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CORRESPONDENCE

This department is for the publication of informal communications that are of interest because they are informative and stimulating, and for the discussion of controversial matters.

Carcinogenic Activity of Dapsone

TO THE EDITOR:

The summary of Bergel's report on the carcinogenic activity of 4,4'-diaminodiphenyl sulfone (dapsone, DDS) in the section on "Current Literature" in this JOURNAL [**43** (1975) 280] should not be considered the first test of this effect of DDS, nor to have firmly established that DDS is carcinogenic for rats. In 1960, Morris *et al* ([8]) reported that after feeding the DDS derivative 4,4'-diacetamidodiphenyl sulfone (acedapsone, DADDS) to 17 female Buffalo rats for ten months at a level of 0.025% in the diet, no greater target spectrum or tumor incidence was found over that in the control group. Later, Griswold *et al* ([4]) reported no tumors in two groups of 19 young female Sprague-Dawley rats receiving either a single oral dose of 100 mg of DDS or a total of ten oral doses of 30 mg of DDS given every three days. The rats receiving the two dosage schedules were autopsied at six and nine months, respectively. Clearly, these reports do not suggest that either DDS or DADDS was carcinogenic as were benzidine, 2-anthramine, 2-fluoroenylacetamide, and 2, 7-fluorendiamine when these compounds were tested concurrently.

Bergel's original article ([1]) indicates that young male Wistar rats received progressively higher dietary levels of DDS (0.025 to 0.30%) during the first four months and that they were continued on the highest dietary level for 24 to 25 months. Assuming that each rat weighed an average of 200 gm and consumed 15 to 20 gm/day, we may estimate that a daily dose of 225 to 300 mg of DDS/kg was ingested. The 13 control rats, which were autopsied at 24 to 25 months, exhibited no tumors. Also, no tumors were found in 11 DDS-fed rats that died or were sacrificed at or before 15 months, in 4 rats after 16 to 22 months, or in 2 rats after 24 to 25 months. Tumors were observed in one rat sacrificed at 17 months and in 7 rats sacrificed at 24 to 25 months. The observation that 8 of 25 exhibited tumors is substantial (32%), but hardly equivalent to the amount noted in Bergel's English summary ("... practically to 100% of the animals..."), or the amount noted in the adaptation of his summary ("... to almost 100% of the animals...") that appeared in this JOURNAL *(loc. cit.)*.

Spontaneous neoplasms are observed frequently in untreated male rats 18 to 24 months old as shown by reports of 23% incidence in the Wistar strain ([2]), 68% in the Fischer strain ([6]), and 34% in the Sprague-Dawley strain ([10]). Would Bergel have observed spontaneous tumors had he used a larger number of control rats than the 13 that were sacrificed at the end of the 25th month?

A possible association between DDS and the incidence of cancer has been suggested in leprosy patients ([3]) and in patients with dermatitis herpetiformis ([7]) receiving long-term therapy with DDS. However, other workers ([9,11]) have concluded in more extensive studies that the incidence of neoplasms was no greater in leprosy patients than in the general population.

DDS undoubtedly will remain the primary drug for the treatment of leprosy in the forseeable future, and it may be speculated that its possible role in cancer etiology in rodents and man is similar to that of isoniazid ([5]). This latter drug is carcinogenic for mice. However, the majority of reports of tests in rats indicate that isoniazid is not carcinogenic. Retrospective studies in man do not indicate any carcinogenic effects of isoniazid

when subjects were exposed, over a period of 15 years, to doses applicable to the treatment and prophylaxis of tuberculosis.

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Reply: *Regarding the carcinogenic activity of diaminodiphenyl sulfone (DDS) we would like to point out the following facts:*

1. In Wistar male rats fed with 0.3% of DDS in the diet we found: 0% tumors at one month; 0% tumors at 10 months; 0% tumors at 15 months; and 100% tumors at 25 months.

2. The only way to know whether or not DDS is carcinogenic for white rats is just to feed such animals with DDS for a period of two years. From theoretical or experimental observations in other animals, or under other experimental conditions, such as rats fed for a short period of time with DDS, it is not possible to know the carcinogenic activity of DDS for rats.

3. In our opinion, and taking into account the type of tumors, the organs in which they appeared, such as the spleen, and other considerations, we feel that DDS is a powerful carcinogenic compound for white rats.

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