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1

Acute Effects of Irradiation in Man

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THE ACUTE EFFECTS of a large dose of irradiation on the blood and marrow in the human being can be described in a general way, although the pattern is not likely to apply strictly in any given clinical situation. Considerable difficulty arises from the fact that the basic information for this generalization is derived from several sources quite widely separated from usual clinical situations:

1. *Laboratory studies in animals.* To extend such information to man one must consider the problems that arise from differences in species response and from the fact that illnesses not present in the animals influence the effects of radiation in man.

2. *Experience with atomic bomb effects in human beings.*[1-3] The opportunity for collection of data during the early phase after explosions was greatly limited by disaster conditions in Japan, and most of the patients had also suffered blast injury and thermal burns.

3. *Industrial reactor accidents* in which uneven dose distribution and severe radiation burns to the skin played an important part in the response.[4]

4. *Clinical therapy.* When external beams are used they do not usually include the whole body and the response to such local irradiation is quite different from that to total-body irradiation.[5, 6] When the whole body is included in the beam, the doses given are small and the response may differ qualitatively from that with large doses.[7-9] Furthermore, repeated doses are usually given with the result that there is a very complicated response to interpret. With radioisotopes, the same problem of protracted dosage is present in addition to the variations related to distribution of the isotope and radiation energies. In many of these clinical situations the illness of the patients treated interferes in variable and unknown degree with the response seen.

In spite of all these problems an attempt is made in figure 1 to chart the hematologic response of a hypothetical patient to a large, but not lethal, dose of total-body irradiation given over a short period of time. This is compiled from many sources and is open to many objections. Nevertheless it does indicate, correctly, that there is a definite sequence of changes with a distinct delay in production of the most profound manifestations of hematopoietic changes. The time intervals involved in the development of these changes are somewhat dependent upon size of dose, but not to as great a degree as one might expect. More striking is the difference related to species, the smaller animals with shorter normal life span showing the same pattern of events at a much more accelerated rate.

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BOX No. 3 of 6

1004290

The mechanisms involved in these changes in the blood picture are complex and not entirely understood. Mature blood cells in vitro are quite resistant to irradiation, although in tissue culture a definite effect on lymphocytes of 350 r. is reported.[10] Within the dose ranges likely to be encountered clinically, the hematologic effects are not thought to result from direct irradiation of circulating blood cells. A few years ago it was believed that most of the changes could be explained by the damage to blood-forming tissues, with failure to replace aging cells as the chief mechanism. Thus it was said, for example, that since lymphocytes have a life in the circulating blood of only a few hours, their prompt disappearance, once formation ceased, was due to normal aging. The granulocytes, with a somewhat longer life span, disappeared more slowly and the red-cell values showed their greatest depression at a still later date, as would be expected. Newer studies on the life of the normal white cells indicate that they survive considerably longer than was formerly believed, although there is still not complete agreement on the time periods.[11-13] The explanation for prompt decrease in number of these cells, especially lymphocytes, after radiation must be attributed to something more than cessation of formation. The other mechanisms must involve hastened removal from the blood stream for distribution in tissues, and possibly actual necrosis of the cells.

The radiation syndrome has repeatedly been compared with the stress reaction. It has been established that whole-body irradiation activates the pituitary-adrenal system,[14-16] but it is not clear to what extent the blood changes are mediated through adrenal stimulation. The adrenals are not necessary for the production of lymphopenia by total-body irradiation.[17]

Neutrophil Response

There may be a temporary leukocytosis after massive total-body irradiation, and this is believed to result from mobilization of cells already formed and available in the marrow. During this period studies using the technique of leukophoresis indicate that there are stores of white cells still available for mobilization and replacement of those artificially removed.[18] The leukocytosis may last 24 to 48 hours and is followed by granulocytopenia developing at a rate depending somewhat on the dose, with the lowest level reached perhaps at 3 to 5 weeks. The initial leukocytosis is usually not seen after multiple smaller doses of radiation or after the internal administration of radioisotopes. During recovery the number of granulocytes may go above normal. It is not known whether this is a true part of the radiation syndrome or evidence of ability to react to pre-existing tissue destruction and infection.

Lymphocyte Response

The very prompt and pronounced fall in lymphocytes is considered the most reliable evidence of acute radiation effect.[19] During the most severe phase of white-cell depression after large, sublethal doses there may be a greater diminution of granulocytes than of lymphocytes so that a relative lymphocytosis exists. A study of thoracic duct lymph[20] in rats and dogs after whole-body

1004291

irradiation showed a transient rise in the number of lymphocytes during the first one to two hours, followed by a precipitous fall. This depression of the number of lymphocytes in lymph seemed to precede the fall in the peripheral blood. At three to ten hours the lymphocytes in the lymph showed pronounced evidence of degenerative changes and necrosis. During recovery at eight to eleven days there was a relative increase in large, young lymphocytes in the thoracic duct. Recovery of normal lymphocyte level may be greatly delayed and there is usually no absolute lymphocytosis during this phase comparable to the granulocytosis sometimes seen.

Characteristic morphologic changes in lymphocytes have been suggested as possible practical aids in the detection of radiation effect, particularly from chronic low-level radiation. One such change reported was the presence of increased numbers of refractile granules[21]; a subsequent study failed to verify the usefulness of this.[22] Another such feature reported is an increase in cells with double nuclei[23]; to detect such a change it is necessary to observe very large numbers of cells.

Platelets

The rate of platelet depression varies with the size of the dose, but the platelet levels tend to parallel those of the granulocytes, without the initial rise. It is presumed that the changes in platelets reflect diminution of production in the marrow plus, with high doses, removal at sites of radiation damage to capillaries.

Red Cells

The red-cell levels shortly after large doses of radiation represent the summation of several influences—decreased red-cell formation, hemoconcentration, and early hemorrhage into lymphatics.[24, 25] A later generalized thrombocytopenic bleeding may contribute to severe anemia. The decreased red-cell formation can be demonstrated with radioiron studies which show a delayed plasma clearance and impaired red-cell "uptake" curve.[26] Reticulocyte depression is also clearly shown in experimental animals, with a distinct reticulocyte peak in the recovery phase. Information on the pattern of reticulocyte response to large doses is not available for the human being. In some of the Japanese atomic bomb casualties reticulocytes above normal were reported during severe hematologic depression.[2] With large doses of internally administered radioisotopes we have noted an absence of reticulocytes during the radiation depression phase.

Marrow

The most salient effect of massive irradiation upon the marrow is reduction in the number of cells. In experimental animals, when observations are made shortly after large doses, necrotic cells are seen and erythrophagocytosis may be prominent. With the smaller doses given to human patients these destructive phenomena are usually not directly observed and the decrease in cellularity is presumably due chiefly to decreased mitosis and is not accompanied by prominent morphologic signs of damaged cells. Variable reports are given on the

1004292

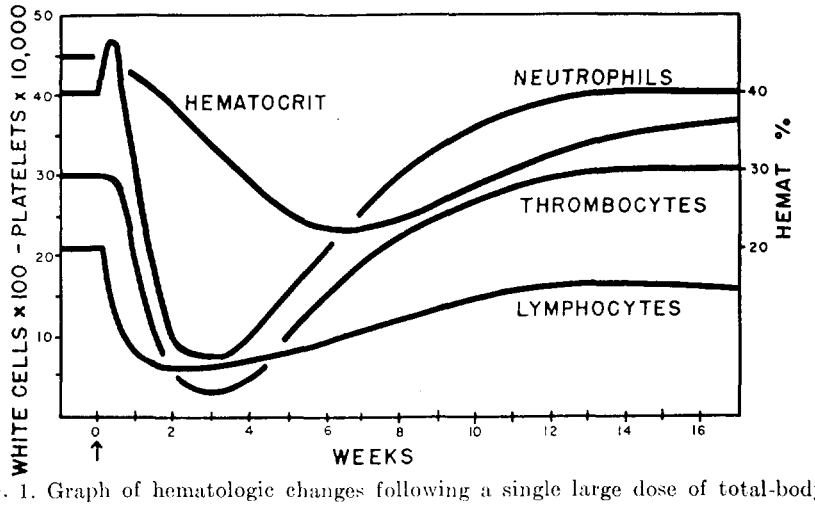

FIG. 1. Graph of hematologic changes following a single large dose of total-body irradiation.

relative sensitivity of the different cell types and this may depend on the species, dose, and rate of delivery of the radiation. The persistence of plasma cells is perhaps the most generally occurring feature.[27] There is also an increase, at least relative, of primitive reticulum cells.[1] Phagocytic cells containing hemosiderin may be plentiful. After internal administration of radioisotopes, we have been impressed by the presence in aspirated marrow of clusters of cells caught in an amorphous meshwork of fibrillar material. These entities may be seen in normal marrow but are much more common in radiation damaged marrow. On an aspirated specimen, presence of these meshworks, plus many small fat spaces, plus a slight relative increase in plasma cells may be quite suggestive of radiation effect, even when the total cellularity seems unimpaired. The relative depression in the granulocyte precursors as compared with that in the red-cell elements is a subject of conflicting reports with most animal studies suggesting that the red-cell precursors are most radiosensitive.[28, 29] Following large doses of radioisotopes we have found red cell forms to persist usually in larger numbers than the granulocytes. They often occur in clusters and an "intermediate normoblast" stage predominates, as if there might be some degree of block at this level of maturity (fig. 3). In the granulocyte series there is frequently a depletion of mature forms with myelocytes remaining the most plentiful stage. Megakaryocytes are reduced in numbers, and damaged forms are sometimes seen. Precipitates of diffusely spread blue staining material, such as are often noted in myeloma and aplastic anemia, may be prominent. An example of aspirated marrow from a patient with severe radiation damage from an internally administered radioisotope is shown in figure 4 and a histologic section from the same patient in figure 5.

With radioisotopes the recovery phase is gradual and has not been very well studied. In the atom bomb victims marrow recovery was variable and often involved only focal areas initially.[1]

1004293

FIG. 2. Photomicrograph of aspirated marrow showing moderate radiation damage from internal radiation with radioiodine (×200).

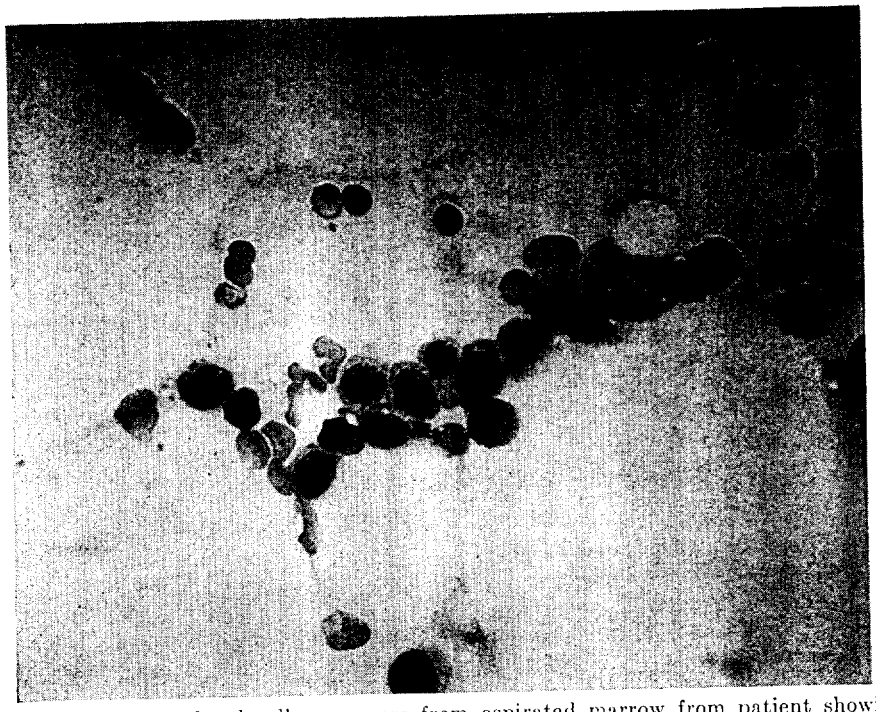

FIG. 3. Cluster of red cell precursors from aspirated marrow from patient showing severe damage from an internally administered radioisotope (×528).

1004294

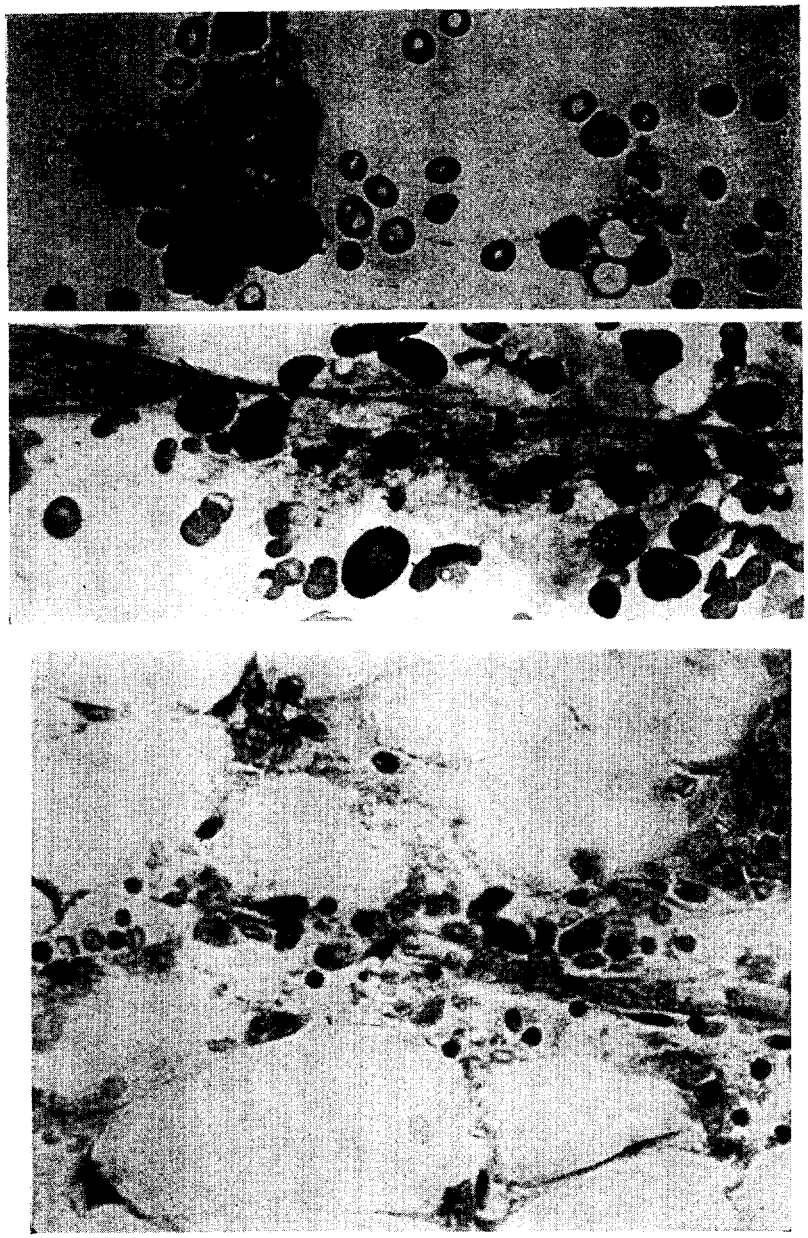

FIG. 4-5. Aspirated marrow (×1080) and histologic section (×528) from marrow showing pronounced radiation effect.

CORRELATION WITH CLINICAL SYNDROMES

Over a considerable range of dose levels hematologic changes are closely correlated with the symptoms in the total-body irradiation syndrome. However, single or repeated doses that are low in terms of immediate effects but

1004295

above the accepted permissible safe levels, are not adequately detected by routine blood studies; such studies are too insensitive and may lead to an erroneous sense of safety.[30] At the opposite extreme, with supralethal doses, central nervous system and gastrointestinal manifestations may predominate. Here the blood will indicate the presence of severe, hopeless radiation damage, but the symptoms present cannot be explained in any direct way by deficiencies of function of cellular blood elements.

It is in the high, but sublethal, dose range where immediate clinical management is important, that the blood changes are a good index of the extent of damage and stage of response. During the initial symptoms of nausea and vomiting the blood may show only lymphopenia and possibly neutrophilia. If direct damage to capillaries is severe, hemorrhage into tissues may account for some early drop in red-cell mass. The lymphocyte depression, although of great prognostic importance, does not appear to be related in a direct way to any clinical symptoms. During the second phase, from about the second to seventh day, the patient may be asymptomatic while the neutrophils and platelets are progressively decreasing. Subsequently, the neutropenia may allow the development of various types of infection. The threshold for serious infection varies a great deal. In using radioisotopes we have had some patients with leukocyte counts below 1000 per cu. mm. without any evidence of infection. It has been our impression that debilitated, bedfast patients are much more susceptible to this complication of leukopenia. It has been suggested that of the peripheral blood values the neutrophil level is most closely correlated with survival after irradiation.[31] At about the same time that the neutrophils are depressed, perhaps 3 to 5 weeks after the dose of irradiation, thrombocytopenia and bleeding may become prominent. The mechanisms involved in the hemorrhagic tendency following irradiation have been the subject of many investigations. Recent information lends emphasis to the thrombocytopenia as the chief factor.[32] If the patient survives these difficulties anemia of the hypoplastic type may be a later problem. Subsequently he may progress, with or without an interval of apparent good health, into the chronic complications of radiation, which are not the subject of this discussion.

Radioisotope Effects

Internally administered radioisotopes, except those with exceedingly short half lives, produce a type of radiation quite different from that usually given externally. The production of continuous ionization over a prolonged period might be expected to yield results very unlike those produced by single or multiple brief exposures, yet the effects in general are quite similar with the expected delay in manifestation of effects of isotopes of fairly long half life. Lamerton[33] has shown that in rats, after the administration of P^{32}, the fall in neutrophils is greater than that of the lymphocytes, whereas the effect of a single dose of x-ray is the opposite. However, such differences are not very striking. Attempts to relate the degree of hematologic effect to the dose rate from the continuous internal radiation are of interest[34]; interpretation is difficult because of the delay in maximal response as shown by the peripheral blood.

1004296

Over the last 10 years it has become increasingly apparent that most internally administered radioisotopes usually exert a profound effect on the bone marrow at doses lower than those necessary for treatment of any type of neoplasm. Even in the treatment of functioning thyroid carcinoma with I^{131}, the bone marrow damage is often a limiting factor. The other types of tumors that show some ability to concentrate one radioisotope or another do not do so to a sufficient degree to make therapy practical. The relatively greater sensitivity of the marrow to radiation is so pronounced as to outweigh any favorable concentration of the isotope in the tumor.

With radioactive iodine there is no specific deposition of the radioisotope in the bone marrow and the effect on blood-forming tissues from the moderate doses used for the treatment of hyperthyroidism is minimal. The large doses used in the treatment of carcinoma of the thyroid produce varying degrees of marrow depression. Rall et al.[35] found lymphocyte depression to be the most sensitive evidence of radiation effect. The degree of depression appeared to depend upon the integrated blood concentration of the isotope plus a factor derived from the amount deposited focally in the thyroid gland and in thyroid tumor tissue. These focal deposits of the isotope would presumably affect the marrow by means of their gamma radiation. Robertson and Godwin[36] have attempted to evaluate the dose to the marrow elements, as influenced by the bone trabeculae, which absorb relatively more radiation per volume than does the less dense hematopoietic marrow.

In treating patients with carcinoma of the thyroid we have seen moderate degrees of marrow depression. In a few patients a persistent leukopenia has developed and persisted long after the cessation of isotope therapy.

Radioactive phosphorus given as soluble phosphate is, of course, notable as a marrow depressant. Although much emphasis has been put on its tendency to concentrate in leukemic and lymphomatous tissue, it is our impression that the clinical effects are largely those of total-body irradiation. It is true that certain tissue, including liver, spleen, and marrow, receive somewhat higher doses than less metabolically active tissues, but the specific localization is slight as compared with that of radioiodine in thyroid tissue. The therapeutic effects are to be considered more as evidence of the radiosensitivity of certain cell types than as the result of well placed radiation.

It is not clear to what extent the bony framework with its ability to take up P^{32} as bone salt contributes to the radiation of the encased marrow. Our data suggest that this is a relatively minor factor and that the incorporation of the isotope into the hematopoietic cells themselves is the chief factor in accounting for the dose delivered.

Colloidal radioactive materials are of great current interest—Au^{198}, chromic phosphate (P^{32}), Y^{90}, Lu^{177}, and others. With these radioisotopes, the route of administration is of prime importance in determining hematologic effects. If they are injected into cavities or solid tissues there may be relatively little of the isotope carried from the site of injection and the effect on hematopoiesis will be negligible for beta emitters and moderate for gamma emitters. On the

1004297

other hand, if these isotope preparations are given intravenously or escape into the blood stream from the site of injection, they are deposited in reticuloendothelial tissues including marrow (the liver usually gets the greatest share) and there is a relatively pronounced effect on hematopoiesis regardless of the radiation characteristics of the isotope. Autoradiograms show that in marrow the distribution of reticuloendothelial tissue is closely correlated with that of hematopoietic tissue. Reports of hematologic effects of colloidal radioisotopes that fail to emphasize route of administration may be misleading. For example, over 200 mc. of Au^{198} may be given into a body cavity without much effect on the marrow, whereas 100 mc. given intravenously in a hazardous, excessive dose, possibly of fatal consequence.

External Irradiation

Total-body irradiation has been studied in detail in animals, and, at lower dose levels, in human beings. The hematologic effects of such general radiation have already been discussed.

On the other hand, there is a lack of adequate information on the mechanisms of the hematologic effects of external *local* port irradiation given to patients for the treatment of neoplasms. With the portals used for most types of disease only a small portion of the total marrow is treated and it is difficult to account for as much hematologic depression as is sometimes seen. Scattered radiation probably is not an important factor. Hutaff and Belding[5] have reported on local and distant bone marrow effects in patients treated for carcinoma of the cervix. They found profound hypoplasia of the treated marrow, with the most pronounced decrease in the erythroid series. Mononuclear cells, lymphocytes, and plasma cells were relatively increased. At distant sites the marrow was hypercellular with a relative increase in red-cell precursors. Thus there was no evidence of an indirect or humoral depressing effect from the radiation.

These findings lead one to question whether the leukopenia occurring during radiation therapy is entirely due to suppression of the blood forming tissues. Perhaps increased removal of white cells is also a factor. This is suggested by the finding that in some cases during the period of blood lymphopenia there are increased lymphocytes in irradiated marrow areas.[5]

It is probable that quite frequently anemia and leukopenia that are caused by the disease process itself are erroneously attributed to the therapy. This may occur especially in Hodgkin's disease and lymphomas.

Studies of platelet levels during and after localized external radiation therapy show extremely variable results, with significant depression of their numbers in an appreciable number of patients.[6]

Discussion

In practical clinical situations several suggestions can be made. Adequate baseline studies are important in attempting to evaluate any radiation effect—preferably several separate blood studies done at the same time of day, and with the same techniques used throughout. Peripheral blood may be much more

1004298

informative than bone marrow in showing mild radiation effects because the blood is more suitable for quantitative study and a given sample is more representative. Furthermore, the lymphocytes, which are the most sensitive index, are believed to be formed chiefly outside the marrow. A careful differential white cell count of the blood is of great value; total leukocyte counts are helpful in following severe degrees of damage; and when the count is much depressed it is, of course, very time-consuming to do differential counts unless some type of white cell concentrating method is used. More emphasis might well be put on platelet levels as a clinical index of radiation effect.

A general uniformity in radiation response is observed clinically. Sometimes one encounters a patient who seems more "sensitive" than others—for example, a patient with polycythemia vera who develops a distinct picture of excessive radiation effect after 4 mc. of P^{32} given intravenously. However, these differences are relatively slight. One patient might show twice as much hematologic effect as another from a given dose, but not four times as much effect. Fortunately, extreme hypersensitivity such as is seen with some drugs does not occur, although unusual sensitivity in the erythema response of the skin to radiation has been reported.

Furthermore, the various aspects of the radiation picture tend to remain relatively in balance; one does not see profound thrombocytopenia without leukopenia as an acute radiation effect. Although there are differences in sensitivity of different cell types, as has been pointed out, at any one level of dosage the picture will show some uniformity from patient to patient, not an isolated extreme effect in one cell series. This is not true, of course, of chronic radiation effects.

Radiation effects on the blood are not sufficiently characteristic to be easily recognized in all cases, and differential diagnosis may be difficult. Careful consideration of the radiation—type, distribution, and dosage—as well as careful study of the whole hematologic picture is needed.

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