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Comparative Medicine

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INTRODUCTION

My decision to become a pathologist was in large part the result of my good fortune in having Francis Schofield as a teacher in special pathology during his last year as an active faculty member at the Ontario Veterinary College. No other teacher before or since has been able to match his stimulation of my enthusiasm and interest in understanding disease phenomena. His lectures on edema disease or enterotoxemia of pigs captured my imagination to the extent that when I entered graduate school at the University of Minnesota I jumped at the chance of making this disease the subject of my thesis research. Consequently, I am grateful for the opportunity of commemorating this great veterinarian and teacher by participating in this lecture. It is also a pleasure to visit my alma mater, one of the world's great veterinary colleges.

Several years ago I pledged myself to become immersed in the field of comparative medicine because I believed that it was not receiving the attention it deserved. I am here today at the beginning of a personal quest to better understand comparative medicine. This enterprise will last at least one year and perhaps the remainder of my professional career. While the wisdom of this course remains to be determined, I can state with certainty that it will be an intellectually exciting experience. The study of disease phenomena in the animal kingdom, wherever that takes one, has to be fascinating. Comparative medicine was of interest to Dr. Schofield but if he were here today he might take me to task for some of my still fuzzy thinking about the subject.

While comparative medicine has been the subject of review from time to time (1-6) its importance merits continued and increased discussion. In the following I plan to discuss the definition of comparative medicine, to review its history in Canada, to give examples of its utility and to speculate as to the objectives that veterinary institutions should pursue in respect to this field in the future. In particular I wish to make the point that comparative medicine should be centered on disease phenomena not on man.

DEFINING COMPARATIVE MEDICINE

Comparative medicine was defined as "a study of phenomena basic to the diseases of all species" (7) by a group of medical scientists in the USA at a conference in 1967 sponsored by the National Institute of General Medical Sciences. This definition is a good one. Unfortunately, in many quarters it has been qualified by assuming that the ultimate objective is improving human health and welfare. This restriction limits the potential of comparative medicine to contribute to medical and biological progress in understanding disease, paradoxically to the detriment of man himself.

Bustad *et al* (2) gave this definition: "Comparative medicine is the study of the nature, cause and cure of abnormal structure and function in people, animals and plants for the eventual application to the benefit of all living things". One can embrace the spirit of this statement but it further begs the definition of "benefit" and "living things". Should an ascarid benefit from comparative medicine?

In 1938, the second year of publication of the Canadian Journal of Comparative Medicine, the editor (8) (probably T.W.M. Cameron) commented as follows:

> "Comparative medicine is an instrument rather than a science and for this reason it is difficult to define it with any degree of accuracy. It includes much of human and more of veterinary medicine, and yet it is bigger than either. It attempts to find underlying principles, and by comparison of disease and disease processes in one animal to understand better the pathology of another. Accordingly, the field must extend beyond that of the medical man and the veterinarian and review the medicine of wild animals".

An address given at the University of Guelph on October 6, 1982.

The editor clearly recognized the importance of wildlife to comparative medicine. Unfortunately he seems to imply that this field lies outside the direct interest of veterinary medicine. In the same journal, Cameron (9) recognizes the importance of experimental medicine:

> "The most significant discovery in the history of medical research was that man is merely an animal — a very special kind of animal perhaps, but still an animal. We do not even know who made this discovery although Darwin, more than anyone else, enlarged its significance and added it to the further ideas of evolution.
>
> The consequences were tremendous, yet it is curious that it was only the leaders of medical thought who really appreciated what these were. They included the use of animals in elucidating the problems of human physiology, anatomy, embryology, pharmacology and above all, in the study of disease processes; they give rise to the whole of our modern conception of experimental medicine.
>
> The normal and pathological processes in the non-human animals were quite strictly analagous to those in man — not quite the same of course, but comparable. From this idea arose Comparative Medicine and with it component parts of comparative pathology, physiology and so on."

In summary, the comparative method seeks to detect differences and similarities that provide insight into disease phenomena. Comparisons are made at many levels; between molecules, cells, tissues, organs or species.

For purposes of analysis, comparative medicine can be divided logically into two large branches, one dealing with experimental medicine and one with diseases in nature.

Experimental Medicine

This branch of comparative medicine is thriving in medical research and is in evidence every time an experimental animal or biological system is used for medical research. The value of animals in medical research is clearly recognized and they are employed in all its fields. If anything this area has been emphasized to the point of obscuring the value of the study of disease in nature. In theory, it should be possible to identify or create disease problems in animals that are comparable or are fundamentally the same as those in man or in any other given species. The veterinary profession has been reasonably aggressive in pointing out examples of animal disease which can serve as models of human disease. While useful, the anthropocentricity of this endeavour is a weakness. A more productive approach would be to give priority to the identification of models of disease phenomena, not models of human disease.

One very positive response of the veterinary profession to the growth of experimental medicine is the development of laboratory animal medicine as a specialty. Despite the importance of this field to medical research, we in Canada have given little priority to fostering its development. A commitment to comparative medicine must inevitably include increased attention to laboratory animal medicine.

University veterinary institutions are a very small presence in the total experimental medical research arena, far too small in proportion to their potential, to make a meaningful contribution to medical progress. For example, scientists at our three faculties of veterinary medicine in Canada received only approximately 0.6% of the more than 300 million dollars allocated to universities by the Medical Research Council and the Natural Sciences and Engineering Research Council in 1981.

Diseases in Nature

If insightful comparisons are to be made about disease in nature then it is a logical necessity to study disease in a wide array of species in order to acquire the requisite knowledge. This fact was recognized by the Canadian Journal of Comparative Medicine in 1938 when it advocated greater attention to wildlife. Given the narrow range of species in which the veterinary profession has shown a sustained interest I submit that it has barely tapped the potential of the study of natural diseases of vertebrates to advance comparative medicine. The multitude of similarities and differences in disease among the species remains a goldmine for study. It is essential therefore for veterinary institutions to take an active interest in the diseases of wildlife both in nature and in captivity if society is to reap the benefits of comparative medicine. Veterinary medicine has a responsibility to show leadership in that branch of comparative medicine which deals with naturally occuring disease in species other than in man.

DEFINING VETERINARY MEDICINE

What is veterinary medicine and how does it relate to comparative medicine? The Oxford dictionary defines veterinary medicine as follows: "The profession occupied with the medical and surgical treatment of animals, especially cattle". This definition is too narrow as the history of our profession has shown. The definition of veterinary medicine is much broader. It deals with health and disease in vertebrates. To give the profession a sufficiently broad perspective it may be necessary to effect a fundamental change in the way the profession is viewed, a paradigm change to use the term in the context developed by Kuhn (10).

Veterinary medicine can best be described by the four broad domains in which it functions. These are: domestic animals, wildlife, public health and biology. The first three are the more applied arm of our profession and the last recognizes our general contribution as a biological science. Comparative medicine is the foundation on which veterinary medicine is built and is shared with human medicine. It is Osler's "one medicine."

The applied domain of domestic animals is extremely important and must be the profession's major commitment at present. Our immediate usefulness to society is in large measure associated with this domain and we neglect it at our peril. Unfortunately it is too dominant at present, perhaps a relative matter because of neglect of the other domains.

Wildlife is important in its own right, as a reservoir of disease for domestic animals and man and as an essential area of concern for comparative medicine. Of immediate practical importance is the current widespread destruction of wildlife habitat coupled with environmental pollution. Many

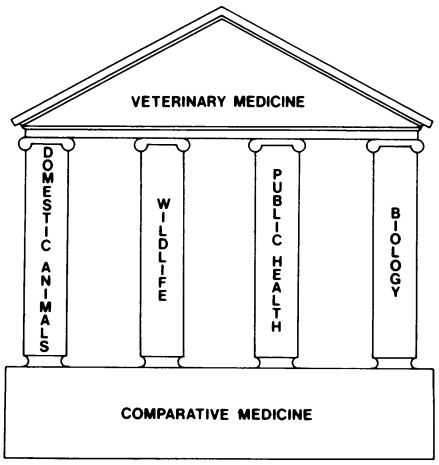

FIGURE 1. Veterinary medicine represented as a Greek temple where the pillars are the principal domains of functional concern to the veterinary profession, all resting on the foundation of comparative medicine.

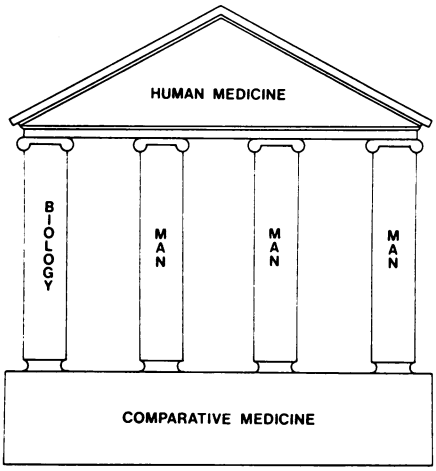

FIGURE 2. Human medicine represented as a Greek temple where the pillars are the principal domains of concern to the human medical profession, largely man, resting on the foundation of comparative medicine.

species of wildlife are at risk and this has become a problem of absolutely vital concern. In the future some wildlife species will be managed as a food source. (In recognition of this, the Western College of Veterinary Medicine at Saskatoon has established research herds of wapiti, bison and musk-ox to help develop the technology required to manage these species under more intensive ranch or farm-like conditions). We need to give more emphasis to wildlife.

In public health the profession is concerned with over 200 diseases transmissable from animals to man (the zoonoses), and is also responsible for assuring the high quality of human food, free from harmful microbes and chemicals.

Let me try to describe diagramatically the relationship of veterinary, comparative and human medicine. In Figure 1 veterinary medicine is illustrated as a Greek temple. The pillars represent the principal domains of functional concern to the veterinary profession, domestic animals, wildlife, public health and biology. All these applications of our science rest on the foundation of comparative medicine. A similar analysis of human medicine is presented in Figure 2. The interests of human medicine are restricted to an over-riding concern with man. Medicine, like veterinary medicine, also has an interest in biology. Comparative medicine serves as the foundation for both human and veterinary medicine. Because of veterinary medicine's responsibility for dealing with disease in the vertebrate branch of the animal kingdom and because knowledge of disease in a wide array of species is necessary to make insightful comparisons, it has a unique role in fostering comparative medicine by the study of disease in nature. The veterinary profession and its institutions have not given sufficient priority to domains such as wildlife, laboratory animals and biology which are necessary elements in building a strong foundation in comparative medicine.

IS THE CONCEPT OF COMPARATIVE MEDICINE A FAILURE?

There is reason to ask "is the concept of comparative medicine a failure"? Consider the following:

1) Notwithstanding the widespread acceptance of experimental medicine, there seem to be few programs, institutions, courses, journals, etc. whose objectives are to exploit that branch of comparative medicine which broadly studies disease in vertebrates in nature for the purpose of defining disease phenomena.
2) In Canada comparative medicine is not a research category in the programs of either the Medical Research Council or the Natural Sciences and Engineering Research Council.
3) It is not possible to distinguish in the Canadian Journal of Comparative Medicine either policy or content which sets it apart from other standard veterinary research journals.
4) A comprehensive review of comparative medicine published a few years ago has not been cited once in journal literature according to a computer search I conducted.
5) The faculty of Comparative Medicine and Veterinary Science of McGill University, which was one of the most academically distinguished in the world, perished in 1903 after 13 years of operation subsequent to 23 years as the Montreal Veterinary College.

Can the term comparative medicine define function or is the term so diffuse as to lose utility in specifying a field of science or a philosophy that is recognized and serves to direct activity within the medical establishments? Despite the observations noted above there are compelling reasons to believe that comparative medicine can provide useful functional objectives worth striving to achieve. Analysis from both first principles and the historical record support this contention.

THE VALUE OF COMPARATIVE MEDICINE

General Principles

There are several powerful arguments from general principles that support the importance of comparative medicine to foster progress in understanding disease. Imagine an intelligent being from another world unlike any creature living on earth who has a fundamental desire to understand disease phenomena of animals on this planet. How would this being go about achieving this goal? The most effective approach to the problem would seem to be to observe disease processes in a large variety of species and then focus on those in which a given process had its most florid and uncomplicated expression. From there, general principles of disease could be established. These principles would be verified by comparative studies. It seems reasonable to posit that an alien intelligence would view the present earthling's

efforts at understanding disease as too centered on man and a few domestic species given the great diversity of species that are available for study.

To what extent has medical science, including veterinary medicine, embraced this wider or more comparative approach to the study of disease? Not very well, it has been overwhelmingly centered on man, probably to his detriment and furthermore veterinary medicine is pervaded by the culture of human medicine with its narrow focus on one species and on the individual. Veterinary medicine's wider role as a biological science is not being recognized.

Shared Genes Beget Shared Diseases

Darwin fathered comparative medicine with his discovery that all animals, including man, are related. Genes are shared throughout the animal kingdom and inevitably shared genes must result in shared diseases or at least comparable disease phenomena. It seems likely that every living creature shares nearly all of its genetic information with other species. For example, evidence suggests that despite some obvious difference in morphology (or at least in most cases) the genetic difference between man and the great apes is less than one percent (11) (Figure 3). There are at least 1.5 million species of animals on this earth of which about 40,000 are vertebrates, including 12-15,000 mammals. The benefits of studying a wider range of species than has heretofore been practiced would seem to have great potential for advancing understanding of basic disease phenomena. Comparative medicine at its broadest, includes the study of disease in the remainder of the animal kingdom and the plant kingdom. Obviously veterinary medicine does not have prime responsibility in these areas. It should however, be alert to the disease phenomena occurring here that can be instructive for understanding disease in vertebrates.

Dose Response

The benefits of comparative study of disease should follow a dose response curve wherein medical progress increases in proportion to the number of species studied (Figure 4). Medical studies to the present have largely involved man, domestic animals, laboratory animals and selected wild and zoo species and represent a very small percentage of the vertebrate animal kingdom. It seems reasonable to suggest that the number of species studied has not remotely approached the potential of comparative medicine for achieving medical progress. Man's preoccupation with man is a severely limiting cultural impediment and hampers the fuller exploitation of comparative medicine and research.

In passing it should be noted that the study of disease is useful in developing an understanding of normal biological processes (physiology). When an organ, tissue or cell malfunctions

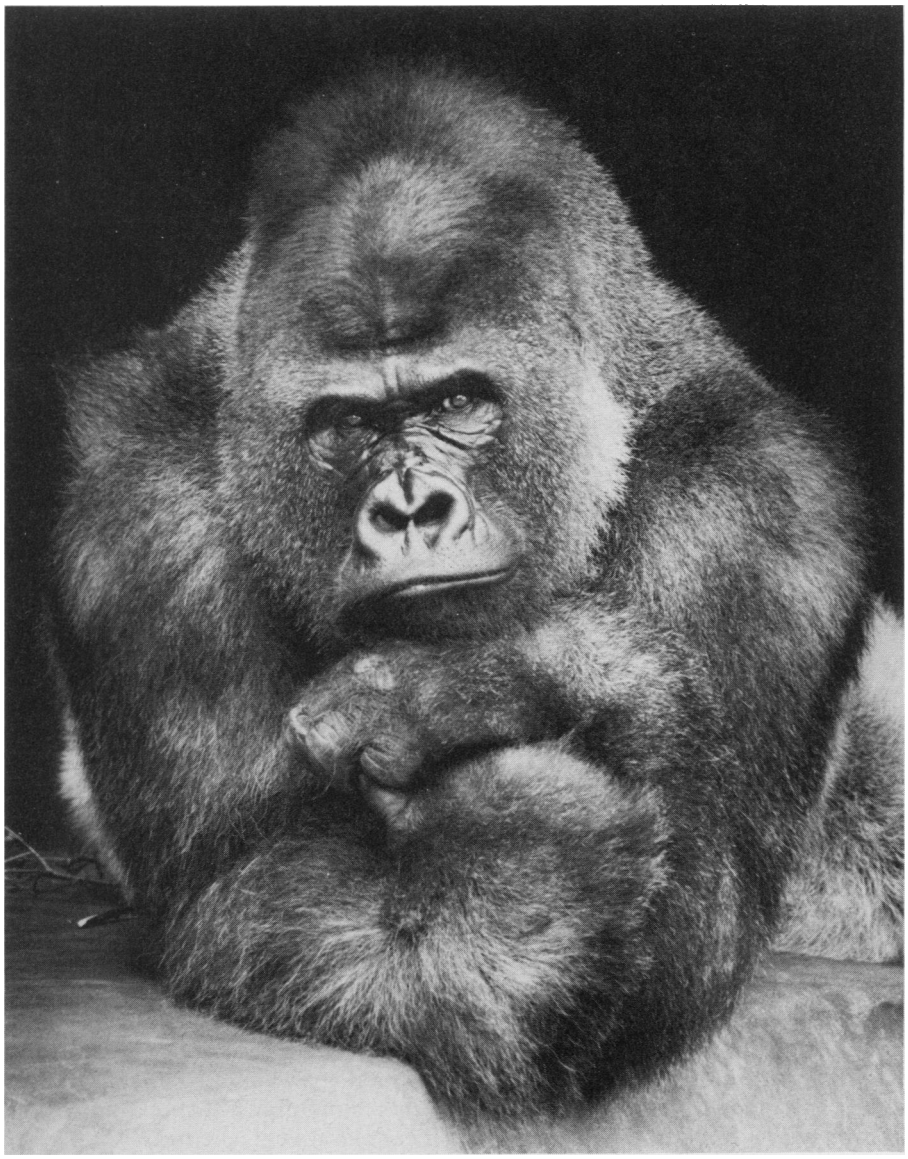

FIGURE 3. A lowland gorilla whose genetic constitution is less than one percent different than man; shared genes beget shared diseases. (Courtesy of The Zoological Society of San Diego — copyright).

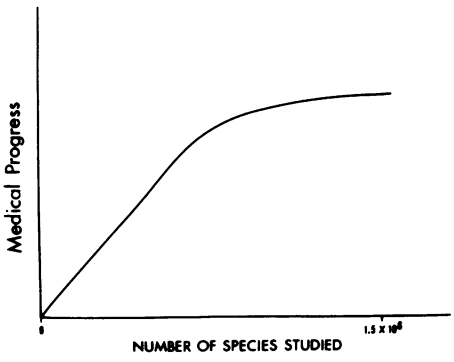

FIGURE 4. A hypothetical dose response curve showing increasing medical progress in understanding disease phenomena in proportion to the number of animal species studied.

by virtue of disease it can be a powerful tool to shed light on normal biological phenomena. For example, the nature of the immune system was partially unravelled by the study of human patients with inherited defects affecting the different genes governing the various components of the immune response. In the absence of experimentation, the comparative medicine of naturally occurring disease is the principal tool available to increase our understanding of disease phenomena.

HISTORY

The history of medicine has proven the value of the comparative approach. For example, the vast majority of phenomena of importance to the understanding of infectious disease (germ theory) was discovered in species other than man either by observation or by experimentation. Viral carcinogenesis, conditioned reflexes and circulation of the blood, are but a few additional phenomena which were discovered or elucidated in animals. The historical record is in fact so voluminous and supportive that the value of comparative medicine cannot be disputed. Nonetheless the phenomenal growth of experimental medicine has obscured the value of the study of naturally occurring disease to our contemporary medical establishment.

In passing consider the many contributions of the lowly chicken to medical progress; viral carcinogenesis, cancer immunity and vaccination, humeral immunity, virology, vaccine production, nutrition and vascular disease are all fields which have benefitted greatly from observations in this species. Reciprocally, comparative medicine has been instrumental in developing an understanding of the disease of chickens called deep pectoral myopathy. It is analogous to "march gangrene" of man in which there is strangulation of exercised muscle in a tight myofascial compartment. The same explanation holds in the chicken (12).

Historically, Canada can lay some claim to helping establish the importance of the comparative approach to medical science. Canadian tradition in comparative medicine was started by the collaboration of Duncan McEachran, a graduate of the Dick School of Veterinary Medicine, Edinburgh and founder of the Montreal Veterinary College in 1866, and William Osler, one of the world's great physicians (13). McEachran came to McGill in 1866 after falling out with Andrew Smith of the Ontario Veterinary College over matters dealing with education at Smith's new school in Toronto. He became associated with Osler shortly after the latter's arrival at McGill in 1870 as a medical student. McEachran proposed the young student as a member of a microscope club because of Osler's great interest in natural history and parasitology which continued during his years at McGill. Osler joined the medical faculty of McGill and that of the Montreal Veterinary College after graduation and a period of study overseas (14). From that time until his departure some ten years later he worked with McEachran. Together they undertook the first experimental work on animal disease in Canada including work on parasites, swamp fever, food hygiene and tuberculosis.

McEachran has written:

> "In our views of what medical education should be, we fully agreed that medical science was a general science divisible into branches, of which the first was what embraced its application to the human family and the second, to domestic animals in particular, and *would rightly include all vertebrates*,[1] reduced however to human medicine and comparative medicine".

The legacy of Osler's recognition of the importance of comparative medicine are several. It was partly his suggestion that the private Montreal Veterinary College on becoming a faculty of McGill, was named the Faculty of Comparative Medicine. Osler's sojourn at Johns Hopkins University School of Medicine in Baltimore may also have been responsible for this institution having one of the first administrative units identified as "comparative". This is the Division of Comparative Pathology and today includes several veterinarians as staff members.

During the first half of this century there was a great decline in veterinary medicine. Concomitantly, comparative medical research in veterinary institutions became dormant (with notable exceptions) and did not live up to its earlier promise. Promising natural scientists with biological orientation towards disease turned to human medicine as a career rather than veterinary medicine, seemingly because veterinary medicine offered so little scope beyond applied work in domestic animals. For the first 25 years of this century the fate of the veterinary profession was apparently linked to the horse. The folly of this narrow interest and the professions' shallow scientific base became apparent with the demise of this animal as a source of energy for transportation and motive power.

The history of comparative medicine at veterinary institutions in North America, notwithstanding the great success of a few individuals, in most cases is one of lost opportunity. These institutions did not or could not grasp the tremendous potential of veterinary science to build a strong foundation in comparative medicine which could serve both applied veterinary and human medicine and biology.

In Canada, despite the early leadership of McEachran and Osler, veterinary education became divorced from the university and operated as a branch of government. Comparative medicine was all but snuffed out at these institutions. The isolation of veterinary education from the universities ended only recently with the incorporation of the Ontario Veterinary College into the University of Guelph in 1965, L'École de Médicine Vétérinaire, into the University of Montreal in 1968 and the establishment of the Western College of Veterinary Medicine at the University of Saskatchewan in 1964. Our society is still paying the price for these 60 years of lost opportunity to better understand disease phenomena in animals including man.

Thus until 80 years ago the potential of comparative medicine to advance medical science would seem to have been exploited to its full potential given the state of knowledge and the culture of the times. Biology, veteri-

[1] My emphasis.

nary medicine and human medicine were closely interwoven and the comparative medicine of natural disease was a major contributor to medical progress. By the turn of the century the comparative value of the accumulated experience with naturally occurring diseased animals was used up. Meanwhile, medicine was moving more rapidly to the experimental branch of comparative medicine by using laboratory animals to generate new progress. Veterinary institutions did not participate in a substantial way in this new direction and furthermore did not broaden their base of interest beyond a very few domestic species. Attempts to rectify this situation did not begin in earnest until after World War II. While progress has been made in experimental medicine in veterinary institutions, I believe the relative neglect of natural disease means that veterinary medicine still has a long way to go to realize its full potential to contribute to comparative medicine and progress in medicine and biology. Figure 5 illustrates graphically my conjecture about the relative historical importance of experimental medicine and the study of natural disease to medical progress.

Three Canadian veterinarians who helped keep comparative medicine alive during the first half of this century were Charles A. Mitchell, Thomas W. M. Cameron and Francis W. Schofield.

Charles Mitchell, a prominent figure in the Animal Diseases Research Institute of the Canada Department of Agriculture was a champion of comparative medicine throughout his life (Figure 6). He played a major role in helping to found the Canadian Journal of Comparative Medicine. In its pages Mitchell recorded the history of comparative medicine in Canada.

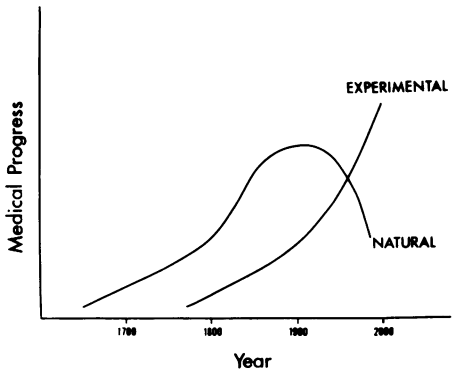

FIGURE 5. A graphic representation of the relative contributions of the study of experimental and of natural disease to medical progress.

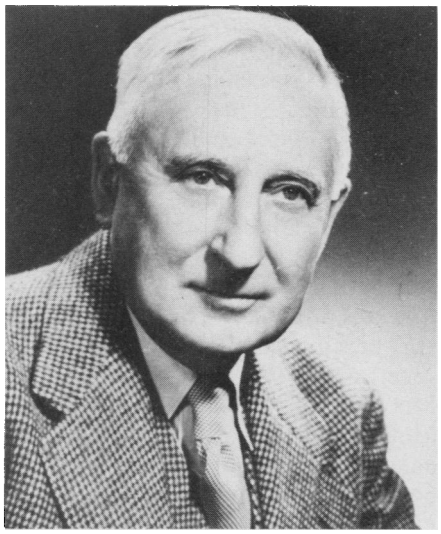

FIGURE 6. Charles A. Mitchell (Courtesy of Agriculture Canada).

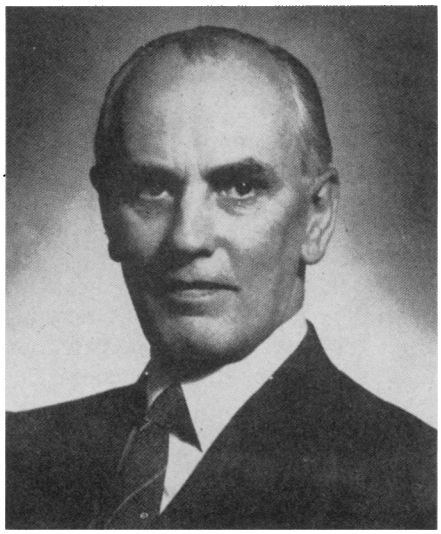

FIGURE 7. Thomas W.M. Cameron. A portrait taken in 1950 when Cameron was President of the American Society of Parasitologists (Courtesy of the American Journal of Parasitology).

The Macdonald College Institute of Parasitology (McGill) seems to have been a bright light for comparative medicine in Canada from 1932 until the academic renaissance at the Ontario Veterinary College after World War II. This institution is the legacy of the McEachran and Osler era at McGill. Its establishment was first advocated by Osler in 1907 (14). T.W.M. Cameron, who died in 1980, became the first director of the Institute (Figure 7). As noted earlier he realized that the study of wildlife disease was essential to comparative medicine and he worked in this domain as well as advocating the veterinary profession to do likewise. He also helped found the Canadian Journal of Comparative Medicine. Cameron had a distinguished career, publishing five books on parisitology and over 200 scientific articles and many of his students played important roles in our profession (15). His academic prowess was widely recognized, *to wit*, he served as president of the Royal Society of Canada. No other Canadian veterinarian has been so honoured.

Another inextinguishable flame that burned in this period was Francis Schofield. Dr. Schofield made several remarkable contributions to comparative medicine at a time when he was sequestered outside the main stream of biology and medicine. This makes his work all the more remarkable. Selected disease processes which were of interest to Dr. Schofield will be discussed now as part of a review of examples of the power of comparative medicine to elucidate disease phenomena.

EXAMPLES OF COMPARATIVE MEDICINE

Mycotoxicosis

Schofield's description of moldy sweet clover poisoning in cattle in 1922-24 (16) based on observation of natural disease and on incisive laboratory studies, proved the existence of the phenomena of mycotoxicosis. While the subsequent isolation, synthesis and medical use of dicoumerol was an important medical development, the demonstration of the phenomenon of mycotoxicosis *per se* is a major medical landmark.

By the comparative approach one can infer that Schofield's discovery predicted the occurrence of a host of other mycotoxic diseases such as hepatitis in dogs, neoplasia in fish, estrogenism in pigs, etc. which were subsequently described in a variety of animal species. It is useful to ask: What would have been the consequences of Schofield's work had a cadre of biological scientists imbued with a comparative philosophy and training

existed in association with Schofield at the time of his discovery? Surely progress in understanding mycotoxic disease and the importance of microbial production of agents with pharmaceutical potential would have been much enhanced. With the wisdom of hindsight one can conjecture that the comparative interpretation of Schofield's work protended not only discovery of other mycotoxic diseases but possibly even the antibiotics. Further, one can conjecture that appropriate research today would discover circumstances under which microbes would produce any one of a wide range of materials with a desired biological activity. Indeed, this is happening.

Enterotoxemia

I have chosen to touch on this phenomenon because of its interest to Schofield. I believe it illustrates rather well the power of comparative medicine and the utility of recognizing specific phenomena that can be extrapolated to several species.

Enterotoxemia denotes a process wherein a harmful bacterial metabolite produced by bacteria resident in the gastrointestinal tract is absorbed and causes disease by effects on other organs or tissues. Overeating disease in sheep is the classic model of the enterotoxemia phenomenon. Bullen (17) showed that *Clostridium perfringens Type D* grew in the intestinal tract under favourable conditions and elaborated a toxic protein designated epsilon toxin. This material increased intestinal permeability, was absorbed, and led to damage in other tissues, particularly the vascular system.

The term enterotoxemia is not fashionable in human medicine, and is not found in standard medical texts. This reluctance to accept enterotoxemia as an important or useful biological phenomena may in part be due to the view that intestinal absorption is a very selective process which allows only the passage of very small molecules. Hence larger molecules such as protein toxins that might be associated with bacterial pathogens would not be expected to gain access to the circulation. Bullen clearly illustrated in a series of elegant experiments on enterotoxemia in sheep that larger protein molecules can indeed be absorbed from the intestine.

Schofield recognized the phenomenon of enterotoxemia in animals and was the first to advocate that edema disease of pigs be designated as such (18). He went on to discover the association of *Escherichia coli* with edema disease (19). Since then studies have shown that edema disease results when specific pathogenic types of *E. coli* proliferate in the small intestine and produce an active principle or metabolite, which when absorbed leads to vascular damage, hypertension, brain damage and death (20). At the time that Schofield associated *E. coli* with edema disease this organism was regarded as a normal inhabitant of the gastrointestinal tract by most and was viewed as a pathogen only of neonatal calves.

It now seems clear that bacterial organisms can produce a great variety of biologically active metabolites, many of which mimic naturally occurring substances important in homeostasis, such as hormones, etc. This mimicry can lead to interference with function and produce disease. On a comparative basis one can conclude that enteric bacteria or microbes have the potential to elaborate a great array of biologically active compounds and that those which resist digestion and act locally or are absorbed may have effects that vary from innocuous to profound.

The importance of enterotoxemia as a disease phenomenon has recently been dramatically demonstrated in the human by the recognition of infant botulism in 1977 (21). In this form of botulism the toxin is produced by bacteria resident in the intestine rather than being preformed in the food. The possibility that such disease could occur was predictable as a consequence of the description of enterotoxemia in sheep and pigs. Infant botulism had likely been an unrecognized component of the "sudden infant death syndrome." One suspects that greater attention to comparative medicine would have advanced this discovery many years.

Adhesins and Enterotoxins

A recent example of the power of comparative medicine is the enormous progress that has occurred in understanding the pathogenesis of bacterial disease as a consequence of the study of colibacillary diarrhea in animals (22, 23, 24). The Ontario Veterinary College has been one of the leaders in this area from the time of Dr. Schofield to the present. As I noted earlier Dr. Schofield clearly recognized that *E. coli* was a pathogen and strains of this organism have been shown to be the cause of a variety of diarrheal diseases in animals and man. This work depended on the development of the means to identify strains of *E. coli* and to characterize the physiochemical attributes of virulent strains. The epidemiological association of specific *E. coli* strains with specific diarrheal diseases established its causal role. Subsequent progress in understanding pathogenesis resulted from of experiments that answered the questions: (1) how do *E. coli* colonize the intestine and resist the flushing action of peristalsis and (2) how do the *E. coli* bacteria induce diarrhea?

Some *E. coli* associated with diarrhea in pigs were shown to possess a specific surface structure with hair-like features which attached the organism to the epithelial surface of the intestine and thereby facilitated colonization. This structure, called pilus or adhesin, was designated K88 and was first described by the Orskovs and their collaborators in 1964 (25). These investigators also showed that this character could be transferred among bacteria as a plasmid, a transposable genetic element (26). Bacteria possessing the K88 plasmid have an attribute of virulence that allows them to colonize the intestine of susceptible pigs. Also, it was shown that the attachment by K88 to intestinal cells required the presence of a specific receptor on the host cell. Not surprisingly, this receptor is under genetic control and as a consequence one can define genotypes of pigs which are resistant to infection by K88 bearing *E. coli* (27). Thus enteric infection with *E. coli* is predicated on the presence of a precise mechanism requiring a specific attachment device, the pili, and an appropriate receptor on the host. In passing it can be noted by comparison that the interaction of macromolecules in a "lock and key" mode is a fundamental mechanism for achieving biological specifity whether it be infection with a bacteria or virus, hormone action or enzymatic digestion of a nutrient.

The comparative implications of the discovery of the mechanism of how *E. coli* colonizes the intestine of the pig are truly enormous in terms of providing understanding of bacterial infections of mucous membranes. Not surprisingly, it has been found that similar but chemically distinct pili are present in a variety of *E. coli* associated with diarrhea in other species such as the calf, sheep and man and that other bacteria such as the gonococcus organism use pili to attach to epithelial surfaces.

The discovery of the K88 adhesin also suggested a rational strategy to control enteric infection by immunization. If the pili could be blocked by antibodies then presumably infection would be prevented. The efficacy of this approach has been proven both experimentally and in practice. Diarrhea caused by *E. coli* has been controlled in pigs and calves using commercially produced pili based vaccines (28,29). The comparative utility of this experience is demonstrated by emerging strategies to control other bacterial diseases of man and animal by a similar approach.

It has also been possible to answer the question of how pathogenic *E. coli* cause diarrhea (27). Such organisms produce specific hormone-like substances that simulate the intestinal mucosa to secrete fluid. These substances are called enterotoxins and have been designated labile toxin (LT) and stable toxin (ST). The demonstration of these substances was founded on a comparative approach. Observations on the existence of enterotoxins were first made in studies of the cholera organism from man. The discovery of *E. coli* enterotoxins by H. Williams Smith and his coworkers and by Gyles and Barnum at this University were important landmarks in unraveling the pathogenesis of colibacillary diarrhea (30, 31).

In summary, the comparative implications of research on colibacillosis, primarily in the pig, have been profound. The definition of specific virulence attributes of microbes and of susceptibility factors in the host have stimulated heightened interest in and increased our understanding of the pathogenesis of bacterial disease.

CHEMICAL CAUSATION OF DISEASE

One of the most significant medical issues of our time is the great increase in the importance of the chemical causation of disease and toxicology. The exponential growth in the use of a wide variety of man-made chemicals has predicated a great increase in the incidence of chemical disease in all species. Comparative medicine has an important role to play in coping with this problem. Indeed events have shown that the detection of the problem has in many cases depended on observations in species other than man, as shown by the following examples. The danger posed by industrial chemicals in nature was brought to society's attention when DDT was first recognized by its effect on reproduction in falcons (32). The exquisite toxicity of dioxins was illustrated when they were found to cause fatal disease in chickens (chick edema disease) fed tallow contaminated with this compound (33). The environmental PCB problem came to light when it was determined that coho salmon from Lake Michigan fed to mink caused reproductive failure and death (34). The problem of organomercurial poisoning in Japan (Minimata disease) was preceded by clinical disease in cats eating contaminated shellfish but unforunately, this was not recognized until there had been human disease. Therefore, the value of comparative medicine in environmental toxicology has been powerfully demonstrated and the monitoring of disease in nature must be an important part of society's strategy to maintain the health of man and the environment.

The importance of environmental toxicology is another reason that makes it imperative for comparative medicine to become less anthrocentric and more concerned with a wide array of species. Wildlife, especially those at the top of the food chain are at high risk and can serve as sentinels of pollution problems of importance to many species. Veterinary medicine must actively assist in monitoring disease in an appropriate selection of wildlife if it is to discharge its responsibility properly. It appears to me that we are making far too little effort in this area. In response to the increased significance of chemically caused disease society must utilize the broad scope of comparative medicine both through the study of disease in nature and by experiment.

It might be useful to cite the old dictum "the description of things caused must precede the description of the cause of things". So must often the description or identification of chemically induced problems occurring naturally in wildlife or domestic animals precede the experimental study of problems which can then yield to specific scientific analysis.

CONCLUSIONS

1. Comparative medicine is the study of phenomena basic to the diseases of all species and is the foundation of both veterinary and human medicine. To flourish it requires a broad biological approach and outlook. This may require a new medical paradigm which focuses on disease phenomena and not on man in an attempt to define principles of disease.
2. The history of medicine shows that observations in nature as well as in experimental animals have been crucial in defining and understanding disease phenomena. This will continue to be so.
3. The relative neglect of the study of natural disease in vertebrates in comparison to experimental medicine needs to be corrected. Veterinary scientists have a major responsibility to ferret out and to induce generalizations about mechanisms of disease based on wide ranging observation in vertebrate animals.
4. Veterinary medicine has a special relationship to comparative medicine because of its unique potential to contribute to this field through the study of both natural disease in vertebrates and experimental medicine. Therefore we must act to develop and strengthen our programs in comparative medicine. It will pay handsome dividends in medical progress.
5. I believe that more emphasis on disease phenomena and on general principles, i.e. comparative medicine, would make the teaching of veterinary medicine a great deal simpler and would also help in coping with the knowledge explosion.

We need to be students of disease phenomena as well as diagnosticians. Such an approach would lay the foundation for more applied work dealing with specific diseases of economically or socially important species.

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