LETTERS TO THE EDITOR

The Descent of Nuclear Medicine

Bravo for Marshall Brucer and Henry Wagner to their articles on the past and future of nuclear medicine in the June edition of the *Journal*. These were so good that, for the first time, I read the *Journal* through from front to back instead of the usual back to front. But I was surprised to see Brucer date the beginning of nuclear medicine to 1815 and Prout's observations on the uric acid content of a boa constrictor's stool. I've been thinking all along that it started with Geoffrey Chaucer (1340?–1400) and Alexander Pope (1688–1744). Pope made the first reference to scintigraphy in "An Essay on Man." Readers will all recognize his famous lines:

"Know then thyself, presume not God to scan
The proper study of mankind is man."

Marshall Brucer could hardly have put it better himself.

And Chaucer must get credit for the first reference to in vitro nuclear medicine, which he made in his poem "Troilus and Cressida." Translated into modern English it goes as follows:

"For my affairs have come to such a pass
That I perceive that Fortune is my foe,
And all who up and down this wide world go
Must take whatever Fortune shall decree,
For as she will, she plays with bound and free."

I'd say that's an unequivocal reference to radioimmunoassay—and 550 years before Berson and Yalow.

And how heartening it was to read Wagner's inspiring article on the future of nuclear medicine and see his graph, which showed a steady decline in the death rate in a university hospital from 1962 to 1972. I could not help noting that in the year when I gave up practicing internal medicine in a university hospital in favor of nuclear medicine, the death rate took the sharpest dive recorded. Readers may draw whatever conclusion they wish from this observation. I know the one I'll choose. Makes a fellow kind of proud.

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Guidelines for the Clinical Evaluation of Radiopharmaceutical Drugs

I. INTRODUCTION

"General Considerations for the Clinical Evaluation of Drugs" should be reviewed before reading this guideline. It contains suggestions that are applicable to investigational drug studies for most classes of drugs and helps to eliminate repetitious material in each of the specific guidelines.

Investigational studies of radiopharmaceutical drug products (RDP's) should be carefully designed to provide the scientific evidence that will substantiate their safety and efficacy for proposed diagnostic or therapeutic indications. These investigations should be conducted so that safety and efficacy are demonstrated with minimum exposure of patients to unnecessary radiation.

Much of the information in this guideline is applicable to the clinical investigation of both diagnostic and therapeutic RDP's. However, the major emphasis in Sections I–III is on the requirements for diagnostic RDP's, whereas the information in Section IV considers the special requirements for therapeutic RDP's.

The evaluation of diagnostic RDP's will differ from that of most therapeutic drugs in several ways because of certain special characteristics:

1. Since diagnostic RDP's do not usually elicit a pharmacologic response, evaluation of safety often requires less detailed study of pharmacologic toxicity and is primarily related to adequate estimation of radiation absorbed dose.
2. A diagnostic RDP is considered to be effective if its use results in information leading to a decision concerning the presence or absence of disease or abnormality. It is recognized that with some diagnostic agents it may not be possible to specify the nature of the disease or abnormality.
3. The diagnostic value of a radiopharmaceutical is a function of its biodistribution and the character of the radiations emitted. The degree to which the biodistribution is altered by disease or abnormalities is of particular importance. Thus, the investigation should demonstrate the normal biodistribution, the pathologically altered distribution, and how the altered distribution is determined in patients—e.g., through imaging studies, in vivo uptake studies, or by in vitro tests.

II. PRECLINICAL STUDIES

Sufficient preclinical animal data, manufacturing information, and quality control information to establish reasonable safety must be available before the administration of a RDP to human subjects. Characterization and quantification of the radiochemical and radionuclidic purity of the radiopharmaceutical are important preliminaries to the evaluation of radiation dosimetry, in order to determine any trace radiocontaminants (including daughter products) and altered chemical forms that might significantly influence biodistribution and radiation absorbed dose.

Preclinical studies will generally include both biodistribution studies and animal toxicity studies.

These data may be obtained from experiments performed by the investigator, the published literature, or other valid sources, provided that the sponsor can demonstrate that the data are applicable to the substance under consideration (i.e., dosage form, route of administration, etc.).

A. Radiation Dosimetry

Preclinical (animal) studies are required to determine the biologic distribution, translocation, and the route and extent of excretion of the RDP. This information is essential for meaningful dosimetry calculations. Dosimetry calculations on these animal data should be determined before initiating human studies. In general, it is desirable to assay for the concentration of the RDP at selected time intervals in all major organs and tissues so that the organs (tissues) receiving the highest radiation absorbed doses can be identified. With a diagnostic RDP used for imaging purposes, the organ (tissue) receiving the highest radiation absorbed