CHRONIC DISEASES IN ANIMALS

Their Significance for Public Health

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service, Bureau of State Services
Communicable Disease Center, Training Branch
Atlanta, Georgia

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A collection of papers presented
on August 21, 1957
at Pennsylvania's Sixth Annual Health Conference,
University Park, Pennsylvania

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FOREWORD

Chronic diseases will continue to receive priority attention in health programs of the future. Logically, one would expect that progress in this sphere will be the result of observations in several specialized fields. Among them, comparative medicine, embracing subspecialities of comparative anatomy, physiology, pathology, and others, will take on added importance.

The matter of relationships between infectious and noninfectious processes and the chronic diseases is of vital interest to the health professions. Such thinking led to the organization of a Seminar, Chronic Diseases in Animals, and Their Significance for Public Health, as an integral part of Pennsylvania's Sixth Annual Health Conference, August 18-22, 1957. The session which was held on August 21st received the full support of Dr. Berwyn K. Mattison, then Secretary of Health. It was planned by Dr. Ernest J. Witte, Chief of the Veterinary Public Health Section, Pennsylvania Department of Health, with the assistance of the Committee on Veterinary Public Health of the Pennsylvania State Veterinary Medical Association, and moderated by Dr. James Lieberman, Assistant to the Chief, Training Branch, Communicable Disease Center, United States Public Health Service.

The panel consisted of three discussions: Virus Induced Tumors by R. F. Gentry, D.V.M., Associate Professor of Veterinary Science at Pennsylvania State University, University Park, Pennsylvania; Experimental Production of Rheumatoid Arthritis in Swine by G. M. Neher, Ph.D., Associate Professor of Veterinary Science at Purdue University, Lafayette, Indiana; and Chronic Heart Disease in Dogs by D. K. Detweiler, V.M.D., Associate Professor of Pharmacology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pennsylvania. Each of these experts explored his area of concentration in the light of possible human health implications. Each emphasized, or implied indirectly, that opportunities for service in this field by the veterinarian and allied scientists are without limit.

With the permission of the sponsors of the Pennsylvania Health Conference, and with the consent of the authors, the Communicable Disease Center is privileged to assemble these papers into a single publication. Perhaps the reader will agree that in the future observations in comparative medicine may contribute markedly to progress in the prevention and treatment of chronic illness in man.

CONTENTS

Virus Induced Tumors 1
Robert F. Gentry

Experimental Production of Rheumatoid Arthritis in Swine 9
George M. Neher

Chronic Heart Disease in Dogs 27
David K. Detweiler

VIRUS INDUCED TUMORS

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Abstract

The theory of virus as the cause of certain tumors has been growing since the first reproduction of a sarcoma by Dr. Peyton Rous in 1911. For a virus to produce a tumor it must live in the host cell, have low virulence, and possess the power to stimulate its host cells to continuous aggressive proliferation. Many viruses have the first two of these requirements but lack the third.

Cytological changes in virus infections include degeneration, cytolysis, and the formation of inclusion bodies. Few animals with tumors show inclusion bodies. Dense areas in some tumor cells may be congregations of virus particles. More complete studies of the normal cell structure and particles seen with the election microscope may allow the identification of particles uncommon to the cells.

How viruses cause cellular proliferation is not known but several theories have been formulated.

A primary characteristic of virus induced tumors is the extended latent period or incubation time. Detection of latest infection is difficult and will depend upon improved techniques with electron microscopy and serology.

Some of the tumors known to be associated with viruses include human skin tumors, mouse mammary carcinoma, tumors of fish and plants, mouse leukemia, and avian tumors, especially visceral lymphomatosis.

Avian visceral lymphomatosis has been studied as much or more than the other tumors and serve as the best subject for the discussion of transmission and control.

VIRUS INDUCED TUMORS

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The cause of cancer has been studied from many aspects. Three theories are worthy of mention, namely: (a) irritation, (b) embryonal, and (c) the parasitic or microbic hypotheses. This discussion will be concerned with the last of these in which a specific type of microbe, the virus, will be considered.

In 1911, Dr. Peyton Rous (1) successfully transmitted a sarcoma in chickens by the use of a cell-free filtrate. Although the theory of virus as a cause of tumors had been considered for some time, this was the first demonstration of virus transmission. The work in the last 45 years has given us answers to many of the basic questions but a full understanding of the problem of tumor etiology has not been resolved.

When we use the term "virus" with respect to tumor causation we must clarify our interpretation of a virus. We usually consider a virus to be a submicroscopic particle requiring living cells for its growth and multiplication, and capable of stimulating an immune response. However, we cannot exclude the possibility of cellular components undergoing mutation and acquiring tumor producing characteristics. Such particles would be submicroscopic, filter passing, and capable of stimulating tumor formation under the proper genetic and endocrine environment. The concept of a virus of the conventional type more fully fits the conditions for the tumors which have been most extensively studied. It is wise, however, to be aware of the possible role of cellular material in the absence of what we consider a conventional type virus.

Realizing the possibility that other factors may be involved, let us use the virus theory as a working hypothesis and consider what would be required in order to produce tumors.

Pinkerton (2) states that the properties they must possess would include: (a) be well-adopted to life in the host cells, (b) be of low virulence and incapable of inducing a high degree of cellular immunity in the host, (c) stimulate its host cells to continuous proliferation. Many viruses have the first two of these properties but lack the third.

If a virus is responsible for the development of a tumor, it is naturally in close association with the cells of that tumor. Virus particles may be liberated from a cell, transported to other cells and set up the proliferative changes in other areas of the body. Examination of some tumor tissues by electron microscopy has revealed the presence of discreet particles within the cells. (3) The number and size of such particles vary but are often found in significant numbers. The differentiation of these particles from normal cellular components is difficult and the observation of such particles cannot be considered as conclusive evidence of the presence of a virus until a complete knowledge of the normal cell structure is obtained. A thorough study of cells infected with other viruses may add to the general knowledge of how cells react to a virus and where within the cells these viruses usually locate themselves. Information of this type will be necessary for the accurate differentiation and identification of virus particles in tumor cells. (4)

We have established the fact that virus must live within the cells. What then is required for their growth? With bacteria we are usually concerned with the ionic and organic composition of the culture medium as well as such factors as atmosphere, light, and temperature. The organisms are presumed to contain the organized catalytic equipment necessary for the transformation and utilization of the growth requirements present in the external environment. The conditions are quite different for viruses. Apparently they do not possess all the enzymes necessary for the breakdown of the various materials necessary for the assimilation of matter and the generation of energy. The presence of virus in a cell may therefore result in a need for special types of nucliec acids and proteins which in turn would require special enzymes not common to the cell. These changes could then lead to an alteration in the cell structure and possibly be a connecting link in the development of tumor cells.

How do we determine when tumor virus is present? Various techniques have been employed with varying success and are listed in Table I.

TABLE I

Methods for Detection of
Tumor Virus Infection

1. Electron Microscope

2. Transplantation

3. Serology
   a) identification of antigen
   b) identification of antibody

The detection of virus within the cells of various tissues is difficult. One possible method is the actual observation of the virus particle within the cells by electron microscopy. This technique, however, requires a thorough knowledge of both the normal structure of the cells and the morphology of the virus particles. In only a few tumorous conditions is the use of such a technique possible at the present time. (5)

Another method to tumor virus detection is the transplantation of tumorous tissues to a susceptible host. If a tumor develops at the site of inoculation within a relatively short period of time, it is usually considered due to the influence of the tumor cell itself. However, if after an extended period of time tumors develop in other parts of the animals body, it is then considered to be virus induced. This is comparable to the preparation of cell-free filtrate of the tumor, which upon inoculation causes the formation of tumors but only after an extended incubation period. In some cases this incubation period may be many months. What happens to the virus and where it locates itself during this time is not known, but the long incubation period is one of the most common characteristics of tumor viruses.

Limited success has been obtained using serological techniques (6) but marked advancement in this field must await methods of production of virus in large enough quantities for use as antigen. Serum neutralization can be employed but at present is useful only as a research tool due to the large numbers of animals and long periods of time required for such tests.

The application of the above mentioned techniques for the determination of virus involvement in various tumors cannot be discussed in detail. However, in Table II are listed some of the tumors for which there is evidence of virus etiology. In some cases the virus has been isolated in relatively pure form and used to produce tumors of the same type in susceptible animals of the same species. In other instances, it is merely transmission by cell-free filtrates while with still others the evidence is obtained from electron photomicrographs where particles have been found associated with the tumor formation.

A brief discussion of one of the more common virus induced tumors should provide an example of how far research has progressed in this field. The condition about which we have as much or more information as any of the virus induced tumor is Avian Visceral Lymphomatosis. This single disease causes an estimated annual loss to the poultry industry of over 75 million dollars. (7)

TABLE II

Tumors for Which Some Evidence of Virus Etiology has been Found

Human	- Skin tumors, Warts and Papillomas Carcinoma of breast
Mouse	- Mammary Carcinoma Leukemia
Fish	- Pox, Papillomas, Lymphosarcoma Lymphocystic disease
Plants	- Wound tumor disease
Chickens	- Sarcoma, Leukemia Visceral Lymphomatosis

What do we know about the disease and its cause? It is a malignant tumorous condition in which the visceral organs, and occasionally the muscles and skin, are invaded by lymphocytes. The lymphocytomas progress until one or more of the vital organs has been severely damaged or completely replaced by the lymphocytes and the bird dies. The causative agent is a virus which can be isolated from tumorous tissues by differential centrifugation. (8) Certain strains of the virus have been grown in embryonated chicken eggs but not in sufficient concentrations for use in immunological studies. (9)

If a bird is infected, how does the virus leave the body? Visceral lymphomatosis virus has been found in the secretions of the nose and mouth, in the feces, and in the egg. (10) The relative significance of these sources with relation to the exposure of other birds has not been determined, but undoubtedly all play an important role.

The route of infection is not definitely known, but it is believed that the respiratory tract is the main portal of entry.

The infective material may come from various sources as shown in Figure I. A chick which has been infected through the egg sheds virus which is then picked up by its pen mates. The rate of infection is not 100 per cent and there are indications that relatively large dosages of virus are required for infection to take place. Also, direct bird to bird contact or mechanical transporting of infected material, principally by the caretaker, is necessary for transmission since there is no evidence that the virus is airborne.

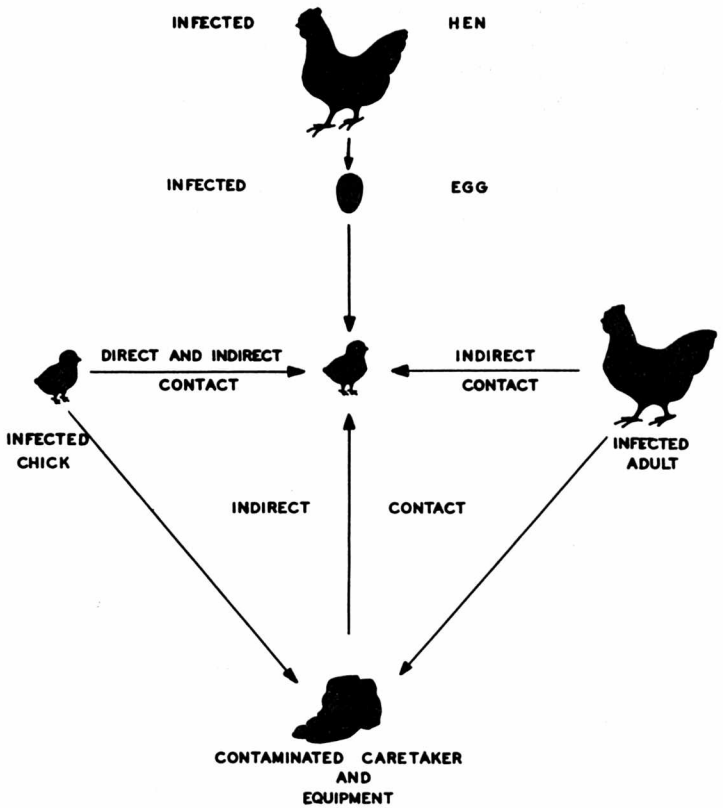

FIGURE I: THE DAM, OTHER CHICKS AND ADULTS, OR THE CARE-TAKER MAY SERVE AS A SOURCE OF VIRUS

Infection does not occur at anytime during the birds life as is found with the respiratory viruses such as Newcastle disease. In order to infect a bird, it must be exposed while very young, usually during the first few weeks of life. (11) The virus then lays dormant for a variable length of time until some unknown factor triggers it into activity and tumor formation starts.

Certain strains of birds have the ability to resist infection due to genetic factors. (12) By the selection of resistant-families the incidence of visceral lymphomatosis can be greatly reduced. The mechanism by which such resistance is possible has not been determined but may hold the secret to the prevention or cure of this and other tumors.

The information concerning visceral lymphomatosis may not prove to be applicable to all other tumors, but it may well serve as a starting point for a better understanding of the problems encountered by workers in the field of tumor research.

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EXPERIMENTAL PRODUCTION OF RHEUMATOID ARTHRITIS IN SWINE

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Abstract

An arthritis comparable in many respects to rheumatoid arthritis in man occurs naturally in swine. It is conceivable that experimentation with swine may facilitate a better understanding of the analogous disease in the human being. The arthritic pig may serve as a valuable test animal on which to evaluate anti-arthritic drugs.

The pathological changes in affected joints are essentially proliferative and non-suppurative with numerous foci of lymphocytes. Severe hyperemia and moderate hypertrophy of the villi and thickening of the synovial lining are characteristic of the acute joint disease. Subsequently, granulomatous proliferations occur with pannus formation, destruction of articular cartilage and subchondral cellular reactions. Intra-articular fibrous adhesions are a common feature.

Roentgenologically a narrowing of the joint spaces, generalized demineralization, osteophyte formation, "punched-out" areas and erosions of the subarticular bony structures are observed as the disease becomes chronic. In advanced cases exostoses occasionally become massive causing an obliteration of joint spaces and a resultant ankylosis. In such cases the pathology may suggest hypertrophic arthritis secondary to rheumatoid arthritis.

Further parallelisms include a lowering of the erythrocyte sedimentation rate with ACTH and amelioration of symptoms with cortisone and ACTH. Pregnancy and experimentally induced icterus likewise appear to have beneficial effects.

Erysipelothrix rhusiopathiae has been clearly incriminated as the cause of swine erysipelas and the arthritis which may or may not result as a sequel to the acute infection. Using 191 swine we reproduced the disease by seven different exposure procedures. Thirty-five percent died and 40 percent of the survivors developed arthritis. Following vaccination (65 vaccinated, 31 controls) and subsequent challenge, marked

anaphylactic reactions were evident in protected swine. Mortality was markedly reduced but arthritis developed in 90 percent of the vaccinated pigs challenged intravenously. Sensitization may play an important role in the etiology of the disease particularly since affected joints (5 months post-exposure) are usually sterile even though the pathology continues unabated.

In current experiments (21 swine) arthritis with frank bony pathology in some instances was produced in hypersensitized swine by intra-articular injections of heat killed cultures. In most cases, the joint pathology was not confined to injected joints. At necropsy all affective joints were negative for Ery. rhusiopathiae. The possiblity that a sub-clinical erysipelas infection had caused the arthritis was off-set by the fact that the untreated swine housed in contact with the hypersensitized pigs proved to be highly susceptible to erysipelas when subsequently challenged. These findings suggest that sensitization plays an important role in the etiology of rheumatoid arthritis in swine.

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Introduction

The architecture of the joint has long been recognized as one of nature's masterpieces of design, and the free and painless movement of its lubricated articulations is included in the essential signs of good health. It is perhaps correct to say that all animals are subject to arthritis, whether it be slight self-limiting inflammation stemming from a general systemic disturbance which subsides with the animal's return to health or joint disease which may progress to frank bony alterations and the eventual loss of function.

Many of the arthritides of domesticated livestock are somewhat analogous to the various differentiated arthritides of the rheumatic disease group. Probably the best known of these, and certainly the one of greatest economic importance, is the rheumatoid-like arthritis of swine which bears many parallelisms to the comparable disease of man. In advanced cases where swine are permitted to remain essentially immobile, extensive osteophyte formations and lipping may occur so that the pathology would appear to suggest osteoarthritis secondary to rheumatoid arthritis. By virtue of its importance to the swine industry and the resemblance it bears to arthritis in man, this disease will receive the bulk of consideration in the following discussion.

In a consideration of degenerative joint disease in farm animals it should be pointed out that geriatric problems in livestock are infrequent, since animals produced for meat purposes (sheep, hogs and beef cattle) are usually slaughtered at a young age, and animals raised for breeding purposes generally are slaughtered when breeding efficiency wanes. Dairy cows are usually kept only as long as they prove to be profitable producers of milk and butterfat. With the widespread practice of artificial insemination, particularly in the dairy industry, and the establishments of bull studs where animals are kept for the commercial production of semen, a degenerative arthritis in aged bulls appears to be an important problem.

The incidence of osteoarthritis appears to be greatest in the Holstein-Friesian breed and may exceed 20 percent in bulls over nine years old according to Bartlett (1). The onset of the disease in some cases may be insidious; however, in many instances it appears to be associated with trauma to a specific joint and later has a tendency to become polyarthritic in nature. Remissions and exacerbations are characteristic of the early disease. In some instances, hydrocortisone therapy (intra-articular) is beneficial. The housing of affected bulls on thick rubber mats in heated pens also appears to induce a temporary remission of symptoms. The pathology may advance to severe destruction of articular cartilage and massive erosions of the subchondral bone. I have observed the loss of an entire distal condyle of a femur in one advanced case. Marginal lipping and massive osteophyte formations are typical features as well as greatly thickened joint capsules and granulomatous proliferation of the synovial villi.

As one would expect, farm animals as well as human beings are subject to acute pyogenic arthritides. The incidence and economic importance of pyogenic arthritis in animals has decreased with the advent of wide usage of the antibiotic drugs. Occasionally articular and periarticular lesions in livestock are associated with brucellosis and tuberculosis infection.

Rheumatoid Arthritis in Swine (A Discussion of the Disease)

A joint disease comparable in many respects to rheumatoid arthritis in man occurs naturally in swine, usually as a manifestation of swine erysipelas, which is an infectious disease caused by the bacterium Erysipelothrix rhusiopathiae. In this disease, great variations occur in the morbidity and the mortality as well as clinical and pathological manifestations. The mortality in a diseased drove of swine on occasion may exceed 30 percent and arthritis may develop in as many as 40 percent of the survivors. Whereas, in other droves arthritis may occur in a few animals to as many as 40 percent apparently without any of the overt signs of acute swine erysipelas, i. e., a marked febrile response and skin lesions.

The clinical manifestations of arthritis are swollen painful joints (figure 1), myalgia and varying degrees of stiffness and lameness. Initially the joint involvement has a tendency to shift to different peripheral joints and within four to six weeks localize in specific joints. The symptoms of arthritis are characterized by remissions and exacerbations, and spontaneous recoveries occasionally occur prior to the development of chronic arthritis. In advanced cases the animals frequently exhibit signs of disuse, atrophy, and inanition (figure 2).

The pathologic changes in the joints are essentially proliferative and non-suppurative with numerous foci of lymphocytes and plasma cells in the synovial villi and adjacent periarticular tissue. Proliferation of the synovial lining cells, hyperemia, and moderate hypertrophy of synovial villi are characteristic of the acute joint disease (figure 3). Subsequently, granulomatous proliferations of the synovial capsule and villi occur with pannus formation, destruction of articulating cartilage (figure 4) and subchondral cellular reactions. Intra-articular fibrous adhesions are a common feature (2, 3, 4, 5) in more advanced cases (figure 5).

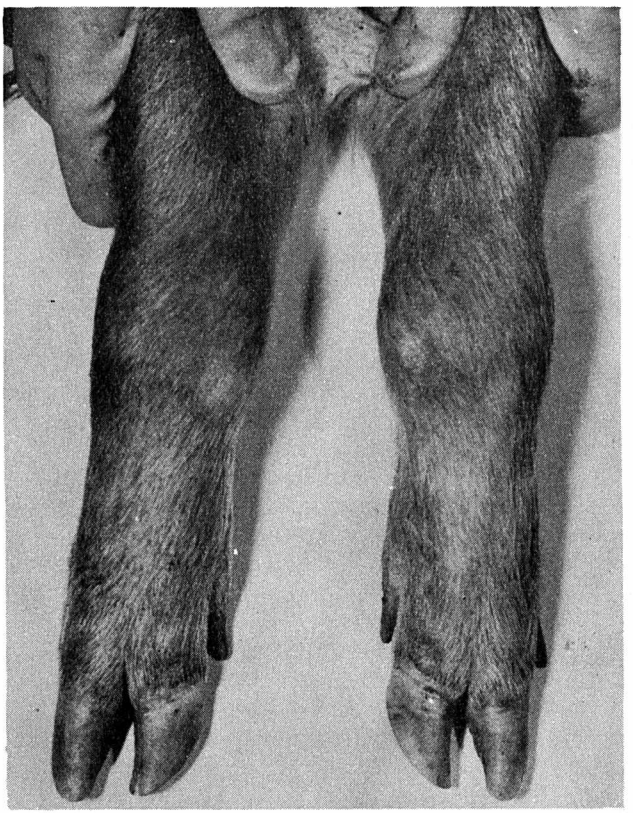

Figure 1. A pair of front legs that were removed from a shoat that was exposed intravenously to Ery. rhusiopathiae three months prior to necropsy. Note the marked swellings in the carpal joints.

Roentgenologically, a widening of the intra-articular space may occasionally be detected during the acute inflammatory phase of the disease. A narrowing of the joint spaces, generalized demineralization of the bone and osteophyte formations on the joint margins are observed as the arthritis becomes chronic, i.e., from the third to the sixth month (figure 6). Cystic-like rarefied areas (often referred to as "punched-out areas") and erosions of the subarticular bony structures are also characteristic.

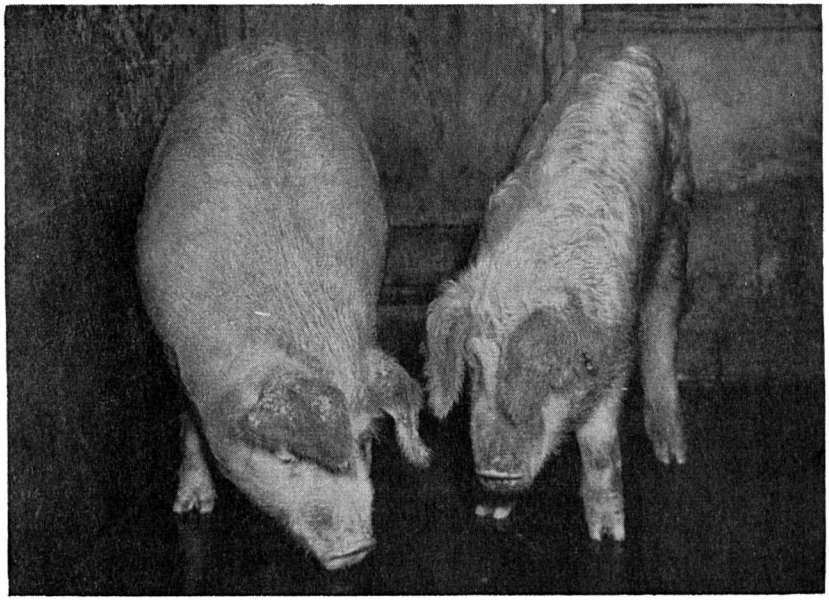

Figure 2. The seven-month-old shoat on the right had been affected for three months with experimentally produced chronic erysipelas with polyarthritis. It weighed 152 lbs.; its unexposed litter mate, 268 lbs.

In advanced cases (one year or more) exostoses occasionally become massive causing obliteration of the joint spaces and resultant bony ankylosis. In some advanced cases the extensive osteophyte formations at the margin of certain joints and apparent lipping would appear suggestive of hypertrophic arthritis secondary to the primary rheumatoid arthritis if comparison were to be drawn with the arthritides of man. It is possible, though speculative, that the osteoarthritis-like pathology may be related to the fact that arthritic swine will not move their painful joints, and thus ankylosis is permitted to develop rapidly (Neher, et al. 3).

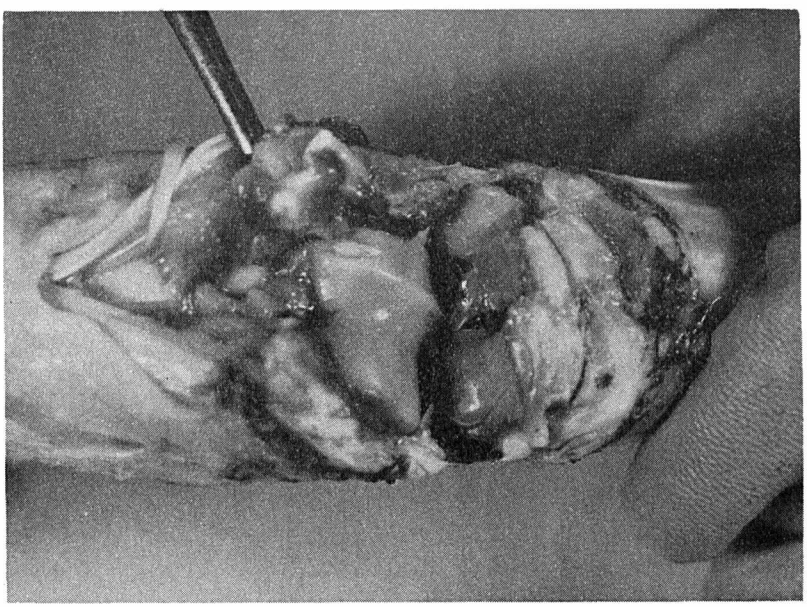

Figure 3. Opened arthritic tarsal joint of a pig two and one-half months after exposure to Ery. rhusiopathiae. Note the thickened joint capsule and the inflamed and hypertrophied synovial tissue.

In addition to the pathologic similarities, further parallelisms to the rheumatoid arthritis in man should include the lowering of the erythrocyte sedimentation rates of arthritic swine with ACTH therapy, and the amelioration of the symptoms of arthritis in swine with cortisone and ACTH treatment (4, 5). Also, pregnancy and experimentally induced icterus, by ligation of the common bile ducts, likewise appear to have a beneficial effect on the symptoms of rheumatoid arthritis in the hog.

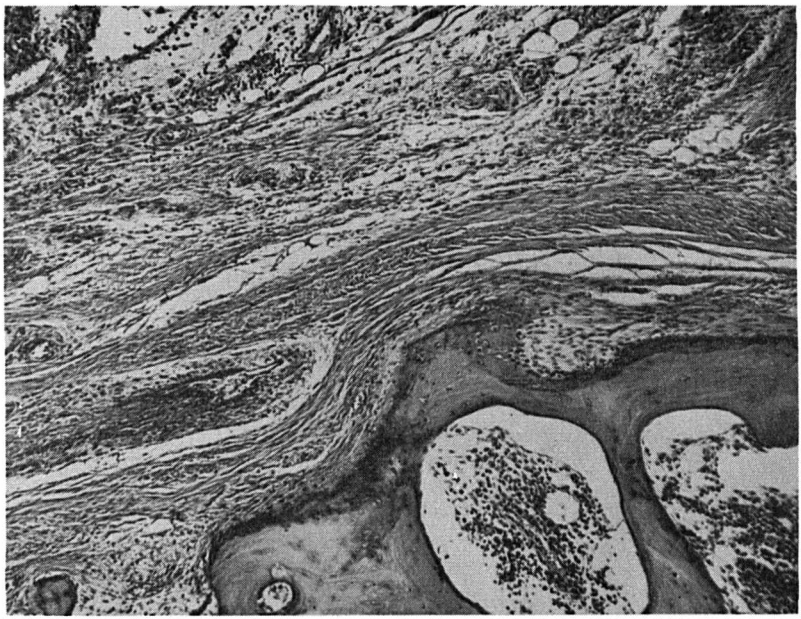

Figure 4. Extensive pannus formation originating from the synovial membrane. Destruction of the articular cartilage is almost complete and fibrous ankylosis had taken place in this advanced case. (14 months).

It would appear that the chief difference between the disease in swine and the corresponding disease in man is that the etiology of rheumatoid-like arthritis in the pig has been established (2, 3, 6, 7, 8, 9). Wernery (10) appears to have been the first investigator (1937) to describe gross and histopathologic changes in the joints of arthritic swine from which Ery. rhusiopathiae could be isolated. Collins and Goldie (1940, 7) described gross and microscopic pathology of experimentally induced erysipelatous arthritis and concluded it to be identical with the naturally occurring disease.

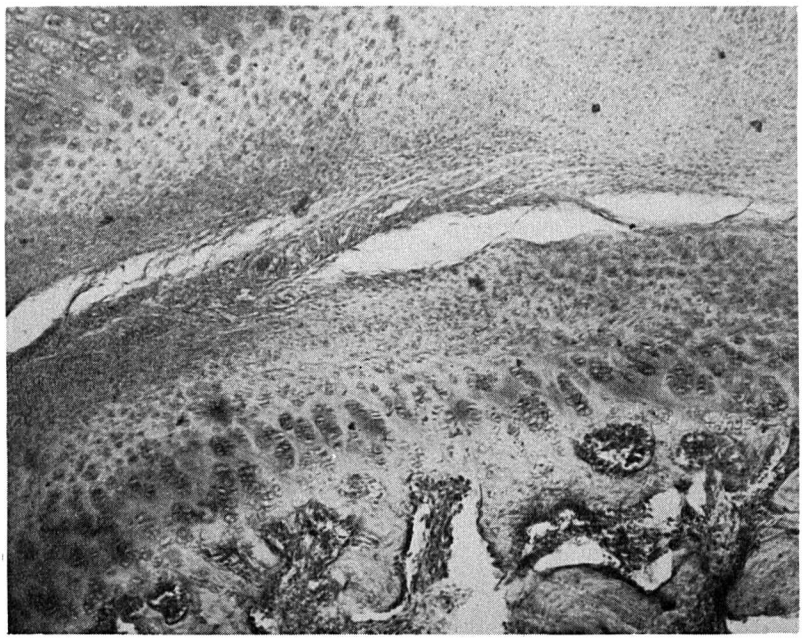

Figure 5. Fibrous ankylosis of a joint in advanced chronic arthritis.

Experimental

In general, attempts to reproduce swine erysipelas have met with limited success. Numerous investigators, Ward (6), Collins and Goldie (7), Hughes (9), and Usdin, et al. (8), have found it necessary to employ repeated injections of the organism. In most instances, arthritis was produced by these workers without apparent signs of acute swine erysipelas, i. e., febrile reactions and skin lesions.

In the initial experiments of Sikes, Neher, and Doyle (2) 21 swine were exposed to tryptose agar cultures of Ery. rhusiopathiae that had been isolated from the joint of a hog with chronic arthritis. Injections were made subcutaneously, intramuscularly, and intravenously into five hogs in each group, and six swine were placed in contact with them. With the exception of moderate

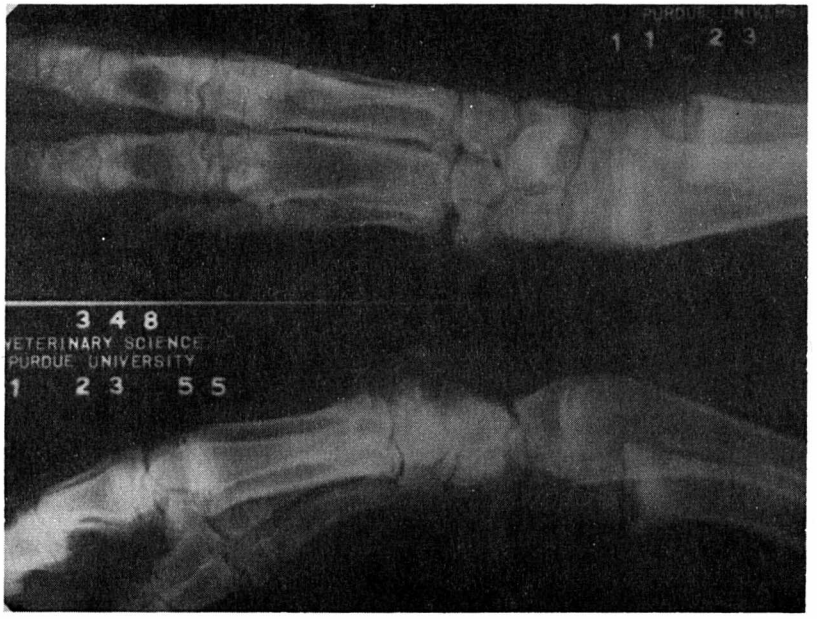

Figure 6. Roentgenogram of the carpus of a hog (anterior-posterior view, top, medial view bottom) showing bony pathology characteristic of the disease in the sixth month. A generalized demineralization of the bone, narrowing of the joint spaces, osteophyte formation and "punched-out" areas are evident.

febrile responses which were apparent for only two days in two of the intravenously exposed pigs, the results were negative. A complete herd history was not available on these swine, and they may have obtained some measure of immunity prior to experimental exposure through a clinical or subclinical exposure.

In subsequent experiments, we were able to reproduce both acute septicemic erysipelas and arthritis when shoats from herds known to be free from the disease were used, by making the exposures with highly pathogenic smooth type colonies of Ery. rhusiopathiae, i. e., isolated from swine that had died of the disease, and by culturing the organism in a semisolid medium which had a reduced oxygen pressure, since the organism is micro-aerophilic. In the following table (figure 7) are summarized the experiments in which acute septicemic erysipelas and arthritis were produced by a single exposure.

METHOD OF EXPOSURE	NUMBER OF SWINE	MORTALITY FROM SWINE ERYSIPELAS	RESISTED EXPOSURE OR RECOVERED FROM ACUTE DISEASE	CHRONIC ARTHRITIS
CONTACT	59	15	35	9
SCARIFICATION	22	7	9	6
INTRADERMAL	13	2	6	5
INTRA-ARTICULAR	35	6	8	21
INTRAVENOUS	34	20	8	6
INTRAMUSCULAR	16	6	5	5
SUBCUTANEOUS	12	4	6	2
	191	60	77	54

Figure 7. A summary of experiments by Sikes, et al. (2) and Neher, et al. (3) in which acute septicemic erysipelas and arthritis were produced in swine by single exposure to Ery. rhusiopathiae.

It is apparent that exposure by pen contact was the least severe form of challenge, since 35 of 59 swine (59%) either resisted the exposure or recovered from the disease. The intravenous exposure was the most severe in that only 8 of 34, or 23%, either resisted exposure or recovered. The intra-articular method of exposure appeared to be the most effective means of producing arthritis, since 21 of 35 (60%) of the swine developed chronic arthritis. It should be pointed out that the arthritis produced in this manner was a systemic disease rather than a local infection, since the overt signs of acute septicemic erysipelas were present and the pathology was by no means confined to the injected joints. In summarizing the results, roughly 32 percent of the swine died following various exposures to virulent cultures of Ery. rhusiopathiae and of the 131 surviving pigs 54, or 41 percent, developed arthritis (2, 3).

Because of the consistency with which we were able to produce acute swine erysipelas and arthritis, the next phase of study was designed to evaluate some commercially available immunizing products. It would seem paradoxical that arthritis continues to rank as one of the primary causes for the condemnation of swine carcasses in federally inspected meatpacking plants in the United States (11) in spite of the widespread use of procedures for the immunization of swine against erysipelas.

In recent studies (12) 65, 150-pound swine were protected against erysipelas with commercially prepared bacterins, and 31 were housed in contact with them and subsequently exposed as unvaccinated controls. Single challenges were made with viable cultures of Ery. rhusiopathiae at various times from six weeks to four months after vaccination.

Marked anaphylactic reactions were evident in the protected pigs at the time of the intravenous challenge; whereas, the reactions were only slight or negative in the unvaccinated animals. The mortality from acute swine erysipelas was reduced from 70 percent in the unprotected pigs to 15 percent in the vaccinated swine.

Although vaccination appeared to have definite merit in preventing the high mortality, the incidence of acute polyarthritis in vaccinated swine approached 90 percent and ultimately over 70 percent developed chronic arthritis.

It appeared that vaccination with bacterin sensitized the swine to the antigens of Ery. rhusiopathiae and the subsequent challenge with viable cultures precipitated joint disease.

If hypersensitivity is involved in the mechanism by which Ery. rhusiopathiae causes joint pathology in the pig, it would

appear that arthritis may result in swine that were sensitized to killed culture as well as those exposed naturally or experimentally to the living organism. This supposition would appear likely since the allergic response in animals of a given species is essentially the same regardless of the antigen to which a particular animal is sensitive (13).

In recent experiments, in which 21, 150-pound swine were used (14), 10 were sensitized by 10 weekly intravenous injections of either heat killed culture, a sterile filtrate of culture, or culture media. Marked anaphylactic reactions were evident in all swine beginning with the fourth weekly injection. However, following the tenth injection no clinical signs of arthritis were evident.

Five sensitized swine were injected intra-articularly weekly for five weeks into the right carpus with 1 cc. of the antigen to which they had been previously sensitized. Four unsensitized swine also received intra-articular injections of sterile antigen (figure 8).

ARTHRITIS FOLLOWING INTRA-ARTICULAR INJECTIONS OF STERILE ANTIGEN

ANIMALS	EXPOSURE	FINDINGS AT NECROPSY	
		SYNOVITIS	PATH. OF BONE
5 (SENSITIZED)	INTRA-ARTIC.	3 MARKED 2 NORMAL	1 MARKED 2 MODERATE
4 (UNSENSITIZED)	INTRA-ARTIC.	2 SLIGHT 2 NORMAL	1 SLIGHT 1 NORMAL
5 (SENSITIZED)	CONTROL	5 NORMAL	EXPOSED TO ERY. RHUSIOPATHIAE
7 (UNSENSITIZED)	CONTROL	7 NORMAL	

Figure 8. A summary of an experiment, Neher, et al. (14), in which arthritis was produced in hypersensitized swine by intra-articular injection of sterile antigen.

Marked lameness was evident in three of the five sensitized pigs and at necropsy between one and three months after the final injection; marked synovitis was present in the joints of these animals. No joint pathology was present in the two animals that failed to show clinical signs of arthritis. Pathology of bone as determined by radiology was marked in one case and moderate in the other two sensitized animals. The pathology was polyarthritic in nature and was not confined to the injected carpal joints. Slight synovitis was evident in two of the four unsensitized pigs that received intra-articular injections and only one of the two showed bone pathology suggestive of arthritis.

The joints of all swine were negative for Ery. rhusiopathiae on bacteriological examination. The five remaining sensitized and seven unsensitized were apparently normal at the time of the intra-articular injections in the previous animals. In order to assure that the arthritis produced was a result of a sensitization to sterile antigen rather than a possible natural exposure, these animals were subsequently challenged to viable cultures of Ery. rhusiopathiae (figure 9).

SENSITIZED AND NORMAL SWINE FOLLOWING I.V. EXPOSURE TO ERYSIPELOTHRIX RHUSIOPATHIAE

ANIMALS	RESPONSE TO CHALLENGE	CONDITION 2 MO. POSTEXPOSURE
7 (UNSENSITIZED)	3 DIED	
	4 FEBRILE, ACUTE POLYARTHRITIS	2 NORMAL 2 ARTHRITIC
5 (SENSITIZED)		
2 KILLED C.	2 ACUTE POLYARTH.	2 ARTHRITIC
1 FILTRATE	1 ACUTE POLYARTH.	1 ARTHRITIC
2 C.MEDIUM	2 DIED	

Figure 9. A summary of an experiment, Neher, et al. (14), in which acute septicemic erysipelas and arthritis were produced in normal and hypersensitized swine by a single intravenous exposure to Ery. rhusiopathiae.

Three of the seven unsensitized shoats died of acute septicemic swine erysipelas. The four surviving animals had marked febrile responses and acute polyarthritis which later assumed a chronic nature in two.

Of the five sensitized swine challenged intravenously, the two sensitized to heat killed culture were protected against the acute form of the disease; however, both developed acute polyarthritis within three days and the joint disease later became chronic.

The animal sensitized to the filtrate likewise developed polyarthritis after challenged with viable organisms. Apparently little, if any, immunity was produced against acute swine erysipelas in the swine sensitized to the sterile culture media since both showed marked febrile responses and died within six days following the challenge.

Discussion

Evidence that sensitivity is involved in this disease is suggested by the fact that numerous investigators have found it necessary to employ repeated injections of viable organism to produce arthritis in the pig.

Recently Hughes (9) was able to produce the disease in all of 16 pigs without apparent signs of acute swine erysipelas by repeated intravenous injections. Only one or two pigs exhibited febrile responses of 104.0 to 104.4 F., and these were exceptional.

Similarly, Usdin, Ferguson, and Birkeland (8) produced arthritis in seven of eight animals without overt signs of acute septicemic erysipelas, i.e., marked febrile responses and skin lesions. Sikes, Neher, and Doyle (15) produced chronic arthritis in all of four swine which resisted an initial intravenous exposure by giving repeated weekly injections of Ery. rhusiopathiae. It is of interest to note that three of the four developed vegetative endocarditis, and death of two of these animals was attributed to these lesions.

Recently Goldie and Collins (16) have been successful in producing arthritis in rabbits that was pathologically similar to the disease in swine by giving repeated intravenous injections of Ery. rhusiopathiae. These authors emphasized that in most instances the exposures were too small (total doses of seven to twenty-eight million organisms) to produce other pathogenic effects. Hypersensitivity induced in rabbits by massive injections of horse serum occasionally results in arthritides in conjunction with cardiovascular lesions (17). Pearson (18, 19) recently reported the

development of arthritis, periarthritis and periostitis in rats that received adjuvants of allergenic emulsions. It was believed that hypersensitivity was probably the basis for these reactions; however, the possibility of pleuropneumonia-like organisms had not been excluded.

According to Usdin et al. (8) arthritis is common in horses being hyperimmunized with living cultures of Ery. rhusiopathiae for the commercial production of anti-swine erysipelas serum.

The production of arthritis in swine through a technique involving repeated exposure to Ery. rhusiopathiae and by vaccination and subsequent challenge where overt signs of acute erysipelas are absent would seem analogous to the arthritis which arises naturally in pigs which have never been visibly ill from the acute disease. Because of the very widespread distribution of the organism in species other than swine (20, 21) and in swine which are apparently healthy (22, 23) it would seem probable under farm conditions that some pigs develop arthritis (without showing the clinical signs of acute swine erysipelas) through sensitization by multiple natural exposures.

Whether joint disease results from an attack of acute swine erysipelas or develops without the symptoms of acute erysipelas it is reasonable to assume, according to Hughes (9) that under natural conditions arthritis arises as a result of a bacteremia. Although Ery. rhusiopathiae reaches the joints via the peripheral circulation we do not know whether the pathology is a direct result of the presence of the organism. Hughes further postulates that if arthritis results from a single exposure the joints may receive repeated doses from some other focus in the body which was set up by the exposure.

The sensitivity theory may explain in part the pathology in affected joints which are apparently sterile. Numerous investigators (2, 3, 7, 8, 9, 24) have reported that only a portion of the typically affected joints of experimental swine are positive for Ery. rhusiopathiae on bacteriological examination. We have been able to isolate the organism from roughly 60 percent of the affected joints examined from experimental cases in which infection was established less than five months previously. However, isolation of Ery. rhusiopathiae from arthritic joints becomes increasingly difficult after this time even though the pathologic process usually continues unabated. In no instance were we able to isolate the organism after 226 days following experimental exposure (2).

In the light of recent work (12) it is apparent that vaccination against swine erysipelas may be beneficial in reducing the mortality in outbreaks of the acute septicemic form of the disease; however, it is conceivable that this procedure may contribute to,

rather than solve, the arthritis problem.

Summary

An economically important disease that bears many similarities to rheumatoid arthritis occurs naturally in swine. We have produced arthritis in roughly one-third of 191 susceptible pigs following exposure to the bacterium Erysipelothrix rhusiopathiae.

Following vaccination with commercially available bacterins and subsequent intravenous challenge marked anaphylactic reactions were evident. The mortality was greatly reduced; however, the incidence of arthritis in surviving vaccinated swine approached 75 percent.

In current work arthritis with frank bone pathology indistinguishable from the naturally occurring disease was produced apparently in the absence of viable Ery. rhusiopathiae by hypersensitizing hogs and subsequently injecting them intra-articularly.

We believe that these experiments clearly indicate that sensitization plays a role in the etiology of rheumatoid-like arthritis in swine.

Various forms of arthritis occur naturally in livestock and some appear to bear a close resemblance to comparable arthritides of man. Since certain fundamental facts may be the same regardless of the species, the field of arthritis is common to workers in human and veterinary medicine. It would appear that research workers in the latter group may enjoy a greater opportunity to follow the experimental approach through the application of strictly controlled scientific principles.

Although rheumatoid arthritis in man and the analogous disease in swine do not have a common etiologic agent, the mechanism by which the joint disease evolves may in certain respects be similar. The arthritic pig may, in any event, prove to be a useful test animal for the screening of new anti-arthritic drugs and hormone preparations.

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CHRONIC HEART DISEASE IN DOGS

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Abstract

Dogs are subject to a variety of cardiovascular disorders and clinical syndromes. In a series of 268 cases the following types of heart disease were found: congenital heart disease, pericarditis, myocarditis, and myocardial degeneration, acute bacterial endocarditis, chronic valvular disease, and such myocardial diseases as infarction, necrosis, fatty degeneration, abscess, and neoplastic metastases. In the middle and south Atlantic and Gulf States, heartworm (Dirofilaria immitis) infestation is common with from 10 to 90 percent of the dog population harboring microfilariae. Chronic valvular disease (chronic valvulitis) and arteriosclerosis are associated with aging and are often found in animals with congestive heart failure syndrome. Arterial hypertension, with and without associated chronic renal disease, has been found in about 0.9 percent of experimental dogs studied. These diseases are of interest from the standpoint of comparative pathology and have a bearing on the usefulness of dogs in cardiovascular research.

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Dogs are subject to a variety of chronic cardiac and vascular disorders. These are of interest to public health scientists because of the importance of the dog as an experimental animal in cardiovascular research and because a comparative study of these diseases may ultimately contribute to the understanding of similar diseases in man.

Incidence and Types of Heart Disease

During a seven year period, 39,378 dogs passed through the Small Animal Clinic of the School of Veterinary Medicine, University of Pennsylvania. Heart disease was diagnosed in 268 of these animals (1). This tabulation excluded all cases of filariasis, "heart-base" tumors, trauma, myocardial degeneration and inflammation in association with specific infectious and metabolic diseases, and cardiac damage associated with severe anemia. Thus, the incidence of primary heart disease in this series was approximately 0.68 per cent.

The various types of heart disease found in this group are listed in Table I. Many of the diagnoses are based on clinical examination only. On post-mortem examination histological sections of cardiac tissue were not made unless gross lesions were seen. For these reasons the frequency of vascular disease involving the cardiac vasculature was not determined.

Owing to a lack of thorough clinical and post-mortem studies on cardiovascular diseases in dogs, the pathological processes now recognized are not well characterized. This is especially true with respect to chronic diseases such as chronic valvulitis and arteriosclerosis. Because of the difficulty in obtaining valid resting blood pressure determinations in the veterinary clinic, arterial hypertension is seldom recognized although dogs are known to develop high blood pressure. A complicating factor which must always be borne in mind when considering dogs as cardiac patients or as subjects for cardiovascular research is the

TABLE I

The Incidence of Various Types of Heart Disease
Among 39,378 Dogs Examined Clinically

(Excluding cases of filariasis, heart base tumors, trauma, myocardial degeneration and inflammation in association with specific infections and metabolic diseases, and cardiac damage associated with severe anemia.)

			Number	Percent
A.	Congenital Heart Diseases		30	11
	Patent ductus arteriosus	13		
	Pure pulmonary stenosis	8		
	Persistent right aortic arch	5		
	Aortic stenosis	2		
	Intraventricular septal defect	1		
	Tricuspid valve hypoplasia	1		
B.	Diseases of the Pericardium		8	3
	Chronic pericarditis with massive sanguinous effusion	6		
	Acute pericarditis	2		
C.	Diseases of the Heart Muscle		53	20
	Myocardial degeneration and inflammation	22		
	Neoplastic metastases			
	Carcinoma	13		
	Sarcoma	8		
	Infarct	4		
	Myocardial necrosis	3		
	Fatty degeneration	2		
	Abscess	1		
D.	Acquired Valvular Lesions and Endocarditis		120	45
	Chronic valvular disease (sometimes with chronic parietal endocardial scars)	103		
	Acute and subacute endocarditis	9		
	Chronic, parietal endocarditis	8		
E.	Uncertain Diagnosis		57	21
			268	100

high incidence of heartworm infestation, particularly among dogs in the southern part of the United States. Finally, the high incidence of renal disease in dogs (exceeding 80 per cent in animals over eight years of age (2)) requires that the possible relationship between kidney and cardiovascular disorders be closely scrutinized.

Despite occasional spurious statements in the literature, lesions identical with rheumatic myocarditis and endocarditis in man have not been demonstrated in the dog. However, the frequent occurrence of chronic valvular lesions in older dogs suggests a disease process which may have a similar pathogenesis.

Myocardial infarction of embolic origin is a rare post-mortem finding and occlusion of a large coronary artery by thrombus formation at the site of an arteriosclerotic lesion is uncommon in the dog. Since the clinical signs of congenital heart disease, chronic valvular disease with valvular deformity, and myocarditis (when the lesions are extensive enough) are often not difficult to detect, it is not surprising that these diagnoses predominate in our clinic. Acute or subacute bacterial endocarditis is rarely incriminated as the cause of death in dogs, and less often diagnosed clinically. Gross myocardial infarction is an unusual finding at necropsy and is less often diagnosed ante mortem. The clinical syndrome of chronic congestive heart failure frequently develops in dogs with serious heart disease and may respond temporarily to appropriate therapy. The most common arrhythmia associated with heart disease in dogs is ventricular extrasystole. Ventricular premature beats are seldom, if ever, unassociated with heart disease in the dog, in contradistinction to man. This finding has been confirmed in other clinics (3). Auricular fibrillation has been found only in severe heart disease in dogs and is a grave prognostic sign (4). In 13 dogs the duration of life after the arrhythmia was first diagnosed in the clinic was from a few hours to 28 weeks.

Chronic Valvular Disease

Valvular lesions, which have been variously described as chronic valvular endocarditis, chronic valvulitis, chronic fibrous endocarditis, and senile involvution of the valves occur in up to five per cent of adult dogs which are examined post mortem (5). Because there is a lack of general agreement regarding the nature of these pathological changes the nondescriptive term chronic valvular disease will be used.

The occurrence of chronic valvular disease has not been shown to be related to sex or breed, but is definitely related to age (6), being most common in dogs over six years old. The mitral valve is by far the most commonly affected. Next in frequency is the tricuspid valve, then the aortic, and last the pulmonic valve.

Grossly (7), the valves are thickened and deformed. The entire valve membrane or only the part of the valve-leaf toward the free margin may be involved. The atrial surface of the auriculoventricular valves and the ventricular surface of the semilunar valves may be smooth, but often are uneven owing to the presence of small tubercles and indurated striations. Sometimes the surface is roughened by delicate vegetations in the region of the line of closure. In advanced cases involving the mitral or tricuspid valves, the leaflets may be reduced to a circle of hard protuberances.

Histologically (7), the prominent change is a connective tissue proliferation in the subendothelium underlying the auricular side of the auriculoventricular valves or the ventricular side of the semilunar valves. This change is most common in the region of the line of closure. The proliferated connective tissue may be rich in cells or poor in cells. Hyaline degeneration may be present. Fine elastic fibers, small blood vessels, plasma cells, leucocytes, and hemosiderin containing cells or free blood pigment are often present. New blood vessels of both normal and pathological appearance (endothelial necrosis, intimal hyperplasia, obliteration) are seen in the intermediate layers of the valve. This vascular and connective tissue proliferation leads to a thickening and hyaline sclerosis of the connective tissue layers.

The subendothelial layer underlying the opposite side of the valve (away from the flow of blood) is only slightly altered. There is an increase in elastic fibers, circumscribed thickening of the insertions of the chorda tendinae and here and there mucoid degeneration, leucocytic infiltration, and groups of pigmented cells.

The proliferation of the connective tissue leads to sclerosis with loss of normal structure and elasticity. Ackerknecht states that owing to early disappearance of blood vessels, incomplete reparative processes, and extensive damage to the arrangement of the elastic elements the predominantly elastic valve membrane is converted to a compact, collagenous sheet.

Chronic valvular disease is usually attributed to repeated bacterial endocarditis followed by healing and scar formation (8). This hypothesis assumes a high frequency of bacterial endocarditis with few deaths and disappearance of bacteria in most of the lesions seen on post-mortem examinations. The recent findings of Shouse and Meier (9) lend support to this argument. These authors report an incidence of acute vegetative endocarditis of 6.6 per cent among 600 dogs and cats examined post mortem. They suggest that chronic valvular disease represents the healed phase of the acute process. Further, it has been shown experimentally that the single

injection of virulent organisms will often induce acute bacterial endocarditis in experimental dogs (10, 11). The concept developed by von Albertini and Grumbach (12, 13) on the basis of experiments with rabbits, serves to explain the bacterial endocarditis hypothesis. They produced both the subacute bacterial endocarditis type and "rheumatic type" lesions with single massive injections of streptococci. In the bacterial endocarditis lesions the local tissue reaction (leucocytes, fibrin) was relatively poor and bacteria remained. In the "rheumatic-type" the cocci were walled-off with masses of fibrinoid and a wide leucocyte zone.

However, these observations fail to provide an entirely satisfactory explanation of the pathogenesis of the valvular changes. Prior to this recent paper (9) on bacterial endocarditis, veterinary pathologists have failed to report a similar high incidence of these lesions. Moreover, deaths resulting from acute or subacute bacterial endocarditis are rare, although the disease is seldom diagnosed nor treated with antibiotics. If repeated bacterial endocarditis is the cause of subsequent chronic valvular disease, it must be assumed that pathologists have formerly often overlooked the lesions of vegetative endocarditis and that, as in the experiments of von Albertini and Grumbach, chronic lesions result when local tissue resistance is high enough to prevent subacute bacterial endocarditis.

That these valvular changes may be induced in part or entirely by an antigen-antibody reaction is, of course, a strong possibility. As pointed out by Böhmig and Klein (14), animal experiments have shown that the subendothelium of the heart valves possess an astonishing readiness to react allergically. Most workers have employed the rabbit to demonstrate this phenomenon (for literature see reference 14, pages 256 to 260).

An interesting relationship between the occurrence of valvular endocarditis in dogs and increased cardiac work load produced by large arteriovenous fistulae made surgically has been reported by Lillehei and coworkers (15). Endocarditis was found in ten out of twenty dogs with large arteriovenous fistula load and in eight out of ten dogs with large distulae existing for more than four weeks. Some of the lesions described by the authors as "rheumatic-like" were similar to chronic valvular disease and at least a portion of these might have been present before the experimental procedure. However, the frequent occurrence of lesions and the presence of friable vegetations containing bacteria support the conclusion that the procedure induced endocarditis. The possibility that valvular lesions in dogs with chronic congestive heart failure may be secondary to the increased cardiovascular stress rather than the cause of it has been suggested by Andrē (16) on the basis of this work. A weakness in this argument is that the firm smooth vegetations seen in these experimental dogs may not have

induced by the experiment and it is this type of lesion which occurs most often in dogs with congestive heart failure.

Arteriosclerosis

Although dogs are subject to non-inflammatory arterial disease the common type affecting man, intimal atherosclerosis, does not occur spontaneously (8). Lindsay and co-workers (17) have reviewed the literature on arteriosclerosis in dogs. They examined the aortas from 26 dogs, 14 of which were 8 to 17 years old. Coronary arteriosclerosis was present in 10 of the 14 aged dogs. Five of the 26 dogs had chronic congestive heart failure. The earliest evidence of aortic disease was an alteration of the internal elastic lamina (reduplication, splitting, fragmentation). The first abnormality in the intima consisted of fibroblastic proliferation with deposition of mucoid ground substance. At this stage lipids were not demonstrable in the lesions. Thus in the dog, lipids are not involved in early aortic disease. Lipid infiltration does occur as a late phenomenon, being limited to the deeper and older portions of the larger plaques. Refractile material is absent in these plaques, indicating that there is no relation to cholestrol deposition. In the diseased coronary arteries a variety of lesions were found. In two dogs, there were small elevated fibrous internal plaques in major coronary arteries. Two large coronary arteries were occluded by organizing thrombi. In two dogs intimal fibrous thickening with considerable hyaline degeneration was observed in medium sized coronary arteries. In the small coronary arteries of four animals eccentrically placed hyaline intimal plaques projected into, and partially occluded, the vascular lumens. An occasional small artery showed muscular hypertrophy, at times with Anitschkow myocytes in the adventitial layer.

Further studies are needed before conclusions can be drawn regarding the incidence and significance of arteriosclerotic disease in dogs. Aortic disease is not rare in older dogs and apparently coronary artery disease occurs more frequently than suspected before the report of Lindsay et al. Cholesterol infiltration does not appear to play a part in canine arteriosclerosis.

The clinical significance of arteriosclerosis in dogs is not clear. In contrast to man, death from occlusion of large arteriosclerotic arteries with consequent infarction is rare in dogs as are instances of cerebral hemorrhage. Thus arteriosclerosis is a post-mortem finding which has not been correlated with clinical disease in canines.

The effect of coronary artery lesions such as those described in the foregoing on myocardial function has not been evaluated. Lindsay et al. suggest that secondary lesions of the myocardium, such as infarction and myocardial fibrosis, readily explain cardiac disability seen in old dogs. There is need to extend and confirm their findings in a larger series of animals so that correlations between vascular lesions and heart disease can be made.

Hypertension

Evidence from a variety of sources indicates that arterial hypertension occurs in dogs, with or without accompanying renal disease.

Blood pressure determinations on 1,000 trained, unanesthetized experimental dogs 1 to 4 years of age were obtained over a period of 18 years by Katz and coworkers (18). In this series of dogs, the upper limit of normotension was 145 (134-155) $\pm$ 7.5 mm. Hg. mean femoral arterial pressure. An average femoral arterial pressure of 150 (140-160) $\pm$ 7.5 mm. Hg. or more was considered hypertension. On the basis of this criterion, 9 dogs had high blood pressure. In three of the animals there was an associated chronic pyelonephritis (i.e., probably the chronic interstitial nephritis of veterinary pathologists (2, pp. 110-111)). In the other six animals spontaneous hypertension was unassociated with renal disease. In all these dogs hog renin and autirenin had a hypotensive action not seen in normotensive dogs. This indicates a qualitative difference between normotensive and hypertensive individuals which further supports the hypertension criterion established and suggests a pathogenetic role for renin in both types of high blood pressure.

Stamler et al. (19), defining hypertension as over 185/100 mm. Hg. reported 10 cases among experimental dogs and McCubbin and Corcoran (20) found two dogs with high blood pressure among 400 street dogs.

In a clinical study Doeglas (21) discovered 17 dogs with systolic blood pressure exceeding 180 mm. Hg.

McIntyre and Montgomery (22) observed elevated blood pressure (about 200/160 mm. Hg.) in dogs infected experimentally with Leptospira canicola. Dogs over five years of age were excluded and most of them were under two years old.

That hypertension may be associated with chronic renal disease in dogs is well known (18, 19, 22, 23). In Doeglas (21) series of 17 dogs with hypertension, six had nephritis and nine uremia.

The frequent occurrence of left ventricular hypertrophy or relative increase in heart weight: body weight ratio in dogs with chronic renal disease suggests that high blood pressure often develops in these cases. Platt (24) found cardiac hypertrophy in six out of 16 dogs with chronic nephritis and an elevated left ventricle: right ventricle ratio in chronic nephritis cases. Dahme (25) reported left ventricular hypertrophy in 17 out of 23 dogs with chronic interstitial nephritis. In their experimental studies, McIntyre and Montgomery (22) found hypertension and muscular hypertrophy of the left ventricle associated with chronic interstitial nephritis in canine leptospirosis. In contrast to this apparent relationship between chronic nephritis and high blood pressure are the findings of Robin (26). He failed to detect high blood pressure in dogs with nephritis and an associated left ventricular hypertrophy and suggests that both the nephritis and hypertrophy may have a common cause.

Congenital Heart Disease

Since the compilation in Table I was made (1) two additional cases of patent ductus arteriosus, two of aortic stenosis, and one of pure pulmonary stenosis have been observed. Thus in a total of 35 cases of congenital heart (and great vessel) disease, the types were distributed as follows:

Patent ductus arteriosus	15
Pure pulmonary stenosis	9
Persistent right aortic arch	5
Aortic stenosis	4
Intraventricular septal defect	1
Tricuspid valve hypoplasia	1

It is not certain whether the cases of aortic stenosis represent a developmental defect or a lesion acquired in utero or during the early months of life.

This series may give a distorted view of the actual incidence of various types of congenital heart disease for several reasons. The series is too small and the addition of only a few cases could change the percentages significantly. The large number of patent ductus arteriosus cases may be, in part, owing to the ease of diagnosis of this defect. The presence of persistent right aortic arch (or similar vascular ring anomalies) is diagnosed because of an associated massive dilatation of the esophagus with consequent regurgitation and emaciation. Great vessel anomalies not disturbing tracheal or esophageal function probably go unnoticed. Congenital anomalies not compatible with life or causing no clinical signs (e. g., patent foramen ovale) would seldom be brought to a veterinary clinic.

Although it was often not possible to obtain a complete litter history, none of the litter mates or parents of any of these dogs were known to have congenital anomalies of any kind.

Filariasis

The adult heartworm (Dirofilaria immitis) which varies in length from 15 cm. (male) to 25 cm. (female), normally lives in the right heart of dogs. The eggs hatch in the uterus of the female and microfilariae (218 to 329 microns in length by 5 or 6 microns in diameter) pass into the blood stream. The microfilariae develop into infective larvae in several species of mosquitoes (and possible fleas) which act as vectors in the spread of the parasite. Microfilariae survive in the blood stream for several months; possibly as long as two years. Larvae transferred from an insect vector to a new host require about eight months to reach the adult stage.

The parasite is widely scattered over southeastern United States, especially along the Atlantic and Gulf coast. Microfilariae may be found in from 50 to 90 per cent of hunting dogs and strays in Florida and Georgia. In the Small Animal Clinic of the University of Pennsylvania in Philadelphia, the incidence of microfilaria (identified as D. immitis) infestation has been found to be approximately ten per cent.

As many as 300,000 microfilariae per cubic centimeter of blood may be found. The presence of microfilariae in the circulating blood does not give rise to any diagnostic clinical signs, although the possible influence on capillary circulation and hemodynamics has not been studied. When there are large numbers of adult worms in the right heart mechanical circulatory interference may result in signs of congestive heart failure as well as pulmonary embolism and infarction.

Recently the presence of another filariid in dogs in the United States has been established (27, 28). It was tentatively identified as a species of Dipetalonema, which is thought to be a tissue filariid. Since from these studies it appears that microfilariae from this species comprise a significant percentage of all infestations, the incidence of true heartworm disease may be lower than previous observations indicate.

Comment

Chronic cardiovascular diseases in dogs are of interest from the standpoint of comparative pathology and have a bearing on the use of these animals in cardiovascular research.

That investigators are sometimes unaware of the influence spontaneous cardiovascular disease in experimental dogs may have

on their results is evident from the published literature. Apparently account is seldom taken of the possibility that microfilariae may be present in the blood stream of animals obtained from areas where the disease is endemic. It has been stated that the accidental finding of endocarditis in dogs is extremely rare (15) and that systolic murmurs are common in "normal" dogs (29). Such statements require qualification and reflect the need for improved dissemination of knowledge already available and for further study of the occurrence of heart disease among experimental dogs.

Insufficient study has been given cardiovascular diseases in dogs to make possible clear delineation of their pathogenesis and interrelations. In dogs with chronic congestive heart failure, valvular disease, coronary artery disease and myocardial degeneration may all be found in a given case. These animals usually also have chronic interstitial nephritis. The incidence of hypertension among these dogs is not known. All of these lesions are more common in older dogs and are therefore associated with aging. Individual variation is great and there are no data which permit an evaluation of environmental and hereditary factors and the effects of infectious diseases.

The pathogenesis of chronic endocarditis in man and animals is not clear despite considerable study. The problems involved in seeking a more complete understanding of these pathological changes have been discussed in the book by Böhmig and Klein (14) and in recent articles by Böhmig (30), Klein (31), Hegglin (32), and Wuhrmann (33). The relatively common occurrence of spontaneous chronic valvular disease in dogs suggests they should be useful in experimental studies on the pathogenesis and etiology of chronic valvular endocarditis. Thorough pathological, physiological, and biochemical study of the spontaneous disease itself would provide information which should increase knowledge of the fundamental organ, tissue, and humoral alterations associated with the development of chronic endocarditic lesions.

Information gained from further study of cardiovascular diseases in dogs will increase the usefulness of the dog as an experimental animal, contribute to an understanding of this group of diseases from the comparative point of view, and provide a background of value in the treatment and possibly in the prevention of these diseases in dogs.

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