antibodies to *Klebsiella* species with cells, mainly lymphocytes, bearing HLA-B27. A few specific serotypes of *Klebsiella* spp have been shown to induce antibodies in rabbits which are capable of inducing the killing of cells in complement-dependent cytotoxic tests positive for B27 lymphocytes from patients with ankylosing spondylitis, but not of cells negative for B27 from patients with disease or cells positive for B27 from normal persons. The phenomenon is unusual in that the cytotoxic effect is detectable only using an assay based on radioactive chromium and seems to be weak or absent when the classical "tissue typing" methods are used which rely on dye uptake by dead cells. Furthermore, rabbit antibodies prepared by immunisation against Gram-negative bacilli or their products are often difficult to evaluate in their reactivity against human cells, possibly because of the presence of heterophil antibodies (some of which behave like anti-A blood group antibodies). These preliminary observations on lymphocytes from patients with ankylosing spondylitis need to be extended with antibodies prepared against purified HLA-B27 material in species other than the rabbit. New studies described at the eighth workshop, using a specific component extracted from selected serotypes of *Klebsiella* (K43), show that B27-positive lymphocytes from patients with spondylitis are specifically killed by an antiserum prepared against a 40-52K band obtained by polyacrylamide fractionation of solubilised bacterial sonicates. B27-positive lymphocytes from healthy donors were not affected, but when these lymphocytes were incubated with culture filtrates from the relevant organism they became susceptible to the cytotoxic effect of the rabbit antiserum.[7 8]

A third mechanism proposed for HLA and disease association is that HLA antigens may act as receptor sites for viral or hormone attachment.[9] For viral infection, this might be a very specific effect (as with influenza and neuraminidase) or might depend on some degree of "mistaken identity" or cross-reactivity. Hormonal attachment is postulated on a different basis—competitive binding by the HLA site and consequent loss of normal hormonal function—but again presupposes some kind of molecular mimicry.

Possibly another, separate group of disorders may exist which have a different association with the HLA system and to which none of the current explanations will be applicable. One of the most comprehensive studies undertaken as part of the workshop dealt with the relation between the HLA system and the virilising syndrome characterised by deficiency of 21-hydroxylase enzyme[10] (generally referred to as adrenal hyperplasia syndrome). A large series of families with cases of adrenal hyperplasia had been studied in detail and the reported association between HLA haplotype and 21-OH deficiency was confirmed. Affected siblings were HLA identical when more than one case occurred in a family, in accordance with a recessive mode of inheritance. Recombinants found in the workshop (and others previously reported) suggest a site for the 21-OH gene close to the HLA-D or DR locus. At least one haplotype seems to predispose to the presence of 21-OH deficiency, including the antigens A2, Bw47, Cw6, DRw1 or DRw7, and BfF. Adrenal hyperplasia due to 21-OH deficiency is clearly the result of a specific mutation, but the relationship with HLA could be quite fortuitous. A variant form of the disease with late onset in young adults was also reported to show association with HLA inheritance, but with a different haplotype that includes HLA-B14, DRw1, and Bf_s. Probably some structural genes important for steroid hormone synthesis are located within the HLA region.

The proceedings of the eighth workshop and the conference which followed will be published shortly; but many problems remain unresolved, and these will form at least part of the basis for succeeding workshops, the next to be held in early 1984 (in Germany). Let us hope that by then the mechanisms of HLA and disease association have been clarified so that they are not still encoded in "newspeak."[11]

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Antibiotics and the liver

With some drugs, such as paracetamol, the risk of hepatic damage is related to the amount taken. More commonly, the toxic response is independent of the dose and is unpredictable, occurring in only a few patients. Such idiosyncratic reactions usually develop within a few weeks but they may appear after several years of treatment or even within a few days of stopping it. The illness may resemble viral hepatitis or obstruction of the biliary tract and in severity may range from an asymptomatic rise in the serum concentration or activities of bilirubin, alkaline phosphatase, and transaminases to deep jaundice or fulminant hepatic failure.

Drug-induced liver disease is occasionally accompanied by features of a hypersensitivity reaction: fever, rash, eosinophilia, or eosinophilic infiltration in the liver biopsy specimen. More often the diagnosis is based on the history of drug ingestion, improvement on stopping the drug, and exclusion of other causes of liver disease such as alcoholism, gall stones, or infection with hepatitis B virus. Further administration of the drug may produce severe toxicity, and challenge tests should not be undertaken merely to confirm the diagnosis.[1]

Many antimicrobial agents may produce acute hepatitis or cholestasis. The list includes carbenicillin, chloramphenicol, clindamycin, erythromycin, isoniazid, nitrofurantoin, para-aminosalicylic acid, rifampicin, and sulphonamides. For some antibiotics the association is based on a few case reports, and since bacterial infections can themselves produce liver dysfunction[2] proof that the drug was responsible for the liver damage is not always possible. Some less common forms of liver disease are also produced by antibiotics.[3] Tetracycline

given intravenously may induce fatty liver, novobiocin and rifampicin may interfere with the conjugation of bilirubin, griseofulvin may precipitate attacks of acute intermittent porphyria in susceptible people, and penicillin may produce hepatic granulomas.

Some antimicrobial drugs produce both acute and chronic liver disease. In one survey of almost 14 000 patients treated with isoniazid, 114 patients developed hepatitis and, of these, 13 died from liver failure.[4] Symptoms usually developed within three months of starting treatment. Histological studies in 33 patients most often showed features of acute hepatitis, but three patients had chronic active hepatitis and one patient had cirrhosis. Some of these patients may possibly have had chronic liver disease even before taking isoniazid. One patient has developed chronic active hepatitis after having taken several courses of sulphonamides over three years.[5] Again, the occurrence of chronic liver disease could be coincidental, but the serum transaminase activities rose slightly when the patient was challenged with a single dose of the drug.

Several reports have appeared of patients found to have chronic active hepatitis while having long-term treatment with nitrofurantoin. Sharp *et al* reviewed 15 cases already published and added a further five of their own.[6] All the patients were women and they had been taking nitrofurantoin for between one month and four years. They usually had jaundice and enlargement of the liver with raised serum concentrations of globulin and transaminases and positive tests for smooth muscle antibody and antinuclear factor. Liver biopsy specimens were taken from 17 patients: all showed chronic active hepatitis and four had superimposed cirrhosis. Most patients improved when treatment with nitrofurantoin was stopped, but reintroducing the drug provoked relapse, which in two cases proved fatal. Chronic active hepatitis may complicate treatment with other drugs such as methyldopa, propylthiouracil, and perhexiline.[3]

What precautions are reasonable? A recommendation that liver function tests should be performed routinely during treatment with isoniazid[7] seems unnecessary; though an asymptomatic rise in serum transaminase activities occurs in one-fifth of patients, the risk of developing serious liver disease is small. Indeed, enzyme activities may return to normal even if treatment is continued. Certainly the risk that long-term treatment with some drugs can produce chronic active hepatitis needs to be recognised, since continued administration of the drug to patients with hepatomegaly or jaundice will allow the hepatic necrosis to become more extensive and increase the risk of progression to cirrhosis.[8] Liver function will, however, usually improve when the drug is discontinued, and any persisting small rise in serum transaminase activities or minimal inflammatory changes in the liver biopsy specimen may be safely ignored.[8] Treatment with corticosteroids has not been shown to be beneficial, but probably these should be given to those few patients who continue to deteriorate after the drug has been withdrawn.[8]

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Priorities at Newcastle

The dominant themes in the Health Service during the 1979-80 session have been those ubiquitous three Ms—money, management, and manpower. Yet the profession's collective response to cash limits, further NHS reorganisation, and threatened medical unemployment has so far been remarkably restrained, with no demands for special representative meetings or militant action. This can reasonably be judged as a responsible rather than an apathetic posture, for doctors have been well aware of the problems, while in their first year of office the BMA's new Chairman of Council and Secretary have brought commendably analytical skills to bear on trying to solve them. In contrast to some unions, which have reacted with reflex hysteria to the consequences of Britain's struggles to live within its means, the BMA has preferred to await firm evidence on which to act. But the time has come for the profession to define its attitude to the Government's policy on NHS resources and the Annual Representative Meeting's first priority motion, which expresses "grave concern" at the NHS's financial problems and the inevitable consequences on standards of patient care,[1] will give the Representative Body an opportunity to do this. The effects of the cuts vary widely and a constructive Association policy sensitive to local needs is more likely if speakers bring facts rather than rhetoric to the rostrum; emotional blunderbuss decisions will not help the profession's leaders in the difficult year ahead.

One welcome event this year has been the Review Body's award,[2] which should mean that more time at the ARM and craft conferences can be devoted to other matters—though the hospital junior staff conference will have to decide whether to return to the Review Body's fold—and the range of controversial topics competing for time is catholic: alcoholism, audit, career structure, certification, complaints procedures, confidentiality, the Flowers Report, related ancillary help, smoking, and work load, to name but a few. While the 586 motions on the agenda at Newcastle Civic Centre on 7 to 11 July will disappoint those who hoped that flourishing craft conferences would reduce ARM agendas to manageable proportions, one encouraging aspect is the strength of the science section. That will maintain the notable scientific tradition of the Association's four Tyneside meetings since 1870, described by a former chairman of the Representative Body, Dr J S Noble, at p 1550.

"Scientific activities" open with a priority motion on audit in which the Sheffield Division, with Yorkshire bluntness, asks the meeting to instruct "Council and the Chairman of the Representative Body to stop surveying any method of medical audit." The Junior Members Forum, following up their demand at Liverpool for Council to produce a practical scheme for audit,[3] asks for audit to be "introduced forthwith." This debate will be a test of the profession's nerve and foresight. The Representative Body should avoid the trap of accusing the Government of cutting standards of care for patients in one breath while in the next refusing the oppor-