

SECTION IV

**ROLE OF COMPUTERS IN MANAGING
INFORMATION FOR PHARMACOLOGY
TEACHING AND RESEARCH**

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Role of Computers in Managing Information for Pharmacology Teaching and Research: Medical Informatics

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INTRODUCTION

Rapid advances in the biomedical sciences, including veterinary pharmacology, have led to an explosion in the volume of medical knowledge. The rate of growth far outstrips the rate in any previous period of time. The first volume of *Index Medicus* contained about 17,000 citations from 700 periodicals. Today, each month's issue averages about 21,000 citations from over 3,000 publications. The textbook on veterinary hematology by Schalm that I used in the '60s contained 664 pages. The current edition has 1241 pages to cover the same discipline. It is predicted that medical knowledge will continue to grow at a faster pace than either the population or the economy (1).

Information growth is not simply addition to previous knowledge. Veterinarians are also faced with the responsibility of identifying and replacing knowledge that has become outdated or obsolete. This process of keeping current is increasingly difficult. Veterinary medical curricula are particularly affected by this proliferation of knowledge. Each year the amount of knowledge within each discipline increases, and the pressure increases to include more information in that discipline's courses. This has resulted in the students being submerged in details and memorization of facts with little opportunity and little encouragement from faculty to do other than rote learning during the basic science years. In most schools this has precluded the teaching of problem-solving skills, even though many of us give lip service to the concept.

Medical Informatics

Fortunately, recent advances in information science, and in computer science and technology, offer some solutions to the problems caused by the proliferation of knowledge. The application of these advances is becoming known as medical informatics. The advances range from the design of data bases and their query through artificial intelligence language interfaces to new very high-speed parallel processing machine architectures (supercomputers). The technological advances in computers have led to significant advances in their capabilities at greatly reduced cost. The functional power of the personal computer I used to compose this manuscript is

greater today than the university computer that filled an entire room at Iowa State University 25 years ago. The ability and the cost of storing information has enjoyed similar progress. Just 10 years ago, when I first started working with computers, hard disk storage cost about \$10,000 for one megabyte of storage. Today, I use optical disks in our informatics laboratory that store over 200 megabytes on a 5.25 inch diameter removable disk and the cost is about \$.75 for one megabyte. This combination of increased functionality and decreased costs is fostering a widespread dissemination of computers throughout our society. Even some of the reticent are becoming computer literate and the use of the computer to help solve needs of veterinary medicine is accepted today.

Medical informatics encompasses a wide range of efforts to apply advances in computer science, statistics, mathematical modeling, information science and educational theory to the goal of providing better and more efficient delivery of medical services, whether those be in patient care or other equally important areas of veterinary medicine. As with most emerging disciplines, a precise definition of medical informatics is difficult to get accepted by all involved. One definition is that "Medical informatics comprises the theoretical and practical aspects of information processing and communication, based on knowledge and experience derived from processes in medicine and health care (2)." I rather like an operational definition as proposed by Reichertz (3) which defined it as "being concerned with the documentation, analysis, evaluation, regulation, control and synthesis of information processes in medicine." It is also important to understand the role of specific tools used in a developing field. The field of medical informatics has come into prominence only since the advent of the use of computers. The computer is the primary tool used by investigators in medical informatics to address the areas of information acquisition, retrieval, analysis and dissemination.

Medical informatics and the power of its tools have great potential for affecting most areas of veterinary medicine. Practice management functions have received the most attention to date where appointment scheduling, admission records, pharmacy records, accounting functions, cost analysis and cost control have all been made available to practi-

tioners through specialized computer programs. Areas such as diagnostic decision assistance, expert consultant systems for diagnostic and management assistance, and drug information systems are also being developed for use in veterinary medicine. Another area of increasing importance is the development of large computerized data bases of medical literature and other specialized medical information such as drug information. The ability of veterinarians to use a personal computer to obtain current information through national and international communication networks will have a significant impact on the delivery of veterinary medical services. Recent advances in text query and retrieval processes and the use of simple English statements for queries, rather than having to use computer language terminology are having significant influences in this area. Another significant area involves the use of computers to aid in decision-making. Studies of how health professionals make decisions are leading to knowledge about underlying assumptions and the processes employed. Knowledge advances in decision theory are providing a better understanding of the methods by which veterinarians ought to make rational decisions about diagnosis and therapy. Sophisticated models are being developed that will assist in building computer applications that will provide assistance to veterinarians in many types of professional endeavor.

For purposes of this discussion, I have arbitrarily selected the areas of biomedical data bases; medical information systems; computer assisted instruction; and biomedical research. I shall attempt to provide examples of medical informatics in each of these areas and touch briefly on some of the expectations for the future.

BIOMEDICAL DATA BASES

The development of modern main frame computers that accommodate many simultaneous users, operate at very high speeds and have massive amounts of quickly accessible information has made possible the use of computerized data bases of information. Today, not only the airlines, banks and the Internal Revenue Service use large data bases, we in the sciences and professions make extensive use of these resources. There are over 2,000 bibliographic data bases ranging from law to education to nuclear physics.

MEDLINE from the National Library of Medicine represents the state-of-the-art in medical bibliographic data bases. It provides the most comprehensive coverage of medical literature in the form of citations and abstracts available today (4). A variety of commercial data bases provide access to MEDLINE and include additional services such as helpful assistance for nonexpert users. One service provides access to over 200 medical journals prior to their inclusion in MEDLINE (5).

The future holds even more promise for use of information from large medical data bases. In the past, the primary reason for having large data bases on main frame computers

was a lack of storage capacity on smaller computers. Development of optical disc storage technology is changing this. It is estimated that the entire contents of MEDLINE could now be stored on two or three optical disks, each of which has the capacity to record 100,000 pages of text. Optical disks are now being connected to microcomputers and the drives cost less than \$1,000. This results in a drastic reduction in the cost of accessing the data and more and more libraries are beginning to purchase bibliographic material on optical disks. Optical disk technology also provides for the inclusion of graphics such as diagrams or photographs as well as text, thereby expanding the information base. Another important development that will influence the use of medical data bases is improvement in the ability to query the data bases. Current queries depend upon manual indexing of key words in each citation. Computer programs have now been developed that automatically index appropriate words in the text, significantly reducing the amount of costly manual indexing and increasing the number of indexed words (6,7). Programs are being developed that not only interpret the syntactic content of a search request but also the semantic intent. Retrieval of information will be based not only on matching index terms but also on the intentions of the searcher. On-line publishing is another advancement that will be expanded. Many publications will bypass print media and be published in electronic form. A current example is in veterinary pharmacology where the widely read international newsletter *AnimalPharm* is now available both in printed form and on-line through a dial-up service in London (8).

Large computerized data bases of medical information are also becoming available in veterinary pharmacology. Examples of these include the Food Animal Residue Avoidance Database, a joint effort of North Carolina State University, the University of Florida, and the University of California-Davis. Another is the InterAmerican Compendium of Veterinary Drugs developed in our laboratory at Virginia Polytechnic Institute and State University.

The future holds the potential for expanded use of medical data bases. Expanded distribution will occur because of technologies such as the optical disk. Graphic information in the form of photographs, diagrams and charts will accompany the text material. Significant advances in the techniques of indexing and searching these data bases will allow more natural language retrieval of data and on-line publishing will become a new means for distribution of medical knowledge.

MEDICAL INFORMATION SYSTEMS

Patient information and clinical data has become much more voluminous and its management much more sophisticated in the past two decades. Veterinary medical records now include not only patient and owner data but also progress notes, laboratory results, radiographic interpretations, medi-

cation records, dietary records, owner instructions, state and federal reporting forms as well as financial and accounting data.

An important part of medical informatics is the design, development, analysis and evaluation of computer-based medical record information systems. These are of special interest to clinical pharmacologists where computer assistance in designing individual patient therapeutic regimes can be helpful.

The state-of-the-art in veterinary medical information systems is represented predominantly by the various practice management systems being used today in private practices and a few teaching hospitals. These systems have developed simultaneously with the development of low-cost personal computers and are largely the result of entrepreneurs providing office automation functions for client tracking, accounting and other fiscal functions and patient reminder notices. Some of the more sophisticated systems are now beginning to include capabilities for medical data management.

At the same time the practice management systems were being developed by commercial interests, other medical information systems have been under development primarily in academic settings. These have been focused on computer-assisted medical decision-making (CMD). The majority of those developed to date have been stimulated by L. L. Weed's pioneering work in the problem oriented medical record and his subsequent computer software programs called "Knowledge Couplers." Faculty at Mississippi State, Cornell, and Tuskegee have pioneered in these activities. These programs, which associate the signs and symptoms in an individual patient with the probabilities of being associated with a particular disease syndrome, are now also beginning to be marketed in conjunction with the practice management programs. A few other types have been or are being developed but have yet to enjoy the popularity of the knowledge coupler programs. The latter include an expert system for clinical pharmacology decision-making in veterinary medicine being developed by a team of veterinary pharmacologists and computer scientists at Virginia Polytechnic Institute and State University (9).

The rationals for development of CMD systems have been summarized by Shortliffe (10):

- to improve the accuracy of clinical diagnosis through approaches that are systematic, complete, and able to integrate data from diverse sources;
- to improve the reliability of clinical decisions by avoiding unwarranted influences of similar but not identical cases and by making the criteria for decisions explicit and hence reproducible;
- to improve patient management and therapies by balancing the expenses of time, inconvenience or funds against benefits and risks of definitive action;
- to improve understanding of the structure of medical knowledge, with the associated development of

techniques for identifying inconsistencies and inadequacies in that knowledge; and

- to improve understanding of clinical decision-making in order to improve medical teaching and to make computer programs more effective and easier to understand.

CMD systems focus on making the most appropriate diagnostic and/or therapeutic decision for a given patient, herd, or flock. The approaches used are varied and include clinical algorithms, statistical pattern classification, decision-analysis and expert systems. All of these approaches have been developed in fields other than veterinary medicine and medicine. They are, however, being used quite prevalently in medical informatics today and they offer means for advancing veterinary pharmacology, both basic and clinical.

Clinical Algorithms

Clinical algorithms are unambiguous step-by-step protocols for decision-making. Simply, they are flow diagrams to instruct a person about information that needs to be obtained, decisions that result from that information and procedures to follow as a result. A number of teaching hospitals use these today, particularly for veterinary technicians and students beginning their clerkships in a clinical service. The computer has been used as a means of presenting the algorithm to the decision-maker and requesting the needed information.

A system developed for use by primary care physicians for management of complex chemotherapy is an example often cited as one of value in extending specialist knowledge to nonspecialist practitioners (11).

Clinical algorithms can make significant contributions to the delivery of veterinary medical services. They are, though, most appropriate where the logic associated with diagnosis and treatment is straightforward. Other methods of decision-making are necessary in more complex situations.

Statistical Pattern Classification

Medical informatics research using statistical pattern classification employs statistical technics to identify relationships of signs and symptoms indicating the presence of disease. They identify sets of signs and symptoms that are statistically associated with a distinct syndrome. The methods used involve collecting information on large groups of patients. Then, one of several statistical technics is applied to identify relationships between independent variables such as symptoms and the criteria or disease classifications. The statistical technics range from simple linear regression to complex discriminant analysis or Bayesian classification. The final product is a numeric index that provides the most likely diagnosis or most effective treatment when applied to the data from a single new patient. Bayesian classification is an interesting subset of statistical pattern classifiers and has been pursued in the work of White at Cornell (12). This technic makes use of conditional probabilities. The underlying

ing assumption is that it is possible to predict the probability of a patient having a disease, given the patient's signs and symptoms, the prevalence of the disease in the population, and the frequency with which the signs and symptoms are observed in patients known to have the disease. The work of deDombal (13) is an example of a Bayesian classification system for acute abdominal pain in humans. In a study of 304 patients evaluated retrospectively by specialists to determine the correct diagnosis, clinicians reached the correct diagnosis less than 80% of the time while Bayesian classification system was correct in 92% of the cases.

The best of the statistical pattern classification schemes have been able to outperform clinicians consistently. They have been remarkably successful in using mathematical models to classify individual patients with specific sets of signs and symptoms into specific disease categories.

Decision Analysis

Another approach that uses computers to assist medical decision-making uses rational human decision-making within the structure of the process. This system lays out options and possible outcomes in explicit detail, stopping at each step in the decision process to assess the probabilities and values of each outcome and then selecting the most desirable outcome. Along the decision tree are chance nodes over which the decision maker has no influence. The success of decision analysis depends upon the ability to estimate the probabilities associated with the chance nodes. The uniqueness of decision-analysis in medical informatics is that it is a process for making rational decisions that specifically take into account probability aspects over which no known control can be exercised as well as the values associated with specific judgments made during the process.

Because a variety of sophisticated economic technics such as cost-benefit analysis (14) and cost-effectiveness analysis can be used to estimate the utility of outcomes, this technic offers potential for use in animal health decision making, especially for animals of economic importance such as food-producing animals. Decision-analysis technics in the hands of decision makers can assist in determining the relative benefit or value of decision outcomes such as treatment regimens for large herds and flocks.

Expert Systems

Expert systems attempt to emulate expert's problem-solving technics through computer based nonnumerical symbol manipulation. In contrast to clinical algorithms and decision analysis technics, computer technology is a central component of expert systems. The underlying assumptions are that it is possible to separate the knowledge of the particular discipline or expert from the problem-solving method used to apply that knowledge and that it is possible to represent that knowledge in a form that can be manipulated by computers using symbolic knowledge or similar approaches. These systems seem especially useful in such areas as

differential diagnosis and therapeutic decision-making. An example of the latter is the being developed by Roach, et al. at Virginia Tech (9).

A major type of expert system used in medicine is rule-based. These types represent the knowledge base as a set of IF-THEN rules or as they are called in one of the computer languages commonly used, antecedent-consequence rules. For example, a rule could state: IF the animal's temperature is elevated AND leucocytosis is present, THEN infection is probable. The systems typically have a large number of interrelated rules linked together. Consequents of some rules are often antecedents of other rules. Decisions are binary in that a consequent is true only if all its antecedents are also true.

The classic example of an expert system developed for medical decision-making is one called MYCIN (15). The MYCIN expert system uses over 500 rules relating signs, symptoms, and culture information to diagnostic conclusions and appropriate antibiotic therapy for meningitis. Since the development of MYCIN, a number of rule-based systems have been developed using a variety of languages and approaches. One of the more recent developments in veterinary medicine is the RORI system developed by Smith at Georgia (16). RORI is analogous to the inference engine in other expert systems in that it manages the process for using rules developed to assist in particular veterinary medical problem-solving areas.

Expert systems assist in and simulate the processes of medical decision-making through the use of computer programs. Successful applications in well-defined areas have equaled the performance of experts.

Summary

Clinical algorithms, statistical pattern classification, decision-analysis, and expert systems currently represent the major approaches to computer assisted medical information systems. These approaches hold promise of major contributions of medical informatics to veterinary pharmacology.

COMPUTER ASSISTED INSTRUCTION

Computer assisted instruction (CAI) is an area of medical informatics that attempts to adapt the technology of computers to provide educational experiences beyond the traditional lecture and laboratory. CAI takes many forms, from simple presentation of text material to complex simulations of biological processes. Programs designed to assist in the memorization of factual material are at the simplest level. At this level, CAI provides little more than a "page turning" system, simply presenting textbook material in computer form. Slightly more complex are testing systems for evaluation of knowledge and competence. More sophisticated programs use complex branching technics to guide the learning process and often integrate slides, video tapes or video disks to

simulate real situations.

CAI has been available in veterinary colleges for almost two decades; it is present in some form or another in most today. The earliest of these was the PLATO system developed at the University of Illinois. PLATO was originally based on mainframe computers but now is available for use on microcomputers. A variety of individual tutorials using computers is available today at most schools. Mississippi State appears to have made the strongest commitment to using computers for instruction. All entering veterinary students are required to purchase Apple Macintosh microcomputers and a significant number of courses in the curriculum utilize the computers for instructional assistance. The College has also committed itself to developing all course syllabi in hypertext format for distribution to all students.

The future for CAI is especially promising because of new developments in computer technology and data storage, reduced costs of equipment and by progress in medical informatics in general. The ability to store large volumes of information on optical disks has already been mentioned. The costs of these are decreasing rapidly and soon will be as common on personal computers as their counterpart compact disk players are on music systems.

The challenge for medical informatics is to provide intelligent software to interface between students and the large volumes of data that can now be made available. A merging of the techniques used in medical decision-making with instructional methods seems likely. Such programs could present a situation to a student, allow the student to make a decision based on the information available, and then compare the student's decision with that of the computer system.

The use of computer programs for continuing education and recertification offers much potential. In the long run, CAI may have its greatest benefit in these areas since it can provide instruction and evaluation at the convenience of the veterinarian rather than the instructor. It greatly extends the options available for learning other than the currently overused and inefficient seminar paradigm.

BIOMEDICAL RESEARCH

The implications for medical informatics in biomedical research are as varied as the research itself. An obvious use of computers is to help the researcher manage and analyze large volumes of data. *In vivo* monitoring systems of physiologic parameters can provide voluminous data points that can be analyzed only by computer assistance. The development of large data bases have extensive implications for epidemiological research. Such data bases can provide means for studying relationships among disease processes, treatment outcomes and other biomedical parameters not possible with previous methods and tools.

Medical informatics is also defining new areas of basic biomedical research. These include medical decision-making,

knowledge acquisition and representation, and the development of new biomedical models. Certain programs can become research tools in themselves. Pharmacokinetic modeling programs are an example. Such tools can facilitate certain research decisions by assisting the investigator in selecting the most appropriate experiment and methodologies for the particular research.

SUMMARY

Developments in medical informatics have had significant effects on instruction, clinical practice and biomedical research. The opportunities offered by the future are even greater. How we adapt to the use of computers as tools to extend our abilities and how we develop medical informatics as a discipline to advance the theoretical and practical aspects of information management will determine many of the advances veterinary pharmacology will make.

ADDITIONAL PAPERS

The remainder of this session has been designed to provide you with examples of how computers and information management technics are being used in veterinary pharmacology today. Our next paper will demonstrate the use of computerized data base management techniques to manage and utilize large volumes of information about drugs. This will be followed by a presentation of research that uses computer management of complex pharmacokinetic models for clinical and research purposes. Then, we will hear about the use of a microcomputer program to teach students basic principles of pharmacokinetics and clinical pharmacology. Our last paper will be a discussion of current work in medical decision-making and the use of expert systems in pharmacology.

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Coping With the Information Explosion in Pharmacology: The Food Animal Residue Avoidance Databank

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Introduction

We are living in an age of information. Today, the unprecedented rate at which new information is generated far exceeds the capacity of the human mind to assimilate all of these new facts and concepts. It has become increasingly more difficult and time consuming to remain current in one's specialty area, and this problem will continue to grow in the future. To avoid drowning in a sea of information it has become important to develop the tools and skills to manage large amounts of data. Efficient management involves the identification of information sources; selective acquisition of information which is scientifically valid and pertinent to the needs of the individual; elimination of information which is trivial, invalid or irrelevant; and integration of the information to yield new concepts and knowledge. This idea of sifting through vast amounts of data to arrive at meaningful in-

formation was probably best expressed by the physician William Osler who wrote: "The knowledge which a man can use is the only real knowledge, the only knowledge which has life and growth in it and converts itself into practical power. The rest hangs like dust about the brain or dries like raindrops off the stones (1)." More recently, the concept of efficient information management has been described in the form of an equation (2):

$$\frac{\text{Scientifically valid and useful literature of the area of interest}}{\text{Literature of the area of interest}}$$

Literature of the area of interest

When the area of interest covers a broad scope or when vast amounts of information exist for a narrower subject

area, additional tools are needed to efficiently manage the data. Early tools developed to aid in the organization of information include the bibliographic citation indexes such as *Index Medicus* and *Index Veterinarius*. More recently, the information contained in these bibliographic indexes has been transferred to magnetic media, stored and accessed by large computers and is available to the public via remote computer terminal. This new form of storage offers tremendous advantages over the "hard copy" form in that topics can be searched at speeds which are several orders of magnitude greater than can be achieved by manually searching the indexes. For example, searching for a single subject through *Medline* which contains more than 5 million citation references, generally requires less than 1 minute. Another advantage over manual searching is that the user does not need a library to access information. In fact through information services like Dialog Information Services, a personal computer, modem and telephone line are all that are necessary to have access to the information contained in the National Library of Medicine, the National Agriculture Library and the Library of Congress.

The disadvantage to the large bibliographic citation databases is that they only point the user to sources of information without interpreting, summarizing, condensing or integrating the information into a standard format conducive to assimilation by the user. In most cases the user is still faced with an overwhelming amount of information and must rely on other management strategies to achieve his intended goals. One approach to taming the information beast has been the development of specialized databases containing information pertaining to specific subject areas. The Food Animal Residue Avoidance Databank (FARAD) is an example of a specialized database. Only information which is relevant to the area of drug and chemical residues in foods of animal origin is contained in FARAD. Although all information contained in the FARAD databases is fully referenced, FARAD differs from a citation database in that FARAD contains actual information which has been selectively extracted from original research articles. The information is maintained in a structured uniform format and this consistent uniformity allows the user to rapidly compare similar experimental data among several different studies. Using this comparative approach, large amounts of data can be evaluated efficiently, and useful knowledge obtained.

Developmental History of FARAD

In February 1982, USDA's Food Safety and Inspection Service and the Extension Service signed a cooperative agreement to establish a Residue Avoidance Program (RAP) (3). The purpose of the program was to gather existing data pertaining to residue avoidance and to assemble this information into programs aimed at livestock producers, livestock extension specialists, and food-animal veterinarians. The information was intended to be used by these professionals to reduce the incidence of drug and chemical residues in red

meat and poultry. In all, 49 projects in 33 states were funded under the Residue Avoidance Program (3). In 1983, FARAD was established as a RAP program through the cooperative efforts of pharmacologists and toxicologists at veterinary colleges in California, Florida, Illinois, and North Carolina. The objective of the FARAD project was to compile into a single source large amounts of information on those drugs and other chemicals which may persist as residues in foods of animal origin. In order to effectively manage this large compilation of data, a decision was made to take advantage of existing micro computer technology. FARAD was initially developed using dBase II running under a CP/M operating system on an Osborn II micro computer. Presently, FARAD is maintained on a Microvax minicomputer but is programmed to operate on micro computers which run MS-DOS. The program is now written and compiled in a super set of dBase III programming language (Clipper) with certain segments of the program being written in C. More than 15,000 records presently comprise the FARAD databases, and the entire system including database and program files consumes 13 megabytes of disk storage. Despite the changes in software, hardware and volume of information, the basic concepts upon which FARAD was conceived have been preserved.

Structure of FARAD

Because FARAD was specifically intended to serve as a comprehensive source of information on residues and residue avoidance, it was first necessary to identify those data elements which were critical to addressing the problems of residue avoidance. Ultimately, it was decided that six different databases were necessary to accommodate those various types of data which are fundamental to residue management. These data files include: 1) proprietary information on all pharmaceutical products approved by the FDA for use in food animals in the United States; 2) physicochemical information on more than 200 chemicals contained in the databank; 3) regulatory information pertaining to tolerance and action levels of chemical residues in animal products and allowable concentrations of drugs in feed; 4) pharmacokinetic rate and volume constants pertinent to residue depletion modeling in a variety of species; 5) summary information on educational materials developed under the USDA's Residue Avoidance Program; and 6) bibliographic citations to which all of the information contained in the databank is referenced.

The Trade Name file is a comprehensive listing of specific information on all pharmaceuticals currently approved in the United States for use in food-producing animals. More than 800 products are included in this file, and as new products are approved or older products are withdrawn from the market, the file is updated to reflect these changes. An example of the information available for each product is presented in Table 1. All of the information contained in the Trade Name file has also been published in book form (4).

Table 1. Sample entry from the FARAD trade name file.

CEFTIOFUR SODIUM

Product name	Naxcel	NADA 140-338
Sponsor	Upjohn Co.	
Active ingredients	Ceftiofur sodium	
Classification	Cephalosporin—antibacterial	
Formulation	Sterile powder for reconstitution to a solution containing 50 mg ceftiofur/ml	
Product type	Therapeutic drug, Rx Route, Injectable—IM	
Approved species	Nonlactating dairy cattle and beef cattle	
Withdrawal time	None	
Indications	Use for the treatment of bovine respiratory disease (shipping fever, pneumonia) associated with <i>Pasteurella hemolytica</i> , <i>P. multocida</i> and <i>Haemophilus somnus</i> .	
Directions	Administer 0.5 mg/lb bwt by intramuscular injection. Treatment should be repeated once every 24 hours for 3 days. Treat an additional 2 days if animals do not show a satisfactory response.	
Misc. information	Do not use in animals previously found to be hypersensitive to the drug. Use of doses in excess of those indicated may result in illegal residues in tissues.	
References	21 CFR 522.313; <i>Fed Reg</i> 02/24/88 (5369)	

The Generic file contains physiocochemical information on all generic drugs, pesticides and environmentally persistent chemicals included in the FARAD priority list of compounds. The data compiled for each chemical compound include the generic and chemical names, molecular formula and weight, the pK_a/pK_b , solubility data, partition coefficients, and analytical methods for residue detection.

The Tolerance/Action level file contains regulatory information pertaining to specific drugs, pesticides, and other chemicals in food-animal species. For each compound, established tissue tolerance or action levels are listed in all tissues, eggs, and milk for which tolerances have been established. In addition to tissue, egg, and milk tolerances, allowable feed concentrations of those compounds considered as feed additives are included. All of the information in this file was obtained from Title 21 of the *Code of Federal Regulations* (5).

The pharmacokinetic file is comprised of various first or-

der rate constants and values relating to the disposition of specific chemicals in domestic animal species. Table 1 lists the rate, volume, and other constants included in the pharmacokinetic file. The values listed in Table 1 either were extracted directly or were calculated from data reported in the scientific literature. A unique set of pharmacokinetic values was extracted or calculated for each reported study, and in many instances, several sets of values were derived from a single literature source. Presently, there are more than 10,000 records in the pharmacokinetic file. Although emphasis was directed at compiling pharmacokinetic data from studies involving food-producing species, data from all domestic animal species as well as human beings were included in this file for purposes of interspecies comparison.

Table 2. Pharmacokinetic values listed in the FARAD Pharmacokinetics File.

$t_{1/2} 1$	Half-life of phase 1
$t_{1/2} 2^*$	Half-life of phase 2
$t_{1/2} 3^{**}$	Half-life of phase 3
k_a	Absorption rate constant
F	Fraction of the dose absorbed
V_c	Apparent volume of the central compartment
V_d (beta)	Apparent volume of distribution—Extrapolated
V_d (Area)	Apparent volume of distribution—Area under the curve
V_d (SS)	Apparent volume of distribution—Steady-state infusion
A_1^*	Intercept of phase 1
A_2^{**}	Intercept of phase 2
A_3	Intercept of phase 3
1	Slope of phase 1
2*	Slope of phase 2
3**	Slope of phase 3
Cl	Clearance Constant
C_{p0}	Plasma concentration at time = 0
C_{pmin}	Min. plasma concentration - Multiple dose
C_{pmax}	Max. plasma concentration - Multiple dose

* Applies to 2 and 3 compartment models only

** Applies to 3 compartment models only

A large proportion of the research publications used to build the Pharmacokinetic file contained data relative to depletion of drugs and other chemicals in domestic animals, but no attempt was made by the authors to estimate pharmacokinetic rate constants. For these data to be of use, it was necessary to derive estimates of the rate constants from the raw data presented in the articles. These raw data were extracted and forwarded to North Carolina State University for statistical evaluation and estimation of the desired pharma-

cokinetic constants using computer-assisted nonlinear regression algorithms.

All of the information entered into the data files was referenced to a literature source. These reference citations are maintained in the Bibliographic file. Information in the FARAD data files was gathered from a number of sources including the USDA, FDA, EPA, and manufacturers of veterinary pharmaceuticals, but most of the information was obtained from research publications.

Summary

The Food Animal Residue Avoidance Databank is a unique system in many respects. It represents the first attempt to assemble a large, diverse body of information pertaining to residues into a standard format within a single system. Because it is computerized, rapid and selective retrieval of the information is facilitated. This feature is essential because a rapid response to a residue problem is often critical to preventing further losses. The system utilizes pharmacokinetic models to predict residue depletion times. Although this method has been suggested by others (6) as a means of predicting residue depletion times, the FARAD system is the only program to utilize pharmacokinetics on a large scale.

Unlike many databases which merely list reference citations, FARAD, in addition, contains information which has been extracted from scientific publications and transformed into a standardized format of pharmacokinetic rate and volume constants. This allows comparison of drug or chemical disposition across species and across studies conducted by various investigators. Perhaps the most innovative feature of

the FARAD system involves the data reduction process. Many of the research publications used in generating data for the Pharmacokinetic File contained no calculated pharmacokinetic rate parameters. Some were written by residue chemists reporting new analytical methods for detecting drugs or chemicals in tissues or fluids of domestic animals. Others were written as drug distribution studies, and still others were written as pharmacokinetic studies but only raw tissue/fluid concentration data were reported. Utilizing the FARAD data reduction and statistical analysis programs, these data were ideally suited for deriving pharmacokinetic models and have contributed substantially to the pharmacokinetic database.

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Development of an Automated Clinical Pharmacokinetic Dosing Program for Therapeutic Drug Monitoring in Veterinary Medicine

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Introduction

It is well established that the dose of drug administered to an individual clinical patient is often poorly correlated with the serum concentrations achieved. Therapeutic Drug Monitoring (TDM) has recently been advocated for use in monitoring drug concentrations in veterinary patients in order to adjust dosage regimens to compensate for this variability. Pharmacokinetic principles have been applied to this problem in a research setting in an effort to quantitate this lack of prediction. With the advent of microcomputers and relatively inexpensive minicomputers, the full power of pharmacokinetics can be applied to veterinary TDM allowing clinicians to individualize dosages based on pharmacokinetic parameters and assayed drug concentrations.

Our laboratory has been involved in using computers to individualize drug dosage regimens in a research and clinical setting for the past five years and has developed two strategies to address this problem. The first, which is ideally suited to a research and intensive care setting, is to utilize computer driven infusion pumps to precisely achieve targeted serum drug concentration-time profiles in individual animals (1,2). The second approach was to develop a software program to calculate multiple dosage regimens based on individual pharmacokinetics and a targeted serum concentration time profile (3,4). This program, PETDR (Pharmacokinetic Estimation of Therapeutic Dosage Regimens), is an outgrowth of software development for the FARAD (Food Animal Residue Avoidance Databank) program (see preceding Sundlof contribution). The goal of developing automated software systems for veterinary clinical pharmacokinetics is to make the mathematical computations transparent to the user and provide a tool by which TDM can be easily applied in a clinical setting for drugs warranting close surveillance.

Background

In order to fully appreciate the direction of software development followed in our laboratory, a brief overview of the projects requiring these tools will be provided. We have served as the Data Analysis and Support Center for the FARAD network and have been responsible for writing this microcomputer-based software package. This involved three

tasks requiring computer analysis.

First, a software package for microcomputer access to FARAD datafiles allows the user to search for tabulated pharmacokinetic parameters, compute a depletion half-life estimate and "time to threshold" estimate (withdrawal time) where the threshold is obtained from a residue tolerance file, and compare this computed "time" to the legal withdrawal time obtained from a regulatory file. This simple pharmacokinetic algorithm assumes a one compartment pharmacokinetic model with the terminal half-life being rate limiting (i.e. true elimination or rate limiting absorption half-life). The program resides on IBM-compatible PCs and is written in a compiled version of dBASE III+ and CLIPPER.

Secondly, a statistical software package for processing "raw" FARAD data from the literature was developed to estimate pharmacokinetic parameters. This utilizes a Fortran curve stripping routine (CSTRIP) for initial estimates and a nonlinear regression program for final parameter estimates (SAS-NONLIN). It automatically selects the optimal number of exponential phases based on C_p statistic and F-test, provides output on residual analyses, plots the serum drug concentration-time profile, and computes the pharmacokinetic parameters from these estimates. This package has been used to process over 5,000 individual pharmacokinetic analyses and resides on a DEC micro VAX II minicomputer running VMS.

Finally, because many compounds are not "ideal" (one compartment, IV administration, non-protein bound), dose predictions using a simple algorithm may be incorrect. We have written PETDR for handling up to three exponentials to compute a dose regimen based on pharmacokinetic parameters and a user-defined target serum-concentration-time profile.

Research in our laboratory has been focussed on correlating the shape of a serum-concentration profile to primarily toxicological effects in the presence of abnormal disease. We have designed a computer controlled infusion pump which allows drug to be infused according to multiexponential rates to precisely produce defined target profiles when the intravenous disposition profile of a drug is known. This software uses linear systems deconvolution analysis and is fully de-

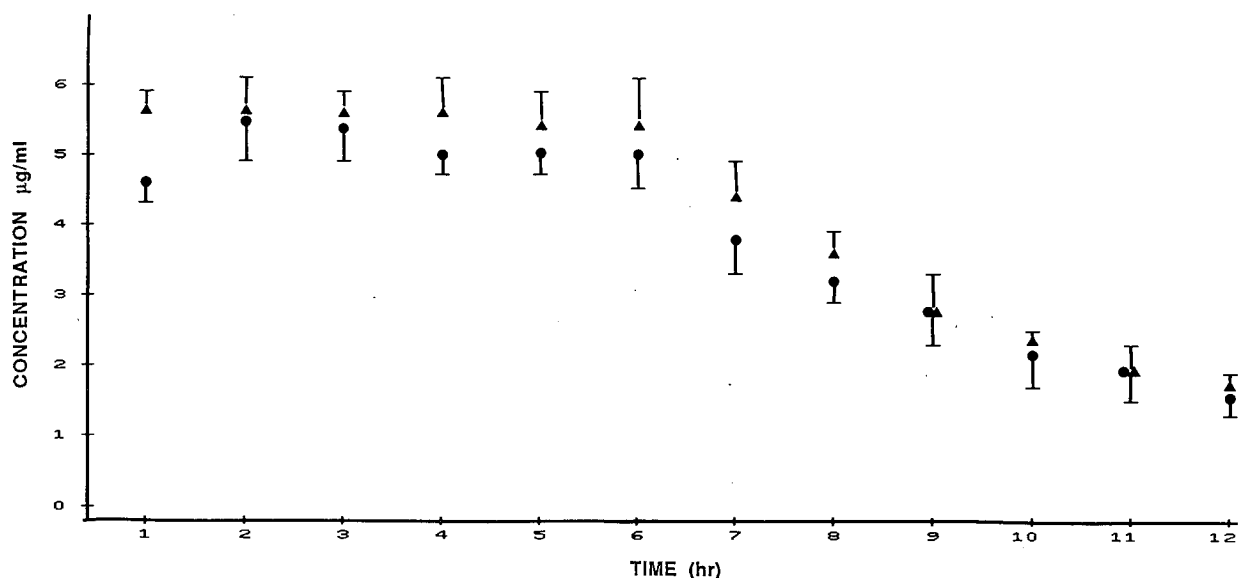


Figure 1. Mean infusion profiles for intact and nephrectomized dogs (N=5/group) following a protocol for maintaining a six-hour plateau followed by a six-hour declining phase (5).

scribed elsewhere (1). Figure 1 illustrates the profiles obtained in normal and 7/8 nephrectomized dogs administered gentamicin by this route. Note that although pre-infusion half-lives were 61 and 116 minutes in normal and diseased dogs, respectively, terminal decay rates in this protocol had pump-controlled half-lives of 3.5 hours and identical steady state serum concentrations of 5 mcg/ml.

This approach is an optimal solution for producing defined serum drug-concentration time profiles based on individual pharmacokinetic analysis. Similar pumps are under development for human clinical use and it is likely that they will leave the research laboratory and be routinely used for intensive care situations in the ensuing decades.

PETDR Approach

In order to practically utilize pharmacokinetics to design dosage regimens, PETDR was implemented (3). Figure 2 is a flowchart of such an automated dosage program.

In this program, a "therapeutic window" is defined (Peak, Trough, Average C_p , Maximum Interval) which describes the desired shape of a patient's serum concentration-time profile. Pharmacokinetic parameters are then obtained from either FARAD mean population estimates for the species at hand or are calculated from serum concentration-time data for the individual patient using the statistical software described earlier. The program iteratively attempts to derive an optimal dosage regimen (dose and interval) using Newton's method to achieve this endpoint. It outputs the user with the computer derived regimen and compares it to the desired endpoints. The user may then adjust dose, interval or loading dose as he/she pleases. A plot and table of serum concentrations versus time post-dosing for any dose is then produced

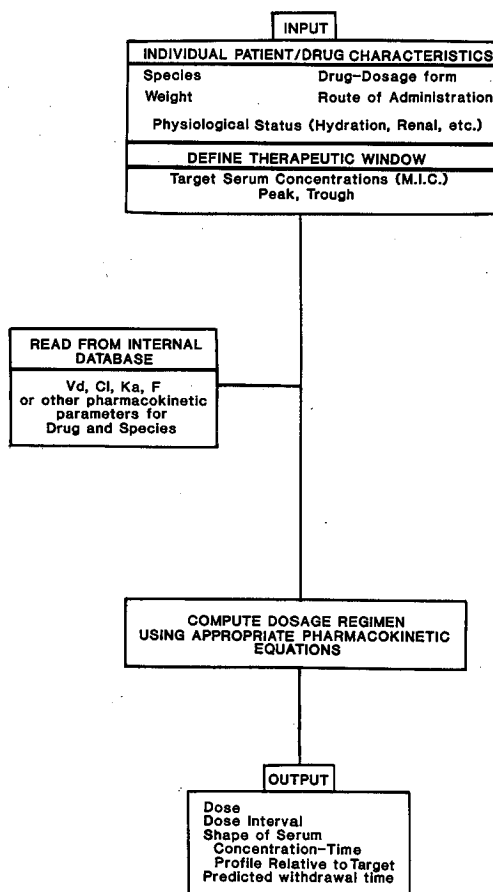


Figure 2. Conceptualized approach to a computerized clinical pharmacokinetic dosing program (See reference 6).

against which samples may be collected for validation. This is PETDR's major strength for use in TDM. A future version will use Bayesian techniques to change the parameter estimates based on this new data. At present, the user has to manipulate parameters based on guesstimates obtained from clinical data until the predicted matches the measured serum concentrations. The program also allows one to compute the time required to reach a threshold concentration based on this dosage history which is useful for estimating drug depletion times. As in FARAD, tolerances and approved withdrawal times are electronically available. A full flow chart of the options available in this program follows.

Options

1. Compute a dosage regimen.
2. Determine a multiple-dose serum concentration-time profile.
3. Predict serum concentration for any time after any dose.
4. Predict a "time to tolerance."

Select Method of Kinetic Data Input

- A. Calculate pharmacokinetic parameters by FARAD nonlinear regression program.
- B. Input known pharmacokinetic parameters.
- C. Access FARAD mean population pharmacokinetic parameters for species to be treated.
- D. If species or disease state files do not exist in FARAD, attempt interspecies extrapolation or disease prediction using AI algorithms (prologue) from pharmacokinetic and physiologic data (future version).

Pharmacokinetic Parameters Required

K, K₁₂, K₂₁

Cl, V_c, V_d(area), V_d(ss)

A, B, Alpha, Beta, Half-lives

One or Two Compartment Model

Computer will automatically calculate values of all parameters (including AUC and AUMC) once minimal data set has been entered. Program will then request that all data entered is correct. This is an essential step since dosage regimen becomes part of the medical record.

Dosage Regimen Calculation

1. Input maximum, minimum, or average steady state serum concentrations desired.
2. Input target MIC or threshold concentration (FARAD).

Program then calculates a dosage regimen (dose and interval) focussing on achieving desired peak concentration and adjusting interval to arrive at trough "near" target value entered. Forces interval to be clinically acceptable (4, 6, 8, 12 hrs). Recommends loading dose if steady state is greater than 5 half-lives.

Output

Prints: Calculated dosage regime.

"Target" and "calculated" peak, trough and average steady state concentrations.

Allows user to then adjust dose or interval if desired.

Based on calculated regimen or inputted regimen, and number of doses administered, outputs:

- Serum concentration-time profile for last two doses (plot and table for use in TDM),
- Predicted serum concentration at time T,
- If MIC inputted, % of time above MIC,
- If threshold tolerance, time to tolerance,
- If IV and non-IV serum concentration data entered, calculates bioavailability based on AUC.

Future Developments

The present program is based on intravenous drug administration. Under development are algorithms for drug administration by nonintravenous routes which will make the program more generally applicable. An intelligent interface program to FARAD is also being designed which would scan all of the pharmacokinetic files in FARAD and obtain a best estimate of the kinetic parameters relevant for an individual patient or generate an interspecies extrapolation if data for the species at hand is not available. This program should also take into account any disease or physiological states which exist. Initial work has utilized the AI language Prologue. However, different approaches may be adopted as development continues. Finally, PETDR as currently configured was designed to maximize data accuracy and integrity and thus has numerous mandatory data-checking sequences built into it to insure that the dosage and medical record output is correct. This makes it cumbersome to use. The VMS program has also not optimized the user interface as the other FARAD programs have in a microcomputer environment. We have felt that up to this point, substance over style has been important but when the substance is completed, the style must be likewise optimized.

PETDR and FARAD are only one approach to implementing automated clinical pharmacokinetic dosing programs for therapeutic drug monitoring in veterinary medicine. As with many programs which evolved out of necessity, our approach has been biased to available equipment and individual needs. There are numerous other valid approaches which can be taken to arrive at the same goal.

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PharmTools: A Computer Technique for Pharmacokinetic Modeling and Replacement of Teaching Animals

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Introduction

A pharmacokinetics laboratory has been included in the sequence of basic pharmacology laboratories taught at the Virginia-Maryland Regional College of Veterinary Medicine. Originally, sheep were dosed with various sulfonamides, blood and urine samples were collected and analyzed using the Bratton-Marshall colorimetric method. Although some of the data was certainly representative of the pharmacokinetic profile for a given sulfonamide, much of it could not be analyzed appropriately. Dosing, sampling, and analytical errors lead to results inconsistent with the known behavior of the various sulfonamides in sheep. In many cases, determinations of total urine sulfonamide eliminated suggested that the sheep "manufactured" considerable amounts of sulfonamide.

In 1983, data were developed, by computer simulation, from known pharmacokinetic models for sulfonamides in sheep. The emphasis of the laboratory shifted from sheep handling, sample acquisition, concentration determinations

and finally, pharmacokinetic profiles; to data analysis, the development of appropriate models, multiple compartment procedures, and the simulation of the altered pharmacokinetic behavior of clinical situations. In the latter simulations, students were encouraged to use the pharmacokinetic models they developed in the laboratory and speculate about altered drug distribution and/or elimination. The simulations were done using CONSAAM (1) which is essentially an operating environment for SAAM27A. Unfortunately, it is a very cumbersome way to manipulate the requests from 12 laboratory groups who wished to run 2 to 5 simulations. Further it requires some expertise in CONSAAM, an understanding of simulation by the SAAM27A package, and in our case, access to a VAX 11/785 mainframe computer. Simulations for the laboratory required up to 12 hours of faculty and computer time which was expensive and made the faculty member unavailable to consult with the students on the validity of the simulations they were developing, or to answer questions about their pharmacokinetic models.

In 1987, two senior veterinary students (who, as sophomores, participated in the revised laboratory described above) agreed to develop a computerized modeling system as a project assignment in an elective Clinical Pharmacology rotation. PharmTools is the fruit of their academic labor. I simply made the request; set the guidelines for basic features; and, until the fun of evaluating their unique product, stayed out of the way.

Goals for the Teaching System

Ease for novice user. Because the purpose of the system is to distribute the ability to simulate among the participants in the laboratory, everyone in the laboratory, including instructors, should be able to make it go. An easy-to-use "interface" should require a minimum of keyboard interaction and virtually no commands.

Ability to upgrade and integrate. We envisioned a core system to which other models would be attached (multiple compartment, noncompartmental) and which could interact with computerized databases to give the user graphical simulations from documented pharmacokinetic profiles of specific drugs in animals.

Single and multiple dose simulations. Graphical depiction of such things as accumulation to steady state and slow rate constants of absorption depends on the ability to simulate the administration of repeated doses of the drug.

Automatic Scaling of Graphs. In our opinion, eye-pleasing and easily interpreted graphs were a key feature in acceptance by veterinary faculty and students of the system we planned.

The Programming Environment

Basic was the first language available to personal computer users and is generally included in a personal computer purchase. Its commands are fairly plain, and structure and syntax are simple. Fairly complex applications (programs which perform specific kinds of tasks) can be written using Basic. Pharmacokinetic programs for personal computers began to appear with the introduction of the Apple II computer. Nearly all were written in Basic. Basic is however, a very cumbersome language (a large number of commands are necessary to perform complex operations), and large Basic programs require considerable execution time. As a consequence, sophisticated applications are difficult to produce and may not perform well. As a teaching tool, Basic is only really suited for teaching elements of logic, programming, and Basic itself.

With the introduction of the IBM-PC and IBM's policy which allowed programmers access to "secrets" of the IBM operating system (and the data processor which it manipulates) it became possible to develop user-oriented software (think programs). Individuals outside of the company providing the computer could develop software that performed sophisticated manipulations of text and data (word processors, spread-

sheets, databases) using relatively few key strokes and no programming at all on the part of the user. Development of teaching software that interacted with the student was facilitated, but it was still in the hands of people with specialized programming skills. The number and sophistication of such programs increased. Still, there are many potential approaches to computerized teaching which may not have appeal to the marketing interests of software companies; or simply are part of the imagination of individuals who do not possess sufficient programming skills or programming time.

An Engine for Graphical Analysis of Pharmacokinetic Data

PharmTools, a computerized teaching tool has been developed by Drs. Neal Bataller and Carl Osborne, two recent graduates of the Virginia-Maryland Regional College of Veterinary Medicine. The program was developed using HyperCard (2), a "software authoring" system, and HyperText, its associated programming language. The system was chosen for this project, specifically because it is relatively easy to author useful "programs" and to share this software with other users. Computer users with limited resources can develop job-specific and sophisticated software. While a program for pharmacokinetic teaching may have limited commercial value, it is precisely the kind of program that appeals to a small audience of specialized users. PharmTools an example of this kind of development.

Essentially, PharmTools is a generic system which allows a student to enter rate constants, volumes and doses pertaining to any drug in any species. PharmTools then calculates concentrations of the drug versus time and displays the concentrations graphically. Values for minimum, maximum, and average concentrations are also displayed. Online help is also available, instructing the student in the use of the program as well as describing the pharmacokinetic constants and other model parameters. The system currently supports intravenous administration, routes which require an absorption rate constant, a loading dose, and single or multiple doses using a one-compartment open model. Programming has also been included which will facilitate the addition of two and three compartment models.

PharmTools is offered to the "public domain" in prototype form (certain functions are under construction). Users are encouraged to see how it works, improve it, attach it to other devices of their own creation, and pass it on to others.

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Future Applications of Computer Technology in Pharmacology: Roles for Artificial Intelligence, Hypertext, Networking, and Interactive Video

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Introduction

Because the title includes topics that could each serve as subjects for separate symposia, this paper will be limited to introducing the concepts and giving some sample applications of interactive video, hypertext, and artificial intelligence. The goal is to create interest that will lead to widespread application of these new tools in teaching veterinary pharmacology and in creating drug-related information systems for veterinarians.

Major topics to be considered are general considerations, interactive video, hypertext, and artificial intelligence. Although superficially disparate, the latter 3 topics are related by an underlying concept that can be expressed by a question. Namely, how can we enhance acquisition and use of data, information, knowledge, and wisdom in pharmacology? In this context, "acquisition" refers to acquisition in a computer manipulable form. "Use" refers to applications in education and professional practice. "Data", "information", "knowledge", and "wisdom" refer to the level of organization of the symbols (facts or information), that we might expect to obtain from a computer system. It is obvious that with current levels of technology and understanding, we are going to be much more successful at creating computer systems to help us at the "data" end of this spectrum than at the "wisdom" extreme.

Our considerations of what human "knowing" entails at various levels of sophistication and organization, prompted my colleague, Dr. James B. Morrison, to rhetorically ask "If your specialty is pharmacology, why worry about epistemology?" This might seem to be a rather arcane issue, but it is a legitimate question. Why, indeed, should pharmacologists be concerned with how information and knowledge are symbolized and organized?

Among the reasons is that we have exceeded the limit of our ability as humans to ingest and use the information being made available to us at an ever increasing rate. Yet, if we cannot handle it, we still cannot afford to ignore it (1). Therefore, we need a cadre of scientists in our discipline who can organize and compress (2) the information into a more digestible and retrievable form for use by students and professionals alike.

Two major categories of technology will help us accomplish the task of organizing and compressing pharmacologic information to facilitate its use. The two categories are machines and concepts. Computers and audio/video equipment form the mechanistic foundation. The concepts are implementable in software including interactive video, hypertext/hypermedia systems, and artificial intelligence/expert systems. The importance of rapid advances in computer and audio/video technology combined with lower cost in making the entire concept viable cannot be overemphasized. Success in creating a future we prefer will depend on our own human efforts and intellect more than on these technologies. We have our work cut out for us.

Interactive Video

Interactive video will be especially useful in increasing the efficiency of information and knowledge acquisition by students, but it can also be an integral part of tools for other uses to be mentioned later. Interactive video instruction essentially consists of a student, an image/information source, and a controller which is, in one of the levels of interactive video, a computer. Although not an absolute requirement, one of the current hallmarks of interactive video is the video disk. A single 8 inch diameter video disk can store over 50,000 individual slides or 30 minutes of television video per side in extremely high quality form. Furthermore, the access time for retrieval of a specific frame or sequence of frames is in milliseconds. This is the time required to move from one part of the disk to another, so response to user desires is essentially instantaneous.

How is interactive video used? In 1985, Dr. O.F. Roesel from Purdue University, received a Student American Veterinary Medical Association (SAVMA) award for a program entitled "What's Your Diagnosis." This program was built around a case of tetralogy of Fallot in a miniature poodle that was a patient in our small animal clinic. Key events in the diagnosis, surgery, and necropsy of the case were video taped. A case simulation authoring system developed by Dr. Roesel was used to create a branching simulation of the case with both correct and incorrect options. Where applicable, the program caused a modified Betamax video tape player to

present auditory and visual information about the case, then paused and forced the student to make a decision that was recorded by the computer. The student could replay the sequences as needed. The video tape included diagnostic radiographs as well as the other sequences required to present the case completely. The interactive program, i.e., under student control and forcing students to answer questions before proceeding, allowed students to request information that would be answered with text, images, or sound. It encouraged the student to make a diagnosis and recommend treatment. Since its primary reason for existence was to enhance the teaching of basic physiological principles of the cardiovascular system, it was appropriate for students early in their professional education.

"What's Your Diagnosis" was one of the early, if not the first, applications of interactive video concepts to veterinary medical education despite the fact that it used video tape as opposed to a laser video disc to present the images. Since the concepts were developed from "real" cases that the students could readily follow, one could hypothesize that the learning would be more efficient and that it would be retained longer. Studies must be done to determine whether or not this hypothesis is correct.

Potential interactive video projects for those of us in pharmacology include putting an entire pharmacology course in this medium, demonstrations of the effects of drugs on animal behavior, and effects of drugs on physiological parameters. Dr. Charles Branch of Auburn University has prepared an impressive series of physiology laboratories in the interactive video format. He is comparing learning and student responses of first-year veterinary medical physiology students doing the traditional wet-laboratory experiments with those doing the same laboratories with the interactive video program. The results of this experiment will be valuable for all of us.

Realizing the enormity of the task of creating interactive video lessons for all of veterinary medicine and the impossibility of each school doing it alone, some of us have formed a consortium called "CONVINCE." CONVINCE, a Consortium of North American Veterinary Interactive New Concept Education, is a not-for-profit organization allied with the American Veterinary Medical Association and includes representation from all schools of veterinary medicine in North America that wish to participate. The goals of CONVINCE as outlined in its brochure are as follows: "CONVINCE is dedicated to implementing change in veterinary medical education by encouraging: involvement of American Colleges of Veterinary Medicine and allied groups in collaborative efforts to incorporate interactive video and hypermedia into educational programs; excellence in program development; hardware and software standards to assure that materials which are developed can be shared; coordination of program development to minimize duplication of effort; development of evaluation systems that will help universities recognize and reward faculty for scholarly program

development; and financial support from corporations and foundations to support development efforts." CONVINCE will work with specialty groups like ours to help them get started in creating interactive video programs. Fulfilling this goal was, in fact, one of the motives for the establishment of AAVPT's Education for the Twenty-First Century Committee.

Hypertext/Hypermedia

Whereas interactive video is primarily of interest because it promises to increase the efficiency of instruction, hypertext is important because it promises to increase one's ability to obtain information at the time it is needed.

After being restricted for 10 years to backroom enthusiasts (3), hypertext and its embellishment, hypermedia, are currently hot buzzwords. Apple's Hypercard-Hypertalk system which is being distributed with every Macintosh computer has played a major role in the increased awareness of this software technology.

The key to understanding hypertext is to understand the concept of "linking" pieces of information so they can be easily retrieved. For example, one can envision a manuscript that contains some keywords. Each keyword could be associated with code of some sort that tells one where to find more information on that keyword. The code could be called a "link." It is possible to link these keywords to other documents that contain more information on those keywords. These secondary documents could also contain keywords or concepts that, in turn, point to still other documents that expand on them. This tertiary level of documents could contain ideas that could be linked to each other or back to one of the higher level documents, thus converting what originally might have been a hierarchical arrangement of information into a network of information. In the context of a computer, the manuscripts or independent "atoms" of information are called "nodes" and the information directing a user from one node to another constitutes the "link." The set of links by which a user moves from the start to the information desired is referred to as a "path." Paths to frequently used information could be stored as the programs become more personalized.

This is not much different from using multiple books and their indexes, except that it is faster, more complete, and less bulky. It is also much easier to change and to keep current. Theoretically, the various pieces of information could exist physically on different computers at different locations or universities. However, it will be some time before we reach this level of integration which is envisioned in T. Nelson's Xanadu project (3).

Information in this context is not limited to text, but also includes sound and images. It could also include graphics, animations, speech, and film-clips. Someday, it may even include smell! Inclusion of such non-textual information converts hypertext to hypermedia. Soon computers will be available that will be able to handle these various modes in a

way that is transparent to the user, but for now we will have to rely on such expedencies as video discs for the non-text information. However, this is one place where effort expended on behalf of interactive video educational programs can be exploited for the purpose of creating ideal information sources. Major and well-known Hypermedia projects involving sciences, humanities, and the arts are underway at a number of universities (4).

Commercial hypertext systems are currently available. Hypercard, the proprietary name for Apple Corporation's entry, is defining the standard of performance now, but operates only on the Macintosh. At Purdue, we have been using PC Hypertext created by the creator of MaxThink and Houdini (MaxThink). This runs on IBM personal computers and compatibles (IBM PCs) and is currently text-oriented although the creator, Neil Larsen, is altering it so that we can integrate laser disks and digitized images with it. Guide (Owl International, Inc.) is a sophisticated hypertext system that operates on both IBM PCs and MacIntosh computers.

Hardware limitations aside, hypertext as currently conceived is not perfect and will not immediately solve all of our problems. One problem that has become apparent is that to fully use this new conceptual approach, we may have to re-learn how to organize information. What is the size of an "atom" (the smallest divisible unit) of information? How does one write the text? We may have to go back to grammar school and learn how to construct good paragraphs with good topic sentences.

Another problem with hypertext is that one can develop "link-mania." If the browsing and user interface are not well thought out, one can get lost in the maze of nodes. This and "cognitive overload," constitute two of the major problems with hypertext (5).

There are also the problems of how one gets the information into the system in the first place and how it is kept current. Ultimately, we will have to find ways to automate information acquisition by the system, but this will require significant advances in artificial intelligence and natural language.

Academicians may be sceptical of such electronic information sources because they have excelled at using the traditional sources of information or they would not have been successful. Other groups, e.g., farmers and pork producers, were not so prejudiced in a recent study and just wanted clear, concise information as fast and conveniently as they could get it (6).

At Purdue, we currently have the following ongoing projects involving interactive video and/or hypertext/hypermedia: creation of an alternative to the use of animals in education (G.R. Dodge Foundation project); putting the veterinary curriculum on computer; creation of multimedia case simulations; creation of a "snippets" database; and creation of student personal hypertext systems (7). It is not possible to go into the details of each of these here.

Artificial Intelligence/Expert Systems

Artificial intelligence may be defined as "...the study of mental faculties through the use of computational models." (8) This definition, obviously the product of a cognitive scientist, does not really help us much. Wags have defined it as "...anything people can do that computers can't (yet)." This tongue-in-cheek definition, at least, captures the idea that artificial intelligence is in the early stages of becoming something useful and that there is little agreement on what it is.

The study of artificial intelligence has had its major impact on medicine through its influence on the creation of expert systems. One of the very earliest expert systems was MYCIN created by Edward Shortliffe and others at Stanford University. MYCIN provided advice on appropriate antibiotic usage for microbial infections (see 9). This program, which equalled the ability of good residents, has inspired many other efforts to create medically oriented expert systems that could provide assistance in diagnosis and therapy.

Expert systems are usually "rule" based (see 9). That is, they are composed of "if x then y" kinds of statements, where x is the premise and y is the conclusion. There may be thousands of rules in an expert system's knowledge base. The expert system engine uses information obtained from the user and these rules to reach a conclusion.

Hypertext systems do nothing automatically and cannot help the user. Expert systems handle browsing and free text very awkwardly. Therefore, it is not surprising that the two approaches have been combined into what can be called "hypertextexpert" systems. Commercial programs available now that embody the principles of both approaches are Knowledgepro (Knowledge Garden, Inc.) which runs on IBM PCs and MacSmarts (Cognition Technology Corporation) which runs on MacIntosh computers.

We recently acquired a combination of tools for hypertext and expert system development from NASA at Houston. The program is called CLIPS and can be purchased with source code compilable for MSDOS (IBM PCs), UNIX, and MacIntosh systems. We are extremely excited about the prospects offered by this software in facilitating the creation of an information system for veterinary medicine.

Conclusion

The Red Queen said "You have to run as fast as you can to keep in place. If you want to get somewhere, you have to run faster." Many of us are on that treadmill today, working as hard as we can to remain abreast of a wide variety of subjects in such a way that we can use the new information available. For some of us, information is coming faster than it can be absorbed, but we cannot run any faster. We must make a paradigm shift, i.e., we must obtain and store information differently. Practitioners are in an even more precarious information-flow situation than those of us in universities. We must provide them with good tools and teach them

how to use them, particularly while they are receiving their formal education in the university.

The computer will play a major role in the future of veterinary medicine and will one day be an accepted tool. A quotation I have in my files of unknown origin says it all. "Ultimately, a computer should do for a surgeon's mind what a scalpel does for his/her hands." It is up to us to fulfill the promise embodied in that statement.

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