

Microbes, Men, and Animals



Dr. Charles Benson (left) and Dr. Jon Palmer.

Unlike gregarious human beings, animals do not hold conventions, and are therefore spared the discomfort, and death, visited upon some of the people who convened in Philadelphia in 1976. As you probably recall, this was the infamous American Legion convention held at the stately Bellevue Stratford hotel and the disease outbreak brought about the demise of a Philadelphia landmark. Naturally, the malady was quickly labelled "Legionnaires Disease." Subsequently, there have been some well publicized outbreaks of this disease in other parts of the world, and the causative organism has been identified as *Legionella pneumophila*.

It now appears that animals may be carriers of this organism, and Dr. Charles E. Benson has begun a screening study to determine whether this is true. Dr. Benson is associate professor of microbiology in the School of Veterinary Medicine, whose laboratory is located at New Bolton Center. Dr. Benson has been involved in some basic studies on the characteristics of *L. pneumophila* which is an organism that invades body cells. *L. pneumophila* itself has never been isolated from animals, but, antibodies, produced in response to the organism, have been detected. Dr. Benson's work is concerned with direct isolation of the bacterium, a difficult chore. The organism can be isolated from human beings where it causes an atypical pneumonia, and Dr. Benson has it growing in cell culture in his laboratory. Dr. Benson's quest for this organism in animals is illustrative of one of his basic philosophies, to wit, "we only find what we look for." Despite some great strides, Dr. Benson points out that we are still on the frontier in our efforts to specifically identify bacteria that cause many infectious diseases in animals. There are a number of clinical syndromes in animals that appear to be of an infectious nature, but for which a causative organism has not been identified. With this in mind, Dr. Benson and various clinicians at New Bolton Center have teamed together in the hope of gaining a better understanding of the pathogenesis of certain of these perplexing syndromes. The clinicians with whom he has been working most closely are Dr. Robert Whitlock, Dr. Robert Dyer, and Dr. Jon Palmer. Prior to Dr. Benson's arrival at New Bolton Center in January 1981, this sort of cooperative effort in the study of infectious diseases had been neglected. Dr. Whitlock, who is associate professor of medicine and chief of medical services at New Bolton Center is quite enthusiastic about the future of this field.

Another major research interest of Dr. Benson is the study of the organism, *Salmonella*. This is a pathogen that has long been the plague of animals and humans. Interestingly, it was first discovered by a veterinarian, Dr. Daniel E. Salmon, who was the first Chief of the Federal Bureau of Animal Industry. One problem in any study of *Salmonella* is that there are over 1,200 strains of the organism. While certain strains have been identified as the cause of the disease in animals known as salmonellosis, it is possible that other, unidentified strains may also be involved. One of the objects of Dr. Benson's work will be to attempt to define mechanisms of pathogenesis. The particular strain now most commonly associated with colitis in horses is *Salmonella typhimurium*. The common clinical signs are hyperthermia, diarrhea, colic pain, and occasionally a rapidly developing septicemia. One characteristic of equine salmonellosis is that it strikes horses that are in stressful situations, including transport, weaning, worming, or any other situation that lowers resistance. Surgery may predispose horses to salmonellosis, and one aspect of the work of Drs. Benson and Palmer is to examine horses post-surgically for the presence of *Salmonella*. Salmonellosis is highly contagious at the local level; it can become entrenched on a particular farm. Horses with salmonellosis at New Bolton Center are placed in isolation.

Dr. Benson states that some *Salmonella* strains have the capability of producing toxins. This is related to the genetic make-up of a particular organism. Horses with toxemia, associated with salmonellosis, have been observed at New Bolton Center, and the search for strains that produce this phenomena will be part of the Benson/Palmer study.

In the past ten years there has been an increase in the incidence of *Salmonella* infections in both humans and animals. Recently there have been outbreaks of the disease in humans following the consumption of cooked beef. One problem in the spread of salmonellosis is the fact that most species, including humans, can act as carriers of the bacteria without exhibiting overt clinical signs. It is estimated that at least ten percent of the horse population are carriers of *Salmonella*.

Diagnosis of salmonellosis is based upon identification of organisms in fecal culture. This may be difficult in carrier animals, and Dr. Benson hopes to improve diagnostic methods.

A cooperative study in which Dr. Benson is involved with Dr. Dyer, concerns the etiology of "shipping fever" in cattle and horses. Dr. Benson is also conducting basic research on metabolic pathways in *Salmonella* and other organisms. While he is relatively new to the faculty of the School of Veterinary Medicine, Dr. Benson has been at the University of Pennsylvania since 1975, with the School of Allied Medical Professions. In addition to research he teaches in the core and elective portions of the veterinary curriculum, and is administrator of the clinical laboratory at New Bolton Center.

Canine Epilepsy

Epilepsy is one of the most common canine neurological complaints, yet control of seizures in dogs remains a difficult, frustrating, and often unrewarding task for veterinarian, owner, and patient. In an effort to remedy this situation, the Veterinary Hospital of the University of Pennsylvania has recently instituted an epilepsy foundation for dogs called the Canine Epilepsy Service under the directorship of Dr. George C. Farnbach, V.M.D., Ph.D., assistant professor of neurology. This canine epilepsy center has the ambitious goals of improving the control of seizures in epileptic dogs and, if possible, eliminating seizures altogether through a cooperative effort involving pets, their owners, their local veterinarians, and the facilities of the Canine Epilepsy Service (CES).

Dogs, like people, suffer from epilepsy of varying intensities and types. Like the physician, a veterinarian is generally forced to attempt to control epilepsy through the use of anticonvulsant drugs. The control of seizures in humans is more often successful than it is in dogs because considerably more information about the use and effectiveness of anticonvulsant drugs in humans is available to the physician. The process of controlling human seizures has been considerably advanced by the study of large numbers of epileptic patients on a variety of treatment regimens, which was made possible by centralized epilepsy study groups. These groups have developed a wealth of knowledge about the efficacy of specific drugs, the blood levels required to control seizures, and the toxic and long-term effects of these drugs. Modern technology now permits relatively inexpensive monitoring of serum drug levels, enabling the physician to adjust or switch anticonvulsants for maximum effect and minimum toxicity based on the knowledge of each drug and the individual patient's blood levels. No such body of knowledge exists in veterinary medicine, leaving the practitioner to determine the appropriate anticonvulsant for the patient on a limited and basically blind trial-and-error basis. This can be a costly and frustrating process.

"There are a variety of drugs and drug combinations which can be used in control protocols, yet accurate information about the effective and toxic blood levels of these drugs or about their long-term side effects in the dog does not exist," Farnbach explained. "At the CES we hope to collect this kind of information over a long period of time. Our goal is to monitor at least 1,000 dogs for at least three years."

To illustrate the importance of drug information, Farnbach cited Dilantin, a drug commonly used in both humans and dogs to control seizures. "In humans, Dilantin is effective in many patients, but to control seizures, blood levels above 10 ug/ml are required. An effective dose for an adult human is about 300 mg/day. We do not know

Service

"Anyone with a loved one—pet or human—that suffers from epilepsy has serious medical and emotional problems to face. In the past, we (the veterinarians and pet owners) have faced them alone and basically in the dark. If we can get together both people and information we will not be alone and, hopefully, the future will be brighter."

if Dilantin is effective in the dog, but we do know that the dog metabolizes Dilantin about 10 times faster than humans. In over 100 serum dilantin assays sent in from epileptic dogs, none showed more Dilantin than 7.2 ug/ml and none of the dogs were controlled. Three hundred mg/day might be an effective dose for a small dog like a Chihuahua, but a German Shepherd would need about 3,000 mg/day to reach 10 ug/ml in its blood. And we don't know yet whether that would be effective."

In humans, where effective blood levels of Dilantin are known and patient blood levels can be monitored, the daily dosage can easily be adjusted to fit the metabolic characteristics of each individual patient. If a human patient has adequate blood levels of Dilantin but continues to seizure, it becomes immediately clear that a new drug and not a new dose should be tried. The veterinarian however, without blood level measurements, must arbitrarily decide when to stop increasing dosages and change to or add different drugs. To improve the techniques in veterinary seizure control, the Epilepsy Service utilizes information collected from three sources: 1) the pet owner, 2) the local veterinarian, and 3) the routine monitoring of blood levels of anticonvulsant medications in epileptic animals.

A computer-based data management facility has been established to carefully record and monitor each patient. Initial information about each patient is recorded as their names are sent to the registry by the local veterinarian. Pet owners are sent explanatory literature and forms to record the characteristics of each subsequent seizure. These forms are filled in as seizures occur and are mailed to the CES in order to monitor both frequency and severity of each pet's seizure pattern. When an anticonvulsant drug protocol is started by the local veterinarian, the name of the drug or drugs and their dosages and blood samples are sent to the CES. The name and dosage of each drug and the corresponding serum level is added to the data base for each individual patient. In this way, changes in seizure patterns (or lack thereof) can be correlated with serum drug levels and dose patterns in hundreds of individual animals and the efficacy and toxicity of drug protocols can be evaluated.

The computerized data management system has been developed by Dr. Farnbach specifically for the CES. Drug level measurements are made using the EMIT system which has been validated for use with dog serum by the SYVA Co. of Palo Alto, CA in conjunction with the Canine Epilepsy Service. This system represents a technological advance which has proven advantageous in monitoring human anticonvulsant therapy and which will be cost-effective in monitoring veterinary anticonvulsant therapy.

"Computers and high technology are not the answer," Farnbach emphasized. "What is needed is a massive cooperative effort between animal lovers, veterinarians and research workers. Anyone with a loved one—pet or human—that suffers from epilepsy has serious medical and emotional problems to face. In the past, we (the veterinarians and pet owners) have faced them alone and basically in the dark. If we can get together both people and information we will not be alone and, hopefully, the future will be brighter."

Owners of epileptic dogs are a very important part of the program. They not only provide the veterinarian with the initial information but they also provide the CES with continuing information about the dog and its improvement or the nature and frequency of recurring seizures. The CES provides more than record keeping for the owner. It provides support and information and answers questions on both an individual basis and through a Newsletter which will be published shortly. In this way owners can see that they are not alone and that their pet's problems are not unique. Further, the questions and observations of the owners may provide clues about seizure patterns and triggers which may have been previously missed and ignored.

Participating veterinarians also play an obviously important role. Their observations regarding efficacy, toxicity and long-term side effects are essential to the development of more rational drug protocols. In return for their participation, veterinarians receive several benefits: serum drug level measurements are provided inexpensively; each animal's seizure and drug history is immediately available by computer for consultation with the staff of CES, if they desire; and new concepts regarding seizure control are disseminated as soon as they are extracted from the collected records of all dogs in the program. A Veterinary Newsletter is also being published for professional members of the Canine Epilepsy Service.

The services of the Canine Epilepsy Service are available to all pet owners free of charge. Veterinarians are asked to make a small annual contribution to cover the costs of publications and computer maintenance. Serum drug level measurements are provided at cost for member veterinarians. The medical data (but not the personal data) are available to any legitimate research organization wishing to use them in medical research. Those interested in more detailed information or in contributing to the program should contact George C. Farnbach, V.M.D., Ph.D., Director, Canine Epilepsy Service, School of Veterinary Medicine, University of Pennsylvania, 3800 Spruce Street, Philadelphia, Pa. 19104.

