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STUDY OF THE POST-IRRADIATION SYNDROME IN HUMANS

Period of Report:
November 1, 1957 - October 31, 1958

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Abstract

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Our aim is to determine physiological alterations resulting from total body irradiation administered in known doses to patients whose general condition is as close to the physiologic normal as possible. Pre-irradiation baselines ~~are~~ established for hematology, creatin-creatinine excretion ratios, pentose excretion, and properdin levels, and post-irradiation changes in these parameters are followed and charted.

During the report period, four patients received total body irradiation in calculated absorbed doses of from 50 to 150 r, at midplane, from a 1 Mev generator, and one of these patients also received internal irradiation from Na^{24} . Alterations in the formed elements of the circulating blood ~~are~~ the most consistent index of radiation effect. Because of the appearance in one patient of a bleeding diathesis (subsequently controlled by protamine sulfate), clotting mechanisms will continue to be studied. Results of observations of pentose excretion, creatin-creatinine excretion ratios, and properdin levels ~~are~~ suggestive enough to warrant further investigation.

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FINAL REPORT

Four patients have received five courses of total body irradiation. The selection of patients was in accordance with the criteria previously described. An attempt is made to utilize patients whose general condition is as near to the physiologic normal as possible. Although rigid adherence to these criteria has limited the number of patients suitable and available for study it has permitted an orderly investigation of many parameters in the post-irradiation state.

All external irradiations were done with the 1 MEVP resonant generator using exposure ports as follows: upper and lower halves of the body, anteriorly and posteriorly. The upper and lower fields were separated by 5 cm. to compensate for divergence of the edge of the beam. This has resulted in a fairly uniform dose distribution throughout the body. Previously all doses were expressed as air dose measured at the mid-plane of the body. In the present report all doses are expressed as calculated absorbed dose at the mid-plane of the body. The mid-plane was 290 to 300 cm. from the target. Dose rate was approximately 6 r per minute. In collaboration with Drs. Bond, Kronkite and Robertson at the Brookhaven National Laboratories, Upton, L. I., one patient received Na^{24} by mouth for a calculated midplane dose of 70 r.

TABLE I

STUDIES REPORTED

| Patient | Hematology | Creatin Ratios | Pentose | Proper.in |
|---------|--------------------|----------------|---------|-----------|
| M. W. | Fig 1, 2, 3, 4, | Fig 5 | * | |
| D. V. | Fig 6, 7 | Fig 8 | Fig 9 | |
| K. M. | Fig 10, 11, 12, 13 | * | Fig 14 | |
| A. M. | Fig 15, 16, 17, 18 | Fig 19 | Fig 20 | * |

*where no Fig. # appears, data appears in the text.

Patient M. W. had already received 18 millicuries of Na²⁴ for a calculated midplane dose of 50 r approximately six months prior to the new study. During the year, November 1957 to October 1958, this patient received two courses of total body irradiation. Initially she received 27 millicuries of Na²⁴ for a calculated midplane dose of approximately 70 r. (As mentioned above, this was done at the Brookhaven National Laboratory Medical Department.) There appeared to be an appreciable difference in the hematologic response to the second course of total body irradiation as compared to the initial course given by Na²⁴ seven months prior to this admission. In the second study there was a less striking fall in the total leukocyte count and in the platelet counts.

Six months later this patient was admitted to Memorial Center and after a suitable period to establish baselines she was given a third course of total body irradiation consisting of 50 r midplane dose delivered by the 1 MEV x-ray generator. The hematologic data showed a modest fall

in the total leukocyte count within the first week post-irradiation which did not change appreciably thereafter. However, in contrast to the previous total body irradiation administered by an internal emitter, this course of external irradiation produced a profound depression of the platelet count which reached a minimum on the 44th day post-irradiation.

However, because of the appearance of metastases in the lumbosacral spine, it was necessary to deliver external radiation to the lumbosacral spine commencing on the 56th day post-total body irradiation. Interestingly, the therapeutic course of irradiation depressed the platelet count even further with the appearance of petechiae and ecchymosis. Metastases in the lungs, which had been observed previously, began to grow rapidly. Biochemical tests showed marked liver abnormalities. The patient developed a respiratory alkalosis secondary to ammonium toxicity and expired 24 weeks post-total body irradiation. Properdin studies were done on this patient pre- and post-irradiation by Dr. Southam and revealed a level of less than one prior to radiation with no change from this value for as long as 30 days post-irradiation.

During the study of the third course of total body irradiation in this patient the levels of urinary excretion of creatin and creatinine were determined. (The ratio of creatin to creatinine excretion has been calculated for these urine specimens.) When the ratio for the first 18 days post-irradiation was compared with that of the 16-day period prior to irradiation there is seen to be a decrease in this ratio. This would indicate that there was an increase in creatin during this period of time.

Pentose excretion was followed. There was a 125% increase in the excretion of pentose following total body irradiation as compared to the baseline established in the 13 day pre-irradiation period.

Patient D. V., a 33 year old white male with widespread metastatic melanoma, received 100 r total body irradiation, measured at the mid-plane in tissue, from the 1 MEV generator. Hematologic data for the short period of observation post-irradiation showed little change in the hemoglobin or platelet count. There was a slight drop in the total white cell count. The absolute granulocyte count remained essentially constant. The lymphocytes fell significantly on the fourth day post-irradiation. At the same time the monocytes increased. These alterations were maintained during the 17 days of observation.

In this patient the creatin-creatinine ratios showed a profound drop immediately post-irradiation and remained depressed until the 10th day post-irradiation. Pentose excretion during this period of time showed no consistent variation. Following the patient's return to his home, a letter from the family physician did not indicate any observable hematological dysfunction prior to his death three months post-irradiation.

K. M., a 42 year old white female with metastatic carcinoma of the breast, received 150 r total body irradiation on the 1 MEV apparatus. This patient showed a prompt hematologic depression. By the 13th day post-irradiation her platelet count fell from a baseline of 350,000 to less than 100,000. The white count fell from a baseline of 8500 to less than 1000 on the 20th day post-irradiation. A bleeding

diathesis appeared on the third week post-irradiation. The bleeding time was prolonged to 8 minutes and clotting time to 14 minutes. During this time multiple petechiae and ecchymosis became apparent over the entire body. Hemorrhage from the nasopharynx became a major problem and required anterior and posterior packing. On one previous occasion in a patient who had received total body irradiation, intravenous protamine sulphate had been administered with apparent amelioration of the bleeding diathesis. Because of previous experience and of the work of Jacobson and Allen on this problem, 50 mgm. of protamine sulphate were given to this patient on the 26th day post-irradiation. The results are summarized in figure 13. Twenty-four hours after the first injection of protamine and just prior to the second injection blood was drawn for more detailed hematologic study in Dr. Zucker's laboratory (Clotting Mechanisms Section). It was found at this time that the factor V content was increased, proconvertin was diminished, prothrombin consumption time was 79% of normal, clot contraction was nonexistent, the clotting time in glass was 8 minutes, and in silicon at 37 degrees, it was one hour and 45 minutes. (The normal time as determined in this laboratory should be under 50 minutes.) The thromboplastin generation test showed only a slight abnormality. The patient continued to lose ground, developing what appeared to be acute pulmonary edema, and expired on the 32nd day post-irradiation. Postmortem findings included acute subendocardial hemorrhages. These may have contributed to the development of acute pulmonary edema and death. The urinary excretion of creatinine and pentose following total body irradiation was studied. There was a 25%

increase in the urinary excretion of creatinine in the 4 to 8 day period post-irradiation. There also was a three-fold increase in urinary pentose during the first three days post-irradiation with a second two-fold increase in the 10 to 12th day period post-irradiation.

Patient A. M., age 48, with disseminated carcinoma of the cervix, received 100 r total body irradiation midplane dose from the 1 MEV generator. In the 75 days during which this patient was studied following total body irradiation, the hematologic pattern showed a fall in the total white count reaching a minimum on the 35th day. The absolute lymphocyte count fell during the first three days post-irradiation. It never returned to the pre-irradiation level. An initial drop in the absolute monocyte count occurred. Return to the pre-irradiation level occurred by the 14th day post-irradiation. Interestingly there was a second depression at the time of the maximal leukopenia between the 28th and 35th days post-irradiation. The platelet counts fell during the third week post-irradiation reaching a minimum between the 28th and 35th day post-irradiation. Although the platelet count rose above 100,000 by the 65th day post-irradiation, it never returned to the pre-irradiation level. Between the 20th and 34th days post-irradiation, bleeding time was prolonged to a maximum value of 18 minutes. It is of interest that even though the platelet count remained depressed, the bleeding time returned to normal by the 34th day. This appears to indicate a nonplatelet mechanism of importance in determining bleeding time. Only transient petechiae were observed in this patient. One crop was seen when the bleeding became prolonged initially. No others occurred even

though fibrinolytic time remained prolonged. The prothrombin time and prothrombin consumption fell as the platelet count fell. However, the determination of factor V, proconvertin and thromboplastin generation showed that these remained within normal ranges throughout the 75 days of observation.

Properdin levels were followed in this patient. Pre-irradiation, the properdin value was 3 units. Eighteen hours post-irradiation, the value rose to six units and returned to the pre-irradiation level of 3 units by the fourth day post-irradiation. These levels have been substantiated on replicated determinations. The changes appear to be significant. The biological significance of these changes will await further study in other patients.

The urinary excretion patterns which were followed in this patient revealed a transient 25% increase in pentose excretion during the 3rd and 6th day post-irradiation. The creatin-creatinine ratios were significantly lower for the first 30 days post-irradiation. A pre-irradiation average of 9.7 fell to 5.7 and then 4.6 by the 25th day post-irradiation.

DISCUSSION

I. Hematologic studies

The documentation of the alterations in the formed elements of the circulatory blood remains the most consistent index in the post-irradiation state. The disparity in response noted in one patient in this report who received total body irradiation both from external emitters and an external generator should be further studied in more patients.

There would appear to be no particular change in most of the blood clotting mechanisms so far elucidated in the patients given total body irradiation, such as Factor V, Factor VII concentration, thromboplastin generation, antihemophilic factor and PTC. Prothrombin time and prothrombin consumption do vary as platelet counts fall, as would be anticipated. No explanation for the bleeding diathesis which responded to protamine is yet forthcoming. It appears worthwhile to study intensively each patient receiving total body irradiation in all of these parameters. Although only a small portion of the patients developed serious bleeding problems, it will still be necessary to follow all of the patients so that in case it does occur the course of all of the known hematologic coagulation factors would be documented before, during and after the post-radiation bleeding diathesis.

II. Urine excretion patterns

The pentose excretion and creatin-creatinine excretion ratios in the patients appear to be of some interest. However, many more will have to be done with varying radiation dosage levels before any conclusions can be reached. At the present time they appear to warrant our continued attention.

III. Immune Mechanism

The interesting small rise in properdin in the one patient so far observed who had any level of properdin whatsoever has made it appear worthwhile to continue this area of investigation. However, the zero levels of properdin which have been found in the other patients

selected for total body irradiation may mean that this may not be too fruitful an area of investigation in the future. Perhaps cancer patients selected for total body irradiation may not be suitable for immune mechanism investigation. However, until more data have accumulated, this area of investigation will receive considerable attention in the near future.

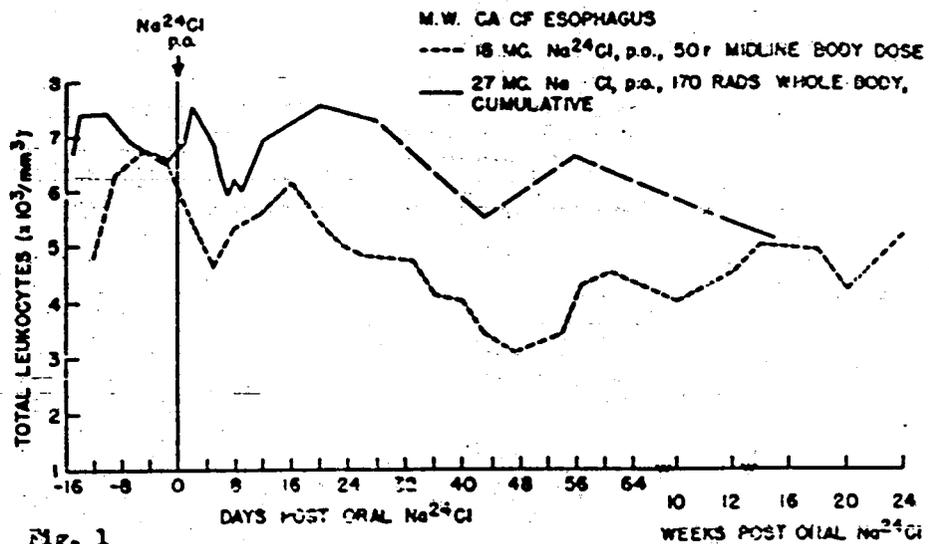


Fig. 1

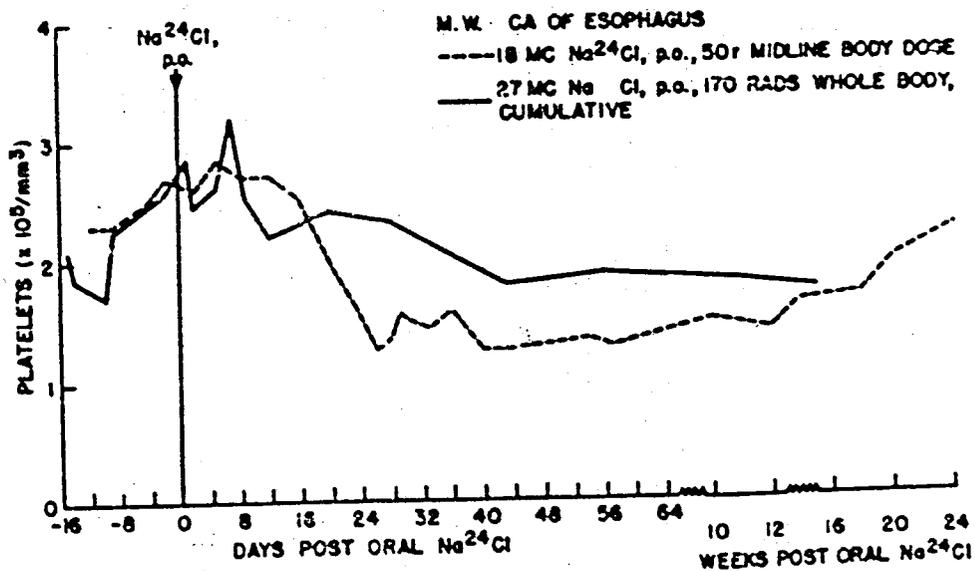
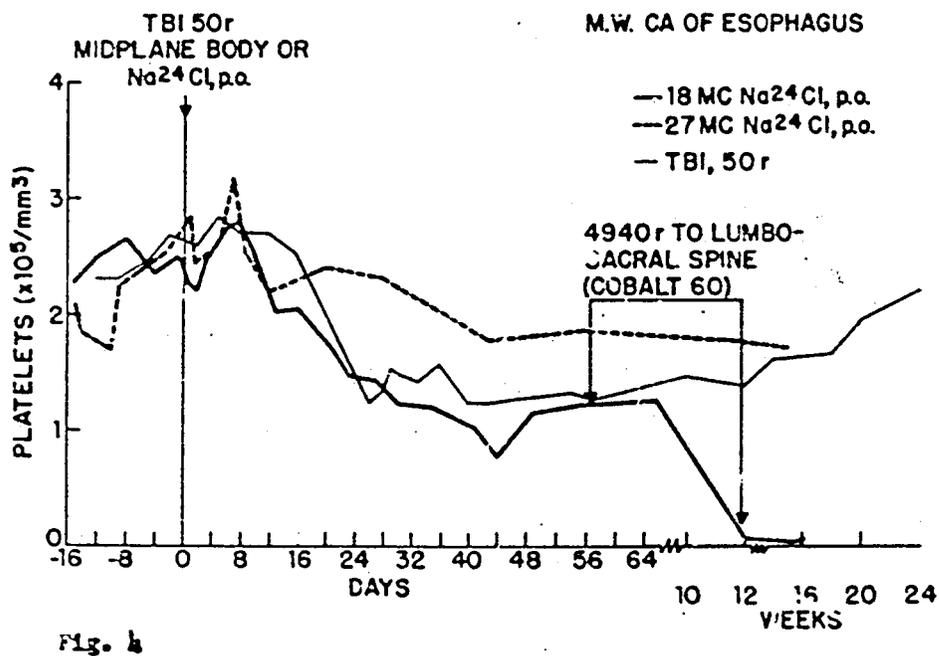
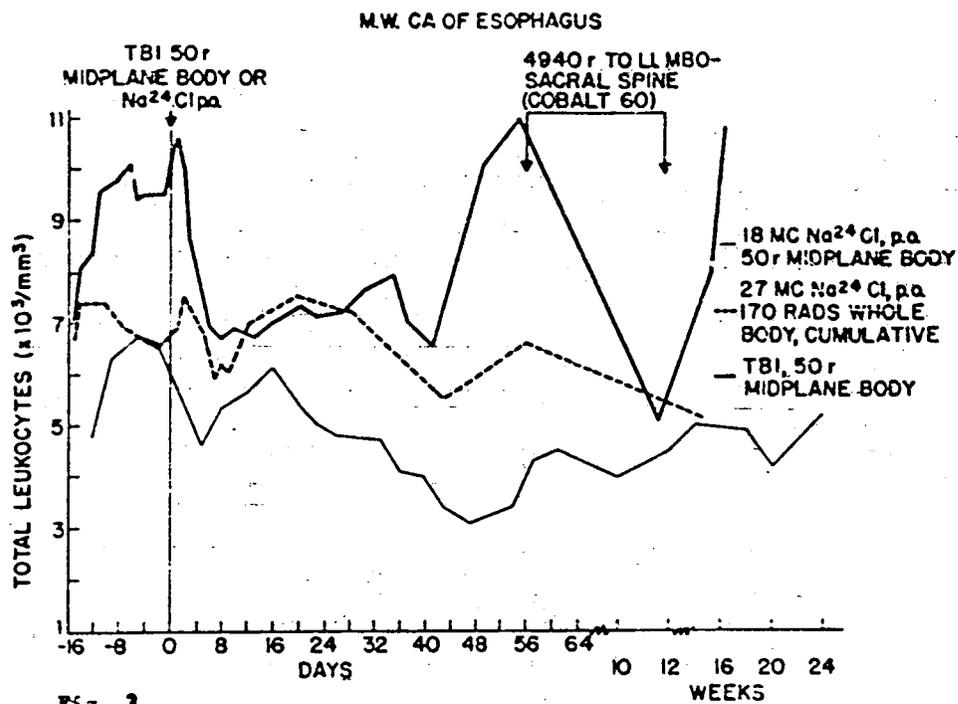
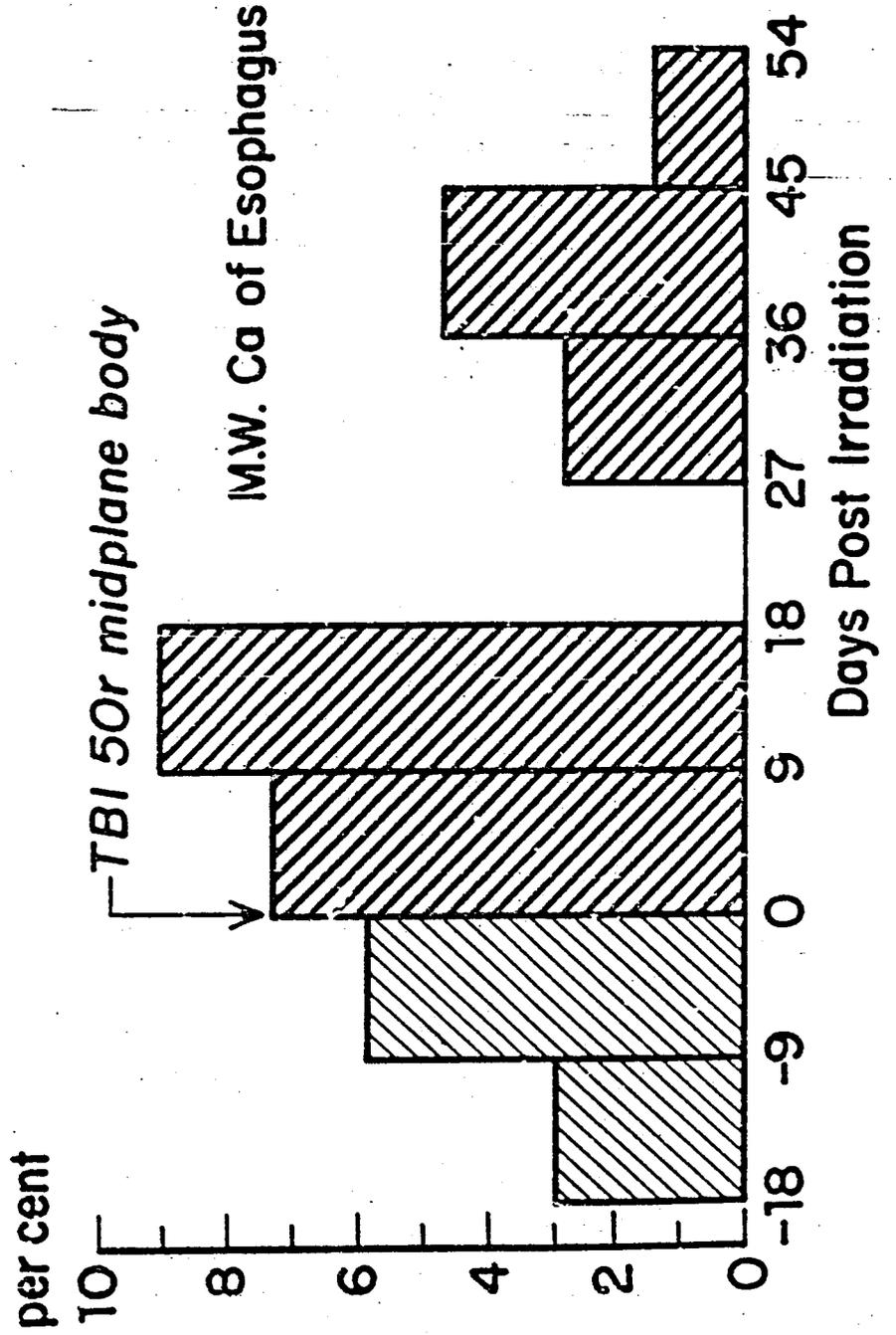
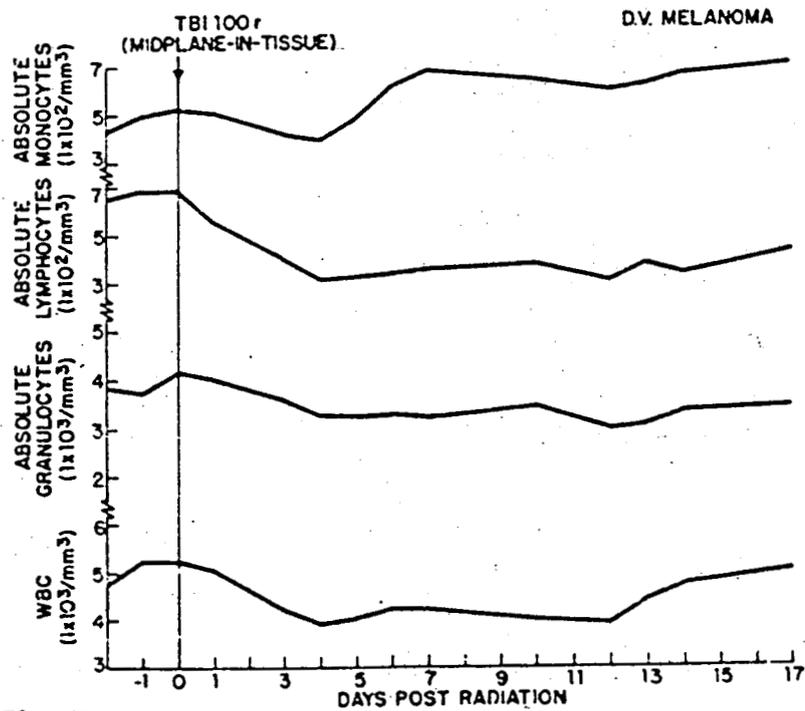
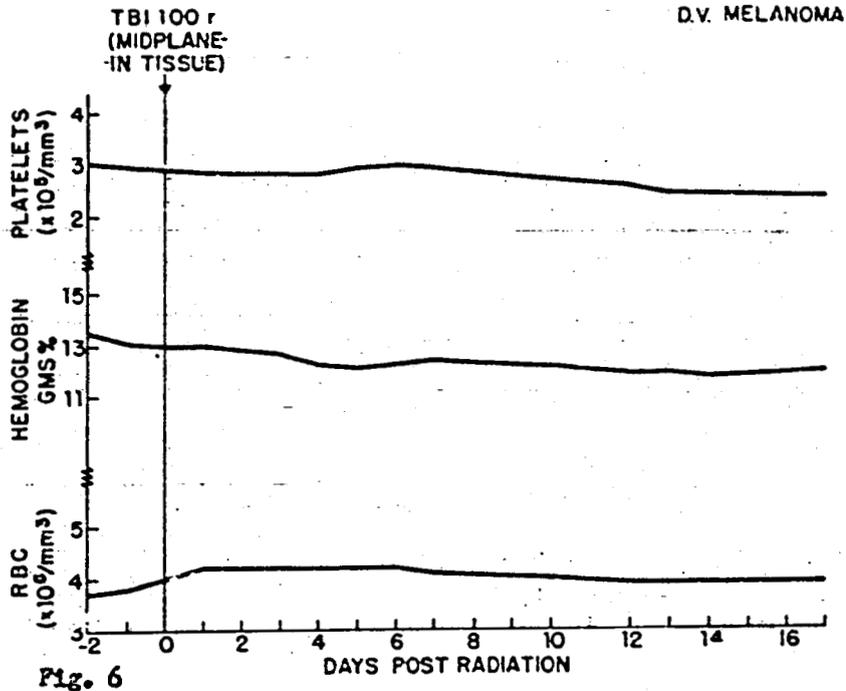


Fig. 2

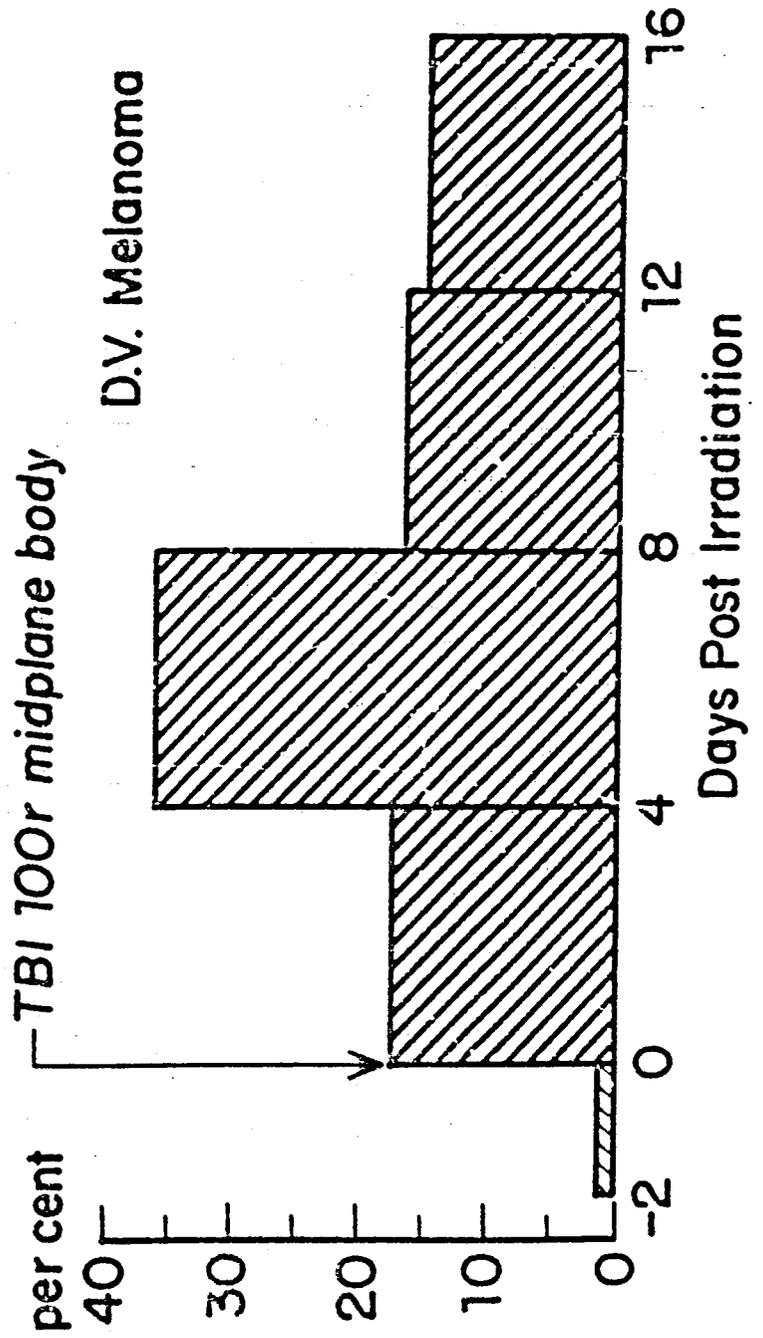


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PER CENT CREATINE OF TOTAL URINARY CREATINE AND CREATININE



D.V., Melanoma

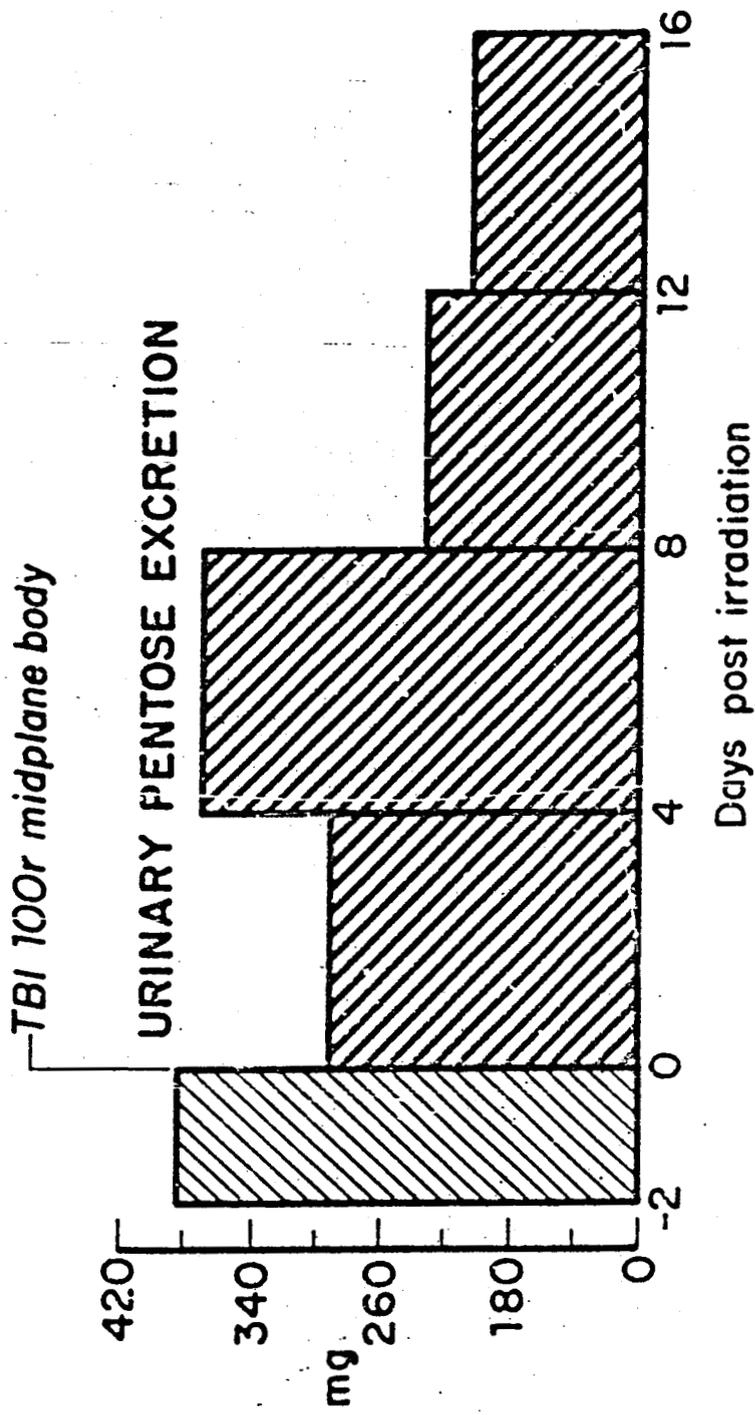


Fig. 9

K.M. CA OF BREAST

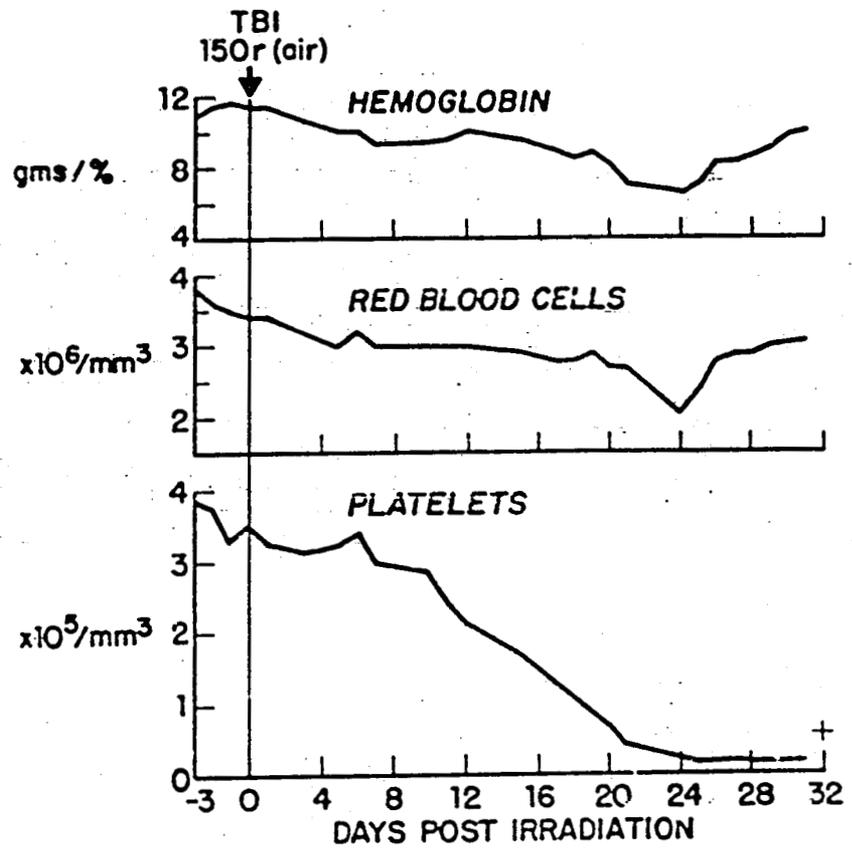


Fig. 10

K.M. CA OF BREAST

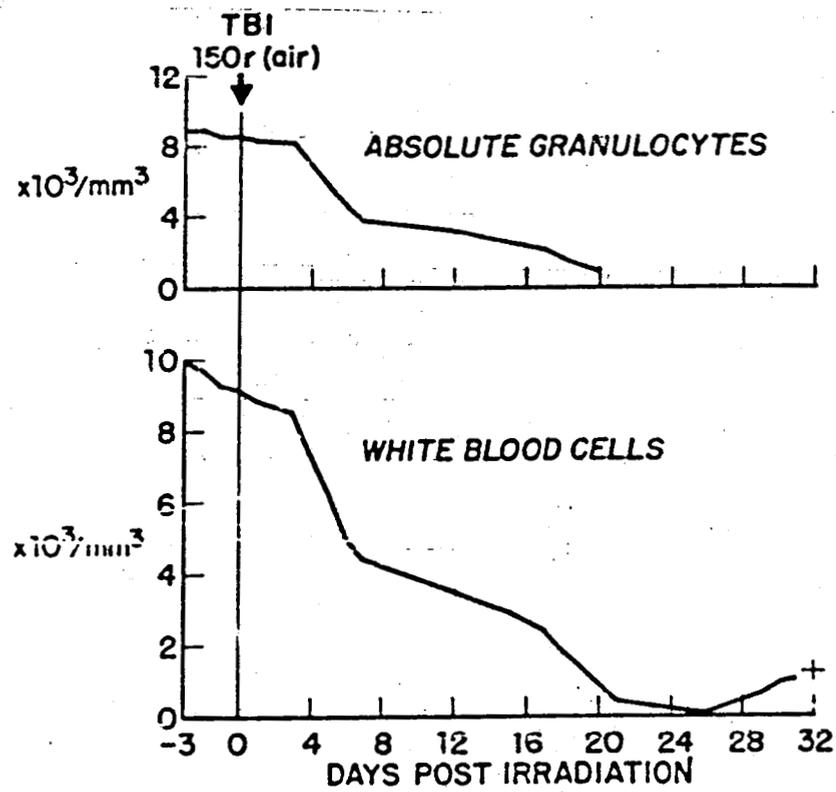


Fig. 21

K.M. CA OF BREAST

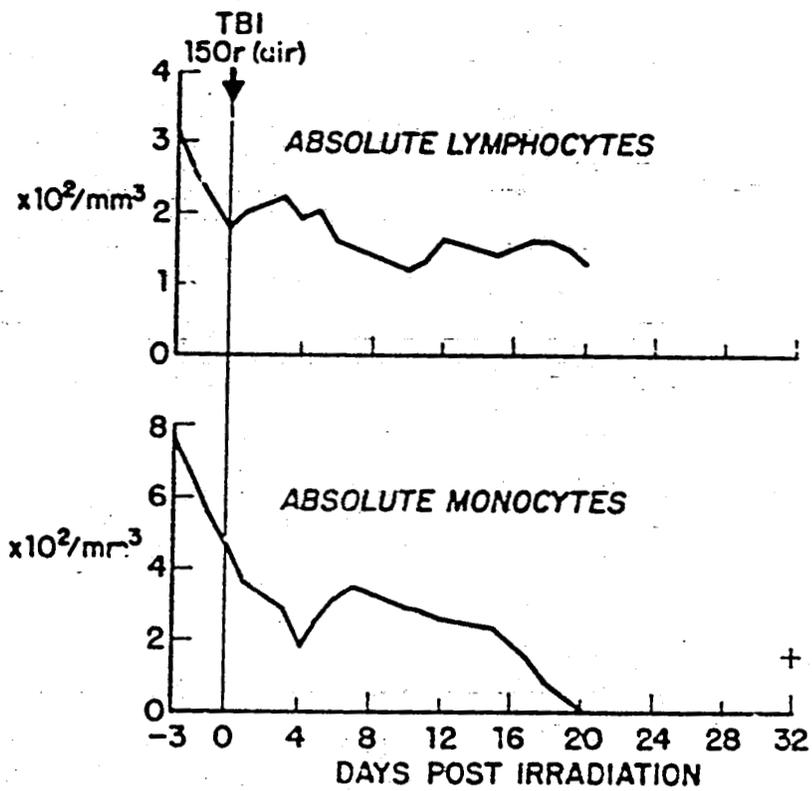


Fig. 12

**EFFECT OF PROTAMINE SULFATE ON HEMORRHAGIC
DIATHESSES OBSERVED FOLLOWING TOTAL BODY IRRADIATION
K.M. Ca of Breast.**

50 mgm Protamine Sulfate, I.V.

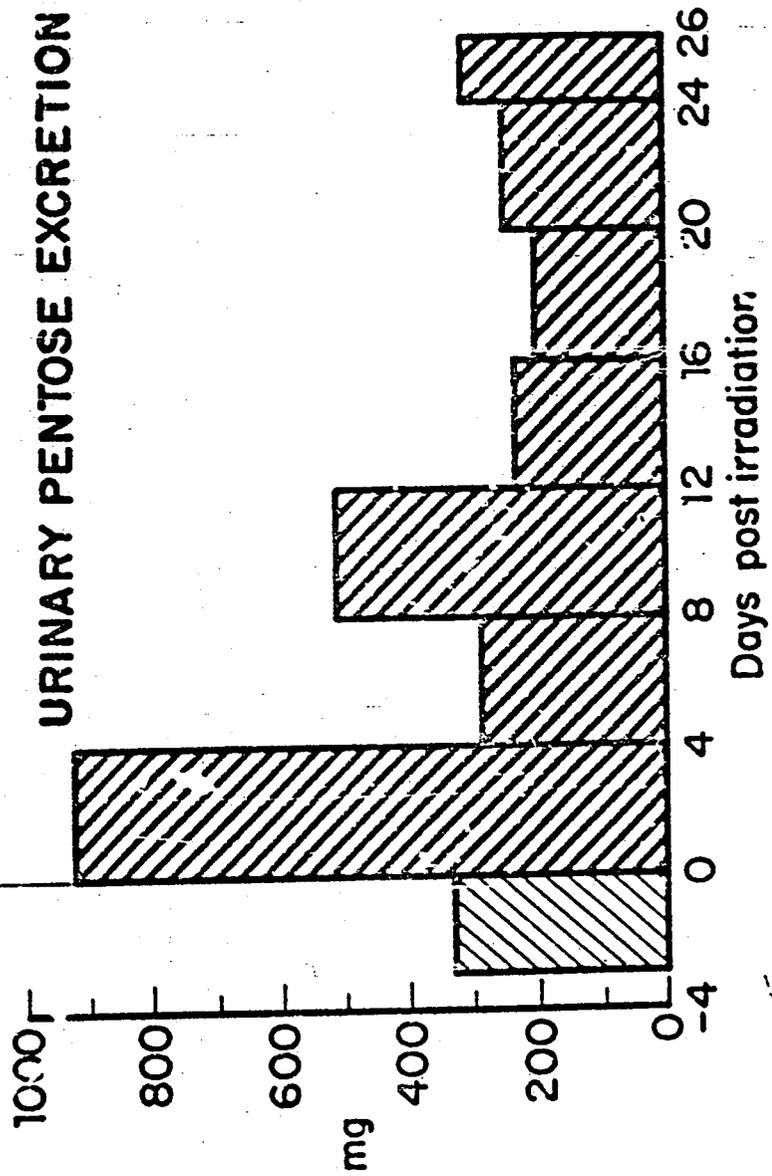
| Diathesis | Days Post Radiation | Pre-Injection | Time Post Injection (min) | | | |
|-------------------------|---------------------|---------------|---------------------------|------|------|---------|
| | | | 10 | 30 | 60 | 18 hrs. |
| Bleeding Time (minutes) | 26 | 7.0 | 5.0 | 2.75 | 3.0 | 11.25 |
| | 27 | 11.25 | 11.25 | 8.75 | 2.75 | 7.0 |
| Clotting Time (minutes) | 26 | 24.0 | 40.0 | 29.0 | 38.0 | 13.0 |
| | 27 | 13.0 | 37.25 | | 20.0 | 10.5 |

Fig. 13

K.M., Ca. of Breast

TBI 150r midplane body

URINARY PENTOSE EXCRETION



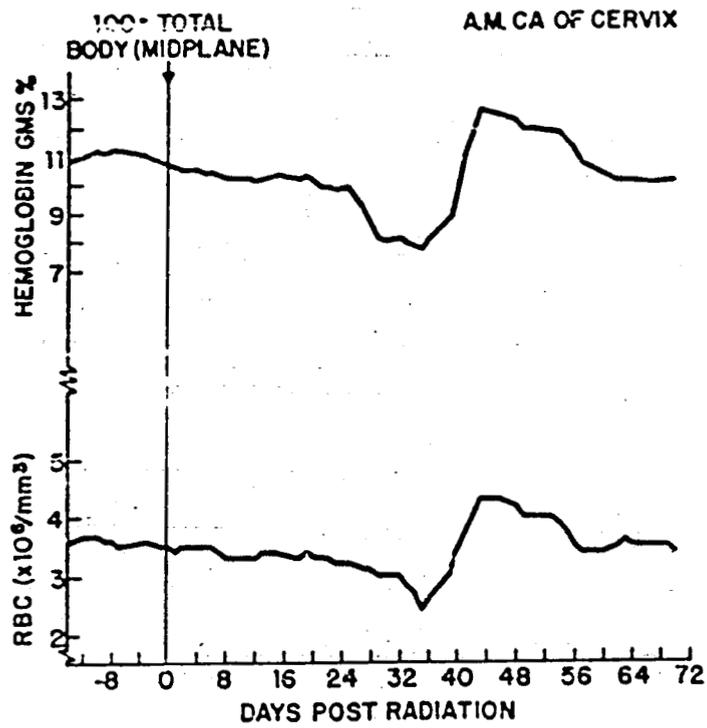


Fig. 15

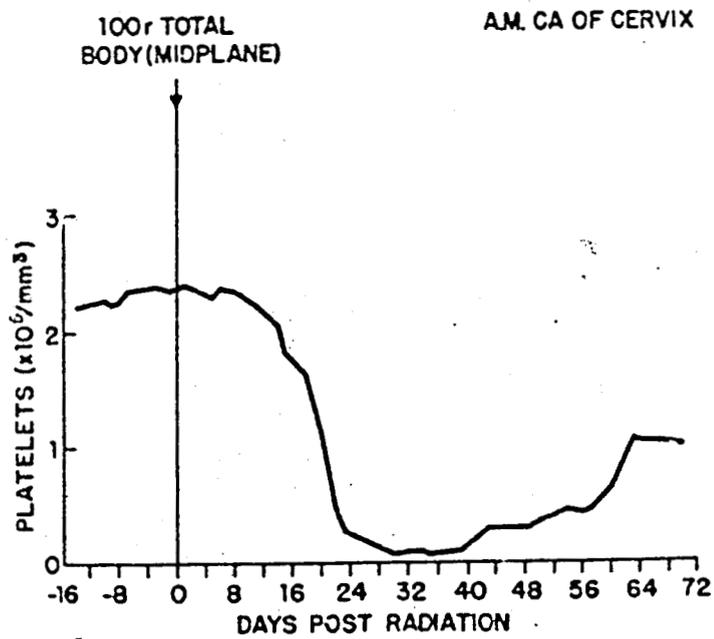


Fig. 16

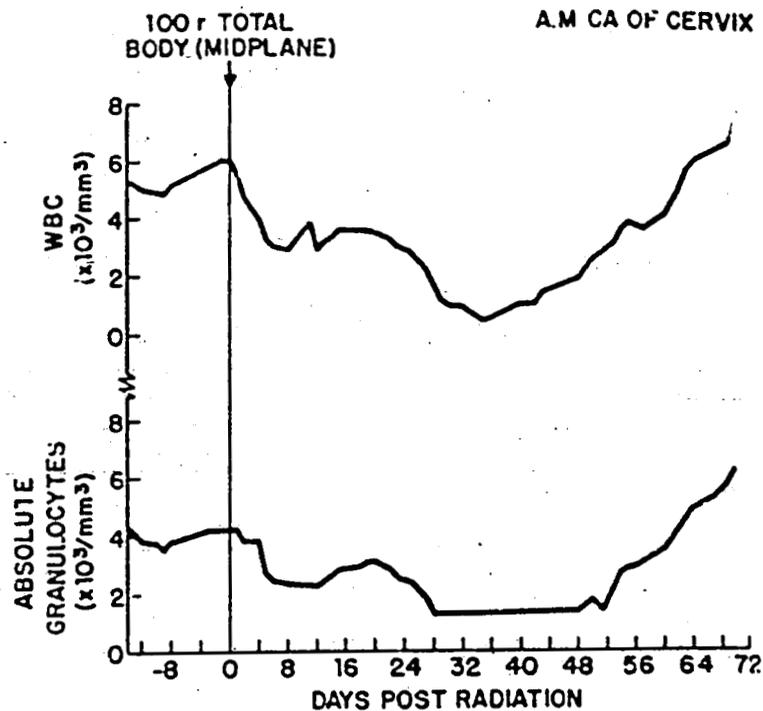


Fig. 17

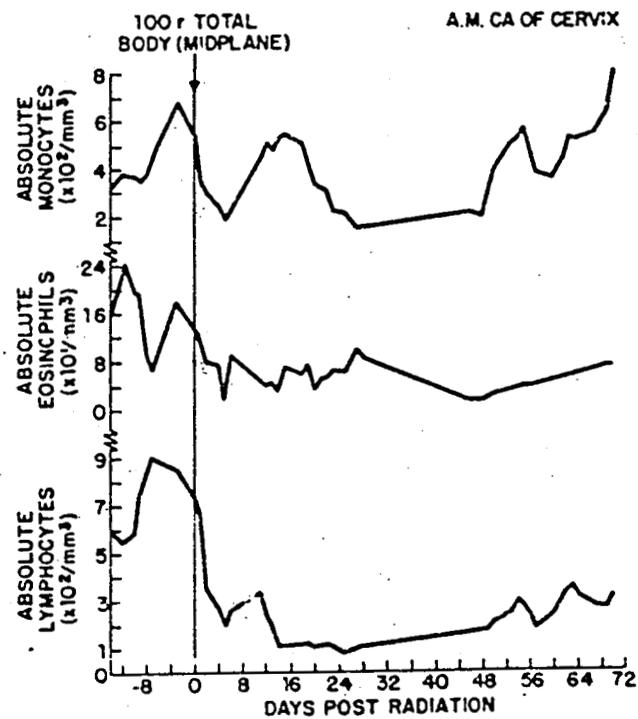


Fig. 18

PER CENT CREATINE OF TOTAL URINARY CREATINE AND CREATININE

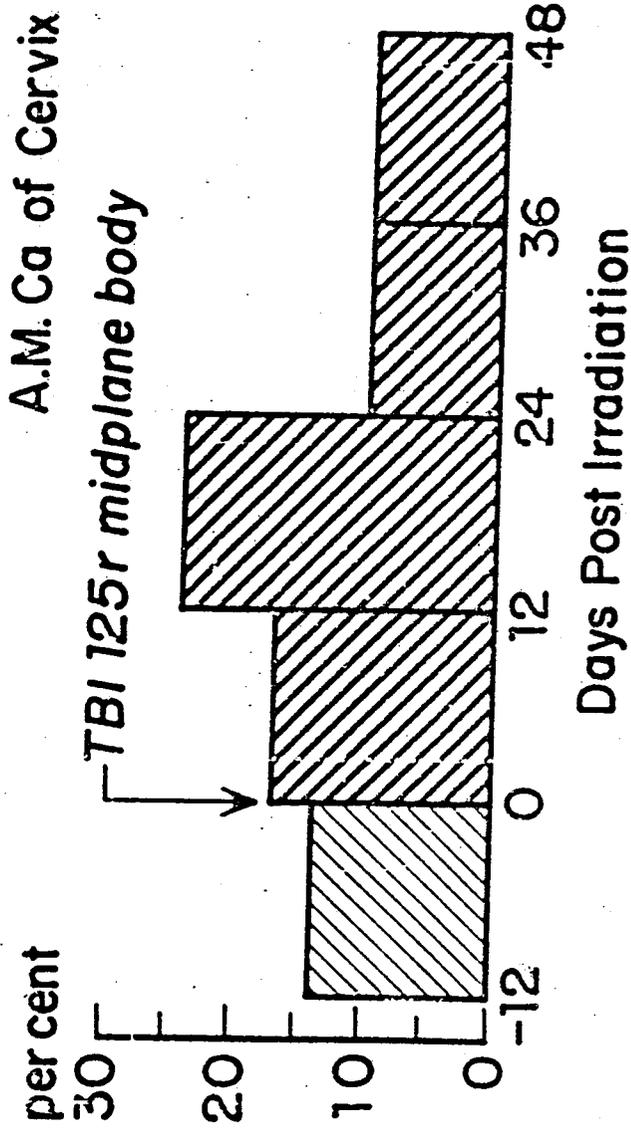


Fig. 19

A.M., Ca. of Cervix

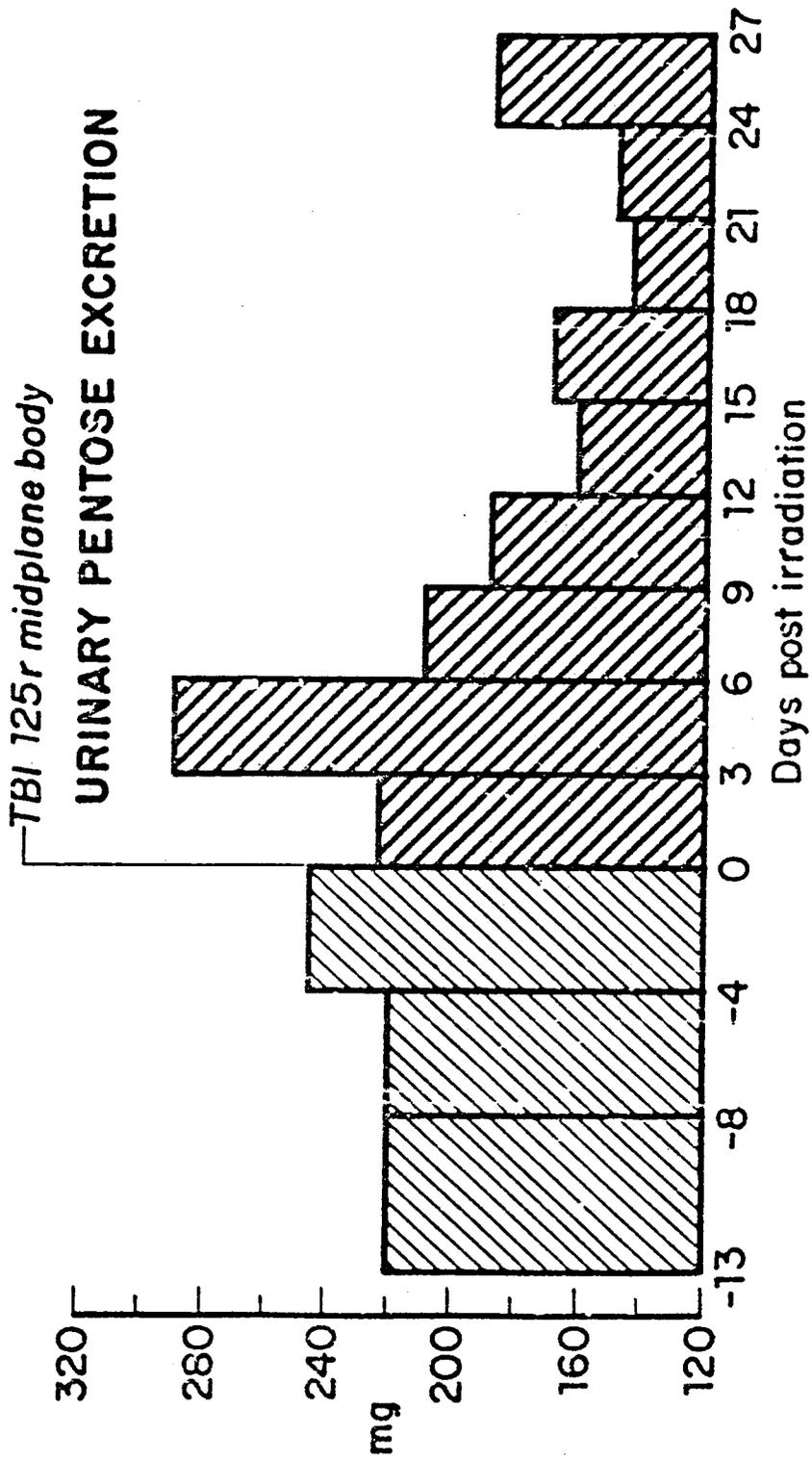


Fig. 20

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