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FOR BIOMEDICAL RESEARCH - IV

NATIONAL RESEARCH COUNCIL, WASHINGTON, D.C.

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Selected Abstracts on ANIMAL MODELS FOR BIOMEDICAL RESEARCH—IV

INSTITUTE OF LABORATORY ANIMAL RESOURCES
ASSEMBLY OF LIFE SCIENCES
NATIONAL RESEARCH COUNCIL
NATIONAL ACADEMY OF SCIENCES

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Preface

Animal models have become increasingly important as a means by which disease processes occurring in humans can be investigated. Some specific strains and stocks have biologic and pathologic processes bearing similarities to humans, and their study can lead to a better understanding of mechanisms.

The great number and diversity of publications relevant to animal models in different biomedical disciplines make advantageous the availability of a service that highlights the animal model concept. This publication, *Selected Abstracts on Animal Models for Biomedical Research*, is the fourth in a series intended to be a useful current-awareness tool for scientists but does not represent a verification of an author's recommended use of a particular species as a model, or as the best model, for a specific biologic process. The publication serves as a vehicle through which current research utilizing animal models can be compiled and disseminated periodically for evaluation. All entries are either authors' abstracts or their summaries and conclusions. Thanks are due to the publishers of the cited journals for granting permission to reprint this material. Readers are encouraged to refer to the original articles, the majority of which appeared in the biomedical literature during 1973 and 1974.

Selected Abstracts on Animal Models for Biomedical Research is a publication of the Animal Models and Genetic Stocks Program, an information-exchange service conducted by ILAR. The program informs the biomedical community of the various animal models available and assists investigators in selecting and locating particular strains or stocks.

Information accumulated within the program includes key references, major characteristics of specific animal models or genetic stocks, and a registry of names and locations of sources of supply. The data are made available to interested individuals by response to specific inquiries and through bibliographies features in the *ILAR News*. A Committee on Animal Models and Genetic Stocks serves in an advisory capacity to the program.

ILAR considers this program to be important for improving communication among biomedical personnel within the research community. The success of an information-exchange program, however, depends largely on the acceptance and participation of the scientific community it serves. Researchers are requested to assist in the further development and dissemination of information by providing data relative to animal models or genetic stocks maintained within their institutions. Pertinent reprints, colony information, inquiries, and other correspondence should be addressed to:

Animal Models and Genetic Stocks Program
Institute of Laboratory Animal Resources
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Charles B. Frank
Nancy A. Muckenhirn
Editors

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ALIMENTARY SYSTEM

1. Avery, B. E. (8401 Osuna Road, N.E., Albuquerque, N. Mex. 87111), and D. M. Simpson. 1973. *The baboon as a model system for the study of periodontal disease: Clinical and light microscopic observations*. J. Periodontol. 44:675-686.

The baboon has been examined both clinically and histopathologically as a possible primate model for human periodontal disease. Young adult males and middle-aged males were used. The clinical features of periodontal disease in the baboon were found to be quite similar to those in the human and consisted of severe gingival inflammation resulting in edema, erythema, hyperplasia, increased crevicular fluid flow, and spontaneous bleeding. As the disease progresses, pocket formation and marginal bone loss occur, resulting in gingival recession and osseous defects resembling those found in advanced human periodontal disease. Gingival inflammation is related to the accumulation of extensive plaque and calculus.

The histopathologic appearance of periodontal disease in the baboon strongly resembles what is seen in the human. In our study, the cellular infiltrate in established lesions consisted primarily of cells of the lymphoid series, i.e., plasma cells, small and medium-sized lymphocytes, and other mononuclear cells, some of which could be identified as macrophages. Lymphoid cell types were also observed within the intercellular spaces of the crevicular epithelium. The numbers of neutrophils varied greatly in different specimens, but neutrophils were frequently found within vessels adjacent to the crevicular epithelium and migrating through the intercellular spaces of the epithelium toward the sulcus.

Thus, the baboon appears to be an excellent model for periodontal research due to the following factors: (1) naturally-occurring osseous defects; (2) a large oral cavity providing easy accessibility; (3) oral structures which generally resemble those in the human; (4) a gingival inflammatory infiltrate which appears identical to that of the human; (5) direct correlation between disease and local irritants. [*Papio anubis*]

2. Coop, K. L. (Radiation Research Laboratory, Department of Radiology, College of Medicine, University of Iowa, Iowa City 52242), J. G. Sharp, J. W. Osborne, and G. R. Zimmerman. 1974. *An animal model for the study of small-bowel tumors*. Cancer Res. 34:1487-1494.

An animal model for the study of small-bowel tumors has been investigated. Tumors were induced in male Holtzman rats by X-irradiation of only the hypoxic, temporarily exteriorized ileum and jejunum. Following an exposure of 2000 R, 56% of the rats developed adenocarcinoma somewhere in the irradiated segment. Macroscopic metastases were not observed outside the small intestine; however,

metastases or direct extensions were observed histologically in the mesentery, pancreas, and abdominal wall. An anemia associated with the intestinal tumors was investigated in detail; the erythrocytes were found to be hypochromic and macrocytic. The anemia appeared to be the result of blood loss from the tumors into the intestinal lumen. Other pathological features associated with these rat intestinal tumors were weight loss, diarrhea, obstruction of the small bowel, and intestinal perforation and hemorrhage. These features are similar to those described in the literature for malignant tumors of the small intestine in humans. This animal model, therefore, would appear to be potentially useful for studies relating to humans with small-bowel tumors.

3. Nigro, N. D. (Department of Surgery, Wayne State University, Detroit, Mich.), N. Bhadrachari, and C. Chomchai. 1973. *A rat model for studying colonic cancer: Effect of cholestyramine on induced tumors*. Dis. Colon Rectum 16:438-443.

Dimethylhydrazine, azoxymethane, and methylazoxymethanol are highly efficient intestinal carcinogens in the rat. Azoxymethane is the best, producing tumors in all rats. The lesions occurred in significant numbers in the small intestine when given at high dosage levels over a period of six months or more. The tumors tend to occur more in the proximal halves of both segments of the intestine.

When the animals are fed a 2 per cent cholestyramine diet, there is a marked increase in the tumor yield and the increase is, for the most part, in the large intestine, especially its distal half. Investigations of the mechanisms whereby cholestyramine enhances tumor formation in the large intestine of the rat are continuing.

We conclude that the rat given azoxymethane subcutaneously at weekly intervals while on a 2 per cent cholestyramine diet is an excellent experimental model for studies of colonic cancer. [Sprague-Dawley rats]

4. St. John, D. J. B. (Monash University Department of Medicine, Alfred Hospital, Melbourne, and the Department of Pathology, Repatriation General Hospital, Perth, Australia), N. D. Yeomans, and W. G. R. M. De Boer. 1973. *Chronic gastric ulcer induced by aspirin: An experimental model*. Gastroenterology 65:634-641.

Investigations were performed in the rat to examine the effects of prolonged administration of aspirin on the gastric mucosa. Groups of rats received aspirin by esophageal intubation in doses of 120, 250, or 500 mg per kg per day for 6 months. Chronic gastric ulcers were found in the antral mucosa in 9 of 16 rats given 250 or 500 mg per kg per day of aspirin. In addition, there were multiple erosions in the glandular mucosa in all of the aspirin-treated rats surviving the treatment period. In a control group, gastric histology was normal in every instance. Mucosal recovery was virtually complete in rats in the 120 and 250 mg per

kg groups allowed to survive for an additional 3 weeks, without aspirin; but in the 250 mg per kg group, some healed chronic ulcers were identified. Despite the extensive morphological damage at the end of treatment, the only observed biochemical change was an increase in sialic acid output in the 250 mg per kg group. The investigation has established a model of aspirin-induced chronic gastric ulcer. The model may have a clinical counterpart in the chronic gastric ulcers which develop in association with habitual ingestion of aspirin-containing preparations. [Sprague-Dawley rats]

CARDIOVASCULAR SYSTEM

5. Boorman, G. A. (Institute for Experimental Gerontology, Organization for Health Research TNO, 151 Lange Kleiweg, Rijswijk (TNO, Netherlands), C. Zurcher, C. F. Hollander, and V. J. Feron. 1973. *Naturally occurring endocardial disease in the rat*. Arch. Pathol. 96:39-45. (Copyright 1973, American Medical Association)

Forty cases of a spontaneous endocardial disease occurring in three different rat strains are described. The incidence varied from 1% to 7% and had a tendency to increase with age. In one strain, predominantly males were affected, and, in another strain, mostly females were affected.

The lesion consisted of a proliferation of fibroblastlike cells within the endocardium and was usually restricted to or was more severe in the left ventricle. In six cases, large tumorlike masses were found.

This lesion has some features in common with the endocardial disease in man reported by Davies, and apparently cases in the rat have not been reported before. As in man, the cause or pathogenesis is as yet unknown. [CIVO, WAG/Rij inbred, and BN/Rij rat strains]

6. Chesney, C. F. (Department of Pathology, University of Wisconsin Medical School and the Regional Primate Research Center, University of Wisconsin, Madison 53706), and J. R. Allen. 1973. *Monocrotaline induced pulmonary vascular lesions in non-human primates*. Cardiovasc. Res. 7:508-518.

Alterations in the pulmonary vasculature of infant *Macaca arctoides* (stumptail monkeys) were induced by subcutaneous injection of the toxic pyrrolizidine alkaloid, monocrotaline. At necropsy these animals exhibited myocardial hypertrophy and a marked dilatation of the right ventricle. Light microscopically, partial to complete obliteration of pulmonary vessels due to enlargement of the endothelium and hypertrophy of the medial musculature, was observed. Ultrastructural features of the lung included the presence of numerous fibrin and platelet thrombi within interalveolar

capillaries and swelling of endothelial cells. Lesions observed in human infants with vasoconstrictive primary pulmonary hypertension correlate closely with those seen in this study, and it is suggested that monocrotaline-intoxicated non-human primates provide a suitable experimental model with which to study this malady.

7. Koletsky, S. (Department of Pathology, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106). 1973. *Obese spontaneously hypertensive rats—A model for study of atherosclerosis*. Exp. Mol. Pathol. 19:53-60.

Probably as the result of a mutation a new type of spontaneously hypertensive rat has been obtained which, in addition to elevated blood pressure, exhibits genetic obesity, endogenous hyperlipemia, endocrine gland malfunction and metabolic abnormalities and develops premature atherosclerosis. The animals also showed marked and persistent albuminuria which appears at an early age and is often associated later in life with a progressive nephrosclerosis which leads to azotemia or uremia.

The animals have been designated as obese spontaneously hypertensive rats. They may provide a useful model to explore the relation of endocrine and metabolic abnormality of obesity and also for investigating the pathogenesis of atherosclerosis, especially in regard to the roles of high blood pressure and hyperlipemia. In addition the animal may also be of value in the study of human type 4 hyperlipoproteinemia of which it appears to be an experimental analog.

8. Maneche, H. C. (Departments of Pathology and Cardiology, McGill University, Montreal, Quebec, Canada), S. P. Woodhouse, P. F. Elson, and G. A. Klassen. 1973. *Coronary artery lesions in Atlantic salmon (Salmo salar)*. Exp. Mol. Pathol. 17:247-280.

One hundred and fifteen hearts and dorsal aortas were studied in anesthetized or moribund salmon for presence of histological alterations associated with spawning and changing environmental conditions. The control group consisted of 26 fish hatched and raised under experimental and controlled conditions. The study group included 61 prespawners and 23 postspawners. The lesions observed were divided into three grades in increasing order of severity. They consisted of focal or diffuse intimal proliferation of cells resembling smooth muscle cells and frequent alteration of the underlying elastica. The changes were more frequently seen in larger branches of coronary arteries, arterial conus, and atrioventricular sulcus regions. Both the relative incidence and severity of lesions appeared greater in prespawners as compared to postspawners. This study indicates a high incidence of coronary lesions in spawning Atlantic salmon. In addition, the severity of the lesions appeared reduced in postspawners exposed to prolonged starvation. It is suggested that the Atlantic salmon

with its exposure to varying environmental conditions may be a useful model to study the epidemiology of coronary artery disease.

9. Manning, P. J. (Sinclair Comparative Medicine Research Farm, Columbia, Mo. 65201), S. S. Lee, and W. K. Yamanaka. 1974. *Coronary lipophyalinosis. Dietary induction in guinea pigs.* *Atherosclerosis* 20:437-445.

Male guinea pigs were fed for 9 to 16 weeks an atherogenic diet containing 1% cholesterol with either 10% butter or 10% corn oil. The intramyocardial arteries of 25 of 31 experimental guinea pigs had a stenotic to occlusive, acellular to hypocellular intimal lesion appearing similar to hyalin and rich in lipid. Histochemically the lipohyalin contained cholesterol, neutral lipids and fibrinoid. The apparent acellular character of lipohyalin, its location in small intramyocardial arteries and renal arterioles and its possible thrombogenic origin are unique characteristics which suggest that the guinea pig would be a useful model to study morphologically and histochemically similar lesions in man.

10. Mersereau, W. A., S. Moore (Department of Pathology, McMaster University Medical Centre, Hamilton, Ontario, Canada), and H. Fernandez. 1972. *Renal renin in experimental nephrosclerosis.* *J. Pathol.* 108:319-327.

Hypertension and a lesion resembling human arteriolar nephrosclerosis were produced in rabbits by placing an embolic source in the thoracic aorta.

In the acute stage of the disease (8-15 days), an increase in renal, arteriolar, renin granules was demonstrated by thioflavin-T stain. Renal renin rose from a control mean of 178.5 to 395.2 units per g kidney. At 5 wk, there was a marked extension of the arteriolar granularity, from the afferent arterioles to the intertubular arterioles, in areas of atrophy produced by embolism. The mean renal renin was markedly elevated, at 555.3 units per g kidney. At 3 mth, all animals showed less than normal renin granularity and had subnormal renal renin, 86.4 units per g kidney. The persistence of at least a 20% increase in mean blood pressure, in 25 of the 35 animals for 3 mth, without histological or assay evidence for increased renal renin, suggests that in the chronic phase of this disease the renin-angiotensin system may not be responsible for maintaining the hypertensive state.

11. Satava, R. M. (c/o Section of Publications, Mayo Clinic, 200 First Street S.W., Rochester, Minn. 55901), and D. C. McGoon. 1974. *A model for cardiogenic shock by coronary artery microembolization in calves.* *Surgery* 76:454-460.

A model for severe cardiogenic shock was produced by se-

lective microembolization of the left coronary artery in calves. Criteria were established for shock so severe that death routinely followed within one half hour. A review of the literature and a critique of previous models are presented. Although requiring close monitoring and several precautions, this model permits assessment of various cardiac-assist devices with respect to their ability to support life.

12. Stier, F. M. (Department of Surgery and Medicine, University of North Carolina School of Medicine, Chapel Hill 27514), J. W. Woods, and L. K. Dahl. 1973. *Contraceptive steroids and hypertension: An experimental model.* *Proc. Soc. Exp. Biol. Med.* 143:561-564.

The effect of contraceptive steroids (CS) on a strain of rats genetically predisposed to develop hypertension from ingestion of an excess of NaCl has been examined. Rats given CS grew more slowly and had a lower weight regardless of salt intake. CS enhanced the hypertension of rats receiving the high-salt diet. CS had no effect on survival but salt intake did. This model offers the opportunity of studying the mechanism by which gonadal steroids enhance hypertension.

EAR

13. Davis, G. L. (Departments of Pathology and Laboratory Medicine and Otolaryngology, The Jewish Hospital of St. Louis and Washington University School of Medicine, St. Louis, Mo. 63110), and M. Strauss. 1973. *Viral disease of the labyrinth. II. An experimental model using mouse cytomegalovirus.* *Ann. Otol. Rhinol. Laryngol.* 82:584-594.

Investigation of the routes of infection of viral labyrinthitis was undertaken using mouse cytomegalovirus (CMV) and CMV-free Swiss-Webster mice. Intraperitoneal and intranasal inoculation caused no CMV infection of the ears or central nervous system. Intraperitoneal inoculation of pregnant mice yielded no evidence of fetal infection. Intracerebral inoculation of newborn mice resulted in viral infection of the ear by extension: (1) from the arachnoid into cochlear periotic connective tissue via the cochlear aqueduct and (2) along the perineurium of the acoustic nerve into the modiolus. There were neither changes in the stria vascularis nor endolymphatic labyrinth in spite of vasculitis and viremia. This experimental labyrinthitis resembles that found in human temporal bones infected with herpes zoster rather than the endolymphatic labyrinthitis seen in rubella, rubeola, mumps, and cytomegalovirus. The chronic effects of the mouse CMV labyrinthitis are under study.

ENDOCRINE SYSTEM

14. Dunson, W. A. (Department of Biology and Poultry Science, Pennsylvania State University, University Park 16802), E. G. Buss, W. H. Sawyer, and H. W. Sokol. 1972. *Hereditary polydipsia and polyuria in chickens*. *Am. J. Physiol.* 222(5):1167-1176.

Hereditary polydipsia and polyuria (diabetes insipidus, DI) in an inbred strain of chickens (Penn State strain) was studied in an effort to determine the cause of the disorder. These chickens show a variable but high degree of polyuria and polydipsia, and a low cloacal fluid osmotic pressure and Na concentration. When on water ad lib., plasma concentration was normal or slightly above normal and remained so after restriction of water intake to 200 ml/day or 5 months. During short-term (15 days) restriction of drinking to 100 ml/day, most polydipsic and normal birds maintained normal body weights and plasma Na concentrations. On 50 ml/day drinking water, both types of birds lost about 0.6% body wt/day and plasma Na levels increased. When denied access to drinking water, normal and polydipsic birds lost weight at the rate of about 2.2%/day. Antidiuretic activity of the DI neurohypophysis was reduced, but there was no change in pituitary oxytocic activity or in antidiuretic activity of the hypothalamus. Aldehyde-fuchsin-stained material in the DI neurohypophysis was normal or subnormal. The nuclei in hypothalamic supraoptic neurons of DI birds placed on restricted water intake (200 ml/day) for 4 months were enlarged. Short-term intramuscular injection of as much as 153 U of vasopressin tannate in oil had no effect on drinking or on the volume or concentration of the cloacal fluid of DI birds. On saline drinking solutions (100, 150, 175, 200 mm NaCl), DI birds produced cloacal fluid of normal concentration. However, when offered solutions between 150 and 200 mm, the DI birds achieved this by reducing their intake and thus lost weight more rapidly than normal. The lack of a normal response to drinking of hyperosmotic NaCl solutions and to injection of exogenous antidiuretic hormones suggests a defect resembling hereditary nephrogenic diabetes insipidus. However, the polydipsic birds show a remarkable resistance to dehydration not characteristic of nephrogenic DI in mammals. This may indicate that the manifestations of DI in chickens are less severe than in mammals. However, other possible causes of polyuria, especially primary polydipsia, cannot be ruled out.

15. Finklestein, J. Z. (Department of Pediatrics, University of California at Los Angeles-Harbor General Hospital, Torrance, Calif.), E. Arima, P. E. Byfield, J. E. Byfield, and E. W. Fonkalsrud. 1973. *Murine neuroblastoma: A model of human disease*. *Cancer Chemother. Rep. (Part 1)* 57:405-412.

The C1300 murine neuroblastoma system was evaluated as a model of human disease. Drug toxicity studies were car-

ried out in adult A/J mice. Cyclophosphamide, BCNU, and cytosine arabinoside prolonged the median lifespan of animals with palpable disease. Actinomycin D, methotrexate, 5-(3,3-dimethyl-1 triazeno)imidazole-4-carboxamide, and cyanocobalamin were inactive in the regimens used. The sensitivity of the murine neoplasm to cyclophosphamide correlates with clinical observations in children with active disease.

16. Wise, P. H. (Department of Medicine, Guy's Hospital Medical School, London S.E. 1, England), B. J. Weir, J. M. Hime, and E. Forrest. 1972. *The diabetic syndrome in the Tuco-tuco (Ctenomys talarum)*. *Diabetologia* 8:165-172.

A syndrome of diabetes, which appears to be dependent upon diet, is described in an Argentine rodent, the tuco-tuco. Hyperglycaemia and cataract are shown to be inversely related to age and associated with excess mortality. Pancreatic islet, renal glomerular and lens changes are similar to those of human diabetics. It is suggested that this species forms a useful model of human maturity onset diabetes.

EYE

17. Gaasterland, D. E. (Clinical Branch, Rm. 10N313, Bldg. 10, National Eye Institute, National Institutes of Health, Bethesda, Md. 20014), and C. Kupfer. 1974. *Experimental glaucoma in the rhesus monkey*. *Invest. Ophthalmol.* 13:455-457.

Repeated, circumferential argon laser photocoagulation of the trabecular meshwork area of the anterior chamber angle of normal Rhesus monkeys causes a sustained elevation of the intraocular pressure and marked reduction of the outflow facility. During the observation period of this study, cupping of the optic nervehead developed. Preliminary histopathologic examination revealed localized scarring of the anterior chamber angle structures. Retinal and optic nerve changes, similar to those seen in human chronic, open-angle glaucoma, were seen. The method to produce this experimental glaucoma is reported.

18. Herron, W. L., Jr. (Department of Ophthalmology, University of Florida, Gainesville 32601). 1974. *Retinal dystrophy in the pigmented rat*. *Invest. Ophthalmol.* 13(2):87-94.

The genetic pattern for obtaining a darkly pigmented Royal College of Surgeons' (RCS) rat is described. The rat dystrophy initially shows a build-up of rod outer segment material because the pigment epithelium does not phagocytize it. The progressive ophthalmoscopic appearance of the fundus of the pigmented dystrophic eye is described. The first abnormal finding is a lightening of the retinal appear-

ance. Thereafter, the choroid and pigment epithelium become obscured. Finally, as the accumulated old rod outer segment debris is removed, the retina thins and pigment clumping is observed. In some pigmented dystrophic rats, a zone of thinned retina with pigmentary changes can be seen to abruptly thicken to the white appearance which hides deep retinal and choroidal detail. Histologic evaluation of this zone shows that the difference is in the amount of remaining old rod outer segment debris. Autoradiography confirmed that the pink-eyed rat and the pigmented dystrophic rat both exhibit an inability of the pigment epithelium to remove their old rod outer segment material. Similarities between human retinitis pigmentosa and the dystrophic rat are noted.

19. Schwartz, J. N. (Department of Pathology, Duke University Medical Center, Durham, N.C. 27710), C. A. Daniels, J. C. Shivers, and G. K. Klintworth. 1974. *Experimental cytomegalovirus ophthalmitis*. *Am. J. Pathol.* 77:477-492.

Cytomegalovirus can produce a severe necrotizing chorioretinitis in patients on immunosuppressive therapy and infants born with congenital cytomegaloviral inclusion disease. To study the effect of cytomegalovirus on the eye, murine cytomegalovirus was injected into the eyes of non-immunosuppressed Swiss CD-1 weanling mice. The eyes were then prepared for virus titer, as well as light and electron microscopy at variable periods after inoculation (1 to 28 days). From days 2 to 6, the hallmarks of cytomegalovirus infection, intranuclear and intracytoplasmic viral inclusions, were evident within cytomegalic cells. The major site of reaction was in the uveal tract, where necrosis and inflammation were prominent. Viral particles budding through the nuclear membranes into the perinuclear cisternae and vacuoles with viral particles could be seen in the cytoplasm of infected cells. In lesions older than 2 weeks, only a mild mixed inflammatory infiltrate and fibrosis were observed. Morphologic alterations unaccompanied by inflammation occurred in the outer sensory retina overlying infected retinal pigment epithelial cells. Multiple necrotic foci with inclusion-bearing cells in the liver indicated the systemic spread of virus from the eye. The titer of virus recovered from the eye peaked at day 4 and then declined to low levels, but infectious virus could still be isolated at day 28, even though viral particles were not seen morphologically at or after day 14. Many of the alterations seen in the model resemble those found in the human cytomegaloviral ophthalmitis.

HEMATOPOIETIC SYSTEM

20. Manning, J. R. S. (California Primate Research Center, University of California, Davis 95616), and R. A.

Griesemer. 1974. *Spontaneous lymphoma of the non-human primate*. *Lab. Anim. Sci.* 24:204-210.

A review of spontaneous lymphoma in the nonhuman primate revealed that 59 cases have developed in 8 different species in the past 4 years. A viral etiology is suspected for 2 lymphomas developing in owl monkeys, 6 in gibbon apes, and 44 in rhesus monkeys. Forty of the 44 cases in rhesus monkeys occurred in a single colony. A known oncogenic herpesvirus, *Herpesvirus saimiri*, was isolated from 1 of the owl monkeys. C-type RNA virus was isolated from lymphoma tissue of a gibbon ape. The occurrence of lymphoma in an adult rhesus and her offspring was discussed.

21. Morley, A. (Department of Medicine, University of Adelaide, Adelaide, South Australia 5000), and J. Blake. 1974. *An animal model of chronic aplastic marrow failure. I. Late marrow failure after busulfan*. *Blood* 44:49-56.

An animal model of chronic aplastic marrow failure was produced by administering busulfan to mice in high dosage for a prolonged period. Mice which survived 60 or more days following cessation of the drug appeared well: in 59% the blood was normal, and in 35% the marrow cellularity was within the normal range; those mice with evident abnormality in the blood and marrow showed only minimal cytopenia in the peripheral blood and moderate decreases in marrow cellularity. Nevertheless, by 240 days 80% of the mice had become ill and died. Sacrifice prior to death showed that aplasia of the marrow and cytopenia (most often pancytopenia) were present in the majority of mice. These syndromes of persistent mild marrow hypoplasia and late severe marrow failure, which followed busulfan, may be suitable experimental models for studying the late effects of myelotoxic agents and the syndrome of chronic aplastic marrow failure in man. [Swiss mice]

22. Perk, K. (National Cancer Institute, National Institutes of Health, Bethesda, Md. 20014), J. A. Torgersen, and M. A. Chirigos. 1974. *An animal model for meningeal leukemia*. *Int. J. Cancer* 13:863-866.

An experimental model of arachnoid leukemia has been developed from a transplantable guinea pig leukemia. The meningeal leukemia develops after chemotherapeutically induced primary remission. The histopathological pattern observed was similar to that seen in central nervous system involvement in childhood leukemia. [Guinea pig]

23. Pinkerton, P. H. (Department of Laboratory Haematology, Sunnybrook Medical Centre, 2075 Bayview Avenue, Toronto, Ontario, Canada), S. M. Fletch, P. J. Brueckner, and D. R. Miller. 1974. *Hereditary stomatocytosis with hemolytic anemia in the dog*. *Blood* 44:557-567.

An autosomal recessive mutant (symbol, *dan*) in the dog

causes chondrodysplastic dwarfism and mild anemia as pleiotropic effects. The anemia is characterized by stomatocytosis, macrocytosis, low MCHC, increased osmotic fragility, shortened red cell survival, reticulocytosis, erythroid hyperplasia, and increased iron turnover. Minor changes can be detected in the red cells of heterozygous carriers of the *dan* gene, but red cell survival is normal and chondrodysplasia is not present. Red cell sodium concentration and water content are increased in anemic dogs and to a lesser degree in carriers. Glutathione deficiency is present. The disorder described here resembles a number of human hemolytic anemias with stomatocytosis, glutathione deficiency, and disordered red cell cation and water content, and further study of the *dan* mutant, together with investigations of the hereditary human conditions, will elucidate the maintenance of normal red cell cation balance. [Alaskan malamute dogs]

24. Shen, S. M.-C., D. I. Feinstein, and S. I. Rapaport (Department of Medicine, University of Southern California School of Medicine, Los Angeles 90033). 1973. *The effects of injection of human factor VIII antibody into rabbits*. Blood 42:509-521.

Rabbits were injected with an immunoglobulin fraction of human serum containing a factor VIII antibody. Factor VIII levels fell abruptly, persisted below 10% of a rabbit plasma standard for 12 hr, and returned to normal by 120-168 hr. The factor VIII antigen-antibody reaction did not result in intravascular clotting as evaluated by kinetic studies with ¹²⁵I-fibrinogen. However, small falls in factor V and factor VII levels were observed over a 6-hr period after the injection. Platelets fell to about one-half of initial values within 15 min, rose to 80% of initial levels over 2 hr, and subsequently declined to 65%-70% of initial levels. WBC levels fell to below 20% of initial values 2 hr after the injection but returned to about 75% of initial values by 6 hr. Total hemolytic complement activity was unaffected. Animals made granulocytopenic with nitrogen mustard and animals with hereditary C₆' deficiency behaved similarly to normal animals. One may conclude that the injection of human factor VIII antibody into rabbits produces a rabbit model with impaired intrinsic coagulation suitable for studies of the mechanism of endotoxin-induced intravascular clotting.

MUSCULOSKELETAL SYSTEM

25. Gershuni-Gordon, D. H. (Orthopaedic Department Research Laboratory, "Asaf Harofe" Government Hospital, Zrifin, Israel), and A. Axer. 1974. *Synovitis of the hip joint—An experimental model in rabbits*. J. Bone Joint Surg. 56B:69-77.

1. Synovitis was induced in the hip joints of fifty-six rabbits by the intraarticular injection of surgical talc. The opposite hip joint and eleven suitable "sham" operations served as controls.

2. The results in the hips injected with talc were as follows. Widening of the medial joint space and sometimes acetabular changes were seen; enlargement of the femoral head and neck in two planes was found, with, in most cases, flattening of the superior aspect of the head; there was thickening of the joint cartilage and sometimes deformity of the capital epiphysis; and thickening of the cartilage was the main cause of the coxa magna, cervix magna, and ischium magnum.

3. The embryology, micro-anatomy and development of the hip joint is reviewed and attention is drawn to the configuration of the layers of germinal cartilage cells. The effect of an induced synovitis in producing hyperplasia of the joint cartilage, incongruity of the articulating surfaces and subsequent subluxation is discussed.

26. Moskowitz, R. W. (Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106), W. Davis, J. Sammarco, M. Martens, J. Baker, M. Mayor, A. H. Burstein, and V. H. Frankel. 1973. *Experimentally induced degenerative joint lesions following partial meniscectomy in the rabbit*. Arthritis Rheum. 16:397-405.

Degenerative lesions characterized by osteochondrophyte spur formation and cartilage degeneration were induced by partial meniscectomy in the rabbit knee. Cartilage degenerative lesions included ulceration, fissure and cyst formation, and diminished concentration of matrix protein-polysaccharide. Proliferation of chondrocytes represented efforts at repair. Osteophytes increased in size with time. Changes resembled certain components of degenerative joint disease. The partial meniscectomy animal may be useful in studies of osteoarthritis pathogenesis, pathology and treatment.

27. Smith, D. E. (Rheumatic Disease Group, Department of Medicine, University of California, San Francisco), P. G. James, J. Schachter, E. P. Engleman, and K. F. Meyer. 1973. *Experimental bedsonial arthritis*. Arthritis Rheum. 16(1):21-29.

A bedsonia isolated from the joint of a patient with Reiter's syndrome produced arthritis when injected into the knees of *Macaca mulatta* or New Zealand white rabbits. The monkeys developed an acute self-limited arthritis that resolved within 11 to 49 days. Symptoms were limited to the injected joints. Reinoculation of the same joints produced a similar arthritis, indicating that repeated exposure neither enhances nor diminishes clinical response. Repeated intra-urethral inoculation produced urethritis in one macaque, and the organism was recovered from the urethra. Infected rabbits developed a chronic arthritis. Bedsonial infection

and disease in the rabbit were disseminated from joint to eye and from joint to selected viscera. Viable multiplying organisms were essential to produce arthritis, and treatment with tetracycline before agent inoculation prevented disease. Bedsonial organisms other than those recovered from Reiter's syndrome also caused arthritis when injected into the knees of monkeys or rabbits.

NERVOUS SYSTEM

28. Ayers, M. M. (Department of Pathology, University of Melbourne, Melbourne, Australia), and R. McD. Anderson. 1973. *Onion bulb neuropathy in the trembler mouse: A model of hypertrophic interstitial neuropathy (Dejerine-Sottas) in man*. *Acta Neuropathol.* 25:54-70.

The trembler mouse is a spontaneous mutant showing dominant inheritance. Clinical symptoms become manifest from 10 to 14 days of age as an action tremor affecting the head, neck and limbs, convulsions which decrease with increasing age, and weakness and rigidity of the limbs. Histological examination revealed a normal central nervous system, and a peripheral onion bulb neuropathy similar to hypertrophic interstitial neuropathy in man. Peripheral nerves of 14 day old and adult affected and control animals were examined with the electron microscope. The young mice showed retardation of myelin development, generalized myelin degeneration and early onion bulb development. Adult animals presented a picture almost identical to hypertrophic interstitial neuropathy in man with hypomyelination, segmental demyelination and well-developed onion bulbs, and an increase in endoneurial and perineurial connective tissue.

This animal is presented as a valuable experimental model of hypertrophic interstitial neuropathy in man.

29. Denlinger, R. H. (Department of Veterinary Pathobiology, Ohio State University, Columbus, Ohio 43210), A. Koestner, and J. A. Swenberg. 1973. *An experimental model for selective production of neoplasms of the peripheral nervous system*. *Acta Neuropathol.* 23:219-228.

Ninety-three tumors of the peripheral nervous system (PNS) were produced in 30 male Fischer (CDF) rats following intravenous injection of 10 mg/kg of *N*-methyl *N*-nitrosourea (MNU) twice weekly for 9 weeks. The high susceptibility of CDF rats to an optimal dose of MNU provides a useful experimental model to study induction and pathogenesis of tumors of the PNS. In this model PNS tumors occur in a high percentage of animals, multiple PNS tumors are com-

mon, the sites of development are predictable, and the well-differentiated morphology is similar to the morphology of naturally occurring neurinomas of man and animals.

30. Fitzgerald, J. E., J. L. Schardein, and S. M. Kurtz (Department of Toxicology, Research and Development Division, Parke, Davis, and Company, 2800 Plymouth Road, Ann Arbor, Mich. 48106). 1974. *Spontaneous tumors of the nervous system in albino rats*. *J. Natl. Cancer Inst.* 52:265-273.

A retrospective review of necropsies of 7803 albino rats revealed 34 tumors originating in the brain or meninges for an overall incidence of 0.44%. In addition, 4 tumors of ganglion cell origin were found. The most frequent brain tumor was the astrocytoma. Other tumor types included oligodendroglioma, ependymoma, meningioma, ganglioneuroma, and optic nerve glioma. The tumors had a predilection for male rats and occurred at an average age of 17-18 months.

31. Grabow, J. D. (Mayo Clinic and Mayo Foundation, Rochester, Minn. 55901), G. M. Zurhein, R. J. Eckroade, P. E. Zollman, and R. P. Hanson. 1973. *Transmissible mink encephalopathy agent in squirrel monkeys. Serial electroencephalographic, clinical and pathologic studies*. *Neurology* 23:820-832.

Our study revealed that the squirrel monkey is an excellent model for serial EEG and clinical investigations of slow-virus disease. The EEG abnormalities precede clinical findings in TME-inoculated squirrel monkeys. The early involvement of synapses and the decrease in the number of neurons that occurs later may account for the decrease in voltage and frequency noted on the EEG tracings. Similar EEG (including periodic complexes), clinical and pathologic findings have been observed in Jakob-Creutzfeldt disease—a human slow-virus disorder. Our data indicate that the TME agent behaves in primates as Jakob-Creutzfeldt disease agent behaves in man and therefore suggest that the agents may be closely related.

32. Marks, M. I. (Department of Pediatrics, McGill University, McGill University-Montreal Children's Hospital Research Institute, Montreal, Quebec, Canada), and S. Carpenter. 1973. *Experimental animal model for encephalitis due to herpes simplex virus*. *J. Infect. Dis.* 128:331-334. (Copyright 1973 by the University of Chicago Press)

Investigations of the pathophysiology and therapy of encephalitis due to herpes simplex virus have been hampered by the lack of appropriate experimental animal models, the relatively small number of human cases, and the variable spectrum of clinical disease. An animal model was developed in the adult hooded rat for encephalitis caused by type I herpes simplex virus; the disease is reproducible, restricted to the brain, and has histopathologic features similar to

those produced by the disease in humans. Two hundred twenty-two animals, including appropriate controls, were studied. The model provides a clear mortality endpoint with reproducible results and an inoculum-dependent response. Infection is characterized by a two- to four-day period of incubation followed by signs of infection of the central nervous system; the average survival time of infected rats is seven days.

33. Rauch, H. C. (Department of Medical Microbiology, Stanford University School of Medicine, Stanford, Calif. 99035), E. R. Einstein, and J. Csejtey. 1973. *Enzymatic degradation of myelin basic protein in central nervous system lesions of monkeys with experimental allergic encephalomyelitis*. *Neurobiology* 3:195-205.

Experimental allergic encephalomyelitis (EAE), considered a model for multiple sclerosis (MS), was induced in rhesus monkeys with modified myelin basic protein (HNB) (which was found to be encephalitogenic) and with homologous white matter. Macroscopic lesions, visibly distinguished by evidence of necrosis, were removed from the brain and studied histologically and biochemically. An increase was observed in acid proteinase in parallel with a decrease in the basic protein of the myelin. It is presumed that the acid proteinase derives from the inflammatory cells (mononuclear, polymorphonuclear, and eosinophilic) found in abundance around the blood vessels in the affected area of the white matter, and that the decrease (and, in some cases, near disappearance) of the basic protein is due to the degradative action of this enzyme on the basic protein, resulting in the loss of myelin. Thus, the present study suggests that the breakdown of myelin in both EAE and MS may be related to increased proteolysis, reported before in MS and demonstrated here in EAE.

34. Woodard, J. C. (Department of Pathology, College of Medicine, University of Florida, Gainesville 32610), G. H. Collins, and J. R. Hessler. 1974. *Feline hereditary neuroaxonal dystrophy*. *Am. J. Pathol.* 74:551-556.

A newly recognized neurologic disorder of cats is described. It is characterized clinically by an abnormal coat color and development of progressive ataxia during infancy. Breeding experiments indicate that the disease is inherited in an autosomal recessive manner. Pathologically, neurologic lesions closely resemble those described in infantile neuroaxonal dystrophy of children. The most prominent microscopic alterations were marked ballooning of nerve cell processes within specific regions of the brain stem and atrophy of the cerebellar vermis. Ultrastructural studies demonstrated that dystrophic axons contained electron-dense flocculent material, multilaminated membrane-bound osmiophilic bodies and filaments. Examination of the inner ears revealed depletion of neurons in the spiral

ganglia and homogeneous eosinophilic bodies within the spiral ganglia, nerve fiber tracts and organ of Corti. The concept that the disease represents an inborn error of metabolism was supported by finding axonal dystrophy in neonates prior to development of cerebellar atrophy or recognition of clinical symptoms.

RESPIRATORY SYSTEM

35. Brentjens, J. R. (Departments of Microbiology and Pathology, State University of New York at Buffalo, Buffalo 14214), D. W. O'Connell, I. B. Pawlawski, K. C. Hsu, and G. A. Andres. 1974. *Experimental immune complex disease of the lung. The pathogenesis of a laboratory model resembling certain human interstitial lung diseases*. *J. Exp. Med.* 140:105-125.

Membranous and/or proliferative pneumonitis, similar in certain features to human interstitial pneumonitis, developed in rabbits making hyperactive antibody response to daily injections of bovine serum albumin (BSA) administered in multiple large doses sufficient to maintain the state of relative antigen-antibody equivalence. The pulmonary lesions were associated with deposition in alveolar capillary walls and interstitium of antigen, host globulin, and complement, presumably in immune complexes. In some rabbits chronic interstitial pneumonitis, characterized by thickening of alveolar capillary walls, interstitial fibrosis and deposition of fibrinogen was observed.

The production of immune complex pneumonitis seems to depend on the degree of the antibody response because rabbits developing chronic serum sickness with low doses of BSA, rabbits with acute serum sickness as well as non-responders, showed no pulmonary alterations. This observation is comparable to that described by Dixon in his studies on experimental immune complex glomerulonephritis. It is conceivable that the pulmonary pathology shown here is produced by formation of larger amounts of complexes which may persist longer at critical levels in the circulation than in rabbits immunized with a single daily injection of BSA.

In conclusion this study suggests: first, that experimental chronic serum sickness can be used as a model, not only for glomerulonephritis, but also for experimental systemic disease, comparable to human systemic diseases produced by circulating antigen-antibody complexes; and second, that the pathogenesis proposed here offers an alternative to using antilung basement membrane pneumonitis for the experimental approach to the study of human lung immunopathology.

36. Kasdon, E. J. (Department of Pathology, Beth Israel Hospital, 330 Brookline Ave., Boston, Mass. 02215),

and S. F. Schlossman. 1973. *An experimental model of pulmonary arterial granulomatous inflammation*. Am. J. Pathol. 71:365-374.

An experimental method to investigate pulmonary granuloma formation in the guinea pig was established. Animals sensitized to human serum albumin (HSA) and challenged intravenously with HSA covalently linked to Sepharose 2B beads developed a specific granulomatous response. This intense pulmonary arterial, focally necrotizing, but mainly granulomatous inflammatory reaction developed 5 to 7 days after the administration of the HSA-bead conjugate. Unsensitized animals did not show such extensive inflammation, but rather exhibited a typical foreign body reaction to the bead. In both the experimental and control groups, the inflammatory response was indistinguishable at 14 and 21 days. Thus the initial acute inflammatory reaction was seen only in specifically sensitized animals. On the other hand, HSA alone produced no demonstrable inflammatory lesion. These observations suggest that locally retained antigen may trigger antigen-specific T (thymus-dependent) lymphocytes to release mediators which contribute to granuloma formation.

37. Mercola, K. E., and J. E. Hagadorn (Custom Reagent Lab. Inc., 7270 Clairemont Mesa Boulevard, San Diego, Calif. 92111). 1973. *Complement-dependent acute immunologic lung injury in an experimental model resembling Goodpasture's Syndrome*. Exp. Mol. Pathol. 19:230-240.

Rabbit antiserum to rat lung injected into normal rats elicits acute pulmonary lesions characterized by alveolar and perivascular hemorrhage and edema resembling the acute lung injury in patients with Goodpasture's Syndrome. Within 1 hr after injection of antilung antibodies, rat serum complement activity decreases significantly. Fluorescent anti-rabbit IgG and fluorescent anti-rat C3 stain alveolar septa and glomeruli in a linear membrane-like pattern suggesting localization of IgG on either basement membranes or endothelial cells of alveolar capillaries and on basement membranes of glomerular capillaries. Anti-lung antibodies are not pathogenic when given to rats de complemented with a purified cobra venom factor. This finding supports the hypothesis that immunologic lung injury requires localization of anti-lung antibodies followed by activation and fixation of complement at the site of impending injury.

The acute lung lesions elicited by sublethal doses of anti-lung serum are transient, disappearing within 24 hr. Four days after injection, lung-localizing heterologous IgG, but not host C3, is demonstrable immunohistochemically in target organs. This is an experimental counterpart of some of the reported immunohistochemical studies of lung tissue specimens from patients with Goodpasture's Syndrome, wherein the tissue localization of C3 was not observed, suggesting that C3 may be involved only at certain stages of the disease. [CD rats/Charles River]

38. Stenback, F. (The Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha 68105). 1973. *Glandular tumors of the nasal cavity induced by diethylnitrosamine Syrian golden hamsters*. J. Natl. Cancer Inst. 50:895-901.

The morphologic pattern and biologic characteristics of diethylnitrosamine (DEN)-induced glandular tumors of the nasal cavity in hamsters were studied. DEN-induced papillary tumors of the surface epithelium, and acinar tumors of the submucous glands. Adenomas, and ultimately papillary adenocarcinomas with squamous metaplasia, were preceded by papillary hyperplasia of the respiratory epithelium. Most of the acinar tumors in the anterior nasal cavity were weakly mucin-producing, in contrast to those in the posterior part with mucosa covered by olfactory epithelium, which were strongly mucin-producing. The tubular type, a subtype, was composed of cylindrical cells with little mucin production. These findings show that the DEN-induced tumors originating from the surface epithelium and the submucous gland in Syrian golden hamsters are in many respects similar to such tumors in man.

SKIN AND ADNEXA

39. Blakely, G. A., B. Lourie (Viral Exanthems Unit, Center for Disease Control, Atlanta, Ga. 30333), W. G. Morton, H. H. Evans, and A. F. Kaufmann. 1973. *A varicella-like disease in macaque monkeys*. J. Infect. Dis. 127(6):617-625. (Copyright 1973 by the University of Chicago Press)

A cell-associated herpesvirus was isolated from macaque monkeys suffering from a disease similar to varicella. The agent can be differentiated from *Herpesvirus varicellae* by its distinct CPE, its inability to replicate well in human fibroblasts, and its antigenic composition. The virus appears distinct from herpesviruses previously isolated from monkeys with vesicular exanthems in its characteristics of growth in tissue culture and in the low case-fatality ratio of the associated disease. Epidemiologic evidence indicated that the virus originated in Southeast Asia. The disease may serve as a model in animals for study of human infections with *Herpesvirus varicellae*.

40. Packchianian, A. (Department of Microbiology, University of Texas Medical Branch, Galveston). 1973. *Experimental cutaneous leishmaniasis in the hairless mouse, Mus musculus*. Tex. Rep. Biol. Med. 31(1): 108. (Abstr.)

Cutaneous leishmaniasis was produced in 46 hairless mice (*Mus musculus*) with cultures of *Leishmania tropica* isolated from an exogenous human case in Texas. The mice were inoculated intradermally and subcutaneously in five areas

of the dorsal side of the body (head, center of the back, sides and on the base of the tail). The early lesions were small, red papules appearing within 1 to 2 months following inoculation, which gradually enlarged into nodules, measuring 10 to 20 mm in diameter. The edges of the lesions were thicker and pink; the adjacent skin showed no visible reaction. Some of the lesions ulcerated; the center of the ulcer was either moist or covered with dry crust. In a few cases the lesions were very extensive and merged with other lesions, covering nearly two-thirds of the dorsal body surface. Smears for the edges of the lesions were positive for the aflagellar form of *L. tropica*, which produced infections when inoculated into other hairless mice and were readily cultured *in vitro* on NNP-2 medium in the presence of suitable antibiotics.

Although the mice were inoculated intradermally with *L. tropica*, at times the animals had generalized infection in addition to dermal leishmaniasis. This was proved by positive blood culture tests for flagellates and by demonstration of the aflagellar form of *L. tropica* in various organs such as the liver, spleen, lymph nodes, etc. In three mice spontaneous recovery of the skin lesions occurred. The remaining mice were kept under observation for 200-300 days before they were sacrificed or died from fulminating infection. Most typical and extensive lesions were photographed, and at the autopsy histological sections of the skin and organs were made and examined. The results of this investigation have demonstrated that the hairless mouse (*Mus musculus*) is an ideal animal for studying experimental cutaneous leishmaniasis.

URINARY SYSTEM

41. Boorman, G. A. (Institute for Experimental Gerontology, Organization for Health Research TNO, 151 Lange Kleiweg, Rijswijk (ZH), the Netherlands), and C. F. Hollander. 1974. *High incidence of spontaneous urinary bladder and ureter tumors in the Brown Norway rat*. J. Natl. Cancer Inst. 52:1005-1008.

The incidence of spontaneous urinary bladder and ureter tumors was unusually high in the Brown Norway (BN/BiRij) rat. Tumors of the bladder epithelium were found in 28% of the males and 2% of the females; 20% of the females and 6% of the males had ureter tumors. Most bladder neoplasms were papillary tumors covered by a thickened and moderately pleomorphic transitional epithelium. Many of the ureter tumors were squamous cell carcinomas with marked keratinization. Metastasis occurred in 4 rats with ureter tumors and 1 rat with bladder tumor. Another rat strain kept at our institute at the same time under identical conditions did not develop these tumors. Preliminary data suggest a

correlation between the occurrence of tumors and the urinary calculi frequently found in this strain. The Brown Norway rat may thus be a useful animal model for the study of urinary bladder tumors.

42. Essner, E. (Division of Cytology, Sloan-Kettering Institute for Cancer Research, New York, N.Y. 10021), and C. Oliver. 1973. *A hereditary alteration in kidneys of mice with Chediak-Higashi syndrome*. Am. J. Pathol. 73(1):217-228.

The beige mouse is considered to be a homologue of Chediak-Higashi syndrome (CHS). Cytochemical and electron microscopic studies have revealed an inherited lesion in the kidneys of these mice. The alteration was confined to the distal segments (S3) of the proximal tubules and was characterized by the accumulation of numerous massive polysaccharide-rich granules. These granules were reactive for acid phosphatase and β -glucuronidase activities and were therefore considered to be lysosomes. Small numbers of lymphocytes were also observed in the perivascular spaces and within the tubules of the S3 segment. The fine structure of S3 cells was also markedly altered. In addition to the massive lysosomes, dense material was found associated with the brush border and was present in pinocytotic vesicles at the base of the brush border and between basal invaginations of the plasma membranes. Despite these changes, reabsorption of exogenous peroxidase by S3 cells appeared to be normal. The presence of a congenital defect in the kidney of the beige mouse appears to provide a useful model for studying the morphology and function of the S3 region of the nephron.

43. Filmer, R. B. (Department of Urology and Pathology, Northwestern University Medical School, Chicago, Ill. 60611), F. A. Carone, R. G. Rowland, and J. R. Babcock. 1973. *Adrenal corticosteroid-induced renal cystic disease in the newborn hamster*. Am. J. Pathol. 72:461-472.

A new model of renal cystic disease was developed in newborn Syrian hamsters by the repeated injection of 9-fluoroprednisolone acetate (9-FPA), a long-acting adrenal corticosteroid. Kidneys harvested from the 10th to 14th day of age showed diffuse cystic dilatation of nearly all cortical convoluted tubules. Microdissection revealed that cystic changes primarily involved proximal convoluted tubules and, to a lesser degree, the distal tubules. Electron microscopy showed immaturity of development and varying degrees of degeneration of the cells of the proximal convoluted tubule. Intraluminal obstruction was not detected and, therefore, could not account for the cystic changes. Analysis of electrolytes in serum and selected tissues showed a significant reduction in potassium and sodium of serum, and significant depletion of potassium, magnesium and calcium in the skeletal muscle. Thus, there was no direct rela-

tionship between an electrolyte deficiency and the cystic changes.

44. Granoff, A. (Laboratories of Virology and Immunology, St. Jude Children's Research Hospital, Memphis, Tenn. 38101). 1973. *Herpesvirus and the Lucké tumor*. *Cancer Res.* 33:1431-1433.

Rana pipiens is host to a renal adenocarcinoma (Lucké tumor) that occurs with high frequency in a wild heterogeneous animal population. There is a relationship between temperature and the presence or absence of herpesvirus in tumor cells. Tumor cells of frogs either in hibernation or maintained at low temperature (4 to 9°) in the laboratory contain intranuclear inclusion bodies (Cowdry type A) and herpesvirus. In contrast, neither inclusions nor virus are found in tumor cells of frogs captured in the spring or summer or maintained in the laboratory at 20 to 25°. Lucké tumors can be induced in developing frog embryos by cell-free tumor extracts containing herpesvirus or by ascitic fluid containing this virus. A number of cell cultures (from insect to mammalian) have been tested for susceptibility to the Lucké tumor herpesvirus, but none has been found that will support multiplication of the virus. A number of other viruses have been isolated, including a herpesvirus distinct from the one seen in tumor cells, but none of them induce tumors.

The Lucké tumor provides an opportunity to study the natural history of a high-frequency, spontaneously occurring viral tumor and offers the additional opportunities of a broad range of experimental design not possible with other virus tumor systems. Significant advances await the isolation and propagation of the etiological agent in tissue culture. When this is accomplished, this experimental model may provide new and relevant information on viral carcinogenesis in humans.

45. Miller, T. E. (Department of Medicine, Auckland Hospital, Park Road, Auckland, New Zealand), and K. B. Robinson. 1973. *Experimental pyelonephritis: A new method for inducing pyelonephritis in the rat*. *J. Infect. Dis.* 127(3):307-310. (Copyright 1973 by the University of Chicago Press)

Induction of renal infection with *Escherichia coli* has been a problem in the investigation of experimental pyelonephritis. A consistent and reproducible infection was induced in the rat by use of a micropipette that introduced bacteria directly into the kidney. The gross appearances and histopathologic changes were similar to those seen during the course of pyelonephritis in man and were confined to the sites of inoculation. Bacteria persisted for extended periods in the kidney, but in contrast to other reports, infection was not confined to the medullary region. This model appears to have advantages over other models available and permits the establishment of a pyelonephritic process in prescribed areas of renal parenchyma.

46. Murphy, G. P. (Institute Director, Rosewell Park Memorial Institute, 666 Elm Street, Buffalo, N.Y. 14203), and W. J. Hrushesky. 1973. *A murine renal cell carcinoma*. *J. Natl. Cancer Inst.* 50:1013-1025.

A renal cell carcinoma animal model was developed and characterized in BALB/cCr mice. Although transplantable by different routes (intramuscular, intraperitoneal, intravenous, subcutaneous), it was most effective intrarenally. The tumor was transferred with as few as 1,000 live cells, but not by a tenfold concentration of a cell-free tumor extract. The renal tumor increased hematocrit and erythropoietin, but did not consistently alter other serum chemistries. Tumor growth was enhanced by testosterone or di-ethylstilbestrol but was unaffected by a progestational agent. The growth of the tumor was reproducible both in terms of the size and weight of the primary lesion, and in terms of the distribution and number of metastatic lesions. Survival interval and death from tumor were also consistent and reproducible.

47. Rashid, H. A. (Division of Urology, Department of Surgery and Department of Pathology, University of Rochester School of Medicine and Dentistry, Rochester, N.Y. 14642), C. A. Linke, T. Bonfiglio, and M. S. Wu. 1974. *Renal cortical necrosis: A model for the study of juxtamedullary nephron physiology*. *J. Appl. Physiol.* 37:228-234.

An experimental model for studying juxtamedullary nephron physiology was produced by inducing necrosis of the outer two-thirds of renal cortex by surface hyperthermia in the rabbit. Data were presented indicating that the model is histologically and functionally intact. The functional studies performed also revealed that: (1) under basal conditions the mean nephron GFR of juxtamedullary nephrons is significantly higher than that of cortical nephrons; (2) in dehydration, the mean nephron GFR of juxtamedullary nephrons is preserved, while that of cortical nephrons is significantly decreased; (3) saline loading increases the mean nephron GFR of both populations of nephrons, the increase being proportionately more in cortical nephrons; (4) the mean nephron Tm_g is higher in juxtamedullary nephrons than in cortical nephrons; and (5) the splay in glucose titration curves is probably due to the presence of these two heterogeneous populations of nephrons in the renal cortex.

48. Stavric, B. (Health Protection Branch, Department of National Health and Welfare, Ottawa, Canada), E. A. Nera, W. J. Johnson, and F. A. Salem. 1973. *Uric acid kidney stones induced in rats by oxonic acid, a uricase inhibitor*. *Invest. Urol.* 11:3-8.

Uric acid calculi were found in the kidneys of rats fed a diet containing potassium oxonate (5%) and uric acid (1%) for 10 months. The treated rats developed multiple kidney stones, hyperuricemia, hyperuricosuria, and elevated blood

urea nitrogen. Kidneys of treated animals were markedly affected, with distortion of the normal renal architecture by fibrosis and cystic formation. The oxonate-treated rat with renal uric acid calculi may serve as a useful animal model for a study of disease and disorders associated with uric acid kidney stones.

49. Texter, J. H. (McGuire Veterans Administration Hospital, and Department of Surgery, Urology Division, Medical College of Virginia, Richmond, Va.). 1973. *The isolated ureter. A model for study of ureteral rejection.* Urology II:244-248.

An animal model is demonstrated in which it is possible to study the histologic and functional characteristics of the isolated ureter. This is possible by means of a staged procedure and demonstrates that blood flow sufficient to maintain a viable ureter will develop from the bladder by 4 weeks following reimplantation. This isolated ureter, if not obstructed or dilated, will continue to produce normal action potentials and contractions when stimulated and will have normal histologic appearance when biopsied. This model is suggested as a means to investigate the problem of ureteral allograft rejection without the influence of renal rejection. [Dog]

NUTRITIONAL-METABOLIC DISEASES

50. Cuadrado, R. R. (Departments of Medical Technology and Health Sciences, Florida International University, Miami, Fla. 33144), and L. A. Bricker. 1973. *An abnormality of hepatic lipogenesis in a mutant strain of "acatalasemic" mice.* Biochim. Biophys. Acta 306: 168-172.

Previous work demonstrating a relationship between acatalasemia and hypolipidemia prompted the present investigation, in which an *in vitro* assessment of rates of sterol and fatty acid synthesis was undertaken. A mutant strain of mice harboring the acatalasemic defect was studied, together with normal control animals and mice heterozygous for the abnormality. Incubation of liver slices from homozygous animals with [¹⁴C] acetate demonstrated an approximately 80% mean depression in rates of incorporation of isotope into cholesterol (as digitonin-precipitable sterol) and *de novo* fatty acid, and less but still significant depression in heterozygotes. Formation of metabolic ¹⁴CO₂ was not significantly reduced by the presence of the acatalasemic defect. The data indicate that the hypolipidemia of acatalasemia is closely related to a diminished rate of lipogenesis in the liver of the affected animal.

51. Levin, E. Y. (Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Md. 21205),

and V. Flyger. 1973. *Erythropoietic porphyria of the fox squirrel* *Sciurus niger*. J. Clin. Invest. 52:96-105.

Uroporphyrin I is found in high concentration in the bones, teeth, blood, soft tissues, and urine of the fox squirrel, *Sciurus niger*. The concentration of uroporphyrin in fox squirrel spleen is much higher than in liver, kidney, or bone marrow, probably because of accumulation from phagocytosed red cells. Bleeding causes a marked increase in the uroporphyrin concentration of red cells and spleen, and a 3-8-fold increase in uroporphyrin excretion. Urinary excretion of δ -amino-levulinic acid and porphobilinogen is not greater in fox squirrels than in nonporphyric gray squirrels, *Sciurus carolinensis*, used as controls. In all these characteristics, as well as in the previously demonstrated deficiency of the enzyme uroporphyrinogen III cosynthetase in red cells, the physiological porphyria of fox squirrels resembles congenital erythropoietic porphyria, a hereditary disease of man and cattle. Fox squirrels differ in showing no evidence of cutaneous photosensitivity or hemolytic anemia.

Uroporphyrinogen III cosynthetase activity is present in fox squirrel bone marrow at 0.1 its concentration in gray squirrel marrow. The fox squirrel enzyme is much more unstable than the gray squirrel enzyme, which provides a possible explanation for its low activity and for the overproduction of uroporphyrin I. It is unlikely that the deficiency of cosynthetase is due to its inactivation by excessive amounts of uroporphyrinogen I synthetase, because activity of the latter enzyme is the same in blood from fox and gray squirrels.

Fox squirrel porphyria provides a convenient model for studies of pathogenesis of human congenital erythropoietic porphyria.

CANCER RESEARCH

52. Martin, M. S. (Lab. Med. Exp., Fac. Med., F-21000 Dijon, France), F. Martin, R. Michiels, H. Bastien, E. Justrabo, M. Bordes, and B. Viry. 1973. *An experimental model for cancer of the colon and rectum: Intestinal carcinoma induced in the rat by 1,2-dimethylhydrazine.* Digestion 8(1):22-34.

1,2-Dimethylhydrazine (DMH) was administered s.c. to a group of 20 inbred BD-IX rats at a dose of 15 mg/kg body weight, weekly for 7 months. Intestinal adenocarcinoma was found in all of the treated animals, often associated with hyperplastic or dysplastic lesions. The intestinal cancers gave metastases in 14 animals. The low incidence of extraintestinal malignancies, the relatively short induction time, and the similarity to human colorectal adenocarcinoma make the DMH-induced intestinal cancer a highly effective experimental model.

53. Maruyama, Y. (Department of Radiation Medicine, University of Kentucky, Lexington), T. Mariani, E. P. Engles, and R. A. Good. 1973. *Analogies between experimental and human lymphoma cutis*. *Cancer* 31: 1106-1113.

An experimental model system of cutaneous lymphoma has been developed in an inbred mouse system. This utilizes skin isografts from donors which received transplants earlier of a passage ascites lymphoma. Tumor develops in the graft site and follows a development pattern which shows many analogies with human *lymphoma cutis*.

BACTERIAL DISEASES

54. Storrs, E. E. (Gulf South Research Institute, New Iberia, La. 70560), G. P. Walsh, H. P. Burchfield, and C. H. Binford. 1974. *Leprosy in the armadillo: New model for biomedical research*. *Science* 183 (4127):851-852. (Copyright 1974 by the American Association for the Advancement of Science)

Eight of twenty armadillos (*Dasypus novemcinctus L.*) developed severe lepromatous leprosy 3 to 3.5 years after inoculation with viable *Mycobacterium leprae*. A total of 988 grams of lepromas containing an estimated 15 to 20 grams of leprosy bacilli has been harvested from these animals. The large amounts of material now available will permit in-depth studies of the biochemistry and metabolism of the leprosy bacillus, and the animal model should make possible definitive studies on the immunology, chemotherapy, and epidemiology of the disease.

PARASITIC DISEASES

55. Judge, D. M. (Department of Pathology, Pennsylvania State University College of Medicine, Milton S. Hershey Medical Center, Hershey 17033), J. T. La Croix, and P. L. Perine. 1974. *Experimental louse-borne relapsing fever in the grivet monkey, Cercopithecus aethiops. I. Clinical course*. *Am. J. Trop. Med. Hyg.* 23:957-961.

Fifteen grivet monkeys, *Cercopithecus aethiops*, were infected with an Ethiopian strain of *Borrelia recurrentis*, the causative agent of louse-borne relapsing fever. An initial spirochetemia occurred in all. Inactivity, fever, and leukocytosis accompanied the infections. Eight of the monkeys experienced 1 relapse and 1 monkey had 2 relapses. The relapses tended to be less severe than the initial infections. The only deaths, however, occurred in 2 of the 3 monkeys

with severe relapses. The clinical course of the experimental infection in grivet monkeys closely resembles that of natural infections in man.

56. Voller, A. (Nuffield Institute of Comparative Medicine, London School of Hygiene and Tropical Medicine, London, England), D. R. Davies, and M. S. R. Hutt. 1973. *Quartan malarial infections in Aotus trivirgatus with special reference to renal pathology*. *Brit. J. Exp. Pathol.* 54:457-468.

This paper describes the renal immunopathology of *Aotus trivirgatus* (owl monkeys) infected with *Plasmodium malariae* or *Plasmodium brasilianum*.

The glomerular changes in the acute infections are different from those of the chronic infections. In the acute group there was evidence of endothelial cell damage and there was an increase in mesangial cells and matrix. IgM deposition was prominent, with a mesangial distribution and fibrin occluded some glomerular capillaries. In the animals with chronic infections mesangio-capillary lesions of variable extent were seen. These were of the membranoproliferative type and were most marked in the animal which developed the nephrotic syndrome. The immunofluorescence patterns were not so consistent in the chronic cases but IgM or C3 deposition was shown in the glomeruli of most cases.

The glomerular pathology noted in the infected animals, particularly in the one which developed nephrotic syndrome, shows close similarities to that seen in human cases of nephrotic syndrome associated with quartan malarial infections.

57. Welde, B. T. (Department of Medical Zoology, Walter Reed Army Institute of Research, Washington, D.C. 20012), A. J. Johnson, J. S. Williams, and E. H. Sadun. 1972. *Experimental infection with Plasmodium falciparum in Aotus monkeys. I. Parasitologic, hematologic, and serum biochemical determinations*. *Am. J. Trop. Med. Hyg.* 21:260-271.

Aotus monkeys infected with the Camp strain of *Plasmodium falciparum* were studied with emphasis on hematologic, parasitologic and serum biochemical changes occurring during the course of infection. For most monkeys the infection was lethal, with survival times ranging from 4 to 18 days depending on the size of the inoculum. Decreases in red blood cell parameters occurred as the infection progressed, but were not accompanied by a pronounced reticulocyte response. Leucocyte levels appeared to be depressed early in the infection, but rose to high levels in some animals that survived for relatively long periods. This rise was accounted for by an increase in mononuclear leucocytes. Platelet levels were reduced to extremely low levels in most monkeys and were sometimes accompanied by hemorrhagic phenomena. Both serum transaminase and urea

nitrogen levels increased while glucose levels decreased. Usually a gradual decrease in total serum protein was accounted for by decreases of both albumin and gamma globulin. Aggregates of erythrocytes containing schizonts and large trophozoites were found throughout the vasculature and were especially prominent in impression smears of the heart and liver. Many aspects of *P. falciparum* infections in *Aotus* were similar to infections with this plasmodium in man.

VIRAL DISEASES

58. Falk, L. A. (Departments of Microbiology, Rush-Presbyterian-St. Luke's and University of Illinois Medical Centers, Chicago, Ill. 60612). 1974. *Oncogenic DNA viruses of nonhuman primates: A review*. Lab. Anim. Sci. 24(Part II):182-192.

Studies of experimental infection of nonhuman primates with 4 members of the herpesvirus group were reviewed. *Herpesvirus saimiri* and *Herpesvirus ateles*, indigenous in *Saimiri sciureus* and *Ateles* sp., respectively, caused no recognized disease in the natural hosts but caused fatal, malignant lymphoproliferative disease in other nonhuman primate species. Epstein-Barr virus (EBV) and *Herpesvirus hominis* (HVH) of man have been implicated as the etiologic agents of several human neoplasms. Recent studies indicate that nonfatal EBV and HVH infections can be established in certain nonhuman primate species, and several features of these infections, i.e., antibody formation and shedding of virus, resemble latent infections in humans that are caused by EBV and HVH.

MISCELLANEOUS

59. Cohen, N. (New York University Medical Center, Institute of Environmental Medicine, Long Meadow Road, Tuxedo 10987), T. J. Kneip, D. H. Goldstein, and E. A. S. Muchmore. 1972. *The juvenile baboon as a model for studies of lead poisoning in children*. J. Med. Primatol. 1:142-155.

Lead toxicity has been studied in the juvenile baboon using both daily intravenous injections of lead chloride and ingestion of leaded paint and lead paint pigments. Approximate steady state blood lead concentrations of 0.9 and 0.08 mg% were obtained after one week of intravenous injections of either 5.0 and 0.5 mg of lead per day, respectively. The onset of clinical symptomatology was noted after only one week of 5.0 mg/day injections culminating in convulsions and blindness after 40 days.

The interrelationship of variations in the blood lead concentration, the clinical symptomatology of toxicity, and the biochemistry of heme formation, have been explored in response to controlled exposures to lead.

60. Fox, R. R. (The Jackson Laboratory, Bar Harbor, Maine 04609), and D. D. Crary. 1973. *Hereditary diaphragmatic hernia in the rabbit*. Genetics and pathology. J. Hered. 64:333-336.

Fifty-five cases of left diaphragmatic hernia were observed in three related strains of rabbits under normal colony conditions; this is suggestive of hereditary transmission. Associated abnormalities included hypoplasia of the ipsilateral lung and an increased incidence of ventricular septal defects. Death was attributable to respiratory insufficiency.

Genetic analysis suggests recessive inheritance. The condition is neither sex-limited nor sex-linked. We believe that two autosomal recessive genes are involved and have proposed the symbols *dh-1* and *dh-2* for the two genes that must both be present in homozygous condition for the development of diaphragmatic hernia in these rabbit strains.

61. Julian, M. (Service d'Anatomie pathologique, UER Medecine Rangueil, Toulouse, France), M. T. Pieraggi, and H. Bouissou. 1973. *Chronic lathyrisms. Experimental model of the ageing of the connective tissue in man*. Gerontologia 19:220-239.

In man, a parallelism between the subepidermic connective tissue and the vascular (aorta and coronary) changes with age was noted. The vascular state is reflected by the alterations of the papillary dermis-normal vessels correspond to a normal skin, whatever the patient's age; a damaged aorta and coronary artery correspond to a damaged skin. The study of the cutaneous fibroblasts during human ageing reveals a progressive lack of microfibrillar secretions and signs of cytoplasmic suffering. The more intense the vascular injury, the more pronounced is the cutaneous change. The detection of the subepidermic connective tissue injuries is particularly interesting for the diagnosis of early arteriosclerosis. Above age 45, vascular and cutaneous alterations increase. They are linked to normal ageing. This parallelism between vascular ageing and the degree of the cutaneous damage also appears in chronic lathyrisms.

In the rat, the administration of lathyrin toxic agents at weak and prolonged doses caused simultaneous alterations of aortic and cutaneous connective tissues in the eighth week of intoxication. In the aorta, a dislocation of the elastic framework, an increase of the interstitial tissue, a dedifferentiation of muscle cells are observed. In the skin, the papillary dermis presents a collagenic tissue with thin and fragmented bundles, a progressive disappearance of the elastic framework and alterations of the fibroblasts with signs of damage and a deficient secretion. In experimental lathyrisms, the changes of the elastic fibres are accompanied by a dedifferentiation of the muscular cells

of the aorta and an alteration of the cutaneous fibroblasts. These damages correspond to the modifications observed during ageing in man.

This experimentation reveals chronic lathyrisms as an experimental pattern of the human connective tissue ageing. This toxic agent causes connective tissue (fibrillary and cellular), aortic and cutaneous injuries rather similar to those observed in senescent man. [strain not identified]

62. Millar, M., and C. D. Graber (Department of Microbiology, Medical University of South Carolina, Charleston). 1974. *Experimental Mycoplasma hominis I infection in the pregnant rat*. Gynecol. Invest. 5:73-82.

Mycoplasma hominis I is known to spread systematically and to cause occasional illness in humans. *M. hominis I*, a common commensal in the vagina of women, was used in a rat model to create intravaginal infection as a means of elucidating a route toward possible teratogenesis. *M. hominis I* was cultured from the vagina of one of eleven rats 3 days following a series of intravaginal inoculations of the organism. Intraperitoneal injections of *M. hominis I* with Freund's complete adjuvant (FCA) in the same rat model caused an increasing humoral antibody response in all rats injected and produced a 17-day sepsis in one rat. Three pregnant rats inoculated intraperitoneally with *M. hominis I* in FCA yielded mycoplasma from uterine blood at 1 or 2 days; and 14 of 30 placentas and 8 of 30 fetuses. The route of mycoplasma infection to the fetus appears

to be from maternal blood to placenta and not via ruptured membranes.

63. Prieur, D. J. (Department of Veterinary Pathology, Washington State University, Pullman 99163), H. M. Olson, and D. M. Young. 1974. *Lysozyme deficiency—An inherited disorder of rabbits*. Am. J. Pathol. 77: 283-298.

A genetic disorder of rabbits consisting of a deficiency of the enzyme lysozyme is characterized. The condition appears to be inherited as an autosomal recessive trait. Most of the tissues of lysozyme-deficient rabbits including bone marrow, liver, lung, spleen and bone had levels of lysozyme which were 1% or less of the levels in the corresponding tissues of normal rabbits when measured with the lysoplate method. Levels of lysozyme in the kidney and serum were 6% of controls, but the thymus of the lysozyme-deficient rabbits had normal levels of the enzyme. All leukocytes of the lysozyme-deficient rabbits were negative for lysozyme when examined by a histobacterial technic. No morphologic lesions could be detected in any of the tissues of the lysozyme-deficient rabbits. Although several species of animals have been reported to be lysozyme deficient, this appears to be the first report of lysozyme deficiency occurring as a mutant condition. It is suggested that these mutant rabbits may be useful as a resource for experiments designed to delineate the biologic role of lysozyme.

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