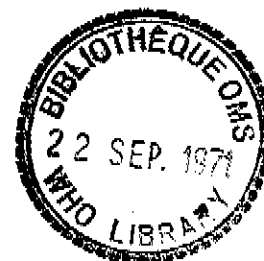




MEETING ON INTERNATIONAL DRUG MONITORING -
The Rôle of National Co-ordinating Centres

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THE PLANNING OF A NATIONAL MONITORING SYSTEM

by

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For more than a decade now, the United States Food and Drug Administration has participated in a number of programmes directed toward the acquisition and management of adverse drug reaction information. These have ranged from the most fundamental procedures for assimilating individual case reports to the more complex methodologies utilizing an integral systems approach. With the wealth of experience gained from these investigations, the Agency is currently formulating a comprehensive plan that will be designed to meet the future requirements for ensuring drug safety. Beyond this objective a broadened safety information system now can be visualized.

On the basis of data configurations, previous FDA studies can be divided into three general categories. These are the spontaneous or isolated case report programmes, the intermediary drug reaction incidence studies, including the more recent intensive monitoring techniques, and the most comprehensive surveillance efforts that have been incorporated into major health plans. Each has been found to have the potential for providing unique segments of data, plus qualitative or quantitative advantages in applied methodologies. In addition, there have been characteristic patterns of reporting and wide economic variances in costs per unit of useful information.

The initial category of individual case report systems can be further divided into those providing drug experience data which have been assimilated through contractual agreements as opposed to sources submitting reports by voluntary initiative or as the result of regulatory requirements. Within the United States, the former consisted primarily of the FDA Hospital Reporting Program while the latter included data from the industrial complex, military hospitals, professional organizations and spontaneous communications from the clinical community. One especially funded study was a completely retrospective survey using hospital charts reviewed by medical record librarians as an alternate approach to the acquisition of drug reaction information. During the ten and one-half years of experience with the hospital programmes, several hundred institutions participated and more than 100,000 such reports were elicited. To institute the desired uniformity of case reports, a continuous effort has been made to retrieve a standard unit of information within the category. Since a reporting criterion in the United States has been a single communication to obtain data, the objectives of the format which evolved over the past decade have been optimum brevity to secure co-operation, combined with the acquisition of adequate information for professional interpretations.

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Although the origins of isolated case reports received by the Agency were diverse, many general characteristics of these as a data category have become evident. Using the guidelines for "significant" cases as defined by the FDA a relatively constant level of reporting for example, was observed. For funded institutions, the receipt of drug reactions affecting approximately five to seven percent of the hospital patients "observed" was found through experience to be a sustained quantity. This average reporting performance is believed to closely reflect the actual occurrence of significant adverse effects. The numerical relationship would vary however under any other given definition of a "reaction". Qualitatively and quantitatively the contractual hospital programme may in fact be considered as having provided the actual numerator (only) of an intensive monitoring system. As anticipated, a direct quantitative variance was observed between funded and non-funded sources. The materials received however were quite comparable qualitatively. While the stipends for the professional services obtained could be described as conservative and there may have been additional variables, a gross ratio of 10-1 was observed from these origins. Of particular significance within the systems within this first category has been the World Health Organization Pilot Research Project for International Drug Monitoring^{1,2}. While primarily based on spontaneous reporting, this programme has demonstrated the feasibility of collaboration between a number of nations and has developed a unique system of "signals" for critical cases based on preselected criteria. It stands today as a single operational programme with exchange and search capability.

As a category of data, isolated reports were found to yield a relatively high incidence of unprecedented, or comparatively undocumented suspected associations of drugs and side effects. Consequently, this type of reporting is believed to be readily amenable for incorporation into a total monitoring system. Its utilization for the "early warning" sector of a comprehensive programme has the further benefit of an economic advantage for identifying new problems of potential significance as opposed to other methodologies. Attempts have been made to subject this type of reporting to statistical analyses through the establishment of trends on which predictions could be based. Due to the complexity of drug reaction cases however, even relatively large quantities of material have not yet proven satisfactory for this purpose.

The second general category of studies is defined as those in which the basic methodology provides a numerator and a denominator, thereby yielding incidence information within adverse reactions and drug usage/patient data. These programmes have demonstrated the potential for providing the next level of documentation for unprecedented ("early warning") reports or drug/reaction associations of particular interest where preliminary numerical perspectives are needed. Instances of primary suspicions of new reaction entities have thus far been rare in such systems since the logistics and economics required to project populations of sufficient proportion have restrained the ultimate employment of this category. Many contemporary systems have amassed data that are closely related to the subject matter in question, but the desired specificity per unit of information processed has not evolved. The Food and Drug Administration has directly funded three investigations within this total surveillance category and maintained an active interest in at least two other established programmes. One of the earliest of the funded studies was implemented in 1965 utilizing records of prescriptions and physician recorded drug reactions.³ Within the geographical

limits of a 367 square mile county (population 115,000), 30 pharmacies and a medical society of 83 physicians were the sources of data. A relatively low yield of drug reactions was obtained during the survey. Another early project of several years duration was undertaken within a major hospital utilizing two approaches to drug side effects⁴. This investigation provided a comparison between the results of intensive surveillance procedures employing nurse surveillance officers and reporting on a voluntary basis from other wards using the protocols specified by the FDA hospital programme. During a subsequent phase of this study special monitoring projects were conducted on classes of drugs or individual agents specified by the Food and Drug Administration. In another medical centre, a study that has been in progress since 1967 has developed an intensive surveillance methodology that is considered to have shown maximum accuracy for retrieving clinical information. Employing a basic pharmacist/physician team for the direct monitoring of in-patients these investigators have established a consistent rate of drug reactions and established a protocol that is readily applicable to other centres. Other studies in which the Agency has had interest have utilized nurse monitors as the basic team for the collection of clinical material or have used a central pharmacy service between several hospitals as a focal point for collecting drug reactions reported by attending physicians.

Rather than providing large quantities of significant information to the Agency the practical value of these studies has been to demonstrate the comparative merits of each methodology. It is envisioned that those with potentially productive protocols can be geographically applied in the future to establish the necessary intermediate level of documentation within a total system. This capability can be enhanced through the techniques of monitoring classes of drugs that have been demonstrated in certain ones of the studies.

The third category of investigations is allotted to those surveys which were designed for major population segments or the compiling of data from an unusually large number of hospitals. Positive interest in these was expressed as early as 1963, but such repositories as existed were found to assemble clinical information of a more general administrative nature. Since the medical literature as a potential source of data has the dimensions discussed here, it could be considered within this general grouping. As with the statistical surveys, an early difficulty was found to be the absence of an existing category of information that would be analogous to the necessary subject matter standards. In addition to the successful efforts that evolved within the Agency, one or more commercial services were subsequently addressed to this need. In 1966, the Food and Drug Administration began its funding of a major programme directed toward epidemiologic surveillance for drug reactions using computer based medical records. The results of this study have been promising and are notably unique in having monitored an outpatient population⁵. With the advent of an increasing emphasis on comprehensive health plans this type of epidemiologic approach may be the most fundamental methodology for the detection of major problems within the population.

Contrary to the earliest projections, the "adverse reaction" entity has been the more difficult aspect of frequency ratio. The academic diversity of interpretations and forensic constraints of such information have been described elsewhere⁶. Experience has shown these limitations to volume to be compounded by qualitative selectivity. As the methodologies progress across the three categories, a consistent

indirect relationship has in fact been observed between the specificity of the subject matter and volume of both the numerator and denominator data. Consequently, while the direct use of professional expertise in the subjective detection of cases has restricted the breadth of any survey, epidemiological approaches that incorporate large segments of general clinical information have not effectively isolated the precise data that are necessary. When further developed the latter class of systems will advantageously supersede the limitations of isolated clinical conclusions, but their exclusive employment would be made at the cost of precluding the numerous professional assessments that are readily apparent and directly adaptable to the task. A comprehensive monitoring system then, as an intelligence programme, must incorporate a spectrum of techniques. The use of each procedure must be measured by the specified objectives of the system. The alternatives to be balanced include early knowledge of isolated "first" cases vs. depiction of statistically significant hazardous products which endanger the public health, monitoring drug categories used predominantly by out-patients vs. in-patients, and consideration of an approach that attempts to monitor all products as opposed to selected categories, e.g. newly approved drugs. The design of a proposed system may be further directed by economic factors since the cost of usable entities has been observed to increase exponentially when progressing through the three categories. Therefore, while the methodology to produce unprecedented conclusions by means of epidemiologically derived hypotheses with confirming statistical data has ample justification academically, a design compromise may be mandatory if an essential criterion of a system is drug interaction surveillance over all agents.

In planning the next generation of surveillance systems, considerable attention must be directed toward the inclusion of a new pattern of disciplines. Drug safety has been assumed to be closely correlated with adverse drug reactions, which have in turn been considered synonymous with the content of monitoring and surveillance programmes. Likewise, injuries may have become the prime criterion for evaluation in the area of product safety. While side effects as now interpreted may occupy a major segment of the subject matter, the premise supporting their exclusive identity can no longer be concluded. Future systems to ensure safety when marketed products are utilized by the populace, must therefore be designed to co-ordinate adverse drug reaction data, toxicological findings, records of the misuse of drugs, adverse effects from potentially hazardous products and a series of allied subjects. Drug surveillance, while still new as a science has now been explored to the degree where a total system can be planned, using the past experience as a foundation.

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