

Addendum

Substituted Malononitriles in Neoplastic Diseases in Man

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Gal, Fung, and Greenberg (1) showed that certain substituted malononitriles partially inhibited the growth of some transplantable tumors in mice. Clinical trial of two chemicals from their series was therefore undertaken.

Nine patients, as given in Table 1, were selected. All had advanced neoplastic disease, substantiated by relevant biopsy. Periodic clinical examinations, including measurement of accessible tumors, were performed. Weekly examinations were carried out on the blood and urine, as well as chemical deter-

minations of the blood for albumin, globulin, nonprotein nitrogen and bilirubin.

Following a single injection of 0.7 gm. of *p*-nitrobenzalmalononitrile, the blood thiocyanate rose from 0.1 to 0.8 mg/100 cc within 24 hours in one patient; in the second patient, the blood thiocyanate level rose steadily from 0.6 to 3.6 mg/100 cc during a course of 5.35 gm. given in 13 days. No significant or consistent rises were seen in three patients who received 1.5, 1.8, and 2.0 gm. of 5-nitrofurandalmononitrile, respectively.

In none of the patients was there an observable effect upon the primary tumor or its metastases. No toxic effects were seen,

TABLE 1
SUBSTITUTED MALONONITRILES IN PATIENTS WITH CANCER

CASE NO.	SEX	AGE	DIAGNOSIS	DOSE/DAY (GM.)	DAYS USED NO.	TOTAL DOSE GM.
<i>p</i> -nitrobenzalmalononitrile						
1	M	39	Carcinoma, nasopharynx	0.7	1	0.7
2	M	62	Carcinoma, lung	0.03-0.15	18	1.61
3	M	19	Osteogenic sarcoma	0.1-0.9	13	5.35
<i>5</i> -nitrofurandalmononitrile						
4	F	47	Carcinoma, antrum	0.1 2.0	10 1	1.0 2.0
5	M	49	Carcinoma, nasopharynx	0.1-0.2 0.3-1.0	10 9	1.1 7.0
6	M	40	Carcinoma, nasopharynx	0.1-0.9	10	5.4
7	M	25	Carcinoma, testis	0.1-0.5	5	1.5
8	M	20	Osteogenic sarcoma	0.3-1.0	8	1.8
9	M	47	Carcinoma, lung	0.1-0.9	11	6.8

minations of the blood for albumin, globulin, nonprotein nitrogen and bilirubin.

p-Nitrobenzalmalononitrile was dispersed as a 5 per cent suspension in sesame oil, and 5-nitrofurandalmononitrile was dispersed as a 10 per cent suspension in propylene glycol. The chemicals were injected intramuscularly, once a day in 7 patients and every other day in one patient; one patient received a single dose only. Thus, daily doses of *p*-nitrobenzalmalononitrile were up to 15 mg/kg body weight; and of 5-nitrofurandalmononitrile, up to 40 mg/kg body weight.

All patients complained of considerable pain at the site of injection, but no severe local reactions were observed. There were no acute effects upon pulse, respiration, temperature, blood pressure, or electrocardiographic patterns. No significant or consistent alterations in the blood cell counts, urine, or chemical constituents of the blood were detected.

Blood levels of thiocyanate were studied in five patients.

and none of the patients derived subjective or objective clinical improvement. All patients died after an expected course of illness. Autopsy examination was available on eight patients, from 1 day to 7 months following completion of injections. No unusual histologic features were present either in the tumors or in the tissues of the body.

It is concluded that *p*-nitrobenzal- and 5-nitrofurandalmononitrile, at the doses, length of courses, route, and vehicles employed had no effect upon the specific neoplasms observed in nine patients, and that no toxic effects were elicited.

REFERENCES

1. GAL, E. M.; FUNG, F. H.; and GREENBERG, D. M. Studies on the Biological Action of Malononitriles. I. The Effect of Substituted Malononitriles on the Growth of Transplanted Tumors in Mice. *Cancer Research*, 12: 565-72, 1952.