Bone Marrow Reactions to Trauma

Stimulation of Erythropoietic Marrow by Mechanical Disruption, Fracture or Endosteal Curettage

By Donald Van Dyke and Norman Harris

That a surrounding of bone provides a unique environment for hematopoietic tissue in adult mammals has been self-evident since Neu mann (1868) demonstrated that the red corpuscles are formed from colorless nucleated elements in the marrow. The 100 years since that discovery has seen every aspect of marrow morphology and function studied by all available technics so that today the marrow is one of the best characterized of all tissues. It is indeed surprising then, that in a century of intense investigation, the relationship of the surrounding bone to marrow function has not been elucidated. Röhlich’s paper in 1941 “On the Relationship Between the Bone Substance and Hematopoiesis in the Bone Marrow” and the studies by Friedenstein et al. are exceptions.

Studies showing a similarity between the distribution of blood flow to the skeleton and the distribution of marrow in the skeleton suggested that marrow grows best in blood which has just passed through bone. If erythropoietic marrow is transplanted to a non-osseous site it either degenerates completely or lies dormant until a surrounding of new bone has formed. If red marrow is removed and the bone allowed to fill with blood, the clotted blood is rapidly and completely converted to hematopoietic marrow. Evacuation of the medullary cavity institutes something akin to reenactment of the embryologic development of the bone marrow, the series of events following closely the pattern of fetal development.

The finding of increased erythropoiesis adjacent to fractures and the report by Knospe et al. that the marrow cavity rendered permanently aplastic by irradiation could be made to regenerate by mechanical disruption plus in-
jection of marrow suggest that trauma to the bone serves as a powerful local stimulus to hematopoietic marrow proliferation.

In the present work transient conversion of completely inert marrow to iron incorporating marrow following endosteal curettage of the tibia of dogs and monkeys strengthens the concept that trauma induces reactions in the surrounding bone which serve as stimuli to growth of hematopoietic marrow.

On the basis of the foregoing evidence, as well as a recent report by Wimer suggesting, from the results in 5 patients, that bone marrow curettage may allow regeneration of prefibrotic type marrow and improved erythropoiesis in appropriately selected cases of myelofibrosis, it was decided to attempt to stimulate regeneration of marrow by endosteal curettage of one femur in two patients with severe anemia, one with aplastic and one with fibrotic marrow.

**Materials and Methods**

Reactions to bone and marrow trauma were studied in New Zealand white rabbits, mongrel dogs, cynomolgous monkeys, and patients with severe anemia due to aplastic or myelofibrotic marrow.

Erythropoietic competence, reticuloendothelial activity, and blood supply to the adjacent bone were studied by isotopic methods, $^{52}$Fe and $^{59}$Fe for hemoglobin synthesis, Te-$^{99m}$sulfur colloid for reticuloendothelial activity, and $^{18}$F for relative bone blood flow. In the living animal or patient, distribution of these isotopes was recorded using the positron scintillation camera. The scintillation camera used simultaneously records the distribution of the isotope at 6 different intensities to eliminate the possibility that differences in intensity could influence the interpretation of the distribution pattern.

All patients had had complete hematologic investigation at the Donner Laboratory clinic, including in most cases complete ferrokinetic studies. In all cases total body marrow distribution studies ($^{52}$Fe and positron scintillation camera) had demonstrated grossly inadequate and abnormal distribution of marrow.

Four monkeys found to have large amounts of active marrow in both tibias, and therefore unsuitable for attempts to convert fatty to red marrow, were used to attempt to stimulate marrow regeneration following irradiation. 2,000 rads x-rays were given to the left tibia in 16 minutes ($230$ Kv, ma-TSD = 30 cm., 1 mm. A1 + 0.5 mm. Cu filters, cone 30/12.5 $\phi$).

**Operation Procedures**

Fractures were not produced experimentally but were studied as they were encountered in patients or in newly arrived animals (2 monkeys and one dog). All fractures discovered in animals were judged to be old on the basis of the roentgenographic appearance.

Rate and completeness of marrow regeneration after evacuation of the femoral shaft was studied in New Zealand white rabbits. In one group marrow was removed “intact” from the shaft of the femur and immediately replaced. In a second group femoral marrow was removed but not replaced. In all cases the unoperated contralateral femur served as the control.

Femoral marrow was removed “intact” by trephining a 7 mm. hole in the distal end of the shaft and forcing marrow out the hole by injecting saline through a needle inserted through the greater trochanter, following a procedure similar to that used by Steinberg and Hufford. As described by those authors, the marrow could be extruded as an apparently intact mass, and by drawing back on the syringe could be immediately sucked back into place in the marrow cavity.

Blood flow to the extruded and replaced marrow was evaluated in rabbits in the early post-operative period by the flow of an isotopic label into the femur. For this purpose $^{59}$Fe
was used and the rabbit killed one minute later. The femur was cleaned of all soft tissue, cut into 7 segments, and the segments counted in a well counter. The unoperated contralateral femur was prepared in the same way to provide the control.

**Endosteal Curettage**

Conversion of fatty to red marrow was accomplished in adult cynomolgous monkeys and mongrel dogs by endosteal curettage of the tibia. The pattern of distribution of erythropoietic marrow in the skeleton was determined using $^{52}$Fe and the positron scintillation camera. Only monkeys or dogs having a pattern comparable to the adult human (no marrow in the peripheral skeleton) were included. Endosteal curettage was done as follows: The monkeys and dogs were anesthetized and a small incision made just medial to the patellar ligament to expose the proximal end of the tibia. With a #24 bit a hole was drilled into the medullary cavity and as far as the bit would penetrate down the shaft of the bone. A small curette made from a piece of 14-gauge spring steel wire was inserted to the distal end of the marrow cavity and withdrawn with pressure applied so as to vigorously abrade the endosteal surface the entire length of the bone. This process was repeated some 20 times in an attempt to abrade the entire endosteal surface. 400,000 units of penicillin with 0.5 Gm. streptomycin were given prophylactically following surgery.

At frequent post-operative intervals relative blood flow to the curetted and opposite untouched tibia was determined using $^{18}$F and the positron scintillation camera. At appropriate times during the study, based on the qualitative data obtained from the scintillation camera pictures, animals were killed to obtain quantitative data on $^{18}$F uptake and radioiron distribution and for histologic examination of bone and marrow.

The effect of endosteal curettage on regeneration of irradiated marrow was studied in 4 monkeys who had been shown to have active marrow in both tibias. One leg (tibia) of each was given 2000 rad. Three months later repeat $^{52}$Fe marrow distribution studies showed active marrow in the non-irradiated leg, but complete absence of uptake in the irradiated tibia. Endosteal curettage was performed on two of the irradiated tibias at that time, and repeat $^{52}$Fe and $^{18}$F studies were done periodically thereafter.

**Case Histories**

**Endosteal Curettage in Severely Anemic Patients**

G.N., a 55 year old white male, was found to have anemia and splenomegaly in October 1967. At that time his bone marrow was found to be fibrotic and his peripheral blood smear showed the morphologic changes characteristic of myeloid metaplasia. Iron kinetics study showed that splenic erythropoiesis was primarily ineffective. In January 1968, the patient was started on high doses of androgens, (Delatestryl—Squibb), 600 mg. twice weekly for 2 weeks followed by 600 mg. weekly and folic acid 15 mg. a day and pyridoxine 200 mg. a day. Despite such therapy the patient's hemoglobin dropped to 5.2 Gm. per cent. Total body marrow distribution studies showed failure of medullary erythropoiesis throughout most of the central skeleton with significant accumulation of hemoglobin synthesizing marrow only in the proximal ends of the tibias. Erythropoietin concentration in serum was elevated, 0.48 IRP units per ml., as measured by the hypertransfused mouse assay at hemoglobin concentration of 5.8 Gm. per cent and hematocrit of 17 per cent. (Serum erythropoietin is not measurable in normal human beings by our method of assay, but has been estimated to be 0.003 units/ml.—ref. 17.) The left femur was entered through the greater trochanter and the atrophic and fibrotic marrow removed by passing a 13 mm. diameter orthopedic reamer to the distal end and subsequent curettment of the endosteal surfaces using long-handled curettes designed for the purpose. Platelets were transfused. Post-operative recovery was uneventful.

During the year following the operation, the patient's hemoglobin concentration fell and then gradually rose to 10 Gm. per cent. In October of 1968, with a stable hemoglobin of 7.6 Gm. per cent, a repeat iron kinetics study was performed which showed increase in effective hemoglobin synthesis associated with splenic sequestration of red cells in excess of splenic erythropoiesis.
P.H., a 10 year old white female, was diagnosed as having Fanconi's anemia in October of 1967. The patient had two older brothers, both of whom had developed classic Fanconi's anemia at ages 3 and 5 years respectively. Physical examination, October 1967, showed pallor, close set eyes and multiple cafe-au-lait spots. Blood count showed a hemoglobin of 6.7 Gm. per cent, hematocrit 18 per cent, red cell count of 1.74 million, retic. count 3.4 per cent, platelets 35,000, white count 2500, primarily composed of mature lymphocytes; one nucleated red cell was seen for every 100 WBC. There was no therapeutic response to pyridoxine, folic acid, B12, or adrenal steroids. By September 1968 the patient's hemoglobin concentration was down to 4.4 Gm. per cent, platelet count was down to 21,000. It was decided to do endosteal curettage of the left femur. Pre-operative total body marrow distribution studies showed patches of marrow in the shafts of the long bone rather than adjacent to the joints as in normal children. Her serum erythropoietin, assayed in hypertransfused mice, was elevated (3.6 IRP units/ml. at hemoglobin concentration of 5.7 Gm. per cent and hematocrit of 15 per cent). On September 27 the left femur was entered through the greater trochanter and the medullary cavity thoroughly curetted the length of the shaft to the distal epiphyseal plate. Two units of platelets were transfused during surgery. Blood loss was minimal and post-operative recovery was uneventful.

Subsequent to the operation, the patient's hemoglobin concentration continued to fall, and by November 1968, it was once again at 4.5 Gm. per cent and the patient was symptomatic and required transfusions. The hemoglobin continued to fall and 2½ months post-operative steroid therapy was recommenced and androgen (Delatestryl—3 ml. IM weekly) was begun. More transfusions were necessary, but 4½ months after surgery and 2 months after institution of steroid and androgen therapy, she developed a remission, maintaining her hemoglobin at 8—9 Gm. per cent.

**RESULTS**

**Fracture**

Increased erythropoiesis has been found in or adjacent to fractures in one dog, two monkeys, and several men. On two occasions newly received adult monkeys were found to have asymmetric distribution of marrow in the legs.
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which corresponded to old and well-healed fractures. Further study showed that not only was there an increase in erythropoietic marrow in and about the healed fracture site, but $^{18}$F uptake (bone blood flow) and Tc$^{99m}$-sulfur colloid (reticuloendothelial marrow) were also markedly increased at the site (Fig. 1).

Stimulation of marrow adjacent to recent fracture in human beings has been observed previously. A patient recently studied for acute idiopathic hypoplastic anemia was found to have abnormal asymmetric peripheral marrow in the legs, which corresponded to the distribution of fractures sustained in an auto accident 12 years previously. $^{18}$F uptake was also asymmetric and similar in distribution to $^{52}$Fe.

Marrow Regeneration after Removal or Removal and Immediate Replacement

In rabbits where marrow was removed and replaced by clotted blood, regeneration, as judged histologically, followed the pattern described first by Röhlich. Regeneration as judged by $^{18}$F (bone blood flow), Fe$^{52}$ (hemoglobin synthesis), and Tc$^{99m}$-colloid (RE phagocytosis) in the group where marrow was not replaced in the evacuated cavity is shown in Figure 2. Bone blood flow ($^{18}$F uptake) increased rapidly to a peak at 10 days. Recovery of reticuloendothelial phagocytosis and hemoglobin synthesis occurred simultaneously at approximately 3 weeks post-operative.

Fig. 1B.—Scintillation camera pictures of the increase in erythropoietic marrow ($^{52}$Fe), bone blood flow ($^{18}$F) and reticuloendothelial marrow (Tc$^{99m}$-colloid) at the fracture site.
Fig. 2.—Rate of regeneration of erythropoietic (52Fe) and reticuloendothelial (Tc99m) marrow and changes in bone blood flow following removal of femoral marrow (open points) or removal and immediate replacement of marrow (solid points).

In the rabbits from which the marrow was removed "intact" and immediately replaced, regeneration was a much slower process and recovery of RE function lagged behind recovery of erythropoietin marrow function (Fig. 2). When rabbits in the marrow replacement group were given 59Fe intravenously and killed one minute later, on the fourth and seventh days post-operative, flow of iron into the bone and marrow at the operated area was 1/100 that of the control femur, indicating infarction of the replaced marrow mass and surrounding bone.

Endosteal Curettage

Dog. Four adult mongrel dogs shown by 52Fe whole body marrow distribution studies to have no erythropoietic marrow in the legs were subjected to endosteal curettage of the right tibia. Pictures of 52Fe distribution taken 30–60 days later showed hemoglobin synthesis in the curetted tibia as compared to the completely inactive unoperated tibia (Fig. 3).

Monkeys. By two days post-endosteal curettage, the earliest time examined, scintillation camera pictures of the monkey's tibia showed a marked increase in bone blood flow (15F uptake) in the curetted tibia as compared to the unoperated leg. This difference became increasingly great until the fourteenth day post-operative. By 30 days the pattern began to revert to normal. No increase in radioiron uptake was observed until 21 days, after which there was a variable increase in radioiron uptake in the marrow of the operated leg, which persisted only transiently (Fig. 4).

Histologic examination at 21 days showed the marrow cavity to be filled with a network of new-formed bone trabeculae, with the first sign of ap-
Fig. 3.—Conversion of completely fatty marrow (left) to red marrow (right) by endosteal curettage of the right tibia of an adult dog. The pictures were taken 45 days post-operative.

pearance of islands of typical hematopoietic cells. Imprints from the fresh tissue were cellular with an occasional typical normoblast. The unoperated tibia contained only adipose tissue.

Four monkeys shown by $^{52}$Fe studies to have erythropoietic marrow in their tibias were given 2000 rad X-rays to one tibia, and in two of them that tibia was subjected to endosteal curettage 3 months later. There was complete absence of $^{52}$Fe uptake in the irradiated tibias prior to curettage and failure of erythropoietic marrow regeneration following curettage. The bone hyperemia (increased $^{18}$F uptake) which characteristically follows curettage of the monkey tibia failed to occur in the radiated portion of the bone (Fig. 5).

Man. In the patient (G.N.) with myelofibrosis receiving endosteal curettage of the left femur, total body marrow distribution studies were repeated 30, 45, and 60 days post-operatively. From the first post-operative examination (30 days) it was apparent that erythropoietic marrow had appeared de novo not only in the distal end of the operated femur but in the opposite femur and throughout the skeleton. The minute amount of marrow previously present in the ankles, shoulder and elbow was increased significantly. The newly
Fig. 4.—Conversion of fatty to red marrow by endosteal curettage. The scintillation camera picture on the left shows the marked increase in bone blood flow ($^{18}$F uptake) in the operated tibia 21 days p.o. The picture to the right shows hemoglobin synthesis ($^{52}$Fe uptake) in the regenerated marrow 32 days p.o.

formed marrow increased somewhat between 30 and 60 days post-operative. Figure 6A shows the total body marrow distribution pre-operatively and Figure 6B shows the pattern 60 days post-operatively. The patient has not required transfusion in 14 months since surgery, the hemoglobin having stabilized at approximately 10 Gm. per cent (Fig. 7).

In this patient $^{18}$F studies done 14 and 37 days post-operative showed slightly decreased uptake in the shaft of the curetted femur. Failure to increase bone blood flow ($^{18}$F uptake) in response to trauma distinguished this patient from normal animals studied (Fig. 8). While the temporal relationship of the patient's hematologic improvement coincided with endosteal curettage, the complexity of this patient's case and this disease in general precludes unique interpretation with regard to therapeutic benefits attendant to this procedure.

Patient P.H., subjected to endosteal curettage of the left femur in an attempt to stimulate marrow regeneration as a therapeutic measure (one of 3 siblings with Fanconi's syndrome), showed the increase in $^{18}$F uptake characteristically seen following trauma to bone (Fig. 9). Following surgery the anemia be-
Fig. 5.—Effect of radiation on hyperemic response of bone to trauma. The monkey on the left had endosteal curettage of the left tibia, resulting in a marked increase in $^{18}$F uptake. The monkey on the right was given 2,000 rad to the proximal 2/3 of the tibia three months prior to curettage. The radiated portion of the bone failed to show the characteristic hyperemia seen in the non-irradiated distal portion.

came more severe and $^{52}$Fe studies showed no stimulation of marrow locally or at other sites, the pattern in the spine being less well defined than prior to surgery. Not only was there no evidence of immediate benefit from curettage in this patient, but the small amount of marrow present in the left femur prior to operation (Fig. 10A) was destroyed by the procedure (Fig. 10B). The remission 4½ months post-operative is attributed to steroid and androgen therapy.

DISCUSSION

Understanding of the mechanisms involved in the control of red blood cell formation has been greatly advanced in recent years by development in the field of endocrine hematology. The erythropoietic marrow is an endocrine target organ. Erythropoietic hormone is not only essential for erythropoiesis to proceed$^{18}$ but the rate of erythropoiesis is dependent on the level of erythropoietin in the blood,$^{19}$ the level of erythropoietin being in turn dependent on the degree of hypoxia present in the tissues.$^{20,21}$

Erythropoietin is distributed by the blood to all parts of the body but erythropoietic marrow is found only in part of the skeleton and often only in a portion of the medullary cavity of a bone. Local non-endocrine factors are clearly of importance in regulation of erythropoietic growth and deserve more
careful scrutiny. Röhlisch’s studies of the relationship between the bone and hematopoiesis in the marrow, demonstrations by Huggins and Blocksom\(^{22}\) that hematopoiesis can be stimulated by heating of the extremities, and Petrakis\(^{23}\) evidence that temperature per se is not the factor, the demonstrations by Knospe et al.\(^{10}\) of the importance of the microcirculation, and Van Dyke’s\(^{4}\) finding of similarity in distribution of skeletal blood flow and erythropoietic marrow suggest that the rate of flow of blood through the bone may be an important factor in regulating the growth of hematopoietic marrow. The existence of a bone-bone marrow portal system of fundamental importance in the regulation of marrow growth has been proposed.\(^{2,4}\) As a result of a series of experiments, Röhlisch concluded that hematopoiesis must be linked to local factors present only in the bone substance, taken up by blood while flowing through the compact bone to be delivered into the bone marrow.
Fig. 6B.—Distribution of $^{52}$Fe (erythropoietic marrow) in patient G.N. 60 days post-endosteal curettage. Note appearance of erythropoiesis in distal ends of femurs and in ankles with some increase in pelvis and shoulder, as compared to pre-operative pattern.

With development of the positron scintillation camera$^{14}$ came methods for in vivo visualization of the relative blood flow to bones (using $^{18}$F ref. 13) and the whole body distribution of erythropoietic marrow (using $^{52}$Fe ref. 24). From the similarity in distribution of marrow in the skeleton and blood flow to the skeleton it was postulated that marrow grows best in blood which has just passed through bone, and the stimulating or essential factor(s) produced in bone are carried directly to the marrow via bone-bone marrow portal vessels. In its simplest form this concept implies that all one would have to do to convert the fatty marrow contained in relatively avascular bones to red marrow would be to achieve chronic stimulation of bone blood flow. Scraping of the endosteal surface of the bones of dogs and monkeys with a sharp curette was found to produce a marked, transient increase in blood flow to the
Fig. 7.—Hemoglobin values on patient G.N. before and for one year following endosteal curettage of one femur.

operated bone accompanied by transient replacement of completely fatty marrow with marrow having some hematopoietic function.

Studies by Röhlich and others\textsuperscript{2,3-10} have demonstrated the series of events and completeness of regeneration in the medullary cavity of rat, rabbit, and dog. Of particular interest in the present studies is the observation that in the rabbit replacement of the marrow (which subsequently becomes infarcted) either specifically inhibits regeneration or replaces some specific stimulatory effect of the blood clot which would otherwise fill the cavity. It should be noted that in the rabbit stimulation of $^{18}$F uptake (bone blood flow) was also delayed when marrow was removed and immediately replaced, as compared to removal without replacement. Brown et al.\textsuperscript{25} have presented evidence of factors present in red cells which are stimulatory to erythropoiesis. Knospe et al.\textsuperscript{10} found in rats that mechanical disruption plus \textit{local injection with bone marrow} obtained from the opposite leg was necessary to induce regeneration of marrow rendered permanently aplastic after irradiation. The effect on regeneration of filling the cavity with different blood and tissue fractions might provide further insight into the mechanisms involved.

Loss of hematopoietic marrow from the extremities occurs as a normal part of maturation in many species including dog, monkey, and man, with conversion of hematopoietic to fatty marrow. Reconversion to hematopoietic marrow frequently occurs in man in response to chronic demand for increased red cell production, such as hemolytic anemia or severe chronic blood loss, or in a variety of diseases where anemia results from destruction or mechanical displacement of central marrow\textsuperscript{26} and in the absence of anemia in polycythemia.
Huggins and Blocksom succeeded in converting fatty marrow to red marrow in the tails of rats by abdominal implantation. Our observation that conversion of fatty marrow to hemoglobin synthesizing marrow occasionally occurs adjacent to fracture suggested that mechanical disruption and irritation with its associated marked increase in bone blood flow might induce such a conversion. Endosteal curettage was chosen as the method for testing this idea. Marked increase of blood flow in the curetted bone was uniformly achieved in the monkeys and in 3 of them small amounts of hematopoietic marrow appeared transiently during the healing process. In 4 dogs curettage resulted in conversion of completely fatty to erythropoietic marrow. These results provided some experimental support to the idea that fatty involution of peripheral marrow results from gradual involution of the blood supply in the peripheral skeleton, a natural process of aging. In dogs and monkeys con-
Fig. 9.—Relative bone blood flow in 10 year old girl 14 days after endosteal curetage of left femur. Note marked increase in blood flow as compared to unoperated right femur. This degree of bone hyperemia was characteristically seen in normal monkeys (Fig. 4), dogs, and rabbits 2 weeks post-endosteal curetage. Version of fatty to red marrow was presumed to result from the marked local increase in bone blood flow resulting from the endosteal irritation.

Chronic Marrow Suppression Following Irradiation

Knospe et al.10 have demonstrated that bone marrow recovery after irradiation occurs only if the sinusoidal microcirculation is not damaged beyond repair. At levels causing radiation fibrosis and irreversible disruption of the microcirculation, the bone marrow remained inactive. Edwards et al.28 have shown complete failure of marrow regeneration in a patient following a less than fibrosing local dose of radiation. The medullary cavity in the radiated area of the pelvis was occupied by completely inactive fatty marrow. Radiation had induced the same change that occurs normally in the peripheral skeleton with age, i.e., replacement of active marrow by fat. Weinstein and Crosby29 have concluded that "the marrow's adventitia is not aggressive: it does not propagate into irradiated areas by its own initiative. Hemopoietic
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Fig. 10A.—Pre-operative distribution of erythropoietic marrow in a 10 year old girl with Fanconi’s syndrome and severe anemia. In children of this age marrow is characteristically distributed throughout the central skeleton and adjacent to joints in the peripheral skeleton. Distribution in this case was abnormal in that peripheral marrow was not found adjacent to joints but in patches in mid-femur and mid-tibia.

tissue, on the other hand, seems to develop wherever there is adventitia to support it.”

Radiation does more than destroy the marrow cells; it renders the site unsuitable for repopulation with marrow. The delayed or permanent radiation inhibition of marrow may be analogous to delayed radiation necrosis in the central nervous system which is thought to be due primarily to slowly progressive vascular degeneration. It is postulated that permanent radiation damage to the marrow can be explained as permanent damage to the bone-marrow portal vessels, diminishing flow below that needed to support marrow growth. Kenner and Jee30 and Jee et al.31 have demonstrated a marked decrease in vascularity in dogs given bone-seeking isotopes. The reduction in vascularity was dose and time dependent.

In the present study radiation abolished the characteristic hyperemic response of monkey bone to trauma (endosteal curettage). To what extent radiation-induced injury to the microcirculation of the bone is responsible for permanent failure of the contained marrow deserves further study.

Endosteal Curettage as a Therapeutic Measure

To date 8 patients with severe anemia secondary to marrow failure have been subjected to endosteal curettage in an attempt to stimulate marrow regeneration, 2 in this study and 6 from the Lovelace Clinic. Those previ-
Previously reported by Wimer from the Lovelace Clinic have been reevaluated and a sixth case added. Four of Wimer's cases and one from this laboratory have improved significantly following endosteal curettage. In only one of the patients studied by the \( ^{52}\text{Fe} \) total body marrow distribution technic has there been regeneration of erythropoietic marrow at the operative site (Wimer's case #5, ref. 32). The one patient in this series who clearly improved following endosteal curettage showed an increase of marrow in peripheral sites in the skeleton. It is apparent that the response in this patient was quite different from that in the dog and monkeys and was unpredicted. In the dog and monkeys new marrow formed in or immediately adjacent to the area of operation. In this patient stimulation of marrow bilaterally symmetrically at several sites distant from the curetted area (ankles, distal femur, and to some extent pelvis, shoulder, and elbow) was unpredicted. By comparing Figures 6B (marrow distribution) and 8 (bone blood flow) it is apparent that marrow regeneration occurred in those parts of the skeleton receiving the greatest blood supply.

If improvement in this patient resulted from the operation and was not just coincidental, the explanation must assume a generalized effect such as a blood borne effect.

Since it is well-known that removal of the marrow institutes a series of events morphologically comparable to embryologic development of the mar-

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**Fig. 10B.—Distribution of erythropoietic bone marrow in patient P.H. 5 weeks post-endosteal curettage of left femur. Note curettage resulted in loss of the small amount of marrow present in the operative area without gains elsewhere.**
row, it is remotely possible that endosteal curettage induced proliferation of primitive marrow precursor or "stem" cells which in this patient migrated to areas throughout the skeleton most richly supplied with blood. Lord has found a 1500 times enrichment of the repopulating cells in the buffy coat cells of rats irradiated 6 days earlier with both hind limbs shielded. Perhaps endosteal curettage has stimulated a similar outpouring of stem cells into the circulation of these patients. This reasoning implies that the defect in these patients was an inadequate stem cell population which was somehow improved by endosteal curettage, medullary or extramedullary sites being adequate to support them after dispersal through the bloodstream.

**Summary and Conclusion**

The present series of studies were designed to examine the effect of artificially altered bone blood flow on activity of the contained marrow. In normal animals bone blood flow was increased locally by fracture, endosteal curettage, and following mechanical disruption of the marow. Local stimulation of erythropoietic marrow was demonstrated following each procedure. Local injury to bone circulation followed high doses of radiation and resulted in permanent marrow aplasia.

Attempts to apply the implications of these studies to therapy of two patients with marrow failure produced inconclusive results. One patient with severe anemia due to idiopathic myelofibrosis improved abruptly and significantly following endosteal curettage of one femur. Unexpectedly there was no demonstrable increase in blood flow in the operated bone and improvement in marrow occurred in skeletal areas other than the operative site.

In a second patient with severe anemia and Fanconi’s syndrome, endosteal curettage of one femur resulted in a marked local increase in bone blood flow with no evidence of stimulation of marrow locally or at other sites and no improvement in clinical condition until institution of androgen therapy.

Further clinical trials of endosteal curettage as a therapeutic measure would appear to be justified.

**SUMMARIO IN INTERLINGUA**

Le serie de studios hic presentate esseva concipite con le objectivo de examinar le effecto de un artificialmente alterate fluxo ossee de sanguine super le activitate del continite medulla. In animales normal, le fluxo ossee de sanguine esseva augmentate localmente per fractura e curettage endosteal e post un disruption mechanic del medulla. Le stimulation local del medulla erythropoietic esseva demonstrate post cata-un del proceduras. Alte doses de radiation esseva sequite de disturbationes del circulation ossee e resultava permanente aplasia medullari.

Effortios de applicar le lectiones de iste studios al therapia de duo patientes con disfallimento medullari produceva resultatos inconclusive. Un patiente con anemia sever causate per myelofibrosis idiopathic se meliorava abruptemente e significativemente post curettage endosteal de un femore. Inexpectatemente, nulle demonstrabile augmento del fluxo de sanguine occurreva in le osso operate, durante que le melioration del medulla occurreva in areas del skeleto altere que le sito del operation.

In un secunde paciente con anemia sever e syndrome de Fanconi, le curettage endosteal de un femore resultava in un marcate augmento local del fluxo ossee de sanguine con nulle evidentia de stimulation del medulla al sito del operation o alterubi e nulle melioration in le condition clinic.
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**ADDENDUM**

Since preparation of this manuscript, endosteal curettage has been applied unsuccessfully to two additional patients. A 74 year old woman with idiopathic myelofibrosis and myeloid metaplasia died with pneumonia 7 weeks post-operative. Histologic examination of the curetted femur showed unresolved clot.

A 70 year old man with acute idiopathic myelofibrosis and myeloid metaplasia deteriorated progressively following curettage of the left ilium. He developed acute leukemia 5 months post-operative and died 2 months later.

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**REFERENCES**

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