CLINICAL SECTION

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Modern Methods for Quantitation of Red Blood Cell Production and Destruction: Erythrokinetics

PARTICIPANTS


EDITOR: It is generally considered that anemia results from an imbalance between production and loss of red blood cells. Methods used to evaluate production consisted at one time chiefly of bone marrow examinations and reticulocyte counts. Loss of blood was detected by obvious signs of hemorrhage, or presumed from indirect evidence. Destruction of erythrocytes has been estimated by such determinations as serum bilirubin, erythrocyte fragility, fecal and urinary urobilinogen, and the Ashby differential red cell agglutination test. In recent years, with the development of isotope technics, new methods have been devised and old ones modified, to probe further into the mechanism of the various anemias. These methods have also enabled us to semi-quantitate erythropoiesis and hemolysis. Thus, the anemia of thalassemia major, which has been looked upon as mainly a result of increased hemolysis now appears, on the basis of these isotope studies, to be largely due to ineffective erythropoiesis. The importance of extramedullary hemopoiesis as a compensatory mechanism needs also to be reconsidered in the light of the concept of "effectiveness" of the hyperplastic marrow rather than on its quantity alone.

In table 1 are listed the methods commonly used in studying erythrokinetics, the general term designed to indicate the quantitation of red blood cell production and/or destruction. We are indebted to Dr. Clement Finch for assistance in planning this discussion and in formulating the questions. We shall begin by asking the members of the panel: What technics do you consider useful in the clinical study of the "problem" anemic patient? Which ones, in your hands, supply you with the greatest information in the majority of such patients?

FINCH: The clinical approach to a quantitation of erythropoiesis has been recently summarized (J. A. M. A. 1961). Briefly, it consists in the evaluation of effective erythropoiesis by the reticulocyte count, and when necessary total erythropoiesis from the erythroblast/myeloid (E/M) ratio or plasma iron turnover (when elevated), and red cell utilization (when depressed). The re-
ticulocyte count, expressed in absolute numbers and corrected for marrow shift when present, is usually adequate to indicate whether there has been a normal response to anemia. Thus, if the corrected reticulocyte count is three to six times normal in the anemic patient, marrow function is adequate. If it is below this figure, the erythroid/myeloid ratio is estimated by inspection of the stained smear of marrow aspirate to determine total erythroid marrow activity. Such a ratio is valid, of course, only in the presence of a normal white cell mass. Plasma iron turnover and red cell utilization are employed when marrow examination is unsatisfactory, or when a higher degree of quantitation is required. The reticulocyte count, marrow examination, and plasma iron turnover are preferred in the clinical evaluation of anemia because they may be completed without time delay.

WASSERMAN: In our laboratories the technics used in the clinical study of obscure anemias include all those noted in table 1 except for cholinesterase and CO elimination. In addition, specific metabolic deficiencies or derangements, viz., vitamin B12, folic acid, hemoglobinopathies, etc., or immunologic problems, are investigated by additional methods (microbiologic assay of serum, hemoglobin and serum electrophoresis on paper, starch gel and acrylamide; red cell enzymes, antibodies, etc.) when indicated by initial screening examinations. Although no single examination or battery of tests can be relied upon consistently to give all the information required, we have found careful evaluation of the peripheral blood and bone marrow, fecal urobilinogen and red cell survival and sequestration studies to be the most useful. Thus, the morphology of the red cells, whether there be target cells or spherocytes, macrocytes or microcytes or the bizarre forms seen in extramedullary hemopoiesis, may be the first clue to the subsequent tests required for elucidation of the underlying cause of the anemia. Fecal urobilinogen excretion, which measures total heme production rather than peripheral erythrocyte destruction as commonly interpreted, may reveal increased pigment turnover in the absence of reticulocytosis and only slight alteration in the mean cell life of the red cell; pernicious anemia is an example of this type of derangement. In those anemias where minimal aberrations exist in hemoglobin production, in delivery of erythrocytes into the circulation, or in peripheral hemolysis, every test available may be required to resolve these borderline problems.

CROSBY: In contemplating any case of anemia, one's approach may be systematized by recollecting that the mass of circulating red cells (M) is a function of the rate of production (I = input) and the average life span of the cells (T = time).

\[ M = IT \]

Anemia represents decreased M; therefore it is a result either of decreased population, as in hypoplastic disease of the marrow, or of shortened life span as in hemolysis or hemorrhage, or both. When M remains constant it can be assumed that production and destruction are equal. Anemia does not necessarily imply an imbalance. With this concept as a background, the procedure which provides the greatest information is measurement of the red cell life
span. It is of help in dividing the anemias into two categories, those in the basis of “I” and those in the basis of “T”.

HAURANI: Currently we are using six measurements, namely reticulocyte count, bone marrow examination, fecal urobilinogen, plasma iron turnover, radioiron utilization and Cr$^{31}$ red cell survival, in the study of anemia. Limitations inherent in the employment of these diagnostic tools and in the interpretation of the results representing erythropoiesis or red cell destruction in all types of anemia have made it advisable to rely on as many technics as possible. As a state of equilibrium is reached between production and destruction of red blood cells, any of the measurements mentioned above could express production or destruction if it is related respectively to the patient’s expected hemoglobin mass (or red cell mass) or to his actual hemoglobin mass. For example, a patient with a red cell count of 2.5 mil./cu.mm. (assuming a normal of 5 mil./cu.mm.) who has a destruction rate of 4 (times the normal) as computed from the Cr$^{31}$ red cell survival technic, must have a production rate of 2 to be able to maintain a red cell count of 2.5 million (about 50 per cent of normal).

STOHLMAN: A distinction should be made between the investigation of mechanisms (e.g., thalassemia as referred to in the opening remarks) and routine clinical study for diagnosis and treatment. I shall confine my remarks to the management of patients. Generally, the relative importance of hemolysis and decreased production in the anemic patient can be established from a careful history, physical examination, and laboratory tests including indices, reticulocyte count, morphology of the peripheral blood, serum iron and iron binding capacity, serum bilirubin and, when indicated, electrophoresis of the hemoglobin. Bone marrow examination is helpful in distinguishing the “refractory anemia” with a hypercellular marrow from true aplasia, but adds little to management. In a patient with marked reticulocytosis and clear-cut evidence of hemolysis, the bone marrow examination contributes little. Evaluations based on transfusion requirements are particularly useful but occasionally may be misleading, since transfusions alter not only the steady state but the rate of cell production. Even in the anemic subject, an increase in hemoglobin from e.g. 7 to 9 Gm. will affect the rate of erythropoiesis. Accordingly, changes in the steady state must be taken into account or erroneous conclusions will be reached. Since hemoglobin derived from intramarrow destruction of cells (ineffective erythropoiesis), hemolysis or “internal” hemorrhage all contribute to fecal urobilinogen, this measurement is of limited value in assessing the relative roles of “production” and “destruction”. Usually there is no single test which will give the answer, rather the diagnosis is based on an evaluation of facts derived from a number of sources.

EDITOR: Through most of us employ essentially the same methods in studying the “problem” anemic patient, there seem to be personal preferences for different tests as being the most informative. How much, then, do the measurements listed in table 1, contribute to the differential diagnosis of anemia?
Table 1.—Methods for Quantitation of Red Cell Production and/or Destruction

<table>
<thead>
<tr>
<th>Determination</th>
<th>Normal values</th>
<th>Probable principal function tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroid myeloid ratio</td>
<td>1:3</td>
<td>Production; total erythropoiesis</td>
</tr>
<tr>
<td>Plasma iron turnover (mg./day)</td>
<td>25–50</td>
<td>Production; total erythropoiesis</td>
</tr>
<tr>
<td>Red blood cell iron utilization</td>
<td>20–40</td>
<td>Production; effective erythropoiesis</td>
</tr>
<tr>
<td>Reticulocytes (%)</td>
<td>0.1–1</td>
<td>Production; effective erythropoiesis</td>
</tr>
<tr>
<td>Cholinesterase (μM per min. per ml. RBC)</td>
<td>9.7–10.5</td>
<td>Production; effective erythropoiesis</td>
</tr>
<tr>
<td>Fecal urobilinogen (mg. day)</td>
<td>150–250</td>
<td>Destruction</td>
</tr>
<tr>
<td>Red cell survival* T 2 (days)</td>
<td>23–33</td>
<td>Destruction</td>
</tr>
<tr>
<td>CO elimination (COHb)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.54 ± 0.02%</td>
<td>Destruction</td>
</tr>
<tr>
<td>Women</td>
<td>0.47 ± 0.02%</td>
<td>Destruction</td>
</tr>
</tbody>
</table>

*Cr51 method.

Under what circumstances are they of help in supplementing the more conventional morphologic studies?

FENCH: Morphologic studies are of use in detecting general abnormalities in erythropoiesis characterized by increased intracellular hemoglobin production (macrocytic anemias) and decreased intracellular hemoglobin production (microcytic anemias) and in detecting certain structural abnormalities associated with hemolytic disorders (sickle cell, spherocyte, etc.). Erythrokinetic measurements are of greatest use in the normocytic group of anemias and serve to differentiate between anemias due to inadequate stimulation of marrow, those due to marrow abnormality, and those due to increased red cell loss through hemolysis or hemorrhage. More specifically, measurements of total erythropoiesis (E/M ratio and plasma iron turnover) indicate whether the magnitude of marrow response is normal and, therefore, whether proper stimulation of the marrow has occurred and whether the marrow has the capacity to proliferate. Measurements of effective erythropoiesis (reticulocyte count and red cell utilization of radioiron) indicate whether the marrow activity is reflected in a similar production of circulating red cells. A comparison of measurements of effective and total erythropoiesis indicate whether marrow dysfunction is present. Increased red cell loss may be evaluated by the Cr51 technic, but the differentiation between hemorrhage and hemolysis involves the demonstration of pyrrol pigment excess in the latter.

WASSERMAN: These tests are helpful in semi-quantitating and delineating those anemias due to heme production failure from those due to increased destruction of blood. It is, of course, implicit in any discussion of laboratory tests that one understands the physiologic function to be tested by a particular technic. Thus, "total erythropoiesis" (or heme turnover) may be measured by:

(a) myeloid/erythroid ratio and marrow cellularity;
(b) fecal urobilinogen excretion;
(c) plasma iron turnover.
Whereas "effective erythropoiesis" can be studied by:

(a) reticulocyte count;
(b) red cell radioiron utilization;
(c) red cell survival.

These tests supplement the more conventional studies when a disparity exists between morphologic evidence of marrow activity and the presence of a diminished circulating red cell mass (as in "refractory" anemia with a hyperplastic marrow). It is obvious that a modest decrease in red cell survival to 70 or 80 days should not bring about an anemia unless some degree of "marrow failure" is present. Similarly a reticulocytosis of 5–15% may be seen in leukoerythroblastic anemia associated with myelofibrosis or metastatic marrow involvement, without any significant change in mean red cell life-span. In these and similar instances, every parameter possible must be measured and evaluated.

CROSBY: The other measurements listed in table 1 are also of value in studying the rate of red cell turnover, provided one is aware of their limitations. In the same patient without variation of erythrokinetics as determined by other parameters, the fecal urobilinogen may vary from 400 to 2000 mg per day even when four-day collections are pooled. Reticulocyte counts may be normal when red cell production is more than five times the normal rate. Plasma iron turnover is not an adequate index of hemoglobin synthesis when large numbers of siderocytes are involved. It is unfortunate that these crude measurements are sometimes used in formulas and the results dignified by the term "index," with its implication of mathematical precision which may be misleading.

STOHLMAN: In part this has been considered above. Some of the values in table 1 would not be considered normal in our laboratory. Our reticulocyte values vary from ~0.5–1.5% per cent. Occasionally a value outside of this range is seen in a normal individual. Repeated reticulocyte counts of 0.3 per cent, however, would be considered abnormal while values of 1.2 per cent would not. The E/M ratio has a range of perhaps 1:2–1:4. While fecal urobilinogen measurements are not done too frequently, the values given by Watson and Wintrobe of 40–280 mg per cent are considered within normal limits. The value of a technic varies with the disease. One of the most useful tests among those listed is the reticulocyte count. The bone marrow examination gives useful qualitative but rarely quantitative information. The relative proportion of erythroid-myeloid elements depends upon a number of factors, including generation times, maturation rate, extent of intramarrow cell death, and time of release of cells. Measurements of cholinesterase activity in our hands have been most unsatisfactory. Cr51 and Fe59 are primarily of value in clinical research but seldom provide information essential for diagnosis or treatment.

HAURANI: Employment of the technics listed in table 1 in the study of various types of anemia has enabled us to quantitate destruction and production of
the red blood cells and how much each contributes to the level of the anemia. The term "high output failure of the bone marrow" has been introduced to describe anemias where in spite of an increase in erythropoiesis, the bone marrow is still unable to compensate for hemolysis. As a result of these techniques, the term "ineffective erythropoiesis" or dysfunction of the bone marrow, has been introduced to describe certain hematologic disorders. In these, there is a discrepancy between the total red cell mass and/or hemoglobin mass in the peripheral circulation (effective erythropoiesis) and red cell production in the bone marrow (total erythropoiesis) unexplained by hemolysis or hemorrhage. For example, a marked increase in fecal urobilinogen despite a slightly altered Cr tagged red cell survival time indicates a state of ineffective erythropoiesis. In this instance, the increased fecal urobilinogen does not necessarily mean an increased destruction of circulating red cells. The same thing applies if an increased plasma iron turnover is associated with poor red cell utilization of iron.

**EDITOR:** It seems that most of the participants feel that some of the tests listed in table 1 do have a place in the study of anemias, especially in the group in which other diagnostic clues are unavailable or of equivocal significance. Three techniques have been often mentioned, the reticulocyte count, the plasma iron turnover and the Cr tagged red cell survival. What manner of expression of these findings do you prefer and what do you consider to be the chief limitations of each method?

**FINCH:** Measurements of erythropoiesis must be so expressed as to permit comparison between individuals of different size, and with different degrees of anemia. One is not interested in the absolute amount of blood produced or destroyed per day, but in the amount in relation to normal. Our preference is to express plasma iron turnover as mg./100 ml. whole blood/24 hours (normal 0.6 mg.). Reticulocyte count is corrected to its value with the patient's hematocrit over normal (Patient's reticulocyte count × patient's hematocrit / normal hematocrit).

Cr red cell survival is similarly corrected for red cell mass in expressing the amount of blood destroyed:

\[
\frac{60}{\text{Cr}^{51} \text{ survival corrected for elution (T} \frac{1}{2} \text{ in days)}} \times \frac{\text{patient's hematocrit}}{\text{normal hematocrit}}
\]

The limitation of any given method in general relates to the specific aspect of erythrokinetics which it measures, i.e. production or destruction, effective or total erythropoiesis. The reticulocyte count is certainly the best all around clinical measurement. Plasma iron turnover is only useful for quantitating increased erythropoiesis. The Cr red cell survival is of limited usefulness because of the time required for its performance.
WASSERMAN: Plasma iron turnover is expressed in mg./24 hours, or in half-time of plasma radioiron disappearance, reticulocyte count in per cent or index, and chromium survival in half-time or mean cell life. The plasma iron turnover is influenced by many factors, viz., plasma iron, size of iron stores, diurnal variation, rate of hemolysis, plasma volume, etc. In hemochromatosis the plasma clearance of radioiron may be normal yet the turnover per day derived from the plasma iron, the rate constant, and the plasma volume, may indicate increased hemoglobin synthesis which is at variance with all other studies. Conversely, in extramedullary hematopoiesis the plasma radioiron turnover may be extremely high in the presence of marked marrow fibrosis. In blood dyscrasias the clearance of plasma iron is rarely, if ever, exponential and complicated multiple pool analysis is required to obtain accurate quantitative information.

The limitations to the method are: (1) There must be an erythropoietic steady state during the study. (2) Plasma volume must be determined directly and not derived indirectly from measurement with tagged red cells. (3) One-pool analysis does not consider the varying rates of iron exchange from different pools in complicated cases; complex three and four-pool analysis is required to obtain quantitative data.

Reticulocyte counts are reliable indices of “effective erythropoiesis” only when there is normal production, maturation and delivery from the marrow into the circulating blood. Chromium tagged red cell survival may be affected by varying elution times from abnormal red cells and particularly by blood transfusions administered during the period of observation.

CROSBY: I prefer that plasma iron clearance and Cr$^{51}$ RBC survival be expressed as half-time and reticulocyte counts be expressed as percentage of red cells. Any more elaborate analysis should be made by the hematologist himself. The shortcomings of the iron clearance and reticulocyte counts as measures of red cell turnover were mentioned in the answer to the previous question. The Cr$^{51}$ method is flawed by the problem of “elution” of the isotope. However, when the life span of the cells is short, the contribution of elution to the biological decay of radioactivity is relatively small. When 50 per cent of the cells are lost in a week, it is of little significance that in addition 10 per cent of the isotope is also lost.

HAURANI: For practical purposes it will suffice to express the plasma iron turnover in terms of mgs./day and the Cr$^{51}$ tagged red cell survival in terms T/2 in days. However, for quantitation and comparison it would be more consistent, if not precise, to express the plasma iron turnover in terms of mgs./day/Gm. of Hb. (patient’s actual or expected hemoglobin mass) and the Cr$^{51}$ red cell survival in mean days, where the normal is 120 days. There are tables that could be used for the conversion of Cr$^{51}$ half-life survival of red cells to mean cell life. The reticulocyte count could be expressed either in percentage or in absolute numbers.

Since the plasma iron turnover is a function of total plasma iron and the
clearance rate of radioiron, then limitations inherent in the measurement of plasma volume and plasma iron would influence the plasma iron turnover determination. Large spleens do not seem to influence directly the radioiron clearance rate. Diseases that primarily influence the iron storage do make interpretation of plasma iron turnover difficult, e.g. in iron deficiency and primary hemochromatosis, the plasma iron turnover is not a correct measure of total erythropoiesis. The same thing applies to extramedullary hemopoiesis where in most cases is low normal, if not actually low.

STOHLMAN: It is not possible to quantify erythropoiesis with either the plasma iron turnover or the iron turnover technic originally described by Huff and co-workers (J. Clin. Invest. 29:1041, 1950). The best estimates are gained with a multicompartment model necessitating a mathematical analysis which is beyond the scope of most clinical laboratories. The removal of iron from the plasma is not a simple exponential function but involves recycling from the tissues; this leads to a curvilinear plot on semilog paper; the degree of non-linearity or recycling varies between individuals, but in our experience has been most marked in pathologic studies. The serum iron varies substantially throughout the day, indicating changing clearance and recycling rates. The Fe59 estimates depend upon the assumption that all of the iron eventually appearing in labeled cells is incorporated during the period in which plasma clearance is measured; in many instances, particularly in pathologic studies, this is not the case. When there is substantial intramarrow cellular death, much of the Fe59 reaching the periphery may have been recycled either within the marrow by rouphoecytosis (Policard and Bessis: C. R. Acad. Sci. 246:3194, 1958) or through the plasma. Marked hemolysis affects the interpretation of iron studies in a similar fashion. The main clinical use of Fe59 is the evaluation of extramedullary erythropoiesis, or to derive a rough estimate of the extent of effective erythropoiesis in the patient with reticulocytopenia and a cellular marrow. Due to the above restrictions, the plasma iron turnover is not an accurate guide in evaluating ineffective erythropoiesis (intramarrow cell death); the reticulocyte count or red cell iron incorporation curve together with bone marrow examination are generally more reliable. Ineffective erythropoiesis can occur in several forms: (A) cells die primarily in the later stages of erythropoiesis, (B) cells die in the earlier stages producing "Maturation arrest", e.g. at the pronormoblast level; (C) cells die throughout the maturation process. The plasma iron clearance will be affected by the type of "ineffective erythropoiesis" occurring. In one patient of type B the T/2 of clearance was ~270 minutes; in another with type C the T/2 was ~30 minutes. In both, the red cell incorporation was <10 per cent and the serum iron ~180 y. Whether C is more ineffective than B is perhaps a philosophical question. However, I view the earlier destruction as being more ineffective. In most instances the reticulocyte count and bone marrow examination will give enough information for the clinical evaluation of red cell production in anemias. In following drug responses, whether for toxic effects, e.g., from chloromycetin or specific therapy (e.g. B12), reticulocyte counts are quite valuable. The best estimates of the rate of destruction of red cells are gained
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with DFP^{32} labeling. The expense and potential toxicity, however, limit its general clinical application. Due to elution, Cr^{51} does not permit precise quantitative estimates of red cell destruction. When hemolysis is severe the rate of elution may not substantially change the estimate of destruction, provided one can be assured that Cr^{51} does not affect cell survival and the pathologic state does not affect Cr^{51} elution. However, there is really no need for survival measurement under such circumstances; it should be evident from a variety of studies that the patient is hemolyzing (or bleeding). Any significant change in the rate of cell loss is also easily recognizable. When mild hemolysis is present, accurate survival studies are helpful. It is unfortunate that under such circumstances Cr^{51} determinations are least reliable; the normal variation of Cr^{51} elution between individuals together with skewing of the cell age distribution in chronic hemolysis may lead to erroneous conclusions. Cr^{51} studies may help in evaluating a patient for splenectomy, where indications from the general clinical picture are not clear-cut. It is also useful in determining the significance of rare blood antibodies and in deciding whether hemolysis is limited to the patient's cells (intracorpuscular defect) or whether donor cells will be similarly affected. We express chromium values as the initial apparent half-time.

EDITOR: The manner of expression of the results obtained from the chief tests of red cell production varies from worker to worker. The limitations of the technics appear to depend largely on the particular use made of them by each observer and his own interpretation of the meaning of the tests. Now, we should like to ask what do you consider to be contraindications to in vivo studies with radioactive iron and chromium?

FINCH: This question relates to the permissible dosage of isotopes in the pregnant woman or infant. Radiation exposure is always a relative matter depending on the amount of isotopes given, and the importance of the information to be obtained. Our calculations of total radiation from the usual dose of 0.1 μc./Kg. of Fe^{59} would be 0.33 roentgens total radiation to marrow.

WASSERMAN: Contraindications to the use of radioiron and chromium are few, assuming AEC regulations are followed. It is important that an erythropoietic steady state exist, if such studies are to be meaningful. Changes in blood volume incident to transfusions may disturb the results and hence should be avoided, if possible.

CROSBY: We consider as contraindications to the use in vivo of radioactive iron and chromium: (a) infancy, (b) pregnancy, (c) prior use of isotopes to limit of permissible dose and (d) inadequacy of counting equipment. Fe^{59} and Cr^{51} should not be used both at once if the available equipment cannot differentiate between the two.

HAURANI: We have observed no immediate toxic reactions from the use of Fe^{59} and Cr^{51}. That these agents in minute amounts may have some delayed
carcinogenic or myelo-depressive effect is very unlikely. However, we have not used them in children who have non-malignant diseases.

STOHLMAN: Two risks are associated with the use of Fe59 and Cr51: hepatitis, when homologous cells or plasma are used, and radiation. The risk of hepatitis can be estimated from its incidence after transfusion; the possible hazards from radiation are more difficult to assess. Nevertheless, the use of isotopes is warranted whenever information essential to diagnosis or treatment can be obtained only with isotopes and the measurements can be adequately interpreted. The use of an isotope should not be considered as an isolated event but rather as contributing to a total radiation exposure, which in many patients may be appreciable. Accordingly, the dose used should be kept as low as possible.

EDITOR: It seems that efforts to approach the problem with the modern technics discussed will prove rewarding in certain anemias due to obscure causes. It must be acknowledged, however, that the "tried and true" methods of evaluating the causes of the anemias must still depend, in a large measure, on the information obtained from a careful, painstaking history, physical examination and a few simple, well-chosen laboratory procedures. The narrow range of general usefulness of the more elaborate studies tends to restrict their general application and suggests that they be resorted to only when the exhaustive use of the simple methods has failed to provide the information desired. Dr. Dameshek, with your clinical and investigative experience in mind, what do you think of this discussion?

EDITOR-IN-CHIEF: I must say it has been of unusual interest. There can be no question as to the growing value of the isotopes in hematology, as in other fields. Whether or not they are always essential for the appropriate or "complete" study of a case with anaemia may be debated. Certainly they should not be used routinely in every case, which implies that careful selection of tests and indications should always be made. Many times, isotope studies give us results which are simply confirmatory of other findings—which is all to the good, of course. That they are actually far superior to other diagnostic methods may be debated, at least in some instances. It seems that to doubt the perfection of the electronic machine of today is almost tantamount to doubting the religious dogma of two or three centuries ago. One realizes that this is a reactionary attitude, but reaction seems necessary at this point.

Let it not be said that we do not use the isotope machines or heed the oracular results obtained from these sleek and beautiful instruments. For example, in the tests for red cell survival, iron clearance, and iron incorporation, we have important methods which are not only confirmatory, not only of value in studying pathophysiologic mechanisms, but occasionally of more practical diagnostic and therapeutic importance. This is particularly true when the bone marrow examinations do not give the entire picture regarding the degree of erythropoiesis present within the body. Active centers of red cell
formation may elude the bone marrow aspiration or biopsy in cases of hypoplastic anemia, yet be detected by the results of the Fe\textsuperscript{59} clearance determination. On the other hand, such testing can be overdone and although numbers are plain enough, results may not be quite as accurate as they seem. The interpretive brain is still a much needed commodity. Thus one would agree with both the forthright and implied comments of Stohlman, Crosby, and Wasserman that indices of red cell production and the like are alright in their place, but that they must be based upon something more solid than quicksand.

The increasing availability of the isotopes and their associated paraphernalia (and perhaps their importance as status symbols) have led to their use in many non-university centers, even in relatively small local or regional hospitals. One would not wish to decry the wisdom of the internists and hematologists of these and other areas in using these tests, but how often are they really necessary? Isn't it about time, therefore, to have a thoughtful reappraisal—as has been done in this panel—of what isotopes can do for us, rather than what we can do with the isotopes.—W. D.