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Increased Prothrombin Consumption Following Total Body X-Irradiation in Man. (23459)

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In a preliminary investigation of the hematological effects of a single exposure to therapeutic total body x-irradiation in cancer patients, an increase in prothrombin consumption during blood coagulation was observed. The average of postirradiation serum prothrombin time values was significantly elevated over the pretreatment average. The incidence of individual serum prothrombin time prolongations was also significantly increased after irradiation. In addition, it was found that in duplicate tests of serum prothrombin time in which the only known variable was the alternate use of prothrombin-free plasma (Cappel)†, and of purified bovine fibrinogen (Warner-Chilcott)‡, the latter reagent resulted in a significantly more sensitive test in the elevated range.

Materials and methods. Forty-one patients having neoplastic lesions with metastases requiring the use of the total body x-ray therapy according to the Radiation Therapy Committee of M. D. Anderson Hospital were studied. All were ambulatory and, apart from their primary disease, were in general good health and not cachectic. X-ray dosages, delivered in a single total body exposure in each case, (400 kv; 200 cm focal skin distance; 4.1 mm copper half value layer) ranged from 25 r through 150 r in 25 r steps. Dosage in each case depended on medical requirements of the patient. Complete hematological studies were performed daily in a 3- to 5-day baseline period immediately prior to therapy. Similar tests were performed immediately postirradiation and through a 10-day follow-up period before any further radiation therapy was given. Only platelet counts, clotting time, and plasma and serum prothrombin time tests are considered in this report. *Platelet counts* were performed in the Neubauer counting chamber with Rees-Ecker diluent (1). Clotting time tests were made by the 3 tube modified Lee-White procedure(2). Plasma prothrombin time was determined by the Link-Shapiro modification(3) of Quick's one-stage method, using Simplastin (Warner-Chilcott). Serum prothrombin tests were done by a previously reported modification (4,5) of the Quick one-stage method using Simplastin (Warner-Chilcott) and Fibrinogen (Warner-Chilcott). When no end-point was reached within 3 minutes, a reading of 180-plus seconds was recorded. Prothrombin-free plasma (Cappel) was used in place of fibrinogen in duplicate tests in 33 cases.

Results. There was no significant alteration from baseline levels in platelet count, clotting time, or plasma prothrombin time. Also, there was no evidence of relationship of these test results to the serum prothrombin time when the latter was prolonged above average. There was no significant relationship of serum prothrombin time changes to air dose or to integral dose in megagram-roentgens.

Serum prothrombin time. A. *Comparison of pre- and postirradiation averages.* It will be seen in Table I that the posttreatment serum prothrombin time averages, determined by the fibrinogen technic, increased over pretreatment times at the .001 significance level.

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TABLE I. Comparison of Serum Prothrombin Times (SPT) Obtained Using Fibrinogen (F) Technic in Subjects before and after Irradiation.

Radiation dose (r)	No. of cases	Preirrad. SPT avg (sec.)	Postirrad. SPT avg (sec.)	Postirrad. SPT increase	
				No.	%
25	5	41.8	54.3	5	(100)
50	9	56.1	99.8	7	(83)
75	6	56.5	64.4	4	(67)
100	13	47.5	54.0	11	(85)
125	4	40.7	52.2	4	(100)
150	4	35.2	52.2	2	(50)
Total	41	48.1	65.2	33	(80)

Postirradiation averages are statistically significantly larger than preirradiation ones at a level of about .0001. Avg increase of serum prothrombin time (fibrinogen technic) irradiation is 26.2%.

B. *Comparison of frequency of prolonged serum prothrombin times pre- and postirradiation.* Sixty seconds was used as the approximate upper end of the average range(5). The proportion of all readings which fell above this level was determined. The average proportions were: preirradiation = .191; postirradiation = .353; difference = .162. The average difference is statistically significantly larger than 0. ($P<.01$). The number of subjects with negative difference is 4; with zero difference, 20; and with positive difference, 17.

C. *Comparison between serum prothrombin times obtained using prothrombin-free plasma and those obtained using fibrinogen.* In 33 subjects duplicate determinations were made using the fibrinogen and the prothrombin-free plasma methods. The preirradiation average serum prothrombin time with prothrombin-free plasma was 34.8 seconds, 8.9 seconds below the average time with fibrinogen. The postirradiation average time with the plasma reagent was 41.5 seconds, 16.2 seconds below the average time with fibrinogen. The average percentage increase in time with the plasma reagent after x-ray therapy was 16.1%, while the fibrinogen reagent showed 24.3% increase. To test the hypothesis that the fibrinogen technic yields higher values when the prothrombin-free plasma method itself gives elevated results, the correlation between the two technics was analyzed statistically. The hypothesis of no correlation was rejected at a P value of less than .01 in favor of positive correlation. In 24 out of the 33 subjects, the correlation was positive.

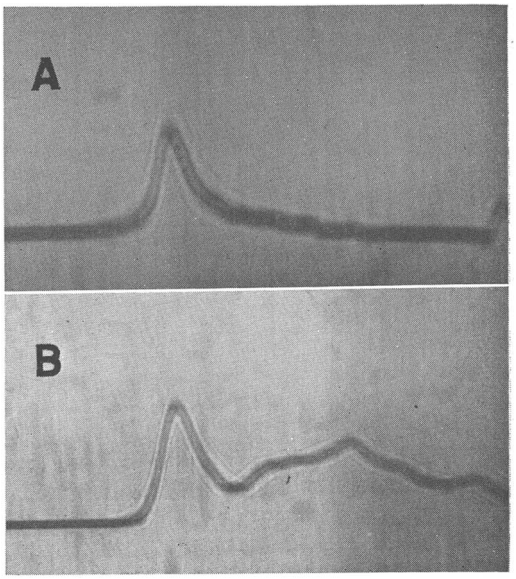

FIG. 1. Electrophoretic pattern of (A) fibrinogen, bovine (Warner-Chilcott) and (B) prothrombin-free plasma (Cappel).

D. *Electrophoretic analysis of fibrinogen (Warner-Chilcott) and of prothrombin-free plasma (Cappel)* is presented in Fig. 1. It will be noted that the former reagent contains fibrinogen in a single pure peak, while the latter reagent contains fibrinogen in a mixture of other plasma protein constituents.

Discussion. Our data indicate the development, in cancer patients, of an alteration in blood coagulation, *i.e.*, increased prothrombin consumption, occurring within 10 days following one dose of therapeutic total body x-irradiation. No reports of similar findings have been found in the radiation hematology literature. In fact, in most of the instances in which prothrombin consumption was studied, reduction was noted at some time following radiation(6,7,8). It is to be noted, however, that the data of Jackson *et al.*(6) indicate that in those of their dogs whose prothrombin consumption was not 100% in the control period (6 out of 8), an increase to 100% occurred at least once in the first 4 days following 600 r whole-body x-irradiation. Also, the mean consumption was in-

TABLE II. Comparison of Serum Prothrombin Times (SPT) Obtained Using Fibrinogen (F) and Prothrombin-Free Plasma (PFP) Technics in the Same Subjects before and after Irradiation.

Radiation dose (r)	No. of cases	Preirradiation SPT avg		Postirradiation SPT avg		Postirradiation SPT increase			
						No.	%	No.	%
		F	PFP	F*	PFP†	F		PFP	
25	3	49.1	38.7	66.6	42.4	3	(100)	2	(67)
50	4	39.6	31.6	49.2	38.7	2	(50)	3	(75)
75	4	50.3	40.8	71.9	55.6	3	(75)	3	(75)
100	13	47.5	37.5	54.0	42.9	11	(85)	11	(85)
125	4	40.7	32.5	52.2	37.3	4	(100)	3	(75)
150	4	35.2	27.5	52.2	32.0	2	(50)	1	(25)
Total	32	43.7	34.8	57.7	41.5	25	(77)	23	(67)

* Avg increase of serum prothrombin time (fibrinogen technic) = 24.3%.
† " " " " " " (prothrombin-free plasma technic) = 16.1%.

creased over baseline on the first and second day postirradiation. Subsequently a marked decrease was found, however, when thrombocytopenia ensued.

Certain limitations of this study should be considered. The number of cases studied was small because of the relative rarity of a therapeutic indication for whole body radiation. For practical reasons the patients studied served as their own controls prior to irradiation and a parallel control series was not run. In addition, the control observation period could not be carried on as long as the postirradiation one. The possibility of a general time-trend effect over the entire experimental period cannot be separated completely from that of radiation effect as the cause of the statistically significant difference in serum prothrombin times before and after irradiation. However, the time-trend differences are not statistically significant by t-test or by a sign test, most of them yielding a P value of about 0.1. Also, clinical experience with the test procedure employed(3,4) did not suggest any time-trend in serial observations heretofore.

Assuming that the observations in this preliminary report are substantiated by similar studies of a large number of cases, an attempt to explain the apparent contradiction of the data in recent pertinent literature is indicated. The frequently noted decrease in prothrombin consumption following irradiation is based primarily on studies of animals, usually after large doses of x-ray at least approaching the lethal range and not always in the immediate period following exposure. Our subjects were humans, receiving a comparatively low exposure and studied promptly. Also, thrombopenia is generally present in animal studies, while it was not found in our series. Court Brown and Abbat noted a similar absence of thrombopenia in their patients receiving one 200 to 425 r skin dose over the spinal column (12). In addition, all of our subjects had metastatic neoplastic disease upon which the radiation may have acted somewhat selectively.

Another difference between our study and those reported in the literature lies in the SPT technic employed. The commonly utilized prothrombin-free plasma may add other protein substances besides fibrinogen to the test system used, as shown by electrophoresis (Fig. 1). That these additional substances might act to mask abnormalities is suggested by the comparative results of serum prothrombin determinations performed by the 2 technics, and by the statistical analysis thereof. The use of pure reagents, when possible, in order to reduce the variables of coagulation test systems is advocated for this reason.

Although the reduction of prothrombin consumption and of serum prothrombin time has been studied extensively by Quick(9) and others, the clinical significance of an alteration in the opposite direction remains to be determined. It has been observed that the average serum prothrombin time in the geriatric age group is higher than that of young adults(4). Dreskin(10) reported a normal range of 25 to 50 seconds but did not account for higher prothrombin consumption evident in a number of normal and diseased subjects

included in his data. Sussman *et al.*(11) reported the average serum prothrombin time in a number of disease states. In many instances this was well above the 30-second level interpreted as the lower limit of normal range. No upper limit was suggested, however.

The reason for the apparent absence of any correlation between onset, magnitude or duration of serum prothrombin time change and either air or integral radiation dose is not readily apparent. Similar lack of quantitative relationship between one large x-ray dose and consequent blood count changes in man has been reported by others(12). Differences in the radiosensitivity of individuals and of neoplasms in our series may be responsible. The selection of the radiation dosage for each case according to medical indications based on the nature and distribution of neoplastic disease may also have helped to obscure any dose effect by introducing bias errors.

It seems possible that alterations in homeostasis produced by disease or by extrinsic agents, such as radiation, could result in imbalances of the many factors involved in the formation of thromboplastin or in the conversion of prothrombin to thrombin. The increase in prothrombin consumption reported here may be an indication of the summation of these alterations, occurring at a time and under conditions of study which have not been carried out previously. This preliminary report is made in the hope that further observations along these lines will aid in the interpretation of the coagulation alteration noted herein.

Summary. 1. Hematological studies were carried out on 41 patients with disseminated neoplastic disease receiving therapeutic whole body x-irradiation. 2. Increased prothrombin consumption, evidenced by an increase in the average serum prothrombin time, and in the incidence of prolonged serum prothrombin times, was found after irradiation. 3. Greater sensitivity resulted when pure fibrinogen was used in place of prothrombin-free plasma in the one-stage serum prothrombin time test. 4. Possible explanations for these findings were discussed.

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