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.[1] 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.[2] 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.[1,3] 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.[2]

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 hepatic failure.

We would like to thank Professors P. I. Folb and R. E. Kirsch and Drs A. Cavvadas, D. J. M. Jenkin, L. Pilkington, A. H. Robins and J. L. Straughan for participating in the meeting and for their contribution to the report.

F. S. E. Monteagudo
P. I. Pillans

Department of Pharmacology
University of Cape Town and
Groote Schuur Hospital
Cape Town

1. Cohen CD, Sayed AR, Kirsch RE. Hepatic complications of antituberculosis therapy revisited. *S Afr Med J* 1983; **63:** 960-963.
2. Davidson CS, Leevy CM, Chamberlayne EC, eds. *Guidelines for Detection of Hepatotoxicity due to Drugs and Chemicals* (NIH Publication No. 79-313). Washington, DC: DHEW, 1979.
3. Rossouw JE, Saunders SJ. Hepatic complications of antituberculous therapy. *Q J Med* 1975; **173:** 1-16.

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.[3,4] In South Africa, the vital statistics of Africans have been labelled 'a black hole'.[5]

Recently we have been studying 50% survival times of series of black cancer patients in Soweto, as diagnosed at Baragwanath Hospital.[6] 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[3]). Crucial local points to be taken into reckoning are: (*i*) in Johannesburg over a quarter of total death certificates of blacks are signed by police as from 'natural causes'; and (*ii*) a variable proportion of the deceased are listed as dying from 'other causes'. In Pretoria in 1981, 40% of deaths of those aged over 5 years were thus listed.[7] This unsatisfactory situation confirms the urgent need for the recently inaugurated National Cancer Registry,[8] based at this Institute. Although initially it will be a pathology-based registry, it will subsequently include clinically diagnosed tumours and hence in time will provide much needed information on inter-ethnic incidences of particular cancers.

Although our enquiries on death certificates are still in progress, the situation depicted is alarming. We next looked into intercity variability in inter-ethnic rates of death from cancer. Marked differences are apparent in crude rates. Among blacks, in 1983 the crude mortality rate for total cancer was far higher in Cape Town[9] than in Durban.[10] For the coloured population, the crude death rate for bronchial and lung cancer in Cape Town[9] was roughly double that in Durban.[10]

We comment as follows:

1. To preserve balance it must be reiterated that in Western populations numerous investigations have revealed major discrepancies between known and certified causes of death.[2-4] Since no examination of this type appears to have been made on any population in South Africa, enquiries are obviously desirable. Understandably, authoritative opinion overseas is urging greater care in the filling in of death certificates.[4,11]

2. When reporting cancer mortality among blacks (or similar populations), sources of error must be detailed, as urged by others.[5]

3. Although interregional differences in cancer mortality rates (as in the UK[12]) are well recognized, it would be profitable to look more closely into the validity of our intercity differences.

4. Because of the uncertainties described, restraint must be exercised (especially by enthusiasts, including ourselves) over maintaining that this or that mortality rate for a particular cancer is extremely low, or the converse. In this respect mortality rates from cancer in developing populations as listed by the Segi Institute[13] must be interpreted with reserve.

We are grateful to Professor C. Isaacson, Head of the Department of Anatomical Pathology, SAIMR, for permission to use the records at Baragwanath Hospital, and to Professor B. R. Richards and Mrs Shirley Pryer, of the City Health Department, for death certificate information. Help was given by Mrs M. Kadwa, M. Verardi and D. Siwedi. The cancer survival studies are being supported by a grant from the Chairman's Fund of Anglo-American and De Beers.

A. R. P. Walker
B. F. Walker

Department of Tropical Pathology
School of Pathology
University of the Witwatersrand and
South African Institute for Medical Research
Johannesburg

1. Editorial. The death certificate — fact or fiction? *S Afr Med J* 1986; **69:** 402-403.
2. Kircher T, Nelson J, Burdo H. The autopsy as a measure of accuracy of the death certificate. *N Engl J Med* 1985; **313:** 1263-1269.
3. Coggon D, Acheson ED. The geography of cancer of the stomach. *Br Med Bull* 1984; **40:** 335-341.
4. Knight B. The causes of death. *J R Soc Med* 1986; **79:** 191-192.
5. Botha JL, Bradshaw D. African vital statistics — a black hole? *S Afr Med J* 1985; **67:** 977-981.
6. Walker ARP, Walker BF, Tshabalala EN, Isaacson C, Segal I. Low survival of South African urban black women with breast cancer. *Br J Cancer* 1984; **49:** 241-245.
7. Medical Officer of Health, Pretoria. *Annual Report,* 1980-1981.
8. Simpson IW. The National Cancer Registry. *S Afr Med J* 1986; **69:** 2-3.
9. Medical Officer of Health, Cape Town. *Annual Report,* 1981-1984.
10. Medical Officer of Health, City of Durban. *Annual Report,* 1980-1983.
11. Carter JR. The problematic death certificate. *N Engl J Med* 1985; **313:** 1285-1286.
12. Gardner MJ, Winter PD, Taylor CP, Acheson ED. *Atlas of Cancer Mortality in England and Wales, 1968-1978.* New York: John Wiley, 1983.
13. Segi M, Fukeshima T, Mikami Y *et al. Age Adjusted Death Rates for Cancer for Selected Sites (A-Classification in 46 Countries in 1978).* Nagoya, Japan: Segi Institute of Cancer Epidemiology, 1984.

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 to 'exclude' colorectal carcinoma in patients complaining of non-specific abdominal pain. These patients arrive with the knowledge that the 'cancer test' performed on them was positive and therefore demand a full diagnostic work-up, including barium enema examination and colonoscopy.

The circulating blood level of CEA has not fulfilled its initial promise as a sensitive and specific biological marker for the detection of colorectal cancer. Elevated CEA levels occur in a wide variety of benign conditions such as liver disease, ulcerative colitis, Crohn's disease and pulmonary infections and also in other malignant conditions such as carcinoma of the pancreas, breast, liver or lung. Elevated levels have also been found in heavy cigarette smokers. Estimation of the CEA level is not mentioned 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