SERUM PROTHROMBIN TIME PROLONGATION FOLLOWING TOTAL-BODY X-IRRADIATION IN MAN

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In an investigation of the hematological effects of a single exposure to therapeutic total body x-irradiation in cancer patients, a coagulation change was observed. The average of postirradiation serum prothrombin time (SPT) values was significantly elevated over the pretreatment average. The incidence of individual SPT prolongations was also significantly increased after radiation. In addition, it was found that in duplicate tests of SPT 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 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 three to five-day baseline period immediately prior to therapy. Similar tests were performed immediately postirradiation and through a ten-day follow-up period before further radiation therapy. Only platelet counts, clotting time, and plasma and serum prothrombin time tests are considered in this preliminary report.

Platelet counts were performed in a Neubauer counting chamber with Rees-Ecker diluent (1, p. 239). Clotting-time test used was the three-tube modified Lee-White procedure (1, p. 256). Plasma prothrombin time was determined by the Link-Shapiro modification (2) of Quick's one-stage method, using Simplastin (Warner-Chilcott). Serum prothrombin tests were done by a previously described modification (3, 4) 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+ seconds was recorded. Prothrombin-free plasma (Cappel) was used in place of fibrinogen in duplicate tests in the 100, 125, and 150 r groups.

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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 in any instance in which the latter was prolonged above average. There was no significant relationship of SPT changes to air dose or to integral dose in megagram-roentgens.

Serum prothrombin time

Comparison of pre- and postirradiation averages. It will be seen from the data in table 1 that the posttreatment SPT averages are significantly increased over pretreatment times at the .0001 significance level.

Comparison of frequency of prolonged SPT pre- and postirradiation. Sixty seconds was used as the approximate upper end of the average SPT range (3). The proportion of all SPT 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 is 17; with positive difference is 20.

Comparison between SPT using prothrombin-free plasma (PFP) and using fibrinogen (F).

The preradiation average PFP - SPT was 30.8 seconds, 10.3 seconds below the average F-SPT. The postradiation average PFP - SPT was 37.4 seconds, 15.4 seconds below the average F - SPT. The average percentage increase in PFP - SPT following x-ray therapy was 15.2 percent while the F - SPT showed a 30.1 percent increase. To test the hypotnesis that F - SPT yields higher values when PFP - SPT itself is elevated, the correlation between the two techniques 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 33 subjects, the correlation was positive.

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

DISCUSSION

The data presented 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 (5-7). It is to be noted, however, that the data of Jackson et al. (5) indicate that in those of their dogs whose prothrombin consumption was not 100 percent in the control period (6 out of 8), an increase to 100 percent occurred at least once in the first four days following 600 r whole-body x-irradiation. Also, the mean consumption was increased over baseline on the first and second day postirradiation. Subsequently a marked decrease was found, however.

Certain limitations of this study should be considered. 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 irradiation 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 further studies, 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. 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 technique employed. The commonly utilized prothrombin-free plasma may add other protein substances besides fibrinogen to the test system used, as shown by electrophoresis (figure 1). That these additional substances might act to mask abnormalities is suggested by the comparative results of SPT performed by the two techniques, 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 SPT has been studied extensively by Quick (8) and others, the clinical significance of an alteration in the opposite direction remains to be determined. It has been observed that the average SPT in the geriatric age group is higher than that of young adults (3). Dreskin (9) reported a normal range of 25 to 50 seconds but did not account for the

TABLE I

Serum prothrombin time tests

Radiation level (r)	n	$\bar{x}-$	$\bar{x}+$	$\bar{n}+$	P+
25	5	41.8	54.3	5	1.00
50	9	56.1	99.8	7	.83
75	6	56.5	64.4	4	.67
100	13(13)	47.5(37.5)	54.0(42.9)	11(11)	.85(.85)
125	4(4)	40.7(32.5)	52.2(37.3)	4(3)	1.00(.75)
150	4(4)	35.2(27.5)	52.2(32.0)	2(1)	.50(.25)
Total	41(21)	48.1(32.5)	65.2(37.4)	33(15)	.80(.62)

n – Number of subjects.
$\bar{x}-$ – Average of pretadiation SPT in seconds (fibrinogen technique).
$\bar{x}+$ – Average of postradiation SPT in seconds (fibrinogen technique).
$\bar{n}+$ – Number of subjects with $\bar{x}+$ greater than $\bar{x}-$.
P+ – Proportion of subjects with $\bar{x}+$ greater than $\bar{x}-$.
() – Cases studied by prothrombin-free plasma technique in addition to fibrinogen technique.

The $\bar{x}+$ values are statistically significantly larger than $\bar{x}-$ values at level of about .0001.

higher prothrombin consumption evident in a number of normal and diseased subjects included in his data. Sussman et al. (10) reported the average SPT 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.

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. 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

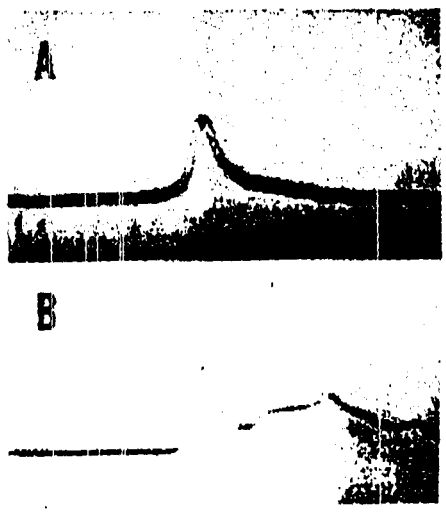

FIGURE 1

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

dose is not readily apparent. However, differences in the radiosensitivity of individuals and of neoplasms may play a role. This preliminary report is made in the hope that further observations along these lines will aid in the proper interpretation of the coagulation alteration noted herein.

SUMMARY

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

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