Correspondence

Letters to the Editor should not exceed 500 words.

Carcinogenesis of Isoniazid in Mice

Str,—Reports in the last few years that isoniazid in very large doses can produce pulmonary tumours in several strains of mice led to speculation that it might be carcinogenic for man. The need for investigation of the question has most recently been pointed out in these columns (12 June, p. 1508). The difficulties of obtaining valid information are, however, perhaps not at first obvious. It could be as tragic for the world to discard isoniazid on the basis of spurious evidence that it was carcinogenic for man as it would be to fail to detect its carcinogenicity. The soundness of investigations of the question thus becomes of tremendous importance.

It is, however, odd that such techniques as randomization and double-blind readings, which are widely accepted as essential for the control of bias, are never mentioned in the published reports on the carcinogenicity of the drug in mice.

In man any investigation requires comparison of the incidence of cancer (or cancer mortality) in a large group of persons who have received isoniazid and in another entirely similar group who have not received isoniazid. Thus the suggestion that the experience of tuberculosis patients treated with isoniazid be measured against the experience of a “so-called” control group, either (i) the general population, or (ii) tuberculous patients not treated with isoniazid, has serious defects, and wholly spurious correlations between isoniazid and cancer might result.

It is not satisfactory to use the general population, because tuberculous patients differ from the general population in at least four critical respects in addition to the fact that they have received isoniazid. Firstly, they have tuberculosis, a disease which itself has been suspected since at least the 1846 of predisposing to cancer. Second, cigarette consumption has been reported to be greater in tuberculosis patients than in matched controls. Third, they have been under roentgenographic surveillance during diagnosis and treatment, with a consequent increase in radiation over the general population, and, even more, greater opportunity for the detection of cancer. Finally, if, as generally accepted, the less-privileged members in the general population have more tuberculosis and also, as reported, more cancer, comparison of the incidence of cancer in tuberculosis patients with that in the general population may show a relationship actually linked neither to tuberculosis nor to isoniazid.

Proposal number (ii) would require the comparison of patients who have been treated since 1952 with patients who have not been treated since that year, when isoniazid first became available. There are several irreducible defects in such a proposal. First, the general increase in incidence of certain types of cancer alone should produce a higher incidence of that disease in tuberculosis patients who have received isoniazid than those observed before the drug became available. Further, the survivors of tuberculosis in the chemotherapy era are very probably qualitatively different as well as more numerous than survivors of the earlier generation, when only the hardest recovered.

A programme undertaken by the United States Public Health Service for a different purpose will, we hope, provide unique and definitive information on the possibility of a carcinogenic effect of isoniazid. Since 1955 we have been engaged in a series of carefully controlled trials designed to test the value of isoniazid in preventing tuberculosis. More than 70,000 persons in eight major trials have been randomly assigned to receive daily for a year either isoniazid or a matching placebo. The 5 mg./kg. dose of isoniazid is comparable to that used for the treatment of tuberculous patients. We now plan to extend our period of observation to at least 15 years. Each year we determine where each person is, whether he has developed tuberculosis during the year, and, if he has died, obtain a copy of the death certificate. The length of observation since the end of the medication year ranges now from nine years in the earliest trial to a few months in the latest trial.

The population admitted to the trials ranged in age from 2 months to over 100 years, and includes household contacts of active cases, inmates of mental institutions, Alaskan and Puerto Rican villagers, and silicotics. Less than 1% of the total population of the trials has been lost from observation.

Observation to date shows that isoniazid prophylaxis reduces the incidence of tuberculosis by 80% during the medication year and by 50% in subsequent years. Thus far, deaths from cancer of all sites have occurred equally among those who received isoniazid and those who received placebo. I am, etc.,

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Ampicillin in Chronic Bronchitis

Str,—In your pointers for 16 October (p. 889) you state that Dr. P. C. Elmes and his colleagues find “no conclusive evidence” that ampicillin is beneficial in the hospital treatment of acute exacerbations of chronic bronchitis. This indeed is the conclusion of the summary of the paper by Dr. Elmes and his colleagues (p. 904), but study of the substance of the report reveals a number of points which suggest that this conclusion is unjustifiably severe.

A major reason for carrying out Dr. Elmes’s trial was that “the routine use of antibiotics...gives rise to the danger of cross-infection by antibiotic-resistant organisms”; and the demonstration that such organisms appeared in the sputum significantly more frequently in patients treated with ampicillin than in controls seems to have weighed heavily with the authors in their condemnation of routine chemotherapy for acute exacerbations. It is not clear, however, what is meant by “cross-infections” in this context. The frequent appearance of resistant organisms—such as coliform bacilli, Pseudomonas pyocyanea, Proteus, and staphylococci—after the sputum of bronchitis suffering chemotherapy is, of course, well recognized, but such evidence as is available indicates that they play little or no pathogenic role in these patients, with the exception that Staphylococcus aureus occasionally cause pneumonia. This possibility, together with

Tropical Diseases in Britain

Str,—In the B.M.J. of 17 July (p. 167) Dr. K. C. Willett made the important point that in patients in Britain who are suffering from tropical diseases the diagnosis may be missed unless the possibilities are constantly kept in mind. He instanced the chronic Gambian form of trypanosomiasis.

There have been many such instances recently and several other tragic cases have occurred. Cerebral malaria has been diagnosed in patients who had returned from brief visits to the East or to West Africa and were morbund before it was even suspected. Another patient had jaundice, liver disease, which was overlooked; he developed persistent pyrexia and upper abdominal pain after a holiday in Portugal; the diagnosis was made post mortem. Another was a man who had been in a Spanish prison and who some months later developed upper abdominal pain and tenderness. At operation for suggested acute cholecystitis a uniform smooth enlargement of the liver was found, the gall-bladder was removed, but the patient’s condition remained until there was a sudden discharge of "mucous pus" from the drainage tube. Vegetative Entamoeba histolytica were found in the discharge, and at operation the peritoneal cavity was full of yellow exudate, and a huge abscess cavity was found on the under surface of the liver. With appropriate treatment he recovered.

Similar cases have often been reported over the years. The implications of these cases are obvious—namely, the need to ask all patients where they have been, to remember that tropical diseases exist, and to realize that expert opinion is readily available at the tropical diseases hospitals in London, Liverpool, and Edinburgh. The Services, of course, are well aware of these matters.—We are, etc.,

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