LETTERS TO THE EDITOR

SNM Drug Problem Reporting System

The SNM Drug Problem Reporting System was established in February 1976 as a cooperative arrangement among the Society of Nuclear Medicine (SNM), the U.S. Pharmacopoeia Convention (USP), and the Food and Drug Administration (FDA). All three organizations are interested in defining the types, the characteristics, and the incidence of adverse reactions to radiopharmaceuticals. They are also interested in documenting any problems caused by defective radiopharmaceutical products. To assist this collaboration, a single reporting form that would supply the data needed by all three groups was developed. The new reporting system replaces SNM's original adverse-reaction registry.

The SNM Drug Problem Reporting System is one of several related FDA programs for assuring the quality of marketed radiopharmaceuticals. The other programs are the New Drug Application Approval process, the monitoring of the regulated industry for current good manufacturing practices, and the surveillance of the products once they reach the market by periodic regulatory analysis of selected samples.

The current reporting form was developed jointly by the SNM and the FDA and first mailed in February 1976, with a cover letter from the SNM president, to approximately 7,164 members of SNM. This type of mailing took place three times during 1976. The forms were also made available to any interested health professional who wished to report radiopharmaceutical-related incidents of drug defect or adverse reaction. Whenever the USP received a report, it sent a copy to the SNM Headquarters, another copy to the manufacturer for information, and a third to FDA for followup action. In addition, replacement forms and postage-paid envelopes were automatically mailed to the reporter for future use.

One hundred reports had been received as of February 1977. There were 57 reports of adverse reactions in patients and 43 drug-defect reports. We do not assume that this represents all of the drug problems that have occurred, but we do assume that it provides a sampling that can serve the purpose of pointing out incipient problems before they assume serious proportions. The reports also provide evidence of adverse reactions whose incidence would be too small to be picked up without a program of the nationwide survey type.

The radiopharmaceuticals to which reactions have occurred and have been reported are listed in Table 1. In some cases, more than one patient was involved in reactions to a particular lot of a product. In such instances we have included the total number of patients. Most of these reactions were of an allergic type, and some involved a vasomotor collapse. Only a few could possibly be attributed to pyrogens (e.g., In-DTPA and possibly Tc-99m sulfur colloid). In a few instances the relationship of the radiopharmaceutical to the adverse reaction was very uncertain, since the patient was on other medications as well.

The most commonly encountered reaction was to Tc-99m-labeled human albumin microspheres. The response was allergic in type, and the cause is unknown. While the incidence is low compared with the number of administrations, a very determined effort is under way to elucidate and correct this problem. No fatalities attributed to radiopharmaceutical administration were reported.

Reported drug defects are listed in Table 2. Poor Tc-99m labeling efficiency was the major defect reported for imag-

TABLE 1. ADVERSE REACTIONS TO RADIOPHARMACEUTICALS (1976)

	No. of patients	Allergic	Pyrogen	Drug effect	Unknown
A. Radiopharmaceuticals—approved for market					
1. Tc-99m human albumin microspheres	20	13		6	1
2. Tc-99m sulfur colloid	10	3	5	1	1
3. Tc-99m pyrophosphate	7			7	
4. Tc-99m diphosphonate	2	1	1		
5. [^{131}I] rose bengal	2			2	
6. [^{131}I] sodium iodide	2	2			
7. In-111 DTPA	2		2		
8. Tc-99m macroaggregated albumin	1			1	
9. [^{131}I] orthoiodohippurate	1			1	
10. Tc-99m human serum albumin	1			1	
11. Ga-67 citrate	1	1			
12. [^{99m}Tc] sodium pertechnetate	1	1			
13. Tc-99m iron ascorbate—DTPA	1			1	
14. Tc-99m DTPA	1				1
Subtotal	52				
B. Radioactive drug—other status					
1. Tc-99m dimercaptosuccinate	2			2	
2. [^{131}I] 6β-iodomethylnorcholesterol	2			2	
3. Tc-99m glucoheptonate	1			1	
Subtotal	5				
Total	57				

TABLE 2. RADIOPHARMACEUTICAL DRUG DEFECTS (1976)

		No. of reports
A.	Radiopharmaceutical—approved for market	
	1. Tc-99m macroaggregated albumin	8
	2. Tc-99m sulfur colloid	8
	3. [^{131}I] sodium iodide	4
	4. [^{99m}Tc] sodium pertechnetate	3
	5. [^{57}Co or ^{58}Co] cyanocobalamin	1
	6. [^{32}P] chromic phosphate	1
	7. Tc-99m standard	1
	8. Tc-99m diphosphonate	2
	9. Tc-99m pyrophosphate	1
	10. Tc-99m polyphosphate	1
	11. [^{131}I] rose bengal	1
	12. Tc-99m iron ascorbate DTPA	1
	13. Tc-99m DTPA	1
	14. I-125 human serum albumin	1
	Subtotal	34
B.	Radiopharmaceutical—other status	
	1. Tc-99m phytate	1
	2. In-111 chloride	1
	3. Tc-99m glucoheptonate	1
	Subtotal	3
C.	Others—In-vitro kits (various radioimmunoassays)	6
	Subtotal	6
	Total	43

ing agents designed for liver (sulfur colloid), lung, and bone. Other reported problems were incorrect radioassay, wrong particle size, inadequate radiochemical purity, external contamination of immediate containers, etc.

Since the reporting rate of adverse reactions and drug defects have increased with the advent of the new reporting form, this is taken as evidence that this procedure is being accepted by the nuclear medicine community as a viable way of communicating such problems. The following is a list of some of the kinds of response that ensued upon receipt of an SNM Drug Problem Reporting Form:

1. A (diagnostic test) package insert had an error in a formula for administered dose computation, which could have led to gross misinterpretations of test results and a serious consequence in making a diagnosis of, for example, pernicious anemia. When notified, the manufacturer immediately ceased distribution of the product until all the faulty inserts could be replaced with corrected inserts. We received only one report, but one was enough to bring about correction in this case. Incidentally, many physicians and paramedical personnel must have read this label; (*please do not assume that someone else will report a needed change.*)
2. The specifications in a compendial drug monograph were questioned. Here a seeming conflict existed between the allowable Mo-99 in a sodium pertechnetate injection based on (a) μCi per mCi of Tc-99m, and (b) total administered dose, when the usual dose range was taken into account. Conceivably, a product could meet one USP specification but not the other, and therefore might not have been suitable for two types of recommended scanning (thyroid and brain). The USP radiopharmaceutical panel considered the SNM report and decided to lower the permissible tolerance for μCi Mo-99 per mCi Tc-99m.
3. A drug defect was traced to faulty instructions in a diagnostic kit. Later the manufacturer voluntarily instituted certain changes in the formulation instructions which, it is hoped, will alleviate the problem.
4. The incidence of adverse reactions reported were judged to be unexpectedly high for a particular product, and the firm voluntarily contacted FDA. Changes were made in the "Warning" and "Adverse Reactions" sections of the package insert so as to reflect accurately the incidence of adverse reactions.
5. A firm that markets a lung aggregate reagent kit voluntarily recalled the product because tests conducted by the firm indicated the need for further evaluaction of the product formula. The USP has received several SNM Drug Problem Reports that highlighted the problem by citing the low tagging efficiency of the product.
6. Upon reconstituting a commercial MAA kit, a physician noted that particles of around 3,000 microns were present. His findings were corroborated by two FDA laboratories on the same lot of material. A followup inspection as a result of this report showed numerous deviations from good manufacturing practice by the firm, and appropriate corrective action was taken.

These are only a few illustrations from the collection of reports, and the actions taken, that show the value of the cooperation that exists among all the parties concerned.

The long-term objectives of the program are to provide answers to the following four questions:

1. What is the reported incidence of receipt of defective radiopharmaceuticals?
2. What is the reported incidence of adverse reactions to radiopharmaceuticals?
3. What symptoms are characteristic of adverse reactions to particular radiopharmaceuticals?
4. Which adverse reactions are related to use of defective radiopharmaceuticals?

The information received to date establishes a data base for an overall estimate of the magnitude and significance of problems caused by defective radiopharmaceuticals and by adverse reactions to radiopharmaceuticals. In the future, all the data will be computerized. This will allow for an analysis of problem trends and manufacturers' profiles, as is currently done with FDA's reporting system for problems with nonradioactive drug products. It is anticipated that by 1978 sufficient data will be available to initiate the first computerized programs.

We believe that the nationwide reporting of radiopharmaceutical problems is benefiting both the scientific medical community and the pharmaceutical industry. We believe that this reporting system establishes a kind of multifaceted feedback loop that allows for the correction of mistakes before the problems reach significant proportions and before the necessity of invoking stiff procedures of a regulatory type.

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