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LUNG TUMORIGENESIS BY ISONIAZID (INH), ITS METABOLITE HYDRAZINE SULPHATE (HS) AND DERIVATIVES OF HYDRAZINE

Introduction

INH and HS have been shown to be carcinogenic in various substrains of mice, and some derivatives of hydrazine have proved equally effective in BALB/c/Cb/Se mice.

Since INH is widely used in human pathology, in January, 1966 experiments following two main lines were put before the Council for Tobacco Research:

- an investigation of the carcinogenic action of INH and HS in species of laboratory animals other than mice, and
- research on the carcinogenic action of other hydrazine derivatives in susceptible and resistent mice.

The work plan was approved by the Council and April 1, 1966+ was established as the starting date. This report covers the experiments already under way and those which will be started next.

I. Carcinogenic action of INH and HS in species of laboratory animals other than mice.

A. Carcinogenic action of INH and HS in rats

In previous (unpublished) investigations rats of both sexes were treated with INH added to their drinking water; the dose (35 mg per day) proved toxic, so that these experiments will be repeated using a smaller dose of the drug and with the addition of vitamin B6, which is recommended to counteract the side-effects produced by INH.

Experiments to be started

150 rats of both sexes, born 25th-30th August, 1966: 50 will be treated with INH and vitamin B6, 50 with HS, and 50 will be untreated controls.

+ *See* letter written by W.T. Hoyt, March 14, 1966

Treatment: to begin 30th October, 1966. INH, 20 mg in drinking water associated with 2 mg of vitamin B6 daily; HS, 1.0 ml of 1.13 per cent aqueous solution daily by stomach tube.

If the dose of INH is not tolerated, either it will be decreased or the amount of vitamin B6 will be increased. The carcinogenic action of HS has already been shown in the rat (relevant papers are in press), but it is considered of interest to repeat this experiment parallel with an experiment using INH. Such differences as occur in the results will be analyzed.

B. Carcinogenic action of INH and HS in golden hamsters.

Experiments in progress

90 golden hamsters of both sexes: 60 born 15th April, 1966 treated with HS, 30 born 1st January, 1966 untreated as controls.

Treatment: HS administrations started 4th June, 1966: 0.3 ml of a 1 per cent aqueous solution daily by stomach tube. Treatment was stopped 26th September, 1966. A total of 100 doses were administered, because treatment was alternated with rest periods. Tolerance of the drug was poor. The total dose for the surviving animals: 280 mg. The proposed total dose of 300 mg was not reached because 0.1 ml of the solution was administered at the beginning.

Golden hamsters are being prepared for INH treatment.

C. Carcinogenic action of INH and HS in rabbits.

The animals are being prepared and the treatment will be started as soon as possible.

II. Carcinogenic action of other derivatives of hydrazine in mice.

D.B. Clayson et al. ("Lung Tumours in Animals", pp. 869-880, ed. L. Severi, Division of Cancer Research, Perugia, 1966) have shown that benzoyl hydrazide, 2-methoxybenzoyl hydrazide and 4-methoxybenzoyl hydrazide may be judged carcinogenic because, after oral administration, the proportion of BALB/c/Cb/Se mice bearing tumours and also the number of tumours per affected mouse are increased. Phenylhydrazine hydrochloride is less effective when assessed by these two criteria, but induced pulmonary tumours of a greater degree of malignancy than the other compounds tested. The carcinogenicity of iproniazid must be considered equivocal.

Experiments in progress.

A. Carcinogenic action of P-nitrobenzoyl hydrazide.

Treatment of 33 virgin female BALB/c/Cb/Se mice was started on 1st August, 1966. Tolerance of the drug was very poor:

the tolerated dose was 1 mg in aqueous solution daily by stomach tube.

B. Carcinogenic action of phenylethyl hydrazine sulphate.

Treatment of 63 virgin female BALB/c/Cb/Se mice was started on 1st August, 1966. Poor tolerance. The tolerated dose was 1 mg in aqueous solution daily by stomach tube.

In both experiments A and B a large number of mice died during the testing of the tolerable dose. Untreated mice, the controls, are present in each group. Treatment was started at 8 weeks of age.

Other quantities of these two hydrazine derivatives are in preparation and will be tested in male BALB/c/Cb/Se mice and in C57BL/Cb/Se mice of both sexes.

Another three hydrazine derivatives: symmetrical dimethyl hydrazine hydrochloride, unsymmetrical dimethylhydrazine hydrochloride and 2-(2-Formylhydrazino)-4-(5-nitro-2-2 furyl)thiazole will be administered in aqueous solution by stomach tube to BALB/c/Cb/Se mice of both sexes as soon as possible.

Preliminary tests will be made to establish the tolerable dose.

Papers in press relevant to this project

1. Pulmonary tumours in rats by oral hydrazine sulphate. (In collaboration with F.E. Giornelli-Santilli, U. Milia and L. Severi) Nature, 1966 (in press)

2. Cancerigenesis by isoniazid, hydrazine sulphate and derivatives of hydrazine. Ann. Med. Perugia, 1966 (in press)

3. The relation of isoniazid (INH) and allied compounds to carcinogenesis in some species of small laboratory animals. (In collaboration with L. Severi) Brit. J. Cancer, 1966 (in press)

4. Isoniazid and allied compounds as related to lung tumours in animals. (In collaboration with L. Severi) Submitted for publication to Growth