Stimulation and Retardation of Neoplastic Growth by Sulfhydryl Compounds*

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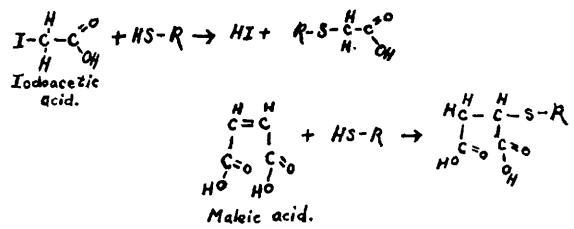
Among the possibilities envisaged by chemotherapy of malignant neoplasms are: (a) specific necrosis of the malignant cells; (b) retardation of mitoses by direct action; (c) maturation of the neoplastic cells, which in turn might lead to arrest of rapid growth.

Recent experiences with alloxan (1, 2) were discouraging insofar as concerns the use of results of laboratory experiments on lower animals as indications for the efficacy of certain compounds as chemotherapeutic substances for cancer in man. Alloxan was shown to cause specific necrosis of the beta cells of the islets of Langerhans of the pancreas and of the epithelium of the convoluted tubules of the kidney in rabbits, rats, and dogs. It was possible to adjust the dosage so that dogs were rendered diabetic. Yet, when alloxan in doses of 1 gm. per kilo (5 times the lethal dosage for dogs, which was 200 mgm. per kilo) was injected into a patient with insulin-producing islet-cell carcinoma of the pancreas, only remissions of attacks of hyperinsulism lasting for 10 to 20 days were observed. After the death of this patient necropsy revealed no histologic evidence of injury to the cells of the carcinoma or to the normal islets of the pancreas.

The importance of the sulfhydryl radical (–SH) in intra-cellular enzyme systems, especially those associated with growth and reaction to injury has long been recognized (6). Experiments reported below were carried out to determine if the addition of –SH might stimulate growth of a transplantable rat tumor, and conversely, if retardation of growth is observed when –SH already present is inactivated by certain agents such as iodoacetic and maleic acids since 3, 4



White rats of inbred strain received subcutaneous injections of fragments of tumor 256 approximately $2 \times 1 \times 1$ mm. in size and thereafter daily intraperitoneal injections of the substances to be tested. The rats, kept 4 to 6 in a cage, in most instances weighed approximately 150 gms. each. At the end of 12 to 17 days the animals were killed, the tumors excised and weighed. As caloric intake affects the growth of neoplasms the animals were weighed at intervals and this factor was controlled in the interpretation of results. Where stimulation or retardation of growth was observed, weight loss or gain of the animals was not a factor.

Since the rate of growth of transplantable neoplasms varies widely among individual rats and appears to be influenced by temperature, diet, season, etc., these factors were controlled. For each group of experimental animals, a parallel control series was maintained in an adjacent cage.

Three preliminary control experiments were carried out using a total of 31 rats. Each experiment consisted of maintaining 3 to 6 rats with tumor transplants in adjacent cages for 2 weeks and at the end of this period the tumors were excised and weighed. The three groups with the heavier average tumor weights were compared with the three groups of lighter tumor weight. The difference was 16.5 per cent, hence it was assumed that variation in weight in the experiments reported below should exceed 20 per cent to be interpreted as significant. Experiments C to G inclusive summarized in Table I and including an additional 104 rats are also control experiments.

To test the possible stimulation of tumor growth by –SH, the following compounds were injected intraperitoneally; sodium thioglycollate, disodium thiomalate, sodium thiolactate, cystein and methionine. Cystin was also injected. The results are summarized in Table I.

The relationship D/H expressed in percentage denotes the ratio of the difference between the average tumor weights in the test and control groups to the heavier of the average weights.

DISCUSSION

The results as summarized in Table I show stimulation of tumor growth by injection of the –SH compounds sodium thioglycollate and disodium malate

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since the neoplasms in the animals receiving these agents averaged 30 to 36 per cent heavier than the controls. The failure of thiolactate to stimulate growth might be explained by an inhibitory effect of lactate (5). The failure of methionine to afford stimulation may be explained by the fact that much of this amino acid was preferentially metabolized to cystin (with its –S–S) and therefore afforded little available –SH. The failure of cystein to stimulate growth can be accounted for by its relative insolubility in saline solution, which necessitated its injection as a suspension thus resulting in slow absorption, and also quite probably by partial conversion to cystin which would further reduce available –SH. Since cystin includes –S–S and not –SH it was not anticipated that it would afford stimulation of tumor growth.

Both iodoacetate and maleate afforded appreciable inhibition of tumor growth as evident from Table II, which shows that the neoplasms in the animals receiving these agents weighed on the average 32 to 44 per cent less than the controls. The inhibition of growth was not very pronounced, however, since the inoculated transplants were not prevented from becoming established as the injections began with the day of transplantation.

The results shown in Table III are corollaries to the

TABLE I: EFFECT OF INTRAPERITONEAL INJECTIONS OF —SH COMPOUNDS ON TUMOR GROWTH

Experiment	No. rats	Compound injected	Daily quantity of S as —SH per 150 gm. rat, gm.	Duration of exper. days	Av. wt. tumors, gm.	D/H %
A	16	Sod. thioglycollate	.003	16	6.70	
	20	No inj. in 9 rats			4.60	30
		Sod. glycollate* in 11 rats				
B	12	Disod. thiomalate	.003	13	7.55	
	11	No inj. in 3 rats			4.80	36
		Disod. malate* in 8 rats				
C	17	Sodium thiolactate	.003	12	4.36	
	16	No injections			3.67	13.5
D	9	Methionine	.0006	15	3.70	
	12	No injections			4.0	5.5
E	9	Methionine	.003	15	5.06	
	10	No injections			6.30	19
F	11	Cysteine	.003	14	6.49	
	11	No injections			5.66	12.7
G	8	Cystin	.003	15	1.99	
	6	Disod. glutamate	.06 (of amino acid)		1.82	9

*In quantities equimolar to those injected in test group.

TABLE II: RETARDATION OF TUMOR GROWTH BY IODACETATE AND MALEATE

Experiment	No. rats	Compound injected	Daily quantity Injected per 150 gm. rat, gm.	Duration of exper. days	Av. wt. tumors, gm.	D/H %
H	16	Sod. iodoacetate	.001	13	4.06	
	17	No inj. in 4 rats			5.99	32
		Sod. acetate* in 13 rats				
I	12	Disod. maleate	.045	15	7.20	
	10	No injections			12.80	44

*In quantities equimolar to quantity of iodoacetate.

TABLE III: NEUTRALIZING EFFECTS OF TUMOR STIMULATORS AND INHIBITORS *

Experiment	No. rats	Compound injected	Daily quantities injected per 150 gm. rat, gm.	Duration of experiment, days	Av. wt. tumor, gm.	D/H %
J	6	Sod. thiolactate+	.006 (sulphur)	12	1.50	
		Sod. iodoacetate	.001			
	6	No injections			2.20	36
K	4	Sod. thioglycollate+	.001 (sulphur)	17	15.80	
		Sod. iodoacetate	.001			
	5	No injections			20.00	20

*Quantities of iodoacetate injected were less than equimolar to quantities of thiolactate and thioglycollate because of the toxicity of iodoacetate which resulted in weight loss (caloric restriction).

results described above. In Experiment J thiolactate and iodoacetate were injected subcutaneously and intraperitoneally respectively. Since thiolactate afforded no stimulation, the full effects of iodoacetate should have obtained and this proved to be the case as the tumors averaged 35 per cent less in weight than the controls. In Experiment K thioglycollate and iodoacetate were injected subcutaneously and intraperitoneally respectively. Since the former afforded stimulation and the latter inhibition to about the same degree, it would be expected that no essential difference would be noted between injected and control groups of rats. This proved to be the case since the difference of 20 per cent, as stated above, is not interpreted as significant.

SUMMARY

1. The injection of certain –SH compounds (thioglycollate and thiomalate), which afford available –SH radicals, showed mild stimulation of growth of the transplantable rat tumor 256. The explanations of failure of other –SH compounds (methionine, cysteine, thiolactate) to cause such stimulation are discussed.

2. The injection of –SH inhibitors, iodoacetate and maleate, was followed by retardation of growth of rat tumor 256 but did not inhibit the establishment of the transplants.

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