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Comparative Biology: Animal Models of Human Hematologic Disease

A Review

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Introduction

The concept of biological unity implies that comparison of homologous disease processes in man and other animals will reveal the existence of fundamental mechanisms common to all species affected by a given disease. There are numerous examples of diseases occurring spontaneously in animals which are similar to or even counterparts of pathological aberrations of man. On the other hand, many biological processes which are found concurrent with diseases in man exist without detrimental effect in animals or plants, or even appear in them as part of a normal metabolic pathway. The understanding of normal biological phenomena and of the spontaneous diseases in animals which mimic human aberrations can be as valuable to medical research as have been the use of 'inborn errors of metabolism' or the study of diseases induced in animals.

The editorial 'Biomedical Models in Veterinary Medicine' by CORNELIUS and ARIAS [38] gave many examples of animal diseases having counterparts in man. GAY has provided an excellent summary of a workshop conference on comparative medicine convened by the National Institute of General Medical Sciences [62]. In his paper he considered the potentials of comparative medicine and projected possible future developments. LEADER's article 'The Kinship of Animal and Human Diseases' [103] pointed out several intriguing lines of investigation and emphasized a number of highly significant findings which have evolved from observations on diseases of animals. In light of the current emphasis on all aspects of comparative medicine and the use of biomedical models, investigators can profit from an awareness of some of the hematological phenomena in animals which simulate human diseases. This review will consider some of the more interesting biological models in animals, the study of which offers promise of contributing to a fundamental understanding of disease in man. Primary diseases of animals that involve erythrocytes, leukocytes and the plasma proteins will be considered. Table I summarizes the germane literature.

Erythrocytes

Shape

Upon comparing erythrocytes of the invertebrates and vertebrates, it is apparent that there is a great difference in their number, size and morphology. While in invertebrates, the various respiratory pigments may be found in the plasma and infrequently in simple cells, the vertebrates have developed a specialized cell containing hemoglobin, the erythron. The erythrocytes of nonmammalian vertebrates are characterized by the presence of a nucleus, whereas in mature mammalian erythrocytes there is none. Observation of the shape and size of red blood cells of various vertebrates creates two major impressions. First, there is a marked species variation in red cell morphology among the submammalian forms. Second, mammalian erythrocytes are all relatively similar in size and quite similar in shape with the exception of those from the families *Cameliadae* (llama, camels) and *Cervidae* (deer) [70, 96].

The peculiar shapes of the erythrocytes of these animal families have been compared to the aberrant shapes associated with some human disease. Elliptocytosis is an abnormality of the normally biconcave human red blood cells [15]. In the camel and llama, the normal erythrocyte is a biconvex ellipsoid resembling a football. This peculiarly shaped erythrocyte is associated with an unusual survival time of approximately 235 days [120].

The occurrence of *in vitro* sickling in the erythrocytes of most species of deer [96] might have remained a

laboratory curiosity had it not been for the existence of similarly shaped cells in a human disease, sickle cell anemia [72]. In contrast to the limited racial and geographical distribution of sickle cell anemia in man, the sickling phenomenon occurs in most species of deer, representing a variety of ecological and geographical areas of the world. In the deer, sickling is an *in vitro* phenomenon which occurs under high oxygen tension and elevated pH and has no apparent pathologic consequences. The propensity to sickle under appropriate conditions has been related to certain polymorphic hemoglobin types in the white-tailed deer [101].

Even though the peculiar cells of the families *Cameliadae* and *Cervidae* can be considered taxonomical characteristics not associated with pathology of the hematopoietic system, they offer morphological and genetic markers for experiments involving bone marrow transplants, alteration of hemoglobin type and other programs.

An outstanding example of this type of relation has been provided by the excellent work of STEINMULLER and MOTULSKY using spherocytosis of deer mice [149]. Spherocytosis and neonatal jaundice were described in *Peromyscus moniculatus* (deer mouse) by HUESTES and ANDERSON in 1954 [77] and established as an inherited abnormality of the erythroid cells by ANDERSON *et al.* in 1960 [3] with pathophysiology identical to that of human hereditary spherocytosis. The defect in the deer mouse is transmitted as an autosomal recessive trait, as contrasted to the dominant mode of transmission of human hereditary spherocytosis. In the mouse, as in man, the defective erythrocytes of affected individuals are spherocytic, have a short life span, an increased osmotic fragility and increased susceptibility to destruction by the spleen. Because the deer mouse used for laboratory work represents a genetically heterogenous population, the same problems of histocompatibility exist in this species as in a human population. The heterogenous origin of these animals, in addition to the fact that spherocytosis represents the confinement of a genetically abnormal tissue to one organ system, has made this animal an ideal model in which to study the potential therapeutic benefits of tissue transplant. Using allogenic bone marrow transplants, STEINMULLER and MOTULSKY [149] demonstrated that animals which survived three months after radiation maintained marrow and peripheral blood phenotypes identical to that of the donor. At present, this type of experiment can only be attempted in such animal models.

Hemoglobin

Hemoglobinopathies have been documented in no species other than man; nevertheless, multiple and polymorphic hemoglobins have been well identified in most domestic and in many wild animals [65, 78, 96, 101, 142]. Several features of the phenomena of quantitative control of hemoglobin synthesis have been studied in mammals [20, 79, 81, 159]. Animals which produce fetal hemoglobin and amphibians which change hemoglobins concomitant with metamorphosis can both serve as models for experiments designed to increase our understanding of the mechanism of the change from fetal to adult hemoglobins. Animal models offer not only an opportunity to study this event but also permit *in vivo* experiments that would be impossible in man. Rather than considering the transition from fetal to adult hemoglobin as a simple switching mechanism within erythrocytes, many investigators now believe that the change involves a change of erythrocyte clone complete with new hemoglobin type and enzymes. If this is true, then all of the proteins within the fetal erythrocytes may be representative of one clone of cells, while those within adult erythrocytes may represent another. Further research directed toward the study of the production of the whole erythrocyte and all its proteins will clarify many details of these theories.

Several models appropriate for the study of hemoglobin synthesis have been identified.

In adult sheep with hemoglobin AA or AB phenotypes, a new hemoglobin, designated 'C', not normally present as a major hemoglobin type, can be induced by establishing severe anemia. Structural comparisons of sheep hemoglobins indicate that an identical α chain is common to sheep hemoglobin A, B and C and that the respective β chains represent three unique cistrons [7, 21, 22, 97, 164]. Hemoglobin C is, therefore, the result of the activation of the β chain for C at the same time that production of the β chain for A ceases. Several laboratories are now investigating means whereby synthesis of this new gene product is initiated [22, 98, 159]. It is unknown whether all erythrocytes can contain all three hemoglobin types, or whether specific erythropoietic cells are necessary for production of each type. Nevertheless, a full understanding of this unique phenomenon in sheep may serve to clarify control mechanisms responsible for quantitative differences in hemoglobin synthesis which occurs in certain diseases of man, such as thalassemia.

It has been reported that activation of a hemoglobin D can occur in sheep of phenotype AB [160]. These findings suggest the activation of yet another gene for another structurally different polypeptide chain.

The initiation of hemoglobin C synthesis in sheep appears to be influenced by environment. This contrasts with the naturally occurring quantitative differences in the concentrations of fast and of slow hemoglobins in the stump-tailed macaque [99] and in the horse [100]. A study of these quantitatively different hemoglobins may increase our understanding of the

controls governing the proportion of human hemoglobins, such as A and E or A and S, which occur in the same heterozygous individual. A comparative study has been carried out on the quantitative differences among hemoglobins in the stump-tail macaque [99]. The proportion of slow and of fast hemoglobins in several animals is different from that seen in the majority. Quantitative differences in the concentration of the individual hemoglobins have been established even though all animals have hemoglobins which are qualitatively identical in electrophoretic characteristics. This finding suggests that there must exist special mechanisms other than those responsible for the shift of synthesis from fetal to adult forms or those which control the concentration of minor components of A_2 in humans. Although the peptide maps of these hemoglobins are identical, precise structural comparisons must be made before the stump-tailed macaque becomes an appropriate model in which to test the structure-rate hypothesis of ITANO [81] or to consider the several levels of control that have been the subject of speculations by BOYER [20] and INGRAM [79].

The existence of multiple hemoglobins in animals such as fish and frogs provides other opportunities to study whether quantitative differences change under environmental stress. In fish, differences may depend largely upon the salinity or the oxygen tension of their environment. For example, the salmon changes hemoglobin type when migrating from salt to fresh water [158].

It is intriguing to speculate that, in the future, it may be possible to correlate specific physiological parameters with the presence of certain amino acids by studying animals with virtually identical hemoglobins but living under different environmental conditions. Through structural comparisons, the type and position of the amino acid residue susceptible to modification could be determined. Although this is not now possible, attempts will probably be made in the near future.

Porphyrin Metabolism

Aberrant porphyrin metabolism has been described in cattle [1, 32, 59, 85, 86, 88, 117, 128, 129, 162], swine [33, 85, 86, 88] and squirrels [157]. The porphyrias of cattle are inherited as a simple mendelian recessive trait and have been studied more extensively than have the porphyrias of other species. The aberrations in Holstein-Friesian, Hereford and shorthorn cattle [59, 129] have been tentatively classified as examples of congenital erythropoietic porphyria. The disease is characterized by the presence of discoloration of teeth and urine, photosensitivity of those areas of skin with lighter color, failure to thrive, anemia, and weakness. There is increased destruction of erythrocytes within bone marrow [87]. The survival time of the erythrocytes of affected cows is 25–47 days, in contrast to the normal red blood cell life span of 140–160 days. Uroporphyrin I and coproporphyrin I are readily demonstrable within the reticulocytes and are excreted in excess in the urine [161, 162]. Variable concentrations of uroporphyrin I and coproporphyrin I have been demonstrated in the plasma and in human congenital erythropoietic porphyria. Although there is an apparent overproduction of uroporphyrin I and coproporphyrin I in cattle as well as in man, SMITH and KANEKO [146] have also reported protoporphyrin III (type IX isomer) to be in excess in reticulocytes. They speculate that bovine porphyria may involve a partial block in the conversion of protoporphyrin to heme. The presence of high levels of protoporphyrin reported in bovine reticulocytes suggests a metabolic similarity between the bovine porphyria and erythropoietic protoporphyria in humans [161, 162]; however, bovine porphyria has not been shown to be an exact metabolic counterpart of human congenital disease, erythropoietic porphyria, or erythropoietic protoporphyria.

In erythropoietic porphyria of man [140], the overproduction of type I isomer of porphyrin is limited to erythropoietic cells. In the case of erythropoietic protoporphyria, however, the overproduction of type III isomer may also involve the liver or other tissues. In cattle, the metabolic defect of the heme pathway involving mainly type I isomer is limited to erythropoietic cells. The production site of type I isomers in swine has not been clarified.

The cow, with large surface areas of thick skin including both pigmented and nonpigmented regions, may offer an ideal model in which to study comparative photosensitivity *in vivo*. By comparing the accumulation of metabolic products in the light and dark skin areas of affected cattle, it may be possible to assess the effect of light upon the mechanisms of photosensitivity. The variability of the severity of symptoms in swine suggests that it may be possible to design experiments for exaggerating the defect by blocking those metabolic pathways suspected of involvement.

Porphyria has been recognized in swine, and in contrast to the cattle-porphyria type, the disease in swine is inherited as a dominant characteristic and produces very little effect on the general health of the affected animals [85, 86, 88]. Photosensitivity is not seen even in pigs having only white hair. Affected newborn animals have discolored teeth which usually exhibit red fluorescence under ultraviolet light. Uroporphyrin I levels in blood have been reported to be elevated. Another dark pigment of unknown nature accumulates in the liver, spleen, lungs, bones and kidneys [85, 86, 88]. In the fox squirrel *(Sciurus niger)*, uroporphyrin accumulates and is excreted in large amounts [157]. The Florida fox squirrel has been examined

clinically at this laboratory. These animals have very dark teeth which fluoresce red under ultraviolet light; the spleen, feces and urine fluorescence slightly. The urine appears normal in color when voided, but darkens after exposure to air. In the fox squirrel, uroporphyrin must be a physiological end product of normal metabolism rather than the result of some aberration.

GRANICK and LEVERE [64b] have given a hypothetical scheme for the control of heme and hemoglobin synthesis based upon the operator-regulator gene model formulated by JACOB and MONOD [82]. GRANICK and LEVERE speculate that the pattern of inheritance for bovine porphyria suggests a regulator gene abnormality, while that of swine suggests an operator gene defect. They have also postulated that the basic defect in human erythropoietic porphyrias, both congenital porphyria and protoporphyria, results from increased activity of the enzyme δ-aminolevulinic acid synthetase.

We must acquire a full understanding of the pathways for and control of normal mammalian heme synthesis before the metabolic aberrations in the porphyrins can be completely characterized. Comparative studies of both the abnormal and normal pathways in these animal models may contribute to comprehension of the fundamental control mechanism. Characterization of δ-aminolevulinic acid synthetase activity and structure in normal cows and those with porphyria would appear to offer possibilities for further studies.

Potassium and Sodium Ions within Erythrocytes

Polymorphism, with respect to potassium concentration within sheep erythrocytes, has been observed by EVANS [54]. The inheritance by sheep of erythrocytes with low or high concentrations of potassium is not directly associated with hemoglobin A or B but is associated with the induction of hemoglobin C [55]; however, high frequencies of A hemoglobin with relatively high frequencies of high potassium erythrocytes has been noted. In contrast to the erythrocytes of man, the horse, and the rabbit, in which the concentration of potassium (~ 140 mEq/l) is much higher than that of sodium (~ 15–25 mEq/l), those of the cat and the dog are high in sodium (~ 130–145 mEq/l) and low in potassium (~ 8–10 mEq/l) [48]. The significance of the potassium polymorphism in sheep and species variation of relative potassium-sodium concentration within red blood cells is unknown. Some investigators have speculated that the presence of high potassium concentration erythrocytes in sheep may be associated with life at high altitudes [107] and may possibly be related to M system of red cell antigens [86b]. The difference in the potassium level in these animals may reflect qualitative differences and changes in K^+-Na ATPase.

Polycythemia

Familial polycythemia in cattle has been the subject of a report by TENNANT *et al.* [154]. Isolated cases of primary polycythemia have been observed in dogs [36, 49] and in a Hereford steer [60]. In Jersey calves studied by TENNANT *et al.* [154], no pathological defect could be found. This suggested that the polycythemia was of a secondary nature. Animals were from an inbred herd, and the genetic pattern reported was consistent with a simple autosomal recessive mode of inheritance.

Anemias

As in man, anemias which are secondary to other diseases are common in animals. Examples of anemia due to hemorrhage (acute blood loss and chronic blood loss, i. e., blood sucking parasites), toxins, or nutritional deficiencies (i. e., iron in baby pigs) are documented for most mammals [137]. Of special interest, however, are several acquired anemias, such as equine infectious anemia [71, 80], hypoplastic anemia associated with consumption of bracken fern [144] or trichlorethylene-extracted soy bean meal [126], isoimmunization of newborn foals and swine [16], and those resulting from the presence of various parasites of the erythrocytes.

Haemobartonella felis and canis are seen in the cat and the dog respectively. In the cat [58], infection by Haemobartonella is characterized by a hemolytic anemia, without hemoglobinemia, emaciation, or depression; it can be an acute or chronic illness. In the dog [137], the Haemobartonella is nonpathogenic, but the disease can be produced experimentally after splenectomy [30]. In man, Oroya fever, a severe, acute hemolytic anemia, is produced by Bartonella. Protozoal parasites of domestic animals include anaplasmosis in cattle, eperythrozoonosis of sheep, cattle and swine, piroplasmosis of dogs, cattle and horses, theileriasis and ginderiosis of sheep, cattle and goats, and trypanosomiasis of cattle and other mammals [137]. An interesting finding is a significant incidence of malaria in penguins [67].

Bracken fern poisoning is common among cattle after prolonged feeding of bracken fern [137, 144]. This hypoplastic anemia, thought to result from high levels of thiaminase, is characterized by marked granulocytopenia and thrombocytopenia, and bleeding from the body openings. Another type of hypoplastic anemia occurs in cattle, horses and chickens fed soybean extracted by trichlorethylene [126].

Equine infectious anemia, a progressive normocytic normochromic anemia, the result of a recurrent hemolytic process, appears to be of viral origin and is currently an important problem to the horse industry [71, 80].

Table I. Reference list of animal disease models[1]

	Horses	Cattle	Dogs	Cats	Sheep and goats	Swine	Rodents	Others[2]
Erythrocytes								
Shape							3, 77, 149	70, 96, 101
Hemoglobin	23, 24, 65, 96, 97, 100	65, 96, 97, 142	65	65	7, 21, 22, 65, 78, 96, 97, 98, 142, 159, 160, 164	65	65, 96	65, 96, 97, 99, 101, 158
Porphyrin		1, 32, 59, 85, 86, 87, 117, 128, 129, 146, 161, 162				33, 85, 86		157
Sodium-potassium					18, 54, 55			
Lifespan					120			120
Inclusion bodies	138, 156	34, 50		12, 136				
Mosaicism	150, 152							
Blood groups	35, 56	35, 56, 151	35, 56, 168	35	35, 56	35, 56, 63, 135	35, 56	35, 56
Siderocytes	71							
Anemia								
Hemolytic	16, 27, 45, 46	34, 50	30, 106, 168	58		16, 63	866	
Hypoplastic		126, 144						
Polycythemia		60,154	36, 49					
Parasites								67
Hemorrhagic disorders	11, 117		4, 25, 26, 28, 31, 57, 64, 89, 109, 131, 132, 133, 167					
Thrombocytopenia			30, 106					
Leukocytes								
Leukemia	148	51, 115, 130, 147, 148, 155	29, 112, 114, 118, 145, 147, 148	84, 141, 147, 148	148	148	47, 68, 148	2, 8, 9, 10, 13, 14, 52, 123, 148
Plasma cell	42	124	17, 37, 110	76		53	66	91, 92, 93, 94, 121, 163
Chediak-Higashi		125, 173						125, 172
Pelger-Huet		122	137					176
Sprue			90					
Lupus erythematosus			105					
Megakaryocytes			134					
Plasma								
Proteins	23, 24, 42, 107	5, 83, 107	107	107	107	73, 102, 107	107	91, 92, 93, 94, 107, 108, 127
Hyperbilirubinemia		41			39, 40, 43		69, 77	

[1] Numbers refer to reference number.

[2] Deer, camels, penguins, chicken, squirrels, etc.

Inclusion Bodies

Heinz bodies and other inclusions within erythrocytes have been found in association with pathological processes and have been the subject of clinical and laboratory investigation in man. Heinz bodies and other inclusion bodies, some of which are characterized by their refractile nature, have been observed in horses [138, 156], cats [12, 136, 139] and cattle [34, 50, 116]. Erythrocyte refractile bodies (ER) were observed in cat blood by SCHALM and SMITH [139] when the cells were stained with new methylene blue. These authors stated that up to 10 % of the cells of healthy cats contain ER bodies. In some sick cats, 50 % of the cells contain ER bodies. BERITIC [12] indicated that these ER bodies were probably the same inclusion bodies recently reported by the German pathologist SCHMAUCH. The Schmauch or ER bodies have been noted by numerous authors and have been tabulated by BERITIC. BERITIC's study concluded that there was no hemolytic anemia in cats in spite of the high occurrence of inclusion bodies that had morphological and staining characteristics identical with those of Heinz bodies in man. The bodies were demonstrated in 93 out of 94 randomly examined domestic cats.

In the horse, Heinz bodies occur spontaneously following splenectomy [156] and as a result of phenothiazine toxicity [138]. Many cattle that have been feeding on kale [34, 50] and winter rye [116] develop severe anemia, hemoglobinuria and icterus. Heinz bodies were demonstrated in the erythrocytes of affected cows [34, 116]. In Florida [116], Heinz body formation associated with anemia and hemoglobinuria has been seen in cattle grazing on winter rye. Unfortunately, none of the reports dealing with Heinz body formation and hemolytic disease in cattle has included a systematic study of the metabolism of the red blood cells. The relation, therefore, to any human disease remains uncertain.

Blood Groups

As in the case of man, blood groups have proved to be a useful genetic marker for studying the evolutionary origin, the geographic distribution, and the natural selection of the gene pools of an animal population. Many extensive and excellent reviews on erythrocyte antigens in animals are available [35, 56, 151]. Among topics considered are the numerous antigenic blood group types and the naturally selected serum isoagglutinins for several species of domestic animals and for a number of primates.

In a study of newborn twin calves, STORMONT *et al.* [152] used differential hemolysis to separate the different erythrocyte populations found in each animal. They were able to demonstrate, by analysis of the separated erythrocytes, that one population of erythrocytes was homozygous for one hemoglobin genotype while the other population was homozygous for another hemoglobin type. They postulated that a sharing or transfer of blood-forming tissues through a chorionic vascular anastomosis had occurred in early fetal life and resulted in the observed hemoglobin mosaicism. This is directly opposed to the findings in a naturally occurring single fetus heterozygote pregnancy in which both hemoglobin types are found in all erythrocytes.

STONE *et al.* [150] reported on chimerism in cattle twins and used blood typing techniques to document the changes over a period of time in the proportions of two antigenically distinct cell populations. Ultimately, these authors concluded that 96 % of the persisting erythrocytes were of a 'hybrid' type. They postulated that the 'hybrid' cell type resulted from 'mating' between the two hematopoietic tissues in the chimeric mixture and speculated that the 'hybrid' type had a distinct selective advantage.

Hemolytic Anemia

Isohemolytic disease has been described in foals [16, 27, 45, 46] and piglets [16, 63, 135]. These babies are born healthy; only after the intake of colostrum is erythrocyte destruction initiated. In acute and severe cases, hemoglobinuria is present. Icterus is not a constant finding. In horses, the hemolytic process results from antibodies in the mare's colostrum which have formed in the dam due to difference of blood types between the foal and the mother. The foal's erythrocytes leak through the placental barrier initiating the formation of antibodies by the dam. These do not pass through the placenta to damage the foal *in utero*, but are secreted in colostrum [46]. In swine, the major cause of antibody formation in the sow can be related to repeated vaccination against hog cholera using crystal violet vaccine [63]. Although this phenomenon does appear to occur spontaneously, it is more common in certain breeds. The crystal violet swine fever vaccine is prepared from pig blood taken at the height of virus infection. Consequently, the source may contain incompatible red cell antigens and may lead to sensitization of vaccinated pigs [63]. The ability of the newborn to absorb orally administered antibodies, in both foals and piglets, is limited to the first 36–48 hours of life. Kernicterus has not been reported. Avoidance of ingestion of mother's milk for 48 hours will prevent the disease in foals.

Although an experimentally-produced hemocytic disease of the newborn has been produced by YOUNG *et al.* [168], naturally occurring isohemolytic disease of puppies has not been verified.

Hemorrhagic Disorders

Blood coagulation disorders have been described in dogs [89, 131, 132, 133], horses [119, 133], and swine [44, 113] and have been studied in greatest detail in the dog. The most commonly recognized, canine hemophilia, resembles classical hemophilia A or factor VIII deficiency of man [64, 89, 133]. Several laboratories have maintained breeding colonies of hemophilic beagles [133], Irish setters [64] and German shepherds [133] with known pedigrees and used them for genetic studies. Although genetic and biochemical studies have been carried out only in these breeds, cases of clinical hemophilia have been described in the following breeds: Irish setters [57, 64], German shepherds [131, 133], collies [133], Shetland sheepdogs [167], greyhounds [143], weimaraners [89], chihuahuas [89], beagles [28, 133] and Labrador retrievers [4, 133].

Classical Hemophilia (Factor VIII)

Inheritance of canine deficiency of factor VIII follows an X-linked recessive pattern [133]. Most of the affected puppies die before three months of age if left untreated. Affected dogs develop hemarthrosis, multiple hematomas and spontaneous hemorrhages in the spinal cord, muscles, joints, and soft tissues; there is excessive bleeding after minor surgical procedures, dental extraction and nail clipping [133]. The disease is characterized by prolonged clotting time, slow prothrombin utilization during clotting and prolonged partial thromoplastin time, but normal bleeding time [89].

Through immunological studies, McLester and Wagner [109] have demonstrated that the lack of factor VIII in the dog is due to failure of production.

Early reports of canine hemophilia concluded that this disorders in dogs was indistinguishable from human hemophilia. This assumption was based on the observation of an X-linked recessive genetic pattern of inheritance in controlled breeding studies. Through the use of this experimental model and karyotype studies verifying sex [25, 31], investigators were able to successfully demonstrate hemophilia A in a female dog. Although it had been considered theoretically possible to demonstrate hemophilia in the human female [166], documented cases were only reported subsequent to the laboratory demonstration of the disease in female dogs [25, 111].

In the horse, factor VIII deficiency has been reported in both the standardbred and thoroughbred. Nossel, Archer and MacFarlane [119] reported a single case of equine hemophilia in a mare. The clinical findings and laboratory results were consistent with the absence of factor VIII. This disorder was presumed to be congenital because of a history of early death of male foals from this mare; however, convincing evidence for any hereditary pattern is unavailable.

In a study of the coagulation mechanism of normal horses, Bell, Tomlin and Archer [11] found that, in comparison with human values, coagulation studies of horse blood reveal prolonged clotting time, poor clot retraction despite normal platelet count, and prolonged one-stage prothrombin time. These authors concluded that there is a relative deficiency of factor VIII in normal horses of both sexes and showed that the deficiency could be corrected by administration of normal human plasma. Further qualitative and quantitative comparative studies of the coagulation mechanism would be useful in assessing the relative contribution of each step in the normal sequence.

In swine (Poland, China), a hemophilic disorder due to low levels of factor VIII [75, 113], with the characteristics of von Willebrand's disease [44] and classical hemophilia A, has been observed. The disease exhibits a recessive mode of inheritance [19], and affected animals have a prolonged bleeding time and levels of factor VIII about 6 % of normal [26].

Factor VII Deficiency

A small colony of beagles has been maintained with factor VII deficiency inherited in an autosomal recessive pattern [133]. Excessive bruising is the primary clinical sign noticeable among the affected animals. A prolonged prothrombin time is the principle abnormality noted [133].

Leukocytes

Leukemia

Leukemia is defined as a neoplastic disease involving one or more of the cell types of the hematopoietic tissue. The nomenclature in the veterinary literature is extremely confusing. Lymphocytic leukemia is the type most frequently reported in animals. Such terms as lymphosarcoma, malignant lymphoma, lymphadenosis and lymphoblastoma are also commonly used.

The leukemia complex has been studied extensively in fowl [10, 52], mice [68, 95], cattle [148, 165] and dogs [114, 145, 148]. Even though avian leukosis of the chicken is not identical with human leukemia, it has offered certain advantages as a model. Studies of avian leukosis gave the first evidence for the viral transmission of neoplastic diseases [52]. In addition, the chicken has also been found ideal for studies of genetic transmission of viral neoplasia [10].

In contrast to avian leukosis, the leukemic diseases of other animals [148] resemble the human disorder so closely that the dog has often been used as a model for screening therapeutic agents [29]. While the value of cattle as models is limited because of size, the accurate records maintained for purebred herds provide vital

information for studies of geographic distribution [155] and genetic susceptibility of the disease. The large size of cattle can even be an advantage when large blood or tissue samples are needed.

The extensive studies of fowl leukosis currently available warrant review since this will permit examination of the evidence implicating a viral mode of production. Avian leukosis is a group of diseases of viral origin characterized by neoplastic proliferation [14]. A number of distinct conditions have been recognized: visceral lymphomatosis, myeloblastosis, and erythroblastosis. Even though much of the work on this disease was initiated because of the economic implications of lymphomatosis in chickens, the information gathered can be related directly to the epizootic features of neoplastic and viral diseases in other species and in man. Therefore, avian leukosis has been studied to further the understanding of viral induction of neoplasia within organisms. These investigations have contributed to the understanding of the general principles of the induction of tumors by viruses. As long ago as 1908, ELLERMANN and BANG [52] demonstrated that the leukosis of domestic chickens could be transmitted by inoculating healthy birds with cell-free extracts. They succeeded in propogating the disease through several generations. The viruses of erythroblastosis and myeloblastosis were later isolated and characterized by BEARD *et al.* [8, 9]. These viruses have been visualized under the electron-microscope and some of their physical characteristics have been determined [2, 13]. Although certain specific strains of virus have been reported to produce one type of leukosis, that is, lymphomatosis, erythroblastosis, or myeloblastosis, BEARD [10] has presented evidence that certain homogeneous laboratory virus types have caused each of the pathological entities characteristic of the leukosis complex. Since none of the strains can be designated as the virus for lymphomatosis, erythroblastosis, or myeloblastosis, it follows that these diseases must be identified on the basis of pathological patterns rather than on the basis of specific virus types. The importance of interaction of virus strains in producing this disease complex cannot be estimated at this time. It is clear, then, that this avian disease complex is a useful model for the study of the influence of genetic and environmental factors and age upon host response, as well as for the study of modes of transmission.

A thorough review of hematopoietic tumors of domestic animals [148] emphasizes the close clinical and anatomical correspondence of animal leukemia to human counterparts. The obvious impetus for comparative studies of leukemia is the hope that a common etiology may be involved in all. Two recent publications [148, 165] tabulate the majority of clinical, pathological, and genetic aspects of these diseases in most animals. However, certain comparative features of leukemia in animals are important enough to be reemphasized. In domestic animals, lymphocytic leukemia is most common; monocytic, basophilic and eosiophilic variants are infrequent; and erythroblastic leukemia, with the exception of erythroblastosis of chickens, is rare.

Lymphocytic leukemia in man is often associated with anemia; however, in domestic animals, marked anemia has only been reported as a constant feature in the disease of the cat. In the dog, only moderate anemia has been associated with lymphocytic leukemia. The severity of anemia in cattle is variable, and anemia is not a constant characteristic of the disease. It is apparent that the majority of studies of animal leukemia have been directed toward characterizing the lesions, clinical aspects, and morphological variations. Although several studies have been directed toward understanding such factors as etiology, transmission, epidemiology and host susceptibility, with the exception of studies on murine and guinea pig leukemia, little or no definitive proof has been provided directly implicating a virus as the causative agent of mammalian leukemia. Epidemiological studies have been made in various leukemias of animals. Of importance is the recent report [141] of possible horizontal transmission of the disease in cats. Five of six cats with leukemia were related and lived in a household with 28 other unrelated cats.

ROSENBERG [130] produced leukosis in cattle by injecting infectious material. HOFLAND *et al.* [74] reported the transfer of leukemia to calves using cell-free extracts of lymphomotous tissue. JARRETT *et al.* [84] successfully produced leukemia in a newborn kitten. Whereas canine lymphoma could not be experimentally produced in irradiated puppies [118], cellular transmission of canine lymphosarcoma in irradiated newborn puppies was demonstrated by MOLDOVANU *et al.* [112].

While a viral origin has not been satisfactorily proven for most mammalian leukemias, the identification of a virus responsible for fowl leukosis is well accepted. A number of virus-like particles have been observed in various animals species, but thus far none has been directly related to the production of leukemia. Virus-like particles have been characterized in mice [47] and guinea pigs [177], and similar particles have been observed in tissue biopsies, plasma, and milk of both man and cattle [51, 115]. These particles have been transmitted in tissue cultures [115]. The etiological significance of a herpes-like virus, formerly thought to be associated with Burkitt's lymphoma, is now in question [104]. The particles associated with this specific lymphoma have been found in a number of other disease states. For example, it has been seen in leukemia, in lymphomas, in tumors of nonhematopoietic tissue, and

even in apparently healthy individuals. This virus may have a predilection for neoplastic tissue or it may be a causal virus rather than a direct inducer of malignancies. Immunological evidence of experience with the virus has been found among individuals having no clinical evidence of malignant disease. Thereis, inaddition, a high frequency of seroreactors among primates other than man. These observations increase the difficulty in establishing the viral theory of etiology of leukemias in higher animals.

Although some work has already been done on the transmission of animal leukemias, further studies of immunological aspects appear in order. In addition, direct isolation of a causative agent such as a virus must be achieved if we are to have a better understanding of the disease process in all mammals. The fact that these diseases occur in animals suggests a ready source of tissue for experiments designed to investigate the pathogenesis of neoplasia.

The immediate potential, using animal leukemias as models, is the designing of experiments to prove etiology and the screening of possible drugs in human therapy. In this aspect of research lies the importance of developing colonies of small animals such as dogs or cats with a predictably high frequency of leukemias.

Abnormal Leukocytes and Proteins

Multiple myeloma is a disease characterized by a generalized proliferation of the plasmocytes. Clinical features include the demonstration of elevated levels of plasma proteins and Bence-Jones proteinuria. The homogeneous nature of the myeloma protein in man has stimulated extensive structural studies of these immunoglobin counterparts. The occurrence of myeloma or plasma cell proliferative disease has been reported in the horse [42], calf [124], pig [53], rabbit [123], dog [17, 37, 110], cat [76], mouse [66], mink [91, 94] and ferret [93].

In some mink, Aleutian disease, a chronic, progressive disease of the plasma cells with high mortality, has been reported [93]. It is thought that Aleutian disease is caused by a virus [93]. The type of pathological alteration of the bile ducts, as well as of the glomeruli and tubules of the kidney, is reminiscent of some connective tissue diseases of man. Hypergammaglobulinemia is a nearly constant feature of Aleutian disease; however, the presence of Bence-Jones protein as reported by one group [121] could not be confirmed [94]. KENYON *et al.* [94] were able to demonstrate a low-molecular-weight (2.2S) protein in the urine, similar in immunoelectrophoretic properties to that of 7S gamma globulins, but the proteins did not have the thermosolubility properties of Bence-Jones proteins.

KENYON observed that in most mink with Aleutian disease, the abnormally elevated species of gamma globulin was heterogeneous [92], a situation similar to that found in some of the autoimmune diseases of man. In some infected mink which survived for extended periods of time, however, the gamma globulins became homogeneous and at this stage the illness was similar to that observed in man [178].

It is interesting to note the high incidence of myeloma-like syndromes in mink and ferrets and to contrast this with the incidence of myelomas in domestic animals.

Other anomalies of the leukocytes have been reported. These include Chediak-Higashi syndrome of cattle [125, 173] and mink [125, 172], acquired Pelger-Huet anomaly in cattle [122], dogs [137] and rabbits [176], sprue [90], cyclic neutropenia [174, 175], and lupus erythematosus cell phenomenon in dogs [105].

Plasma

Polymorphism of the plasma proteins of animals has been reported nearly as frequently as has the heterogeneity of animal hemoglobins. Polymorphic forms of transferrin [24, 83], haptoglobin [23, 73] and albumins [5, 102, 127] have been reported for most domestic animals. LUSH [107] has recently published an excellent review of most of the known polymorphic plasma proteins. Bialbuminemia has been reported in healthy people [61]. A similar polymorphism of chickens [108] and pigs [102] has been studied.

Hereditary hyperbilirubinemia has been investigated in the Gunn Strain rat [69]. The primary defect in those rats affected involves the glucuronyl transferase system of the microsomes [6]. Icterus has been observed in two mutant strains of sheep [39, 40, 43]. In some sheep of the Southdown breed, a failure of hepatic uptake from the blood of organic anions such as bilirubin and sulfobromophathalein was reported [40]; in a strain of Corriedale sheep, an abnormality that is clinically and morphologically similar to that of Dubin-Johnson syndrome has been studied [39].

Discussion

This review has identified many of the animal diseases which are models for human hematological disorders. Numerous examples of animal diseases of other organ systems also exist, indicating the scope of these model systems. This review leads one to conclude that the full potential of these animal diseases as laboratory prototypes susceptible to study and manipulation is at an early stage of exploration. Physiological, pathological, and clinical analyses of animal disease models have been a profitable undertaking; however, the exact homology

of these diseases to their human counterparts is of secondary importance. Primary emphasis must now be given to the study of disease mechanisms. The knowledge gained will provide insight into the basis of human illnesses. The laboratory approaches required for elucidating the mechanisms of disease will require experimental designs which are impossible or severely limited in man, but which are feasible in animals.

A full understanding of both the genetic and the biochemical bases of the aberrations in animals offers a starting point for development of curative or palliative procedures for similarly affected humans. The future development of corrective therapy may involve 'genetic engineering' [153]. The possible achievement of 'genetic engineering' in mammals is suggested by the success in manipulating the genetic endowment of bacteria, viruses, and simple cells. The spontaneous occurrence of genetically controlled diseases in animals presumably reflects alteration in a unique cistron. It follows that any 'genetic engineering' must affect only this cistron. The effectiveness of therapy can be evaluated by examining the specificity of the manipulation; the ultimate beneficial result would become apparent when the induced change and the amelioration of the disease could be maintained beyond a single generation. The implications for human illness are almost limitless if the techniques can be established unambiguously in animal models. The future development of corrective therapy is dependent upon exploitation of animal models in which the genetic and biochemical lesions have been defined.

References and Notes

1. AMOROSO, E.C.; LOOSMORE, R.M.; RIMINGTON, C. and TOOTH, B.E.: Congenital porphyria in bovines: First living cases in Britain. Nature (Lond.) *180:* 230 (1957).
2. ANANO, S and IWAKATA, S.: Peculiarity of leukemia and cancer viruses based on our recent investigations utilizing ultra-thin sections by electromicrography. Acta Path. Jap. *8:* 615 (1958).
3. ANDERSON, R.; HUESTIS, R.R. and MOTULSKY, A.G.: Hereditary spherocytosis in the deer mouse, its similarity to the human disease. Blood *15:* 491 (1960).
4. ARCHER, R.K. and BOWDEN, R.S.T.: A case of true hemophilia in a Labrador dog. Vet. Rec. *71:* 560 (1959).
5. ASHTON, G.C.: Serum albumin polymorphism in cattle. Genetics *50:* 1421 (1964).
6. AXELROD, J.; SCHMID, R. and HAMMAKER, L.: A biochemical lesion in congenital non-obstructive non-haemolytic jaundice. Nature (Lond.) *180:* 1426 (1957).
7. BEALE, D.: A partial amino acid sequence for sheep haemoglobin A. Biochem. J. *103:* 129 (1967).
8. BEARD, J.W.: Isolation and identification of tumor viruses. Tex. Rep. Biol. Med. *15:* 627 (1957).
9. BEARD, J.W.: Etiology of avian leukosis. Ann. N.Y. Acad. Sci. *68:* 473 (1957).
10. BEARD, J.W.: Viral tumors of chickens with particular reference to the leukosis complex. Ann. N.Y. Acad. Sc. *108:* 1057 (1963).
11. BELL, W.N.; TOMLIN, S.C. and ARCHER, R.K.: The coagulation mechanism of the blood of the horse with particular reference to its 'Haemophilioid' status. J. comp. Path. *65:* 255 (1955).
12. BERITIC, T.: Studies on Schmauch bodies. I. The incidence in normal cats *(Felis domestica)* and the morphologic relationship to Heinz bodies. Blood *25:* 999 (1965).
13. BERNHARD, W.; BONAR, R.A.; BEARD, D. and BEARD, J.W.: Ultrastructure of viruses of myeloblastosis and erythroblastosis isolated from plasma of leukemic chickens. Proc. Soc. exp. Biol. (N.Y.) *97:* 48 (1958).
14. BIESTER, H.E. and SCHWARTE, L.H., eds.: Diseases of poultry, 4th ed. (Iowa State University Press, Ames, Iowa 1962).
15. BLACKBURN, E.K.; Jordan, A.; LYTLE, W.J.; SWAN, H.T. and TUDHOPE, G.R.: Hereditary elliptocytic hemolytic anemia. J. clin. Path. *11:* 316 (1958).
16. BLOOD, D.C. and HENDERSON, J.A.: Veterinary medicine (Williams and Wilkins, Baltimore, Md. 1960).
17. BLOOM, F.: Intramedullary plasma cell myeloma occurring spontaneously in a dog. Cancer Res. *6:* 718 (1946).
18. BLUNT, M.H. and EVANS, J.V.: Changes in the concentration of potassium in the erythrocytes and in haemoglobin type in Merino Sheep under a severe anaemic stress. Nature (Lond.) *200:* 1215 (1963).
19. BOGART, R. and MUHRER, M.E.: The inheritance of a hemophilia-like condition in swine. J. Hered. *33:* 59 (1942).
20. BOYER, S.H.; HATHAWAY, P. and GARRICK, M.D.: Modulation of protein synthesis in man: An *in vitro* study of hemoglobin synthesis by heterozygotes. Cold Spring Harbor Symposium on Quantitative Biology *39:* 333 (1964).
21. BOYER, S.H.; HATHAWAY, P.; PASCAIO, F.; BORDLEY, J.; ORTON, C. and NAUGHTON, M.A.: Differences in the amino acid sequences of tryptic peptides from three sheep hemoglobin β chains. J. biol. Chem. *242:* 2211 (1967).

22. Boyer, S.H.; Hathaway, P.; Pascasio, F.; Orton, C.; Bordley, J. and Naughton, M.A.: Hemoglobins in sheep: Multi differences in amino acid sequences of three beta-chains and possible origins. Science *153:* 1539 (1966).
23. Braend, M. and Efremov, G.: Haemoglobins, haptoglobins and albumins of horses. Blood groups of animals. Proceedings of the 9th European Animal Blood Group Conference, Prague, August 1964 (Publishing House of the Czechoslovak Academy of Sciences, Prague 1965).
24. Braend, M. and Stormont, C.: Studies on hemoglobin and transferrin types in horses. Nord. Vet.-Med. *16:* 31 (1964).
25. Brinkhous, K.M. and Graham, J.B.: Hemophilia in the female dog. Science *111:* 723 (1950).
26. Brinkhous, K.M.; Morrison, C., Jr., and Muhrer, M.E.: Comparative study of clotting defects in human, canine and procine hemophilia. Fed. Proc. *11:* 409 (1952).
27. Britton, J.W.: A method of handling hemolytic icterus of newborn foals. J. Amer. Vet. med. Ass. *116:* 345 (1950).
28. Brock, W.E.; Buckner, R.G.; Hampton, J.W.; Bird, R.M. and Wulz, C.E.: Canine hemophilia. Arch. Path. *76:* 464 (1963).
29. Brodey, R.S.; Old, L.; Fidler, I.J.; Boyse, E.A. and Campbell, H.A.: The use of L-asparaginase in the treatment of canine lymphosarcoma. Section 72, 104th Annual AVMA Meeting, Dallas, Texas, July 1967.
30. Brodey, R.S. and Schalm, O.W.: Hemabartonellosis and thrombocytopenic purpura in a dog. J. Amer. Vet. med. Ass. *143:* 1231 (1963).
31. Brown, R.C.; Swanton, M.C. and Brinkhous, K.M.: Canine hemophilia and male pseudohermaphroditism, cytogenetic studies. Lab. Invest. *12:* 961 (1963).
32. Chu, T.C. and Chu, E.J.-H.: Porphyrins from congenitally porphyric (pink-tooth) cattle. Biochem. J. *83:* 318 (1962).
33. Clare, N.T. and Stephens, E.H.: Congenital porphyria in pigs. Nature (Lond.) *153:* 252 (1944.)
34. Clegg, F.G. and Evans, R.K.: Hemoglobinemia of cattle associated with the feeding of Brassical species. Vet. Rec. *74:* 1169 (1962).
35. Cohen, C., Ed.: Blood groups in infrahuman species. Ann. N.Y. Acad. Sci. *97:* 1 (1962).
36. Cole, N.: Polycythemia in a dog. North Amer. Vet. *35:* 601 (1954).
37. Cordy, D.R.: Plasma cell myeloma in a dog. Cornell Vet. *47:* 498 (1957).
38. Cornelius, C.E. and Arias, I.M.: Editorial. Biomedical models in veterinary medicine. Amer. J. Med. *40:* 165 (1966).
39. Cornelius, C.E.; Arias, I.M. and Osburn, B.I.: Hepatic pigmentation with photosensitivity: a syndrome in Corriedale sheep resembling Dubin-Johnson syndrome in man. J. Amer. Vet. med. Ass. *146:* 709 (1965).
40. Cornelius, C.E. and Gronwall, R.R.: A mutation in Southdown sheep affecting the hepatic uptake of sulfobromophthalein (BSP) indocyanine green, rose bengal, sodium cholate and phylloerythrin from blood. Fed. Proc. *24:* 144 (1965).
41. Cornelius, C.E.; Gazmuri, G.; Gronwall, R. and Rhode, E.A.: Preliminary studies on experimental hyperbilirubinemia ane hepatic coma in the horse. Cornell Vet. *55:* 110 (1965).
42. Cornelius, C.E.; Goodbary, R.F. and Kennedy, P.C.: Plasma Cell Myelomatosis in a horse. Cornell Vet. *49:* 478 (1959).
43. Cornelius, C.E. and Gronwall, R.R.: Congenital photosensitivity and hyperbilirubinemia in Southdown sheep in the United States. Amer. J. vet. Res. *29:* 291 (1968).
44. Cornell, C.N. and Muhrer, M.E.: Coagulation factors in normal and hemophiliac-type swine. Amer. J. Physiol. *206:* 926 (1964).
45. Cronin, M.T.: Hemolytic disease in foals. Irish vet. J. *4:* 138 (1950).
46. Cronin, M.T.I.: Hemolytic diseases of new born foals. Vet. Rec. *67:* 479 (1955).
47. De Harven, E. and Friend, C.: Structure of virus particles partially purified from the blood of leukemic mice. Virology *23:* 119 (1964).
48. Dittmer, D.S., ed.: Blood and other body fluids (Federation of the American Societies for Experimental Biology, Washington, D.C. 1961).
49. Donovan, E.F. and Loeb, W.F.: Polycythemia rubra vera in the dog. J. Amer. Vet. med. Ass. *134:* 36 (1959).
50. Dunbar, G.M. and Chambers, T.A.M.: Suspected kale poisoning in dairy cows. Vet. Rec. *75:* 566 (1963).
51. Dutcher, R.M.; Larkin, E.P.; Tumilowicz, J.J.; Marshak, R.R. and Szekely, I.E.: Recent studies on bovine leukemia. In comparative leukemia research. 6. International Symposium, Wenner-Gren Center (Pergamon Press, New York 1966).
52. Ellermann, V. und Bang, O.: Experimentelle Leukämie bei Hühnern. Vorläufige Mitteilung. Zbl. Bakt. *46:* 595 (1908).
53. Englert, H.K.: Die Leukose des Schweines. Zbl. Vet.-Med. *2:* 607 und 764 (1955).
54. Evans, J.V.: Electrolyte concentrations of red bloods of British breeds of sheep. Nature (Lond.) *174:* 931 (1954).
55. Evans, J.V.: The variability of potassium con-

centrations in erythrocytes in relation to anaemia in sheep. Aust. J. Agric. Res. *14:* 540 (1963).
56. FERGUSON, L. C.: The blood groups of animals. Advanc. vet. Sci. *2:* 106 (1955).
57. FIELD, R. A.; RICHARD, C. G. and HUTT, S. B.: Hemophilia in a family of dogs. Cornell Vet. *36:* 293 (1946).
58. FLINT, J. C.; ROEPKE, M. H. and JENSEN, R.: Feline infectious anemia. I. Clinical aspects, Amer. J. vet. Res. *19:* 164 (1958). – II. Experimental cases. Amer. J. vet. Res. *20:* 33 (1959).
59. FOURIE, P. J. J.: The occurrence of congenital porphyrinuria (pink tooth) in cattle in South Africa (Swaziland). Onderstepoort J. vet. Res. *2:* 535 (1936).
60. FOWLER, M. E.; CORNELIUS, C. E. and BAKER, N. F.: Clinical and erythrokinetic studies on a case of bovine polycythemia vera. Cornell Vet. *54:* 153 (1964).
61. FRANGLEN, G.; MARTIN, N. H.; HARGREAVES, I.; SMITH, M. J. H. and WILLIAMS, D. I.: Bisalbuminemia: A hereditary abnormality. Lancet *1:* 307 (1960).
62. GAY, W. J.: Comparative medicine. Science *158:* 1220 (1967).
63. GOODWIN, R. F. W.; SAISON, R. and COOMBS, R. R. A.: The blood groups of the pig. II. Red cell iso-antibodies in the sera of pigs injected with crystal violet swine fever vaccine. J. comp. Path. *65:* 79 (1955).
64. GRAHAM, J. B.; BUCKWALTER, J. A.; HARTLEY, L. J. and BRINKHOUS, K. M.: Canine hemophilia. Observations on the course, the clotting anomaly and the effects of blood transfusions. J. exp. Med. *90:* 97 (1949).
64b. GRANICK, S. and LEVESE, R. D.: Heme synthesis in erythroid cells. Progr. Hemat. *4:* 1 (1964).
65. GRATZER, W. B. and ALLISON, A. C.: Multiple hemoglobins. Biological Rev. *35:* 459 (1960).
66. GRAY, W. R.; DREYER, W. J. and HOOD, L.: Mechanism of antibody synthesis: Size differences between mouse kappa chains. Science *155:* 465 (1967).
67. GRINER, L. A. and SHERIDAN, B. W.: Malaria *(Plasmodium relictum)* in penguins at the San Diego Zoo. Amer. J. vet. clin. Path. *1:* 7 (1967).
68. GROSS, L.: 'Spontaneous leukemia' developing in C_3H mice following inoculation, in infancy, with AK-leukemic extracts or AK-embryos. Proc. Soc. exp. Biol. (N.Y.) *76:* 27 (1951).
69. GUNN, C. H.: Hereditary acholuric jaundice in a new mutant strain of rats. J. Hered. *29:* 137 (1938).
70. GULLIVER, G.: Observations on certain peculiarities of form in the blood corpuscles of the maniferous animals. O. Proc. Zool. Soc. London *17:* 325 (1840).
71. HENSEN, J. B.; MCGUIRE, T. C.; KOBAYASHI, K. and GORHAM, J. R.: The diagnosis of equine infectious anemia using the complement-fixation test, siderocyte counts, hepatic biopsies and serum protein alterations. J. Amer. Vet. med. Ass. *151:* 1830 (1968).
72. HERRICK, J. B.: Peculiar elongated and sickle shaped red blood corpuscles in a case of severe anemia. Arch. intern. Med. *6:* 517 (1910).
73. HESSELHOLT, M.: Haptoglobin polymorphism in pigs. Acta vet. scand. *4:* 238 (1963).
74. HOFLAND, S.; THORELL, B. and WINQVIST, G.: Experimental transmission of bovine leukosis. 3. International Symposium on Comparative Leukemia Research, p. 2 (1963).
75. HOGAN, A. G.; MUHRER, M. E. and BOGART, R.: A hemophilia like disease in swine. Proc. Soc. exp. Biol. (N.Y.) *48:* 217 (1941).
76. HOLZWORTH, J. and MEIER, J.: Reticulun cell myeloma in a cat. Cornell Vet. *47:* 302 (1957).
77. HUESTIS, R. R. and ANDERSON, R.: Inherited jaundice in peromyscus. Science *120:* 852 (1954).
78. HUISMAN, T. H. J.: VAN DER HELM, H. J.; VISSER, H. K. A. and VAN VLIET, G.: Investigations on different hemoglobin types in some species of animals; in Abnormal hemoglobins, p. 181 (Thomas, Springfield, Ill. 1959).
79. INGRAM, V. M.: The hemoglobins in genetics and evolution, p. 80 (Columbia University Press, New York 1963).
80. ISHII, S.: Equine infectious anemia or swamp fever. Advanc. vet. Sci. *8:* 263 (1963).
81. ITANO, H. Y.: The synthesis and structure of normal and abnormal hemoglobins; in Abnormal hemoglobins in Africa (CIOMS) (ed. JONXIS, J. H. P.), p. 3 (Blackwell, Oxford 1965).
82. JACOB, F. and MONOD, J.: Genetic regulatory mechanisms in the synthesis of proteins. J. molec. Biol. *3:* 318 (1961).
83. JAMIESON, A.: The genetics of transferrins in cattle. Heredity *20:* 419 (1965).
84. JARRETT, W. F. H.; MARTIN, W. B.; CRIGHTON, G. W.; DALTON, R. G. and STEWART, M. F.: Leukemia in the cat. Nature *202:* 566 (1964).
85. JOERGENSEN, S. K. and WITH, T. K.: Congenital porphyria in swine and cattle in Denmark. Nature (Lond.) *176:* 156 (1955).
86. JOERGENSEN, S. K. and WITH, T. K.: Porphyria in domestic animals: Danish observations in pigs and cattle and comparison with human porphyria. Ann. N. Y. Acad. Sci. *104:* 701 (1963).
86b. KALES, A. N.; FRIED, W. and GURNEY, C. W.: Mechanism of the hereditary anemia of Sl^m mutant mice. Blood *28:* 387 (1966).

87. KANEKO, J.J.: Erythrokinetics and iron metabolism in bovine porphyria erythropoietica. Ann. N.Y. Acad. Sci. *104:* 689 (1963).
88. KANEKO, J.J.: Porphyrins and porphyrias, in Clinical biochemistry of domestic animals (ed. CORNELIUS, C.E. and KANEKO, J.J.), p. 203 (Academic Press, New York 1963).
89. KANEKO, J.J.; CORDY, D.R. and CARLSON, G.: Canine hemophilia resembling classic hemophilia A. J. Amer. Vet. med. Ass. *150:* 15 (1967).
90. KANEKO, J.; MOULTON, J.E.; BRODEY, R.S. and PERRYMAN, V.D.: Malabsorption syndrome resembling non-tropical sprue in dogs. J. Amer. Vet. med. Ass. *146:* 463 (1965).
91. KENYON, A.J.: Immunologic deficiency in Aleutian disease of mink. Amer. J. vet. Res. *27:* 1780 (1966).
92. KENYON, A.J. and HELMBOLDT, C.F.: Solubility and electrophoretic characterizations of globulins from mink with Aleutian disease. Amer. J. vet. Res. *25:* 1535 (1964).
93. KENYON, A.J.; HOWARD, E. and BUKO, L.: Hypergammaglobulinemia in Ferrets with lymphoproliferative lesions (Aleutian disease). Amer. J. vet. Res. *28:* 1167 (1967).
94. KENYON, A.J.; NIELSEN, S.W. and HELMBOLDT, C.F.: Urinary proteins in mink with Aleutian disease. Amer. J. vet. Res. *26:* 781 (1965).
95. KIRSCHBAUM, A.: Etiology of the leukemias: Chemical and hormonal factors in mice. Proceedings of the 3rd National Cancer Conference, p. 331 (Lippincott, Philadelphia, Pa. 1957).
96. KITCHEN, H.: Physical and chemical studies of deer hemoglobins; Ph.D. thesis Florida (1965).
97. KITCHEN, H.; EASLEY, C.W.; PUTNAM, F.W. and TAYLOR, W.J.: Structural comparism of polymorphic hemoglobins of deer with those of sheep and other species. J. biol. Chem. *243:* 1204 (1968).
98. KITCHEN, H.; EATON, J. and TAYLOR, W.J.: Rapid production of a hemoglobin by induced hemolysis in sheep: Hemoglobin C. Amer. J. vet. Res. *29:* 281 (1968).
99. KITCHEN, H.; EATON, H. and STENGER, V.G.: Hemoglobin types of adult, fetal and newborn subhuman primates: *Macaca speciosa*. Arch. Biochem. *123:* 227 (1968).
100. KITCHEN, H.; JACKSON, W.F. and TAYLOR, W.J.: Hemoglobin and hemodynamics in the horse during physical training. 11th Proceedings of the American Association of Equine Practitioners, Miami, Fla., p. 97 (1966).
101. KITCHEN, H.; PUTMAN, F.W. and TAYLOR, W.J.: Hemoglobin polymorphism in white-tailed deer: Subunit basis. Blood *29:* 867 (1967).
102. KRISTJANSSON, F.K.: Fractionation of serum albumin and genetic control of two albumin fractions in pigs. Genetics *53:* 675 (1966).
103. LEADER, R.W.: The Kinship of animal and human diseases. Sci. Amer. *216:* 110 (1967).
104. Leading Article: Virus and Barkitt's lymphoma. Lancet *2:* 872 (1967).
105. LEWIS, R.M.: Clinical evaluation of the lupus erythematosus cell phenomenon in dogs. J. Amer. Vet. med. Ass. *147:* 939 (1965).
106. LEWIS, R.M.; HENRY, W.B., Jr.; THORNTON, G.W. and GILMORE, C.E.: A Syndrome of autoimmune hemolytic anemia and thrombocytopenia in dogs. Proceedings of the 100th Annual Meeting of the American Veterinary Medical Association, New York, N.Y., p. 140 (1960).
107. LUSH, I.E.: The biochemical genetics of vertebrates except man (Saunders, Philadelphia, Pa. 1966).
108. MCINDOE, W.M.: Occurrence of two plasma albumins in the domestic fowl. Nature (Lond.) *195:* 353 (1962).
109. MCLESTER, W.D. and WAGNER, R.H.: Antibody to antihemophilic factor and its lack of reaction with hemophilic plasma. Amer. J. Physiol. *208:* 499 (1965).
110. MEDWAY, W.; WEBER, W.T.; O'BRIEN, J.A. and KRAWITZ, L.: Multiple Myeloma in a dog. J. Amer. Vet. med. Ass. *150:* 386 (1967).
111. MERSKEY, C.: Hemophilia occurring in the human female. Proceedings of the International Society of Hematology, p. 441 (1950).
112. MOLDOVANU, G.; MOORE, A.E.; FRIEDMAN, M. and MILLER, D.G.: Cellular transmission of lymphosarcoma in dogs. Nature (Lond.) *210:* 1342 (1966).
113. MUHRER, M.E.; LECHLER, E.; CORNELL, C.N. and KIRKLAND, J.L.: Antihemophilic factor levels in bleeder swine following infusions of plasma and serum. Amer. J. Physiol. *208:* 508 (1965).
114. MULLIGAN, R.M.: Comparative pathology of human and canine cancer. Ann. N.Y. Acad. Sci. *108:* 642 (1963).
115. NAZERIAN, K.; DUTCHER, R.M.; LARKIN, E.P.; TUMILOWICZ, J.J. and EUSEBIO, G.P.: Electron microscopy of virus-like particles found in bovine leukemia. Amer. J. vet. Res. *29:* 387 (1968).
116. NEAL, F.: Personal communication. Unpublished observation.
117. NESTEL, B.L.: Bovine congenital porphyria (pink tooth), with a note on five cases observed in Jamaica. Cornell Vet. *48:* 430 (1958).
118. NIELSEN, S. and COLE, C.: Homologous transplantation of canine neoplasms. Amer. J. vet. Res. *22:* 663 (1961).

119. NOSSEL, H.L.; ARCHER, R.K. and MACFARLANE, R.G.: Equine haemophilia: Report of a case and its response to multiple infusions of heterospecific AHG. Brit.J.Haemat. *8:* 335 (1962).
120. NOYES, W.D.; KITCHEN, H. and TAYLOR, W.J.: Red cell life span of white-tailed deer, *Odocoileus virginianus*.Comp.Biochem.Physiol. *19:* 471 (1966).
121. OBEL, A.: Studies on a disease in mink with systemic proliferation of the plasma cells. Amer.J.vet. Res. *20:* 384 (1959).
122. OSBURN, B.I. and GLENN, B.L.: Acquired Pelger-Huët anomaly in cattle. J.Amer.Vet.med.Ass. *152:* 11 (1968).
123. PASCAL, R.R.: Plasma cell myeloma in the brain of a rabbit. Cornell Vet. *51:* 528 (1961).
124. PEDINI, B. e ROMANELLI, V.: Il plasmoatoma negli animali domestici. Osservazioni e considerozioni su di un caso riscontrato nel vitello. Arch.Vet., Italy *6:* 193 (1955).
125. PHILLIPS, L.L.; KAPLAN, H. S.; PADGETT, G.A. and GORHAM, J.R.: Comparative studies on the Chediak-Higashi syndrome. Coagulation and fibrinolytic mechanisms of mink and cattle. Am. J.Vet.clin.Path. *1:* 1 (1967).
126. PRITCHARD, W.R.; REHFELD, C.E.; MIZUNO, N.S.; SAUTTER, J.H. and SCHULTZE, M.O.: Studies on Trichlorethylene-extraeted feeds. I.Experimental production of acute aplastic anemia in young heifers. Amer.J.vet.Res. *17:* 425 (1956).
127. QUINTEROS, I.R.; STEVENS, R.W.C.; STORMONT, C. and ASMUNDSON, U.S.: Albumin phenotype in turkeys. Genetics *50:* 579 (1964).
127b. RASMUSEN, B.A. and HALL, J.G.: Association between potassium concentration and serological type of sheep red blood cells. Science *151:* 1551 (1966).
128. RHODE, E.A. and CORNELIUS, C.E.: Congenital porphyria (pink tooth) in Holstein-Friesian calves in California. J.Amer.Vet.med.Ass. *132:* 112 (1958).
129. RIMINGTON, C.: Some cases of congenital prophyrinuria in cattle: Chemical studies upon the living animals and post-mortem material. Onderstepoort J.vet.Res. *7:* 567 (1936).
130. ROSENBERGER, G.: Successful Transmission Trails of leukosis in cattle. 3rd International Symposium on Comparative Leukemia Research, Hanover, p.1 (1964).
131. ROSWELL, H.C.: Hemorrhagic disorders in dogs: their recognition, treatment and importance. 12th Gaines Veterinary Symposium, Michigan State Univ., East Lansing, Mich., January 1965, p.6.
132. ROSWELL, H.C. and MUSTARD, J.F.: Blood coagulation in some common laboratory animals. Lab.Anim.Care *13:* 752 (1963).
133. ROSWELL, H.C. and MUSTARD, J.F.: Hemostasis in domestic animals. Canad.J.med.Technol. *28:* 2 (1966).
134. ROSZEL, J.; PRIER, J.E. and KOPROWSKA, I.: The occurrence of megakaryocytes in the peripheral blood of dogs. J.Amer.Vet.med.Ass. *147:* 133 (1965).
135. SAISON, R.; GODWIN, R.F.W. and COOMBS, R.R.A.: The blood groups of the pig. I. The interaction of pig red cells of group A and the naturally occurring A iso-antibody in the serum of pigs of blood group 0. J.comp.Path. *65:* 71 (1955).
136. SCHALM, O.W.: Inclusion bodies in the erythrocytes of the cat. Calif.Vet. *17:* 34 (1962).
137. SCHALM, O.W.: Veterinary hematology (Lea & Febiger, Philadelphia, Pa. 1965).
138. SCHALM, O.W.; RHODE, E.A. and ABRAHAMS, J.W.: Hemolytic anemia in the horse associated with Heinz body formation. Calif.Vet. Jan.-Feb. (1963).
139. SCHALM, O.W. and SMITH, R.: Some unique aspects of feline hematology in disease. Small Animal Clinician *3:* 311 (1963).
140. SCHMID, R.: The porphyrias; in The metabolic basis of inherited disease, 2nd ed. (ed. STANBURY, J.B.; WYNGAARDEN, J.B. and FREDRICKSON, D.C.), p.813 (McGraw-Hill, New York, N.Y. 1966).
141. SCHNEIDER, R.; FRYE, F.L.; DEE, O.N.; TAYLOR, D.O. and DORN, E.R.: A household cluster of feline malignant lymphoma. Cancer Res. *27:* 1316 (1967).
142. SCHROEDER, W.A. and JONES, R.T.: Some aspects of the chemistry and function of human and animal hemoglobins. Fortschr.Chem.Org.Naturst *23:* 113 (1965).
143. SHARP, A.A. and DIKE, G.W.R.: Hemophilia in the dog-treatment with heterologous anti-haemophilic globulin. Thrombos.Diathes.haemorrh. (Stuttg.) *10:* 494 (1963).
144. SIPPEL, W.L.: Bracken fern poisoning. J.Amer. Vet.med.Ass. *121:* 9 (1952).
145. SMITH, H.A.: Leukemic neoplasia in the dog. Ann.N.Y.Acad.Sci. *108:* 633 (1963).
146. SMITH, J.E. and KANEKO, J.J.: Heme and porphyrin synthesis by porphyric bovine erythrocytes. Life Sciences *4:* 1745 (1965).
147. SQUIRE, R.A.: A cytologic study of malignant lymphoma in cattle, dogs and cats. Amer.J.vet. Res. *26:* 97 (1965).
148. SQUIRE, R.A.: Hematopoietic tumors of domestic animals. Cornell Vet. *54:* 97 (1964).
149. STEINMULLER, D. and MOTULSKY, A.G.: Treatment of hereditary spherocytosis in peromyscus by radiation and allogeneic bone marrow transplantation. Blood *29:* 320 (1967).

150. STONE, W..H; FRIEDMAN, J. and FREGIN, A.: Possible somatic cell mating in twin cattle with erythrocyte mosaicism. Proc. Nat. Acad. Sci. *51:* 1036 (1964).
151. STORMONT, C.: On the applications of blood groups in animal breeding. Proceedings of the X. International Congress on Genetics, p. 206 (1951).
152. STORMONT, C.; MORRIS, B.G. and SUZUKI, Y.: Mosaic hemoglobin types in a pair of cattle twins. Science *145:* 600 (1964).
153. TATUM, E.L.: Molecular biology, nucleic acids and the future of medicine; in Reflections on research and the future of medicine (ed. LYGHT, C.E.), p. 31 (McGraw-Hill, New York 1967).
154. TENNANT, B.; ASBURY, A.C.; LABEN, R.C.; RICHARDS, W.P.C.; KANEKO, J.J. and CUPPS, P.T.: Familial polycythemia in cattle. J. Amer. Vet. med. Ass. *150:* 1493 (1967).
155. THEILEN, G.H.; APPLEMAN, R.D. and WIXOM, H.G.: Epizootiology of lymphosarcoma in California cattle. Ann. N.Y. Acad. Sci. *108:* 1203 (1963).
156. TORTEN, M. and SCHALM, O.W.: Influence of the equine spleen on rapid changes in concentration of erythrocytes in peripheral blood. Amer. J. vet. Res. *25:* 500 (1964).
157. TURNER, W.J.: Studies on porphyria. I. Observations on the fox squirrel *(Sciurus niger)*. J. biol. Chem. *118:* 519 (1937).
158. VANSTONE, W.E.; ROBERTS, E. and TSUYUKI, H.: Changes in the multiple hemoglobin patterns of some Pacific salmon genus oncorhynchus during the parr-smolt transformation. Can. J. Physiol. Pharmacol. *42:* 697 (1964).
159. VAN VLIET, G. and HUISMAN, T.H.J.: Changes in the hemoglobin types of sheep as a response to anemia. Biochem. J. *93:* 401 (1964).
160. VASKOV, B. and EFREMOV, G.: Fourth hemoglobin type in sheep. Nature (Lond.) *216:* 593 (1967).
161. WASS, W.M. and HOYT, H.A.: Bovine congenital porphyria: Hematologic studies inducing porphyrin analyses. Amer. J. vet. Res. *26:* 659 (1965).
162. WATSON, C.J.; PERMAN, V.; SPURRELL, F.A.; HOYT, H.H. and SCHWARTZ, S.: Some studies of the comparative biology of human and bovine porphyria erythropoietica. Tr. A. Am. Physicians. *71:* 196 (1958).
163. WILLIAMS, R.C., Jr.; RUSSELL, J.D. and KENYON, A.J.: Anti-*Gamma*-Globulin factors and immunofluorescent studies in normal mink and mink with Aleutian disease. Amer. J. vet. Res. *27:* 1447 (1966).
164. WILSON, J.B.; EDWARDS, W.C.; MCDANIEL, M.; DOBBS, M.M. and HUISMAN, T.H.J.: The structure of sheep hemoglobins. II. The amino acid composition of the tryptic peptides of the non-α chains of hemoglobins A, B, C and F. Arch. Biochem. *115:* 385 (1966).
165. WINQVIST, G., Ed.: Comparative leukemia research. Wenner-Gren Center International Symposium Series, vol. 6 (Pergamon Press, New York 1966).
166. WINTROBE, M.M.: Clinical hematology, 6th ed. (Lea & Febiger, Philadelphia, Pa. 1967).
167. WURZEL, H.A. and LAWRENCE, W.C.: Canine hemophilia. Thrombos. et Diathes. haemorrh. (Stuttg.) *6:* 98 (1961).
168. YOUNG, L.E.; CHRISTIAN, R.M.; ERVIN, D.M.; DAVIS, R.W.; O'BRIEN, W.A.; SWISHER, S.N. and VUILE, C.L.: Hemolytic disease in newborn dogs. Blood *6:* 291 (1951).
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172. LEADER, R.W.; PADGETT, G.A. and GORHAM, J.R.: Studies of abnormal leukocyte bodies in the mink. Blood *22:* 477 (1963).
173. LEADER, R.W.; PADGETT, G.A. and GORHAM, J.R.: Hereditary leukomelanopathy (Chediak-Higashi syndrome of man, mink and cattle). NINB Monograph *2:* 393, Nat. Inst. Neurologic Disease and Blindness, USPHS (1965).
174. LUND, J.E.; PADGETT, G.A. and OTT, R.L.: Cyclic neutropenia in grey collie dogs. Blood *29:* 452 (1967).
175. CHEVILLE, N.F.: The grey collie syndrome. J. amer. Vet. med. Ass. *152:* 620 (1968).
176. NACHTSHEIM, H.: The pelger-anomaly in man and rabbit. J. Hered. *41:* 131 (1950).
177. OPLER, S.R.: Observations on a new virus associated with guinea pig leukemia: Preliminary note. J. Nat. Cancer Inst. *38:* 797 (1967).
178. PORTER, D.D.; DIXON, F.J. and LARSEN, A.E.: The development of a myeloma-like condition in mink with Aleution disease. Blood *25:* 736 (1965).