Antituberculosis drug-induced hepatitis —
the dangers of rechallenge

To the Editor: There has been concern in our hospital about the issue of antituberculosis drug-induced hepatitis and the dangers of rechallenge. After a meeting between interested parties from Groote Schuur and Brooklyn Chest hospitals, the following report was formulated, which may be of interest to readers.

Approximately 0.3% of patients on commonly used antituberculosis therapy (streptomycin, isoniazid, pyrazinamide and rifampicin) develop drug-induced hepatitis, most often within 3 months of starting treatment. In descending order of probability, the most likely offending agents are pyrazinamide, rifampicin and isoniazid. Streptomycin is not likely to be implicated in this problem.

The diagnosis of drug-induced hepatitis is made on clinical and biochemical grounds. The patient is usually ill and may develop jaundice, fever, nausea and right upper quadrant pain, and the results of liver function tests are abnormal (confirmed on two occasions). For this purpose an abnormal result is considered to be an aspartate aminotransferase or alanine aminotransferase value more than 3 times the upper limit of normal, an alkaline phosphatase level more than 1.5 times the upper limit of normal, or a bilirubin level more than 2 times the upper limit of normal. Transient mild elevation of these values is not uncommon during the initial period of antituberculosis therapy, typically does not cause symptoms, and should not be confused with drug-induced hepatitis. Other causes of hepatitis should be carefully sought, e.g. alcohol and other hepatotoxic drugs, or hepatic enzyme-inducers such as anticonvulsants. Viral hepatitis should be considered.

Once the diagnosis of drug-induced hepatitis is made, all antituberculosis therapy should be stopped until clinical and biochemical recovery takes place. The issue of substitution or drug rechallenge must then be considered. Deaths have been reported after patients have been rechallenged with drugs that have previously induced hepatitis. As a result, a careful risk/benefit assessment is mandatory. Care should be taken that the diagnosis of tuberculosis is firmly established before continuing with therapy. Rechallenge should not be considered without the advice of a regional expert on tuberculosis therapy.

Since there are alternative agents, it is recommended that patients should be rechallenged only if the tuberculosis is considered to be of such severity that this dangerous step is essential. Certain authorities would go so far as to say that it should only be done if the tuberculosis is considered to be potentially fatal. In that event, the precautions outlined below should be strictly adhered to. An alternative therapeutic regimen could be streptomycin, ethambutol and ethionamide.

In severe tuberculosis (e.g. tuberculous meningitis or miliary tuberculosis) the risk of the disease may be more serious than the risk of drug-induced hepatitis. In this event it may be necessary to rechallenge with one or more drugs. The following regimen is recommended at Groote Schuur Hospital:

1. Additional advice must be sought from the University Liver Clinic or the Clinical Pharmacology Unit.
2. The patient must be admitted to hospital and monitored closely, and informed consent must be obtained.
3. The following drugs could be used (after fulfilling the above two recommendations): (i) streptomycin; (ii) ethambutol or ethionamide (as new drugs); and (iii) isoniazid (or rifampicin) rechallenge.

It is recommended that rechallenge be carried out by giving once only a quarter of a single dose of the drug and monitoring the patient's clinical state closely. Liver function tests should be performed at 6, 24, 48 and 96 hours. If the test dose is well tolerated, the full dose could be given for 3 days and the patient monitored daily for 4 days and again at 1 week. If there are no problems, continuation at full dosage is justified.
The patient should be carefully monitored during the rest of his antituberculosis therapy if rechallenged. The most important aspect of this monitoring is the patient's clinical condition, in addition to his or her reporting any untoward effects.

In conclusion, it should be emphasized that rechallenge in drug-induced hepatitis is dangerous. It is recommended that whenever possible patients should not be rechallenged. Should rechallenge be considered essential this should only be done in a major hospital and by experts in the management of fulminant hepatitis.

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Problems over death certificates

To the Editor: In the editorial entitled 'The death certificate — fact or fiction?'1 attention was drawn to the results of a recent American autopsy study which indicated that in 29% of cases there was major disagreement on the underlying causes of death.2 Other reports indicating similar findings have been published.3-5 In South Africa, the vital statistics of Africans have been labelled 'a black hole'.6

Recently we have been studying 50% survival times of series of black cancer patients in Soweto, as diagnosed at Baragwanath Hospital.7 When we investigated the extent to which the cause of death (known to us) correlated with death certification data as recorded at the Johannesburg City Health Department, it transpired that certification was correct for only 38 of 65 blacks with known breast cancer. Conversely, of 64 deaths certified as from breast cancer, 44 were verified from records at Baragwanath Hospital. On attempting to visit the remaining 20 patients' relatives to enquire about antecedent medical attention, in only half of the few cases in which satisfactory information was provided was there a measure of certainty about the diagnosis. Hence, breast cancer (and probably other cancers) is being both undercertified and overcertified (as also reported for stomach cancer in the UK).8 Crucial local points to be taken into reckoning are: (i) in Johannesburg over a quarter of total death certificates of blacks are signed at Groote Schuur Hospital,9 when we investigated the extent to which the cause of death (known to us) correlated with death certification data as recorded at the Johannesburg City Health Department, it transpired that certification was correct for only 38 of 65 blacks with known breast cancer. Conversely, of 64 deaths certified as from breast cancer, 44 were verified from records at Baragwanath Hospital. On attempting to visit the remaining 20 patients' relatives to enquire about antecedent medical attention, in only half of the few cases in which satisfactory information was provided was there a measure of certainty about the diagnosis. Hence, breast cancer (and probably other cancers) is being both undercertified and overcertified (as also reported for stomach cancer in the UK).

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Raised carcino-embryonic antigen levels

To the Editor: Recently an increasing number of patients have been referred to us for investigation of slightly raised carcino-embryonic antigen (CEA) levels. The CEA level is often measured as a screening test for colorectal cancer by the American Cancer Society.1 The unselected use of CEA measurements in patients with minimal abdominal symptoms will result in what we have