ANIMAL MODELS OF HUMAN DISEASE

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THE REGISTRY OF COMPARATIVE PATHOLOGY
ARMED FORCES INSTITUTE OF PATHOLOGY
WASHINGTON, D. C. 20305

ADVISORY COMMITTEE

The publication of these models is supported by Public Health Service Grant No. RR00301 from the Division of Research Resources, U.S. Department of Health, Education, and Welfare, under the auspices of Universities Associated for Research and Education in Pathology, Inc.

Produced by Information Services, Inc.
9650 Rockville Pike, Bethesda, Maryland 20014

THE REGISTRY OF COMPARATIVE PATHOLOGY

The Registry of Comparative Pathology provides a national resource for consultative assistance and information exchange among scientists concerned with comparative pathology. Its major activity is the collection of pathologic specimens of comparative value for research and education from a wide range of species—nonhuman primates, domestic, laboratory, marine, wild, and zoo animals; reptiles, birds, fish; and to a limited extent, invertebrates. The collected material, recorded in an automatic data-processing system for retrieval, is used in the preparation of:

Loan study sets describing specific diseases in various animals that are of comparative interest. Each set is accompanied by a syllabus, microslides, and color transparencies.

Loan study sets on the histology of various animals. Organs and tissue structures illustrate comparative histologic variations among species.

Exhibits that compare lesions in diseases among animals with those seen in man. Exhibits are displayed at appropriate scientific meetings and may be borrowed if available.

Lectures and publications on comparative pathology from the accessioned material.

Other key functions of the Registry are:

Quarterly publication of the Comparative Pathology Bulletin. Each issue serves as a forum for the exchange of news of interest to comparative pathologists and contains a description of a useful animal model of a human disease.

Maintenance of a catalog of animal models of human diseases. Information is continuously added to the catalog, and is available to all interested investigators.

Facilities for visiting scientists. This service is available to scientists who wish to conduct comparative studies of diseases in animals or those that have a similar counterpart in man. Prior notification of visit is recommended.

Consultation in comparative pathology. This ongoing function of the Registry offers cases for consultation representing a wide range of animals and birds affected with various diseases.

Symposia, workshops, and seminars. These activities sponsored by the Registry are instrumental in establishing better means of communication among investigators in comparative pathology.

Handbook of Animal Models of Human Disease. The Registry publishes a cumulative collection of animal models, to which new models are added periodically, reprinted from The American Journal of Pathology, The Comparative Pathology Bulletin and other professional publications.

THE AMERICAN JOURNAL OF PATHOLOGY

The American Journal of Pathology is published under the auspices of The American Association of Pathologists and Bacteriologists and The American Society for Experimental Pathology, and is edited by a Board appointed by the Councils of the two Societies. For the benefit of those concerned with comparative pathology, The Journal periodically presents studies of animal models of human disease under the sponsorship of the Registry of Comparative Pathology.

PREFACE

The search for new or improved approaches to the study of human disease is never ending. Although the use of experimental animals for this purpose is very well established, the utilization of natural diseases of various animals as models for human disease has not been exploited nearly as fully as it might be. This is in part due to the difficulty that a specialized investigator may have in finding an animal model.

One of the principal goals of comparative pathology is to make meaningful comparisons between pathological processes in different species in order to gain new knowledge about obscure disease entities. This is of particular promise in developing concepts of diseases in man in which the human animal is less than satisfactory as an experimental subject.

The Advisory Committee of the Registry of Comparative Pathology at the Armed Forces Institute of Pathology has devoted much of its effort toward finding ways of making comparative pathology more useful to the study of human disease. A comprehensive catalogue of animal models was proposed as one of the means toward this end. It was envisioned that each proposed animal model would be carefully studied and compared with similar diseases in man. Similarities and differences would be evaluated and described. A brief description of the morphological and biological characteristics of the animal disease would be noted. Also included would be information on the availability of the model animals and a few selected references to the literature. The aim is to provide investigators with a readily accessible, critically prepared but succinct, reference to animal diseases, experimentally induced or occurring naturally, which could be used for comparison with human disease. This concept has now matured as the *Handbook, Animal Models of Human Disease*, of which this is the first fascicle.

The articles in this *Handbook* were initially published in the Bulletin of Comparative Pathology or the American Journal of Pathology. We are particularly grateful to the authors who have prepared these descriptions. These short articles have been reproduced by permission of the two Journals to make up this first fascicle of the *Handbook*. The *Handbook* is loose leaf and the pages punched in order for the reader to make his own indexing arrangements and to provide for the addition of new fascicles which will be published subsequently.

The Registry of Comparative Pathology is involved in many other activities designed to increase interest and accelerate progress in comparative pathology. These include the sponsorship of symposia and workshops, the preparation and dissemination of study sets and exhibits, the publication of the Bulletin of Comparative Pathology and of articles with descriptions of new animal diseases, and the collection and registration of examples of unusual animal diseases for future comparative study.

This *Handbook* is a new venture and may have imperfections. The Committee and Staff would be grateful for the reader's candid comments and criticisms on the usefulness of this *Handbook*. We would particularly welcome suggestions as to how future fascicles might be improved.

T. C. JONES, DVM
Editor-in-Chief
Handbook, Animal Models
of Human Disease

ROBERT W. WISSLER, PH.D., M.D.
Chairman, Advisory Committee of the
Registry of Comparative Pathology

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Reprinted from:
THE AMERICAN JOURNAL OF PATHOLOGY
66:1, 189-192, January 1972

Model No. 1

Idiopathic Polyneuritis

Human Disease: Guillain-Barré Syndrome

Animal Model: Coonhound Paralysis, Idiopathic Polyradiculoneuritis of Coonhounds

Contributed by: J. F. Cummings, DVM, Department of Anatomy, New York State Veterinary College, Cornell University, Ithaca, NY, and D. C. Haas, MD, Department of Neurology, Upstate Medical Center, State University of New York, Syracuse, N.Y.

Clinical Features

This syndrome, first described by Kingma and Catcott,[1] is primarily an occupational hazard for coonhounds (Fig 1) although it occurs in other dogs that encounter raccoons. A raccoon bite or scratch precedes the onset of signs by 7–14 days. The onset is marked by weakness and hyporeflexia in the hind limbs. Paralysis progresses rapidly, resulting in a flaccid symmetric quadriplegia. While recumbent, dogs remain alert and afebrile. Motor impairment is more pronounced than sensory changes. In severely affected animals, at the peak of their illness, one finds a complete absence of spinal reflexes, facial weakness and labored respiration. Electromyographic findings include fibrillations, positive-sharp waves and other evidence of denervation. Although 2 hounds in our care have died of respiratory failure, paralysis usually abates and recovery is to be expected (Fig 1), but the rate and extent of recovery is variable.

Pathologic Features

Pathologic changes are concentrated in the ventral roots and the spinal and peripheral nerves.[2] In keeping with clinical signs, ventral roots are affected more severly than dorsal roots (Fig 2). The lesions consist of segmental demyelination with axon preservation (Fig 3), Wallerian degeneration with disintegration of axons as well as myelin and, often, perivenular leukocytic infiltration. The constituents and prominence of the leukocytic infiltration appears to vary (Fig 4). Neurogenic muscle atrophy and retrograde chromatolysis in neurons of the ventral horn of the spinal cord occur secondary to axonal disruption.

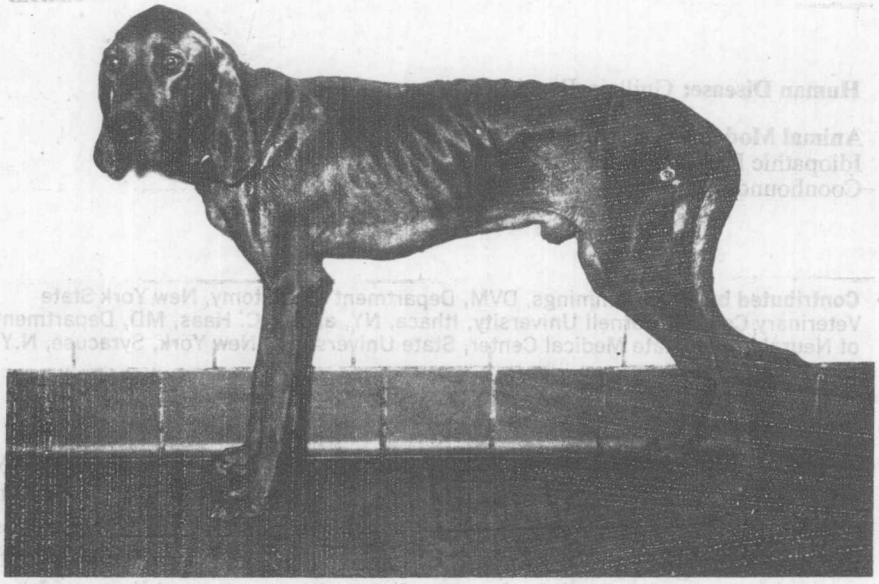

Fig 1—Red bone coonhound during recovery phase of paralysis. Note marked muscle atrophy and decubital ulcers that developed during the quadriplegic phase of illness. This hound subsequently sustained three more attacks of coonhound paralysis, each preceded by a raccoon bite.

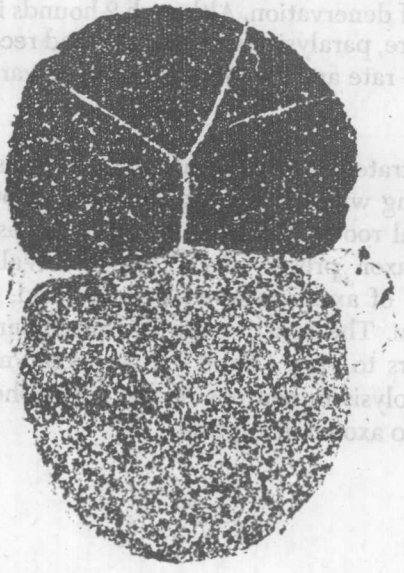

Fig 2—Transverse section of a lumbar spinal nerve. Note marked demyelination in the ventral root component. The dorsal root component above appears normal at this magnification (Luxol fast blue—cresyl echt violet, × 45).

Fig 3—Single myelinated nerve fiber isolated from a lumbar ventral root of a dog that died 110 days after the onset of signs. Osmic acid stain demonstrates the restoration of myelin that occurs in areas of segmental demyelination. The short, partially remyelinated internodal length with prominent infundibuli appears thinner and paler than adjacent internodes (× 400).

Comparison with Guillain-Barré Syndrome

The clinical features of coonhound paralysis are very similar to those reported in the Guillain-Barré syndrome.[3] In man, however, the onset is preceded by an infection which often involves the upper respiratory tract. The initial symptom is usually weakness of the lower extremities which extends rapidly to the upper extremities and facial muscles.

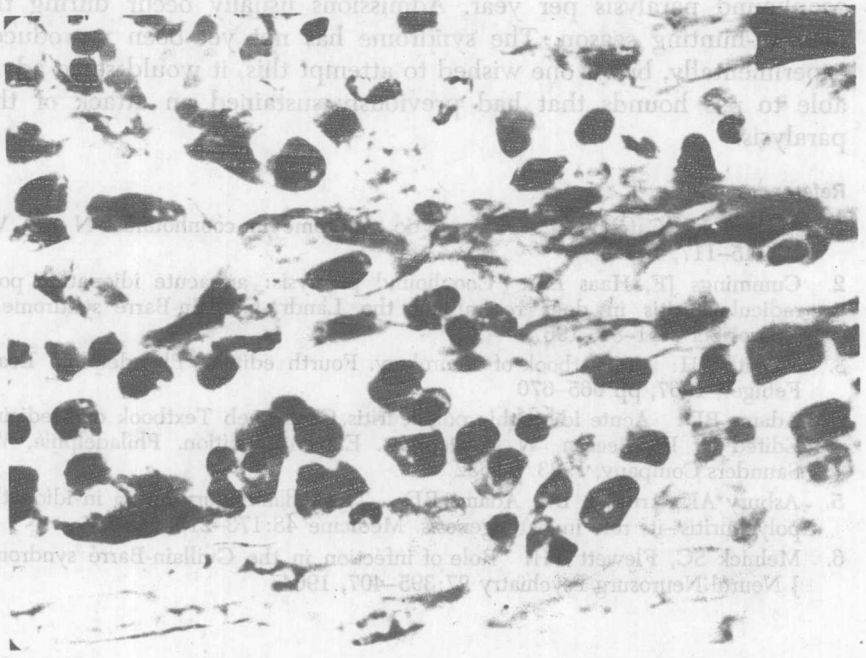

Fig 4—Section from a lumbar ventral root of a hound which died 20 days after the onset of signs. Note the perivenular infiltration of plasma cells (× 1000).

Flaccid quadriplegia is not uncommon and in about one-fourth of the cases a respirator is required because respirations are weak. Sensory changes are not usually prominent. The recovery rate varies from a few days or weeks to months.

Pathologic changes in coonhound paralysis resemble those found in the Guillain-Barré syndrome both in type and location.[4,5] Changes in roots and nerves include perivenular leukocytic infiltration; degeneration of myelin sheaths, both Wallerian and segmental types; swelling and fragmentation axis cylinders, and chromatolysis of ventral horn cells.

The cause of the Guillain-Barré syndrome is unknown. It has been postulated that autoimmune processes may be involved in the etiology.[6] To date, no infectious agent has been isolated from dogs afflicted with coonhound paralysis. Since the lesions in these dogs resemble the changes found in the Guillain-Barré syndrome and also, to some extent, those described in experimental allergic neuritis, an immune disturbance may be considered. However, the raccoon's role in initiating such a demyelinating neuritis remains enigmatic.

Availability

The clinic at Cornell rarely receives more than three or four cases of coonhound paralysis per year. Admissions usually occur during the raccoon-hunting season. The syndrome has not yet been reproduced experimentally, but if one wished to attempt this, it would seem advisable to use hounds that had previously sustained an attack of this paralysis.

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Reprinted from:
COMPARATIVE PATHOLOGY BULLETIN
2:3, August 1970

Model No. 2

Congenital Hyperbilirubinemia, Dubin - Johnson Syndrome

Human Disease: Dubin-Johnson (Sprinz-Nelson) Syndrome: Congenital hyperbilirubinemia (conjugated, "direct-reacting" bilirubin) due to an organic anion excretory defect of the liver.

Animal Model: Dubin-Johnson Syndrome in Corriedale sheep.

Contributed by Charles E. Cornelius, DVM, PhD, Department of Physiological Sciences, College of Veterinary Medicine, Kansas State University, Manhattan, Kansas 66502.

Biologic Features: This syndrome is characterized by a congenital hepatic excretory defect for organic anions such as bilirubin, sulfobromophthalein sodium (BSP), phylloerythrin, metepinephrine glucuronide, etc. The mode of inheritance is not known at present; however, the condition is most likely inherited as a single autosomal recessive. The condition is lethal under natural field conditions due to photosensitivity from phylloerythrin retention. Clinical signs are acute photophobia and phytodermatitis at the time of weaning due to the ingestion of chlorophyll in green feed which is converted to phylloerythrin in the intestinal tract. Phylloerythrin is not adequately excreted from the portal blood by the liver. Photosensitivity can be prevented by housing mutants indoors. Jaundice is not apparent, but elevated levels of bilirubin diglucuronide (direct-reacting) are present in the plasma.

Pathologic Findings: Livers at birth are free of pigment but become grossly dark brown to black by a few months of age from the accumulation of a melanin pigment in the hepatic lysosomes. Pigment deposition is pericanalicular and more centrolobular in distribution. Pigments isolated from human and ovine cases are nearly identical in their elemental analyses and electron spin-resonance characteristics. After the administration of DL-epinephrine-7-^{3}H bitartrate, radioactivity was accounted for chromatographically as metepinephrine glucuronide. Incorporation of radioactivity into the hepatic pigment occurred by three days and was followed by a very slow turnover rate. The hepatic pigment is postulated to result from impaired hepatic excretion of metabolites of epinephrine which are oxidized to insoluble melanin polymers.

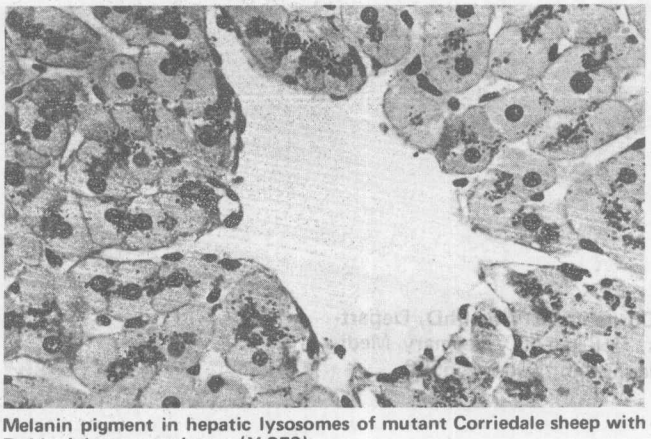
Physiologic Observations: This chronic non-hemolytic hyperbilirubinemia is characterized by the accumulation of the conjugated pigment, bilirubin diglucuronide, in the plasma due to a transport defect in its excretion from the liver cell. Defects in the excretion or T_m of many organic anions (bilirubin, BSP, iopanoic acid, indocyanine green, etc.) occurs; however, their hepatic uptake and storage are normal. This ovine mutant has no defect in taurocholic acid excretion. After bile salt infusion and subsequent choleresis, a persisting defect in BSP excretion was present.

Comparison with Dubin-Johnson Syndrome in Man: The livers of mutant Corriedale sheep with this syndrome appear functionally and morphologically identical to those observed in the human counterpart disease. The syndrome in the ovine mutant is unlike man in being lethal under field conditions due to the complication of photosensitivity from the ingestion of chlorophyll in green feed.

Availability: At present, one flock of Corriedale mutants exist and is maintained at Kansas State University. The present

Photodynamic dermatitis around eyes and ears of Corriedale sheep with Dubin-Johnson syndrome. Photosensitivity occurs due to retention of phylloerythrin, one of many organic anions inadequately excreted from the portal blood by the mutant's liver.

breeding program should provide parent breeding stock for establishing additional colonies by 1971. Limited plasma and tissue samples can be provided upon request.



Melanin pigment in hepatic lysosomes of mutant Corriedale sheep with Dubin-Johnson syndrome (X 350).

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Pathologic features of the liver in non-human primates has been observed mainly in captive animals. A report prepared by Cesar A. Maruffo, M.D., Manuel R. Malinow, M.D., Juan R. Depaoli, Ph.D., and Samuel Katz, M.D., from the Oregon Regional Primate Research Center, Beaverton, Oregon, and the Academia Nacional de Medicina and Hospital Churruca, Buenos Aires, Argentina, deals with the findings in the livers of a large series of free-ranging howler monkeys (Alouatia caraya, Humboldt, 1811). Most of the animals exhibited a peculiar hepatic pigmentation, similar in certain respects to that described in man as familial chronic idiopathic jaundice or Dubin-Johnson syndrome.

Reprinted from:
COMPARATIVE PATHOLOGY BULLETIN
2:1, February 1970

Model No. 3

Acute Toxoplasmosis

Human Disease: Toxoplasmosis

Animal Model: Toxoplasmosis

Contributed by K. Benirschke and R. J. Low, Department of Pathology, Dartmouth Medical School, Hanover, New Hampshire 03755.

Toxoplasma gondii, the protozoan responsible for this disease, is an ubiquitous parasite. In man the disease is usually innocuous when acquired in adulthood. Its descructive effects in the fetus, particularly on the central nervous system, are the principal medical concern. Treatment, transmission, diagnosis, and particularly pathogenesis are of great medical interest.[1,2] Many animals have been used in past studies,[3] and the disease occurs also spontaneously in a wide variety of species;[3,4,5] South American primates appear to be uniquely susceptible to this organism however. The following recent accession to the Registry of Comparative Pathology illustrates the common findings.

Case Report. A juvenile male woolly monkey *(Lagothrix sp.)* died in January 1969 after a 2-day respiratory illness with convulsions and after a period of inanition. The only macroscopic findings noted were pulmonary edema and hemorrhages, swollen liver and spleen, and generalized lymphadenomegaly. A tissue culture (from a minute specimen of skin biopsied after death) planted for other reasons yielded not only excellent fibroblastic growth but also an abundance of *Toxoplasma* organisms, free and as cysts. These were sent to Dr. J. K. Frenkel (University of Kansas Medical Center) who confirmed the diagnosis.

Microscopic examination revealed the organisms in almost all tissues sampled, including the biopsied skin (Figs. A-G). Areas of necrosis found in the lung, heart, liver, and pancreas bore no direct relationship to the presence of organisms as has been noted by others. In all respects the pathologic findings are identical to those described by McKissick *et al.*,[6] and the pertinent questions raised by these authors cannot be answered from this further case of spontaneous acute toxoplasmosis.

The animal had been caged with three squirrel monkeys. Those monkeys, as well as a variety of other animals (ocelot, pumas, macaws, spider monkeys) wintering in the same room, remained healthy. Dirt scraped from various areas of the room and from the animal's cage were examined by Dr. Frenkel but failed to yield *Toxoplasma* organisms. On many occasions all animals had been fed raw meat (horse, deer, hamburger), samples of which (some of it frozen) contained no cysts on sections.

The relative frequency with which spontaneous acute toxoplasmosis is found in South American primates[6] is as yet unexplained. Although experimental infection of rhesus monkeys has been achieved, various studies indicate that Platyrrhini are more readily infected and that they would be a useful group of animals in which to study transmission and pathogenesis of the disease.[7] Because of a recent small epidemic in man, apparently caused by ingestion of infected meat,[8] there may be a renewed interest for animal models such as this.

Classically, intraperitoneal propagation in immature mice is used for diagnosis and as a means for maintaining the

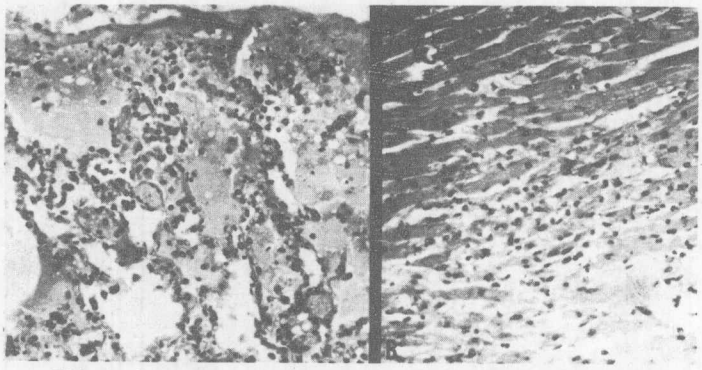

FIG. A. Pulmonary edema and fibrinous pleurisy in woolly monkey with fatal acute toxoplasmosis. Free and encysted organisms were found at higher magnification (H&E X200).

FIG. B. Focal necrosis of myocardium in same case. No organisms were found in this area. (H&E X200).

organisms. Recent experience[9,10,11] indicates however, that *Toxoplasma* can be maintained in various cell cultures for long periods. No toxins seem to be elaborated by the organisms in culture, and cells die only after they are completely filled with the protozoan. The appearance of cysts in culture is characteristic and they are easily identified by this means.

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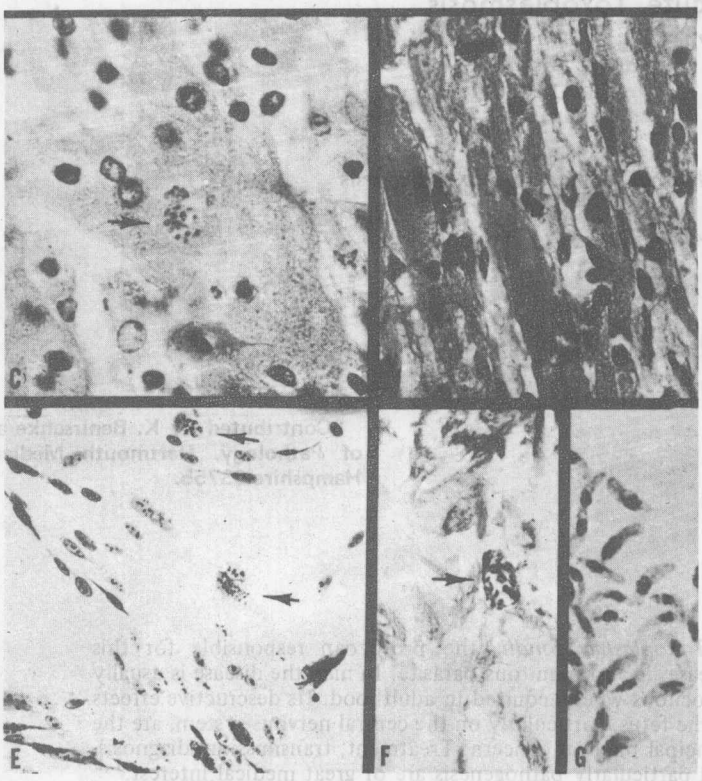


FIG. C. Toxoplasma gondii cyst in liver. No apparent reaction or necrosis is evident. (H&E X800).

FIG. D. Cystic form of Toxoplasma organism in myocardium (arrow) in no immediate relationship to necrosis (H&E X800).

FIG. E. Fibroblastic tissue culture from F, second trypsinized passage, with numerous organisms at arrows (H&E X200).

FIG. F. Section of remains of skin explant, 4 weeks after initiation of culture, to illustrate typical Toxoplasma cyst (H&E X600).

FIG. G. Squashed cyst from culture in F, showing typical protoza, serologically identified as Toxoplasma gondii by Dr. J. K. Frenkel (Giemsa. X2,000).

Model No. 4

Reprinted from:
COMPARATIVE PATHOLOGY BULLETIN
2:3, August 1970

Bacterial Endocarditis

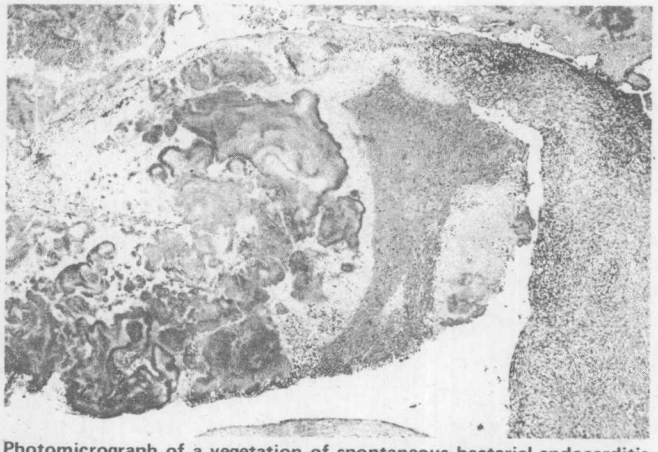
Human Disease: Bacterial endocarditis appears in humans as vegetations on any or all of the heart valves. The order of frequency of involvement of the heart valves is mitral, aortic, tricuspid, and pulmonic valves. Numerous microorganisms including *Streptococcus viridans* have been identified as causative agents in bacterial endocarditis. The valvular vegetations often give rise to emboli which lodge in spleen, kidneys, brain, and mesenteric vessels.

Animal Disease: Suitable experimental animal models are few and induction of bacterial endocarditis in most animal species requires multiple injections of bacteria often with addition of hemodynamic alterations or stress.

Animal Model: Captive opossums *(Didelphis virginiana)* have a high incidence of bacterial endocarditis and a similar disease can be produced experimentally in normal opossums using a single injection of *Streptococcus viridans.*

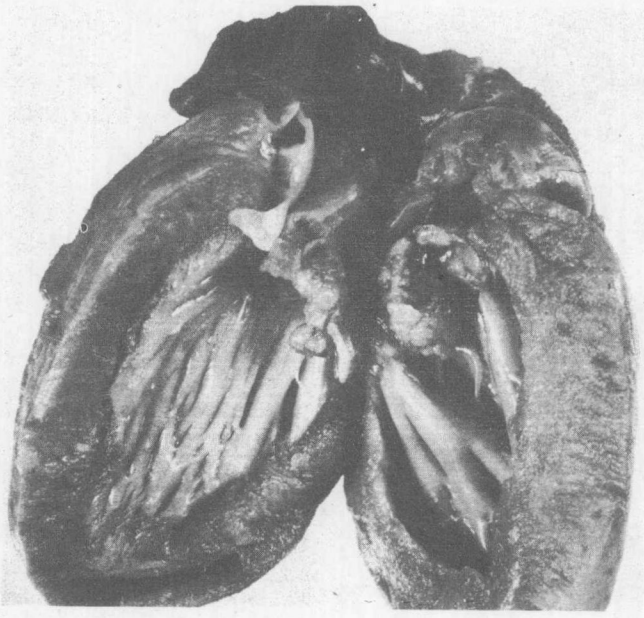
Contributed by David T. Rowlands, Jr., M.D., Department of Pathology, Duke University Medical Center, Durham, North Carolina.

Biologic Features: At least three separate laboratories have now recorded the spontaneous occurrence of bacterial endocarditis in opossums in captivity (1-3). Eighteen of 33 adult animals which died in our laboratory had bacterial valvular vegetations (3). Its occurrence seemed unrelated to sex or to season of the year. The lesions were confined to the mitral valve in seven animals, the mitral and aortic valves in ten opossums, and they were on both mitral and tricuspid valves in one case. These lesions were soft and friable and attached to the atrial surfaces of the atrioventricular valves; they commonly involved both surfaces of the aortic leaflets. The valves underlying the vegetations were often eroded and edematous, containing moderate numbers of chronic inflammatory cells. Gram positive cocci could be identified in the vegetations and *Streptococcus viridans* was isolated from three of seven cases in which positive cultures were obtained from vegetations. Since bacterial endocarditis was not found in animals which were sacrificed immediately after capture, it is believed that bacterial endocarditis in opossums is related to exposure of susceptible animals to human or animal carriers of pathogenetic organisms.



Photomicrograph of a vegetation of spontaneous bacterial endocarditis from an opossum. The valve has been partially destroyed.

We have attempted to establish a colony of opossums free of bacterial infections for use as an experimental model for bacterial endocarditis (4,5). Newly captured adult animals were placed in individual stainless steel cages in a room with



Gross photograph of bacterial endocarditis in the oppossum. The vegetations are large and friable being localized to the mitral valve.

constant temperatures (24° C) and humidity (50-60%) where they were maintained in apparent good health. Only three of 33 of these animals developed bacterial endocarditis.

Twenty-one "clean" opossums were given 52 x 10^6 *Streptococci viridans* intravenously and 12 were given an equal volume of saline intravenously. Twelve of the 21 test animals died of their infection and the remaining nine were sacrificed after three weeks. Two of the control animals (16%) and 12 of the test animals (52%) developed endocarditis. Streptococci could not be recovered from either of the control animals but these organisms were found in the vegetations of 75% of the affected test animals. The mitral valve was the seat of valvulitis in all 12 of the affected animals. In five opossums mitral valvulitis was associated with aortic valvular endocarditis, in one with aortic and tricuspid disease, and in another with aortic and pulmonic valvulitis. The vegetations were grossly and microscopically identical in these animals with those occurring spontaneously. Brain abscesses were found in eight test animals.

Naturally occurring and induced bacterial endocarditis in opossums is similar to that in humans both with regard to the morphology of the individual lesions and their distribution on heart valves. The use of opossums for the experimental induction of bacterial endocarditis is unique in that it requires only a single injection of bacteria in unmodified animals.

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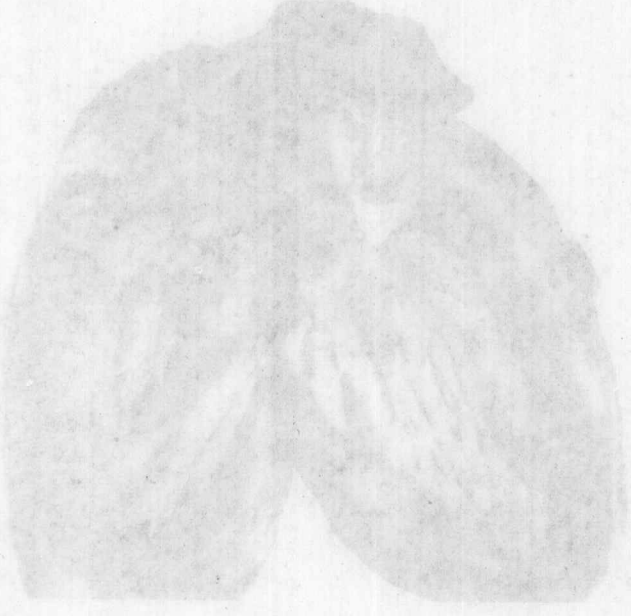

Reprinted from:
COMPARATIVE PATHOLOGY BULLETIN
1:1, November 1969

Model No. 5

Sex Chromosome Anomaly, Klinefelter's Syndrome

Human Disease: Klinefelter's Syndrome; Sex chromosome anomalies.

Animal Model: Tortoiseshell male cat, sex chromosome anomoloies.

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Biologic Features: Two sex-linked alleles in the domestic cat (*Felis catus*) determine alternate colors in the hair coat, orange (0) and black (0+). These alleles are co-dominant, each is expressed in the heterozygote, called the tortoiseshell ("tortie"). In the presence of white spotting ("piebald") (S, an autosomal dominant) the phenotype is often described as tortoiseshell and white, tortie and white, "tricolor" or "calico." Many modifying genes affect the intensity and pattern of the orange or black, necessitating care in identifying the phenotype.

The hemizygous male may be orange (O) or black (O+), the female may be black ((O+O+) or orange (OO) in the homozygous state. The heterozygous female (O+O) is the tortoiseshell. The rare occurrence of male tortoiseshell cats (Fig. 1) has been an enigma for many years and has only recently been explained on the basis of anomalies of sex chromosomes. Evidence for such chromosome anomaly was first presented by Thuline and Norby, (1961) on the basis of chromosome counts in two male torties, in which one additional chromosome, postulated to be an X was found in each case. Subsequent studies have demonstrated that one or more additional X chromosomes (Fig. 2) are present in male torties but more complex anomalies also occur. A diploid/triploid chimera 38XX/57XXY tortoiseshell male has been described by Chu, Thuline and Norby (1964); another chimera 38XY/39XXY by Biggers & McFeely (1966); an XX/XY chimera with normal chromosome number (2n 38) by Malouf, Benirschke, and Hoefnagel, (1967); and two chimeric torties were reported by Jones (1969). These latter were 38XX/XY/39XXY/40XXYY and 38XY/39XXY/40XXYY respectively. The frequency of chimeric individuals among the few animals studied so far is remarkable.

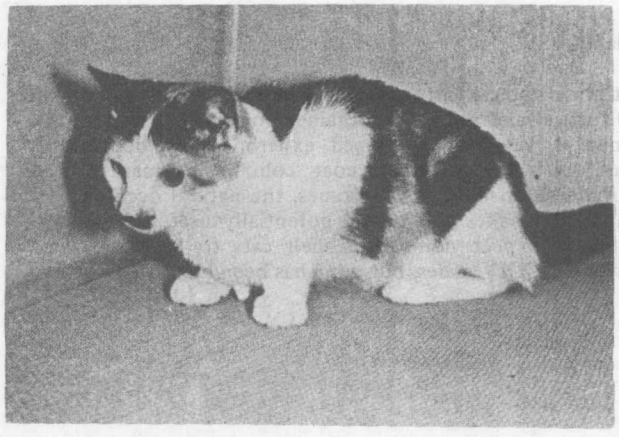

Fig. 1. Male "tortoiseshell and white" cat. The orange or yellowish coat color and the black are controlled by allelic, sex-linked codominant genes. The white color, "piebald" is inherited as an autosomal dominant.

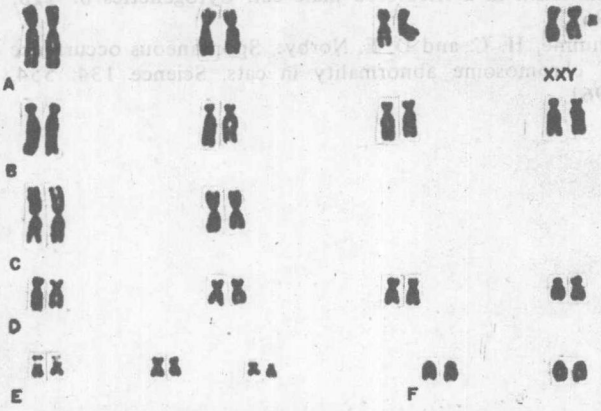

Fig. 2. Karyotype of an XXY cell from a male tortoiseshell cat. The model number of cells from skins and blood were of this karyotype.