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SELECTED ABSTRACTS ON ANIMAL MODELS
FOR BIOMEDICAL RESEARCH - III

Marilyn J. Anderson, et al

National Academy of Sciences-National Research
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Institute of Laboratory Animal Resources
National Research Council
National Academy of Sciences

Washington, D.C. 1974

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INSTITUTE OF LABORATORY ANIMAL RESOURCES

The Institute of Laboratory Animal Resources (ILAR) was founded in 1952 and is a working body of the Division of Biological Sciences within the Assembly of Life Sciences. It serves as a coordinating agency to disseminate information, survey existing and required resources, establish guidelines, promote education, hold conferences, and, generally, to upgrade laboratory animal resources.

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V

PREFACE

Animal models have become increasingly important as a means by which disease processes occurring in humans can be investigated. Many species of animals show syndromes bearing similarities to their human counterparts. Some specific strains or stocks have biologic and pathologic processes that can lead to better understanding of mechanisms in higher organisms. Thus, literature published on experimental animals is very important to investigators in many phases of study.

The great number and diversity of publications relevant to animal models in different biomedical disciplines make imperative the availability to investigators of a service that highlights the animal model concept. Selected Abstracts on Animal Models for Biomedical Research is intended to be a useful current-awareness tool for scientists engaged in such research. It serves as a vehicle through which current documentation of research utilizing animal models can be compiled, condensed, and disseminated periodically. Thanks are due to the publishers of the cited journals for granting permission to reprint authors' abstracts or summaries. Readers are encouraged to refer to the original articles for more thorough coverage to obtain additional information or data of special interest to them.

This publication is the third in a series designed to present abstracts or summaries of selected papers focusing on research utilizing animal models. The majority of abstracts in this volume appeared in biomedical literature during 1972, although some entries date from late 1971 or early 1973. Authors' abstracts have been reprinted from the original papers except for several in the behavior section that were written by Dr. Duane M. Rumbaugh of Georgia State University.

This edition of Selected Abstracts also contains an appendix featuring a list of 201 references relating to animal models for cardiovascular research (p. 49). A more comprehensive listing of reference citations on potential animal models for biomedical research appears in the ILAR News, a quarterly newsletter available from the Institute of Laboratory Animal Resources (ILAR).

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 and Genetic Stock Market Reports featured 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:

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SELECTED ABSTRACTS ON ANIMAL MODELS FOR BIOMEDICAL RESEARCH - III

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ALIMENTARY SYSTEM

1. Campbell, C. B. (Royal Brisbane Hospital, Herston Road, Brisbane 4029 Queensland, Australia), P. Burgess, S. A. Roberts, and R. H. Dowling. 1972. The use of Rhesus monkeys to study biliary secretion with an intact enterohepatic circulation. Aust. N. Z. J. Med. 2(1): 49-56.

An experimental model, originally designed to study the effects of controlled interruption of the enterohepatic circulation (EHC), has been extensively modified and adapted to study the applied physiology of an "intact" EHC of bile in Rhesus monkeys. Basically, the model consists of a surgically exteriorised extrahepatic biliary circuit in which an electronic stream splitter is interposed. This diverts every twentieth drop of bile which provides a representative sample for analysis while returning the remaining 95 percent of bile to the upper intestine. During these studies, the monkeys were comfortably restrained in specially designed chairs whose construction is described in detail. Animal maintenance and the design of the electronic stream splitter are also described. Analysis of the glycine:taurine and the dihydroxy:trihydroxy bile salt ratios both in gallbladder bile and in bile obtained with an "intact" EHC (by using the stream splitter), showed that the Rhesus monkey secretes a bile similar in composition to that of man. The bile salt:cholesterol:phospholipid ratios in monkey gallbladder bile (81:6:13) were also similar to those found in human bile, indicating that this animal is suitable for studies of cholesterol solubility in bile--a factor of major importance in gallstone pathogenesis. The model has been used to measure bile volume, bile salt secretion, pool size and the frequency of circulation of the bile salt pool. The diurnal variation in these variables has also been studied.

2. Kelly, M., D. G. Butler, and J. R. Hamilton (Research Institute of the Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada). 1972. Transmissible gastroenteritis in piglets: A model of infantile viral diarrhea. J. Pediat. 80(6):925-931.

Piglets infected with transmissible gastroenteritis virus, compared to matched-fed litter mates, had massive diarrhea characterized by increased quantities and concentrations of sodium, potassium, and chloride. Determinations of Na-K-ATPase in mucosal homogenates from small and large intestine revealed decreased activity of this enzyme in the upper small bowel. The data indicate that a defect in active sodium transport in this region may be an important factor in the pathogenesis of the diarrhea. Further studies using this model should help to define the mechanisms producing diarrhea in acute infantile gastroenteritis.

3. Levy, B. M. (The University of Texas Dental Science Institute at Houston), S. Drexler, and S. Bernick. 1972. Effect of aging on the marmoset periodontium. J. Oral. Path. 1:61-65.

The periodontium of old marmosets is characterized by a narrow, serrated cribriform plate of alveolar bone, a loss of tinctorial identification of Sharpey's fibers and a decrease in the cellular elements of the periodontal ligament. The attachment fibers are frequently calcified. In contrast to the blue periodontal ligament and pink alveolar bone in alcian blue-PAS stained sections of adult marmosets, the periodontal ligament stains pink and the alveolar bone deep red in old animals. Aged marmosets also have degenerative changes in the periodontal vasculature not seen in younger adults. The changes are similar to those described in aged human periodontal tissues.

4. Loux, J. J. (Department of Pharmacology, Cooper Labs, Cedar Knolls, New Jersey), R. Alioto, and S. L. Yankell. 1972. Effects of glucose and urea on dental deposit pH in dogs. J. Dent. Res. 51(6):1610-1613.

Preliminary experiments on the use of beagles to study dental deposits demonstrate that the responses of dog dental deposits to glucose and urea were not unlike those seen clinically and in primates. The activity after the application of 5 percent glucose indicates that microbial potential exists for the production of acid materials in an environment that is considered highly selective to urea. The similarity between the responses of the dental deposits in the clinical model primarily used for caries studies, and this animal model, primarily used for periodontal studies, indicates that dogs can serve as useful laboratory models in dental deposit research.

5. Misra, M. K. (Department of Surgery, University of Cambridge, Cambridge, England), F.-K. P'eng, A. Sayhoun, A. Kashii, C. D. Derry, T. Caridis, and M. Slapak. 1972. Acute hepatic coma: A canine model. Surgery 72(4):634-642.

A canine model for fulminating hepatic necrosis with hepatic coma has been described. Its main advantages are the fully ambulant state of the animal when the lesion is produced and the reproducibility together with the flexibility of the imposed damage. A number of tests of hepatocyte function, hemodynamic status, and metabolic, respiratory, and reticuloendothelial function have been measured and the results found to simulate those described clinically in fulminant hepatic coma.

6. Seibold, H. R. (Tulane University, Delta Regional Primate Research Center, Covington, Louisiana 70433), T. H. Clewe,

and R. H. Wolf. 1972. Enteropathy resembling sprue in nonhuman primates. *Lab. Anim. Sci.* 22(3):353-361.

An enteropathy resembling sprue was found in 3 *Cercopithecus talapoin* and a *Macaca arctoides*. Clinical signs were progressive weight loss and intermittent diarrhea. Steatorrhea was not observed, but the amount of fat in the diet was low compared with the average diet of people. Anatomical changes were partial to subtotal villous atrophy and glandular hyperplasia in the mucosa of the entire small intestine. The affection differed from idiopathic sprue in the severe involvement of the ileum which has not been reported in the latter disease. It also differed from tropical sprue in the absence of macrocytic anemia.

7. Spjut, H. J. (Department of Pathology, St. Luke's Hospital, Houston, Texas 77025). 1972. Newer concepts of cancer of the colon and rectum: Similarities between human and experimentally induced tumors of the large intestine. *Dis. Col. Rect.* 15(2):94-99.

Several points of similarity between human colorectal adenomatous polyps and those induced in rats have been discussed. Morphologically and in distribution, the polyps and carcinomas bore a resemblance to the point of being nearly indistinguishable. One point in deviation was the absence of metastases. Different methods of dosing have altered the frequency of occurrence of the tumors and, in the case of oophorectomy, the distribution. The variations may well be relevant to the epidemiologic differences in human colonic tumors, in relation to diet and exposure to possible carcinogenic agents, for example. Even though similarities exist, implications as to etiology are not intended. It is felt that experimental methods may contribute to our understanding of colorectal adenomatous polyps and carcinomas.

8. Tsui, C-Y., G. E. Burch (Department of Medicine, Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans, Louisiana 70112), and J. M. Harb. 1972. Pancreatitis in mice infected with coxsackievirus B1. *Arch. Path.* 93:379-389.

Coxsackievirus B1 experimentally produces damage to both the acinar cells and islet cells of the pancreas of mice of different ages. Pancreatic damage ranged from moderate to severe scattered and widespread lesions, with cell degeneration and necrosis and atrophic changes in the islets beginning about the fourth day after inoculation. Ultrastructurally, the damage ranged from vacuolation of the cytoplasm, with formation of membranous vesicles, to severe necrosis and breakdown of cells. In addition, viral crystals of coxsackievirus B1 are demonstrated in cells of the pancreas. Such viral crystals have never been described previously. Thus, mice

infected with coxsackievirus B1 provide good models for studying pancreatic disease due to viruses with a further possibility of elucidating the relationship between diabetes mellitus in man and viral infections with coxsackievirus B and other viruses. (Copyright 1972, American Medical Association)

9. Van Kruiningen, H. J. (Department of Animal Diseases, University of Connecticut, Storrs), and C. B. Williams. 1972. Mucoid enteritis of rabbits. Comparison to cholera and cystic fibrosis. Vet. Path. 9:53-77.

Fourteen cases of spontaneous mucoid enteritis, five cases that occurred after transmission of material from natural cases, and 13 control animals were studied to define disease characteristics and lesions. Prominent clinical features included diarrhea with passage of mucus, polydipsia, crouched stance, distended abdomen, succussion splash, and subnormal temperature. Transmission of the disease was unequivocally successful. Rabbits with mucoid enteritis had moderate leukocytosis, hyperglycemia, azotemia, serum globulin alterations, and electrolyte imbalance. Autopsy consistently revealed distended stomach, fluid-filled small bowel, impacted cecum, and mucus-filled colon. In the small intestine there was mucus-cell hyperplasia and in the colon mucous casts, glandular dilatation, and depletion of acidic mucus. The small-bowel changes in mucoid enteritis are similar to those in enterotoxin-induced secretory diarrheas, and the excessive discharge of mucus is comparable to that of cystic fibrosis.

10. Witzeleben, C. L. (Bidwill Memorial Research Laboratory, Cardinal Glennon Memorial Hospital, St. Louis, Missouri). 1972. Physiologic and morphologic natural history of a model of intrahepatic cholestasis (manganese-bilirubin overload). Am. J. Path. 66:577-588.

Study of the morphologic and physiologic features of the biliary excretory apparatus of SD rats at 24 and 48 hours after the induction of intrahepatic cholestasis by manganese-bilirubin overload shows that at the same time that physiologic cholestasis is rapidly waning, morphologic features of cholestasis are, in fact, increasing. These observations, therefore, provide the first direct proof of the proposal that such features are not, in fact, causes of cholestasis, at least at its outset. Although morphologic and physiologic features do not parallel one another in time, they do seem to parallel one another in severity. Morphologic features in manganese-bilirubin cholestasis closely resemble those in human cholestasis, and so reaffirm the validity and potential value of manganese-bilirubin overload as a model for the study of cholestasis. However, a review of information available about these features, reveals little conclusive evidence as to their pathogenesis and biochemical connotations.

CARDIOVASCULAR SYSTEM

11. Constantine, J. W. (Departments of Pharmacology and Pathology, Medical Research Laboratories, Pfizer, Inc., Groton, CT 06340), G. L. Coleman, and I. M. Purcell. 1972. Inversion of an arterial branch: A technique for inducing thrombosis. *Atherosclerosis* 16:31-36.

Arterial thrombosis was induced in anesthetized dogs by inverting a branch of the carotid or femoral artery into the lumen of the main vessel to cause endothelial damage without introducing foreign material into the circulation. Platelet-fibrin thrombi and platelet plaques were attached to necrotic endothelium on and close to inverted vessels. This technique is suggested as a model of thrombosis.

12. Freedman, L. R. (Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510), and M. L. Johnson. 1972. Experimental endocarditis. IV. Tricuspid and aortic valve infection with *Candida albicans* in rabbits. *Yale J. Biol. Med.* 45:163-175.

Methods are described for the production of *Candida albicans* endocarditis in rabbits. Infections were easily produced in the right or left sides of the heart in association with placement of indwelling intravascular polyethylene cannulas. The infections were well tolerated and were not accompanied by positive blood cultures or splenomegaly despite the finding of large numbers of microorganisms in the endocardial vegetations and foci of metastatic infection in the kidneys. Multiplication of fungi was greater in the left side of the heart than in the right side. This model reproduces circumstances similar to those in which infection is seen in man and appears suitable for the study of the pathogenesis and therapy of *C. albicans* endocarditis. (Copyright 1972, Academic Press, Inc.)

13. Grauer, L. E. (National Heart and Lung Institute, Bethesda, Maryland), and L. L. Waters. 1972. Studies on atherogenesis: The reaction of the model to repeated injections of lipoprotein-rich and lipoprotein-poor homologous serum. *Yale J. Biol. Med.* 45:93-103.

The potential of the serum-injected rabbit cornea as an experimental model for pertinent reactions of the arterial intima is noted. Utilizing the corneal model, it has been possible to elucidate further certain controversial mechanisms of atherogenesis. Thus it has been clearly demonstrated that after a single infiltration of avascular connective tissue by lipoprotein-rich serum lipid appears initially as fine granules closely associated with collagen fibers. In only four days lipophagocytic cells appear. There is a steady progression of the lipid from and extra- to an intra-cellular location. During

a full year of observation no necrosis of foam cells or release of lipid into the intercellular stroma could be seen. Over the course of a year there is gradual decrease in the lipid content of the plaque, suggesting that the foam cells slowly metabolize the phagocytosed lipid. Microhemorrhages, as advancing capillary aneurysms burst, are a regular feature of neovascularization of corneal lipid-connective tissue plaques, and a similar phenomenon may be a source of the larger hemorrhages in developing atheromata. By the removal of water from serum-infiltrated connective tissue, serum lipid is concentrated to such an extent that even four episodes of infiltration by lipid-poor serum leads to the development of a fatty, foam-cellular lesion. This observation suggests that repeated concentration of filtered serum lipids, and not *in situ* synthesis, may be responsible for the massive amounts of lipids regularly present in the atherosclerotic lesions of arteries in man. (Copyright 1972, Academic Press, Inc.)

14. Kaln, K. (1200 Druid Road South, Clearwater, Florida 33516). 1972. The natural course of experimental cerebral infarction in the gerbil. *Neurology* 22(5):510-515.

The gerbil is highly susceptible to cerebral infarct following ligation of a single common carotid artery. This was accomplished in 30 mature gerbils weighing between 50 and 81 gm. Sixteen animals (53 percent) showed evidence of infarction and all died within five days. The gerbil has no significant connection between the basilar-vertebral system and the carotid system and appears to be an excellent animal for cerebral infarction studies.

15. Keys, T. F. (Department of Medicine, University of California, Los Angeles, CA 90024), F. L. Sapico, R. Touchon, M. Barenfus, and W. L. Hewitt. 1972. Experimental enterococcal endocarditis. I. Description of a canine model. *Am. J. Med. Sci.* 63:103-109.

Eighteen medium-sized mongrel dogs were used to study experimental enterococcal endocarditis. Aortic valve injury was accomplished by needle punctures through a catheter in the left carotid artery. Thirteen dogs survived the procedure and one week later received a suspension of 10^7 enterococci intravenously. In 10 dogs a sustained bacteremia of 10^2 organisms per milliliter of blood or greater occurred within one week and rose to 10^3 in all but one animal shortly before death or sacrifice. Necropsy was performed in the dogs from 3 to 103 days after inoculation. Vegetative endocarditis involving both aortic and mitral valves occurred in 9 of 10 canine subjects. Bacterial counts on affected valves ranged from 10^7 to 10^9 per gram of tissue. Thromboembolic and hemorrhagic lesions were noted in the kidneys, myocardium, spleen, and lungs. The simplicity of this technique should prove this a useful model for therapeutic and pathophysiological studies.

16. Lindsay, S. (Department of Pathology, University of California, School of Medicine, San Francisco, California 94122), and C. W. Nichols, Jr. 1971. Arteriosclerosis in the pigeon: Naturally occurring disease of the coronary arteries and aorta. Exp. Med. Surg. 29(1-2):42-60.

Two forms of arteriosclerosis have been described in the coronary arteries and aortas of 166 pigeons of six breeds. A primary lipid infiltration with uncommon and minimal secondary intimal reaction was characteristic of thoracic aortic lesions, but was less prominent in other parts of the vascular system. A primary degenerative process with secondary lipid and cholesterol infiltration and eventual atheroma formation was a more severe form of vascular disease that was found most prominently in the upper abdominal aorta just above the origin of the coeliac artery. Atherosclerotic disease of the upper abdominal aorta occurred in all six breeds of pigeons. Although severer lesions were found in White Carneau, White King, and Silver King pigeons, almost as pronounced aortic atherosclerosis was observed in some Racing Homers and Show Racers despite the younger ages of birds of these two breeds. Coronary sclerosis was almost absent, however, in the racing breeds.

17. Ruiz, U. (Departments of Surgery and Pediatric Surgery Service, Tufts-New England Medical Center, Boston University Medical Center, Boston, Massachusetts 02115), G. J. Piasecki, K. Balogh, B. J. Polansky, and B. T. Jackson. 1972. An experimental model for fetal pulmonary hypertension. Am. J. Surg. 123:468-471.

To produce an experimental model for pulmonary hypertension in the fetus, the ductus arteriosus was ligated in fetal lambs of approximately 120 days' gestation. An implanted telemetry device was used for recording the fetal vectorcardiogram. Postoperative survival ranged from nine to thirty-six days. Marked anatomic changes were observed in the heart consistent with myocardial hypertrophy. The pulmonary vascular bed showed changes in the media of the small muscular branches of the pulmonary artery, presumably due to pulmonary vascular hypertension. The measurement of the vascular pressures by means of implanted catheters in the pulmonary artery and the aorta revealed significant increase in pulmonary arterial pressure relative to aortic pressure.

18. Santerre, R. F., T. N. Wright, S. C. Smith (Department of Animal Sciences, Kendall Hall, University of New Hampshire, Durham, NH 03824), and D. Brannigan. 1972. Spontaneous atherosclerosis in pigeons. A model system for studying metabolic parameters associated with atherogenesis. Am. J. Path. 67:1-22.

The interpretation of metabolic studies related to early changes in spontaneous atherosclerosis has been hampered by the focal nature of the disease and by the lack of a well-defined model system of the disease process. Gross, histologic and ultrastructural observations of lesion development at the celiac bifurcation of the aorta in atherosclerosis-susceptible White Carneau and atherosclerosis-resistant Show Racer pigeons are compared and discussed in terms of hemodynamics, muscular aggregation and altered metabolism of smooth muscle cells. Detailed knowledge of the morphologic sequence of events in lesion localization makes the celiac bifurcation in White Carneau and Show Racer pigeons a useful model for genetic comparisons of arterial wall metabolism and for investigating metabolic alterations occurring with atherogenesis.

19. Solez, K., and G. W. Richter (Department of Pathology, University of Rochester Medical Center, Rochester, New York 14642). 1972. Microembolic renal disease in rats induced with Sephadex. *Am. J. Path.* 66(1):163-180.

Sephadex particles (20-80 μ in size) were injected into the abdominal aorta of 134 male Sprague-Dawley rats near the renal arteries. In 31 rats, the right kidney was then removed. The Sephadex particles lodged in glomerular capillaries, afferent glomerular arterioles and interlobular arteries, creating renal infarcts, some of which were grossly visible. Shortly after injection, arterial blood pressure rose significantly in most animals. The hypertension in uninephrectomized rats was not demonstrably different from that in rats with 2 kidneys. Severity and duration of hypertension (up to 8 mo.) were positively correlated with the number of Sephadex particles in renal vessels, and there was also a positive correlation between the degree of hypertension and serum urea nitrogen levels, and between degree of hypertension and degree of cardiac hypertrophy. The vascular permeability in acutely hypertensive rats was abnormal, as judged from penetration of iron-dextran into vessel walls. This experimental model resembles atheromatous microembolic renovascular disease, which may play a significant role in the pathogenesis of unexplained hypertension in patients with advanced aortic atherosclerosis.

20. Stemerman, M. B. (Department of Pathology, University of Washington, School of Medicine, Seattle, Washington 98195), and R. Ross. 1972. Experimental arteriosclerosis I. Fibrous plaque formation in primates, an electron microscope study. *J. Exp. Med.* 136:769-778.

Arteriosclerotic lesions have been produced in monkeys (*Macaca nemestrina*) by selective removal of the vascular endothelium with an intra-arterial balloon catheter. Immediately after de-endothelialization a platelet layer covers the denuded area. This thrombus is gradually removed and by 7 days the vessel appears to be largely reendothelialized.

Beginning at day 4, smooth muscle cells undergo modification and migrate through fenestrae in the internal elastic lamina into the intima where they proliferate. By 28 days, the intimal lesion consists of multiple layers of smooth muscle cells surrounded by collagen and elastic fibers and basement-like material. After 3 months the lesions are markedly hyperplastic and contain new extracellular connective tissue elements. In contrast, with no further injury after 6 months the lesion has decreased markedly in size suggesting that it may be reversible in the absence of continued endothelial injury. The importance of endothelial "injury" exposing medial smooth muscle to plasma constituents may be the principal factors associated with the migration and proliferation of the smooth muscle cells into the intima resulting in the lesion. The smooth muscle cells do not contain lipid. The similarities of this lesion to the fibromusculo-elastic lesion or preatherosclerotic intimal hyperplasia in man makes it a useful model for the further study of atherosclerosis.

21. Waters, L. L. (Department of Pathology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510). 1972. Insoluble lipoproteins in the pathogenesis of experimentally induced atherosclerosis. Arch. Path. 93: 525-529.

Embolization of the pulmonary arteries of rabbits with insoluble plasma lipoproteins of human origin results in a prompt lipophagic, mononuclear, and sclerosing lesion at the involved arterial site. The lesions at certain stages reproduce many of the morphologic features of experimentally induced atherosclerosis. The observations direct attention to denatured plasma lipoproteins rather than to platelets or to components of thrombus as a source of lipids in atherogenesis. A virtually "instant" model for experimental atherogenesis is provided. (Copyright 1972, American Medical Association)

ENDOCRINE SYSTEM

22. Boorman, G. A., M. J. van Noord, and C. F. Hollander (Institute for Experimental Gerontology, TNO, 151 Lange Kleiweg, Rijswijk ZH, The Netherlands). 1972. Naturally occurring medullary thyroid carcinoma in the rat. Arch. Path. 94:35-41.

A series of necropsies of 334 older WAG/Kij rats (84 percent were older than 2 years) revealed 124 thyroid neoplasms. Medullary thyroid carcinoma accounted for 123 neoplasms; one follicular carcinoma was seen. The incidence increased with age. Multiple endocrine neoplasia was common, but no increased association with thyroid neoplasia could be found. Definite malignant tendencies with either extensive invasion or distant metastasis were seen in four cases. Electron microscopic study demonstrated that the parafollicular cell was the cell of origin of medullary thyroid carcinoma in the rat, as

has been suggested by electron microscopic studies of the medullary thyroid carcinoma in man. Spontaneous high incidence of medullary thyroid carcinoma in rats and its many similarities to this neoplasm as seen in man suggest that the rat may serve as a useful animal model for medullary thyroid carcinoma. (Copyright 1972, American Medical Association)

23. Butler, L. (Department of Zoology, University of Toronto, Toronto, Ontario, Canada). 1972. The inheritance of glucosuria in the KK and AY mouse. *Can. J. Genet. Cytol.* 14:265-269.

Both the KK and the AY mouse exhibit many symptoms of diabetes. Glucosuria is the most satisfactory test for this condition in mice. Glucosuria is inherited as a dominant in both strains, but many factors reduce its penetrance. The penetrance in the KK strain can be increased from 23 to 62 percent by crossing to C57BL/10J and then selecting the most effective background modifiers. The number of modifiers must be small because response was rapid and fixation fast. The cross KK x AY gives yellow and black offspring in equal numbers. The yellows have the dominant genes for glucosuria from both strains, and the males all become glucosuric by the time they are 8 months old, in comparison to 7 percent of the males in the parental yellow strain. Of the yellow females, 88 percent are glucosuric by 1 year in comparison to 0 percent of the yellow strain or 2 percent of the Y's. The black males which lack the gene from the AY strain but do have the gene from the KK have no glucosurics at 8 months and only 2 percent at 1 year. The F1 of the cross KK x AY provides valuable research material since all yellow males will become glucosuric by 8 months of age and none of their black litter mates will.

24. Hamilton, C. L. (Departments of Physiology and Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania). 1972. An observation of long-term experimental obesity and diabetes in the monkey. *J. Med. Prim.* 1:247-255.

Electrolytic lesions in ventromedial hypothalamus were induced in the rhesus monkey to produce a model for experimental study of obesity and *diabetes mellitus*. The animal was observed for 14 1/2 years. The preparation demonstrates the feasibility of long-term studies of diabetes using the non-human primate as a model.

25. Hummel, K. P. (The Jackson Laboratory, Bar Harbor, Maine 04609), D. L. Coleman, and P. W. Lane. 1972. The influence of genetic background on expression of mutations at the diabetes locus in the mouse. 1. C57BL/KsJ and C57BL/6J strains. *Biochem. Genet.* 7:1-13. Plenum Publishing Corporation.

Two new diabetic strains, C57BL/KsJ-db^{2J} and C57BL/6J-db^{2J}, have been developed. C57BL/KsJ-db^{2J} mice are indistinguishable from C57BL/KsJ-db/db mice, the original diabetes mutation. Both have severe diabetes characterized by hyperphagia, obesity, marked hyperglycemia, temporarily elevated plasma insulin concentrations, and typical degenerative changes in the islets of Langerhans. In contrast, C57BL/6J-db^{2J}/db^{2J} mice, although also hyperphagic and obese, have mild diabetes characterized by transitory hyperglycemia and markedly elevated plasma insulin concentrations coupled with marked hypertrophy of the islets and increased proliferative capacity of beta cells. The mild diabetes-like syndrome produced by diabetes-2J on the C57BL/6J background is similar to that produced by the obese gene (ob) on the same background. The islet responses, whether atrophy or hypertrophy, appear to be due to the interaction of diabetes-2J (and possibly obese) with modifiers in the genetic background rather than being peculiar to the specific mutant. The markedly different disease patterns that result when the same gene is placed on different inbred backgrounds emphasize the importance of strict genetic control in biochemical and physiological studies with these and other obesity mutants.

26. Howaru, C. F. (Department of Primate Nutrition and Metabolic Diseases, Oregon Regional Primate Research Center, Beaverton, Oregon 97005). 1972. Spontaneous diabetes in *Macaca nigra*. *Diabetes* 21:1077-1090.

In a closed breeding colony of *Macaca nigra* (black Celebes apes) there was a marked proclivity for a spontaneous diabetic-like state closely analogous to human diabetes. Numerous diabetic signs were present, including abnormal intravenous and oral glucose tolerance tests, hyperglycemia, impaired insulin response, hypertriglyceridemia, increased prebetalipoprotein, retinal vascular aberrations, abnormalities in the islets of Langerhans, and pronounced weight loss in a few severely diabetic monkeys. A classification of diabetic status established primarily on deviation of the intravenous glucose tolerance test from results in normal Celebes apes places over 50 percent of these interrelated monkeys in nonnormal categories.

27. Matsuo, T. (Biological Research Laboratories, R&D Division, Takeda Chemical Industries, Ltd., Osaka, Japan), K. Furuno, and K. Shimakawa. 1971. Factors affecting development of hyperglycemia in KK mice. *J. Takeda Res. Lab.* 30(2):307-313.

Some factors affecting development of hyperglycemia were investigated in KK mice. Semisynthetic diets containing 10.5 or 20.5 percent fat were more effective on elevation of blood glucose levels than those containing 2.5 or 60.5 percent fat. A laboratory chow was also effective when given in powdered form but less effective

when given in pelleted one. Group rearing suppressed the elevation of blood glucose levels. KK mice whose body weight was less than 8.5 g at weaning did not develop hyperglycemia, despite free access to semisynthetic diet containing 10.5 percent fat after weaning. These results indicated that development of hyperglycemia was affected not only by the type or form of diet, but also by the weaning body weight in this strain. In all animals which developed hyperglycemia and glucosuria, increased weight gains were remarkable. These findings demonstrate that the diabetic changes were closely correlated with development of obesity in KK mice

28. Parker, D. C. (Endocrine Division, Scripps Clinic and Research Foundation, 476 Prospect Street, La Jolla, CA 92037), M. Morishima, D. J. Koerker, C. C. Gale, and C. J. Goodner. 1972. Pilot study of growth hormone release in sleep of the chair-adapted baboon: Potential as model of human sleep release. *Endocrinology* 91(6): 1462-1467.

Release of GH in sleep of 2 adolescent male baboons was studied on 7 nights: 2 basal nights, 2 nights during a 72-hr fast, 2 nights during β adrenergic blockade by propranolol and during 1 night of β blockade in which the α agonist, phenylephrine, was also infused. Sleep was video monitored behaviorally, recorded polygraphically and scored by standardized human criteria. GH was measured by a human RIA system. The animals were chair-adapted for 6 months prior to study, housed together in a temperature and light-dark controlled chamber, studied over a 9-hr night in 25-watt illumination and fed once daily. Implanted arterial and venous catheters allowed cardiovascular data recording and sampling at 20-30 min intervals. Each baboon proved to have individual sleep and release patterns: Baboon B slept readily, more continuously and with fewer arousals; he released large amounts of GH in sleep in a repetitive pattern. Baboon Z slept more briefly, lightly, and awakened frequently; he released small amounts of GH infrequently but in relation to his few better organized sleep cycles. Stage 4 sleep release, propranolol had no effect and the infusion of propranolol plus phenylephrine gave inconclusively decreased release since sleep was also disrupted. The similarity of these results to those in humans suggest the baboon may prove a useful model for study of GH release in sleep.

29. Rimoin, D. L. (Harbor General Hospital, School of Medicine, University of California, Torrance, CA 90509), and L. Richmond. 1972. The pygmy (pg) mutant of the mouse - a model of the human pygmy. *J. Clin. Endocrinol. Metab.* 35(3):467.

The pygmy (pg) mutant of the mouse is an autosomal recessive trait resulting in proportionate dwarfism. The growth rate of pg/pg mice was found to be unresponsive to treatment with porcine growth hormone, whereas this same hormonal preparation resulted in marked growth acceleration in hypopituitary mice. These observations suggest that the pygmy mutant of the mouse is associated with a peripheral subresponsiveness to growth hormone, and thus may represent a model of the human African pygmy.

30. Rogers, M. C. and W. H. Bergstrom (750 East Adams Street, Syracuse NY 13210). 1971. Diet-induced hypoparathyroidism: A model for neonatal tetany. *Pediatrics* 47(1):207-210.

Transient hypoparathyroidism in the newborn has been attributed to immaturity of the parathyroid glands, renal tubules, or both. Since fetal uptake of calcium and phosphorus is regulated by maternal and placental mechanisms, parathyroid stimulation is probably minimal *in utero* during normal pregnancies. The present study was designed to induce transient hypoparathyroidism in mature animals by dietary means. Rats kept on a low-phosphate diet (with an elevated Ca/P ratio) were challenged with parenteral sodium phosphate. Their post-load serum calcium and phosphorus concentrations were compared to those of controls on a standard ration. Hyperphosphatemia, hypocalcemia, and fatal tetany were seen in the experimental animals but not in controls. Parathyroid extract was partially protective. Re-feeding the standard laboratory diet reversed susceptibility to phosphate loading within a week. The data indicate that the capacity to defend serum calcium against exogenous phosphate depends upon prior stimulation of the mechanism for calcium-phosphorus homeostasis rather than upon "maturity" *per se*.

31. Sit, K. H., (Department of Anatomy and Embryology, University College, London, Gower Street, London WC1 6BT, U.K.), and R. Kanagasuntheram. 1972. A structural analysis of congenital limb deformities in experimental hyperthyroid tadpoles. *J. Embryol. Exp. Morphol.* 28:223-234.

An experimental model for the study of hyperthyroidism in embryonic development was achieved in the local anuran larvae, *Bufo melanostictus*, by treatment with potassium perchlorate at a critical dose and time of embryogenesis. Phocomely-hemimely and digital deformities of fore- and hind limbs in high percentages of the population were found associated with such critically stimulated tadpoles. Similar deformities were reproduced by exogenous treatment with L-thyroxine sodium. The deformities were severely aggravated if the tadpoles had anti-thyroid treatment before critical stimulation with thyroxine in the sensitive phase of development. Incoordinate cellular differentiation in the malformed limbs was indicated histologically by undifferentiated mesenchyme in the distal extremities although the overlying ectoderm had already

formed mature epidermis with specialized skin glands. Thee differentiated mesodermal components (muscles, cartilages and connective tissues) more proximally were afflicted with degenerative changes. Lytic spinal motor neurones and involuted Mauthner's neurones with precipitate metamorphosis were accompanying features. Embryonic thyrotoxicosis is discussed in relation to congenital deformities of limbs.

32. Stuhlman, R. A. (Department of Laboratory Animal Medicine, School of Veterinary Medicine, University of Missouri, Columbia, MO 65201), J. T. Packer, and R. E. Dcyle. 1972. Spontaneous diabetes mellitus in *Mystromys albicaudatus*. Repeated glucose values from 620 animals. Diabetes 21: 715-721.

The serum glucose values of 1,423 blood samples from 620 *Mystromys albicaudatus* have been determined and defined as orthoglycemic or hyperglycemic. Analyses of variance tests and regression analyses of the data revealed a significant difference between orthoglycemic and hyperglycemic serum glucose means and indicated that serum glucose is not affected by sex, inbreeding, or age in these animals. However, within classifications of orthoglycemic and hyperglycemic, weight did affect serum glucose. Therefore, while obesity did not occur during this study, obese-hyperglycemia syndromes might be expected should the animals become overweight. The data and their analyses are strongly indicative that spontaneous diabetes mellitus in *M. albicaudatus*, as related to hyperglycemia, is very similar to the disease in man.

EYE

33. Albert, D. M. (Sect. Ophthalmol., Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510), M. O. M. Tso, and A. S. Rabson. 1972. Experimental malignant tumors from retinal pigment epithelium. Arch. Ophthal. 88(1):70-74.

Malignant neoplasms of the retinal pigment epithelium (RPE) were produced by infecting pure cultures of hamster RPE *in vitro* with simian vacuolating virus 40, an oncogenic DNA virus. When transformed cells were injected s.c. into irradiated 4-wk-old hamsters, neoplasms developed at the injection site within 3 wk and subsequently killed the animals by generalized metastasis. These experimental tumors resembled morphologically some tumors seen in human eyes arising from the RPE. While extraocular invasion or metastasis of human RPE tumors is not documented convincingly, under experimental conditions retinal pigment can give rise to tumors capable of invasion and metastasis. This provides a model useful in distinguishing histologic characteristics of true malignant tumors of the RPE. (Copyright 1972, American Medical Association)

34. Dasler, W. (Dept. of Biochemistry, The Chicago Medical School, University of Health Sciences, Chicago, IL 60612), and H. L. S. Wang. 1972. Studies on cataracts induced in rats by N²-phenyl-β-hydrazinopropionitrile. Invest. Ophthalm. 11(4):236-240.

When N²-phenyl-β-hydrazinopropionitrile hydrochloride (N²-φ-BHPN · HCL) is fed to weanling rats, cataracts appear in 11 to 17 days. It was found that the mean adenosine triphosphate (ATP) levels in the lenses of such rats began to fall precipitously about one week before cataracts began to appear. ATP levels continued to fall and became minimal at about the time that lens opacities became evident by gross examination. At this time, the mean soluble protein levels dropped sharply and lens weights increased dramatically. The increases in lens weights were accompanied by partial liquifaction of the lenses with complete loss of their crystalline character. Lens weights then rapidly returned to normal levels with the formation of solid, brittle, completely opaque lenses. These changes are similar in some respects to those which have been reported to occur during the development of "sugar" cataracts.

35. Schneider, W. J. (School of Pharmacy, University of the Pacific, Stockton, CA 95207), and J. A. Howarth. 1973. Clinical course and histopathologic features of pseudorabies virus-induced keratoconjunctivitis in pigs. Am. J. Vet. Res. 34:393-401.

To study ocular lesions caused by pseudorabies (PR) virus (*Herpesvirus suis*) in pigs, experimental self-limiting keratoconjunctivitis was produced by placing PR virus directly on traumatized corneas. The initial punctate corneal ulcers spread rapidly, progressing to disciform or geographic forms. These ulcers were accompanied by follicular conjunctivitis, chemosis, blepharospasm, corneal anesthesia, purulent exudate from exposed eyes, transient blindness, edema of the iris, miosis, and fever. Corneal vascularization was well developed by postinoculation day (PID) 12 and coincided with regression of the ulcer. Corneal opacities developed and remained at least through PID 48. Histopathologic examination indicated necrosis and erosion of corneal epithelium through PID 11 and regeneration of a thin epithelial layer by PID 14. Epithelial degeneration was accompanied by corneal edema, deep stromal vascularization, and heavy inflammatory infiltrate of the cornea and bulbar conjunctiva. Transient iritis developed, characterized by edema, perivascular mononuclear cuffs, and stromal infiltration of mononuclear cells. Experimentally induced PR keratoconjunctivitis in the pig resembles the deeper forms of herpes simplex keratitis in man and rabbit.

36. Tissot, R. G. (The Center for Genetics, University of Illinois College of Medicine, Chicago IL 60612), and C. Cohen. 1972. A new congenital cataract in the mouse. J. Hered. 63:197-201.

A new hereditary cataract affecting the eye of the mouse is reported. This condition, first found in a Webster strain Swiss female, is present at birth and differs from other reported inherited cataracts in the mouse. Through the use of breeding experiments involving selection and backcross matings to inbred lines it was found that this defect is controlled by a major dominant gene that is lethal in the homozygous state and by one independent recessive gene. Occasionally, about 6 percent of the time, the cataract will also appear in F₁ animals from outcrosses to certain inbred strains, including DBA/2 and C57BL/6.

HEMATOPOIETIC SYSTEM

37. Burderer, M. C. (Environmental Physiology Laboratory, University of California, Berkeley, CA 94720), and N. Pace. 1972. Hemopoiesis in the pig-tailed monkey *Macaca nemestrina* during chronic altitude exposure. Am. J. Physiol. 223(2):346-352.

Monkeys were studied for 180 days at 3,800 m altitude to examine their hemopoietic response. Plasma volume was found to be reduced while red cell volume increased steadily for 4-5 months. Reduction in mean corpuscular hemoglobin content was observed from *day 30--day 120* at altitude. Total plasma protein concentration was unchanged at altitude, but marked reduction in the albumin/globulin ratio occurred. Total circulating plasma protein and albumin were reduced in amount, whereas nonalbumin protein was unchanged. These results imply loss of albumin coupled with a corresponding loss of water from the blood and maintenance of normal plasma osmotic pressure. The following sequence is postulated: hypoxia → increase in body functional capillary surface area → increase in plasma albumin and plasma water transfer to lymph → decrease in plasma volume. The body/venous hematocrit ratio was found to be reduced at altitude, possibly as a consequence of the expanded capillary volume of the body. The hemopoietic responses of the pig-tailed monkey at altitude require at least several months for completion, and closely resemble those seen in man; thus, the monkey can serve well for long-term studies of high-altitude acclimatization.

38. Cooper, R. G. (Departments of Agriculture, Chemistry and Physiology, University of Missouri, Columbia, MO 65201), C. N. Cornell, M. E. Mutherer, and K. Leimer. 1972.

Sedimentation behavior of fibrinogen from normal and bleeder swine. *Thromb. Diath. Haem.* 27(1):59-62.

The Missouri Bleeder Swine have prolonged bleeding time, low factor VIII levels, reduced platelet adhesion, and respond to plasma and serum transfusions in a manner similar to that of patients with von Willebrand's disease. The swine disease is thus more similar to von Willebrand's disease than to classical hemophilia. The present work demonstrates that the sedimentation behavior of fibrinogen from these bleeder swine is like that of normal swine and does not show the anomalous sedimentation pattern of fibrinogen from classical hemophiliacs.

39. Dimandopoulos, G. I. (Department of Pathology, Harvard Medical School, Boston, MA 02115). 1972. Leukemia, lymphoma, and osteosarcoma induced in the Syrian golden hamster by simian virus 40. *Science* 176:173-175.

Leukemia, lymphoma, and osteogenic and anaplastic sarcomas develop in Syrian golden hamsters inoculated intravenously at 3 weeks of age with simian virus 40, which is a popova virus. Previously, only RNA and herpes DNA viruses have been recognized as capable of inducing leukemia and lymphoma in mammals. The significance of these findings is emphasized in relation to the nature of viral agents that may be involved in analogous diseases of man. (Copyright 1972 by the American Association for the Advancement of Science)

40. Dung, H. C. (Department of Anatomy, The University of Texas Medical School, 7703 Floyd Curl Drive, San Antonio, Texas 78299), and R. H. Swigart. 1972. Histopathologic observations of the nervous and lymphoid tissues of "lethargic" mutant mice. *Texas Rep. Biol. Med.* 30:1-39.

"Lethargic" is a single recessive mutation occurring spontaneously. The affected mice display abnormal behavior, such as instability of gait, seizures, and convulsions; and they are designated as neurological mutations. Results of the study revealed no pathologic changes in the nervous system of the affected mice. However, pathologic changes were found in the thymus, spleen, lymph nodes, and Peyer's patches. Pathologic changes in these lymphatic organs from "lethargic" mice resemble those described for the animals injected with exogenous cortical hormones, for mice with wasting disease due to neonatal thymectomy, and for children with Swiss type of agammaglobulinemia. The cause of abnormal behavior still is undetermined for "lethargic" mice.

41. Gong, J. K. (Department of Oral Biology, School of Dentistry, State University, Buffalo NY 14214), P. G. Brauschweiger, and C. A. Glomski. 1972. Anemic stress as a trigger of myelogenous leukemia in the unirradiated RF mouse. *Science* 177:274-276.

Ninety-six percent of mice that were bled of 50 percent of their blood volume when they were 9 weeks old succumbed to myelogenous leukemia by 15 months after phlebotomy, the majority of them dying between 7 and 10 months after this treatment. These results suggest that (i) anemia is an effective stress for triggering myelogenous leukemia in animals that are predisposed to the disease, (ii) the RF mouse is "naturally" prone to the development of myelogenous leukemia, and (iii) the concept of two-step de novo induction of myelogenous leukemia appears to be applicable in this animal. (Copyright 1972 by the American Association for the Achievement of Science)

42. Richter, C. B. (Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN 37830), P. C. Esters, and R. W. Tennant. 1972. Spontaneous stem cell leukemia in young Sprague-Dawley rats. Lab. Invest. 26(4):419-428.

The pathology of spontaneously occurring acute stem cell leukemia in young outbred rats was studied by light and electron microscopy. The primary focus of these leukemias was the bone marrow, and a high incidence of central nervous system damage resulted from leukemic encroachment. The lymphatic system was only secondarily involved. We were unable to demonstrate associated virus by electron microscopy or by cell-free transmission. We also examined leukemic cells for the presence of mouse leukemia virus antigens directly by complement fixation and indirectly by similar examination of "infected" tissue cultures, and none was found. The leukemias were readily transplantable in the two strains of rats that we tested provided that the recipients were less than 25 days old. A rapidly developing leukemic form of the disease was produced by intraperitoneal inoculation, while subcutaneous implantation produced leukemias or solid tumors. Sera from rats bearing solid tumors for 1 month or longer did not react by complement fixation with Rauscher or Moloney leukemia viruses. The mean age at death of spontaneously leukemic rats was 180 days (± 95 days standard deviation), which differs from previous reports on this species. Leukemia occurred as early as 81 days of age, and in one instance two littermates died of the disease within 1 week of each other. It is concluded that this leukemia in rats may provide a useful model for the study of childhood leukemias for the following reasons: (1) few animal models of acute early life leukemias such as occur in man are available. The type of leukemia that we describe in rats is a common type in children; (2) the absence of readily demonstrable virus parallels experience with man rather than mouse; and (3) the leukemia is readily transplantable and easily maintained.

43. Rosenthal, D. S. (Department of Hematology, Peter Bent Brigham Hospital, Harvard Medical School, Boston, MA 02115), R. Maglio, and W. C. Moloney. 1972. Muramidasuria

and hyperkalemia in the chloroleukemic rat. Proc. Soc. Exp. Biol. Med. 141(2):499-500.

The transplanted rat chloroleukemia cytologically similar to human acute myelocytic leukemia is associated with markedly elevated serum and urinary muramidase levels. Current metabolic studies demonstrate excessive potassium loss in the urine and appears to be related to the degree of muramiduria. The experimental myelogenous leukemia furnishes an excellent model for the investigation of the enzyme effect on the kidney and present studies suggest that muramidase causes a direct tubular damage.

44. Seidel, H.-J. (Center for Basic Clinical Research, University of Ulm, Ulm, Parkstrasse 10, Germany). 1972. Pancytopenia in CBA mice after Rauscher virus infection. J. Nat. Cancer Inst. 48:959-964.

Hematology of female CBA mice was studied 5-30 days after Rauscher virus infection. After 10 days pancytopenia was observed; this included reticulocytes, neutrophils, and thrombocytes. Bone marrow cellularity had decreased. Later there was a partial regeneration in some animals, but most remained anemic and thrombopenic. Spleen tumors developed weighing up to 2.5 g. In the bone marrow, a defect in cellular differentiation in the granulopoietic series with a maturation block was noted; erythropoiesis seemed normal. A leukemic blast cell population was not seen. From these results it is concluded that the underlying mechanism in Rauscher disease is a common disorder in hematopoietic cell differentiation, probably caused by the action of the virus on a common precursor cell. This could be a useful model for aplastic anemia, preleukemia, or both.

45. Takayama, S. (Department of Pathology, School of Medicine, Tokyo Medical & Dental University, Tokyo), T. Yamada, and S. Kamata. 1972. Chronic myelogenous leukemia in rats fed 2,7-diacetylaminofluorene. Acta Path. Jap. 22(2):309-319.

Chronic myelogenous leukemia is said to be difficult to induce in rats. However, there have been reports that granulocytic leukemia was induced by the administration of 3-methylcholanthrene, 7,12-dimethylbenz (a) anthracene, 2,7-diacetylaminofluorene, and N-nitrosobutylurea. 2,7-diacetylaminofluorene is carcinogenic on various organs, including the breast, stomach, and hematopoietic organs. The present authors originally attempted to induce gastric carcinoma in rats by the oral administration of this compound without success, but during this experiment chronic myelogenous leukemia was frequently encountered. This paper reports their observations on the induced chronic myelogenous leukemia.

46. Tschopp, T. B. (Department of Pathology, New York University, School of Medicine, New York City), and M. B. Zucker. 1972. Hereditary defect in platelet function in rats. Blood 40(2): 217-226.

Hemostatic parameters of fawn-hooded (FH) rats with an inherited hemorrhagic diathesis were compared with those of normal rats. Prothrombin time, partial thromboplastin time, plasma factor VIII, plasma fibrinogen, and platelet count and volume were normal. Bleeding time (BT) in FH rats was over 15 min vs. 1-8 min in controls, and platelet retention in glassbead columns was reduced. Transfusion of platelet concentrates from normal rats corrected the BT of thrombocytopenic FH rats, but FH rat platelets did not shorten the BT of thrombocytopenic controls. ADP-induced aggregation, measured turbidimetrically in heparinized FH platelet-rich plasma, was normal. Connective tissue did not aggregate platelets of FH rats and released a subnormal amount of ^{14}C -serotonin. In comparison with control platelets washed FH platelets aggregated by thrombin released virtually no ATP and ADP. Platelets, 10^{11} of normal rats contained 4.49 μmoles ATP, 0.98 μmoles ADP, and 0.88 μmoles serotonin compared with only about one-half as much ATP and ADP and one-third as much serotonin in platelets of FH rats. These low values suggest the absence of the platelet, "release pool" rather than a defective release mechanism. The hemorrhagic diathesis seen in the FH rats resembles the platelet defect with storage pool deficiency observed in man.

MUSCULOSKELETAL SYSTEM

47. Lorenz, M. D. (New York State Veterinary College, Cornell University, Ithaca, NY 14850), A. deLahunta, and D. H. Alstrom. 1972. Neostigmine-responsive weakness in the dog, similar to myasthenia gravis. J. Am. Vet. Med. Assn. 161: 795-800.

A disease similar to myasthenia gravis in man was diagnosed in a 6-year-old English Coonhound. Diagnosis was based on the presence of weakness which progressed on exertion and responded partially to rest and completely to anticholinesterase therapy. The weakness was generalized throughout the axial and appendicular muscles. Four months after a 30-day course of neostigmine therapy, no relapse had occurred.

48. Stringer, J. M., R. A. Kainer, and A. T. Tu (Department of Biochemistry, Colorado State University, Fort Collins, CO 80521). 1972. Myonecrosis induced by rattlesnake venom. Am. J. Path. 67:127-140.

The myonecrotic effect of rattlesnake (*Crotalus viridis viridis*) venom on mouse skeletal muscle was studied. The biceps femoris

muscle was examined with the electron microscope after one-fourth the LD₅₀ of the crude venom was injected into the gracilis and semimembranosus muscles. Focal areas of myonecrosis were abundant. Injured fibers contained dilated sarcoplasmic reticulum, disoriented, coagulated myofilamentous components and condensed, rounded and enlarged mitochondria. The external lamina and sarcolemma remained intact in many fibers. Hemorrhage was apparent in the endomysial connective tissue, and hemolysis was discernible. In areas where the erythrocytes were tightly packed between the muscle fibers, there was disruption of the external lamina and sarcolemma. Degeneration of the fibers in these areas was pronounced. These findings correlate well with the breakdown of muscle fibers by various methods described in the literature. Myonecrosis induced by snake venom may serve as a useful model for studying muscle necrosis because of its rapid onset and relative ease of induction.

49. Taylor, R. G. (2315 Stockton Boulevard, Sacramento, CA 95817), W. M. Fowler, Jr., D. T. Mason, and J. F. Spann, Jr. 1971. Contractile properties of skeletal muscle in dystrophic mice. Arch. Phys. Med. Rehabil. 53(11):511-515.

Hereditary dystrophia muscularis (HDM) in mice provides an important animal model for the evaluation of skeletal muscle performance in muscular dystrophy. Isometric contractile properties were studied in soleus muscles isolated from HDM mice, their normal littermates (LM) and, as a 2nd control, mice from a non-dystrophic strain (CON). Physiologic parameters studied were: maximum tetanic tension, rate of tension development (dP/dT), duration of the active state (DAS), and rate of relaxation. HDM mice were significantly different from LM and CON in all anthropometric measurements: body weight, soleus muscle weight, length and cross-sectional area. The physiologic measurements revealed marked reduction in performance of HDM mice for tension development, dP/dT, and relaxation rate. There was no significant alteration of DAS for HDM when compared to LM or CON. HDM results in a profound depression of contractile properties of skeletal muscle which is not due to an abnormal abbreviation of DAS or to incomplete fusion at stimulus frequencies equivalent to the normal rates of firing of the motor unit in the intact animal. Since dP/dT is a function of the intensity of the active state, this mechanical defect reflects a basic reduction of the intensity of the active state in HDM. Since this altered active state persists *in vitro*, in a controlled environment, this represents an intrinsic contractile abnormality of skeletal muscle of mice with muscular dystrophy.

50. Thomas, L. (Department of Pathology, Yale University School of Medicine, New Haven, CT 06510). 1973. Experimental mycoplasma infections as models of rheumatoid arthritis. Fed. Proc. 32:143-146.

Several experimental models for the production of arthritis and polyarteritis by mycoplasma infection in laboratory animals are discussed. It is suggested that such infections may offer useful models for the study of therapeutic agents in arthritis, in particular, the therapeutic effectiveness of gold salts and tetracyclines. The tissue-specific nature of mycoplasmal toxins, and the special capacity of mycoplasmas to localize within the walls of arteries in certain tissues, as exemplified by the turkey encephalopathy caused by the S6 strain of *Mycoplasma gallisepticum*, provide new approaches to the general problem of the pathogenicity of these microorganisms.

NERVOUS SYSTEM

51. Caviness, Jr., V. S. (Department of Neuropathology, Harvard Medical School, Boston, MA 02115), D. D. K. So, and K. L. Sidman. 1972. The hybrid reeler mouse. J. Hered. 63(5): 241-246.

Hybrid reeler offspring of matings between C57BL/6J and C3H/HeJ mice heterozygous for the reeler gene, may survive to adult life with only mild neurological disability and growth retardation. Affected hybrid mice of both sexes are fertile and the animals will breed. By contrast, inbred reelers of the C57BL/6J strain have profound neurological disability and growth retardation, and rarely survive the fourth week of life. Despite these differences in the phenotype of hybrid and inbred reelers, the cytoarchitectonic anomaly of cortical structures is identical in the two groups within the limits defectable in cresyl violet and Loyez histological preparations. Because of its greater vitality and life expectancy, the hybrid mutant is more suitable than the inbred animal for studies of neural connections as well as for physiological and psychological studies.

52. Molony, V. (Wellcome Neurobiology Unit, Departments of Anatomy and Veterinary Anatomy, University of Liverpool, Liverpool L69 3BX U.K.). 1971. The dogfish as a subject for neurophysiological research. J. Physiol. 219:12-13.

Scyliorhinus is an easily obtainable animal, with a nervous system of generalized pattern displaying all the features expected of a lowly vertebrate. Simple modifications can be made to a standard stereotaxic frame, allowing the fish to be mounted with ear bars in the spiracles. Animals can be anaesthetized by immersion in sea water containing one part in 5000 of MS222 (Sandoz). After gill movements have ceased, they can safely be kept in air for 1/2 hr. Paralysis is obtained by injection of D-tubocurarine into the peri-ocular venous sinus (gallamine produces rigidity in these animals). After stereotaxic fixation, sea water is circulated via a Y-piece inserted into the mouth, and collected into a tank

through a plastic tray whose outlet contains a carbon filter into a reservoir tank. Oxygen is bubbled through this. The water is then pumped round with a small centrifugal pump through a beer cooler to maintain temperature at about 14°C and recirculated through the fish. For an average dogfish, a flow of 1.0-1.5 l./min is used. The brain is easily exposed by pairing away the chondrocranium, following which decerebration can be performed. The metabolism of the animal and the stability of the preparation is such that intracellular recordings can be made without any necessity to seal the system.

53. Murphey, D. L. (Baylor College of Dentistry, Department of Microscopic Anatomy, Dallas, TX 75226), and R. E. Dill. 1972. Chemical stimulation of discrete brain loci as a method of producing dyskinesia models in primates. Exp. Neurol. 34:244-254.

The technique of chemical stimulation of the CNS was utilized in a study designed to develop models of dyskinesias in a primate. Four sites in the extra-pyramidal motor system of squirrel monkeys were stimulated with carbachol, a cholinergic drug. This was achieved by intracranial injection of microgram amounts of the drug via chronically implanted cannulae. Injection of carbachol into the neostriatum, both caudate nucleus and putamen, produced a hyperkinetic choreiform syndrome. Tremor and chorea in the contralateral limbs and facial dyskinesia with sialorrhoea were the most common results of this procedure. Carbachol stimulation of the medial globus pallidus produced an akinetic hyperextension syndrome characterized by an immobile extension of the contralateral limbs. The extended limbs had the appearance of being rigid. Brief bursts of tremor or chorea were rarely superimposed. Carbachol stimulation of the subthalamus produced a hyperactive state consisting of ceaseless ambulation, climbing, and circling. All of the above effects were reproducible and consistent for each cannula site, suggesting that specific dyskinesias can be elicited by cholinergic stimulation of discrete loci in the extrapyramidal system. Such information is critical to the understanding of the physiology of these structures. (Copyright 1972, Academic Press, Inc.)

54. Watanabe, S., (Department of Neurosurgery, School of Medicine, Juntendo University, Tokyo, Japan), H. Shimada, and S. Ishii. 1972. Production of clinical form of chronic subdural hematoma in experimental animals. J. Neurosurg. 37:552-561.

A method for producing a clinical form of experimental chronic subdural hematoma is reported. When blood is mixed with cerebrospinal fluid and incubated a peculiar clot is formed which, when inoculated into the subdural space of dogs or monkeys, grows gradually. Histologically the capsule of the hematoma is comparable to that seen in human chronic subdural hematoma. In some animals progressive hemiparesis develops.

- 55 Webster, H. deF. (Laboratory of Neuropathology and Neuro-anatomical Sciences, Institute of Neurological Diseases and Stroke, NIH, Bethesda, MD 20014), and S. M. Billings. 1972. Myelinated nerve fibers in xenopus tadpoles: *In vivo* observations and fine structure. J. Neuropath. Exp. Neurol. 31(1):102-112.

The differential interference (Nomarski) microscope was used to examine myelinated nerve fibers in the tails of living *Xenopus* tadpoles. Moving axonal mitochondria were observed at nodes of Ranvier and in growing sprouts. Schwann cells traveled toward naked axons and surrounded them. In general, the fine structure of these myelinated fibers was similar to that found in other species during development. In this preparation of living nervous tissue, myelinated fibers can be observed in their natural environment where they are relatively accessible for experimental manipulation. Our results suggest that this model system deserves further study by experimental neuropathologists.

56. Zeller, W. J. (Institut für experimentelle Toxikologie und Chemotherapie), and S. Ivakovic. 1972. Carcinogenic action of a single subcutaneous application of n-butyl-nitrosourea to newborn rats. Z. Neurol. 202:121-127.

17 animals out of a group of 25 Sprague-Dawley rats, injected subcutaneously with 120 mg/kg n-butyl-nitrosourea on their first day of life, developed 29 neurogenic malignancies. The medium induction time of the tumors was about 290 days. Tumors were never seen at site of injection. 5 animals still alive will be observed until their natural death. The single application of n-butyl-nitrosourea (BNU) to newborn rats is considered to give a simple and appropriate model for the induction of neurogenic tumors in neuro-oncological studies.

REPRODUCTIVE SYSTEM

57. Myers, R. E. (Laboratory of Perinatal Physiology, National Institute of Neurological Diseases & Stroke, NIH, Bethesda, MD 20014). 1972. The gross pathology of the rhesus monkey. Acta Endocrinol. (Suppl 166):221-257.

Cases are described which depict the spontaneously occurring abnormalities in attachment and patterns of pathology which afflict the placenta in the rhesus monkey. These findings demonstrate that the rhesus monkey, as a species, is subject to much the same spectrum of pregnancy abnormalities as is the human. The incidence figures for these abnormalities are surprisingly similar among the two species as are the mortality and morbidity figures. These findings recommend

the rhesus monkey as a suitable model for the study not only of normal *in utero* growth and development but also of the disease processes which affect the developing placenta and fetus.

RESPIRATORY SYSTEM

58. Gold, W. M. (Cardiovascular Research Institute, Specialized Center of Research in Pulmonary Disease, University of California, San Francisco, CA 94122), G.-F. Kessler, D. Y. Yu, and O. L. Frick. 1972. Pulmonary physiologic abnormalities in experimental asthma in dogs. J. Appl. Physiol. 33:496-501.

In anesthetized, paralyzed, artificially ventilated dogs, we studied the pulmonary physiologic abnormalities in acute asthma which was induced by aerosols of *Toxocara canis*, *Ascaris suum*, or grass pollen extracts. Respiratory resistance measured by the forced oscillation method increased an average of 262 percent of control after 5-10 min of aerosol and remained increased for 35 min. Pulmonary compliance decreased an average of 23.7 percent below control and returned nearly to control levels within 20-30 min. No significant changes were observed in single breath CO diffusing capacity, alveolar volume, or systemic blood pressure. A single large inflation of the lungs produced temporary, often complete reversal of compliance, but never complete or lasting reversal of resistance. Significant decreases occurred in arterial PO_2 , arterial pH, and heart rate. Tantalum bronchograms showed bronchoconstriction of all airways from trachea to 1-mm bronchi. Although the abnormalities of resistance and compliance were completely corrected by bronchodilators, hypoxemia persisted. These studies indicate that dogs are suitable subjects for the study of experimental asthma; the changes in airway structure and function appear similar to those in human asthmatic patients.

59. Marco, V. (Pulmonary Disease Section, Albert Einstein Medical Center, Philadelphia, PA 19141), D. R. Meranze, M. Yoshida, and P. Kimbel. 1972. Papain-induced experimental emphysema in the dog. J. Appl. Physiol. 33(3):293-299.

Two doses of 3 ml of an 8 percent or 16 percent solution of aerosolized papain were administered to dogs with a 1-week interval. The dogs were killed 5 weeks after the first treatment. Lesions resembling human pulmonary emphysema were observed and consisted of enlargement of terminal airways with destruction and loss of alveoli. Inflammatory reaction was minimal or absent. There was a dose-effect relationship in the extent of destruction and physiologic abnormalities. In the 16 percent group, PC tended to increase by 21.2 percent ($P < 0.1$) and end-expiratory Ppl decreased

significantly by 41.7 percent ($P < 0.05$), indicating loss of elastic rerecoil. V_D tended to increase by 15.9 percent ($P < 0.1$) and steady-state DL_{CO} decreased significantly by 39.6 percent ($P < 0.05$). No appreciable changes were detected in C_{dyn} and R_t . No physiologic changes were observed in the control or 8 percent papain groups. Lesions were produced rapidly and could be detected in acute experiments 3 hr after a single 16 percent papain treatment. Papain heated to 100°C for 10 min produced no lesions. This, and the rapidity of development of lesions suggest that the proteolytic action of papain is responsible. Endogenous enzymatic proteolysis could also be a mechanism in at least some forms of human emphysema. This animal model can serve as an experimental tool for the study of anatomical-physiological relationships in emphysema.

60. McAdams, A. J. (Children's Hospital Medical Center, Elland & Bethesda Avenue, Cincinnati, OH 45229), R. Coen, L. I. Kleinman, R. Tsang, and J. Sutherland. 1973. The experimental production of hyaline membranes in premature rhesus monkeys. Am. J. Path. 73:277-290.

When premature rhesus monkeys are ventilated with oxygen or air, hyaline membranes are formed within 5 minutes in alveolar ducts and respiratory bronchioles. Studies with fluorescein-labeled antiserum to porcine pepsinogen provide evidence that the monkey fetuses have aspirated gastric fluid. The findings suggest that some component of gastric fluid plays an important role in the formation of the hyaline membranes, either directly by causing necrosis of susceptible bronchiolar epithelium or secondarily by sensitizing the bronchiolar epithelium to another necrotizing agent such as oxygen.

61. Ryan, S. F. (Department of Pathology and the Cardiopulmonary Laboratory, St. Luke's Hospital Center, New York, NY 10025). 1972. Experimental fibrosing alveolitis. Am. Rev. Resp. Dis. 105:776-791.

Lung damage induced in the Syrian golden hamster by weekly subcutaneous administration of N-nitroso-N-methylurethane was serially studied by light and electron microscopy on inflation-fixed lungs. The evolution of the lesion closely resembled that in human fibrosing alveolitis, beginning as an acute alveolitis, often with hyaline membrane formation, and progressing through a stage of chronic interstitial inflammation to interstitial fibrosis with honeycombing and epithelial proliferation. The interstitial inflammation and fibrosis were demonstrated by electron microscopy to occur only in the connective tissue part of the interalveolar septum, which normally lies between two networks of capillaries. The capillary basement membrane itself was not thickened. In the later phases of the process, a marked decrease in the number of alveolar capillaries occurred. Damage to alveolar epithelial cells was a prominent feature of the

lesion. The repair of this damage appeared to involve proliferation of type II epithelial cells. Later, the alveoli became lined by bronchiolar type epithelium.

SKIN AND ADNEXA

62. Cho, S. I., F. S. Marcus, and S. L. Kountz (Department of Surgery, 884-M, University of California, San Francisco, CA 94122). 1972. A new model for study of allograft rejection in the rat: Use of skin with an intact vascular pedicle. I. Effect of vascularity on allograft survival. *Transplantation* 13(5):486-492.

A new model was devised in which rat skin with an intact vascular pedicle was used. The model was constructed by microsurgical technique. Ten skin grafts with vascular pedicle were performed from ACI to Lewis rats and another 10 grafts were performed from Fischer to Lewis rats. The survival time of skin grafts with vascular pedicles, which immediately receive a blood supply after vascular anastomosis, was the same as that of full-thickness skin grafts of same strain combinations. This model demonstrated that organ ischemia and vascular pathways do not have an important role in the primary sensitization of the host by skin grafts.

63. Dick, H. M. (Department of Bacteriology, Royal Infirmary, Glasgow, Scotland), and J. E. Baird. 1972. An animal model for staphylococcal toxic epidermal necrolysis. *Br. J. Derm.* 86(Suppl. 8):28-34.

Three strains of phage type "71" coagulase-positive staphylococci, 2 from cases of toxic epidermal necrolysis (T.E.N.) and 1 from a case of impetigo, produced a response clinically and histologically similar to human staphylococcal T.E.N. after subcutaneous injection into 3-day old mice. The experimental lesion progressed from the development of erythema and a positive Nikolsky sign to generalized peeling of the superficial skin and death. The response in mice was shown to be dependent both on the dose of organisms and on the age of the mice. The significance of this mouse model in relation to human staphylococcal T.E.N. is discussed.

64. Dillard, S. H. (Department of Pathology, Vanderbilt University School of Medicine, Nashville, TN 37232), W. J. Cheatham, and H. L. Moses. 1972. Electron microscopy of zosteriform herpes simplex infection in the mouse. *Lab. Invest.* 26(4):391-402.

Superficial inoculation of the depilated skin of young mice with a neurotropic strain of herpes simplex results in a dermatomal cutaneous eruption and infection of segmental nerves, their ganglia, and the

autonomic nervous system. This proposed model of herpes zoster of man was studied using the electron microscope. Major differences in viral replication were observed in the various cell types involved in the neural spread. Efficient production of complete, presumably infectious, viral particles was seen almost exclusively in epidermal cells and in neurons of dorsal root ganglia and autonomic nerves; replication was almost exclusively incomplete in other cells involved, including Schwann cells, endoneurial cells, perineurial cells, and satellite cells. Evidence of viral infection in Schwann cells was seen only in cells associated with unmyelinated axons, and no evidence of infection was seen in Schwann cells of heavily myelinated fibers; no viral particles were unequivocally demonstrated in axons or within extracellular neural spaces. The observations make cell to cell spread in Schwann or endoneurial cells unlikely as an explanation of neural spread of herpesvirus. Although the possibility of transport along tissue spaces of the nerves cannot be excluded, the present findings tend to support the hypothesis that spread occurs via axons to produce a primary infection of neurons. The dorsal root ganglion cells sending unmyelinated afferent branches to the skin and to the viscera are proposed as a possible common pathway for the neural spread of herpes simplex virus in this present experimental situation and for the neural spread of herpes zoster in man.

65. Goldschmidt, F. (Johnson & Johnson Research, North Brunswick, NJ 08903). 1972. Reproducible topical staphylococcal infection in rats. Appl. Microbiol. 23(1):121.

A topical infection model for the study of the effectiveness of antimicrobials was developed. Animals were laparotomized, sutured with braided silk, and inoculated with a strain of *Staphylococcus aureus*. The test organism was phage typed and its antibiotic spectrum was determined. Concentrations of bacteria from 5×10^4 to 10^8 cells per incision produced large body wall stitch abscesses with occasional drainage through the skin. This laparotomy infection is readily reproducible and can be used for evaluation of the ability of topical antimicrobials to prevent *S. aureus* stitch abscesses.

66. Robinson, T. W. E. (Department of Dermatological Histology, University College Hospital Medical School, University Street, London, W. C. 1 U.K.), and J. R. Dover. 1972. Experimental zosteriform herpes simplex virus infection in mouse skin. Br. J. Derm. 86:40-48.

A highly reproducible model in which linear zosteriform lesions are produced in the skin of Webster Schneider mice, using an oral strain of herpes simplex virus, (HSV) is described. The incidence of infection is high, and a large proportion of infected animals develop a highly characteristic ascending paralysis which is invariably fatal.

67. Saymen, D. G. (Departments of Physiology, Surgery, and Microbiology, University of Cincinnati College of Medicine, Cincinnati, OH 45219), P. Nathan, I. A. Holder, E. O. Hill, and B. G. Macmillan. 1972. Infected surface wound: An experimental model and a method for the quantitation of bacteria in infected tissues. Appl. Microbiol. 23(3): 509-514.

Methods for the quantitation of bacteria in infected tissues must be rigidly standardized to insure uniformity of results. In this communication we report on a laboratory animal model for the study of surface wound infection and the development of a standardized method for the quantitative estimation of bacteria in infected surface wound tissue by mechanical tissue homogenization and serial dilution. Parallel comparative studies demonstrated that a moist-swab sampling procedure detected only 10 percent of the bacteria recoverable by a surface-wash procedure. Either tissue homogenization or surface-wash procedures recovered significantly more bacteria from contaminated surface wounds than were obtained by surface-swab sampling techniques.

URINARY SYSTEM

68. Barkin, M. (Hospital for Sick Children, Research Institute, 555 University Avenue, Toronto, Ontario, Canada), R. D. Jeffs, and E. J. Hambley. 1972. A model for the study of hyperacute renal rejection. Invest. Urol. 9(6):475-479.

Hyperacute rejection is a catastrophic occurrence, often predictable by the presence of preformed antibodies in the recipient. Previous research into the therapy of this entity has been hampered by the unavailability of an adequate experimental model that reproduces hyperacute rejection in the absence of superimposed acute rejection. These experiments describe the development of such a model. Hyperacute rejection can be simulated in the autografted canine kidney if it is perfused with a xenogeneic (human) plasma perfusate prior to reautotransplantation. The clinical course and histologic picture are indistinguishable from hyperacute rejection. Moreover, because this is an autograft, cell-mediated acute rejection should not occur.

69. Collins, G. R. (Department of Animal Care, Northwestern University Medical School, 303 East Chicago Avenue, Chicago, IL 60611), C. R. Goodheart, and D. Henson. 1972. Spontaneous heritable hydronephrosis in inbred mice. 1. Description, incidence, and distribution of lesions. Lab. Anim. Sci. 22(3):333-338.

Hydronephrosis, unassociated with the 4 mutant genes known to produce hydronephrosis pleiotropically, and not fitting the description of other reported cases, was discovered in 4 inbred strains of

mice. Statistical analysis of data collected from 1,467 mice was performed by a Univac computer. The afflicted mice were remarkably asymptomatic. Males (32 percent) had a significantly higher overall incidence than females (24.1 percent). Right kidneys were affected more frequently than left kidneys, in both sexes. Age did not appear to influence the incidence or expressivity. Histopathological studies suggest congenital ureteropelvic dyskinesia as the descriptive diagnosis.

70. Elhilali, M. M. (Urology Department, Centre Hospitalier Universitaire, Sherbrooke, Quebec, Canada), S. K. Nayak, and C. Brailovsky. 1972. A transplantable human bladder cancer in the unconditioned Syrian hamster. Invest. Urol. 10(3):230-234.

Human bladder cancer tissues obtained from four patients were cultured. Two cell lines could be obtained. Heterotransplantation to Syrian hamsters with and without cortisone conditioning was carried out. Tumor take-up was obtained in the hamster cheek pouch without cortisone treatment after 3 days. Tumor take-up after subcutaneous transplantation with cortisone treatment was obtained after 10 to 12 days. The group of hamsters transplanted in the subcutaneous tissue but without immunosuppression at any time developed tumors after 18 to 21 days. Subsequent transplantation of this tumor without immunosuppression after the fifth passage resulted in tumor take-up after 12 to 15 days. This human bladder cancer model in unconditioned hamsters lends itself more readily to immunologic and chemotherapeutic studies.

71. Hartenbower, D. J. (Research & Medical Services, VA Hospital (Wadsworth), Wilshire & Sawtelle Boulevards, Los Angeles, CA 90073), and J. W. Coburn. 1972. A model of renal insufficiency in the chick. Lab. Anim. Sci. 22(2):258-261.

A method for producing chronic renal insufficiency in the chick was described. By ureteral ligation, the function of 1 kidney was completely eliminated, and the functional mass of the other was reduced by two-thirds. The method resulted in elevation of plasma concentrations of uric acid, the major product of protein catabolism present in avian plasma, to levels 2-4 times normal for periods as long as 3 weeks. The procedure was relatively simple with a low operative mortality, and it provided a useful and convenient animal model for renal insufficiency.

72. Holter, A. R. (Departments of Surgery and Pathology, University of Chicago, Chicago, IL 60637), T. J. McKearn, M. R. Neu, F. W. Fitch, and F. P. Stuart. 1972. Renal transplantation in the rabbit. I. Development of a model for study of hyperacute

rejection and immunological enhancement. Transplantation
13(3):244-249.

A surgical technique for renal allografting has been developed in the rabbit which permits immediate bilateral nephrectomy of the recipient; postoperative uring output and blood urea nitrogen (BUN) values then become indicators of transplant function. The model was used to determine whether passive immunization with alloimmune antidonor IgG or its pepsin digest F(ab')² fragment would cause hyperacute rejection of a renal allograft. For 13 allograft controls, the onset of uremia began at 5.4 ± 0.2 (SE) days after surgery; they died after 9.0 ± 0.7 (SE) days. Five rabbits that received antidonor IgG i.v. at the time of transplantation sustained massive cortical necrosis of their allografts within 24 hr (hyperacute rejection). Hyperacute rejection was not observed among 5 rabbits that received antidonor F(ab')².

73. Kuntz, R. E. (Division of Microbiology & Infectious Diseases, Southwest Foundation for Research and Education, San Antonio, TX 78228), A. W. Cheever, and B. J. Myers. 1972. Proliferative epithelial lesions of the urinary bladder of nonhuman primates infected with *Schistosoma haematobium*. J. Nat. Cancer Inst. 48:223-235.

Lesions with the morphologic characteristics of papillary transitional cell carcinomas of the urinary bladder were found in a talapoin monkey and a capuchin monkey infected with *Schistosoma haematobium*, and a papilloma of the ureter was found in an infected African baboon. Marked proliferation and squamous metaplasia of the bladder epithelium were seen in 2 squirrel monkeys and in 1 capuchin monkey. These lesions were seen 5-24 months after infection of the monkeys. Epithelial proliferation was topographically related to the presence of *S. haematobium* eggs in the lamina propria of the bladder. This and the absence of reports of spontaneous bladder cancer in monkeys suggest that the proliferative lesions were caused by the schistosome infection. The relatively small number of capuchin, talapoin, and squirrel monkeys at risk during the period in which tumors developed suggests that infected animals of these species may offer useful models for the study of bladder cancer.

74. Machado, E. A. (II Center of Pathology, Faculty of Medicine, University of Buenos Aires, Argentina), and B. B. Iozzio. 1972. Congenital renal structural alterations in a mutant strain of rats. Invest. Urol. 10(1):78-83.

The structural alterations of the urinary tract occurring in rats suffering from a hereditary renal disease are described. The disease is inherited as an autosomal dominant gene. Unilateral and bilateral hydronephrosis with and without obstruction of the lower

urinary tract were the most common abnormalities observed (52.2 percent of 1,824 rats studied). Other kidney lesions, accounting for 6.2 percent, included: cicatricial scars, renal arteriosclerosis, solitary cysts, pyelonephritis, nephroblastomas, and the persistence of connective tissue bundles in adult rats. The remaining animals (41.6 percent) were found to have normal urinary tracts. Despite the severity of renal damage, such as that seen in animals with severe bilateral hydronephrosis, the rats survive, grow, and reproduce in apparently healthy condition. The studies reported are of biomedical importance from both theoretical and practical aspects. Thus, this animal is a useful model for the study of the pathogenesis of hydronephrosis and as a guide for experimental surgical correction of the damaged kidney.

75. McGeoch, J. E. M. (Tenovis Research Laboratory, Southampton General Hospital, Southampton SO9 4XY, U.K.), M. A. Woodhouse, and E. M. Darmady. 1972. Experimental infantile polycystic kidney in rats. The influence of age and sex. Br. J. Exp. Path. 53:322-340.

The nephrotoxic effects of an anti-inflammatory compound 5,6,7,8, tetrahydrocarbozole-3-acetic acid in rats were found to be age and sex correlated. Morphologically the experimental lesion mimicked infantile polycystic disease. Application of the drug produced a lowering of the serum gamma globulins, a rise in the urinary protein and an increase in kidney weight associated oedema and hyperplasia of the proximal and distal tubules.

76. Murray, G., R. G. Wyllie, G. S. Hill, P. W. Ransen, and R. H. Heptinstall (Department of Pathology, The Johns Hopkins Hospital, Baltimore, MD 21205). 1972. Experimental papillary necrosis of the kidney. I. Morphologic and functional data. Am. J. Path. 67:285-302.

Papillary necrosis was produced in rats by a single intravenous injection of bromoethylamine hydrobromide (BEA). The earliest changes as seen by light microscopy were necroses of the limbs of Henle and eosinophilic droplets in collecting ducts. Complete necrosis of the papilla took place between 4 and 7 days and the dead papilla was usually sequestered completely by 21 days. Cortical changes occurred secondary to papillary necrosis. Tubular atrophy and loss was greatest in the deeper parts of the central cortex, the more superficial nephrons frequently being spared. The perihilar cortex was the least involved. This distribution was considered to be related to the respective lengths of the limbs of Henle, nephrons with limbs extending into the papilla being those undergoing change. Increased urine output occurred during the first day and continued thereafter. There was a profound defect in concentrating ability.

77. Roberts, J. A. (Section of Urology, Delta Regional Primate Research Center, Covington, LA), J. D. Clayton, and G. J. Domingue. 1972. Experimental pyelonephritis in the monkey. Invest. Urol. 9(6):449-453.

The technique of hematogenous infection at the time of renal tubular obstruction by oxamide crystals was used to produce acute and chronic pyelonephritis in *Macaca arctoides* (stumptail monkey). As in other animals both tubular obstruction and bacteria rapidly disappear from the kidney and late pathologic change is minimal. The renal concentrating defect of pyelonephritis was found to continue after bacteria were absent from urine and kidney. The L-forms of bacteria were not produced, and antibodies to common antigen were not found following infection.

78. Roberts, J. A. (Urology Laboratory, Tulane University Medical Center, New Orleans, LA), J. D. Clayton, and F. J. Mather. 1972. Ureteral physiology in the monkey. Invest. Urol. 9(4):264-270.

The physiology of the ureter of *Macaca mulatta* and *Macaca arctoides* was studied and compared to data obtained in humans and dogs. The monkey has ureteral pressures quite similar to those of man and shows no vesicoureteral reflux. It would appear, therefore, that the monkey offers an acceptable model for the study of ureteral physiology and pathology found in man.

79. Smith, J. C., Jr. (Trace Element Research Laboratory, VA Hospital, Washington, D.C. 20422), and E. C. McDaniel. 1972. Increased urolithiasis in germfree rats. Invest. Urol. 9(6):518-519.

An increased incidence of urolithiasis in germfree rats has been confirmed. In a total of 41 germfree and 22 conventional animals, 66 percent of the germfree rats exhibited grossly visible calculi in either the bladder, ureters, and/or kidneys. In contrast, only 9 percent of the conventional rats developed urolithiasis when fed the identical diet. There was a higher incidence for males than females in both environments. The calculi as analyzed by X-ray diffraction was composed mainly of weddellite ($\text{CaC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$) plus an organic phase which was not collagen or urea. The germfree rat fed the described calculogenic diet could be a useful model for studying calculi formation.

80. Soloway, M. S. (Department of Surgery, University Hospital), Cleveland, OH 44106, G. H. Myers, Jr., J. A. C. Marrone, P. R. Del Vecchio, and R. A. Malmgren. 1973. Evaluation of urinary cytology as an indicator of bladder neoplasia in mice. J. Urol. 109:249-252.

Urine specimens were obtained periodically from mice receiving a potent bladder carcinogen, FANFT, to determine if urinary cytology could be used to indicate the presence of the tumors. The identification of atypical transitional cells and red blood cells in the specimens coincided with the development of the bladder tumors. Recognition of cellular atypia or microhematuria was equally reliable as an indicator of the presence of bladder neoplasia. It is believed that monitoring for the presence of erythrocytes is a particularly simple and accurate method to indicate the presence of bladder tumors in this experimental model.

81. Tomashefsky, P. (Department of Urology, College of Physicians and Surgeons, Columbia University, New York, NY), J. Furth, J. K. Lattimer, M. Tannenbaum, and J. Priestley. 1972. The Furth-Columbia rat Wilms tumor. J. Urol. 107:348-354.

This study presents a description of a Wilms tumor in rats which grows morphologically and biologically in a manner closely parallel to the Wilms tumors found in children. The tumor metastasized to the lung, preferentially, as in humans and chemotaxis tests verified the fact that lung tissue is more acceptable to the tumor than other tissues. The animal tumor thus provides a reasonable tool for the further study of this neoplasm in controlled systems.

AUTOIMMUNE - ALLERGIC DISEASES

82. Malley, A. (Oregon Regional Primate Research Center, 505 Northwest 185 Avenue, Beaverton, OR 97005), and L. Beacher. Hyper-sensitivity induced in rhesus monkeys. Oregon Regional Primate Research Center, Publ. No. 536, 42(1):36-42.

The present study demonstrates that intracutaneous inoculations of bacterial enzymes (Novo alcalase and Monsanto DA-10) used in laundry detergents induce significant levels of homocytotropic antibody in rhesus monkeys. None of the animals immunized with these bacterial enzymes developed either Arthus or delayed skin reactions during the duration of this study. The ability to induce atopic reactions in rhesus monkeys with bacterial enzymes used in laundry detergents provides an animal model which permits evaluation of: (1) the relative allergenicity of bacterial enzymes and (2) the changes in bronchial or alveolar functions at various stages after sensitization.

83. Wick, G. (Department of General and Experimental Pathology, University of Vienna, Medical School, A-1090, Vienna, Austria), and R. Steiner. 1972. Simultaneous induction of experimental

allergic encephalomyelitis in obese strain (OS) chickens with spontaneous, hereditary autoimmune thyroiditis. J. Immunol. 109(3):471-474.

Experimental allergic encephalomyelitis (EAE) was elicited in Obese strain (OS) chickens, which develop a spontaneous autoimmune thyroiditis, and in normal White Leghorn (NWLH) chickens by immunization with bovine spinal cord and complete Freund's adjuvant alone or Freund's adjuvant and pertussis vaccine. Control groups were similarly immunized with bovine liver. OS chickens developed severe EAE without any influence on the frequency and severity of spontaneous thyroiditis and on the occurrence of circulating thyroglobulin autoantibodies. The use of pertussis vaccine as a coadjuvant led to slightly more severe EAE in both NWLH and OS birds as compared to Freund's adjuvant alone. Immunization with bovine spinal cord resulted not only in the formation of antibodies to this antigen but also to the appearance of circulating brain autoantibodies in OS and NWLH chickens. This avian model which simultaneously displays a spontaneous and an experimentally induced autoimmune disease should provide a very useful tool for the study of the role of the bursa- and thymus-dependent part of the immune system in the development of these diseases.

BACTERIAL DISEASES

84. Mellins, R. B. (Departments of Pediatrics and Pathology, Columbia University, College of Physicians and Surgeons, New York, NY 10032), O. R. Levine, H. J. Wigger, G. Leidy, and E. C. Curnen. 1972. Experimental meningococemia: Model of overwhelming infection in unanesthetized monkeys. J. Appl. Physiol. 32(3):309-314.

A model of overwhelming infection was developed in the unanesthetized primate by the intracisternal injection of meningococci and 5 percent mucin. Eight out of nine monkeys died. The model is characterized by progressive fall in cardiac output and renal blood flow, maintenance of systemic arterial and central venous pressure close to control values, elevation of systemic vascular resistance, absence of significant changes in clincial tests of hemostasis, development of meningococemia and death in 5-15 hr, and the presence of intravascular aggregates of fibrin, platelets, and polymorphonuclear leukocytes in kidney, liver, and lung at postmortem examination. The intracisternal injection of pneumococci (5 monkeys) resulted in bacteremia and death but without consistent changes in cardiac output or systemic vascular resistance. The intracisternal injection of meningococci (4 monkeys) or mucin (4 monkeys) and the intravenous injection of meningococci (4 monkeys) did not result in significant cardiovascular alterations.

NUTRITIONAL - METABOLIC DISEASES

85. Blake, R. L. (Jackson Laboratory, Bar Harbor, ME 04609), and E. S. Russell. 1972. Hyperprolinemia and prolinuria in a new inbred strain of mice, PRO/Re. Science 176:809-810.

This report describes the discovery of an unusual biochemical characteristic of proline metabolism, hyperprolinemia, occurring in a new inbred strain of mice now designated the PRO/Re strain. An elevation of the blood concentration several times that in the normal animal is indicative of an "overflow" type disorder of amino acid metabolism, perhaps similar to one of the types of hyperprolinemias known to occur in human beings. We believe that the PRO/Re strain may serve as an animal model for similar types of biochemical disorders in man and may also be useful in studies on (i) the comparative biochemistry and physiology of mammalian proline metabolism, (ii) the genetic transmission of biochemical traits, and (iii) the structural and functional organization of the genome in *Mus musculus* (12). (Copyright 1972 by the American Association for the Advancement of Science)

86. Coward, D. G. (Medical Research Council Child Nutrition Unit, P.O. Box 6717, Kampala, Uganda), and R. G. Whitehead. 1972. Experimental protein-energy malnutrition in baby baboons. Attempts to reproduce the pathological features of kwashiorkor as seen in Uganda. Br. J. Nutr. 28:223-237.

The object of this investigation was to produce an animal model of kwashiorkor like that seen in Ugandan children. In the initial studies the baby baboons were weaned at 8-10 weeks of age and given a full-cream milk diet for 2 weeks. The milk intake was then gradually reduced and local staples with a low-protein, high-carbohydrate content were provided instead. Maintaining the baby baboons for as long as 100 d on this diet markedly impaired body growth but it did not result in a 'kwashiorkor-like' appearance. Subsequent stressing of the animals by the introduction of periods of energy restriction did apparently precipitate them into a clinical condition in many ways reminiscent of kwashiorkor. The baboons exhibited extreme mental apathy, and had sparse hair, oedema of the limbs and face, and skin lesions similar to the flaky-paint rash found in severely malnourished children, but there was no gross accumulation of fat in the liver. The basal diet was subsequently modified by the addition of sucrose to bring the carbohydrate composition more into line with that in food eaten by local Ugandan children. This relatively minor change seemed to cause a more rapid clinical deterioration and the animals did develop fatty livers as well as the other pathological changes. The final condition resembled marasmic kwashiorkor and further modification to the experimental design is required if an animal model truly representative of the more typical Ugandan type of kwashiorkor is to be reproduced.

87. Falk, J. L. (Department of Psychology, Rutgers University, New Brunswick, NJ 08903), H. H. Samson, and G. Singer. 1972. Behavioral maintenance of high concentrations of blood ethanol and physical dependence in the rat. Science 177:811-813.

Rats maintained on an intermittent food schedule with an available ethanol solution drink to excess (13.1 grams of ethanol per kilogram of body weight, daily). Removal of ethanol produces symptoms of physical dependence including death from tonic-clonic seizures. Overindulgence in oral self-administration of an aqueous ethanol solution, resulting in unequivocal physical dependence, approximates a model of human alcoholism. (Copyright 1972 by the American Association for the Advancement of Science)

88. Jakob, W. (Abteilung für Pathologie des Institutes für Vergleichende, Pathologie der Deutschen Akademie der Wissenschaften zu Berlin, Berlin). 1971. Spontaneous amyloidosis of mammals. Vet. Path. 8:292-306.

Spontaneous amyloidosis is known in more than 30 mammalian species. Various patterns of mammalian amyloidosis are reviewed. On the basis of the anatomical distribution of the amyloid deposits a distinction is made between patterns with typical amyloid distribution, patterns with atypical distribution, and so-called intermediate or mixed patterns. Staining, histochemical, and electron microscopic properties of amyloid and possible etiological factors of amyloidosis in different mammalian species are briefly discussed.

89. Pieper, W. A. (Yerkes Regional Primate Research Center, Emory University, Atlanta, GA 30322), M. J. Skeen, H. M. McClure, and P. G. Bourne. 1972. The chimpanzee as an animal model for investigating alcoholism. Science 176:71-73.

Young chimpanzees (*Pan troglodytes*) will accept ethanol in quantities sufficient to produce symptoms of withdrawal when ethanol is subsequently discontinued. Mild to severe symptoms of physical dependence, including grand mal seizures, are observed when ethanol is abruptly withdrawn after 6 to 10 weeks of chronic oral intake. In addition, the rate of disappearance of ethanol in blood increased during periods of chronic ingestion, an indication of developing metabolic tolerance. These results suggest that the young chimpanzee may be a suitable model for experimental studies of alcoholism. (Copyright 1972 by the American Association for the Advancement of Science)

BEHAVIOR

90. Butcher, R. F. (Children's Hospital Research Foundation, Elland Avenue and Bethesda, Cincinnati, OH 45229), R. M. Stutz, and H. K. Berry. 1971. Behavioral abnormalities in rats with neonatal jaundice. *Am. J. Ment. Defic.* 75:755-759.

Gunn rats are a Wistar substrain in which an enzymatic defect leading to neonatal jaundice and brain damage is inherited as a recessive trait. In 3 experiments, the behavior of homozygous (jj), brain-damaged animals of the Gunn strain was compared to that of asymptomatic littermate controls (JC). Despite the locomotor impairment (ataxia) present in the jj rats, their open field and activity-cage activity levels equalled or exceeded that of controls. In a swimming maze, the jj rats made more errors than JC subjects in learning to escape from water. Because the hyperactivity and learning impairment observed in the jj Gunn rat results from physiological events which closely parallel those found in humans, it is believed that the systematic examination of the behavior of these animals will contribute significantly to the comparative study of mental retardation.

91. Davenport, R. Y. (Yerkes Regional Primate Research Center, Emory University, Atlanta, GA 30322), and Rogers, C. M. 1970. Inter-modal equivalence of stimuli in apes. *Science* 168:279-280.

Apes are capable of equating visual with haptic stimulation. The capability for intermodal communication and perception and the neurological foundations for that capability can be investigated with the ape as an animal model. Results might shed light upon human speech, intelligence, and certain reading disorders. - D.M.R.

92. Davenport, R. K. (Yerkes Regional Primate Research Center, Emory University, Atlanta, GA 30322), C. M. Rogers, and D. M. Rumbaugh. 1973. Long-term cognitive deficits in chimpanzees associated with early impoverished rearing. *Dev. Psych.* 9:343-347.

Early social restriction during the first two years of life has long-term and probably irreversible effects upon the intelligence of chimpanzees (*Pan*). Apes are excellent subjects for studies directed to the effects of early environment upon the development of cognition and social skill. - D.M.R.

93. Gardner, G. T., and R. A. Gardner. 1971. Two-way communication with an infant chimpanzee. In A. Schrier, and F. Stollnitz (eds.), *Behavior of non-human primates*. Academic Press, pp. 117-184.

The results of this research with an infant chimpanzee cause us to reconsider the conclusion that man is the only life form capable of language. The chimpanzee, Washoe, learned a large number of hand signs and, from time to time, chained them appropriately into strings that remind us of sentences. Apes are probably the only reasonable subjects for those who wish to explore non-human primate behaviors relevant to the language processes of man. - D.M.R.

94. Harlow, H. F. (Primate Laboratory, Department of Psychology, University of Wisconsin, Madison, Wisconsin), M. K. Harlow, and S. J. Suomi. 1971. From thought to therapy: Lessons from a primate laboratory. Am. Scien. 59(5):538-549.

The rhesus (*Macaca mulatta*) monkey when raised as a social isolate becomes compromised in the acquisition of social and communication skills. The longer and more complete the isolation, the more profound the behavioral damage. Reversal of behavioral deficits can be achieved through use of young monkey "therapists." The rhesus monkey provides a good model for developmental studies of socialization processes. - D.M.R.

95. Rose, R. M. (Department of Psychosomatic Medicine, Boston University School of Medicine, Boston, MA 02118), T. P. Gordon, and I. S. Bernstein. 1972. Plasma testosterone levels in the male rhesus: Influences of sexual and social stimuli. Science 178:643-646.

Aggression and sexual behavior are demonstrated to be associated with variations in testosterone levels, which, in turn, can be reliably altered by social encounters and exposure to female rhesus (*Macaca mulatta*) in estrous. - D.M.R.

96. Rumbaugh, D. M. (Department of Psychology, Georgia State University, Atlanta, GA 30303). 1971. Evidence of qualitative differences in learning processes among primates. J. Comp. Physiol. Psychol. 76:250-255.

Evidence is presented to support the contention that with evolution of the primate brain there has been the emergence of new learning processes that are abstractive/ideational in character. Data support the conclusion that whereas great apes (*Gorilla*) learn abstractively, talapoin (*Miopithecus*) learn in accordance with more primitive stimulus-response associationistic processes. Dimensions of human intelligence might be better understood through intensive study of learning processes in relation to brain development as found in great variation within the order Primates. - D.M.R.

97. Zimmermann, R. R. (Department of Psychology, University of Montana, Missoula, MT 59801). 1973. Effects of age, experience, and malnourishment of object retention in learning set. *Percept. Mot. Skills* 28:867-876.

The rhesus monkey (*Macaca mulatta*) constitutes a reasonable animal model for studying the long-term effects of protein deficiency upon selected behaviors of man. - D.M.R.

CANCER RESEARCH

98. Bazin, H. (Avenue Chapelle-aux-Champs, 4, 1200 Brussels, Belgium), C. Deckers, A. Beckers, and J. P. Heremans. 1972. Transplantable immunoglobulin-secreting tumours in rats. I. General features of LOU/Wsl strain rat immunocytomas and their monoclonal proteins. *Int. J. Cancer* 10:568-580.

This article describes a peculiar tumour which originates in the ileocecal lymph node of the LOU/Wsl strain rat. The tumour cells usually have the appearance of very poorly differentiated lymphoid cells showing a tendency to develop ribosome-studded ergastoplasmic membranes. In about 60 percent of the cases, such tumours synthesize monoclonal immunoglobulins of the IgG or IgA class, or Bence-Jones proteins. These tumours are readily transplantable in isologous hosts or their F¹ hybrids. The great majority of the transplanted growths retain their capacity for immunoglobulin production during many successive passages *in vivo*. A scrutiny of older and more recent literature has revealed several descriptions of rat tumours having the same macroscopic and microscopic features as the tumours described here, except for the immunoglobulin-secreting properties which were never tested in the earlier studies. It is proposed to call this tumour the rat ileocecal immunocytoma.

99. Cuprak, L. J. (VA Hospital, Leech Farm Road, Pittsburgh, PA 15206), and W. F. Lever. 1972. A hamster fibrohemangiosarcoma: Influence of host sex on tumor mass. *Proc. Soc. Exp. Biol. Med.* 141(2):494-498.

A fibrohemangiosarcoma was produced in hamsters following the injection of cell inocula. These tumors in pregnant, lactating female hamsters attained a wet tumor weight 4-8 times greater than that noted in either adult male or female hamsters within 6-7 wk. Monolayer cell cultures obtained from a fibroma produced by the injection of cells from a Wistar Institute HE-44 culture in its 69th passage was alternately repassaged through inbred Syrian hamsters. Following the fourth animal repassage a culture line was obtained which consistently through the 16th subculture produced tumors composed of spindle cells, endothelial cells and cells intermediate between

these two types of cells. It is considered likely that the culture line consisted of mesenchymal cells that have retained some degree of pluripotentiality. Strong acid phosphatase, β -glucuronidase and nonspecific esterase activity was present in the cells of the tumor tissue as well as in the cells grown in culture for 16 passages. It is probable that hormonal influences associated with growth are responsible for the observed differences in wet tumor weight in pregnant and nonpregnant hamsters. This tumor showed histologic resemblance to the human Kaposi sarcoma.

100. Eulderink, F. (Pathologisch Laboratorium der Rijksuniversiteit, The Netherlands), and Th. G. van Rijssel. 1972. Experimental induction of benign mesenchymal jaw tumours. Path. Europ. 7(2):144-150.

Benign mesenchymal jaw tumours were induced in (WLLf x O₂) F₁ hybrid mice. These mice were treated by röntgen irradiation of the head (one dose of 1000 or 500 rads) and/or chronic mechanical irritation of the intra-alveolar tissues by implanted threads or wires. These tumours closely resemble the benign mesenchymal jaw tumours in man (osteofibroma, cementofibroma) as regards the histological picture, sex ratio, and (probably) their appearance at an earlier age than is found for carcinomas. These tumours were most frequent in mice treated with a combination of irradiation and implantation of nylon threads, especially when the treatment had been started at a relatively young age.

101. Krieg, K. (Institute of Comparative Pathology, German Academy of Science, Berlin, Germany). 1972. Ampullarius australis d'Orbigny (Mollusca, Gastropoda) as experimental animal in oncological research. A contribution to the study of carcinogenesis in invertebrates. Neoplasma 19(1):41-49.

The significance of invertebrates in oncologic research is discussed. Results of investigations so far available indicate that neoplastic growth is exhibited by the so-called "half-stabil" animal species which possesses a limited regenerative capacity. *Ampullarius australis* d'Orbigny, a southern snail species, proved suitable for study. Over a series of eleven experiments 850 snails were injected with a 1 percent oily solution of 20-methylcholanthrene in a dose of 0.1 ml. Following a latency period of 95-150 days neoplastic processes were observed in three percent of the test organisms. Histological examination of these chemically induced tumor tissues showed them to be benign blastomas of epithelial origin. A metastatic process was seen in only one case. Transplantation experiments were carried out on a separate group of 168 snails. A malignant adenopapilloma was passaged successfully through three of the test gastropods. The rate of successful tumor transplant incidence in single passages was 69, 16 and 7 percent. In the transplant group, it was found that prolonged latent periods of the

epithelial tumors of both the induced and transplant category seem to make the gastropods an especially suitable species for further carcinogenic investigation. Invertebrates, by their wide variety of species, phylogenetic position, and readily comprehensible structure present themselves as suitable vehicles for certain types of experimentation. The advantages of using gastropods are discussed in light of their ready availability, ease of maintenance in a laboratory situation and rapid supplementary breeding patterns.

102. Pauley, G. B. (National Marine Fisheries Service, Middle Atlantic Coastal Fisheries Center, Pathology Investigations, Oxford, MD 21655), and C. S. Sayce. 1972. Brief communication: An invasive epithelial neoplasm in a pacific oyster, *Crassostrea gigas*. J. Natl. Cancer Inst. 49:897-902.

In a Pacific oyster (*Crassostrea gigas*) an ulcerative growth was found extending from the external mantle surface through the gonad to the digestive gland. Histologically the lesion was composed of proliferating epithelium-forming, irregular, gland-like or cystic structures that contained deposits of conchiolin and mucin. The lesion is interpreted to be a well-differentiated neoplasm originating from mantle epithelium and retaining the mucus- and conchiolin-secreting functions of that epithelium. While other neoplasms originating from mantle epithelium of oysters have been reported, this is the first example in which conchiolin, the organic matrix of pearl, is produced.

103. Roth, L. M. (Department of Pathology, Tulane University School of Medicine, New Orleans, LA 70112), W. H. Sternberg, R. A. Huseby, A. A. MacPhee, F. E. Cole, and B. F. Rice. 1972. Transplantable luteoma of the mouse -- an ultrastructural and biochemical study. Lab. Invest. 27(1)115-122.

Ultrastructural studies and biochemical characterization of a transplantable mouse luteoma are reported. The tumor cells show fine structural evidence of steroid hormone secretion, as indicated by the presence of abundant smooth endoplasmic reticulum and tubular mitochondrial cristae. Comparison of the fine structure of a transplantable luteoma with that of luteinized stromal cells and granulosa-lutein cells of the mouse ovary suggests an origin of the tumor from luteinized stromal cells. When the luteoma was grown in tissue culture with acetate-1-¹⁴C, labeled 21-OH-pregn-4-ene-3,20-dione (deoxycorticosterone) was identified following crystallization to constant specific activity demonstrating *de novo* synthesis of this steroid. Microgram amounts of this steroid were also measured by gas liquid chromatography. Androst-4-ene-3,17-dione (androstenedione), the major steroid of normal human ovarian stroma and the human luteoma of pregnancy, was measured and was the major androgen found in tissue culture with lesser amounts of testosterone being present. The luteoma possessed

specific receptor sites for luteinizing hormone as demonstrated by a radioligand-receptor assay employing ^{125}I -human luteinizing hormone for binding studies. The ultrastructural studies and the biochemical studies support the gonadal origin of this tumor and its derivation from luteinized stromal cells. The tumor possesses a number of features in common with two human neoplasms, the stromal luteoma and the luteoma of pregnancy.

104. Tashjian, A. H. Jr. (Harvard School of Dental Medicine, Boston, MA 02115), E. F. Voelkel, L. Levine, and P. Goldhaber. 1972. Evidence that the bone resorption-stimulating factor produced by mouse fibrosarcoma cells is prostaglandin E₂. A new model for the hypercalcemia of cancer. J. Exp. Med. 136(6):1329-1343.

A transplantable mouse fibrosarcoma, HSDM₁, produces a potent bone resorption-stimulating factor. The factor can be extracted from the tumor tissue and harvested from the medium of clonal strains of HSDM₁ tumor cells growing in monolayer culture. It has several chemical and biological properties of a prostaglandin. Using radio-immunoassay techniques, we have shown that HSDM₁ cells synthesize and secrete large quantities of prostaglandin E₂ (PGE₂). The specific bone resorption-stimulating activity of the HSDM₁ factor extracted from the tumor is high and approximately equal to that of PGE₂ as measured in bone tissue culture system *in vitro*. Indomethacin, a potent inhibitor of PGE₂ synthesis in HSDM₁ cells, also inhibits production by the cells of the bone resorption-stimulating factor, and has no detectable nonspecific effects on the bone culture assay system. Mice bearing the HSDM₁ tumor have higher levels of both calcium and PGE₂ in serum than control mice. We conclude that PGE₂ is the bone resorption-stimulating factor produced by HSDM₁ tumor cells, and that secretion of PGE₂ by the tumor *in vivo* accounts for the relative hypercalcemia observed in tumor-bearing animals. The HSDM₁ tumor cell system constitutes a new model for studying the pathogenesis of hypercalcemia associated with certain malignant tumors.

TERATOLOGY

105. Warkany, J. (Children's Hospital Research Foundation & Department of Environmental Health, College of Medicine, University of Cincinnati, OH 45229), and H. G. Patterling. 1972. Congenital malformations of the central nervous system in rats produced by maternal zinc deficiency. Teratology 5:319-334.

Teratogenic effects of maternal zinc deficiency in rats have been observed, confirming previous reports. The deficient diet differed in several respects from that used by Hurley and co-workers

but the results were essentially the same. Special attention was given to malformations of the central nervous system and to tissue anomalies not recognizable by gross inspection of the fetuses.

TOXICOLOGY

106. Klein, R. (National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709), S. P. Herman, P. E. Brubaker, and G. W. Lucier. 1972. A model of acute methyl mercury intoxication. Arch. Path. 93:408-418.

A highly reproducible model of acute methyl mercury intoxication in the adult rat is described. Daily subcutaneous injections of methyl mercury hydroxide, 10 mg/kg of body weight were administered for seven days. This dosage schedule initially produced weight loss followed by decreased activity, ataxia, weakness, and the hindlimb-crossing phenomenon. Histological examination of the nervous system revealed advanced peripheral neuropathy, vacuolization and focal neuronophagia of anterior horn neurons, decreased neuron density in selective brain stem nuclei, and pyknotic neurons in the internal granular layer of the cerebellum. Progressive distal convoluted tubular degeneration of the kidney was revealed. Atrophy of malpighian corpuscles, extramedullary hematopoiesis, and increased hemosiderin stores were observed in the spleen. Starved controls were used in order to evaluate the effect of malnutrition. This model should be useful in further animal studies of alkyl mercury intoxication. (Copyright 1972, American Medical Association)

MISCELLANEOUS

107. French, J. W., B. C. Morgan, and W. G. Guntheroth (Department of Pediatrics, University of Washington, School of Medicine, Seattle WA 98195). 1972. Infant monkeys -- a model for crib death. Am. J. Dis. Child. 123:480-484.

Recent reports suggest that sudden infant death syndrome (SIDS) may be related to an inappropriate diving reflex or obligate nose breathing. Immersion of the neonatal monkey's face in (14°C) water, or nasal occlusion resulted in apnea which is occasionally persistent, bradycardia, and relative hypertension. In the same monkeys at an older age, apnea never persisted after removal of the diving stimulus, and there was no obligate nose breathing. The study documents a dive reflex and obligate nose breathing, and concludes that the infant monkey is a suitable model for the study of SIDS. It is suggested, however, that the fatal factor in crib death may be the failure to interrupt apnea however the apnea was initiated. The failure to resume respiration may represent an inappropriate return to the apneic state of the fetus. (Copyright 1972, American Medical Association)

108. Homburger, F. (Bio-Research Institute, Inc , Nine Commercial Avenue, Cambridge, MA 02140). 1972. Models of human disease in inbred Syrian hamsters. Health Lab. Scien. 9(2):103-111.

Continuous inbreeding by brother-sister mating (for from 20 to 50 generations) has developed some 27 inbred lines of Syrian golden hamsters. Among these there occur a number of inherited diseases that are models of human disorders. The susceptibility of these inbred lines to various chemical carcinogens varies, depending on genetic background. The males of some lines (but not of others) develop gastric, colonic and jejunal cancers following methylcholanthrene feeding, and females of five lines (and, to a lesser degree, those of other lines as well) will form metastasizing mammary cancer when given methylcholanthrene. Thus inbred strains of Syrian hamsters provide useful models of major human diseases.

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The following is a list of 201 references that relate to animal models for cardiovascular research. The list covers the latter part of 1971, 1972, and the first half of 1973. The list was compiled and submitted by Drs. J. W. Buchanan and D. F. Patterson, Comparative Cardiovascular Studies Unit, School of Veterinary Medicine, University of Pennsylvania.

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