Studies on the Radiosensitivity of Bone Marrow

I. The Relative Sensitivity of Erythroid and Myeloid Elements

By William N. Valentine, M.D. and Morton Lee Pearce, M.D.

Despite the large amount of experimental work on the effects of roentgen irradiation on the various elements of bone marrow, doubt still exists as to the comparative sensitivity of myeloid and erythroid precursors. It is generally conceded that the macrophages or reticulum cells of hematopoietic tissue have a marked resistance to radiation injury, and that the megakaryocytic, myeloid and erythroid elements are among the more sensitive of the mammalian tissues to the effects of both particulate and short wavelength electromagnetic radiations. It is most generally held that lymphoid tissue is the most radiosensitive of all the hematopoietic tissues. The subject of comparative sensitivity of the various marrow cell lineages has been reviewed in recent years. Snelling and Osgood, in 1938 stated that "aplasia of bone marrow is the typical effect. All parenchymatous elements, leucoblastic, erythroblastic and thromboablastic suffer. They may be involved singly or in any combination and there is considerable variation in the reports of different investigators as to the relative degree to which individual tissues are affected."

Dunlap in 1942 reported that in necropsy specimens erythroblastic foci persist in some marrows after irradiation injury despite disappearance of granulopoietic tissue. Bloom more recently reviewed this subject beginning with the pioneer work of Heineke in 1903 and 1905. On the basis of the histopathology in animal experiments, Bloom came to the conclusion that the erythropoietic cells were more sensitive than the myelopoietic tissue and that the erythroblasts were exceedingly sensitive to irradiation, perhaps almost as sensitive as the lymphocyte. After x-ray exposure of rabbits the erythroblasts were the first cells observed to disintegrate, the myelocytes being affected later and more gradually. Bloom points out, however, that the erythroblasts in spite of their greater sensitivity were the first cells to regenerate. In the chicken basophilic erythroblasts were considered to be even more sensitive than the small lymphocyte. Liebow, Warren, and De Coursey in their studies of the tissues of Japan.
RADIOSENSITIVITY OF BONE MARROW I.

Those exposed to atomic explosions at Hiroshima and Nagasaki were unable to find confirmation of the marked relative sensitivity of erythroblasts. Lawrence, Dowdy and Valentine, utilizing depression of reticulocyte count in the rat as a measure of erythropoietic damage, failed to detect any appreciable difference between the sensitivity of erythroid and myeloid precursors, although in the rat recovery of reticulocytes after LD$_{50}$ doses of x-rays occurred slightly earlier than did recovery of the peripheral leukocyte count. Investigators at Donner Laboratory have recently published studies on the uptake of intravenously injected radioactive iron in irradiated and normal rats. Whole body irradiation in doses up to 250 r resulted in diminished incorporation of Fe$^{69}$ into the red blood cells and this was more marked in the heavily irradiated animals. The iron in one series was injected 24 hours after irradiation and in another series 48 hours after irradiation. In a third series, iron was administered 4 hours after irradiation but radiation dosage greater than 25 r was not given. It was considered that the data confirmed the histologic evidence of sensitivity of erythroid tissue to irradiation.

There are several factors which render difficult an accurate assessment of the comparative radiosensitivity of erythropoietic and granulopoietic tissues. There may, of course, be species differences rather than a constant pattern from species to species. The vast majority of data relative to comparative radiosensitivity are derived from histopathologic sources and represent morphologic observations made at a number of fixed points in time after a radiation injury. Valuable as such data are in the evaluation of radiation pathology, they have certain limitations in estimating function. Rhoads and Miller as well as others have emphasized that bone marrow cellularity is not necessarily an index of the rate of cell delivery to the peripheral blood. Liebow et al. state that the tissues of atomic bomb casualties often showed a marked disparity between peripheral leukocyte count and marrow histology. Lawrence, Dowdy and Valentine have commented on similar findings in irradiated animals. The converse phenomenon may also exist. For example, the number of circulating lymphocytes in lymphatic leukemia may increase during ACTH and cortisone therapy at a time when there is both gross and histologic evidence of marked involutionary changes in the lymphoid tissues. Further, the definition of the term "radiosensitivity" is somewhat abstruse. Comparative radiosensitivity of various tissues may be evaluated in terms of the minimal dosage of radiation resulting in detectable damage, in terms of the maximal apparent injury apparent after a given amount of radiation, and in terms of the duration of evident injury and delay in regeneration. Data obtained in terms of one parameter do not necessarily parallel those obtained in terms of another. In our opinion, it is impossible to characterize radiosensitivity except with multiple parameters.

Lastly, and probably most important in the problem under consideration, the widely differing life span of the erythrocytes and leukocytes in the peripheral blood has made the comparative sensitivity of their precursors difficult to ascertain. There is considerable evidence that the mature circulating erythrocytes and granulocytes are probably little damaged by radiation in dosages compatible with life, and that the peripheral blood changes in these elements occurring after radiation injury largely reflect cessation or impairment of production at the...
hematopoietic centers rather than destruction of circulating adult cells. The level of circulating erythrocytes depends, of course, also upon the presence or absence of a hemorrhagic diathesis and blood loss. Since the leukocytes have a rapid rate of utilization in the peripheral blood, inadequate production is rapidly manifested by peripheral leukopenia, and the severity and duration of that leukopenia can be supposed to be a measure of damage to the precursor tissue. There is, then, a definable reflection in the peripheral blood of the quantitative degree of leukopoietic damage and of the functional state of leukopoietic tissue after a given dose of radiation. The erythrocytes are very long-lived elements, however. Even with complete cessation of production, in the absence of blood loss or hemolysis, the rate of fall in peripheral erythrocyte count is so slow that erythropoietic damage may be masked well into the stage of regeneration. The peripheral erythrocyte count also reflects at certain periods the hemorrhagic phenomenon of the radiation syndrome more than the erythropoietic damage. These factors may prevent an accurate assessment of the functional state of erythropoietic tissue and force reliance solely on histologic examination of the bone marrow.

It is the purpose of this investigation to report data on the comparative radiosensitivity of erythropoietic and myelopoietic tissue in the normal cat. To this end, data are presented on the effect of acute whole body irradiation on the ability of the animal to regenerate erythrocytes in the face of the severe stimulus of a massive bleeding performed immediately prior to irradiation. Control animals were bled but not irradiated. Since with the radiation dosage employed marked depression of the leukocyte count also occurs, it is possible in each animal to observe (1) the ability of the white blood cell picture to return to normal levels after irradiation injury to the marrow precursors in the face of the stimulus of the substantial leukopenia which promptly follows irradiation and (2) the ability of red blood cells similarly to increase to normal values in the face of substantial anemia induced by bleeding immediately prior to irradiation. The degree of damage effected by radiation on the erythroid tissue in the dosage employed is indicated by comparison with the similarly bled but nonirradiated animal; the sensitivity of myeloid and erythroid precursors is indicated by the comparative regeneration curves of white cells and red cells respectively in each animal subjected to irradiation.

Materials and Methods

Animals

Healthy, adult cats were employed as experimental animals. These animals from our colony were maintained on a diet of canned commercial dog food, a small weekly allotment of horsemeat, and an admixture of ground Rockland Rat Chow.

Bleeding

Phlebotomy was performed in a standard manner on both normal controls and experimental animals. Since it was considered important to produce an erythropoietic stimulus of considerable magnitude, a large single phlebotomy was performed as follows. The animals were placed under light ether anesthesia and a small incision made with the usual sterile precautions over the femoral artery. This vessel was isolated, divided and cannulated with
sterile polyethylene tubing. Prior to the phlebotomy, the desired amount of blood withdrawal was computed on the basis of 24 ml. per Kg. of body weight. Clamps were removed and the blood allowed to flow into a calibrated container. When approximately one-half to slightly more of the calculated amount had been withdrawn, blood pressure usually fell to low levels. At this point the tubing was clamped and sterile isotonic saline injected retrograde (by means of a syringe and needle which tightly fitted the tubing) into the femoral artery in the same volume as the previously withdrawn blood. This permitted restoration of blood pressure and the withdrawal of the remaining part of the calculated volume after a short interval allowed for mixing of blood and injected saline. When the calculated volume had been withdrawn a second injection of saline was made, bringing the total amount of saline administered equal to the total amount of blood removed. Since part of the 24 ml. of blood per Kg. of body weight withdrawn was diluted with saline, the phlebotomy did not remove as many circulating cells as if it had been possible to remove the entire calculated volume before intra-arterial reinjection of saline. However, the procedure did permit the removal in a standard manner of a much larger volume of blood at a single bleeding than is possible under other circumstances. Following phlebotomy, the incision was sutured and the experimental group irradiated within approximately one hour of the acute hemorrhage. It was considered that hyperplasia secondary to hemorrhage would be negligible at this time. Control animals were allowed to recover without irradiation. As a result of phlebotomy, a comparatively uniform reduction in circulating hemoglobin and erythrocytes to approximately 60 per cent of the pre-phlebotomy levels was effected as indicated in figures 1 and 2. The erythropoietic stimulus resulting, therefore, was that of the sudden reduction of about 40 per cent in the peripheral hemoglobin level.

Radiation

Irradiated animals were confined individually in a wooden box supplied with a thin lucite top through which radiation was administered subject to the following factors: voltage 250KV, amperage 15 MA, inherent filtration equivalent to 0.21 mm. Cu. 0.5 mm. Cu parabolic filter and 1.0 mm. aluminum filter, target distance 54 cm. to center of cat, dosage 200 r to the whole body calculated in air, average rate of administration 32 to 38 r per minute.

Hematology

Blood for hematologic procedures was obtained from the marginal ear vein at intervals subsequent to phlebotomy and irradiation. Red cell and white cell counts were made in the usual manner employing Bureau of Standard certified pipets and counting chambers. Blood smears were stained with Wright's stain and differential leukocyte counts were made on the basis of counting 100 leukocytes. Hemoglobin determinations were made by standard techniques calibrated on the basis of hemoglobin determination made by the oxygen capacity method as modified by Van Slyke.

Experimental Procedure

The experimental procedure is largely included under the discussion of methods. Prior to phlebotomy each animal had several complete hemograms whose average served as his baseline values. Control groups and experimental groups were then determined by dividing the animals on the basis of matching body weight and matching baseline hemograms as comparably as possible. Results are reported on 11 control animals phlebotomized but not irradiated, and on 13 experimental animals both phlebotomized and irradiated. In addition, two other groups of control and irradiated animals were studied. In one of those groups a coryzal infection with leukocytosis developed in several animals between the tenth and twentieth day after phlebotomy. In the other, studied prior to the contamination of a new colony, infectious feline agranulocytosis appeared and some nonimmune animals were affected in the third and fourth week after bleeding. In subsequent experiments all animals used were immune as evidenced by either recovery from the disease or by failure to develop the disease after prolonged habitation of virus contaminated quarters. Although several
animals in both groups did not develop signs of either condition, these groups are not included in the analysis. However, the data obtained corroborated that found in groups not subject to these variables.

A. Comparative Regeneration of Erythrocytes after Phlebotomy in Control and in Irradiated Animals

The experimental results can best be discussed with reference to table 1 and figures 1 and 2. Table 1 merely indicates the comparative baseline values in the

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Fig. 1.—Comparison of the regeneration of erythrocytes in normal and irradiated animals after a standard phlebotomy. Animals were phlebotomized at day 0 and the experimental group irradiated immediately after phlebotomy. 100 per cent = 6.97 M. RBC/per cu. mm. in the controls and 7.24 M. per cu. mm. in the irradiated group.

experimental and control groups. Nine to ten complete hemograms obtained prior to bleeding and irradiation were averaged to obtain a mean value which served as a baseline. In the figures, these mean values for the various components of the baseline hemograms are represented as 100 per cent for purposes of convenient comparison. The translation to absolute values from per cent can be readily made by reference to table 1 or to the legends of figures 1 and 2.
Figures 1 and 2 indicate the rate of regeneration of circulating erythrocytes and hemoglobin in control and irradiated animals. The data show that for approximately the first fifteen days after phlebotomy, the red cell counts of the two groups return rapidly toward normal values, and that the rate of return is very comparable in both. Subsequent to this time, regeneration in the irradiated animals lags somewhat behind that of controls but the lag remains surprisingly slight. Hemoglobin regeneration in irradiated animals occurs at a slightly slower pace than regeneration of erythrocyte numbers. Hemoglobin and erythrocyte regeneration progressed in this manner despite the fact that the radiation dosage employed reduced the total leukocytes to 20 to 30 per cent of baseline values and the leukocytes remained at this level for more than 30 days. By the twenty-

![Graph: Comparison of the regeneration of hemoglobin in normal and irradiated animals after a standard phlebotomy.](image)

first day, average erythrocyte values were in the neighborhood of 90 per cent of baseline and stayed in excess of this figure for the remainder of the study period. There appeared to be a slight tendency for control animals to attain erythrocyte values in excess of baseline figures between the twenty-fifth and fiftieth day after phlebotomy. Regeneration in both groups can be regarded as practically complete after the twenty-fifth to thirtieth day.

**Discussion:** The results obtained do not indicate marked relative sensitivity of erythroid precursors at this dosage level and under the condition of this experiment. In fact, strikingly adequate erythropoietic function appears to be present in these animals subjected to 200 r whole body irradiation. Comparable function of the myelopoietic tissue will be discussed in the following section of this report.
Data on the normal life span of the erythrocyte in the cat, obtained by the N\textsuperscript{14} labeled glycine technic, indicate that the red cells of the cat survive on the average 75 to 80 days. Taking the latter figure as an approximation, it can be calculated that normal erythropoiesis is geared to replace roughly 1.25 per cent of the circulating red cell mass per day. Phlebotomy in the irradiated group reduced the erythrocyte count to 58 per cent of baseline values. Since the cells present after phlebotomy are a random population, and will die at the rate of 1.25 per cent of their number per day, an initial production rate after bleeding of 58/100 of original productive capacity would suffice to maintain the new erythrocyte level without rise or fall. This means that the erythropoietic tissue would have to operate at 58 per cent of its baseline productive capacity in order to prevent further anemia from developing.

Figure 1 indicates that not only was productive capacity in irradiated animals sufficient to accomplish this, but, in addition, by 20 days after phlebotomy and irradiation it was actually able to raise the erythrocyte level from 58 to 90 per cent of baseline, an average daily increase of 1.6 per cent of the baseline red cell count. This increase amounts to roughly 130 per cent of the prephlebotomy and irradiation operating level of erythropoiesis. Added to the 58 per cent baseline erythropoiesis necessary before any recovery from the anemia could occur, it is apparent that despite radiation injury the erythroid tissue was capable of responding to the stimulus of bleeding by operating at a level nearly twice that in the normal animal. Appreciable reserve capacity was therefore still present in the face of whole body irradiation in the amount of 200 r. As will be seen, this is in marked contrast to the myelopoietic function measured in the same animals with the same radiation exposure.

The mechanism of rate of recovery from anemia in the normal and irradiated cat will be discussed in a separate report. It is common knowledge that in man the rate of recovery from the anemia of hemorrhage, iron deficiency when iron is supplied optimally, and of primary anemia treated with optimal liver dosage is dependent upon the initial severity of the anemia, and that greater daily increments can be expected when the initial count is low. Data in the literature indicate that in man under these circumstances, maximal restoration of erythrocyte and hemoglobin levels rarely exceeds two to three times normal productive capacity even when initial counts as low as 20 to 30 per cent of normal are present. As the count rises there is a progressively smaller daily rise in the erythrocyte level—presumably due to the diminishing stimulus to erythropoietic activity. It can be seen that for this stimulus in normal and irradiated cats (erythrocyte level 58 per cent of normal) an increase in erythropoietic activity of two times is of the same order of magnitude as that expected in man recovering from hemorrhage, iron deficiency or primary anemia under optimal therapy.

The data indicate that in the cat receiving irradiation of this magnitude (200 r), the functional reserve of erythroid tissue for practical purposes is surprisingly satisfactory. The findings are not in agreement with the conclusions of Bloom and Bloom\textsuperscript{5} and are at variance with those of Hennessey and Huff\textsuperscript{9} using uptake of radioactive iron as a measure of erythropoietic function. The reasons for this variance are not clear. Species variation is one possibility.
The disparity sometimes existing between morphology and function may be another. Although radioactive iron uptake by erythroid tissue and its incorporation into hemoglobin represent a highly specific parameter for estimating erythropoietic function, some difficulties in interpretation are inherent in estimating this function in animals receiving the isotope 24 and 48 hours after irradiation. It is current belief that serum iron or transport iron is the source of iron drawn upon for new hemoglobin formation. In the absence of saturation of serum iron binding protein, the intravenous injection of tracer doses of radioactive iron labels this compartment of body iron to a greater degree than it does the pool of body iron as a whole. For a period after injection, therefore, normal erythroid tissue is drawing upon a disproportionately rich source of the isotope for incorporation into hemoglobin. However, under circumstances where erythropoiesis is temporarily depressed, the radioactive isotope would soon become diluted as a part of the body iron pool as a whole. When next presented to a bone marrow resuming function, the ratio of isotopic to nonisotopic transport iron would be much less and might well be no greater than that present in the tissues generally. Erythropoiesis under such circumstances might appear depressed not only on the basis of persistent radiation injury but also on the basis of a more transitory inability to utilize transport iron at a time when the isotope concentration was maximal. Radioactive iron in the reported studies was administered only during the first 48 hours after irradiation. Speculation in this regard could, of course, be resolved experimentally. The nature of the variable results obtained after irradiation of erythroid tissue must await further study for full explanation.

B. Comparison of Sensitivity of Myeloid and Erythroid Tissue in the Same Animals after 200 r Whole Body Irradiation

Figure 3 charts the mean leukocyte and erythrocyte counts at varying intervals of time after phlebotomy and irradiation. It will be noted that 200 r depressed the mean leukocyte values to about 20 per cent of baseline and that they remained in the vicinity of 20 to 30 per cent of their pre-irradiation numbers for almost 30 days. Recovery to levels comparable to nonirradiated controls did not occur until between 42 and 50 days after irradiation. This period of depression of leukocyte values is somewhat longer than that observed in rats after severe radiation injury but differs little from that seen in dogs. In the latter species receiving 350 r, complete recovery of pre-irradiation leukocyte values requires approximately 40 days on the average. In contrast to the leukocytes, the erythrocytes were rapidly increasing in numbers after phlebotomy and the same radiation injury, and had returned to baseline values long before the white blood cells. Further, erythrocyte regeneration appeared to proceed promptly with little latent period after irradiation. The leukocyte values of nonirradiated controls are also plotted in figure 3 for comparison with those of the experimental animals. There appears to be a tendency for the mean leukocyte count in the controls to fall somewhat below baseline values. This is probably the result of diminished animal excitement with training in the bleeding procedures, since the trend was apparent in nearly every animal.

Figure 4 compares the relative percentages of granulocytes and mononuclear
Fig. 3.—Comparison of the effect of whole body irradiation in the amount of 200 r on (a) the recovery of the erythrocyte level after a standard bleeding performed immediately prior to irradiation and (b) the recovery pattern of leukocytes after radiation in the same animals. The leukocyte level of nonirradiated controls is also charted. The values are presented as per cent of the mean of the baseline hemograms. See table 1 for absolute values of these means.

Fig. 4.—Comparison of the relative percentages of mononuclear and granulocytic cells after whole body irradiation at day 0 in amount of 200 r. The initial point on the chart represents the average baseline percentages prior to phlebotomy and irradiation. Each point recorded represents the mean value for the entire group of irradiated animals on the specified day after bleeding and irradiation.
cells at selected intervals after phlebotomy and irradiation. Lymphocytes and monocytes are both included under the designation of “mononuclear cells.” The latter (monocytes) are few in number and in the cat can frequently not be distinguished with assurance in routine preparations with Wright’s stain.

It will be noted that during the first 30 days post irradiation—essentially the period of maximal depression of total leukocyte count—granulocytes constituted relatively less and mononuclears (almost all lymphocytes) relatively more of the total leukocytes than was the case during the baseline period. Granulocytes were relatively more depressed at this time than were lymphocytes. Although the lymphocytes are reduced in number with smaller amounts of irradiation than are any of the formed elements of the peripheral blood and lymphoid tissue is justly regarded as the most radiosensitive of all the hematopoietic organs, it is none the less paradoxically true that during the period of marked leukopenia following a severe radiation injury, the polymorphonuclear leukocytes may constitute a smaller proportion of the total leukocytes than they did prior to irradiation. This has been reported in dogs receiving single L.D./50 doses of irradiation. In the leukopenia developing during radiation therapy in man, it is also common experience to find the percentage of granulocytes disproportionately low. After a 30 day interval when the total leukocyte count was climbing toward baseline values, the relative percentages of mononuclear and granulocytic cells again became about what they had been prior to irradiation.

Discussion: The data presented indicate that under the conditions of this experiment, myelopoietic tissue was damaged functionally to a considerably greater degree than was erythropoietic tissue. While red cell mass determinations were not employed in these experiments, the erythrocyte recovery data can hardly be explained in terms of changes in circulatory dynamics subsequent to hemorrhage or irradiation. The red blood cell counts of both bled controls and bled, irradiated animals were reduced to essentially identical levels after a standard hemorrhage. They remained unchanged or only slightly changed for a three day period and then began to rise. The recovery curves in the two groups were of identical shape with a slight lag evident in the irradiated group. In both instances, by twenty days after bleeding the values have returned to 90 per cent of their pre-bleeding levels, rising more slowly after that time to normal. While some differences in red cell mass may conceivably have been present in the two groups after apparent recovery to essentially normal erythrocyte values, the findings indicate that surprisingly active erythrocyte regeneration occurred in the face of irradiation injury in these animals, and that the functional responses of erythroid tissue after radiation in the amount of 200 r were of an entirely different order of magnitude from those of the myelopoietic tissue as judged by peripheral blood counts.

In the case of the granulocytic leukocytes, peripheral blood values of course are a resultant of the numbers produced daily by the myelopoietic tissues and the number destroyed or utilized in the tissues. It might be argued that the depression of the granulocyte counts in these experiments reflected increased peripheral destruction rather than diminished productivity of the myelopoietic tissue. This possibility cannot be eliminated on the basis of present data. However, no satisfactory evidence of increased peripheral destruction of granulocytes follow-
ing radiation in this dose range has thus far been presented, while ample evidence of a fundamental action of radiation in reducing productivity in the parent marrow tissue is available. It seems likely that the leukocyte producing tissues did not recover even normal productive capacity for a period of greater than one month, while the daily production of erythrocytes was above normal soon after phlebotomy and irradiation.

A partial alternative explanation of the observed disparity in myelopoietic and erythropoietic function after the same irradiation injury might be that erythropoietic tissue had a priority and that granulopoiesis had to await recovery from the anemia of hemorrhage before it could itself return to normalcy. This possibility was assessed specifically and negated by observations on five animals irradiated with 200 r but not bled. The depression of leukocyte count was of the same general order of magnitude as in the bled animals. The comparatively adequate function of erythroid tissue remaining after irradiation in these animals might also have resulted from some protective influence of the bleeding on the subsequent irradiation administered within the hour. If such protection was afforded, it applied only to the erythroid tissues and not to the animal in general, for no differences were noted in the leukocyte responses of bled, irradiated animals and animals irradiated alone. The close time relationship of the bleeding and irradiation largely eliminate simple erythroid hyperplasia as a significant factor.

Of some indirect interest were the observations during the experiment of the abortive rise in leukocyte counts usually some 8 to 12 days after radiation in most animals. This has been commented upon by Jacobson et al., and histologic evidence of similar abortive waves of marrow regeneration have been observed by Bloom.

**Summary**

1. Data are presented on (a) comparison of the regenerative capacity of erythroid tissue in the irradiated and nonirradiated cat after the stimulus of acute hemorrhage resulting in a 40 per cent reduction in the peripheral erythrocyte level; (b) comparison of the relative regenerative capacity of myelopoietic and erythropoietic tissue in the same animals after 200 r delivered to the whole body.

2. Recovery from standard anemia produced by hemorrhage immediately prior to irradiation injury was only slightly less rapid in the irradiated than in the control group. Estimates of functional reserve indicate that the cats exposed to 200 r were still able in the first 20 days after exposure to produce erythrocytes at nearly twice the normal production rate in the nonanemic, normal animal.

3. In sharp contrast to the findings for erythropoiesis, myelopoiesis as judged by peripheral leukocyte counts was severely depressed for about 30 days and final recovery delayed for 40 to 50 days after 200 r. In the face of the stimulus of leukopenia developing shortly after the radiation exposure, myeloid tissue appeared incapable of operating at more than a fraction of its normal productive capacity for a long period of time.

4. The data indicate that on the basis of functional impairment erythropoietic
tissue is significantly less sensitive to radiation injury than is the myelopoietic tissue of the same animal under the conditions of this experiment.

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