was probably provided by the variation in the carbon content of continental crust available for partial melting. Through its oxygen-carbon energy storage cell, the biomass has influenced the patterns of nearly all the ore metals, except perhaps those of chromium, nickel, and titanium.

References and Notes

1. A chart listing individual deposits by type and age may be found in C. Meyer, in *75th Anniversary Volume, Economic Geology*, P. Sims, Ed. (Economic Geology, Lancaster, Pa., 1981), p. 12.
2. First-cycle magma is derived from the partial melting of mantle; second-cycle magma from the partial melting of rock from first-cycle magma, for example, oceanic crust; third-cycle magma from the melting of continental crust.
3. T. P. Thayer, *Geol. Assoc. Can. Spec. Pap. 14* (1976), p. 211; A. J. Naldrett and L. J. Cabri, *Econ. Geol.* 71, 1131 (1976).
4. P. Cotterill, *Econ. Geol. Monogr. 4* (1969).
5. R. Woodall and G. A. Travis, in *Proceedings of the 9th Congress* (Commonwealth Mining and Metallurgical Congress, London, 1969), vol. 2, pp. 517–533.
6. N. Herz, *Science* **164**, 944 (1969).
7. J. M. Franklin, D. M. Sangster, J. W. Lydon, in *75th Anniversary Volume, Economic Geology*, P. Sims, Ed. (Economic Geology, Lancaster, Pa., 1981), pp. 485–627.
8. F. Mendelsohn, Ed., *Geology of the Northern Rhodesian Copperbelt* (McDonald, London, 1961); A. Francois, in *Gisements Stratiforme et Provinces Cupriféres*, P. Bartholomè, Ed. (Société Geologique de Belgique, Liége, 1974), pp. 79–101.
9. P. G. Söhnge, *Geol. Soc. S. Afr. Spec. Publ.* (1964), pp. 367–382.
10. L. B. Gustafson and N. Williams, in *75th Anniversary Volume, Economic Geology*, P. Sims, Ed. (Economic Geology, Lancaster, Pa., 1981), pp. 139–178.
11. S. R. Titley, Ed., *Advances in Geology of the Porphyry Copper Deposits* (Univ. of Arizona Press, Tucson, 1982); J. M. Guilbert and J. D. Lowell, *Trans. Can. Inst. Min. Metallurg.* **77**, 105 (1974).
12. J. D. Lowell, *Econ. Geol.* 69, 601 (1974).
13. V. F. Hollister, *Geology of the Porphyry Copper Deposits of the Western Hemisphere* (Special Publication, American Institute of Mining and Metallurgical Engineers, New York, 1978).
14. H. L. James and P. K. Sims, *Econ. Geol.* **68**, 913 (1973).
15. P. Cloud, *Trans. Geol. Soc. S. Afr.* 79, 1 (1976) (Alex du Toit Memorial Lecture).
16. S. Moorbath, R. K. O'Nions, R. J. Pankhurst, *Nature (London)* **245**, 138 (1973).
17. S. A. Hauk and E. W. Kendall, in *30th Annual Meeting of the Institute on Lake Superior Geology*, G. L. LaBerge, Ed. (Institute of Lake Superior Geology, Wausau, Wisc., 1984), pp. 17–18 (abstract).
18. D. E. Roberts and G. R. T. Hudson, *Econ. Geol.* **78**, 799 (1983).
19. E. S. O'Driscoll, in *Australasian Institute of Mining and Metallurgy Broken Hill Conference* (Australasian Institute of Mining and Metallurgy, Sydney, 1983), pp. 29–47; *Pet. Explor. Soc. Aust.* 1, 11 (1982).
20. G. N. Phillips and D. L. Groves, *J. Geol. Soc. Aust.* **30**, 25 (1983).
21. D. A. Pretorius, in *75th Anniversary Volume, Economic Geology*, P. Sims, Ed. (Economic Geology, Lancaster, Pa., 1981), pp. 117–138.
22. J. T. Nash *et al.*, *ibid.*, pp. 63–116.
23. C. Meyer and J. J. Hemley, in *Geochemistry of Hydrothermal Ore Deposits*, H. L. Barnes, Ed. (Holt, Rinehart, Winston, New York, 1967), pp. 166–235.
24. B. W. Chappel and A. J. R. White, *Pac. Geol.* **8**, 173 (1974); S. Ishihara, *J. Min. Geol. Soc. Jpn.* **27**, 293 (1977).

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Genetic Basis for Species Vulnerability in the Cheetah

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Over 1000 animal species, many of them mammalian, have been recognized by the Convention of International Trade in Endangered Species as being threatened by extinction (*1*). Although 1000 seems a large number, it probably represents a minor part of a larger process (*2, 3*). Myers (*2*) estimated that, of the 5 to 10 million living biological species, as many as 1 million probably will become extinct by the turn of the century. At the present accelerating rate of extinction, this translates to losing one species every hour. Many large mammals already have become extinct in the wild and survive today only under managed breeding programs in zoological parks and wildlife preserves (*4*). The accelerated rate of habitat destruction has led to the prospect that in the next century virtually all exotic wildlife will be managed in captive breeding programs. Several programs have been successful (most notably those involving Père David's deer, the Mongolian wild horse, and the European bison), but other species (such as clouded leopards, penguins, and condors) have done very poorly under captive propagation conditions (*4*). The reasons for success or failure in these programs are obscure, since scientists and curators have almost none of the necessary background information for species that are threatened or rare (*2*).

There are 37 species in the cat family (Felidae), and all except the domestic cat are considered threatened or endangered (*1*). The cheetah (*Acinonyx jubatus*) is the single surviving species of the genus *Acinonyx* and is considered by most taxonomists to be markedly divergent in both anatomy and behavior from the other genera in the Felidae (*5–7*). Cheetahs, the world's swiftest sprinters, have a number of cursorial adaptations that make high-speed pursuit (up to 112 km/hour) possible (*5*): long, slender legs; enlarged respiratory, cardiovascular, and adrenal capacities; specialized muscles for high acceleration; and semiretractile claws (*5, 6*). Because of its swift and elusive character, demographic estimates of wild cheetahs vary considerably (from 1,500 to 25,000 animals) (*8–11*). Most animals are restricted to two remaining wild populations in southern and eastern Africa, where the population density is less than one animal per 6 km^2 (*9*). This low density can be partially explained by the cheetah's solitary nature, for, unlike the lion, the cheetah usually avoids family groups (*8, 11*). In addition, cheetah cubs appear to suffer severe mortality (estimated at as high as 70 percent) due to disease susceptibility, maternal neglect, and insufficient defense against predators (*12*).

In 1971 the National Zoological Gardens of South Africa initiated a comprehensive program for the propagation of cheetahs in captivity (*13*). In 1981 40 semen samples from 18 cheetahs were collected, examined, and compared to the semen of domestic cats (*14*). Spermatozoal concentrations in ejaculates were ten times less in cheetahs than in domes-

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tic cats, and an average of 71 percent of all cheetah spermatozoa were morphologically abnormal, compared to 29 percent in cats. Comparable abnormalities were observed in semen collected from cheetahs in zoos in the United States. In a parallel study in which over 200 isozyme and cellular protein loci of 55 South African cheetahs were analyzed, the population was found to contain 10 to 100 times less genetic variation than other mammalian species (*15*). Both the genetic and reproductive data cast the cheetah in a status reminiscent of highly inbred mice or livestock and prompted us to hypothesize that the species experienced a severe population bottleneck in its recent evolutionary history (*15*). The possible consequences of such genetic uniformity would include high species vulnerability because such circumstances not only allow expression of deleterious recessive alleles but also limit adaptiveness to perturbations of the ecological niche. The studies presented here confirm and extend the reproductive and genetic status of the species and illustrate its vulnerability to at least one ecological challenge, a feline coronavirus.

High Juvenile Mortality

Captive breeding of cheetahs has been notoriously difficult (*13, 16*), resulting in only a limited number of successful captive propagation programs. To our knowledge, the first documented birth of cheetah cubs in captivity did not occur until 1956 at the Philadelphia Zoo (*16*). Since 1970 the proportion of wild-caught cheetahs that have been successfully bred has been only 10 to 15 percent. For the litters that were produced in captivity we determined the incidence of juvenile mortality (including stillbirths, premature births, and deaths of cubs surviving less than 6 months). This statistic was selected because it closely reflects the damaging effects of inbreeding in exotic mammalian species (*17*). Table 1 presents the results of a fecundity and pedigree record survey of 40 breeding facilities that have successfully produced cheetah cubs. In all, 519 offspring were recorded; the frequency of infant mortality was 29.1 percent, a value comparatively greater than that for most exotic animal species.

Cheetah infant mortality was compared to that of 28 other mammalian species bred in captivity (Fig. 1). Infant mortality for each species was characterized as juvenile mortality from matings between unrelated or related parents. Three important points are evident from Fig. 1: (i) as Ralls and colleagues (*17*) have described, inbred offspring of zoo species in general have consistently greater juvenile mortality than their noninbred zoo counterparts; (ii) cheetah mortality from noninbred matings occurs at the high end of the distribution, with only two species (reindeer and dik-dik) having higher noninbred mortality; and (iii) there is no significant difference between infant mortalities from inbred and noninbred matings of cheetahs, which is not surprising in light of the genetic status of the species (*15*). If the cheetah is as monomorphic for those loci that contribute to congenital defects or lethality as it is for biochemical loci, then inbreeding would probably not lead to the expression of any more deleterious recessive alleles than would be observed in genetically variable outbred populations.

Summary. A population genetic survey of over 200 structural loci previously revealed that the South African cheetah (*Acinonyx jubatus jubatus*) has an extreme paucity of genetic variability, probably as a consequence of a severe population bottleneck in its recent past. The genetic monomorphism of the species is here extended to the major histocompatibility complex, since 14 reciprocal skin grafts between unrelated cheetahs were accepted. The apparent consequences of such genetic uniformity to the species include (i) great difficulty in captive breeding, (ii) a high degree of juvenile mortality in captivity and in the wild, and (iii) a high frequency of spermatozoal abnormalities in ejaculates. The species vulnerability of the cheetah was demonstrated by an epizootic of coronavirus-associated feline infectious peritonitis in an Oregon breeding colony in 1983. Exposure and spread of the coronavirus, which has a very low morbidity in domestic cats (approximately 1 percent), has decimated a heretofore productive and healthy captive population. The extreme genetic monomorphism, especially at the major histocompatibility complex, and the apparent hypersensitivity of the cheetah to a viral pathogen may be related, and provide a biological basis for understanding the adaptive significance of abundant genetic variation in outbred mammalian species.

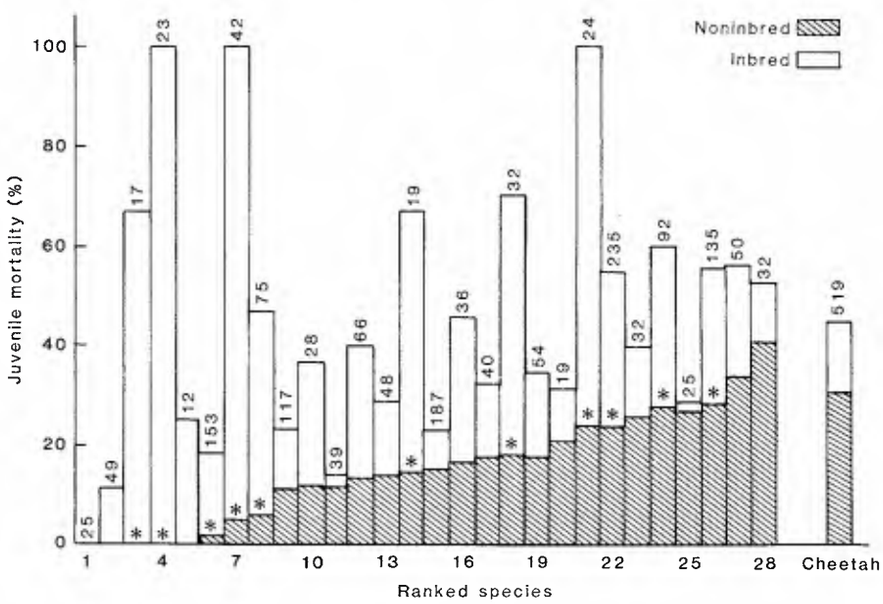

Fig. 1. Infant mortality in 29 mammalian species bred in captivity. Hatched bars are ranked frequencies of juvenile mortality among matings between unrelated parents. All wild-caught animals were considered to be unrelated. Higher values in all cases except species 25 were obtained from consanguineous (inbred) matings (open bars). Species with statistically significant inbred mortalities greater than noninbred mortalities are indicated by an asterisk. The species are (1) four-striped rat; (2) climbing rat; (3) salt desert cavy; (4) Wied's red-nosed mouse; (5) zagoutis; (6) short bare-tailed opossum; (7) scimitar-horned oryx; (8) sitatunga; (9) degu; (10) spiny rat; (11) Père David's deer; (12) punare; (13) wildebeest; (14) Indian elephant; (15) elephant shrew; (16) acouchi; (17) muntjac; (18) sable; (19) boris; (20) giraffe; (21) Eld's deer; (22) pygmy hippopotamus; (23) Grant's zebra; (24) Dorcas gazelle; (25) kudu; (26) Japanese serow; (27) reindeer; and (28) dik-dik. The cheetah data are from Table 1 and the data for the other species are from Ralls and colleagues (*17*). Numbers above the bars give the total number of animals considered in each species.

Table 1. Juvenile mortality in captive-bred cheetahs. Juvenile mortality includes all deaths at 6 months of age or less, including stillbirths, premature births, and cases of maternal neglect, cannibalism, infection and so forth.

Population	Period	Number of litters	Number of offspring	Number of deaths at ≤6 months	Infant mortality (%)
1. De Wildt, South Africa	1974 to 1981	50	183	67	36.6
2. Whipsnade Park, United Kingdom	1964 to 1980	21	73	10	13.7
3. *North American Regional Cheetah Studbook**	1956 to 1982	77	263	74	28.1
Summary of groups 1, 2, and 3	1956 to 1982	148	519	151	29.1
4. Unrelated, North American regional studbook†	1956 to 1982	56	194	51	26.3
5. Related, North American regional studbook†	1956 to 1982	13	43	19	44.2

*Data were compiled by L.M. (*16*). The data represent a composite of pedigree analysis of successful breeding programs at 38 zoos. †Pedigree data for each of the offspring produced by groups 1 and 3 was available. The entire De Wildt population was the result of matings of wild-caught or unrelated animals. Within the survey of the studbook (*16*), all offspring were either one or two generations removed from the wild. Those offspring resulting from matings of related parents (group 5) were compared to those arising from apparently unrelated parents (group 4).

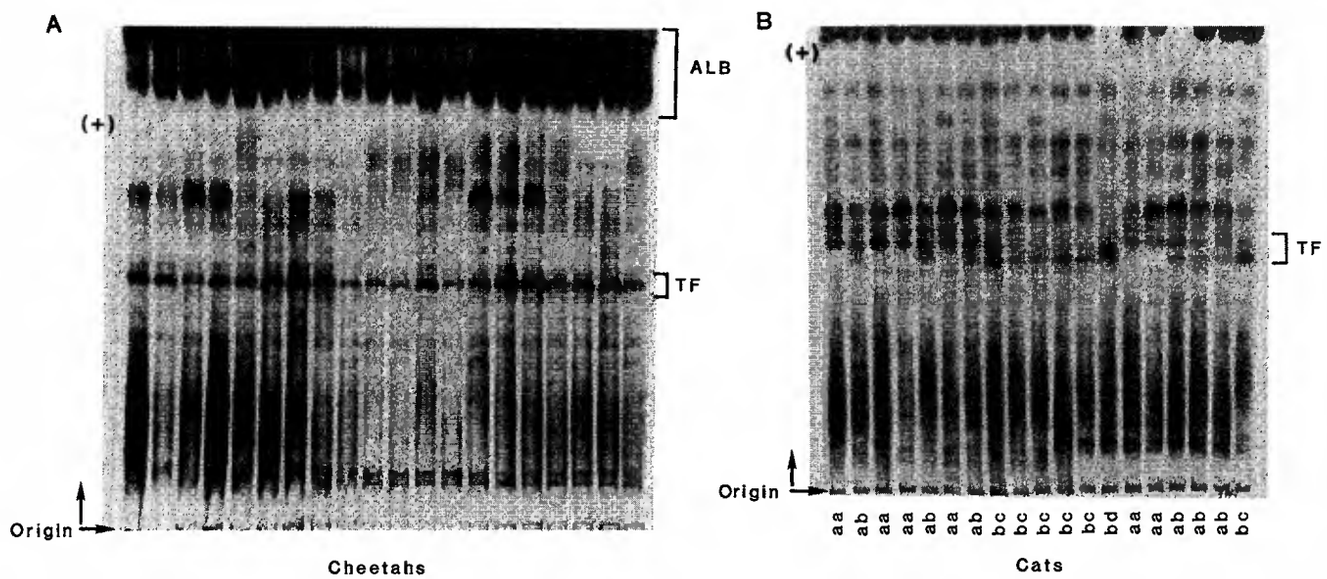

Fig. 2. (A) Polyacrylamide gel loaded with 20 cheetah plasma samples and stained for proteins with Coomassie brilliant blue. Invariant transferrin (TF) and albumin (ALB) bands are indicated. Transferrin was identified in duplicate gels stained with iron-specific Nitroso-R stain (*19*). (B) Polyacrylamide gel loaded with 20 domestic cat samples and stained as in (A). Three domestic cat alleles of TF were observed in the cat survey (*22, 42*).

Table 2. Proportion of loci estimated to be polymorphic and proportion of the genome estimated to be heterozygous in species of Felidae and other selected mammals.

Species	Geographic range	Number of individuals	Number of loci	Polymorphic loci (%)	Average heterozygosity	Reference
Felidae						
Cheetah (*Acinonyx jubatus*)	South and East Africa	55	52	0.0	0.0	This article; (*15*)
Domestic cat (*Felis catus*)	Worldwide	56	61	21.3	0.082	(*38*)
Lion (*Panthera leo*)	Africa, India	20	50	12.0	0.037	(*22*)
Serval (*Leptailurus serval*)	Africa	16	49	12.2	0.033	(*22*)
Leopard (*Panthera pardus*)	Africa, Asia	18	50	8.0	0.029	(*22*)
Caracal (*Caracal caracal*)	Africa, Asia	16	50	10.0	0.029	(*22*)
Tiger (*Panthera tigris*)	India, Southeast Asia, Manchuria, Korea, U.S.S.R.	40	50	10.0	0.035	(*22*)
Ocelot (*Leopardus pardalus*)	North, South, and Central America	6	48	20.8	0.072	(*22*)
Margay (*Leopardus wiedi*)	North, South, and Central America	11	50	16.0	0.047	(*22*)
Other mammals						
House mouse (*Mus musculus*)	Worldwide	87	46	20.5	0.088	(*39*)
Man (*Homo sapiens*)	Worldwide	>100	104	31.7	0.063	(*40*)
	*Two-dimensional gel survey**					
Man (*Homo sapiens*)	Worldwide	28	185	10.8	0.024	(*41*)
Cheetah (*Acinonyx jubatus*)	South and East Africa	6	155	3.2	0.013	(*15*)

*Estimates based on allelic variation at loci coding for soluble proteins resolved by two-dimensional gel electrophoresis of fibroblast extracts.

Genetic Uniformity

In the past 15 years approximately 250 species have been examined for the extent and character of biochemical genetic variation in natural populations (*18*). Electrophoretic analysis of isozyme and soluble protein variation has revealed abundant genetic variation, with frequencies of polymorphic loci ranging from 0.15 to 0.60 and average heterozygosity estimates from 0.0 to 0.26. In an earlier study of 55 cheetahs from two separate South African populations (*15*), we found a total absence of genetic polymorphism in 47 allozyme (allelic isozyme) loci and a low frequency of polymorphism of proteins (polymorphic loci, 3.2 percent; heterozygosity, 0.013) by two-dimensional gel electrophoresis. The allozyme survey of the cheetah population has been extended here to include carbonic anhydrase-2, catalase, phosphoglyceromutase, pyruvate kinase, and transferrin (*19*). All five of these new loci were monomorphic in the sampled cheetahs, including transferrin (Fig. 2), a protein with a high degree of polymorphism in domestic cats, man, and several other mammalian species (*18, 20*). Monomorphism for transferrin in the cheetah extends to 19, the number of "polymorphic cluster loci" (those that tend to be polymorphic in mammals) that are nonetheless monomorphic in the cheetah (*15, 21*).

It was possible that the cheetah's low genetic variation is characteristic of wild species of felids and that the cheetah is only one of several highly monomorphic species. This possibility prompted an examination of genetic variation in other species of the Felidae. A survey of seven cat species was undertaken in which the same 50 allozyme loci that had been examined in the cheetahs were sampled. The species included the leopard, lion, serval, and caracal, which overlap the cheetah's range in Africa. The results are summarized in Table 2 (*22*). All species showed moderate to high levels of genetic variation, further emphasizing the absence of genetic variability in the cheetah.

Isogenicity of the Cheetah at Its Major Histocompatibility Complex

The most polymorphic locus in vetebrates is the major histocompatibility complex (MHC), designated HLA in man, H-2 in the mouse, DLA in the dog, and so forth (*23*). The MHC, ubiquitous among vertebrates, encodes a group of cell surface antigens responsible for strong cell-mediated rejection of allogeneic tissue grafts (*23, 24*). The MHC has been the object of intensive molecular and immunological study in recent years and has been shown to consist of a group of tightly linked loci encoding at least three classes of gene products: class I, serologically defined transplantation antigens expressed on the surface of most types of mammalian cells; class II, cell surface proteins (I region–associated antigens) found on B and some T lymphocytes, which participate in the induction of antibody production; and class III, several components of the complement system (*24, 25*). The MHC system in all species studied to date encodes multiple alleles for class I phenotypes as defined by graft rejection and cytotoxicity reactions with allogeneic antisera. In human populations the variation is so great at the HLA locus that the most common haplotype (combination of alleles of the subloci linked on a single chromosome) has a frequency of less than 1 percent, so that occurrence of the most common phenotype is 10^{-4} (*23*).

Variation of the cheetah MHC was monitored by measuring the timing of allograft rejection between unrelated cheetahs. In man the average survival time of skin grafts between unrelated individuals is 10.5 days (*23*). Rejection of grafts between inbred mouse strains of different H-2 haplotypes occurs between 10 and 12 days (*23, 26*). Similarly, unrelated domestic cats reject skin grafts between 7 and 13 days after grafting (*27*). Rejections at this time occur suddenly, progress rapidly, and are accompanied by the production of cytotoxic alloantisera against donor lymphocytes. Occasionally, and often when grafts are exchanged between related individuals, slower progression and usually much later rejections are observed in these species. Rapid rejections are interpreted as resulting from a difference at the MHC locus, while slow rejections are the result of allelic differences at one or more "minor histocompatibility loci" in the face of identity at the MHC (*23, 25, 27*).

Reciprocal skin grafts were surgically performed on 14 South African cheetahs—four at the De Wildt Cheetah Breeding and Research Center, South Africa, two at the Johannesburg Zoo, and eight at Wildlife Safari, Winston, Oregon. The pedigrees of the cheetahs used in this analysis are presented in Fig. 3. Six graft pairs were between unrelated animals and one pair was between siblings. The cheetahs were immobilized at approximately 5-day intervals and the grafts were monitored for signs of immunological rejection and for gross differ-

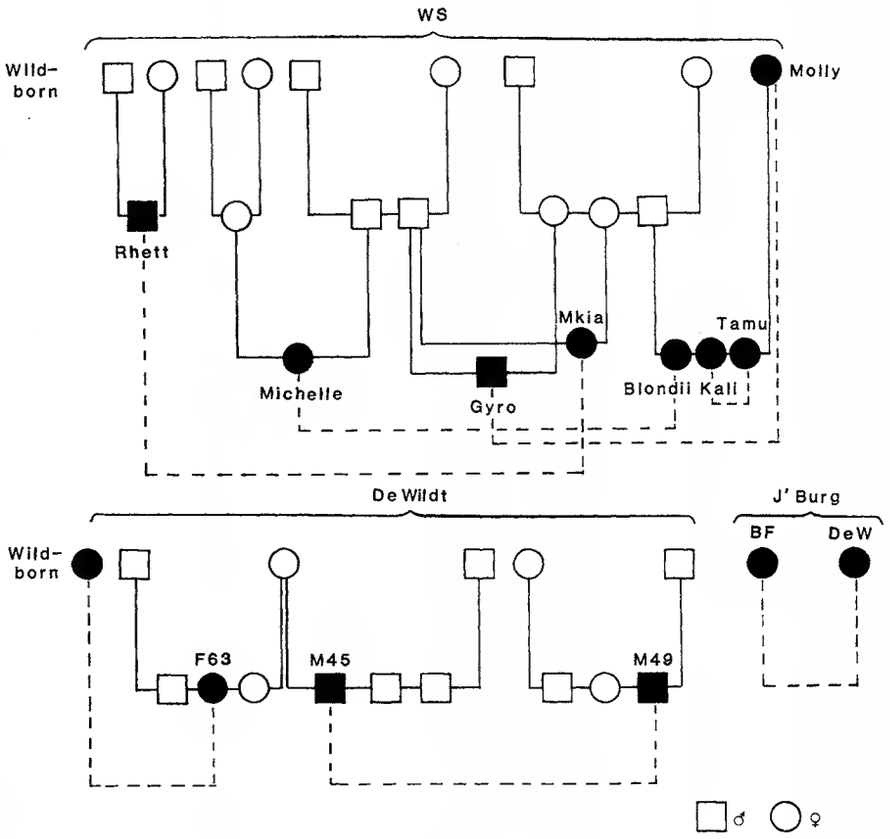

Fig. 3. Pedigree of animals used in reciprocal skin grafts. Filled symbols represent graft animals. WS animals received grafts at Wildlife Safari. Dotted lines connect grafted pairs (Table 3).

ences between allograft and autograft. The characteristics of rejection anticipated from rapid rejections in domestic cats and other species (*23, 26, 27*) include darkening and discoloration, changes in skin pliability, absence of hair growth, and induration, scabbing, and sloughing of skin.

The fate of 14 reciprocal split-thickness grafts are summarized in Table 3 and illustrated in Fig. 4. None of the 14 cheetahs showed rapid graft rejection, and clear evidence of slow rejection was observed in only three animals (Rhett, Mkia, and Blondii). A photographic chronology of the progress of two grafting experiments (Molly and Kali) is presented in Fig. 4. In every case the allograft and autograft were virtually indistinguishable 2 weeks after surgery. The De Wildt and Johannesburg studies were terminated early (day 23), but none of the six animals showed evidence of rejection of allografts, which were similar to control autografts in hair growth, texture, pliability, and appearance.

Since all the allografts were apparently accepted through the rapid rejection stage, the possibility existed that cheetahs were immunologically incapable of rejecting an allograft. To control for this alternative, skin from a domestic cat also was grafted to two of the Oregon cheetahs, Tamu and Kali (Fig. 4). These xenografts were rapidly rejected (after 10 to 14 days) by both animals, while the autografts and allografts survived and were apparently accepted (Table 3). Surgical biopsies of the autograft, allograft, and xenograft of Kali taken on day 14 revealed that the xenograft was heavily infiltrated with mononuclear inflammatory cells, characteristic of a cell-mediated immune reaction, while the allograft and autograft were not. We conclude that 14 of 14 reciprocal skin grafts (12 of which were between unrelated animals) were accepted beyond the rapid rejection stage, suggesting identity of donor and recipient at the cheetahs' MHC locus.

The Cost of Genetic Uniformity: A Case History

The cheetah breeding program at Wildlife Safari is among the most successful in the world. Since 1973, 73 offspring have been born from 18 litters, with an infant mortality rate of 24.7 percent.

In May 1982 a clinically healthy 8-year-old female cheetah developed severe icterus (jaundice), depression, elevated temperature, and diarrhea 5 weeks after being transferred to Wildlife Safari. Despite aggressive therapy, including diuretics, antibiotics, vitamins, corticosteroids, and forced feeding, the animal deteriorated and died within 1 week (*28*). Pathological and serological analysis at necropsy revealed that the animal had the effusive form of feline infectious peritonitis, a generally fatal disease of domestic cats that has only occasionally been reported in exotic felids (*29*). Feline infectious peritonitis (FIP) is caused by a coronavirus, an immunogenic virus with an RNA genome (*30*). The epizootiology and etiology of feline coronaviruses are not well understood, but at least three forms of associated disease are recognized: (i) the effusive or wet form of FIP, which is characterized by fibrinous peritonitis or pleuritis and which is always fatal; (ii) the noneffusive or dry form of FIP, which does not have the fluid but which does have the fibrinous peritoneal deposition and which is also fatal; and (iii) a feline enteritis, which is usually mild (often subclinical) in manifestation. The three conditions are each accompanied by increasing titers of antibody against coronavirus (*29*). In domestic cats the fatal form is rare (approximately 1 percent of cats), and it seldom affects more than 10 percent of the cats in a group under the worst conditions (*29*). The effusive form appears to be immunologically mediated, since induction of effusive FIP in kittens is augmented by the presence of humoral antibodies (*29*).

A retrospective survey of sera from 42 cheetahs at the Oregon colony in 1982 and 1983 revealed that each animal was negative for circulating antibodies against coronavirus before June 1982. By January 1983 every cheetah had developed antibodies (titer, 1:100 to >1:1600) against coronavirus. During 1983 clinical signs (intermittent and chronic diarrhea, weight loss, and de-

Table 3. Fate of reciprocal skin grafts in cheetahs. Grafting procedures previously developed for the domestic cat were used (*23, 26, 27*). Each pair of cheetahs was immobilized with ketamine hydrochloride (7 mg/kg), intubated, and maintained on halothane gas anesthesia. Split-thickness skin pieces (16 cm^2) were removed with a dermatome from a surgically prepared area of the lateral thorax of each animal. The pieces were cut in half under a sterile solution of phosphate-buffered saline. An autograft and an allograft were sutured back into the graft beds. Intramuscular antibiotics were administered and the surgical area was bandaged. Autografts on all cheetahs were accepted throughout.

Recipient (sex)	Donor (sex)	Relation	Location	Fate of allograft*	Day of graft rejection†
Rhett (♂)	Mkia (♀)	Unrelated	Wildlife Safari	S	39 to 49
Mkia (♂)	Rhett (♂)	Unrelated	Wildlife Safari	S	46 to 51
Molly (♀)	Gyro (♂)	Unrelated	Wildlife Safari	A	>78
Gyro (♂)	Molly (♀)	Unrelated	Wildlife Safari	A	>78
Michelle (♀)	Blondii (♀)	Unrelated	Wildlife Safari	S or A	>41
Blondii (♀)	Michelle (♀)	Unrelated	Wildlife Safari	S	70
Tamu (♀)	Kali (♀)	Siblings	Wildlife Safari	A	>52
Kali (♀)	Tamu (♀)	Siblings	Wildlife Safari	A	>52
Tamu (♀)	Heidi (♀)‡	Cheetah (Tamu) and cat (Heidi)	Wildlife Safari	R	9 to 14
Kali (♀)	Heidi (♀)‡	Cheetah (Kali) and cat (Heidi)	Wildlife Safari	R	10 to 16
De Wildt (♀)	B.F. (♀)	Unrelated	Johannesburg	A	>24
B.F. (♀)	De Wildt (♀)	Unrelated	Johannesburg	A	≥24
M45 (♂)	M49 (♂)§	Unrelated	De Wildt	A	>28
M49 (♂)§	M45 (♂)	Unrelated	De Wildt	A	>14
F63 (♀)	Nina (♀)	Unrelated	De Wildt	A	>44
Nina (♀)	F63 (♀)	Unrelated	De Wildt	A	>44

*Abbreviations: S, slow (chronic) rejection; R, rapid (acute) rejection; A, accepted—no sign of rejection. †The symbol > means that this was the last day the graft bed was examined and no sign of rejection had yet occurred. ‡Heidi is a Himalayan domestic cat from the NIH colony. §The allograft-autograft bed in M49 became infected by an abrasion over the bed—a result of surgery and tight bandaging. An inflammatory reaction developed within the first week which subsided with a scaly scab over both the allograft and autograft. The grafts were monitored up to day 24. At all times the appearance, texture, and pliability of both grafts were identical. Nonetheless, the dermatitis reaction complicated the interpretation of this experiment beyond day 14, when the grafts were healthy, showing no evidence of immunological rejection. After this date the grafts were not distinguishable but were both characterized by flaky skin and granulation as a result of dermatitis.

pression) and morbidity were apparent in over 90 percent of the cheetahs. Even with aggressive clinical therapy, 18 cheetahs died from one or more of the following coronavirus-associated diseases: FIP, renal disease, enteritis, hemorrhagic gastroenteritis, renal oxalosis, and FIP-associated kitten mortality complex (*28, 31*). This is, to our knowledge, the most extreme response to an FIP virus infection reported to date in any feline species. For whatever reason, the Oregon cheetahs reacted to the virus in a homogeneously sensitive manner.

One possible reason for the extreme susceptibility of the Oregon colony to the FIP epizootic is that the responsible coronavirus strain was an exceptionally virulent form that happened to be detected first in cheetahs. Certain aspects of this episode, however, tend to preclude this explanation. Attempts to transmit FIP by inoculation of peritoneal fluid or tissue homogenates from diseased cheetahs to three 10-week-old virus-negative kittens were unsuccessful, despite their development of antibody titers against feline coronavirus (*28*). Furthermore, although ten African lions maintained at the Oregon compound were exposed to and developed antibodies against the coronavirus, the antibody titers were all low (never greater than 1:400) compared to those of the cheetahs (often above 1:1600), and none of the lions developed symptoms of FIP. The lack of virulence of the virus in domestic cats and lions suggests that the virus epizootic is specific to the cheetahs.

The high sensitivity of the Oregon colony might be a consequence of the lack of genetic variation. A wide variety of gene classes are normally variable in natural populations and could contribute to disease susceptibility (or resistance) (*23–25, 32*). Most notable of these genes are the products of the MHC (*24, 25, 33*). Class II MHC genes were originally discovered because they varied with respect to ability of certain mouse strains to develop antibodies against synthetic and viral antigens. Class I gene products have been shown to play a key role in T-cell communication (by self-recognition) in mounting an immune response against infectious viruses (*33*). For cytotoxic T cells to recognize and lyse virus-infected cells they must interact with viral antigens and the target cell's MHC product. This "MHC restriction" is well known in several mammals and is probably its most important function (*24, 33*). The extreme polymorphism in class I and class II loci has been interpreted as being an evolutionary adaptation, since (i) MHC variation would expand the T-cell repertoire for flexibility against variant viruses and (ii) polymorphism would ensure species protection against an adaptation of viruses to abrogate a specific haplotype's function (*33, 34*). The possibility that the FIP virus circumvented a specific MHC haplotype present in the entire cheetah colony is a consistent and appealing hypothesis that merits further investigation.

Conclusions

The extreme genetic monomorphism at isozyme and MHC loci in the cheetah is almost nonexistent in wild biological species (*23–25, 35*). Such genetic uniformity might have resulted from a population bottleneck followed by inbreeding (*15*). The timing of such a bottleneck is difficult to pinpoint because of the varia-

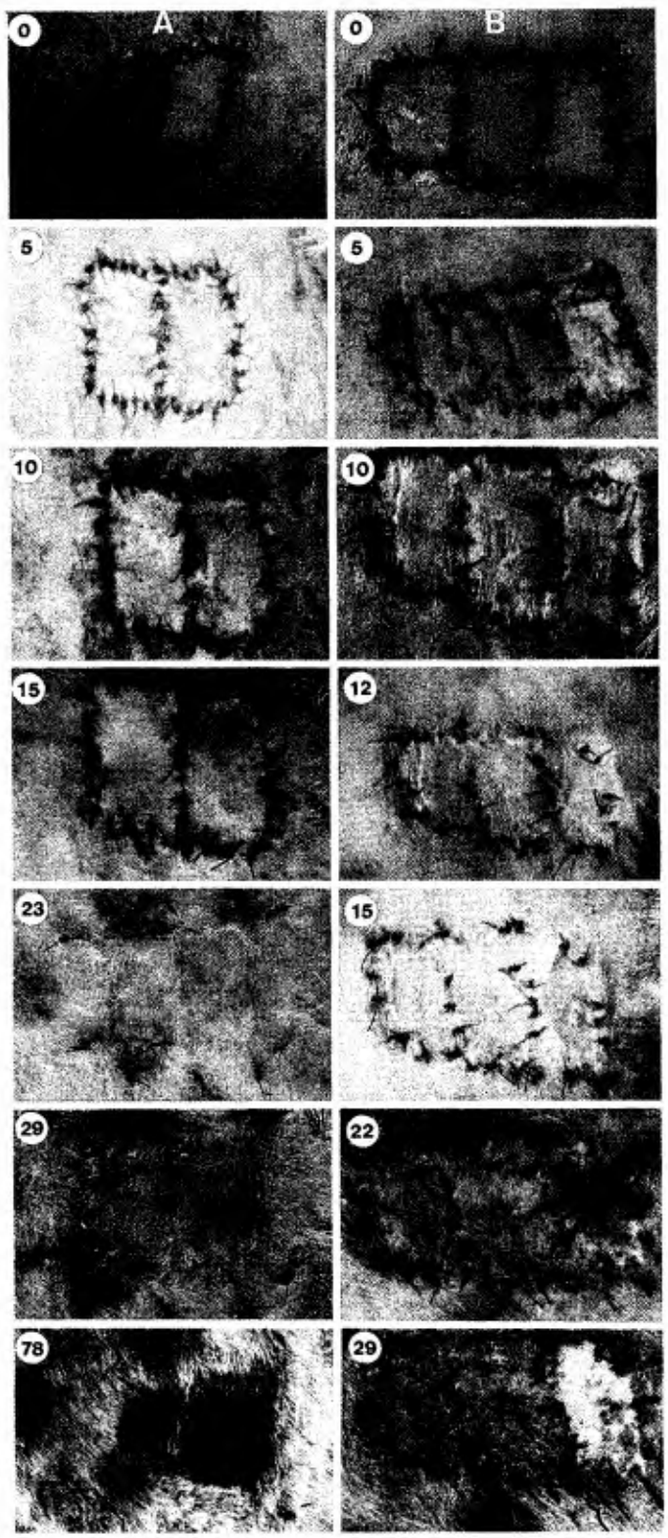

Fig. 4. Reciprocal skin grafts in two cheetahs. The first series (A) was on Molly, who received an autograft (left) and an allograft from Gyro (right). The second series (B) was on Kali, who received (from left to right) an allograft from Tamu, an autograft, and a xenograft from a domestic cat, Heidi. The day after grafting is indicated in the upper left of each frame. Note the strikingly similar appearance of the allograft and autograft throughout the experiment in both series. This is in spite of classical rejection of the xenograft by Kali, first evident by day 10 and completed and scabbed by day 12.

bles that influence population genetic variation (*15, 36*), but it certainly was not a result of captivity, since nearly all the animals in this study are no more than two generations removed from the wild (Fig. 3) (*13, 16*). A possible approach to this question would be a genetic analysis of the East African cheetahs. Allelic differences between East and South African populations would be consistent with a recent bottleneck, while monomorphism and identity of the two isolated populations would be evidence for a more ancient contraction.

The occurrence of a devastating epizootic of FIP at a cheetah compound in Oregon revealed an extreme response to the coronavirus pathogen. A speculative but circumstantially consistent hypothesis is that this virus strain adapted to a particular MHC haplotype that was common among the afflicted cheetahs. This interpretation is based on a well-established proposition that the major function of the MHC locus is self-recognition in mounting immune defense against viruses and that the widespread polymorphism of the MHC reflects the species' protection against more rapid genomic adaptation of pathological viruses (*33*). Whether the vulnerability of the cheetah is in fact the result of MHC monomorphism or the consequence of monomorphism by different types of loci that participate in viral susceptibility cannot be resolved at present. Nonetheless, the catastrophic sensitivity of this genetically uniform species does provide a graphic natural example of the protection afforded to biological species by genetic variability.

The future of the captive breeding programs and even of the species may appear bleak. Nonetheless, there are some hopeful considerations that bear on the management and survival of the cheetah. First, several inbred zoo species (including Père David's deer and Speke's gazelle) that had experienced severe population bottlenecks and inbreeding survived after effective breeding practices were instituted (*4*). Second, at least one other endangered wild species, the northern elephant seal, which also experienced a bottleneck and was shown to have critically low genetic variation, has increased by thousands in the past decade off the California coast since the enactment of protective legislation (*37*). Finally, the East African cheetah may provide a new source of genetic variation that can be introduced into breeding programs.

References and Notes

1. *Convention on International Trade in Endangered Species of Wild Flora and Fauna*, part of the *Endangered Species Act* (PL 93-205, 93rd Congress, 1973) and in 50 appendices. *Code Fed. Reg.*, part 23.
2. N. Myers, *The Sinking Ark* (Pergamon, Oxford, 1979).
3. P. Ehrlich and A. Ehrlich, *Extinction* (Random House, New York, 1981).
4. C. M. Schonewald-Cox, S. M. Chambers, B. Mac Bryde, L. Thomas, *Genetics and Conservation* (Benjamin-Cummings, Menlo Park, Calif., 1983); R. D. Martin, Ed., *Breeding Endangered Species in Captivity* (Academic Press, New York, 1975); J. Perry *et al.*, *ibid.*, pp. 361–362; J. Volf, *ibid.*, pp. 263–270.
5. N. Neff, *The Big Cats: The Paintings of Guy Coheleach* (Abrams, New York, 1983); R. M. Nowak and J. L. Paradiso, *Walker's Mammals of the World* (Johns Hopkins Univ. Press, Baltimore, 1983).
6. J. Kingdon, *East African Mammals: An Atlas of Evolution in Africa*, vol. 3(A), *Carnivores* (Academic Press, New York, 1977).
7. P. Leyhausen, *Cat Behavior* (Garland, New York, 1979); R. F. Ewer, *The Carnivores* (Cornell Univ. Press, Ithaca, N.Y., 1973); H. Hemmer, *Carnivore* **1**, 71 (1978).
8. G. W. Frame and L. Frame, *Swift and Enduring: Cheetahs and Wild Dogs of the Serengeti* (Dutton, New York, 1981).
9. N. Myers, *IUCN (Int. Union Conserv. Nature Nat. Resour. Monogr. No. 4*, 1975).
10. E. Joubert and P. K. N. Mostert, *Madoqua* **9**, 6 (1975).
11. R. L. Eaton, Ed., *The Cheetah: The Biology, Ecology, and Behavior of an Endangered Species* (Van Nostrand Reinhold, New York, 1974).
12. G. B. Schaller, *The Serengeti Lion: A Study of Predator-Prey Relations* (Univ. of Chicago Press, Chicago, 1972); M. G. Hornocker, *Natl. Geogr.* **136**, 638 (1969).
13. D. J. Brand, *Int. Zoo Yearb.* **20**, 107 (1980).
14. D. E. Wildt *et al.*, *Biol. Reprod.* **21**, 1019 (1983).
15. S. J. O'Brien, D. E. Wildt, D. Goldman, C. R. Merril, M. Bush, *Science* **221**, 459 (1983).
16. L. Marker, *North American Regional Cheetah Studbook* (Wildlife Safari, Winston, Ore., 1983).
17. K. Ralls, K. Brugger, J. Ballou, *Science* **206**, 1101 (1979); K. Ralls and J. Ballou, *Lab. Anim.* **16**, 159 (1982); *Int. J. Primatol.* **3**, 491 (1982).
18. J. Powell, *Evol. Biol.* **8**, 79 (1976); E. Nevo, *Theor. Popul. Biol.* **13**, 121 (1978); R. K. Selander, in *Molecular Evolution*, F. Ayala, Ed. (Sinauer, Sunderland, Mass., 1976).
19. H. Harris and D. A. Hopkinson, *Handbook of Enzyme Electrophoresis in Human Genetics* (North-Holland, Amsterdam, 1976); J. O. Mueller, O. Smithies, M. R. Irwin, *Genetics* **17**, 1385 (1962).
20. N. A. Barnicot, C. J. Jolly, P. Eade, *Am. J. Phys. Anthropol.* **27**, 343 (1967); M. Goodman, W. G. Wisecup, H. H. Reynolds, C. H. Kratochvil, *Science* **156**, 98 (1967).
21. S. J. O'Brien, M. H. Gail, D. L. Levin, *Nature (London)* **288**, 580 (1980).
22. A. Newman *et al.*, *J. Mammal.*, in press.
23. G. D. Snell, J. Dausset, S. Nathenson, *Histocompatibility* (Academic Press, New York, 1976); D. Golze, Ed., *The Major Histocompatibility System in Man and Animals* (Springer-Verlag, New York, 1977).
24. J. Klein, A. Juretic, C. N. Baxevanis, Z. A. Nagy, *Nature (London)* **291**, 455 (1981).
25. G. D. Snell, *Science* **213**, 172 (1981).
26. R. E. Billingham and P. B. Medawar, *J. Exp. Biol.* **28**, 385 (1951).
27. C. A. Winkler and S. J. O'Brien, in preparation.
28. M. L. Pfeifer *et al.*, *J. Am. Vet. Med. Assoc.* **183**, 1317 (1983).
29. M. C. Horzinek and A. D. M. E. Osterhaus, *Arch. Virol.* **59**, 1 (1979); R. C. Weiss and F. W. Scott, *Am. J. Vet. Res.* **42**, 382 (1981); N. C. Pedersen, *ibid.* **37**, 1449 (1976); *ibid.* **41**, 868 (1980).
30. S. Siddel, H. Wege, V. TerMeylen, *Curr. Top. Microbiol. Immunol.* **99**, 131 (1982).
31. J. F. Evermann *et al.*, paper presented at the 26th Annual Meeting of the American Association of Veterinary Laboratory Diagnosticians (1984).
32. R. Weiss, N. Teich, H. Varmus, J. Coffin, *RNA Tumor Viruses* (Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1982).
33. R. M. Zinkernagel and P. C. Doherty, *Adv. Immunol.* **27**, 51 (1980); *J. Exp. Med.* **141**, 1427 (1975); M. Cohn, *Cell* **33**, 657 (1983).
34. Any virus that can interfere with the host's immune defenses, possibly by blocking MHC expression or presentation, would possess a selective advantage (*33*). An oncogenic murine adenovirus was recently shown to escape cytotoxic cellular immunity by specifically reducing MHC class 1 molecules [P. 1. Schrier, R. Bernards, R. T. M. J. Vaessen, A. Houweling, A. J. van der Eb, *Nature (London)* **305**, 771 (1983); M. Zijlstra and C. J. M. Melief, *ibid.*, p. 776.
35. A fascinating exception to the generalization that species are polymorphic at the MHC has been described in the Syrian hamster [J. W. Streilein and W. R. Duncan, *Transp. Proc.* **15**, 1540 (1983); J. Streilein, A. Gerboth-Darden, J. T. Phillips, *Immunol. Today* **5**, 87 (1984); F. Csaikl, *Heredity* **52**, 141 (1984)]. This species is apparently monomorphic at class I loci but is polymorphic at class II and at multiple isozyme loci. The species also appears to be especially vulnerable to viral epizootics. Streilein has interpreted this situation to be a consequence of the hermit-like life-style of the species. Because physical contact between individual demes is minimal (unlike the situation in mice, humans, and cats), the selective advantage for abundant MHC polymorphism is slight since virulent viruses simply do not have the opportunities for transmission.
36. M. Nei, T. Marayama, R. Chakraborty, *Evolution* **29**, 1 (1975).
37. M. L. Bonnell and R. K. Selander, *Science* **184**, 908 (1974); C. F. Cooper and B. S. Stewart, *ibid.* **219**, 969 (1983).
38. S. J. O'Brien, *J. Hered.* **71**, 2 (1980).
39. M. C. Rice, M. B. Gardner, S. J. O'Brien, *Biochem. Genet.* **18**, 915 (1980).
40. H. Harris and D. A. Hopkinson, *Ann. Hum. Genet.* **36**, 9 (1972).
41. D. Goldman and C. R. Merril, *Am. J. Hum. Genet.* **28**, 1021 (1983).
42. J. Allan, W. Putt, R. A. Fisher, *Anim. Blood Groups Biochem. Genet.* **12**, 95 (1981).

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