TECHNICAL PAPERS

Regression of Lymphosarcoma Produced by Intraperitoneal Administration of 95% Ethyl Alcohol[1]

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During the process of screening chemicals for the treatment of mouse lymphoma it was found that 95% ethyl alcohol, which was being used as a solvent, produced regression equivalent to that obtained by the test compound plus the solvent. Since it has been shown that stress produced by various techniques causes a lymphopenia (*2, 4*), it seemed possible that we were encountering a similar phenomenon affecting the malignant lymphocyte. Very little attention has been given to the question of the "alarm phenomenon" in relation to lymphoma or the circulating malignant lymphocyte. Selye (*4*) has stated that colchicine, a drug causing destruction of normal lymphoid tissue, is an "alarm"-producing drug. On the other hand, it has recently been reported by Lu and Kirschbaum (*3*) that urethane does not act through adrenal mechanisms in causing regression of experimental lymphoma. Because of such reports it was of interest to us to determine whether the effect of the injected alcohol was due to alcohol per se or to some stimulus or stress initiated by the concentrated drug.

TABLE 1

TUMOR RESPONSE TO INTRAPERITONEAL ALCOHOL

Treatment	Daily dose (cc)	Mice (No.)	Tumor response*			Remarks
			Regression (No.)	Inhibition (No.)	None (No.)	
Alcohol 95%	0.06	9	2	2	0	5 dead in 24 hrs
" 95%	0.04	9	7	1	1	
" 95%	0.02	9	5	2	1	1 dead in 24 hrs
" 19%	0.3	9	0	0	9	
Untreated		9	0	0	9	

* Only changes occurring within the first 48-hr period are included.

Two groups of animals were employed. One was given ethyl alcohol in 19% concentration, and to the other group various amounts of 95% ethyl alcohol were administered. Daily injections were given intraperitoneally, and tumor size was recorded daily. C3H mice obtained from the Roscoe B. Jackson Memorial Laboratory and bearing 6C3HED tumors were used. All animals were fed Purina dog chow ad libitum.

There was a high mortality in the group of animals receiving concentrated alcohol solutions. Gross inflammatory changes were seen in the peritonea and intestines of animals so treated. Usually the process was rather localized, but in a few mice there was a more generalized reaction with a slight amount of bloody fluid present in the abdominal cavity.

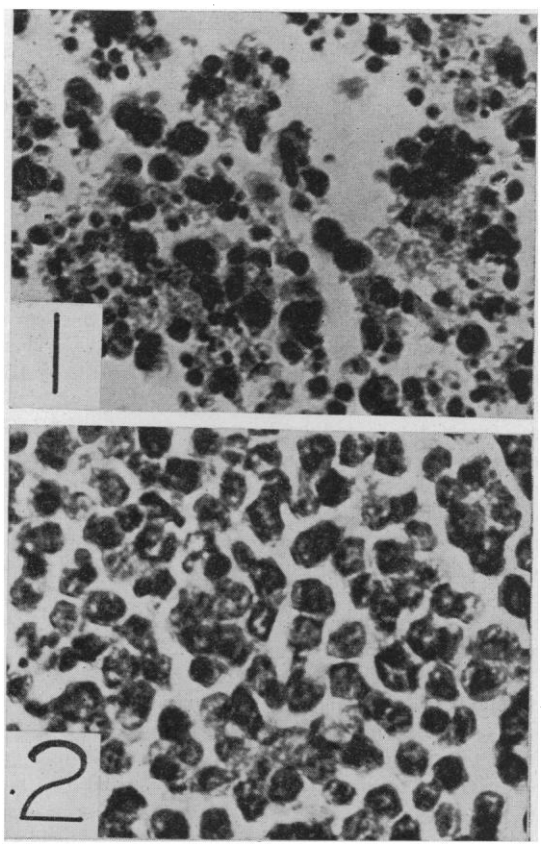

FIG. 1. Histological sections from C3H mice bearing transplanted 6C3HED tumors: (1) Animal was sacrificed 48 hrs after the first of two doses of 0.02 cc of 95% ethyl alcohol, administered 24 hrs apart. Note cellular disintegration. Magnification, x 880. (2) Animal sacrificed 72 hrs after the first of three daily doses of 0.3 cc of 19% ethyl alcohol. Note the absence of any histological abnormality. Magnification, x 880.

No symptoms or signs of toxicity were noted with the administration of diluted alcohol, and no tumor regression was obtained. However, a high percentage of all animals receiving concentrated alcohol showed tumor regression (Table 1).

It was evident that alcohol in itself was probably not responsible for the regression of the tumors, since 0.30 cc

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of 19% ethyl alcohol (equivalent to 0.06 cc of 95% ethyl alcohol) caused no change in the tumor, whereas 0.02 cc of 95% ethyl alcohol produced marked reduction in the tumor size. This was confirmed by histological studies (Fig. 1). The histological changes seen in the tumors of animals receiving the concentrated alcohol resemble those obtained with bis(β-chloroethyl)sulfide (*1*), the main feature of which is diffuse cell necrosis throughout the entire tumor. These changes are qualitatively not unlike spontaneous cellular changes seen in large lymphoid tumors; however, quantitatively the difference is quite striking.

Since there is much current interest in the response of lymphoma to various chemical agents, it is an appropriate time to call attention to the fact that the normal lymphocyte can be affected both in the circulating blood and in lymphoid structures by indirect action of chemical substances. Moreover, the data presented show that this same type of response can be produced in malignant lymphoid tissue. At present we are not prepared to say that this effect of concentrated alcohol on the malignant lymphocyte is mediated through the adrenal, as Selye has suggested for the normal lymphocyte in the case of colchicine-treated animals. However, it appears that the nonspecific damage caused by the concentrated alcohol, and not the ethyl alcohol itself, is responsible in some way for the malignant lymphocyte effect.

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Some Biological Effects Due to Nuclear Fission[1]

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Since direct interaction of neutrons with the atoms and molecules of the animal body is small, most of the biological effects produced by neutrons are due to secondary ionizing radiations. As is well known, fast neutron effects are due mainly to recoil nuclei from elastic collisions in the tissue (*1*). Thermal neutrons exert their effect primarily through ionizing radiations produced in transmutations of the elements composing the body and, to a lesser extent (~ 1%), through neutron-induced radioactivities. The relative importance of various nuclear reactions in causing biological effects has been elucidated by Zirkle (*17*) and his collaborators.

Localized effects may be artificially produced in the animal body or in selected organs if one deposits in the body or organ some element A, the cross section of which is relatively high for a suitable slow neutron-induced transmutation. If the organism is then bombarded with slow neutrons, the action of the disintegration products and of induced radioactivities resulting from the interaction of the neutrons and atoms of element A will be superimposed on the general effects of the neutrons. Several elements with suitable properties for such use are known. Among them is boron, where the $_5B^{10}$ (n, α)$_3$ Li^7 reaction has a high cross section. The lithium nucleus and the alpha particle emitted in this reaction produce ionizations in the tissue. Kruger (*8*) suspended tumor slices in boric acid solution and bombarded them with slow neutrons. With neutron doses above a certain level these tumors would no longer grow after transplantation. On the other hand, control tumor slices untreated with boric acid were not affected by neutron doses up to a much higher level. Likewise, boric acid without neutrons was without effect. Zahl, *et al.* (*15*) infiltrated sarcomata *in vivo* with lithium and boron compounds. Li^6 splits into an alpha particle and tritium on slow neutron bombardment. These disintegration products caused regression of some of the sarcomata. The same authors also showed that azo-dyes containing lithium can be localized to some extent in tumors.

To our knowledge, fissionable materials have not been used thus far in studying the biological effects of fission fragments and their radioactivity produced *in vivo*.[2] The study of such effects is interesting for at least three reasons. First, the knowledge of the specific effectiveness of heavily ionizing fragments may be of importance in understanding the mechanism of radiation effects. It should be mentioned that alpha particles and protons are known to cause change in animal tissue more effectively per unit energy transferred than electrons, and it is not unreasonable to assume that the heavily ionizing fission fragments might be even more effective than alpha particles. Secondly, the use of fission *in vivo* also has potential application in radiation therapy, particularly if fissionable elements can be incorporated into compounds which may localize at specific sites in the animal body. Steps in this direction have been made for example, by McClintock and Friedman (*10*), who were able to combine uranium with certain antibodies. Finally, the knowledge of *in vivo* fission effects is of interest from the point of view of radiation health protection in atomic energy plants and laboratories.

An over-all view of numerical factors involved in a comparison of the properties of neutron disintegration of elements important to this discussion may be ob-

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[2] Zahl, *et al.* (*15*) mentioned the possibility of the use of uranium.