, M., and Williams, R., London, Heinemann, 1971.
[3] Golding, P. L., and Mason, A. S. M., *Gut*, 1971, **12**, 153.
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Solar Flares and the Concorde

"Any person remaining unprotected within the path of the radiation from a major flare at the distance of the Earth from the Sun will almost certainly receive a fatal dose." So writes P. M. Molton.[1] The key words in this statement are "remaining" and "unprotected." Passengers in supersonic aircraft, at the height these vehicles are expected to fly, come within 3% of being full-blown astronauts, since 97% of the atmosphere is below them. But they themselves need not remain there. As to being unprotected, even a space-walking astronaut outside his ship has layer upon layer of clothing around him, not to mention a layer of gas. The occupants of an aeroplane or spaceship are shielded by the vessel wall and any objects stowed within the vessel between the wall and its occupants. All these items have some effect.

Shielding from radiation is usually reckoned in terms of grammes of matter per square centimetre of the surface being bombarded. The grammes are units of mass, not of weight—at least in space travel, where a mass of 1 g may weigh 6 g on take-off but none at all while coasting through empty space. Measured in these units, the shielding effect of the whole atmosphere is rather more than 1,000 g/cm^2. At the cruising height of the Concorde, somewhere between 75,000 and 80,000 ft (22,900 and 24,400 m), atmospheric shielding is reduced to 36 and 29 g/cm^2 respectively.

Solar flares in the form of abnormally bright patches on the sun's surface were first noticed in 1859 but were thought to be extremely rare until in the early 1930s the spectrohelioscope showed them to be fairly frequent. The final surprise came in 1942 with the discovery that they bring not only light from the sun but a high-speed hail of particles of matter, mainly protons, capable of damaging living tissues in outer space or even in the high atmosphere. J. H. Reid,[2] of Houston Aerospace Systems, listed 16 "major" flares detected between 1942 and 1967. They were not evenly spread over the years but were dependent on the "solar cycle"—a period averaging about 11 years, during which the number of sunspots increases to a maximum and then decreases to a minimum. At present we are at the end of a safe period and must expect flares again.

The International Commission for Radiation Protection gives 0·5 rem per year as the maximum permissible radiation dose. According to Reid[2] a supersonic passenger exposed to every major flare during a complete solar cycle would accumulate 4·4 rem in the 11 years, an average of 0·4 rem per year. But the dose is much higher for a pilot, flying for 40 hours a month at 75,000 ft (22,900 m), especially if he flies over the polar regions. He will in addition receive cosmic radiation from the rest of the universe as well as secondary radiation caused by energetic particles hitting the cabin walls, and the total adds up to an average of 1·6 rem per year if he takes no avoiding action by diving. But the most dangerous flares can produce at their onset a high radiation dose.

How much time would be available for diving down to a safer altitude, such as 40,000 ft (12,200 m), where atmospheric shielding is 200 g/cm^2? During the 16 major flares listed by Reid[2] the times taken for the first and most energetic particles to travel from sun to earth vary from 6 hours 40 minutes for the flare of 3 September 1960 to 26 minutes for that of 23 February 1956 and 25 minutes for that of 4 May 1960. Diving at 30° to the horizontal and going at twice the speed of sound, an aircraft would lose height at just the speed of sound, and drop from 80,000 to 40,000 ft (24,400 to 12,200 m) in 36 seconds. In practice, initiation of the dive would have to be gradual, or everything in the cabin would acquire negative weight, and even passengers strapped in and holding on to their glasses would see their drinks rise before them and splash on to the roof. There would be plenty of time to get down provided the onset of the flare on the sun can be observed. But can it? Much has been learned in the past two years, Molton[1] states, about the observable conditions which favour flare formation, so that prediction may be possible.

Astronauts take longer than aircraft to get down, even from earth orbit, and on a moon journey may have to suffer a flare which lasts for 8 hours or so. However, the earliest and most dangerous particles come almost in a straight line from the sun, so the cabin contents can be piled against the thickest part of the wall as partial shielding. Later particles have time to be diverted by the magnetic field between earth and sun and may hit the ship from all directions. It would be impractical to take up an enormous weight of shielding against such a rare event. So Molton[1] mentions several electrical and magnetic methods of deflecting the radiation from a spacecraft. A further possibility is biological shielding, this last being achieved by a layer of *Micrococcus radiodurans*. This micro-organism can tolerate 400,000 rem of radiation without appreciable mortality, which it does by quick repair of radiation damage by means of special enzymes. Travellers to Mars should be all right. E. Öpik[3] assures them that "little or no corpuscular radiation from these disturbances should reach Mars or beyond."

[1] Molton, P. M., *Spaceflight*, 1971, **13**, 220.
[2] Reid, J. H., *Irish Astronomical Journal*, 1969, **9**, 69.
[3] Öpik, E., *Irish Astronomical Journal*, 1963, **6**, 29.

Anticoagulant Interactions

Interactions between oral anticoagulants of the coumarin-inanedione groups and other drugs are common. They lead to an upset in the normal balance of the clotting systems dependent on vitamin K. The result may be serious haemorrhage, occurring either when a drug is given which increases the anticoagulant action or when a drug which reduces this action is stopped.

A wide variety of drugs, including many tranquillizers and antidepressants, barbiturates, and other sedatives such as glutethimide, diphenhydramine, and meprobamate stimulate increased synthesis of the liver microsomal enzymes ("enzyme induction"). The latter are responsible for metabolizing and inactivating many drugs, including most oral anticoagulants. When a patient is given an enzyme-inducing agent the effect of the anticoagulant is reduced. Conversely, when the prothrombin time is being controlled in the therapeutic range in a patient who is taking such an agent, the anticoagulant effect increases when it is stopped. Serious haemorrhage may occur some days later unless the dose of the anticoagulant is reduced. A. Breckenridge and his colleagues,[1] studying dichloralphenazone (a complex of antipyrine and chloral hydrate), have recently found that its enzyme-inducing effects were due to antipyrine. They also confirmed an earlier report[2] that chloral displaced warfarin from its binding sites on the plasma proteins. In both studies the patients' plasma warfarin levels fell, indicating that the free drug, while available for its biological effect, was also available for enzymatic hydroxylation. E. M. Sellers and J. Koch-Weser found that the anticoagulant effect of warfarin was enhanced when chloral was given, but Breckenridge and his colleagues did not confirm this. Conversely, there has been one report of fatal haemorrhage in a patient whom the prothrombin time rose sharply when chloral hydrate was stopped—suggesting that chloral had reduced the anticoagulant effect.[3]

Clearly, therefore, the interplay between anticoagulant displacement and metabolism cannot be predicted in the individual patient when chloral is given. However, these results do show that both chloral hydrate and dichloralphenazone are unsuitable sedatives for patients on oral anticoagulants. But, though chlordiazepoxide is an enzyme inducer in the rat,[4] it does not seem to affect warfarin requirements in man.[5] Nitrazepam is also thought to be a safe sedative during anticoagulant treatment.

A high proportion of a dose of oral anticoagulants becomes bound to plasma protein after absorption. This fraction may be displaced by other highly protein-bound acidic drugs including phenylbutazone, oxyphenbutazone, salicylates, indomethacin, mefenamic acid, probenecid, nalidixic acid, sulphonamides, clofibrate, diazoxide, and ethacrynic acid.[6–9] Serious and fatal haemorrhage has followed the use of some of these drugs in patients taking anticoagulants, suggesting that the drugs have a potentiating effect. However, displacement may not be the only mechanism responsible; phenylbutazone and other pyrazolones may inhibit the enzyme hydroxylating warfarin[10]; and salicylates—some of which also