Medical Informatics

ARAMIS (The American Rheumatism Association Medical Information System)

A Prototypical National Chronic-Disease Data Bank

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ARAMIS is a prototype of a national chronic-disease data-bank system consisting of parallel, longitudinal, clinical data sets from 17 diverse locations; the data describe the courses of thousands of patients with rheumatic disease followed over many years. Chronic-disease data-bank systems include the data themselves, protocols to ensure their quality, computer systems for their manipulation, statistical procedures for analysis and an appropriately skilled staff. Such a data resource facilitates analyzing long-term health outcomes and the factors associated with particular outcomes. Such systems are mandated by the overwhelming prevalence of chronic illness; the variability, complexity and uniqueness of a patient's course; the difficulties of traditional randomized approaches in these areas, and the time span required for studying these problems.

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ARAMIS (the American Rheumatism Association Medical Information System) is based on the premise that many of the most important problems of contemporary clinical medicine require data banks of chronic diseases for their solution. ARAMIS is one such data bank, containing detailed longitudinal patient information collected prospectively and carefully controlled for quality. Information is stored for thousands of patients and tens of thousands of patient-years of observation.[1,2] The system includes the data, the computer systems that allow efficient manipulation of data, a set of evolving investigational methods for approaching the study of such data sets and the appropriate staff to carry out the required activities.

In chronic-disease data-bank systems the complete courses of thousands of patients from different settings are stored on computers and through communication networks become accessible to investigators at many locations. Unlike clinical investigations based in the medical record room, data are collected with a prospective protocol using standard, defined observations. Patients are regularly followed even when they move or change physicians. Measurements include broad health and economic status indicators. In essence, each patient is on a universal prospective research protocol. In this review we present our personal view of the history of ARAMIS, the principles on which it is based and its accomplishments.

The Eight Principles of ARAMIS

The development of ARAMIS has been based on eight principles, discussed in more detail in a previous communication[3]; these principles support the premise with which we introduced this article.

1. *Because the purpose of the medical care system is to improve health outcomes, clinical investigation must include measuring these outcomes.*

A medical care system exists to minimize death rates, to decrease disability, to reduce discomfort, to minimize the drug and therapeutic toxicities of the care itself and to reduce the economic impact of illness and its treatment. These five broad dimensions of health outcome—death, disability, discomfort, drug toxicity and dollar costs—have now been shown to be measurable, relevant and surprisingly discrete.[3] Such measures, rather than merely "process" measures such as antibody levels or sedimentation rate, should serve as the major dependent variables for study.[4,5]

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ABBREVIATIONS USED IN TEXT

ARA = American Rheumatism Association
ARAMIS = ARA Medical Information System
MRFIT = Multiple Risk Factor Intervention Trial
TOD = Time-Oriented Data Base

2. *Chronic diseases now constitute the major national illness burden.*

Over recent decades, the national burden of illness has shifted strikingly from acute infectious disease to chronic illness.[6] Currently the major medical problems in developed nations are atherosclerosis, cancer, arthritis, emphysema, cirrhosis, other chronic diseases and trauma. Chronic diseases at present cause more than 80% of the national mortality and morbidity.[6,7] These illnesses are characterized by slow development, insidious progression, widely varying patient courses and multiple interactions over time with various environmental and medical determinants.[8]

3. *Studies of health outcomes, therefore, require long-term longitudinal studies.*

Variables that are predictive of eventual patient outcome in cases of chronic illness predate the outcomes themselves by many years. Patients with arthritis, for example, are typically treated with a score of different medications by 15 or 20 physicians over a quarter of a century. The effects, good and ill, of treatment programs accumulate over time, and treatment involves many different modalities applied sequentially and concurrently over a period of many years. In such a complex situation, definitive studies require a large number of patients observed for long periods of time. Expensive experimental studies, as with the Multiple Risk Factor Intervention Trial (MRFIT) study,[9] address only a single major question and are thus seldom feasible. Prospective observational studies, therefore, must represent a major approach to the study of chronic disease.

4. *The effective study of long-term outcomes must be systematic.*

A traditional research cycle consists of developing a hypothesis, carrying out an investigation, analyzing the results, forming conclusions and formulating a new hypothesis for subsequent study. With long-term questions, however, the duration of the cycle does not permit the efficient accumulation of knowledge by this approach. One cannot wait for results from one study to be completed before beginning another. A new strategy is needed in which an underlying system allows new data to be collected and new studies to be introduced as soon as a new question arises—and thus for multiple studies to be done simultaneously. A feedback loop is required in which the data being systematically collected gradually evolve in nature as previous results and the emerging new questions lead to increased understanding of future data requirements.[10]

5. *Studying long-term health outcomes requires developing and using new observational analytic techniques.*

Traditional human experimentation, with randomly selected treatment and control groups, often is effective and practical for short-term questions. For long-term studies, however, it is seldom ethical or possible to assign persons to one or another group for life. With time and with many secular influences, the number of dropouts in both treatment and control groups increases to the point where conclusive analysis is no longer possible. The cost is prohibitive, even for medium-term studies. Very expensive studies—such as MRFIT at $115,000,000—have yielded inconclusive results, and no new experiments of this size have been funded in recent years.[9]

Observational studies, on the other hand, are often justifiably criticized for not being true experiments. Good observational study methods, however, can minimize many of the problems. Data-bank systems permit studies to be protocol-driven and prospective, with data collected "blind" (study hypothesis unknown to observer) and of a quality equivalent to that of randomized experiments. Moreover, statistical techniques of analyzing by strata, using several control groups, carefully adjusting for differences between study groups and using matched controls may minimize the difficulties of observational studies.

6. *Long-term data must be collected for more than one purpose.*

The long time and great expense required to undertake long-term studies of chronic diseases necessitate that the collecting of multipurpose data be economically justifiable. The same basic data can support many current and future studies unthought of when the data were initially collected.[3]

7. *The "real world" contains multifactorial influences on outcome.*

The outcome of chronic diseases is influenced by social and economic considerations, patient compliance with therapy and complicated interrelationships among medical treatment, surgical treatment and various other factors. Meaningful analysis of chronic-disease outcome requires a more complicated biologic, psychological and social model of disease, the study of a larger number of patients and the development of new techniques to deal with the complexity. The classic "reductionist" scientific experiment can examine only a small, tightly defined portion of such a complex disease model and thus cannot account adequately for such complex relationships.

8. *Prospective protocol-driven data are required.*

In our view, these principles mandate the development of computer data-bank systems for chronic disease as a major approach to investigating human illness. They also serve to define the characteristics that such a system must have. There must be a large number of patients from diverse settings. Data collection must be standardized using rigorous prospectively applied protocols. Data must be collected serially and over the long term, with intensive efforts at quality control. Follow-up must be as complete as possible. Patients must be enrolled consecutively and the data to be collected must be regularly reevaluated. Reliable and valid measurements of outcome must be made and repeated. Sophisticated information management tools are required and access to the data by many investigators must be possible if many questions are to be addressed and the potential economies of scale realized. Statisticians must develop improved approaches to study design, analysis and interpretation.

On a practical basis, such data banks can be used in establishing a feedback loop between long-term outcome and antecedent factors, determining the natural history and prognostic

factors of illness and defining and classifying diseases. Clinical benefits include identifying subgroups of patients who have different outcomes and the risk factors for particular outcomes, analyzing the costs and benefits of different treatments and better delineating the productive and relatively nonproductive endeavors of medicine.[10]

The History of ARAMIS

Five general stages in the development of ARAMIS can be identified:

1. *Development of the Time-Oriented Medical Record*

Traditional medical records represent a nonsystematic approach to accumulating data that prevents combining data across patient cases without retrospectively abstracting sparse and nonstandard data at the time of a study. We developed the time-oriented record as a framework for systematically and prospectively collecting data that encouraged more complete data recording, with the additional hope that the chart format would assist clinicians in reviewing records efficiently and in determining the trends and the tempo of illness in an individual patient. The time-oriented chart displays clinical information on "flow sheets," with time represented on the horizontal axis (Figure 1) and the variables to be observed on the vertical axis. Time-oriented records are more formally structured than traditional records and are slightly more difficult to complete initially. But as a complex patient course evolves, they rapidly become more effective for reviewing many encounters and are thus easier to use than traditional formats.[11,12]

Many of the data-quality problems of clinical research are a result of incomplete physician observation and recording. The format of our original time-oriented records on rheumatic disease has evolved (through 13 revisions over the years) toward an increasingly "physician friendly" format, resulting in more complete recording of data. With our present records, time-oriented flow sheets are used for laboratory and therapeutic information, as well as other quantitative data, but a single-page form is used for qualitative clinical observations. Medical histories that are self-administered by patients and reviewed by a physician are used extensively.

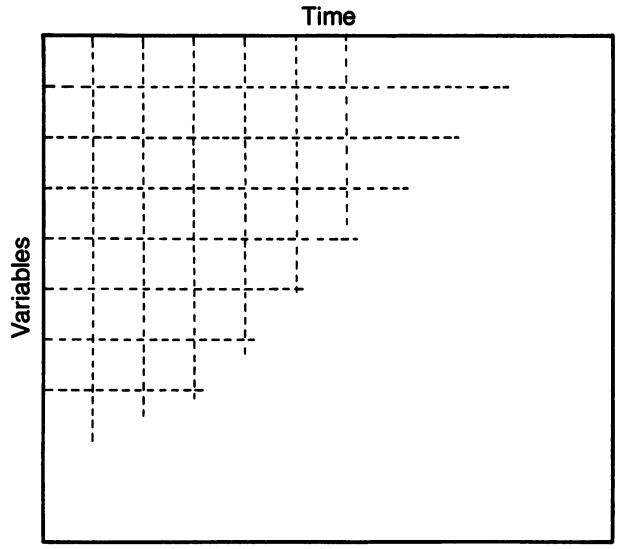

Figure 1.—Schematic representation of a time-oriented medical record.

2. *Development of the Uniform Data Base of Rheumatic Disease*

Data-bank projects in the rheumatic diseases developed nearly simultaneously at four institutions from 1966 to 1968. It soon became clear that each institution would become fixed to its own initial data set, precluding comparison or pooling of data, unless a common descriptive vocabulary could be negotiated. A computer committee of the American Rheumatism Association (ARA) was formed, and a conference involving 29 institutions was held resulting in the initial formulation of the Uniform Data Base of Rheumatic Disease. A common descriptive vocabulary was developed that lists 422 diagnostic, historical, physical examination, laboratory and therapeutic variables to be used, in whole or in part, by all institutions. Institutions were permitted to add variables of their own choosing. The uniform data base was designed to be revised periodically, which has occurred at about three-year intervals. There are now about 40 institutions using the uniform data base.[13]

Next, agreement was sought on the definitions of terms. The ARA Glossary Committee developed a dictionary of rheumatic diseases, which provides definitions and protocols for the data-base variables. Such definition is critical to improved precision in teaching and to the quality of clinical data. Volumes I and II of the dictionary have now been published.[14]

3. *Development of Time-Oriented Data-Base Management Systems (TOD and MEDLOG).*

A data bank[11] was conceived as a collection of individual time-oriented patient records that could be represented as a three-dimensional array (Figure 2). Thus, each data point had a unique address created by the specification of three coordinates. Computations along the time axis were facilitated by this organization. TOD (Time-Oriented Data Base) represents the original mainframe computer data-management system, and MEDLOG, developed by the Information Analysis Corporation with ARAMIS collaboration, is the currently available microprocessor system.[15,16] Both systems have closely comparable architecture.

Data are entered into a main file interactively from the patient record or from another computer through telephone lines, magnetic tape or floppy disk (Figure 3). During a following entry, a number of quality-control features are executed and errors corrected. Periodically, after additional data-quality checks, the file is transposed (inverted and ordered) into a second file, the transposed file, which is used for statistical analysis. The transposed file is not always current with data entry, but is always "clean" with regard to data quality for retrieval and provides a stable data set for analysis.

In the main file, a record consists of a patient visit: a string of numerical values describing the patient's status at that visit. In the transposed file, a record is a long, ordered string of values for a particular variable; these records often include 20,000 to 30,000 numbers. Analysis across patient data, the fundamental data-bank requirement, is facilitated by this file structure because it is no longer necessary to look through each patient record to find the data but only at the records pertaining to the variables of immediate interest.

Analysis programs begin by specifying a patient group (or subset) to be examined. A "patient subset" is a list of numbers that identify persons who fulfill particular criteria. These per-

sons may be specified by any combination of variables, using ranges of values or increases or decreases in value for a particular variable. All Boolean operations are supported. In contrast, a "visit subset" is a collection of only those specific visits at which particular criteria were met. Visit subsetting allows investigation of a particular portion of a patient's course and comparison with other portions of the same patient's course.

After specifying a subset, the user selects a particular retrieval program. These programs analyze data in a basic format, such as a histogram or a scattergram, but are otherwise entirely general; they will operate with any variable and any subset. Programs provide histograms, scatter plots, life-table analyses, comparison of means, comparison of proportions, multiple logistic regressions, multiple linear regression, recursive partitioning and contingency table analyses, among others. Programs also format the data for passage to the standard statistical packages of SAS (Statistical Analysis System), BMDP (Biomedical Data Programs) and SPSS (the Statistical Package for the Social Sciences).[2]

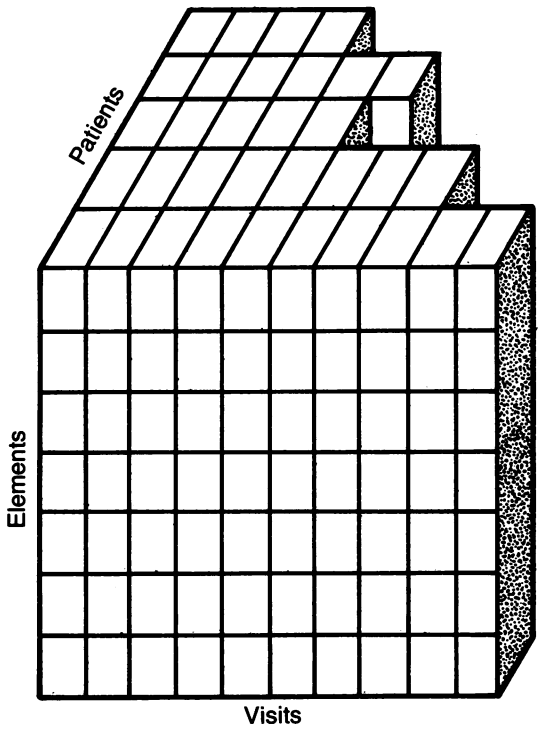

Figure 2.—Schematic representation of a time-oriented data bank.

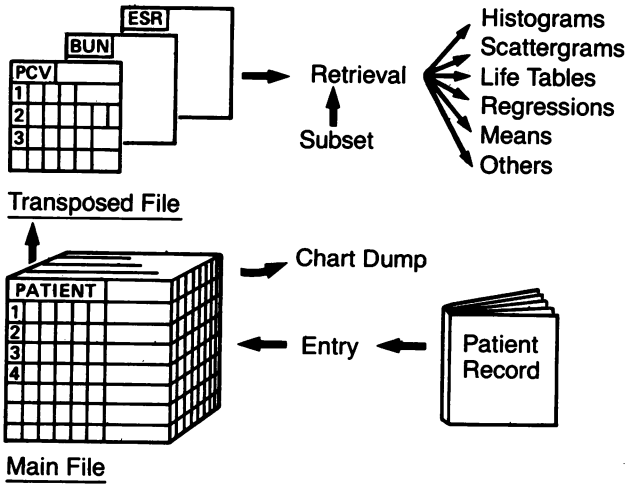

Figure 3.—Overview of a time-oriented data-base system. BUN = blood urea nitrogen, ESR = erythrocyte sedimentation rate, PCV = packed cell volume

The TOD system operates on the Stanford 370/3084A computer and is written in PL/1. MEDLOG is written for the IBM personal computer PC/XT and AT and is programmed in the languages PL/1, assembler and C.[15,16] Most operations, including data entry, are interactive. Microprocessor workstations are configured with 20 to 100 megabytes of additional hard-disk storage. The entire system currently contains about 300 megabytes of data. Data may be transferred between the mainframe and the microprocessor units.

4. *Development of a Pilot National Data Resource for Arthritis (ARAMIS)*

Conceptually, a national chronic-disease data-bank system is simply a collection of data banks with similar variables at different locations. A common schema (dictionary) defines the system and renders the different data banks compatible.

ARAMIS currently has 17 data banks in the United States and Canada. Responsibility for the integrity of data and for maintaining each data bank rests with the principal investigator of that data bank. Common data quality and follow-up protocols are used. Data quality is systematically reviewed by the ARAMIS core staff using audit procedures that compare patient chart data with information in the data bank.

Specific data banks have been selected for particular reasons; each consists of consecutive patient data with defined entry characteristics. One data bank may be strongest in longitudinal data for the disease systemic lupus erythematosus, another on rheumatoid arthritis. Some follow results for orthopedic procedures, and others trace the course of arthritis in children. Some represent urban centers, some tertiary care institutions and others (such as HANES I) represent population-based patient groups. While data are sometimes pooled between data banks, the strength of a system is in the ability to do parallel analyses in several settings and to confirm or contrast findings in different patient populations. ARAMIS currently contains information on more than 23,000 patients and 150,000 patient visits, covering more than 160,000 patient-years of experience, with some 60 million pieces of individual information.

The original configuration linked peripheral centers to the central computer by TYMNET and TELENET communication linkages, allowing access through telephones in the United States or Canada. This system remains in use for analyzing pooled data and for extensive computational tasks. In general, however, data are now entered into MEDLOG microprocessor data banks, and these data banks are then periodically transferred to a large computer over telephone lines or by mailed magnetic tapes. Information from a single data bank may be analyzed directly in MEDLOG or a microprocessor and additional data sets from other institutions may be installed on that microprocessor as well, if desired. The most time-consuming tasks, consisting of data entry and quality control, are thus now done in a distributed manner, with major savings in cost and efficiency.

A basic principle of ARAMIS is open, shared data. ARAMIS data are available to all qualified ARAMIS investigators. Potential projects are reviewed by a projects and publications committee where the study design is sharpened and possible conflicts anticipated. Patient confidentiality is absolutely maintained; identifying information about any patient within ARAMIS is available only to a physician responsible for a particular data bank.[10]

5. *Development of Outcome Measurement Techniques*

Originally, the uniform data base contained only traditional medical variables. It soon became apparent that data on socioeconomic and psychological variables were not adequate and that such variables were clearly important in studies of long-term outcome. Outcome itself was neither defined nor measured adequately. Accordingly, a major effort was applied to defining long-term patient outcome and developing methods for its measurement.[17-20] These measurement instruments (collectively referred to as the Health Assessment Questionnaire), focusing on disability, discomfort, iatrogenic effects, economic impact and mortality (Figure 4), have been developed, tested, revised, validated and widely used.[17-20]

Over the long term, the adequacy of patient follow-up becomes a central criterion of the quality of a system. Physicians' office records usually do not systematically follow patients when care is given elsewhere. Because patients with arthritis typically change physicians (and even cities) with some frequency, accumulating "dropout" percentages weaken study conclusions if patient follow-up has not been aggressively pursued. Developing instruments for measuring outcome, self-administered by patients, makes it possible to follow patients by mail or telephone. ARAMIS has moved toward a concept of a comprehensive visit for each patient each year at which outcome is measured, needed laboratory tests done and a particularly thorough physician assessment carried out. Questionnaire self-assessment is done each six months. The development of a medical record that serially displays overall health status information is felt critical to the clinical management of patients with chronic illness and thus a benefit to the recording physician and the patient.

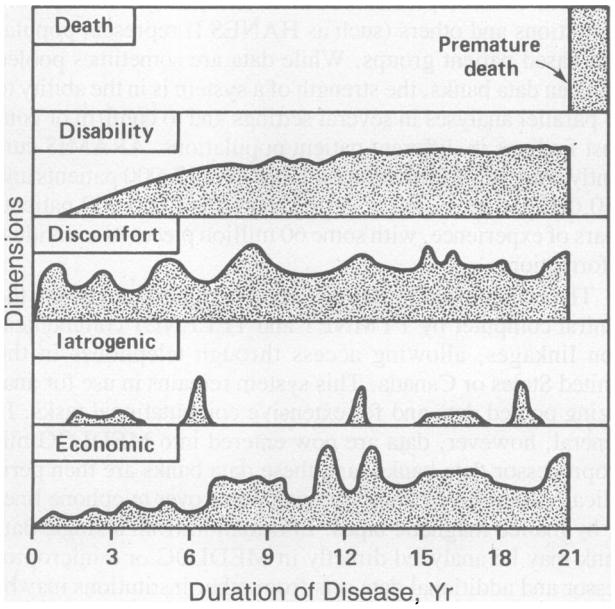

Figure 4.—The concept of cumulative patient outcome. In this schematic representation of a case of rheumatoid arthritis, the effect of the disease on each outcome dimension throughout the course is represented by the stippled areas.

Applications

ARAMIS has 45 associated investigators and about 100 projects under way at any one time; about 40 studies are published each year, and more than 250 ARAMIS publications have emerged to date. Some of these studies have concerned developing methods as described above. The time-oriented medical record,[1-3] the dictionary of rheumatic diseases,[14] documentation of time-oriented data-base software[11,12,15,16] and the development of particular statistical enhancements such as stepwise logistical regression have been described. The concepts of assessing outcome and developing instruments for measurement have been frequent topics.[17-20] More recently, methodologic papers describing postmarketing surveillance for drug toxicity and uses of recursive partitioning for patient stratification have been reported. Periodically, the entire system—its accomplishments and its current status—has been described.[3]

Clinical investigations have become increasingly formal. We have become skeptical of unadjusted tabulations of raw data because of the difficulty in definitive interpretation. Accordingly, ARAMIS has evolved a projects and publications committee that requires a formal investigative protocol before any investigation, review of the protocol and the proposed analysis at several steps by a committee experienced in biostatistical and methodologic evaluation and both internal and external review before publication in a peer-reviewed journal. The major information flow to clinicians is through the medical literature.

Clinical studies can be grouped into several general categories. First, defining the rheumatic diseases themselves has been an important activity. Studies have analyzed the criteria for classifying rheumatoid arthritis and have developed new criteria for juvenile arthritis, scleroderma, systemic lupus erythematosus and osteoarthritis of the knee. Currently under way are revisions of the rheumatoid arthritis criteria and studies of vasculitis and fibrositis. These studies have been done in collaboration with the criteria committee of the American Rheumatism Association.[21-23]

Second, ARAMIS has emphasized identifying subsets of patients within classic diagnostic entities. Such applications have been made in patients with juvenile rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, scleroderma and other conditions. For example, identifying the subset of "late-stage lupus nephropathy"[24] enabled hazardous therapy to be reduced in patients with systemic lupus who had uremia and encouraged the use of renal dialysis and renal transplantation in such patients. In cases of scleroderma renal crisis, successful medical management by aggressive antihypertensive treatment has followed from ARAMIS reporting of the management of the first three survivors of this dramatic syndrome.[25]

Third, many studies have had economic implications. The cost of different categories of disease, the variables predictive of high-cost patients, the identification of the most prevalent and the most expensive services and the effects of different treatment regimens on direct and indirect costs have been

subjects of study.[26,27] A more selective use of laboratory tests has been encouraged by an emphasis on laboratory variability and the marginal benefit of specific procedures.[28]

Fourth, studies of long-term outcome have analyzed the effects of initial variables on patient outcome after ten or more years. Outcome studies have explored mortality in cases of rheumatoid arthritis and systemic lupus, outcomes after total joint replacement and projected disability outcomes in rheumatoid arthritis and other disorders.[3,29,30]

Finally, therapeutic effects have been studied. These studies have been both observational and randomized in type, and both efficacy and toxicity have been described. Whereas ARAMIS is frequently associated with observational studies, trials that are "embedded"—prospective, randomized, double-blind and controlled—are frequently done, as with the use of nonsteroidal anti-inflammatory agents in rheumatoid arthritis, antihypertensive agents in scleroderma and cytotoxic agents in systemic lupus erythematosus.[3,31-34] Observational studies of cytotoxic treatment of systemic lupus, D-penicillamine therapy in scleroderma and others have been reported. The overall impact of therapeutic agents on costs, disability and symptom levels has been studied comparing the effects of commonly used antirheumatic agents.[31-35]

Therapeutic toxicity has been systematically studied by the development of a formal postmarketing surveillance system that serially records drug toxicity each six months. Data are collected in a protocol similar to that used in premarketing studies, which has allowed increased precision in comparing the side effects of different agents, delineating long-term side effects and noting the effects of concurrent factors such as age, race, sex and alcohol on side-effect rates.[3,36,37]

Future Evolution

We foresee that chronic-disease data-bank systems will continue to evolve toward distributed microprocessor networks with increased computational power available at work-stations. Soon to become available will be 32-bit microprocessor units with 1,000 megabytes of desktop data storage. The national arthritis data resource will increasingly evolve toward a series of carefully maintained meta-data banks aggregated from many sources with comprehensive data in particular areas, such as specific disease categories. Such data sets may be easily replicated and made available to investigators both within and outside of ARAMIS. Data acquisition, quality control, follow-up and outcome assessment, carried out centrally, will provide data of extraordinary usefulness. Compatible computer systems are being used increasingly in private practice settings, and larger amounts of data from more diverse clinical settings are becoming available.

Chronic-disease data banks begin to mature as the duration of follow-up approaches the average duration of the diseases under study. With time-oriented data, it becomes possible to examine the cumulative impact of a disease (the areas that are stippled on Figure 4), allowing more sophisticated analysis of the effects of treatment (and other variables) on the overall course of a disease rather than merely on the final status. The ability to compare the successive cohorts of new patients entered in the study each year from diverse centers will allow review of the changing characteristics of diseases, changing approaches to their treatment, changing determinants of cost and changes in outcome accruing to the successive cohorts.

Finally, a combination of the complementary attributes of "expert" systems using rule-based artificial intelligence techniques and the plentiful raw clinical data of chronic-disease data banks offers attractive conceptual opportunities. Rules may be developed by quantitatively analyzing actual experience rather than by armchair tactics, and the relationships between raw data such as "serum creatinine" and "proteinuria" and conceptual syndromes such as "active lupus nephritis" may be explicitly and rigorously defined.

The ability to summarize and display complex patient courses will improve the ability of physicians to effectively review the course of diseases as data-management systems become more compatible in individual clinical practice. Those involved in clinical research may combine effective patient management with the accumulation of valuable research data. Systematically assessing outcome in clinical practice will aid clinicians in appreciating the long-term course of patients with chronic illness.

In the past decade rapid progress has been made in hardware capability, in software support, in analytic techniques and in the volume and quality of available data. These advances combine to make chronic-disease data-bank systems an increasingly valuable part of the armamentarium of clinical research.

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