

SECTION V

**THE FIRST DECADE OF AAVPT
AND NEW FRONTIERS IN VETERINARY
AND COMPARATIVE PHARMACOLOGY**

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Veterinary and Comparative Pharmacology: A Personal Philosophy

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I thank you all for dedicating this Sixth Symposium of the American Academy of Veterinary Pharmacology and Therapeutics to me. It makes me very happy to look around the room and see the faces of many long time friends. Some of you I taught as veterinary students and I was the mentor for several of you in your graduate programs. I have been associated with nearly all of you in the discipline of veterinary pharmacology. Our biennial symposia provide a focus for this fellowship that has developed over the years. There are few organizations that have the cohesiveness that we have and I am very proud of the Academy and what it has accomplished.

I would like to take this opportunity to expound my personal philosophy of veterinary pharmacology. Aspects of this philosophy are closely related to the early development of our Academy and are incorporated in our logo.



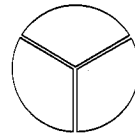
This was designed at the time we formed the college. I have a vivid recollection of constructing the drawing at my desk at Colorado State University. Unlike a number of other efforts I have made over the years, it took very little time (5 minutes) to assemble this logo. It was subsequently adopted by the membership at our meeting in Cincinnati in 1976.



The logo can be reduced to component parts. (See above.) The outer ring, apart from containing the name of the organization, is meant to symbolize unity. Our membership consists of individuals with many different interests and points

of view. Yet, we come together within the Academy to pursue similar interests and to serve a common cause.

Inside the outer ring of the logo are three sectors, each of which contains a symbol. These areas represent the important sectors of veterinary pharmacology. This concept originally was enunciated by Bill Huber at the conference held at Fort Collins in 1975 when he discussed the relationships that exist among academe, industry, and government. As you are aware, many of our activities have revolved around these, sometimes adversarial, relationships.



The Aesculapian staff is to indicate the close relationship that should exist between the science of veterinary pharmacology and the profession of veterinary medicine. It is sometimes convenient to forget this when research funds become available to support pharmacologic studies oriented toward human medicine. As veterinarians we have professional responsibilities above and beyond those of research scientists and this is implied by the inclusion of the staff in the logo.



An aphorism of Aristotle (384-322 B.C.) was "medicine begins in philosophy and philosophy ends in medicine." I agree with this implicitly as I believe that being a veterinarian is what one *is* not what one *does*. To understand why I believe as I do, it may be useful for me to provide a brief description of my background. The personal philosophy of each of us is molded by the sum of our experiences throughout our lifetimes. I was born two months before the stock

market crash in 1929, so I spent my childhood during the Great Depression, my adolescence during World War II and young manhood in the Korean War and college. I was born into a medical family. My grandfather, father, uncle and brother were all physicians. Consequently, I have spent my life immersed in a medically-oriented environment. The table-talk at holiday dinners was often medical in nature and I spent time with my father and grandfather in their offices or riding with them to make house calls. I also have experienced medicine from the point of view of being a patient. This extends from a one-year's illness in 1934 when there were few technologies or effective drugs available to recent coronary bypass graft surgery which utilized a variety of modern technologic innovations and drug therapy. Additionally, I cared for human patients during my service in the Navy and as an x-ray technician while attending veterinary school.

I was influenced by the philosophies of my grandfather, father and brother as well as by my own experiences. So what is this philosophy that has governed my perceptions of veterinary pharmacology? It is one of profession, duty and service. I strongly believe that the practice of our profession is principally an art that employs a foundation of the biomedical sciences to attain medical objectives in patients. This is the reason that I am frequently critical of the laboratory scientist in veterinary schools. It is very easy simply to be led to where the research funding is rather than to be involved with questions that are pertinent to veterinary medicine. Science is considered to be ethically-neutral but I submit to you that pharmacology is a value-laden enterprise when applied within a professional context. As veterinarians we practice a healing art and each time that we accept the care of a patient we are making a profession to the client to do something in a professional manner. The use of drugs is often central to this endeavor.

The central focus of medicine (human or veterinary) that makes it unique is what has been described by Pellegrino as the clinical event (1). This event involves the interaction of the physician with the patient or the establishment of a veterinarian-client-patient relationship with the intent of healing or ameliorating the effects of disease. Within the context of educating veterinarians, pharmacology is simply a science and does not become a part of medicine until the fruits of that science are applied to the patient with therapeutic intent. Even though we frequently must deal with herd or flock situations, animals are still treated individually. It is important to emphasize to our students that each patient that they will encounter is unique. Its particular genome never existed before and will not be duplicated again and the circumstances surrounding similar clinical events are never the same. One of the most fundamental concepts of medicine is the existence of individual variation. The Gaussian curve suggests to us why the practice of medicine will always be, to a great extent, an art. We study dose-response relationships in populations but we administer drug doses to indi-

viduals. Thus, when we give the usual (average) dose of a drug to a given patient there is some uncertainty as to whether the treatment will be toxic or ineffective.

An important attribute of veterinary medicine—and some of you have heard me say this before—is that our greatest strength as a profession lies in our generality. Any tampering we do, that might eliminate this advantage, will be to our great detriment. Some degree of specialization within the profession is necessary but I am unalterably opposed to specialization within the professional curriculum. Jim Voss has said that "veterinary medicine is like a river that is two miles wide and one inch deep." That, perhaps, is an accurate description and I contend that it is an appropriate situation. If we consider our role, in contrast to that of the physician, we find that we are required to provide medical care for all animal species with the exception of human beings. I do not know how this obligation can be met unless we collectively maintain a broad perspective in the education of veterinarians.

I had an experience a few years ago that indicated where we might have come as a profession. It disturbed me profoundly. I was at home on a weekend and received a call from a lady in another state. She said that she raised dairy goats and that some of them had gotten into a storage shed and eaten some fertilizer and were now sick. I told her that she needed the services of a veterinarian because the signs that she was describing were those of nitrate intoxication. The affected animals probably would require an injection of methylene blue and a rumenotomy to clean out the rumen. She told me, "Doctor, I am calling you because I have called a number of veterinarians in my area and they responded by saying that they did not take care of goats." This situation was a poor commentary on the veterinarians in her area and indicates the need for maintaining a general outlook. Many clients view a veterinarian as a person who is trained to care for the health of all animals and not simply dogs or birds or horses or other species that may be of interest to the particular practitioner.

We need to maintain a generalist's perspective for another reason. The sciences have become so fragmented through extreme specialization that these specialists frequently contribute more to the information pool than they do to the understanding of their discipline. At some point this information needs to be incorporated into a medical context; otherwise such efforts merely become a game. I don't know of anyone better prepared to separate the grain from the chaff and to synthesize a body of knowledge in medicine than an astute person who has a perspective that is "two miles wide."

Another reason to maintain a generalized perspective concerns the use of drugs in veterinary therapy. The essence of veterinary pharmacology, in contrast to medical pharmacology, resides in species differences. We should be expected to be experts in terms of variations in drug disposition and pharmacodynamics that occur on a species basis. Very few other scientists are interested. A few years ago we attended

the fall meeting of ASPET in Philadelphia. Dr. Brumbaugh was presenting a paper concerning digoxin in horses. Gordon reported to me later that he had socialized with some graduate students from medical school pharmacology departments and they had expressed that it was beyond their comprehension as to why anyone would be interested in a cardiac glycoside in a horse.

A number of differences have been observed among the various common domesticated animal species. This was clearly delineated in studies of salicylate conducted at the University of Missouri in the middle 1960s (2). At the same time, Dr. Oehme established the basis on which phenolics are particularly toxic to cats. This had been known anecdotically for years but he showed this to be due to impaired glucuronidation. He also found that ruminants and swine had an extraordinary capacity for conjugation of phenol (3). Dr. Baggot found wide variations in rates of elimination of amphetamine from several animal species (4). In humans the rate of elimination of amphetamine is dependent on urinary pH whereas in the horse it is independent of pH. The reason is that the horse completely metabolizes the drug so that amphetamine is not excreted into equine urine. In our studies of quinidine, we observed a species difference in protein binding of the drug (5). The plasma concentrations of quinidine were much higher in swine than other species because of more extensive protein binding. Dr. Short's work (6) demonstrated the course of development of pathways for biotransformation of drugs in neonatal swine. So we not only have species differences to contend with in veterinary therapeutics but also age differences.

Other factors must be considered when we administer drugs to patients. Many animals are raised for breeding purposes and thus are pregnant for most of their life spans. This situation presents added considerations relative to the safe and effective use of drugs in such patients (7). As animals age there are changes in body composition that alter the disposition of drugs. We must be concerned with interactions among drugs and idiosyncratic responses (8). A number of diseases will affect drug disposition in the patient (9). Addison's disease, hyperthyroidism, diabetes, viral infections and cirrhosis of the liver may decrease the metabolic clearance of drugs. Diseases that produce hypoalbuminemia, increased plasma free fatty acids or lipemia will modify plasma protein binding of drugs. Orosomucoid (alpha 1-acid glycoprotein) binds a number of basic drugs in plasma. Its concentration in plasma is increased by inflammatory disorders and decreased by estrogen or pregnancy. Diseases of the kidneys can have profound effects on the rate of elimination of many drugs (10). Receptor sensitivity can be affected by drugs as well as by disease (9). We know that the number of receptors can be up-regulated or down-regulated by chronic exposure to agonists or antagonists. Nutritional status and specific nutrients can modify several pathways for biotransformation (11).

These are all examples of factors that can modify the re-

sponse of a given patient to a drug. They must be considered by the veterinarian in order to prescribe drug therapy that will be safe and effective for the patient. A broad understanding is necessary for making such decisions. Now, I am not implying that all research in veterinary pharmacology must be broadly based and applied. What I am saying is that when we synthesize research data for medical purposes it must be maintained within a context that is broad and general because that is the nature of our profession.

The second component in our logo is the lamp of learning. We are a learned profession and our scientific, teaching and service aspects are all predicated on a devotion to learning.



This symbol was added to the logo because scholarship and learning are absolutely essential to veterinary pharmacology and therapeutics. Additionally, I would comment that the flame from the lamp is eternal. We need to keep our discipline and profession within a historical perspective and convey to our students a sense of continuity in the flow of history. Knowledge about drugs extends back more than 4,700 years. The first drug compilation, the *Pen Tsao*, was written in China, in about 2700 B.C. Our roots extend back many years and through several different cultures.

We are beginning to lose our historical perspective within society. I do not know exactly when it began but it seems that for the past 10 to 12 years, students have had the idea that history started at the moment they were born and that nothing of any significance happened prior to that time. As a teacher, I find this situation difficult to deal with. It is made more difficult because I had twenty years of experience working with veterinary students prior to this period. This lack of a historical view has an impact on our common sense and common knowledge. We no longer share basic understanding that, at one time, served as a beginning for instruction. I recently had an experience that illustrates this point. I loaned my timing light to a neighbor boy who is in high school. He didn't know how to use it to adjust the timing of the engine in his car. I explained to him that the light was a strobe that made the timing marks on the flywheel appear to be in line when the timing was properly set. It was much like looking at a fan blade illuminated by a fluorescent light where the blade appears to be rotating very slowly. He did not have any idea what I was talking about. Without some common understanding in any area it is nearly impossible to communicate and to instruct in that arena.

Even with a historical perspective, we can abandon certain ideas or knowledge by considering them to be obsolete. I remember one day when I was a veterinary student, Dr. C.

Roger Smith mentioned that yohimbine was an alkaloid that once was advocated for use as an aphrodisiac but is now obsolete in medicine. Of course the problem at the time was that we knew nothing about alpha-2 adrenoceptors. Twenty-five years later when we learned about alpha-2 receptors, yohimbine once again became important.

Another problem concerning learning in veterinary medicine that we must guard against in pharmacology is the emphasis on application of technology as opposed to the restoration of health. There are far too many instances of doing things *to* patients rather than doing them *for* patients. I attended teaching rounds a couple of years ago and a senior student was presenting a case of an emaciated ewe that was heavily parasitized. In the discussion I noted that the animal was receiving sodium bicarbonate and asked why this had been prescribed. The student said that she had found that the urinary pH was acidic and that everyone knew that the urine of a ruminant should be alkaline. We see many instances of students treating laboratory data rather than patients. Frequently this is the result of exposure of students to instructors who have a narrow view of their discipline and fail to make the subject relevant within a broader medical context.

A paradigm for learning in medicine consists of the acquisition of blueprints and recipes with respect to our patients (11). The two blueprints that each student must develop are the concept and details surrounding a normal, healthy, functional animal and a blueprint concerning a variety of diseased states. The students should then be able to formulate recipes for converting one blueprint to the other. This involves the ability to find answers to three fundamental questions: 1) What is the problem? 2) What can be done to correct the problem? and 3) What should be done? The classic medical curriculum has served very well as a framework for educating someone in medicine. Specific information changes but the essential conceptual structure of medicine remains relatively constant. Much of the curriculum is concerned with providing students with the mental blueprints. Thus, biochemistry, physiology, anatomy, nutrition, animal science, immunology are oriented largely toward the development of the ability to recognize healthy, normal animals. On the other hand, bacteriology, pathology, pathophysiology, parasitology, toxicology are concerned primarily with the blueprint for diseased animals of each species. There obviously is some overlap, e.g., animals support a normal bacterial flora as well as develop infections by pathogenic bacteria. Since the student is studying for entry into a healing profession, the main operational function is the formulation of recipes (decision-making) that will connect one blueprint to the other. Subjects in the curriculum that are largely concerned with this aspect are radiology, clinical pathology, internal medicine, surgery, pharmacology. The formulation of recipes are concerned with the three questions mentioned above. "*What is the problem?*" involves diagnostic procedures. "*What can be done?*" concerns decisions about drug therapy, surgery, physical therapy, nutrition, etc. "*What should be done?*" pri-

marily is concerned with making ethical decisions.

Veterinary pharmacology is quite broad as a discipline and pertains to much of the paradigm just described. For example, drug receptors, pathways for biotransformation of xenobiotics, endogenous mediators are all part of normal healthy animals. Drugs, themselves, can cause diseases in animals. Pharmacotherapy is an important aspect of the formulation of recipes to restore health.

Lastly, as part of the process of learning in veterinary medicine, our students must be prepared to cope with uncertainty in making decisions. The college at The Ohio State University has been a pioneer by incorporating statistical approaches to decision making in veterinary medicine into its curriculum.



The last symbol in our logo is the balance. It was not included to signify the law but to indicate the weighing of risks versus benefits in the formulation of rational drug therapy. In our teaching as well as practice, it is important not only to consider what a drug will do for a patient but also to appreciate problems that may be created by the therapy (12). I try to approach this in my teaching by approaching the matter of drug selection from the standpoint of formulation of therapeutic objectives. This symbol could also remind us of the need to maintain a balance between art and science and between technology and caring. We must not lose sight of this if science and technology are to be a benefit to our patients and clients rather than a menace. This is an idea that has guided medicine since antiquity—"above all, do no harm." Another aphorism from Hippocrates (460-375 B.C.) is pertinent: "Life is short and the art is long, occasion passing, experiment perilous, judgement difficult." But I began with Aristotle and I will finish with a quotation from the Nicomachean Ethics.

"Even in medicine, though it is easy to know what honey, wine and hellebore, cautery and surgery are, to know how and to whom and when to apply them so as to effect a cure is no less an undertaking than to be a physician."

Things really have not changed that much in their essentials. We are a part of the continuity of flow that extends back throughout the history of mankind.

With that I am finished. Thank you very much.

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Historical Notes on the AAVPT Years 1976-1981

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The American Academy of Veterinary Pharmacology and Therapeutics grew out of the concept that veterinary pharmacology is a unique discipline which would be nurtured by assembling its proponents into an organization to work toward common goals. Events which fostered the idea of a College or Academy of Veterinary Pharmacology must include the First Symposium on Pharmacology in the Animal Health Sector, sponsored by Dr. Lloyd E. Davis at Colorado State University in 1975 and the activities of the American College of Veterinary Toxicology. The former brought many veterinary pharmacologists in the U.S. together in a first-of-its-kind symposium. The latter set an example of what could be done to establish and promote a veterinary discipline.

The first step taken toward organization was to send a letter of interest to approximately 40 known colleagues around the U.S. The response was favorable on the whole, although there were 2 or 3 who felt that specialty organizations detracted from membership participation in activities of the

AVMA. The first effort at organization took place at the CRWAD meeting in Chicago in 1976. I was elected Chairman of a Steering Board, and plans were made to incorporate in Illinois, elect a membership, and write a Constitution and Bylaws to be acted upon by the elected membership.

The Constitution and Bylaws were adapted from those of the American College of Veterinary Toxicology. The Constitution outlined the goals of the organization as follows:

- a. To support and promote education and research in comparative pharmacology, clinical veterinary pharmacology and other aspects of pharmacology of interest to the veterinary profession.
- b. To sponsor a periodical Journal of The College which will publish reviews, summaries and original treatises on all aspects of veterinary pharmacology and therapeutics. The Journal of Veterinary Pharmacology and Therapeutics, hereinafter referred to as "the Journal," shall be an official instrument of the College.

- c. To sponsor and conduct workshops, symposia or other scientific and educational meetings in veterinary pharmacology and therapeutics.
- d. To enhance the exchange of educational materials and ideas among veterinary pharmacologists.
- e. To organize committees of experts to research and make recommendations to the profession on current problems in veterinary therapeutics.

The founding membership of the organization was elected by a vote of all interested parties and certificates of membership were signed and distributed on October 29, 1976. The founding members then elected officers as follows: Lloyd E. Davis (President); Charles R. Short (President-Elect); and Ronald E. Borchard (Secretary-Treasurer). Dr. Davis appointed the first committees (July, 1977) which included the following as chairmen: Membership and Bylaws, Lester Crawford; Program, Charles Short; Professional Liaison, Jerry Brunton. Additional committees appointed in 1978 included: Examination Committee, Gordon Coppoc; and Advisory Committee on Drug Availability, Dan Upson.

Two further committees were added in 1980 with these chairmen: Finance and Budget, Gordon Coppoc; and Board of Veterinary Clinical Pharmacology Review, Lloyd Davis.

The AVMA assisted with incorporation in Illinois and registration with the Internal Revenue Service as a tax-exempt, not-for-profit organization. The American College of Veterinary Pharmacology was incorporated in 1977.

Sifting through old files and re-reading memos and reports of 8 to 12 years ago leaves one impressed that so much could be accomplished through dedication to a goal. The College was active on many fronts and saw most of its early objectives accomplished. To be sure, there were moments when we did not all agree on an issue, and there were periods when we worried about mundane concerns such as nearly non-existent bank balances. But the need for the organization was clear. The critical mass and impetus were there. In retrospect, we played out roles on an idea whose time had come. If it hadn't begun in 1976-77, it probably would have in 1978, or 1979, or 1980.

The most notable events and accomplishments of these years are listed below, in more or less chronological order, with a few notations. My recollections of events in 1976-77 are a bit sketchy, as some earlier files may have been discarded.

Membership

The college intended to serve all veterinary pharmacologists, DVM and/or PhD alike, as well as honor our most distinguished colleagues as elected Distinguished Fellows. There were 74 members in July, 1978, including 3 Distinguished Fellows: Dr. Robert Dougherty, Dr. L. Meyer Jones and Dr. Samuel Scheidy. By July, 1979, there were 71 Fellows, 12 Associate Fellows, and 3 Distinguished Fellows. The majority of the membership was associated with basic pharmacological science in an academic setting (54),

while there were 9 primarily involved in clinical pharmacology, 17 in industry and 6 in government. In 1980, Dr. Frank Alexander and Dr. Roger Link joined as Distinguished Fellows. In May, 1981, the membership was reported to increase slightly to 92. The first Directory was published by Dr. Borchard in 1978, providing a handy reference to affiliations, interests, and telephone numbers.

Journal of Veterinary Pharmacology and Therapeutics

One of the objectives of the College was to publish a scientific journal devoted to veterinary pharmacology. By coincidence, Dr. Andrew Yoxall, a British colleague working at Cambridge, was promoting the formation of a similar society in Britain, and soon afterward, a second representing the European continent. He had already been in touch with a publisher and invited us to join him in persuading Blackwells Scientific of Oxford to publish an international journal of veterinary pharmacology. Andrew ("Drew") and I signed an agreement with Bob Campbell of Blackwells in Oxford in 1977 under which Blackwells would underwrite costs and retain title to JvPT for 2 years. A call for papers was distributed in the Fall of 1977 and the first issue appeared in March of 1978. The first 2-3 years of publication were relatively successful, but difficulties became apparent in 1981 when Andrew became ill and withdrew, and shortly thereafter, died. I continued as sole editor until 1984 when Peter Lees was elected co-editor to fill the responsibilities vacated by Andrew. By this time the Journal was back on schedule (it had fallen at least 6 months behind schedule during Andrew's illness), and had recovered to a reasonable degree from its accumulated debt (which at one point was approximately £17,000). With Dr. Lees on board, manuscript accessions increased once again and the page allotment was increased from 360 to 440 per year in 1985. In the meantime, the Journal was accepted into Current Contents (Agricultural, Biology, and Environmental Sciences), and now also appears in Med-Line and the Science Citation Index. The Journal showed an accumulated profit for the first time in 1986, thanks in part to membership subscriptions purchased by the AAVPT. In spite of a weak U.S. dollar, JvPT continues to work in the black, ensuring the support of the publisher in the future. A ten year index, published in volume 11:1, cites 447 publications. Perhaps the most encouraging and gratifying statistic is that JvPT had the second highest ISI "impact factor" of all veterinary journals in 1986, the most recent year for which this has been calculated.

Topics in Drug Therapy

Dr. Lloyd Davis initiated this feature in the Journal of the American Veterinary Medical Association. The purpose is to provide readers with modern concepts of veterinary clinical pharmacology and therapeutics. The first TDT article ap-

peared in JAVMA 175:1 in July 1979. This publication is a function of AAVPT which Lloyd has nourished and monitored since its inception and is a valuable contribution, especially to veterinary clinicians. Over 40 such articles have been published to date, each generating a \$50 donation to the AAVPT treasury.

First and Second Symposia on Veterinary Pharmacology

The First Symposium was not really the "first" symposium of its kind but it was the first sponsored by ACVPT. Patterned after the one hosted by Dr. Lloyd Davis at Colorado State University in 1975, and with Lloyd's immensely helpful suggestions, the First Symposium was held in Baton Rouge in March, 1978. There were approximately 110 registrants and a very stimulating program dealing with a variety of timely topics. Thanks to industrial contributions, the Symposium costs were covered and in July of 1979, the ACVPT had \$1,255.90 in its treasury.

The Second Symposium was hosted by Dr. Carl Aronson in Philadelphia in June, 1980. Again, this meeting was well attended, informative and enjoyable. Thanks again to corporate donations, the Second Symposium added to the treasury. Proceedings of both symposia were published, and enjoyed a fairly brisk demand by libraries.

Cosponsored Colloquia

Between 1978 and 1981, the ACVPT, sponsored or cosponsored a number of smaller conferences. To the best of my recollection, these included the following:

1. Symposium on Circulatory Shock: Concepts and Management. July, 1978. The University of Texas Health Science Center at Dallas. Host: H.R. Adams.
2. The First Veterinary Respiratory Symposium. November, 1978. University of Illinois. Cosponsored by CVS and ACVIM. Host: L.E. Davis.
3. Symposium on Safety Assessment of Drug Residues. February, 1979. Cosponsored by AHI and ACVT. Host: Dr. Jerry Brunton.
4. Therapeutics in Gastroenterology. July, 1980. Cosponsored by the AVMA, Washington, D.C. Hosts: Dr. Lloyd Davis and Dr. Ed Baker.
5. International Conference on Veterinary Pharmacology, Therapeutics and Toxicology. Cambridge, England, July, 1980. Sponsored by ACVP and AVCPT and hosted and organized by Dr. Andrew Yoxall.

National Board Examination Reviews

Through the efforts of Dr. Gordon Coppoc, a number of ACVPT Fellows participated in reviewing National Board Examination questions dealing with pharmacology and therapeutics. Several annual sessions were held in which members reviewed and revised questions and contributed new questions for future exams.

Liaison with FDA

The need for increased communication between academia, industry and the FDA had been recognized long before the inception of the ACVPT. The meeting sponsored by Lloyd Davis at Colorado State in 1975, however, brought the need into focus and it thus became one of the objectives of the College. The ACVPT began, in the Fall of 1980, to investigate ways and means of interacting with FDA. A meeting was held in October 1980 at Ohio State University to determine what role the College could play in a liaison capacity. Drs. Mercer, T. Powers, and Short met with the Acting Director of the Bureau of Veterinary Medicine, Dr. Jerry Guest. Dr. Guest agreed that the ACVPT, in principle, might serve as an independent scientific resource. Topics for future interaction centered on the sponsorship of workshops in clinical pharmacology involving (and for) colleagues and employees of FDA and the possible use of the College as a peer review group. These initial contacts have since generated a great deal of interaction that has profited both the industrial and governmental sectors. Drs. Tom Powers and John Paul, in particular, are responsible for the organization of workshops in clinical pharmacology that have been highly successful.

Other Issues

Two important issues came to the fore in the Spring of 1981. The first was the need to change the name of the organization from "College" to "Academy" or "Society" to fall within the guidelines of the AVMA. Drs. Decker and Ames of the AVMA had suggested that we (and the American College of Veterinary Toxicology) change the name as the term "College" should be reserved for certifying bodies.

The second issue was whether the ACVPT should work to organize a specialty board in Veterinary Clinical Pharmacology and Therapeutics. The committee appointed to review the question met at the AVMA meeting in Washington, July, 1980. After considerable deliberation, the committee recommended that the ACVPT pursue the establishment of a Specialty Board. They also noted that it would be necessary in doing so to change the name of the ACVPT. At the 1981 AVMA meeting, the membership voted to change the name to "Academy", but the vote to establish a Steering Committee to develop a Board did not pass. As we all know, however, this has now received a favorable vote and the AAVPT is exploring different avenues by which a Board may eventually be established. I will not try to elect any of these activities as a "greatest" accomplishment of the AAVPT (or ACVPT) during its first 5 years. It is enough to say that much was accomplished through the earnest and dedicated efforts of many. In closing, I would like to reiterate the last two sentences of a Newsletter sent to the membership in December, 1980. "Looking to the future convinces me that we have only begun. Indeed, what we can accomplish is only limited by the interest of the Fellows and their willingness to participate." As true today as ever.

History of American Academy of Veterinary Pharmacology and Therapeutics, 1981-1983

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Introduction

I assumed the presidency from Dr. Charles Short in 1981 during the AVMA meeting at St. Louis, Missouri. I received the reins of an organization that had been well founded and that was in a very healthy state. There were 2 critical issues discussed at this meeting: 1) to look into the need for a board in veterinary clinical pharmacology and 2) the possibility of special seminars limited to addressing the problems in the drug approval process. After "heated" discussions, both received approval by the narrowest of margins.

The idea of seminars on the drug approval process had been discussed at a special meeting in Columbus, Ohio on October 10, 1980. I had called this meeting as a function of my duties as President-elect and Chairman of the Program Committee. There were 7 academicians, 3 industrial veterinarians and 1 veterinarian from the Animal Health Institute in attendance. Due to a lack of funds in the AAVPT treasury at that time, the academicians' expenses were paid from The Ohio State University's visiting lecturers' fund. This was possible as each also delivered lectures to our graduate students during their stays at The Ohio State University. The expenses of each industrial veterinarian were paid by their respective companies and AHI paid for the remaining participant. The results of this meeting were in no way conclusive in agreement as to the value of holding such meetings. To read extracts from the 5 pages of minutes for that meeting:

"A free-form, widely ranging discussion ensued. Such questions as 'What is really possible, given pressures on the BVM from consumers, environmentalists, lawyers, and other groups?' There have already been many investigations of the FDA/BVM as well as symposia that supposedly fostered formal dialogue between the BVM and the industry. The fact is, they already know the problems faced by each other. One of the major problems from the industrial point of view is the seeming inability of some BVM personnel to make decisions. This results in a severe problem of 'moving targets' for getting drugs cleared, which puts severe strains on the research and development budgets of the corporations as well as their ability to plan drug development....

"There is a need for an Advisory Council to work

with BVM on scientific issues....Dr. Mercer asked whether the College would take a stand on any issue. The answer from Drs. Powers and Davis was an emphatic yes! There is a need for an advisory group to help investigators and industry deal with a two-year graduate DVM or statistician who tells experienced investigators and statisticians how to do their work....

"The history of previous College attempts was reviewed. The Symposium held in 1976 at Colorado State University prior to the formation of the AAVPT tried to get industry, academia and regulatory people together with modest success...."

In spite of this and after encouragement from several Food and Drug, Center for Veterinary Medicine personnel, the first symposium to study the Drug Approval Process was held in conjunction with the 3rd Biennial Symposium of the AAVPT at The Ohio State University, April 13-15, 1982. The success of this meeting is now history. The report of the Task Forces from this meeting was delivered in person by Dr. Lester Crawford, Dr. Dwight Mercer, and myself to Dr. Arthur Hull Hayes, Commissioner of the U.S. Food and Drug Administration, on June 18, 1982. The report was well received and Dr. Hayes, speaking as a clinical pharmacologist himself, was enthusiastic in his response to the observations and recommendations that it contained. Some of the observations and recommendations were already started and others were immediately put in motion and he assured us that others would follow. The proceedings of this meeting were dedicated to the late Dr. Sam Scheidy, distinguished fellow of the AAVPT and a member of one of the task forces.

Another accomplishment of the AAVPT during my tenure was the inaugural issue of the AAVPT newsletter, as we now know it, in January 1982. At my request, Dr. Carl Aronson became the editor and continues to be its editor. We are all extremely appreciative of Carl's efforts in this regard and we cannot thank you enough, Carl. This newsletter has had a great positive impact upon the progressive development of the AAVPT. Further, through the efforts of Dr. William Jenkins and Dr. J. D. McCrady, our participation in the program of the Chicago Research Workers in Animal

Diseases (CRWAD) was markedly improved to the point that an extra half-day was required for the papers.

During my two-year tenure, several members from the AAVPT and from the industrial veterinarians' organization were organized for the purpose of presentation of scientific seminars. By industry paying the expenses of each participant, very high caliber continuing education courses were offered at a minimum expense to the veterinarian. Two-day courses were given at the Arkansas Veterinary Medical Association, Mississippi State Veterinary Medical Association and Southern Veterinary Medical Federation annual meetings.

In 1983, I presided over my last meeting of the AAVPT at the AVMA meeting in New York. At this meeting Dr. Terry Harvey, representing the FDA, moved that a symposium be sponsored by the FDA/CVM and the AAVPT to discuss the issue of dosage determination for veterinary pharmaceuticals.

This reinforced that we had been successful in our first meeting in Ohio and this certainly pleased all of us very much.

As I reflect on my two years, I believe AAVPT's major accomplishments in addition to membership growth were:

1. A continued increase in communications between ourselves and from ourselves to the rest of the profession. (Newsletter and formation of Industrial Veterinary Continuing Education Program);
2. The initiation of the special meetings involving the FDA, industry, academia, and practicing veterinarians for the sole purpose of studying the drug approval process.

Reflections on the Years 1983-1985 During the First Decade of the AAVPT

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During the period between July 18, 1983 and July 22, 1985, it was my privilege and pleasure to serve as the fourth president of the American Academy of Veterinary Pharmacology and Therapeutics (AAVPT).

At our annual business meeting held in New York City in 1983, the importance of documenting AAVPT's history for posterity was among the many items discussed. Subsequently, the position of "Historian/Archivist" was created and Dario Cappucci, Jr. graciously assumed this important new area of responsibility for our organization. He soon established a firm working relationship with the History of Medicine Division of the National Library of Medicine, National Institutes of Health, Bethesda, Maryland (HMD/NLM) and they agreed to accept and house a collection of materials relating to the history and activities of the AAVPT. This collection presently includes all of the issues of our Newsletter,

AAVPT publications, photographs and other documents relating to the AAVPT since it was founded as the American College of Veterinary Pharmacology and Therapeutics in 1977. I am pleased that this relationship with HMD/NLM continues, and Dario Cappucci welcomes your input and continued support.

Article III of our Constitution, which defines our objectives, states, in part, that we seek to promote education and research in comparative pharmacology and that we sponsor and conduct workshops, symposia or other scientific and educational meetings, and that we organize committees of experts to research and make recommendations to the profession on current problems in veterinary therapeutics. In order to achieve these goals, we have reached out to and worked in concert with other groups representing academia, industry, the Federal Government and the veterinary profession at

large in order to share our views and mutual concerns and to provide a forum for their discussion. In this regard, I believe that we can be proud of our achievements.

On August 8, 1983, the AAVPT met, as a cooperating group, with the American Society for Pharmacology and Experimental Therapeutics (ASPET) at its meeting in Philadelphia. At that time, we sponsored and presented a symposium on the topic "Application of Pharmacology and Therapeutics in the Animal Health Sector." Tom Powers chaired the session and the presentations were made by AAVPT members. During the same meeting, Lloyd Davis chaired an ASPET scientific session on "Comparative Pharmacology and Toxicology."

On November 16-17, 1983, the AAVPT and BVM/FDA cosponsored a symposium on "Dose Determination with Animal Drugs" in cooperation with the American Association of Industrial Veterinarians (AAIV) and the American Veterinary Medical Association (AVMA). This symposium, held in Alexandria, Virginia, examined scientific, statistical, legal, regulatory and clinical issues related to the dose determination process. At the conclusion of the formal sessions, task forces headed by H. Dwight Mercer and Arthur Aronson identified key issues developed during the meeting, and they proposed suggestions for their resolution. Interest focused primarily on antibiotic and prescription drugs. Subsequently, their report was presented to Lester Crawford, Director of BVM/FDA.

Also in November 1983, Charles R. Short, Editor of the *Journal of Veterinary Pharmacology and Therapeutics* (JVPT) reported that the JVPT had been included in Current Contents as well as several other indexes. The AAVPT continued to sponsor "Topics in Drug Therapy" the *Journal of the American Veterinary Medical Association*. This interesting feature concerned with veterinary therapeutics, deals primarily with the clinical pharmacology of various therapeutic agents and it is edited by Lloyd Davis.

We, as an organization, have also taken an active role in supporting continuing education for practitioners. February 19, 1984, John Paul chaired a symposium on "Antimicrobial Therapy" at the Western States Veterinary Conference. At this meeting, AAVPT speakers presented papers on the use of antibiotics in various aspects of veterinary practice including large and small animals and food animals. Through such presentations, we have been able to bring many of the latest developments in therapeutics to the attention of persons regularly engaged in clinical practice.

Another important activity has been AAVPT sponsorship of a biennial symposium on veterinary pharmacology and therapeutics. The fourth such symposium was held on April 24-27, 1984 at Texas A&M University and was hosted by William Jenkins. Eight sessions covered a variety of topics and included the following: 1) Future; 2) Modern Anthelmintics and their Pharmacological Properties; 3) Modern Drug Delivery Systems; 4) Research Reports; 5) Oncotherapy; 6) Veterinary Pharmacy; 7) Therapeutic Aspects of Gas-

troenterology; and 8) Therapeutic Aspects of Cardiology. Session six on veterinary pharmacy was presented by the Society of Veterinary Hospital Pharmacists who met with us in conjunction with our symposium. Those who attended this meeting will long remember the warm Texas hospitality extended to us, the voices of the Texas A&M Singing Cadets, and the country western barbecue and dancing at the Texas Hall of Fame.

On May 10, 1984, I represented the AAVPT and participated in a "Voluntary Compliance Educational Workshop on Illegal Distribution of Veterinary Drugs" sponsored and conducted by CVM/FDA at Rockville, Maryland. Other groups represented included the AVMA, American Association of Veterinary Medical Colleges, American Feed Manufacturers Association, American Veterinary Distributors Association, the Animal Health Institute (AHI) and other divisions of FDA. Candid discussion of the problem identified a number of specific concerns and suggestions were offered by the participants on how best to resolve them.

AAVPT's leadership role in promoting dialogue about issues important to the veterinary profession was officially recognized at FDA's National Awards Ceremony on June 1, 1984. At that time, the AAVPT was awarded a Commissioner's Special Citation "For significant contributions to the agency's animal drug review process by facilitating scientific forums and symposia on contemporary issues in drug therapy." This was the first time that an organization like ours had been so honored by the FDA, and the presentation was made by Mark Novitch, Acting Commissioner of Food and Drugs and Lester Crawford, Director of CVM/FDA.

Over the years AAVPT members have been invited to serve on various committees, and William Jenkins who was then AAVPT President Elect was appointed to the first FDA Advisory Committee, the formation of which was approved by HEW Secretary Margaret Heckler on April 27, 1984.

On September 25-26, 1984, Tom Powers and Glen Hoffis organized an in-depth seminar on "The Use of Drugs in Food Animal Medicine." This program, cosponsored by AAVPT, CVM/FDA and the College of Veterinary Medicine of The Ohio State University, drew over 400 registrants from 32 states and abroad.

Our educational activities in 1985 began on February 17-21 at the Western States Veterinary Conference where an AAVPT sponsored session on "Veterinary Therapeutics" was organized by John Paul. Topics covered included anthelmintics, anesthesia, GI therapy, corticosteroids and antimicrobials.

Another major symposium followed on April 17-21, 1985 on "Clinical Trials with Therapeutic Animal Drugs." This meeting was cosponsored by AAVPT and CVM/FDA in cooperation with the AVMA, the AAIV and the AHI. It focused on issues associated with clinical trials and their design, their management and data evaluation. In a departure from earlier formats, a special workshop for practitioners and

clinicians was conducted and was quite successful. As in earlier symposia, a task force convened at the close of the formal sessions to pinpoint specific problems and offer recommendations concerning their solution. It was also during this meeting that our friend and colleague, Fred Kingma, was made a Distinguished Fellow of the AAVPT and recognized for his many achievements and contributions to the veterinary profession.

On April 21, 1985, we mourned the death of one of our Distinguished Fellows, Roger Link, and remembered his long and distinguished career in veterinary pharmacology.

On May 16-17, 1985, Lloyd Davis and Terry Harvey met at AVMA headquarters with AVMA staff and representatives from 14 professional and producer groups as part of the Food Animal Veterinarians Organized for Results (FAVOR) Task Force. The purpose of this meeting was to discuss issues of concern in the food animal practice sector.

In June, 1985, Council submitted several Constitution and Bylaw changes to the membership for their consideration and subsequent approval, and at the annual meeting held in Las Vegas I completed my term of office and passed the gavel to William Jenkins.

The First Decade of the American Academy of Veterinary Pharmacology and Therapeutics: The 1985-1987 Era

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Introduction

The 1985-87 period was one of continued growth both in numbers and stature for AAVPT. There were no serious difficulties that confronted the Academy and several positive developments occurred. A synoptic overview of the major features of these final two years of AAVPT's first decade will be presented below.

Officers and Councilors

The officers during 1985-86 and 1986-87 were Bill Jenkins, President; Art Aronson, President-elect; John Paul, Secretary/Treasurer; and Carl Aronson, Past President. 1985-1986 Councilors were Desmond Baggot, Charles Short, Gordon Coppoc, Dan Gingerich, John Stoner, and Dick Teske. The 1986-87 Councilors were Gordon Coppoc, Dan Gingerich, John Stoner, Dick Teske, Richard Adams, and Gary Koritz.

Membership

Membership figures were as follows:

	1985	1986	1987
Fellows:	96	101	105
Associate Fellows:	21	24	29
Distinguished Fellows:	6	7	7

It was Dr. Nicholas Booth who was elevated to the Distinguished Fellow category.

AAVPT Sponsored or Cosponsored Symposia

1) *Fifth AAVPT Biennial Symposium*. This was a very successful meeting held at the Lake of the Ozarks under the auspices of the University of Missouri. Richard Adams and his Program Committee produced a fine symposium with the overall theme of "New Perspectives in Veterinary Pharmacology and Therapeutics." The proceedings have been published as part of the on-going AAVPT series.

2) *Special FDA's CVM/AAVPT Cosponsored Symposium*. Because of the pressing nature of the question, a special symposium cosponsored by FDA's CVM and AAVPT entitled "Does the Animal Drug Prescription versus OTC Issue Impact Human and Animal Health?" was held in Alexandria, Virginia. John Paul attended to the logistics of the meeting and Jean and Tom Powers organized the program. As one would have expected, provocative and timely issues surfaced during this symposium. The proceedings are due to be published shortly.

3) *AVMA Colloquium*. Although AAVPT was only a contributor to AVMA's COBTA-sponsored symposium on "Recognition and Alleviation of Animal Pain and Distress" held in Chicago, Illinois, several AAVPT members actively participated in this landmark program. The colloquium addressed an area in which it is hoped AAVPT will become much more directly involved in the future.

Regular Scientific Meetings with AAVPT Participation

During both years under review, AAVPT continued to actively participate in several meetings, either as a sponsor or cosponsor of specific scientific sessions. The Academy's visibility to the veterinary profession at large was clearly enhanced by these efforts. The meetings of note were the Western States Veterinary Conference, the AVMA Annual Convention and the Conference of Research Workers. Pleasingly, during this time we were also asked to sponsor programs at the Eastern States Veterinary Conference as well as at the annual meeting of the American Association of Bovine Practitioners and this indeed was done in 1987 and 1988.

Amendments to the Constitution and By-laws

The few changes made to the by-laws were mostly of a corrective nature to facilitate how AAVPT conducts its business. A proposal that was put forward and agreed to in 1987 was for the creation of a membership category for "Retired Fellows." This amendment is currently going through the adoption process.

Issues of Special Note

A selection of the more significant developments that took place will be briefly recounted below.

1) *Establishment of the Hoechst-Roussel Agri-Vet Graduate Student Award Program*. The academy was the beneficiary of a wonderful gesture by the Hoechst-Roussel Agri-Vet Company (through the good offices of John Paul) which funded a Graduate Student Award Program intended for any graduate student enrolled in a Masters or Doctorate program in the areas of pharmacology or therapeutics. The annual grant of \$1000 must be used by the recipient to attend scientific meetings, in the U.S. or abroad, that are relevant to his/her area of study. The guidelines for the selection process were delineated by AAVPT and the program is in place.

2) *Reduction of outstanding debt on the Journal of Veterinary Pharmacology and Therapeutics*. The Council, with membership approval, agreed to accept an offer from Blackwell Scientific Publications to subscribe, on behalf of each AVPT member, to the Journal of Veterinary Pharmacology and Therapeutics at a reduced rate for just one year. This decision provided each member with copies of JVPT for a year and importantly substantially reduced the remaining outstanding debt on the journal. The journal continues to be available to individual members at the much reduced rate of \$50. Charles Short and Peter Lees, working as coeditors of the journal, were superb and the journal's reputation and popularity continued to grow steadily.

3) *Comments on the bulk drug issue*. AAVPT's Advisory Committee under Art Aronson's able leadership responded to CVM's call for comment on the proposal to make drugs in bulk form available to practitioners. This was a difficult issue for AAVPT but the Academy responded appropriately and responsibly in my opinion.

4) *Establishment of a Speciality Board in Clinical Pharmacology*. A standing AAVPT committee had wrestled with this matter for many years and finally an opinion poll was taken to decide whether the efforts should continue. By a narrow margin, it was agreed to proceed with the development of a formal proposal to AVMA and the clinical Pharmacology Speciality Board Committee has now started its work in earnest.

5) *Observer status at AVMA's COBTA meetings*. Through the efforts of Art Aronson, AAVPT was granted observer (or consultant) status at COBTA meetings. This is proving to be a highly desirable and mutually beneficial arrangement.

6) *Creation of a Long-Range Planning Committee*. The membership suggested at the 1986 annual meeting that a Long-Range Planning Committee be brought into being to review the future disposition of AAVPT's accumulated resources. A committee, under the chairmanship of John Paul, was constituted and several recommendations are already on file.

7) *The Nomenclature Committee and SNOVET*. Gordon Coppoc continued his sterling work on behalf of AAVPT with respect to developing an appropriate veterinary nomenclature system with all pharmacological terminology correctly identified and incorporated. Gordon's contributions to this ongoing process deserve AAVPT's unmitigated gratitude.

8) *Development of the National Board Examination*. Jim Riviere and his AAVPT Examination Committee played a much more significant role than had been the case in the past in the development of the National Board Examination. AAVPT's input and contributions were very much appreciated by the AVMA and the Professional Examination Service.

9) *Liaison with other associations*. Continued contacts with two important European groups with similar interests to AAVPT occurred during the 1985-87 period. These were, firstly, the European Association for Veterinary Pharmacology

gy and Toxicology and, secondly, the Association for Veterinary Clinical Pharmacology and Therapeutics. Great interest was expressed in furthering the relationships with these groups.

10) *Other committee work.* Many other members continued to serve the Academy well through their work on several AAVPT as well as outside committees. Mention should be made of the following: FAVOR Task Force (Lloyd Davis); Professional Liaison Committee (Bill Huber); Finance Committee (Bill Miner); Nominating Committees (1986, Carl Aronson and 1987, Judi Weissinger); and the Constitution and By-laws Committee (Dwight Mercer). Dario Cappucci continued to act in exemplary fashion as AAVPT's Archivist Historian.

11) *The AAVPT Newsletter.* This publication was produced and regularly distributed throughout the 1985-87 period in the superb fashion to which the membership had become accustomed. The thanks for this effort falls almost

totally on the shoulders of the editor, Carl Aronson, and Eleanor Arrington, his able production assistant/secretary.

12) *The 6th Biennial Symposium.* Finally, Dean Peter Eyre through Bill Huber offered to host the 6th AAVPT Biennial Symposium at the Virginia-Maryland Regional Veterinary College in Blacksburg and so it is that we are here today reflecting on the first decade of AAVPT's existence.

For completeness sake, it should also be recorded that the present Council, which was elected in July, 1987 and which now carries AAVPT's banner, is constituted as follows:

President:	Art Aronson
President-elect:	John Paul
Secretary/Treasurer:	Dan Gingerich
Past-President:	Bill Jenkins
Councilors:	Richard Adams, Gary Koritz, John Stoner, Dick Teske, Rainer Muser, Bill Kay.

Inflammation and Joint Disease: Mechanisms, Mediators, and Medicines

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A New Frontier in Veterinary and Comparative Pharmacology: Aquatic Species

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Introduction

The area of pharmacology dealing with animals living in the seas, oceans, lakes, and rivers of this planet is largely underdeveloped. Studies into this area are urgently required due to our increasing dependence on food from the sea, exemplified by growing aquaculture industries, and the changing environmental conditions of aquatic habitats, due to pollution, acid rain, etc.

The administration of drugs to fish and other aquatic species is complicated because of incomplete knowledge of the pharmacokinetics of drugs in these animals. It is also difficult to properly control drug delivery and bioavailability in an aquatic environment. Furthermore, the basic physiological processes of many species are incompletely understood and must be described prior to examining the pharmacology.

The present study has been initiated to understand the receptor populations of fish smooth muscle and how they are affected by environmental changes. The rainbow trout, *Salmo gairdneri* was chosen because it is the major fish species farmed in the Maritime provinces of Canada and the gut chosen because of its ready accessibility. The study can be expanded to look at vascular smooth muscle as well.

Material and Methods

Tissue preparation: Rainbow trout, 14-25 cm in length, raised in the Fish Health Unit of the Atlantic Veterinary College, were killed by decapitation. The intestine was removed and washed with cold trout Ringer's solution (TRS) of the following composition: NaCl 110 mM; KCl 2 mM; CaCl₂ 1.5 mM; NaHCO₃ 1 mM; NaH₂PO₄ 0.4 mM; MgSO₄ 0.5 mM, pH 7.4. Segments approximately 2 cm in length were cut from the intestine and suspended in TRS in 10 ml organ baths by a method similar to that used for guinea pig ileum (1). The position from which the segment was removed from the intestine was noted for future reference. The trout Ringer's solution was maintained at 10°C and aerated with a mixture of O₂ and CO₂ (95:5). The baseline tension on the tissues was maintained under isometric conditions at 2 g, which corresponds to the 1₀, and changes in tension were measured using FT.03 transducers (Grass, Quincy, MA) and recorded on linear chart recorders (Gould, Cleveland, OH). At the end of each day, the tissues were re-

moved from the organ baths, blotted to remove surface moisture, weighed, and the lengths measured. The changes in tension induced by drugs was normalized by dividing the value by the weight and length. The value obtained is the tension developed per cross-sectional area of the tissue (2).

Experimental protocol: The tissues were allowed to equilibrate for approximately 1 hr following set up, with regular changes of the bath fluid. Concentration-response relationships were established for histamine, 5-hydroxytryptamine (5HT), carbachol, and potassium chloride by randomly adding amounts of these agents to the organ baths to achieve concentrations that were capable of inducing contractions, ranging from threshold to maximal. The values were normalized, as noted above, and log concentration-response curves drawn. The EC₅₀ and maximum values were determined using the computer program MEANCURV. The EC₅₀ values were converted to pD₂ values (-log EC₅₀) to facilitate calculations.

The specificity of agonists for their receptors was determined using the selective antagonists, methysergide and atropine for 5HT and muscarinic receptors, respectively. Paired segments of gut from the same fish were used, so that responses to agonists could be compared in the presence and absence of antagonists at identical times. Concentration-response curves were established as above and the EC₅₀ and maximal values compared statistically using Student's t-test for paired data.

Materials: Histamine dihydrochloride, 5-hydroxytryptamine creatinine sulfate, carbamylcholine chloride, and atropine sulfate were purchased from Sigma, St. Louis, Missouri. Methysergide hydrogenmaleate was a gift from Sandoz Ltd., Basel, Switzerland. All other chemicals were obtained from Fisher Scientific, Oshawa, Canada. All drugs were dissolved and diluted in distilled water.

Results

Carbachol, 5HT, and potassium induced concentration-dependent contractions of trout intestinal smooth muscle (Figure 1). Histamine (up to 10⁻⁴M) had no effect. Carbachol and 5HT were equipotent (pD₂ values: 5.36 ± 0.13 and 5.58 ± 0.14, respectively; n=20). They also had similar efficacy (maximal contractions: 185.51 ± 15.83 and 220.55 ± 19.50

Table 1. Potency and efficacy of carbachol and 5HT in the presence and absence of antagonists.

Concentration of Atropine	Maximum Contraction to Carbachol (g/mm ²)	pD ₂ for Carbachol	Sample Size
0	194.1 ± 12.3	5.40 ± 0.08	34
3 × 10 ⁻⁹ M	117.5 ± 25.4*	4.77 ± 0.12*	6
1 × 10 ⁻⁸ M	50.4 ± 14.5*	4.49 ± 0.23*	6
2 × 10 ⁻⁸ M	33.8 ± 17.5*	3.85 ± 0.59*	2

Concentration of Methysergide	Maximum Contraction to 5 HT	pD ₂ for 5 HT	Sample Size
0	229.7 ± 20.1	5.61 ± 0.16	18
3 × 10 ⁻⁹ M	227.7 ± 36.6	5.66 ± 0.28	6
1 × 10 ⁻⁸ M	146.2 ± 42.7*	5.03 ± 0.17	6
2 × 10 ⁻⁸ M	57.6 ± 30.3*	5.00 ± 0.31	4

*P<0.05

mg/mm², respectively; n=20), and were only slightly less effective than the depolarizing agent, KCl (maximal contraction: 259.49 ± 15.82 mg/mm²; n=20), in inducing contraction of the smooth muscle.

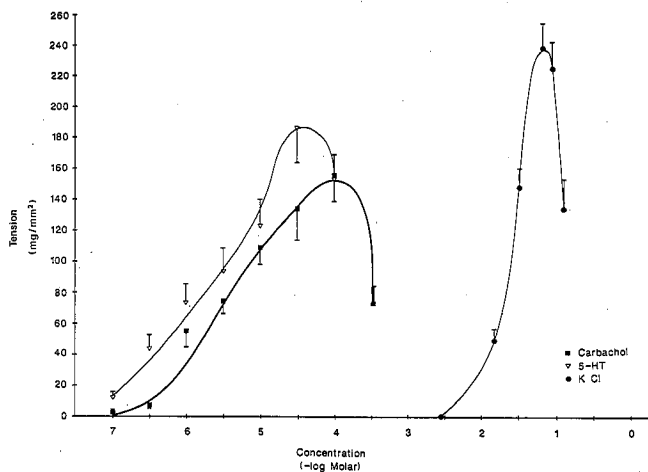


Figure 1. Concentration-response curves for carbachol, 5HT, and KCl.

Both the potency and efficacy of carbachol were reduced by increasing concentrations of atropine (Figure 2, Table 1). Neither the pD₂ nor the maximal values for 5HT or KCl were changed by atropine (data not shown).

5HT, but not carbachol or KCl, was inhibited by methysergide. The CR curves were shifted slightly, but not significantly, to the right with increasing concentrations of methysergide, but there was a clear concentration-dependent inhibition of the maximal contractions (Figure 3, Table 1).

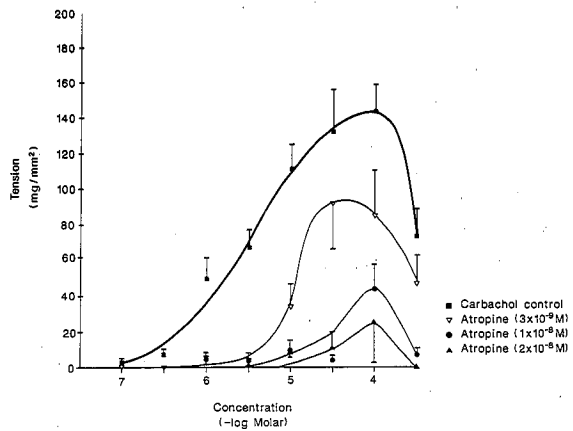


Figure 2. Concentration-response curves for carbachol in the presence and absence of atropine.

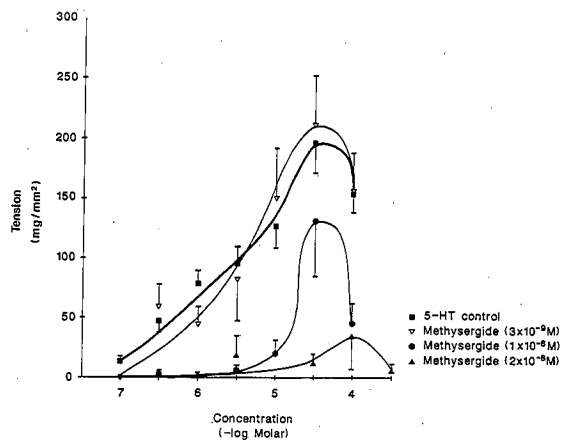


Figure 3. Concentration-response curves for 5HT in the presence and absence of methysergide.

Discussion

The ability of carbachol and 5HT to contract intestinal smooth muscle of the rainbow trout in a concentration-dependent manner indicates the presence of muscarinic and serotonergic receptors in this tissue. The lack of efficacy for histamine suggests an absence of histamine receptors. These findings confirm the earlier observations by Burnstock (3) in brown trout (*Salmo trutta*). Carbachol and 5HT have approximately equal efficacy and potency, but do not contract the tissue to its maximum potential, as is shown by the increased tension attainable with the membrane depolarizing agent, potassium chloride.

The muscarinic and serotonergic receptors can be blocked by atropine and methysergide, respectively. However, the antagonism is not competitive, as is evident by the suppression of the maximal response with these agents. The antagonism by atropine and methysergide is specific, as atropine only blocked carbachol and methysergide only 5HT. This noncompetitive antagonism for muscarinic and serotonergic receptors by atropine and methysergide, respectively, is different from that seen in mammalian smooth muscle. Data further suggest that, in this species, serotonin does not elicit a neurogenic (parasympathetic) response, also different from mammalian preparations. Evidence for multiple types of muscarinic and serotonergic receptors has appeared in the literature in the last few years (4, 5). The type of antagonism observed may reflect that more than one receptor subtype is involved in smooth muscle contraction in trout intestine. Studies are presently underway using selective agonists and antagonists for muscarinic and serotonergic receptor subtypes to determine the classes of receptor involved in contractile responses.

Future Directions in Aquatic Pharmacology

1) *Sources of information and agents for mammalian pharmacology*: In addition to studying aquatic species for their own sake, they also can provide us with information about mammalian species. For example, the Torpedo ray has been a primary source of material for isolation and purification of acetylcholine receptors (6), and tetrodotoxin and saxitoxin, sodium channel blockers, are derived from the Japanese puffer fish and the marine plankton, Gonyaulax, respectively (7). Several pharmacological agents have also been derived from aquatic species. Corals supplied the basic chemicals for the early synthesis of eicosanoids and pharmaceutical firms are actively searching for anticancer drugs in marine organisms. Ingestion of fish containing high levels of eicosapentaenoic acid have also been shown to be of therapeutic advantage in reducing occurrence of myocardial infarctions and stroke (8). The above examples only represent a small part of a vast compendium.

2) *Studies of fish physiology and pharmacology*: The present experiments are an example of this. The effects of changes in a fish's environment on smooth muscle function have previously only received limited attention. Parameters

that can be examined include pH, temperature, and salinity. Effects of pH are of current interest because of the environmental impact of acid rain. Studies on the effects of temperature will be particularly useful to the field of aquaculture where fish are kept in a fixed space and cannot migrate to meet their optimum environmental conditions. Growth rates are dependent on temperature and fish will go off feed when subjected to temperatures above and below an optimum range (9). Water temperatures in Atlantic Canada regularly fluctuate above or below optimum feeding temperatures of salmonids.

Changes in water acidity alter ion exchange mechanisms in the gills (10). In mammals, ionic imbalance alters smooth muscle function (11) and similar changes probably also occur in fish. Temperature changes in mammalian smooth muscle alter ion flux, particularly of calcium, across membranes. This is of particular relevance to hypothermia and hibernation. Preliminary studies in my laboratory indicated that potassium contracts gastrointestinal (gi) smooth muscle of fish at low temperatures, suggesting differences between mammalian and fish smooth muscle. A clearer understanding of this difference and its relationship to calcium channels may provide further information on calcium channel pharmacology, which is significant to medical therapeutics.

The potential for further research in the area of autonomic and smooth muscle pharmacology of fish is great. It has already been shown that trout stomach is innervated by a nonadrenergic noncholinergic (NANC) nervous system with substance P as the primary neurotransmitter which can induce secondary release of 5HT (12). Similar NANC nervous systems occur in mammals and contribute to both contraction and relaxation of smooth muscle. This may be a primitive nervous system, but it appears to have implications in inflammatory diseases, such as asthma (13). Understanding the mechanisms in trout may help us again to understand the mechanisms in humans.

3) *Pharmacy of aquatic species*: Little is known about the pharmacokinetics of drugs administered to fish, particularly in the aquaculture industry. Drugs currently used are fairly nonspecific and consist primarily of antibacterials, antiparasitics, and vaccines. The impact of unused and eliminated drugs on the environment is basically an unknown. More efficient routes of administration must be determined to reduce costs to the industry, to allow the use of more selective agents, and to eliminate damage to the environment. Thus, the pharmacy of aquatic species may be a profession of the future.

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New Frontiers in Veterinary and Comparative Pharmacology for Regulatory Agencies

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I would like to stimulate some thoughts about the future in veterinary clinical pharmacology. My perspective is that of a veterinary drug regulator, and I must begin by saying that from my perspective these are, at once, exciting, depressing, challenging, frustrating times. I believe that we are on the threshold of significant change, particularly in the area of drug distribution and use in food animals.

One of the driving forces causing change in this area is the concern being expressed by consumers for animal-derived food products that are free of drug or pesticided residues. This concern has led to a change in the attitude or philosophy of many livestock producers relative to the products they produce. More and more producers recognize that responsibility for their product does not end when their animals are shipped for slaughter or the milk tanker heads down the lane. They recognize that they are both dependent on and bear a shared

responsibility for, not only the actual but also the perceived, wholesomeness of the product at the retail level.

Evidence of this change is everywhere; in the establishment of the Nutritional Effects Foundation as a nonregulatory human nutrition and health-oriented body that both sets standards for red meat and certifies products that meet their standards; in expansion of the concept of verified production control and other quality assurance initiatives and programs sponsored by producer organizations; and in standards of practice being established by various veterinary practice specialty groups providing veterinary services to the livestock and poultry industry, as well as AHI's animal health product use documentation program.

Thus, I believe that the proper and responsible use of animal drugs and feed additives must become a "bottom-line" issue for veterinary practitioners, particularly food animal

practitioners, in the future. Concern for proper and responsible drug use must be the primary factor in decisions regarding drug use, outweighing such secondary factors as the economics within one's practice, and must reflect not only appropriate medical standards but also the client's sense of ultimate responsibility for consumer perceptions about the wholesomeness of animal-derived food products.

One of the most important considerations relative to proper drug use is being sure that such use does not result in violative residues in edible products derived from treated animals. The best way to do this, of course, is to use only approved animal drugs and use them in strict accordance with their labeling, paying particular attention to stated withdrawal times. Why, because only with approved drugs is one dealing with a product of proven quality with labeling that has been demonstrated under strict scientific standards to assure its safe and effective use.

I recognize the obvious problem with this position. There are not approved drugs available for every indication in every food animal species. Nor is it possible, given current circumstances, to provide approved animal drugs labeled for use by laymen for every indication in every food-animal species. Thus, I think that the only real solution to many of the concerns that are related to the proper and responsible use of animal drugs in food animals is more approved animal drugs that are labeled in such a way as to provide for considerably more flexibility in their use by an informed professional. For example, labeled in such a way as to provide the necessary information to allow the informed professional to exercise his/her professional judgement in deciding on the appropriate dose level or treatment regimen to be employed in a particular case. Flexibility even with respect to indications for use. Of course for this to be a viable solution, a number of things would have to change.

The underlying premise in this idea is that there would be greater control of the distribution and sale of animal drugs and that the use of such drugs would be restricted to those who, by law, have been deemed qualified to exercise the necessary skill and judgment in their use. For example, states would have to adopt appropriate animal drug regulatory procedures providing for adequate surveillance and compliance authority relative to animal drugs. Of course, a number of states are already in the process of adopting or revising their regulations in this area. Interest in the Model Animal Drug Code recently adopted by the Association of Food and Drug Officials is further evidence of the trend in this direction.

Food animal veterinarians, or others who are appropriately certified or otherwise authorized to accept such responsibility, would have to adopt appropriate standards of drug use and be willing to accept, along with the responsibility for the use of such drugs, accountability for their use. Evidencing the trend in this direction are standards for the use, prescribing or dispensing of drugs by veterinarians currently under development by the AVMA's Council on Biologic and Therapeutic Agents (subsequently adopted by the AVMA House

of Delegates meeting in Portland, Oregon.

Veterinary academia will have to provide via both their professional curricula and through continuing education programs an adequate base in veterinary clinical pharmacology both to stimulate research in clinical pharmacology and to assure an adequate knowledge base among veterinary practitioners.

The FDA would have to adopt approval policies that recognize that animal drugs which are subject to greater control in sales and distribution and for which use is generally restricted to those who, by law, have been deemed qualified to exercise the necessary skill and judgment in their use, would require less specific documentation particularly in support of indications for use. In addition the animal drug industry would have to recognize and support the concept that the proper and responsible use of animal drugs and feed additives is now and will continue to be an issue, and that the only real solution is in the assurance that only approved drugs are used in food animals and poultry and that they are used in strict accordance with their labeling. The animal drug industry would also have to recognize that there must be greater supervision and control of the distribution and the use of animal drugs in livestock.

I believe that all of these suggestions are achievable. Some of them will, in fact, occur whether we like it or not. Certainly the trend toward more integration in the red meat industry and the move toward individual animal identification of animals moving to slaughter will drive a much greater attention to quality control at the farm production level. The availability of cost-effective, pen-side tests for drug residues in animals being readied for market will facilitate the inclusion of clinical pharmacology/residue quality control services as what I believe will become an essential component of the full service animal health, diagnostic, production, nutrition, and management service producers of the future will come to rely upon. I draw a distinction between clinical pharmacology and residue quality control because I believe these new rapid test procedures ultimately will have as much utility in monitoring therapeutic blood levels to assure proper dosage regimens, and in evaluating the effectiveness of delivery systems as they do in residue quality control programs.

In conclusion let me reiterate first that proper and responsible use of drugs, particularly in food animals, must supercede economics or convenience in decisions regarding drug therapy. Secondly, in order to assure proper distribution and use of drugs we must have an adequate armamentarium of approved drugs for use in all livestock species and for all needed indications. Finally, I believe that such an armamentarium of animal drugs can be achieved only through development of approved labeling that provides more flexibility for use by an informed professional. This in turn can be achieved only through establishment of processes that limit the distribution and use of animal drugs to and by informed professionals.

New Frontiers in Veterinary and Comparative Pharmacology for Industry

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It appears that the frontier which promises to have a dramatic impact on veterinary pharmacology for industry as well as for the entire animal health community is biotechnology. The term biotechnology is frequently overused and often misused. For the purpose of this discussion biotechnology will be used as it applies mainly to genetic engineering. Biotechnology, if defined this way, will not replace traditional pharmacological agents. Rather, biotechnology will expand the range of available veterinary drugs. It will allow the production of certain substances that cannot be produced economically by other means. It will result in the production of substances with greater specificity and purity than is possible by conventional methods.

During only the past 44 years some very important scientific events have occurred which led into the biotechnology era. In 1944, Avery et al. were the first to determine the role of DNA as the carrier of genetic information. Watson and Crick in 1953 discovered the double helix structure of DNA. Several workers, notably Kelly and Smith, in 1970 developed restriction enzymes that cut the DNA strands in precise locations. In 1973, Cohen and Boyer used the restrictive enzymes to isolate DNA fragments in one bacterium and inserted them into another. The first commercial effort at developing genetically engineered products came about only 12 years ago with the foundation of Genentech. In 1983, Eli Lilly and Company received FDA approval to market the first genetically engineered drug, Humalin—a form of insulin (1).

There are currently several types of biotechnology products under development or with potential for commercial development. Regulatory peptides involved in reproduction, growth and metabolism as well as behavior are ideally suited for genetic engineering. Immunomodulators and immunizing agents are very interesting for commercial development and some biotechnology vaccines are already on the market. Production of highly specific antibodies using biotechnology has led to the development of rapid immunoassay tests; specifically, ELISA (enzyme linked immunosorbant assay) technology has resulted in the availability of several diagnostic products with many more products on the horizon. Finally, animals themselves may have the potential as sub-

jects of genetic engineering. Transgenic farm animals may result in animal populations that are resistant to various diseases, are highly efficient converters of feed to meat and may produce a higher ratio of lean to fat tissue. Undoubtedly many other types of biotechnology developments will surface in the future. (2)

What impact will biotechnology have on veterinary pharmacologists and the animal health industry? It is possible that we are on the brink of a revolution relative to the development of new animal health products. One might predict that more emphasis will be placed on the development of products that prevent diseases as compared to therapeutic agents. Peptide hormones used to regulate reproduction, growth and metabolism at the basic level can be expected to take priority over the development and use of "end point" hormones. Rapid, sensitive and highly specific diagnostics will play important roles in not only detecting disease, but also for drug detection. If the above predictions prove correct, new methods will be needed to develop and evaluate certain animal health products. Veterinary pharmacologists may be required to become reoriented in respect to the use of drugs and may need expertise in a broader variety of scientific skills.

The new technology will require interaction among many disciplines of veterinary medicine. Demarcations between disciplines may shift and adjust to overlapping interests. Pharmacologists working in industry will play a special role in translating this new technology into commercial products to the benefit of diseased animals, animal production and humanity, relying on animals as a food source.

In conclusion, there are at least two major challenges facing the animal health industry and veterinary pharmacologists as we enter the era of biotechnology:

- Development of graduate training centers to attract more individuals to veterinary pharmacology are needed. The graduate student must intertwine training in pharmacology with in-depth training in immunology, microbiology, endocrinology, oncology, biochemistry and possibly other disciplines.
- As a responsible and learned scientific group, we must take a pro-active role to inform the public about the

benefits of biotechnology. This instructive role is vital to counteract the efforts of many consumer and production groups whose apparent goal is to block further development of biotechnology.

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New Frontiers in Veterinary and Comparative Pharmacology for Academia

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Introduction

During the past two days of the symposium, we have heard a number of excellent descriptions of many new frontiers, presented by virtually the entire leadership in veterinary pharmacology in North America. It would be both presumptuous and redundant if I were to attempt to redefine these in the short time available to me.

I would therefore like to take just a few minutes to suggest that there is one frontier (perhaps our most important) which is not new but which certainly needs to be revisited and re-evaluated. And that is *graduate education*. This is an ideal moment for me, at this point in the symposium, to combine my remarks with the AAVPT's first biennial graduate student awards program and I shall return to that momentarily.

As an academy, we have an absolutely unequivocal obligation to promote graduate education in veterinary pharmacology. This, for me, is also a personal matter because graduate students have played a very prominent part in my career. Six of my former graduate trainees are here at this symposium. Many are scattered around the world and I count them among my closest friends and colleagues.

Yesterday, Jim Riviere thoroughly described the many challenges of graduate education. Today John Paul has made a plea for enhanced graduate educational programs to serve industry. I fully agree with what has been said and I would simply like to add a few other perspectives.

One can certainly have excellent research which carries no

direct educational component. However, one cannot have good graduate education for tomorrow's world without excellent research. Academia is the only place in society where research and education are integrated into a common goal: the advanced degree. I would go even farther and suggest that if academic research does not also have educational goals, then an essential component of the University's mission is lacking.

It seems to me that, although there are many variants, one can condense postgraduate education in pharmacology into two categories: 1) the classical MS-PhD track and 2) the applied track which is exemplified in the clinical residency. Academia, practice and industry are served by one or both of these, depending on circumstances.

The MS-PhD Program in Veterinary Pharmacology

In my view one cannot begin to define priority areas of research, nor should we even try. Likewise I feel it is unimportant whether the student holds a veterinary degree or not. And by the same token, it is not important that the faculty supervisor be a veterinarian. However, it seems to me that there are four essential ingredients:

- 1) There must be a well-qualified, committed faculty and administration. Graduate student supervision must be recognized as a high priority in the College and department and must be rewarded in promotion, tenure and salary decisions.

- 2) There must be an adequate supply of high quality formal courses available. The teaching of graduate courses must

be regarded as an activity of equal value to all other academic endeavors and again must be properly rewarded.

3) There must be a stable, well-resourced research program in an appropriate subject area. Such a program must have a solid publication record in leading journals in the discipline. Traditionally, research publication is well recognized in the faculty reward system.

4) There must be a nucleus of well-qualified students who are endowed with a high level of intellectual curiosity and self-motivation.

In my view we must place a high priority on the education of the student in the principles of scientific method and leave as much flexibility as possible in the conduct of the research project. Too often we confuse education with training and there is a growing trend towards the latter at the expense of good basic education: leaving the graduate ill-prepared for the inevitable changes of the future.

I could not even begin to prioritize the new frontiers of research in veterinary pharmacology. They are legion. However, it is safe to make certain generalizations.

We can be sure that the present revolution in biotechnology will profoundly influence pharmacological research and clinical practice. Molecular pharmacology will certainly continue to influence most areas of study. The growing public concern for wholesome food and a clean environment will ensure continued interest in drug and chemical monitoring. We shall certainly continue to discover and evaluate "new" endogenous mediators of body functions and thereby develop additional ways to manipulate biological processes. I also believe that the growing interest in minor and exotic species will continue.

In all the above there is one feature which I feel is most important (and also may be controversial) and that is the definition of veterinary pharmacology which distinguishes it from all other avenues of pharmacological endeavor. I believe, very simply, that veterinary pharmacological research must have a veterinary endpoint: in other words we are the professional group which addresses the actions and uses of drugs in animals as the target species as opposed to using animals as models in fundamental biological research or as models for advancing human biomedical knowledge.

Final Thoughts on Residencies in Clinical Pharmacology

Dr. Riviere described all the features in detail and also pointed out the many frustrations and logistical difficulties inherent in such an enterprise.

The fundamental principle is that clinical training is integrated with postgraduate education and research. Clearly the student will hold a degree in veterinary medicine and will be committed to a clinically-oriented career. The student's clini-

cal advisor will obviously be an appropriate board-certified veterinarian, whereas the educational/research component may well be provided by a basic bioscientist. Indeed this would in most instances, be a desirable arrangement.

In principle there should be no difficulty in combining a study of the patient with a proper understanding of biometrics. I feel that such a program is best if it culminates in a graduate degree (typically an MS, but occasionally a PhD degree). I find it difficult, generally, to support the "no-thesis" master's degree for this purpose, although exceptions will no doubt exist.

I also feel that we have a responsibility to promote the incorporation of clinical pharmacology instruction as a mandatory component of most (if not all) residencies in Medicine and Surgery. It ought to be an indispensable part of all advanced clinical training to better understand the rational use of drugs and drug monitoring in patients.

I support the formation of a College of Veterinary Clinical Pharmacology and Therapeutics as a specialty board. I am very encouraged by Bill Jenkins' rational but bold approach to this. As an academy, let's stop studying the issue and do something. We have all the relevant facts we need, so we should submit our credentials to the AVMA and start the program.

In conclusion I want to congratulate, very sincerely, the thirteen graduate student participants in this symposium. Their papers were uniformly excellent. The topics ranged from molecular mechanisms to clinical applications and, without exception, all the investigations were in veterinary target species.

This graduate student program was a significant feature of the 6th symposium and should be continued and formalized into future programs. The academy should seek funds to support the attendance of graduate students at future meetings. I would also recommend that AAVPT create a category of student membership with a nominal annual retention fee.

All these proposals would show the academy's commitment to and investment in the future of the profession of veterinary pharmacology and the academy would be enhanced significantly in the process.

In order to recognize the graduate student authors in this symposium it is my pleasure to present a certificate of participation to all thirteen individuals. It is also my privilege, for the first time in the academy's history, to award certificates and sums of money as prizes for the best graduate student papers. The first position is awarded to Hassan El-Fawal and the second position to Jean-Luc Rioud.

I would like to thank the academy for supporting this graduate student program and finally to offer congratulations to all the participants.

