match, however, the first day's urine counting seemed to provide enough information to predict the compatibility of the blood. Although all urine samples were grouped into 24-hr collections in this case, if earlier results had been designed as in blood sampling method, it would have been possible to quantitate the first voided specimen separately to rule out major incompatibility and hemolysis.

A potential problem that may cause underestimation of hemolysis is sequestration of the tagged RBC, i.e., disappearance from the blood stream without hemolysis and subsequent ^{51}Cr appearance in the urine. However, in practice, this is unlikely to cause much of a problem, since this test was developed on the basis of differentiation of a series of hemolytic patients with sequestration, normal subjects, and patients with gastrointestinal bleeding.

The urine-counting method can also provide an easy way to monitor the ^{51}Cr-labeled transfused red cells by subtracting the expected counts of the previous cross-match.

We presented a rare case of anti-Ge in which in vivo cross-matching was successfully performed by counting ^{51}Cr from labeled erythrocytes excreted in the urine. This RBC survival test provided an easy and accurate means for in vivo cross-match of donor blood that was incompatible when tested in vitro.

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Editorial
In Praise of the Mighty Red Cell

In the course of examining the formulary of diagnostic radiopharmaceuticals, a few agents stand out for their demonstrated versatility and durability. The radiolabeled human erythrocyte is one such agent. In the 48 years that have elapsed since Nobel Laureate George de Hevesy introduced phosphorus-32- (^{32}P) labeled erythrocytes for the determination of blood volume in patients, investigation of the mechanistic aspects of labeling produced advances in methodology which led to thoughtful application of radiolabeled red cells to routine, as well as unique clinical problems. The fact that this level of interest continues today is demonstrated by two articles in this issue of the *Journal*: Mochizuki et al. describe a case in which the creative application of a diagnostic study with chromium-51-labeled red blood cells (RBCs) was possibly lifesaving for the patient by making available a source of blood for transfusion that would have otherwise been thought to be unusable in this patient, and the second describes the role of anion transport on technetium labeling.

The literature reveals a total of 13 radionuclides that have been used to label human erythrocytes: phosphorus-32, chromium-51, carbon-14, iron-55, iron-59, mercury-197, mercury-203, rubidium-81, carbon-11, indium-111, technetium-99m, gallium-67 and gallium-68. A small number of these have been used in humans for:

1. The measurement of RBC volume.
2. Measurement of RBC survival time.
3. Identification of sites of RBC destruction.
4. Blood pool imaging.
5. Selective spleen imaging with damaged RBCs.
6. In vivo cross-matching of donor blood.

It was the introduction of the chromium-51 technique by Sterling and Gray in 1950 that brought radiolabeled red cells into the clinical arena, paved the way for routine evaluation of red cell volume and

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For reprints contact: Ronald J. Callahan, PhD, Massachusetts General Hospital, 32 Fruit St., Boston, MA 02114.

kinetics, and began the investigation of labeling mechanisms which continues today.

Many aspects of the history of radiolabeled RBCs are impressive and have taught us much about radiopharmaceutical chemistry. Early attempts to label RBCs with technetium were minimally successful and often nonreproducible. It was not until the introduction of the stannous ion as a reducing agent that ^{99m}Tc-labeled RBCs began to flourish. This, in fact, was one of the earliest applications of the now ubiquitous stannous ion in radiopharmaceutical chemistry. Even with the advent of stannous reduction, the methodology was cumbersome and time-consuming. Pioneering work at Brookhaven National Laboratories resulted in the development of an in vitro kit for the labeling of RBC with ^{99m}Tc in 1974. The in vivo behavior of ^{99m}Tc-RBCs labeled by this kit has become the standard to which all other methods are compared. Yet, few institutions use this agent even today. Any objections to the multiple steps, including centrifugation, involved in the original method have been removed by a very clever modification in which extracellular stannous ion is oxidized to stannic ion by the addition of sodium hypochlorite (bleach), thus, eliminating the need for centrifugation. Studies on this kit first suggested that the amount of ^{99m}Tc in a generator eluate could effect the radiopharmaceutical chemistry of a product. This phenomenon is now widely accepted and is a major concern for some of the newest radiopharmaceuticals. Yet, 16 years and many modifications later, there is still no approved product for the in vitro labeling of red cells with ^{99m}Tc. One manufacturer has brought a kit to clinical trials, a major step to drug approval, but historically we know that we have a long wait ahead.

Whereas the in vitro methods were developed along a line of continued research, in vivo methods were the result of insightful applications of a causal observation. One of the first drug interactions reported with diagnostic radiopharmaceuticals was the altered biodistribution of [^{99m}Tc]pertechnetate in patients who had previously received ^{99m}Tc-stannous pyrophosphate for a bone scan. The distribution shift from extracellular to intravascular was described as a potential pitfall to image interpretation and was to be avoided. Later investigations showed that this intravascular retention was due to labeling of RBCs in vivo. The in vivo methods were rapidly applied and quickly became the method of choice. This rapid acceptance of the method is, in part, attributable to the fact that all components are readily available, in approved forms, and are applied without much regulatory scrutiny. Subsequent modifications have attempted to improve the in vivo behavior of labeled RBCs with some success. Clearly, the in vivo methods enjoy the most widespread use today. In fact, with the exception of ^{111}In-labeled plasma proteins, RBCs remain the only radiopharmaceutical which is routinely labeled in vivo or in vitro even in the face of much effort to find in vivo methods for labeling other blood components.

Another unique aspect of radiolabeled RBCs is that their biodistribution can be selectively altered by controlled chemical or thermal damage to permit high resolution imaging of the spleen. Although selective spleen imaging is not commonly performed today, this technique when first introduced was indeed creative, innovative, and of great clinical significance.

The radiolabeled RBC has been carefully studied and has taught us about the sub-cellular and molecular aspects of the product. Whereas a crystal structure of the radiopharmaceutical product might be the end point in its chemical understanding, the red cell provides many different layers for investigation. These include intracellular binding sites, intracellular chemistry of the radionuclide, and membrane transport of reagents. Each of these aspects has been characterized and work in this area continues today, making the radiolabeled RBC one of the best understood radiopharmaceuticals we have in our formulary.

Ronald J. Callahan
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts