

The Guinea Pig, *Cavia porcellus*

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Introduction

The genetics of the domestic guinea pig, *Cavia porcellus*, is not being pursued so ardently (at this time) as that of other laboratory rodents but, notwithstanding, an impressive amount of material has accumulated. The majority of mutant genes which have been investigated are those for coat color or type. However, a number of interesting pathological conditions have been described, several of which have been carefully examined. Reviews of special aspects of guinea-pig genetics are those of Wright (1927, 1960a, 1963) who has, himself, been responsible for much of the research. Only key references to the extensive literature can be given. In particular, many reports which have merely postulated a genetic component of the observed variation or have described polygenic variation (without attempting an analysis) have been regarded as beyond the scope of this review.

There is no obvious wild form of the domestic guinea pig. The species was being kept by the Incas at the time of the Spanish conquests of South America in the 16th century and most probably had been domesticated long before that. Which of the wild species gave rise to the domestic form is contentious, but authoritative opinion tends towards *Cavia apyrea* (Hackinghaus, 1961b; Rood and Weir, 1970).

Color Mutants

In general, the known color genes are comparable to those of other laboratory rodents; merely one or two are unique to the species (see Table 1).

The agouti locus has three alleles: *A*, which is primarily responsible for wild-type *porcellus* agouti (agouti gray dorsum and yellowish venter), *A'*, which produces *Cavia rufescens* agouti (darker, narrow band, agouti dorsum, and grayish venter) and *a*, which produces non-agouti (self-black in the absence of other mutants).

The albino locus contains four alleles, and their relationships for the production of pigment are shown in Figure 1. The wild-type gene is fully dominant to all mutant alleles, but heterozygous combinations of the latter show intermediate grades of expression. Both temperature and age affect the level of pigmentation. Low temperature increases the amount of pig-

TABLE 1. Known Mutants of the Guinea Pig

Symbol	Designation	Symbol	Designation
<i>A'</i>	Ticked belly agouti	<i>H</i>	Histocompatibility
<i>a</i>	Non-agouti	<i>l</i>	Long hair
<i>b</i>	Brown pigment	<i>Lbsa</i>	Immune response to LBSA
<i>c^k</i>	Dark dilution	<i>m</i>	Rough modifier
<i>c^o</i>	Light dilution	<i>n</i>	Congenital palsy
<i>c'</i>	Red-eyed dilution	<i>p</i>	Pink-eyed dilute
<i>cⁿ</i>	Acromelanic albino	<i>Pgiⁿ</i>	PGI variant
<i>ca</i>	Catalase activity	<i>Pgi^p</i>	PGI variant
<i>co</i>	Cornea anomaly	<i>Pll</i>	Immune response to PLL
<i>co-3</i>	C3 complementary deficiency	<i>Px</i>	Polydactyly
		<i>R</i>	Rough
<i>cn-1</i>	C4 complementary deficiency	<i>Rs</i>	Roan spotting
		<i>s</i>	Piebald spotting
<i>dha</i>	Diminished	<i>sh</i>	Sexual hypogenesis
<i>dao</i>	Dwarf	<i>S^{hu}</i>	Immune response to serum factor SHY
<i>eⁿ</i>	Tortoiseshell	<i>si</i>	Silvering
<i>e</i>	Yellow	<i>sk</i>	Sticky coat
<i>f</i>	Fading yellow	<i>sm</i>	Salmon eye
<i>fc</i>	Fuzzy	<i>St</i>	Star
<i>Ga</i>	Immune response to GA	<i>tr</i>	Tremor
<i>gt</i>	Grizzled	<i>W</i>	Whitish
<i>Gpa</i>	Immune response to GPA	<i>wa</i>	Waltzing
<i>Gt</i>	Immune response to GT	<i>Wz</i>	Dominant waltzing

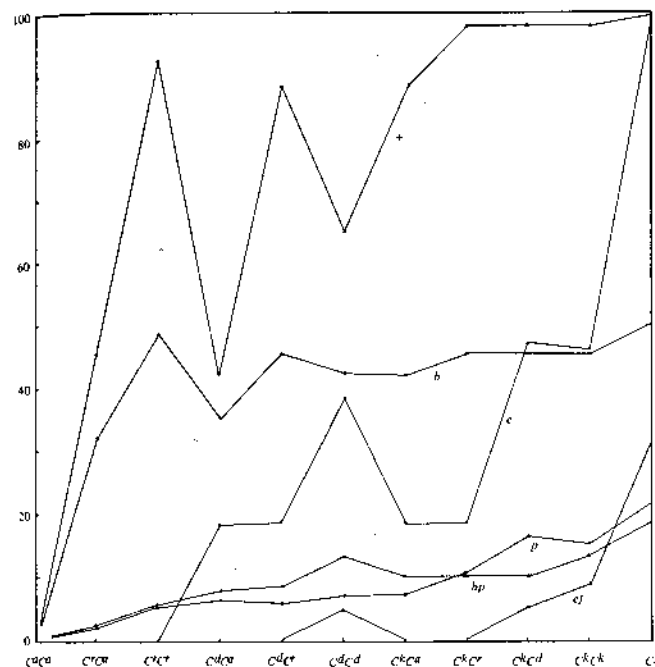


Figure 1. Average expression of eumelanin pigment for genotypes *b*, *p*, and *bp* (shown as percentage of wild type, +) and of pheomelanin pigment for genotypes *e* and *e f* (shown as percentage of maximum expression) for combinations of albino alleles. Based on calculations of Wright (1959d).

ment, the lower alleles (*c'* and *cⁿ*) tending to respond more than the others (Wolff, 1955). Increasing age tends to darken the phenotypes for compounds of *c^d*, *c'*, and *c^o*, but to decrease pigmentation for *c* and *c^k* (Wright, 1960c). The *cⁿ* allele is often referred to as albino, but the mutant is actually an instance of acromelanic albinism (Robinson, 1973) in that pigment forms regularly in the extremities (unless blocked by the action of another gene).

Gene *b* produces brown or chocolate pigmentation. The iris color assumes a slightly lighter shade of brown, while the pupil may have a ruby tint in certain lights. Both hair and skin color are changed.

Two alleles are known for the extension locus, namely, e^p , where the coat is a mixture of wild-type and yellow hairs, usually closely intermingled (brindled) or segregated into black or yellow patches (tortoiseshell), and e , where all of the hairs are yellow. Gene e^p , in fact, combines the action of wild-type and e , as may be seen explicitly in combinations with genes with differential effects on black and yellow pigmentation. The e^p allele is incompletely dominant to e in the sense that $e^p e$ usually has more yellow, on the average, than $e^p e^p$ (Chase, 1939*b*). The transformation of brindled to tortoiseshell is strikingly facilitated by the presence of piebald spotting (s), and this effect has been extensively studied (Chase, 1939*b*; Wright, 1960*b*). The $e e$ animal is self-red or -yellow, the intensity of color varying widely due to the existence of modifying polygenes.

The locus f dilutes yellow to about the same degree as $c^k c^k$; the dilution is not stable, the color paling still further with age; hence, the designation of "fading yellow." The gene is not fully recessive. There is no, or very trivial, effect on black or brown pigmentation.

Gene p produces a pink eye and a marked reduction of intensity of black and brown, but it has no (or very minor) effect on yellow pigmentation. Ibsen (1932) briefly notes that p may dilute slightly the color of reds ($e e$) which have been selectively bred for richness of color.

Salmon eye (sm) is a recessive gene restricting pigmentation of the eye to a variable ring at the pupillary margin of the iris (Gregory, 1923). Unlike p , the hair pigmentation is not strongly affected, although Ibsen (1932) has remarked that the gene can slightly dilute the color of red ($e e$) and cream ($c^a c^a e e$). Genes b and sm interact to produce a pseudo-pink eye in $b b sm sm$ animals. A histological examination of the distribution of pigment in the various forms of salmon eye has been contributed by Gregory (1929).

There are several known forms of silvering (mixture of white and colored hairs). The more well known is stationary silver, described by Wright (1947, 1959*a*). The white hairs are present at birth and do not increase in number with age. The expression is highly variable and accompanied by local concentrations to engender all-white patches. The colored hairs often display a small dilution of color. The degree of expression is strongly influenced by modifying polygenes. Although the gene (si) is formally regarded as recessive, the modifiers can shift the expression toward incomplete dominance. Wright is of the opinion that the dominant gene roan (Ro) depicted by Ibsen and Goertzen (1951*b*) is the same as si , the dominant expression of silvering in this case being a consequence of the polygenic background.

The si gene interacts phenotypically with other color genes, particu-

larly with the albino alleles, details of which are given by Wright (1959*a,b*). Wright's analysis revealed the presence of an incompletely dominant modifying gene, diminished (dm). The $dm dm si si$ animal is mainly white except for a few small spots of color on the cheeks. These silver-whites show greater mortality than normal, 25 percent deficiency of hemoglobin concentration, and impaired fertility in both sexes. The dm gene interacts with the albino alleles to lighten the coat color.

The extreme variability of silvering impelled Pietet and Ferrero (1940) to postulate the involvement of two genes. One, a dominant (V), for ventral silvering and another, recessive (d), for dorsal expression. However, as Wright (1947) has argued, there are grounds for doubting this interpretation.

A progressive silvering has been termed grizzling (Lambert, 1935; Wright, 1947). This form is not present at birth, but first appears at about 2-3 months of age in the form of scattered white hairs. While the number of these hairs increases steadily throughout life, the majority of the white hairs are produced in the second coat. The degree of grizzling is most variable and is confined largely to the dorsum, particularly posteriorly. A single recessive gene (gr) appears largely responsible although other minor genes may be concerned.

It may be remarked that a synthetic silvered phenotype can be produced by the joint action of c' and e^p in $a a c' c' e^p e^p$ due to the removal of yellow from the hair by c' and the brindling induced by e^p . The effect is striking.

The gene for whitish (W), described by Ibsen and Goertzen (1951*a*), causes a reduction of hair pigmentation in the shaft of the hair of brown ($b b$) individuals. The character is variable, ranging from hairs with merely pale brown banding to others in which most of the hair is white, except for a pigmented tip. Whitish is manifest at birth. In blacks, the trait is expressed merely as a few whitish hairs on the forehead in homozygous ($W W$) animals, and these hairs disappear with age. No individuals homozygous for c^a , c' , e^a , or e were observed to show the whitish character.

It is of interest that whitish is remarkably similar to the "silver" of Eaton (1943) and to the dinginess of browns reported by Wright (1947) in regard to expression and their interaction with other genes. However, Wright found that dinginess was inherited polygenically in his breeding material. Ibsen and Goertzen noted that dinginess was present in their stock, but they were unable to relate it to whitish. However, while being *prima facie* independent, it is possible for the two characteristics to be aspects of the same basic failure of normal pigment physiology. Either W

is a major gene of the dinginess polygenic complex (which happened to be absent from Wright's material), or the polygenic background of Ibsen and Goertzen's stock enhanced the expression of dinginess so that one of the genes involved could assume monogenic expression.

R_s is a recent mutant, and it has manifold effects in the heterozygote (Whiteway, 1973). The head and feet are usually solidly colored except for white blazes on the head and distal white on the feet. The body is heavily and irregularly silvered (to the point of roan) with white hairs. The pupil of the eye is distinctly ruby in color. Whiteway (private communication, 1973) has preliminary evidence that *R_s R_s* is microphthalmic and has white fur.

White Spotting

A feature of white spotting in guinea pigs is its extreme variability, ranging all the way from a self animal with white spots on the head or feet to all white (Wright, 1920, 1926; Wright and Chase, 1936; Chase 1939*a*). Despite this, the spotting appears due in the main to a single gene (*s*) which is formally regarded as recessive. The heterozygote *+ s* may show some white spotting, but it is irregular and normally only against a polygenic background which induces very white homozygotes *s s*. Wright has given considerable attention to the factors (genetic and environmental) which contribute to the variability of expression in homozygotes. In two stocks, one random bred and the other highly inbred, the variability was apportioned as indicated in Table 2. The sex difference is manifested as the males showing slightly less white than the females, the magnitude of the difference varying with the stock. Increasing the age of the mother tended to increase the amount of white in the young but, in general, the effect of factors common to siblings was small. Even in the random-bred stock, at least half of the environmental variability was specific to the individual. Chase's study of the presence or absence of white for definite points of the body showed that, while moderate correlations were realized for adjacent points, the correlation coefficients fell quickly to virtually zero for more distant points. The quantity of exogenetic variation has also frustrated attempts to select for definite areas of pigmentation, in spite of the fact that inbred strains can be characteristically spotted (MacCurdy and Castle, 1907; Eaton, 1928).

In addition to the main gene, there is evidence for modifying genes, most presumably only capable of expression in conjunction with *s*, although some may be able to produce minor white spotting in their own right (Pictet, 1931; Ibsen, 1932; Baker and Ibsen, 1942). Some have been

TABLE 2. Variability of Expression in Homozygotes

Source	Random bred, percent	Inbred, percent
Heredity	40	0
Sex	2	3
Environment		
Age of mother	6	4
Other factors common to litter mates		4
Factors not common to litter mates	52	89

designated gene symbols, but whether identification is consistent enough from generation to generation to warrant this is open to question.

Ibsen (1932) has given brief details of numerous modifiers of expression of mutant characters. Most are dignified by the nomination of symbols. Several of these have been confirmed by the later publication of experimental data; whereas many others remain unsubstantiated. It may be wondered if many of the modifications described are due to polygenes rather than to genes with effects stable enough for these to be identified in crosses. Genes controlling intensity of pigmentation of reds (*e e*) and creams (*c^a c^a e e*), the formation of eumelanin tipping to the hairs of reds (*e e*) and whites (*c' c' e e*), and the development of fullness of hair length in long-haired (*l l*) animals would almost certainly fall into this category. Wright (1959*b*) has commented that one of Ibsen's lightning genes (*li*) of creams could be the same as *dm*. A gene (*di*) has been described which causes black and brown hairs to be dilute at the base, while red hairs are not affected; brown is more affected than black. Hence, the gene could be part of the dinginess polygene complex.

Gene Interaction

The coat-color genes display a variety of interactions, some of which may be regarded as curious and unexpected. It is unknown if the guinea pig is unique in this respect. Probably not, since these interactions have been brought out by the painstaking labors of Sewall Wright, who has not been content to simply describe the many phenotypes produced by systematic recombination of the genes but has endeavored to quantify their relationships (Wright, 1916, 1927, 1941*b*, 1949*a*, 1959*c,d*, 1960*b,c*).

The interrelations of the albino alleles have been the focus of much at-

tention, because while these behave in general as expected for chinchillated mutants (greater effect on yellow pigment than on black, so that yellow is diminished or eliminated before black is severely modified) in order of descending dominance, there is a notable exception (Figure 1). The c' allele normally fails to show any yellow but produces more black pigment than c^a , an allele which shows a moderate amount of yellow. It is as if a physiological substrate, normally involved in the production of yellow, had been diverted to supplement the production of black pigment; or, that the processes involved in the production of yellow and black pigment have been competing for a common substrate and one (the yellow) had been interrupted or rendered less efficient, so that more black is produced.

The albino alleles present one of the more remarkable interactions, but others exist, and the papers of Wright (1959*c,d*) should be consulted for details of these. The intensity of both black and yellow are strongly influenced by modifying polygenes, especially the latter, which may vary from bright orange-red to almost mahogany. In this connection, the curves for e and ef in Figure 1 are not based exclusively on the darkest obtainable phenotypes, hence the levels shown are slightly underestimated. Wright (1959*d*) has shown, however, that the relative expression of pigmentation by the different albino alleles is not changed by considering the effects of one or more of the "diluting" genes, dm and si .

The coat of the guinea pig is well developed at birth, and this stage is the obvious choice for quantitative analysis since the pigment has been laid down in the almost constant environment of the mother's uterus. Changes occur after birth, and the magnitude of these have been studied by Wright (1960*c*). The changes are many and sufficiently complicated to defy summary. An important influence is the temperature level, particularly for phenotypes produced by the lower members of the albino alleles. Other phenotypes react differentially to advancing age.

This is not the place for a detailed discussion of the microscopic and chemical studies of color phenotypes, although this work should be noted. The distribution of pigment in the eye tissues has been described by Gregory (1929) and Harman and Case (1942), and in the hair by Schilling (1939) and Harman and Case (1941). Most of the genes induce highly correlated changes in the two structures. The first appearance of pigment in the skin and hair is in the 43-day-old fetus, and no clear distinction can be made between black, brown, or yellow pigment granules at this age. Brown granules are of the same size, shape and distribution as black, but they are of a lighter sepia brown color. Diffuse yellowish pigment is present in the cortex of both black and brown hairs but it is richer in color and more conspicuous in the latter.

Yellow granules are larger than black or brown and are more irregular in shape, while the diffuse pigment is bright orange-red. Two sorts of yellow granules have been observed, dark and light, corresponding to $+e$ and be genotypes. A few pale red granules have also been seen in $b^c e^b$ hair. In $c' e^b$ animals, black or brown granules occur in the eumelanic areas of the coat, but only colorless granules occur in the white areas (potentially phaeomelanic, but white due to action of c'). Mock albinos ($c^a e$) have only colorless granules. The action of f , p , and sm on hair pigment granules has not been ascertained at this time.

The many chemical analyses have been largely concerned with the quantitative determination of amounts of pigment, particularly for the various albino alleles, since this locus is a fundamental modulator of pigment production. Some attention has also been given to the chemical differences between eumelanin and phaeomelanin, as revealed by several standard treatments. This work has involved colorimetric comparisons, observations of the dopa reaction with frozen sections of skin or colorless extracts, permanganate titration, reflectometer readings, oxygen consumption curves, and amount of darkening in a Warburg apparatus (Kronig, 1930*a,b*; E. S. Russell, 1939; W. L. Russell, 1939; Heidental, 1940; Baker and Andrews, 1944; Ginsburg, 1944; Wright, 1949*a*; Wright and Braddock, 1949; Foster, 1956). Concise summaries of some of this work are given by Wright (1941*b*, 1963).

Table 3 gives the genotypes of the principal varieties of guinea pigs

TABLE 3. Genotypes of Fancy Varieties of Guinea Pigs^a

Variety	Genotype	Variety	Genotype
Abyssinian	Rm	Lilac	$a p$
Albino	$c^a c^a e$	Orange agouti	b
Beige	$a b p$	Peruvian	$i R m$
Black	a	Red	r
Black-eyed white	$c' c' e$	Roan	st or Rs
Brindle	$a e^b$	Salmon agouti	p or $h p$
Chocolate	$a b$	Self golden	sp
Cinnamon agouti	$b c' c'$	Shellic	l
Cream	$c^a c^a e$	Silver agouti	$c' r r$
Dutch	$a s$	Tortoiseshell	$a e^b$
Golden agouti	$+$	Tortoiseshell and white	$a e^b s$
Himalayan	$a c^b c^a$		
Lemon agouti	$c' c^a$ or $b c' c^a$		

^aThe names of the majority are surprisingly descriptive. Where there is epistasis, it is possible for the variety to have several genotypes.

bred by fanciers. These varieties serve as a useful reservoir for mutant color genes.

Coat Mutants

One of the oldest known mutants is the long hair which is due to a recessive gene *l*. Indeed, the mutant was among the first to be utilized to confirm that Mendelian assortment applied to mammals (Castle, 1903). In the hands of fanciers, the long hair of the Peruvian variety has been greatly extended in length and is of extreme softness of texture. The differences appear due to polygenes. They have also combined long hair with *R* and *m*, the effect of which is to cause the hair to grow outward in all directions (which they desire) instead of tending to fall from head to tail in conformity with normal hair direction.

"Abyssinian," rosette, or rough coat is characterized by marked changes of hair slope, so that partings, ridges, and hair whorls are produced. There is considerable variation of degree of change of slope, formation of ridges and whorls, and presence and sites of whorls. The genetic basis for the variation has been the subject of considerable discussion (Wright, 1916, 1935*b*, 1949*b*; Pictet, 1934; Pictet and Ferrero, 1934). An embryological study of hair-follicle initiation and development in rough animals has been contributed by Colin (1943).

Wright has postulated the interaction of two major genes, one dominant (rough, *R*) and one recessive (rough modifier, *m*), as the prime mover of the variation. The expression of *m* is dependent upon the presence of *R*, so that normal-coated cavies lack *R*, although they may carry *m*. The highest grade of expression is given *R - m m*, with well-formed primary and secondary whorls on all regions of the animal. The *R - + m* animal often has whorls, but they are fewer in number and less well formed; they may even be devoid of whorls, possessing merely a mid-dorsal crest and roughness of hair on the legs. The *R - + +* animal usually lacks whorls, and the mid-dorsal crest may be present, but this is not invariably the case. The least expression of rough are irregularities of hair slope on the hind legs. Other modifying genes, less well definable as *m*, are responsible for part of the residual variability.

Pictet and Ferrero postulated the presence of a dominant gene for rough and also two dominant modifiers (*D* and *G*): *D* producing well-developed head whorls, as opposed to poorly developed, and *G* producing whorls over most of the body, as opposed to more restricted formation to the trunk or midriff. Wright has criticized this interpretation and has

argued that Pictet and Ferrero's own data can be demonstrated not to be in full agreement with it.

The *St* gene induces a flat whorl or hair on the forehead, with notably little variation (Wright, 1959*c*). There is often a parting, anterior to the center of the whorl, extending for a short distance along the midline of the nose. *St* is genetically independent of *R* and *m* but interacts antagonistically with *R*. Whereas, both *St -* and *R - m m* would be expected to have whorls on the forehead, the combination *R - m m St -* may either lack a whorl or may have it imperfectly formed. In *R - + + St -* or *R - + m St -*, the inhibitory effect of *R* is evident as a distortion of the normally formed *St* whorl. Conversely, *St* appears to interfere with the usual crest and whorl formations of *R* on the body. The original paper should be consulted for full details of this rather surprising interaction.

A "fuzzy"-haired mutant has been reported by Garber (1953). The vibrissae is said to be curly, and the fuzziness of the coat is apparent within two or three days of birth, becoming more pronounced with age. The breeding data are meager but compatible with the assortment of a dominant gene (*Fz*).

A rex coat appeared spontaneously in a closed colony some years ago (Robinson, unpublished). The vibrissae were bent and the coat was unkempt. Backcross matings inferred that the trait was inherited monogenically, but the stock was annihilated by disease before it could be established whether the gene was dominant or recessive. It is possible that the mutant may have been a repeat mutation of *Fz*.

The sticky coat described by Herbertson *et al.* (1959) owes its peculiar appearance to excessive secretion of the sebaceous glands. Preliminary analysis indicates that the secretion differs from normal, containing about four times as much lipid material, with the fatty acid fraction being more fully saturated. The coat appears ruffled and sticky to the touch. The effect is most obvious at birth, when the coat is also wavy. Subsequently, the wave disappears, but the stickiness persists. Loose material and food tends to adhere to the stomach fur and about the muzzle. The condition is due to a monogenic recessive (*sk*).

Immunological and Electrophoretic Variation

Much of the early work in this field would now be regarded as merely exploratory from a genetic viewpoint. Notwithstanding, variation of responsiveness was reported in several experiments. Chase (1911) observed variation between individuals to sensitization to dinitrochloroben-

zene, and Scheibel (1943) observed variation in ability to produce anti-toxin to diphtheria. The interesting aspect is that in these experiments it was possible to breed strains which diverged in their responsiveness, thus demonstrating a genetic component in the variation.

The inbred strains, Wright 2 and 13, have been featured in several studies of histocompatibility. The earliest work is that of Loeb and Wright (1927), whose report on these two strains (among others) showed that they had become sufficiently homozygous for pieces of organs, transplanted subcutaneously between members of the same strain, to be accepted. Strain 2 appeared to have the better acceptability because strain 13 gave the more variable results.

Subsequently, Bauer (1958, 1960) presented results of skin grafting both within and between the two strains. The intrastain transplants were fully successful, with no indication of Y-chromosome incompatibility, as shown by acceptance of male skin by females. All of the interstrain grafts were rejected, with a mean survival time of 8 days. An estimate of the number of histocompatible gene differences was derived by challenging 27 F_2 individuals by grafts from each parent strain. Of these, 14 survived, giving a survival rate of 26 percent. This level of survival would correspond to five independent genes (with 95 percent fiducial limits of about three and seven genes). The distribution of survival dates ranged from 8 to 52 days, with a suggestion of two modes at 8 and 14 days. Thus, it is possible that differences at two major (rapidly reacting) histocompatibility loci could separate the two strains. Recently, in this connection, Ellman *et al.* (1970b) and Bluestein *et al.* (1971c) have demonstrated that differences do exist between the strains for one major locus (provisional symbol *H*).

A locus directly concerned with immune responsiveness to various haptens (both synthetic and natural) has been discovered (Green *et al.*, 1969, 1970; Green and Benacerraf, 1971). One of the first demonstrations of the existence of the locus was the discovery of a discrete difference in the response to the synthetic polypeptide poly-L-lysine. It was found that the response was controlled by the presence of an autosomal dominant gene *Pll* (Benacerraf *et al.*, 1967; Ellman *et al.*, 1970b). Furthermore, strain 2 possesses the gene while strain 13 does not. Studies with these strains revealed that the *Pll* gene is closely linked to a histocompatibility antigen carried by strain 2. Continuation of the studies showed that the linkage is manifested in two stocks of random-bred guinea pigs (Martin *et al.*, 1970; Ellman *et al.*, 1971a).

Strains 2 and 13 were featured in a search to assess immune responsiveness to synthetic copolymers of L-glutamic acid and L-alanine (GA) and of L-glutamic acid and L-tyrosine (GT); the evoked response to these substances was found to be governed by the two dominant genes *Ga* and

Gt, respectively. Strain 2 was homozygous for *Ga* but not *Gt*, while strain 13 was homozygous for *Gt* but not *Ga* (Bluestein *et al.*, 1971a). Experiments with random-bred animals revealed that *Ga* and *Gt*, and *Gt* and *Pll* are totally disassociated, as if they are allelic or pseudo-allelic. However, whereas *Ga* and *Pll* tend to be inherited together, a few animals had *Ga* but not *Pll*, and *vice versa*. The implication is that crossing over had occurred in the ancestry of these exceptional individuals (Bluestein *et al.*, 1971b). As may be anticipated, *Ga* and *Gt* displayed linkage, with the respective histocompatibility alleles differing strains 2 and 13 (Bluestein *et al.*, 1971c,d).

Immune responsiveness to low doses of bovine serum albumin and human serum albumin appeared to be inherited as a simple dominant (*Lbsa*) linked to *Pll* in strain 2 and 13 crosses (Green *et al.*, 1970; Green and Benacerraf, 1971). Conversely, the response to low doses of hapten-guinea-pig albumin conjugates (GPA) was governed by a dominant gene (*Gpa*) linked to the strain 13 histocompatibility allele (Green *et al.*, 1972; Davie *et al.*, 1972).

The above results suggest that the *Pll* locus is complex, governing specific immune responsiveness to a variety of antigens. The fact of linkage to a histocompatible locus has prompted the above authors to stress the transpecies homology of close linkage of *H-2* histocompatibility and the *Ir-1* immune response in the house mouse. Both of these loci of the mouse are known to be complex; remarkably so at this time (although it may be that most gene loci are complex when subjected to prolonged analysis). Notationally, it may prove to be advisable to indicate the immune responsiveness complex by a generalized symbol (say *I^r*) instead of doing so for its components, which are better regarded as specificities.

Preliminary evidence points to the monogenic autosomal dominant inheritance of response to immunization with hydralazine (Ellman *et al.*, 1971b). The number of animals examined are few, but the data imply that the response gene is inherited independently of the strain 13 histocompatibility allele.

Batisto (1963) has described a naturally occurring differential reaction to a "serum factor" present in some stocks of cavies, but not in others. The ability to elicit a response is ascribed to a dominant gene *S^h*. It is of interest that both the inbred Wright 2 and 13 strains lack the factor.

Prima facie evidence for allotypes of γ -globulin has been reported (Benacerraf and Gell, 1961; Kelus, 1969). No breeding results are presented, but the implication is that genetic variants coexist as polymorphisms in random-bred colonies.

Guinea pigs are a useful source of complement, and the system has

been well studied. The first reports to disclose genetic variation were those of Moore (1929), Rich (1923), and Hyde (1923, 1927). The inability to produce the so-called C3 component was inherited as an autosomal recessive (provisional symbol *co-3*). These complement-deficient animals flourished under ideal husbandry, but were less resistant to disease and environmental stress, and the stock eventually died out. Ellman *et al.* (1970a) have queried which complement was deficient in these animals, since the C3 component is now known to be complex.

Ellman *et al.* (1970a) have founded a colony which is deficient in the C4 component and have determined that the deficiency is due to an incompletely recessive gene. No symbol is assigned to the gene, but *co-4* is employed here provisionally.

The experiments of Colten *et al.* (1970) have revealed variants of the C2 component. These showed that the isoelectric point of C2 activity from pooled sera was bimodal, with one peak at about 5.2 and another at 5.5. Serums from individual animals were subsequently found to be of two sorts: those which had one peak of 5.5 and those which had two peaks. The results are interpreted as indicative of polymorphism for two electrophoretic variants. No formal genetic data are presented, and it is clear that a genetic analysis could be rewarding.

Radev (1961) isolated a stock in which the level of erythrocyte catalase activity was unusually low. The lower level was also found in homogenates of kidneys, liver, and spleen from which the blood had been removed. The lower activity was demonstrated to be inherited as a simple recessive trait. However, Lush (1966) makes the point that the assay method employed was inefficient and any differences between homozygous and heterozygous normals could have been easily overlooked. The gene has not been symbolized, but for the purposes of this review will be represented provisionally as *ca*.

An examination of 20 domestic guinea pigs for electrophoretic variants of phosphoglucose isomerase (PGI) failed to detect variation; likewise for three *Cavia aperca* animals (see section on hybridization, p. 297), although the electrophoretic patterns of the two groups were distinctive (Carter *et al.* 1972). Each group gave single bands, sited differently in the electrophoretic spectrum. However, F₁ hybrid offspring of the two species showed a triple-banded pattern corresponding to the parental bands and an intermediate hybrid band. Segregation of the three patterns occurred in the F₂ offspring. Although the number of animals involved was meager, different alleles, *Pgi^a* and *Pgi^b*, were assumed to be possessed by the *porcellus* and *aperca* animals, respectively, for a postulated *Pgi* locus.

Abnormalities

Wright (1960a) has discussed the occurrence of a variety of anomalies in guinea pigs, particularly those with which he has been directly concerned. The frequency of many of these was too low for ideas to be drawn on the modes of inheritance. The only indication of a possible, albeit tenuous, genetic basis was the recurrence of certain anomalies in one family or strain. Those with more or less well-defined modes of inheritance have been the subject of separate reports and are detailed below.

A form of dwarfism was observed by Sollas (1909, 1914) to be inherited as a monogenic recessive (*dw*). At birth, the animal appears more thickset than normal, with short limbs and a curiously shaped head. With increasing age, the small size becomes increasingly apparent. All of the leg bones were found to be short and thickened. The length of the skull was shortened. Mortality of the dwarfs was high, most dying within a few days or weeks of birth.

The eye defect reported by Lambert and Shrigley (1933) primarily affected the cornea. The defect is present at birth and persists throughout life. The more obvious symptoms are a dulling or dryness of the cornea, photophobia, and unusual sensitivity and thickening of the eyelids; however, there is considerable variability of expression. The anomaly is attributable to a recessive gene (*co*) with variable expression. A histological study of the defect has been made by Whitlock (1935).

An instance of waltzing was that reported by Ibsen and Risty (1929) and Ibsen (1932) and was due to a recessive gene *wa*. The guinea pig as a newborn tends to throw its head about, and it tends to run in circles as it becomes older. The pathology of the anomaly has been investigated by Cogan (1940) and Lurie (1934, 1941). Afflicted animals are totally deaf. About ten days prior to birth degenerative changes occur in the vascularis cochleae and in the organs of Corti; later degeneration of the ganglion spirale is apparent. Lurie conjectured that the circling movement is caused by a fundamental disturbance of the central nervous system, and Lurie and Dempsey (1939) were able to produce waltzer phenocopies by surgical destruction of the ganglia of the brain stem.

A second waltzing guinea pig is that of Ernstson (1970). This type is produced by the heterozygote of a dominant gene *Wz* (new symbol, by agreement of Dr. S. Ernstson), which is lethal when homozygous. Death occurs around the time of parturition, the few individuals which did survive birth soon succumbed. *Wz* + animals show whirling and shaking behavior which does not diminish with age. Investigations of the behavior of

the waltzer, together with detailed anatomical and histological investigations of the inner ear, have been completed (Ernstson, 1971a,b, 1972; Ernstson *et al.*, 1969). Hearing is initially near normal, but deafness ensues by approximately 42 days of age. The defect appears to arise from fundamental changes of the organs of Corti. There is a progressive degeneration of the vestibular neuroepithelium. A peculiar rod-shaped inclusion was observed in type I hair cells; it is speculated that it may be an anomalous metabolite concerned in the defect.

A hypoplasia of the sex apparatus (sexual hypogenesis) described by Lone (1932) has been shown to be due to a recessive gene *sh*. Individuals of both sexes may be affected. In males, the penis is infantile, while the testis are small, flaccid, and undescended (although the inguinal ring is open). The seminal vesicles, prostate, and Cowper's glands are diminutive. Spermiogenesis is arrested. There is no external evidence of abnormality in the female except that they tend to display perpetual oestrus. The ovaries are of normal size, but there are few primary follicles and no corpora lutea. Transplants of anterior pituitaries have indicated that the disorder could be due to a deficiency of gonad-stimulating hormones.

A congenital palsy was described by Cole and Ibsen (1920). The condition was obvious from birth despite some variation of symptoms. Many individuals were unable to rise or to stand on their feet, while others could stand but were incapable of walking; still others could walk but were unable to rise unaided while some could both rise and walk. A sharp sound would cause the less severely affected animal to start nervously, while the others would collapse as a result of stiffening of the legs, especially the rear ones. The latter animals would lie on their sides, their whole bodies shaking and their legs showing pronounced clonic spasms. The most severely affected animal would exhibit the same symptoms upon attempting to walk. As the palsy becomes more severe, the animal loses weight and death occurs within a week or two. A hypoplasia of the parathyroid glands was determined. The condition is due to a recessive gene (*n*).

Ibsen (1932) reported an inherited trembling condition due to a recessive gene *tr*. Affected individuals were stated to display a continuous tremor from birth, although there was some abatement upon attaining adulthood. No genetic data were given.

Guinea pigs normally have four digits on the front feet (no thumb) and three digits on the back feet (no big or little toes). It is not uncommon for an extra toe to recur and to be remarkably well formed in some instances. The classic case is that of Castle (1906), who selectively bred a

polydactylous strain in which an extra little toe was regularly manifested and was a perfect or near-perfect duplication of a normal digit. Stockard (1930), Pictet (1932), Kroning and Engelman (1934), Wright (1934b,c), and Kobozieff and Salomon (1943) observed the condition in various colonies.

Wright's meticulous study has shown that the development of the extra toe displays typical behavior of a threshold character, controlled basically by polygenes. The percentage frequency (often stable) will vary between strains, and tolerable Mendelian ratios may even be obtained in some cases. The incidence of the polydactylism will depend upon the distribution of the polygenes relative to the developmental threshold and on the proportion of polygenes which falls across a threshold, leading to partial or complete genesis of the toe.

Wright's analysis of an array of families of an inbred stock led to the conclusion that the prenatal environment was of significant importance. The final analysis was as shown in Table 4. No obvious factor could explain the variation between sibships, but the major factor for the inter-litter variation was age of female. Immature mothers produced more polydactylous young than did mature mothers. Litter parity had little influence, while weight of mother had a slight effect. Again, no obvious factor emerged for differences between individuals. There was a slightly greater propensity for the left foot to be polydactylous than the right. A season influence was recorded in that the incidence increased for autumn, winter, and early spring months of the year for one particular line, but not for another. It follows, of course, that the above partition of the variability may not hold in its entirety for other stocks.

In contrast to the above is the polydactyly reported by Wright (1934d, 1935a), which is engendered by a dominant gene *Px*. The heterozygote *Px +* is polydactylous, while the homozygote *Px Px* is monstrous. The expression in *Px +* is variable. In the main polydactylous

TABLE 4. Analysis of Families of an Inbred Stock for Polydactyly Threshold

Source	Variation, percent
Heredity	19
Environment	
Sibships	24
Litters	24
Individuals	11
Foot affected	22

stock, about 18 percent were normal-toed, 2 percent had one or two big toes, 62 percent had one or both little toes, and 74 percent possessed one or both thumbs. On crossing with a stock with a high manifestation of the polygenic form of polydactyly, the degree of expression of Px was increased (e.g., the incidence of big toes increased to 16 and 50 percent in the initial cross and a backcross, respectively). On the other hand, in crosses with a nonpolydactylous stock, the penetrance of Px fell sharply. These results imply that the manifestation of the Px polydactyly is controlled by a definite polygenic complex, part of which, at least, is the same as that responsible for the threshold form. Only some 8 percent of Px/Px homozygotes survive to term, the majority die as fetuses about the 26th day of gestation (Scott, 1937, 1938). These show an extraordinary variety of gross defects stemming from a profound developmental disorganization which is first apparent about the 18th or 19th day.

Various abnormalities of the forefoot have been described by Kroning (1938), e.g., bent, fused, or split phalanges and syndactylia. There is much variation of expression and manifestation, according to the nature of the strain and crossbreeding between strains. Kroning hypothesized the segregation of a single gene, but this conclusion is debatable.

Otocephaly is the term used to denote a series of teras in which the head is progressively malformed. The abnormalities range from a shortness of the lower jaw, followed by loss of various organs (eyes, ears) and formation of a nasal proboscis, to a condition where the body is rounded off in front of the shoulders, with no sign of a head except for a small ear (Wright and Eaton, 1923; Wright and Wagner, 1934; Wright, 1934a). Wright's very careful study showed that the occurrence of these monsters displays threshold heredity. This incidence in most stocks is extremely low, but can attain frequencies of up to 7 percent in some, as a consequence of chance fixation of polygenes. In a branch of a strain normally producing about 5 percent otocephalies, the incidence suddenly rose to 28 percent. This increase was accredited to the occurrence of a dominant mutation, raising the genetic propensity to near the threshold for abnormality. The present case is interesting in that no obvious environmental factors could be adduced for the appearance of otocephalies, and this is in contradiction to threshold polydactyly, where a number of environmental factors could be isolated. However, twice as many otocephalies were female than male.

The occurrence of anophthalmia has been reported on several occasions (Eaton, 1937; Wright, 1960a; Komich, 1971). In no case has it been possible to pinpoint the mode of inheritance. The influence of heredity is shown by the variable incidence in different stocks. A polygenic-threshold concept is probably the best explanation at this time.

The inheritance of supernumerary mammae (the female normally has two) is discussed by Goertzen and Ibsen (1951). Up to five extra mammae (all rudimentary to various degrees and nonfunctional) was observed in both sexes. Their recurrence in successive generations indicates a definite genetic influence, but it is doubtful if the condition could be attributed to an autosomal dominant gene as these authors seem to imply. The observations are drawn from a closed colony, and no assortment data from systematic crosses are reported. Polygenic heredity, possibly interacting with one or more thresholds, is likely. Table 1 presents a list of mutant genes and their symbols.

Growth and Weight

Except for mutants producing severe metabolic changes, which lead to dwarfism or excessive fatness, the heredity of rate of growth and weight at various age levels is typically quantitative. However, growth is so affected by environmental factors, such as nutritional level of the diet, quantity fed, and the like, that it is difficult to estimate the proportion of the variation which is genetic.

However, Dillard *et al.* (1972) has obtained estimates of heritability (h^2) for several growth parameters, drawn from two distinct stocks of guinea pigs. Average estimates of h^2 for two stocks are: birth weight, 0.25; weaning weight, 0.49; 91-day weight, 0.52; weight gain birth/weaning, 0.46; gain weaning/91 days, 0.25 and gain birth/91 days, 0.48. Certain differences are apparent between the two lines for the components of growth. These may represent differences of growth rate between the stocks, although the authors believe them to be merely sampling errors. A correlation of 0.89 was found between weaning weight and 91-day weight, from which it is concluded that selection for size could be based on the former with only a small loss of efficiency.

Inbreeding

The guinea pig is renowned for the long-term program of inbreeding arranged by G. M. Rommel and conducted by Wright (1922a,b), Wright and Eaton (1929), and Eaton (1932a, 1941). Initially, the project commenced with 23 lines, but many became extinct as a consequence of the inbreeding (poor viability or fecundity) or were otherwise jettisoned. In the later stages, only five lines (families 2, 13, 32, 35, and 39) were maintained. The lines have been studied for changes in various components of fertility, growth, and mortality. They differed among themselves for many

of the components, but in general there was a slow but steady decline. It is a moot point if all of the decline could be attributed to the inbreeding, for an almost similar decline was observed in a control stock in which inbreeding was excluded. Crosses between the inbred lines revealed the existence of heterosis, but not usually to the extent that the F_1 was superior to both parents. The performance of the F_1 could not be predicted from that of the inbred parental line.

The establishment of these inbred lines has meant that interstrain comparisons can be made which would give some idea of the genetic variability latent in random-bred stocks. Comparisons have been made for a wide range of characters: body weight, growth, vigor, and mortality (Wright, 1922a; Wright and Eaton, 1929; McPhee and Eaton, 1931; Eaton, 1932a,b, 1941; Strandkov, 1939, 1942; Jakway, 1959), organs (weight and size of adrenals, heart, liver, lungs, spleen, testes, thyroids, etc.: Eaton, 1938; Strandkov, 1939; Jakway, 1959), skeleton (dimensions of skull and leg bones: Eaton, 1939; Strandkov, 1942), reproduction (Wright, 1922a; Wright and Eaton, 1929; Eaton, 1932a,b), tuberculosis resistance (Wright and Lewis, 1921), anaphylactic reactions (Lewis and Loomis, 1925; 1928), tissue grafting (Loeb and Wright, 1927; Baur, 1958, 1960; Brent *et al.*, 1958; Bluestein *et al.*, 1971c,d), otocephaly (Wright, 1934a), threshold polydactyly (Wright 1934b), oxygen consumption (Riss, 1955; Riss and Goy, 1957; Jakway 1959), sexual behavior (Riss, 1955; Valentine *et al.*, 1954, 1955; Riss and Goy, 1957; Goy and Young, 1957; Jakway, 1959, Goy and Jakway, 1959), immunogenetics (Battisto, 1963; Ellman *et al.*, 1970b; Bluestein *et al.*, 1971a,b,c,d), and allergic thyroiditis (McMaster *et al.*, 1965).

Studies on these strains are of interest because two of them (families 2 and 13, or Wright 2 and 13) have survived to the present day. Most of the more-recent studies have been on these strains (say, from 1939 onward). This work *in toto* enables a profile to be assembled on the characteristics of the two strains. However, the strains are fairly widely distributed and substrain divergence may be appearing. Apart from certain monogenic characteristics (discussed in other sections) the interstrain differences are typically quantitative.

A second experiment in long-term inbreeding with multiple lines has been described by Carstens and Mehner (1938) and Mehner (1950, 1956). This project was launched in 1926 with 14 lines; of these, five were in existence in 1948, and only three in 1953. Poor fertility and low viability were the main factors in the decision to terminate lines. Differences were apparent between the lines but, in general, litter size and birth weight of young decreased, while litter mortality increased as the in-

breeding continued. The more vigorous lines survived 20 or more generations of inbreeding. Crosses between the lines produced F_1 individuals which often surpassed the parents in the above features.

Linkage

Almost all of the long-established mutants have been systematically tested for linkage, and with mainly negative results (Wright, 1941a, 1949c, 1959a; Robinson, 1970, 1972). The absence of linkage for so many genes is probably a consequence of the large number of chromosomes possessed by the guinea pig, compared with the number in other laboratory rodents. The extent of the linkage testing is summarized by Figure 2. Most of the tested combinations are undoubtedly inherited independently, although loose linkage cannot always be excluded.

There is a small probability of linkage between genes *e* and *f*. The combined segregation data for the pair indicates a linkage of 43.9 ± 2.9 percent. However, those crosses yielding the best evidence for linkage are those in which *f* manifests problems of accurate classification (Wright 1941a). In the cross where misclassification is not a problem, the amount of recombination is 47.4 ± 3.7 percent, an insignificant value.

Herbertson *et al.* (1959) have stated that *sk* is inherited independently of several color genes and of *R*. However, the color genes are not specified, nor are any assortment data given.

Two cases of linkage have been established. The first is between *Px* and *R* (group I). Unfortunately, *Px* has variable penetrance, and this fact influences the estimated crossover value. Combining all the data, the amount of crossing over is 45.7 ± 1.6 , while an estimate based on the most consistent data produces an estimate of 44.7 ± 1.7 . The second case of linkage is between *m* and *si* (group II), with a crossover value of 21.7 ± 4.3 percent.

Ellman *et al.* (1970b) and Martin *et al.* (1970) have demonstrated that the histocompatibility locus *H* is closely linked to the immune-response gene *Pll*. Concurrently, Bluestein *et al.* (1971c) found that the similar genes *Ga* and *Gt* are linked to *Pll*. Evidence was obtained for crossing over between *Ga* and *Pll*, but not between *Gt* and *Pll*. Linkage was also found between both *Ga* and *Gt* and *H* (Bluestein *et al.*, 1971c). A later paper in the series (Bluestein *et al.*, 1971d) showed by the aid of *Gt*-responder animals that the *H* locus is composed of at least two major specificities. The fact that some *Gt* animals responded to one of the specificities but not the others could be attributed to crossing over between specificities, although mutation is an alternative explanation. Thus far, in

phology are: Awa *et al.* (1959), Watson *et al.* (1966), Dobrijanov and Goljman (1967), Schmid (1967), Fernandez and Spotorno (1968), Ja-giello (1969), and George *et al.* (1972). A fuller listing is provided by Robinson (1970, 1972).

It is particularly difficult to characterize morphologically the numerous elements comprising the karyotype. Published illustrations show the presence of a large subtelocentric chromosome, easily identifiable, and a similar, but slightly smaller, subtelocentric X chromosome. The second and third largest autosomes are distinguished by many observers but, beyond this, recognition of individual chromosomes becomes increasingly difficult. Even categorizing the chromosomes presents problems because of the almost smooth graduation of relative size. The latest descriptions speak of about 18-22 submetacentric and subtelocentric chromosomes, the remainder being telocentric. The Y is almost certainly a small telocentric.

The large number and uniform size of so many chromosomes, compared with the karyotypes of other rodents, is suggestive of either fission or lack of fusion. However, characterization of individual elements should be possible with the recently perfected techniques of Giemsa treatment and fluorochrome banding.

There is evidence that polymorphism for one or more chromosomes may exist. Ohno *et al.* (1961) described a curious condition for the largest subtelocentric autosome I in mitotic material. The smaller arm of one chromosome appeared to be more condensed, or shorter, than the corresponding arm of the other. The arm stained differentially to give the impression that the chromosome was satellited. The difference could also be seen at meiosis. The condensed portion is represented as a nucleolus organizer.

Cohen and Pinsky (1966) depicted the large chromosome I as being unusually variable. In some individuals, the small second arm appeared to be exceptionally long, while in others the arm was lacking. It is proposed that the former could be the result of a duplicated region, while the latter is a result of a deficiency. Six possible combinations of the two chromosomes (in conjunction with normal) could theoretically exist, and three have been identified. The variation could arise if a small translocation occurs between the two arms.

Dobrijanov and Goljman (1967) have also found heteromorphism for the large subtelocentric. These authors favor a structural difference in the size of the second arm rather than differential condensation. Their material revealed cells with pairs of chromosomes either of one form or the other, in contrast to cells in which only one arm of the chromosome pair was shorter or more condensed than the homologue.

Fernandez and Spotorno (1968) also describe variations of form of chromosome I. These authors are not happy with the hypothesis of a translocation, however plausible the concept may be. They caution that the difference may arise from a differential effect of colchicine treatment in the heterochromatic areas adjacent to the centromere. At present, the number of animals examined is few, but the indications are that the condition may not be uncommon. If so, it will be interesting to ascertain the precise nature of the observed difference and why it should be so widespread.

Manna and Talukdar (1964) described a difference of size for one of the larger submetacentric chromosomes (not the large subtelocentric, but probably chromosome II). In some individuals the chromosome was said to be smaller than usual. The difference was most apparent for possessors of both chromosomes (i.e., for the "heterozygote"). The authors briefly commented that sporadic occurrences of heteromorphism of other chromosomes were noted.

Apparent polymorphism for chromosome 21 was featured by Bianchi and Ayres (1971). One or both chromosomes in different individuals showed excessive pericentric heterochromatinization.

The chromosomes of *C. aperea* have been examined by George *et al.* (1972). A count of 32 was found: 1 large subacrocentric, 29 smaller elements which graded into one another, and 3 microchromosomes. The X is one of the larger medium-sized chromosomes, while the Y is minute. A comparison of the individual chromosomes with those of *porcellus* revealed an almost perfect match. Only the third autosome (chromosome III) gave less than perfect agreement; both are submetacentric, but the relative position of the centromere is different. Close agreement is to be expected, of course, if *aperea* is indeed the wild ancestor of *porcellus*. It is not without interest that one animal possessed a subacrocentric chromosome III while, in the others, the chromosome was more metacentric. This observation implies variability for the element and may explain in part the slight discrepancy noted between the *aperea* and *porcellus* karyotypes.

Studies on chiasma frequency have been merely cursory at this time. Sharma *et al.* (1963) have commented that each of the autosomal bivalents in spermatogenic material had one or two chiasmata. Later, Jagiello (1969) reported a mean frequency of 1.04 chiasma per bivalent in 50 metaphase cells which were chosen for their clarity. The autosomes of *aperea* are stated by George *et al.* (1972) to have one or two chiasmata, with a mean of 1.3 per bivalent. The X and Y chromosomes give a configuration consistent with end-to-end pairing.

Literature Cited

- Awa, A., M. Sasaki and S. Takayama, 1959. An *in vitro* study of the somatic chromosomes in several animals. *Jap. J. Zool.* 12:257-265.
- Baker, M. R. and A. C. Andrews, 1944. The melanins. I. Studies of the hair pigments of the guinea pig. *Genetics* 29:104-112.
- Baker, M. R. and M. L. Ibsen, 1942. Two modifiers of self (S) and white spotting (s) in guinea pigs. *Genetics* 27:130.
- Battisto, J. R., 1963. Genetic control of a guinea pig serum factor toward which natural delayed isohypersensitivity occurs. *Nature (Lond.)* 198:598-599.
- Baur, J. A., 1958. Histocompatibility in inbred strains of guinea pigs. *Ann. N.Y. Acad. Sci.* 73:663-672.
- Baur, J. A., 1960. Genetics of skin transplantation and an estimate of the number of histocompatibility genes in inbred guinea pigs. *Ann. N.Y. Acad. Sci.* 87:78-92.
- Benacerraf, B. and P. G. H. Gell, 1961. Delayed hypersensitivity to homologous γ -globulin in the guinea pig. *Nature (Lond.)* 189:586-587.
- Benacerraf, B., I. Green and W. E. Paul, 1967. The immune response of guinea pig to hapten poly-L-lysine conjugates as an example of the genetic control of the recognition of antigenicity. *Cold Spring Harbor Symp. Quant. Biol.* 32:569-575.
- Bianchi, N. O. and J. Ayres, 1971. Polymorphic patterns of heterochromatin distribution in guinea pig chromosomes. *Chromosoma (Berl.)* 34:254-260.
- Bluestein, H. G., I. Green and B. Benacerraf, 1971a. Specific immune response genes of the guinea pig. I. Dominant genetic control of immune responsiveness to copolymers of L-glutamic acid and L-alanine and L-glutamic acid and poly-L-lysine. *J. Exp. Med.* 134:458-470.
- Bluestein, H. G., I. Green and B. Benacerraf, 1971b. Specific immune response genes of the guinea pig. II. Relationship between the poly-L-lysine gene and the genes controlling responsiveness to copolymers of L-glutamic acid and L-alanine and L-glutamic acid and L-tyrosine in random-bred Hartley guinea pigs. *J. Exp. Med.* 134:471-481.
- Bluestein, H. G., L. Ellman, I. Green and B. Benacerraf, 1971c. Specific immune response genes of the guinea pig. III. Linkage of the GA and GT immune response genes to histocompatibility genotypes in inbred guinea pigs. *J. Exp. Med.* 134:1529-1537.
- Bluestein, H. G., I. Green and B. Benacerraf, 1971d. Specific immune response genes of the guinea pig. IV. Demonstration in random-bred guinea pigs that responsiveness to a copolymer of L-glutamic acid and L-tyrosine is predicated upon the possession of a distinct strain 13 histocompatibility specificity. *J. Exp. Med.* 134:1538-1544.
- Brent, L., J. Brown and P. B. Medawar, 1958. Skin transplantation immunity in relation to hypersensitivity (1958) 11:561-564.
- Carstens, K. and A. Mehner, 1938. Vorläufige Ergebnisse eines Inzuchtversuches mit Meerschweinchen. *Z. Tierz. Züchtungsbiol.* 42:104-123.
- Carter, N. D., M. R. Hill and B. J. Weir, 1972. Genetic variation of phosphoglucose isomerase in some hystricomorph rodents. *Biochem. Genet.* 6:147-156.
- Castle, W. E., 1903. The heredity of Angora coat in mammals. *Science (Wash., D.C.)* 18:760-761.
- Castle, W. E., 1906. The origin of a polydactylous race of guinea pigs. *Carnegie Inst. Wash. Pub.* 49:29 pp.
- Castle, W. E., 1916. An expedition to the home of the guinea pig and some breeding experiments with material there obtained. *Carnegie Inst. Wash. Pub.* 241:1-55.
- Chase, H. B., 1939a. Studies on the tricolor pattern of the guinea pig. I. The relations between different areas of the coat in respect to the presence of colour. *Genetics* 24:610-621.
- Chase, H. B., 1939b. Studies on the tricolor pattern of the guinea pig. II. The distribution of black and yellow as affected by which spotting and by imperfect dominance in the tortoiseshell series of alleles. *Genetics* 24:622-643.
- Chase, M. W., 1941. Inheritance in guinea pigs of the susceptibility to skin sensitization with simple chemical compounds. *J. Exp. Med.* 73:711-726.
- Cogan, D. G., 1940. Waltzing guinea pigs with particular reference to ocular movements and righting reflexes. *Arch. Ophthalmol.* 24:78-82.
- Cohen, M. M. and L. Pinsky, 1966. Autosomal polymorphism via a translocation in the guinea pig, *Cavia porcellus*. *Cytogenetics* 5:120-132.
- Cole, L. J. and H. L. Ibsen, 1920. Inheritance of congenital palsy in guinea pigs. *Am. Nat.* 54:130-151.
- Collin, E., 1943. Hair direction in mammals; Embryogenesis of hair follicles in the guinea pig. *J. Morphol.* 72:191-223.
- Colten, H. R., T. Boros and H. J. Rapp, 1970. Isoelectric focusing of human and guinea pig C2: Polymorphism of guinea-pig C2. *Immunology* 18:467-472.
- Davie, J. M., W. E. Paul and I. Green, 1972. Genetic control of the immune response of inbred guinea-pigs to 2, 4-dinitrophenyl guinea-pig albumin. *J. Immunol.* 109:193-200.
- DeJefson, J. A., 1914. Genetic studies on a cavy species cross. *Carnegie Inst. Wash. Pub.* 205:1-134.
- Dillard, E. U., R. Vaccaro, J. Lozano and O. W. Robison, 1972. Phenotypic and genetic parameters for growth in guinea pigs. *J. Animal Sci.* 34:193-195.
- Dobrijanov, D. S. and I. L. Goldjman, 1967. The normal karyotype of the guinea pig. *Tsitol. Genet.* 1 (5):78-82.
- Eaton, O. N., 1928. The occurrence of nose spots and tail spots in guinea pigs. *J. Agric. Res.* 37:25-41.
- Eaton, O. M., 1932a. A quarter-century of inbreeding in guinea pigs. *J. Exp. Zool.* 63:261-290.
- Eaton, O. N., 1932b. Correlation of hereditary and other factors affecting growth of guinea-pigs. *Tech. Bull. U.S. Dept. Agric.* 279:1-35.
- Eaton, O. N., 1937. Hereditary eye defect in guinea-pigs. *J. Hered.* 28:353-358.
- Eaton, O. N., 1938. Weights and measurements of the parts and organs of mature inbred and crossbred guinea pigs. *Am. J. Anat.* 63:273-295.
- Eaton, O. N., 1939. A comparative analysis of the measurements of the limb bones of inbred families of guinea pigs and their hybrids as affected by family, sex and age. *Am. J. Anat.* 64:485-499.
- Eaton, O. N., 1941. Effect of crossing inbred lines of guinea pigs. *Tech. Bull. U.S. Dept. Agric.* 765:1-19.
- Eaton, O. N., 1943. Silvering in a strain of guinea pigs. *J. Hered.* 34:105-107.
- Ellman, L., I. Green and M. Frank, 1970a. Genetically controlled total deficiency of the fourth component of the complement in the guinea pig. *Science (Wash., D.C.)* 170:74-75.
- Ellman, L., I. Green, W. J. Martin and B. Benacerraf, 1970b. Linkage between the

- poly-L-lysine gene and the locus controlling the major histocompatibility antigens in strain 2 guinea pigs. *Proc. Natl. Acad. Sci. USA* 66:322-328.
- Ellman, L., I. Green and B. Benacerraf, 1971a The P.L.L. gene and histocompatibility genotype in inbred and random bred guinea pigs. *J. Immunol.* 107:382-388.
- Ellman, L., J. Inman and I. Green, 1971b Strain difference in the immune response to hydralazine in inbred guinea pigs. *Chin. Exp. Immunol.* 9:927-937.
- Ernstson, S., 1970 Heredity in a strain of waltzing guinea pig. *Acta Otolaryngol.* 69:358-362.
- Ernstson, S., 1971a Vestibular physiology in a strain of the waltzing guinea pig. *Acta Otolaryngol.* 72:303-309.
- Ernstson, S., 1971b Cochlear morphology in a strain of the waltzing guinea pig. *Acta Otolaryngol.* 71:469-482.
- Ernstson, S., 1972 Cochlear physiology and hair cell population in a strain of the waltzing guinea-pig. *Acta Otolaryngol. Suppl.* 297:1-18.
- Ernstson, S., P. G. Lundquist, W. Wedenberg and J. Wersäll, 1969 Morphological changes in vestibular hair cells in a strain of the waltzing guinea pig. *Acta Otolaryngol.* 67:521-534.
- Fernandez, R. and A. Spotorno, 1968 Heteromorphism in chromosome pair No. 1 of *Cavia porcellus*. *Arch. Biol. Med. Exp. (Santiago)* 5:81-85.
- Foster, M., 1956 Enzymatic studies of the physiological genetics of guinea pig coat coloration. I. Oxygen consumption studies. *Genetics* 41:396-409.
- Garber, E. D., 1953 "Fuzzy," a dominant mutation in the guinea pig. *J. Hered.* 44:232.
- George, W., B. J. Weir and J. Bedford, 1972 Chromosome studies in some members of the family Caviidae (Mammalia: Rodentia). *J. Zool.* 168:81-89.
- Ginsburg, B., 1944 The effects of the major genes controlling coat colour in the guinea-pig on the dopaoxidase activity of skin extracts. *Genetics* 29:176-198.
- Goertzen, B. L. and H. L. Ibsen, 1951 Supernumerary mammae in guinea pigs. *J. Hered.* 42:307-311.
- Goy, R. W. and J. S. Jakway, 1959 The inheritance of patterns of sexual behaviour in female guinea pigs. *Anim. Behav.* 7:142-149.
- Goy, R. W. and W. C. Young, 1957 Strain differences in the behavioural responses of female guinea pigs to alpha-oestradiol benzoate and progesterone. *Behaviour* 10:340-354.
- Green, I. and B. Benacerraf, 1971 Genetic control of immune responsiveness to limiting dose of proteins and hapten protein conjugates in guinea pigs. *J. Immunol.* 107:374-381.
- Green, I., W. E. Paul and B. Benacerraf, 1969 Genetic control of immunological responsiveness in guinea pigs to 2,4-dinitrophenyl conjugates of poly-L-arginine, protamine and poly-L-ornithine. *Proc. Natl. Acad. Sci. USA* 64:1095-1102.
- Green, I., J. K. Inman and B. Benacerraf, 1970 Genetic control of the immune response of guinea pigs to limiting dose of bovine serum albumin: relationship to the poly-L-lysine gene. *Proc. Natl. Acad. Sci. USA* 66:1267-1274.
- Green, I., W. E. Paul and B. Benacerraf, 1972 Histocompatibility-linked genetic control of the immune response to hapten guinea pig albumin conjugates in inbred guinea-pigs. *J. Immunol.* 109:457-463.
- Gregory, P. W., 1928 Some new genetic types of eyes in the guinea pig. *J. Exp. Zool.* 52:159-181.
- Gregory, P. W., 1929 A histological description of pigment distribution in the eyes of guinea-pigs of various genetic types. *J. Morphol.* 47:227-258.
- Harman, M. T. and A. A. Case, 1941 Genetic aspects of pigment production in the guinea-pig. *Genetics* 26:474-486.
- Harman, M. T. and A. A. Case, 1942 The influence of certain genetic factors upon eye color in the guinea pig. *Trans. Kansas Acad. Sci.* 45:344-357.
- Heidenthal, G., 1940 A colorimetric study of genic effect on guinea pig coat color. *Genetics* 25:197-214.
- Herbertson, B. M., M. E. Skinnies and J. A. H. Tatchell, 1959 Sticky: A new mutant in the guinea pig. *J. Genet.* 56:315-324.
- Huckinghaus, F., 1961a Vergleichende Untersuchungen über die Formenannigfaltigkeit der Unterfamilie Cavinac, Murray 1886. *Z. Wiss. Zool.* 166:1-98.
- Huckinghaus, F., 1961b Zur Nomenklatur und Abstammung des Hausmeerschweinchens. *Z. Säugetierkd.* 26:108-111.
- Hyde, R. R., 1923 Complement deficient guinea pig serum. *J. Immunol.* 8:267-268.
- Hyde, R. R., 1927 The complement deficient guinea pig. *Am. J. Hyg.* 7:619-626.
- Ibsen, H. L., 1932 Modifying factors in guinea pigs. *Proc. 6th Internat. Congr. Genet.* 2:97-101.
- Ibsen, H. L. and B. L. Goertzen, 1951a Whiish, a modifier of chocolate and black hairs in guinea-pigs. *J. Hered.* 42:231-236.
- Ibsen, H. L. and B. L. Goertzen, 1951b Roan, a modifier of pigmented hairs of guinea-pigs. *J. Hered.* 42:267-269.
- Ibsen, H. L. and T. K. Risty, 1929 A new character in guinea pigs: waltzing. *Anat. Rec.* 44:294.
- Jagiello, G. M., 1969 Some cytologic aspects of meiosis in female guinea pig. *Chromosoma (Berl.)* 27:95-101.
- Jakway, J. S., 1959 Inheritance of patterns of mating behaviour in the male guinea pig. *Anim. Behav.* 7:150-162.
- Kelus, A. S., 1969 Allotypic marker GP γ -1 of guinea pig immunoglobulins. *Nature (Lond.)* 223:398-399.
- Kobozieff, N. and L. Salomon, 1943 Sur l'heredite de la tetradactylie des membres posterieurs chez le cobaye. *C. R. Soc. Biol. (Paris)* 137:105-107.
- Komich, R. J., 1971 Anophthalmos: An inherited trait in a new stock of guinea pigs. *Am. J. Vet. Res.* 32:2099-2105.
- Krönig, F., 1930a Über der Eichung von Fellfarben auf Grund der Oswaldschen Methode, nach Untersuchungen am Meerschweinchen. *Z. Indukt. Abstammungs-Vererbungsst.* 53:355-367.
- Krönig, F., 1930b Die Dopareaktion bei verschiedenen Farbenrassen des Meerschweinchens und des Kaolinchen. *Arch. Entwicklungsmech. Org.* 121:470-484.
- Krönig, F., 1938 Abnorme Vorderzehen als ein neues erbliches Merkmal des Meerschweinchens. *Biol. Zentralb.* 58:268-272.
- Krönig, F. and C. Engelmann, 1934 Penetranz, Expressivität und Asymmetrie des Überzehens des Meerschweinchens und die Abhängigkeit ihrer Realisation von Ausseinfaktoren. *Nachr. Ges. Wiss. Göttingen (Math. Phys. Kl. Biol.)* 1:123-141.
- Lambert, W. V., 1935 Silver guinea pigs. *J. Hered.* 26:279-283.
- Lambert, W. V. and E. W. Shrigley, 1933 An inherited eye defect in the guinea pig. *Proc. Iowa Acad. Sci.* 40:227-230.
- Lewis, P. A. and D. Loomis, 1925 Allergic irritability. II. Anaphylaxis in the guinea pig as affected by the inheritance. *J. Exp. Med.* 41:327-335.

- and highly inbred strains of male guinea pigs. *J. Comp. Physiol. Psychol.* 47:162-165.
- Valentine, E. S., W. Riss and W. C. Young, 1955 Experimental and genetic factors in the organization of sexual behaviour in male guinea pigs. *J. Comp. Physiol. Psychol.* 48:397-403.
- Watson, E. D., H. T. Blumenthal and W. E. Hutton, 1966 A method for the culture of leucocytes of the guinea pig with karyotypic analysis. *Cytogenetic* 5:179-185.
- Whiteway, C., 1973 A new dominant spotting and silvering factor in the guinea pig. *Heredity* 31:123-125.
- Whitlock, J. H., 1935 A preliminary report on the anatomical study of an inherited eye defect in the guinea pig. *Iowa State Coll. J. Sci.* 9:667-675.
- Wolff, G. L., 1955 The effects of environmental temperature on coat colour in diverse genotypes of the guinea pig. *Genetics* 40:90-106.
- Wright, S., 1916 An intensive study of the inheritance of color and of other coat characters in guinea pigs. *Carnegie Inst. Wash. Pub.* 241:57-160.
- Wright, S., 1920 The relative importance of heredity and environment in determining the piebald pattern of guinea pigs. *Proc. Natl. Acad. Sci. USA* 6:320-332.
- Wright, S., 1922a The effects of inbreeding and crossbreeding on guinea pigs. I. Decline in vigour. II. Differentiation among inbred families. *U.S. Dept. Agric. Bull.* 1090:1-61.
- Wright, S., 1922b The effects of inbreeding and crossbreeding on guinea pigs. III. Crosses between highly inbred families. *U.S. Dept. Agric. Bull.* 1121:1-60.
- Wright, S., 1926 Effects of age of parents on characteristics of the guinea pig. *Am. Nat.* 60:552-559.
- Wright, S., 1927 The effects in combination of the major color factors of the guinea pig. *Genetics* 12:530-569.
- Wright, S., 1934a On the genetics of subnormal development of the head (otocephaly) in the guinea pig. *Genetics* 19:471-505.
- Wright, S., 1934b An analysis of variability in number of digits in an inbred strain of guinea pigs. *Genetics* 19:506-536.
- Wright, S., 1934c The results of crosses between inbred strains of guinea pigs differing in number of digits. *Genetics* 19:537-551.
- Wright, S., 1934d Polydactylous guinea pigs. *J. Hered.* 25:359-362.
- Wright, S., 1935a A mutation of the guinea pig, tending to restore the pentadactyl foot when heterozygous, producing a monstrosity when homozygous. *Genetics* 20:84-107.
- Wright, S., 1935b On the genetics of rosette pattern in guinea pigs. *Genetica (The Hague)* 17:547-560.
- Wright, S., 1941a Tests for linkage in the guinea-pig. *Genetics* 26:650-669.
- Wright, S., 1941b A quantitative study of the interaction of the major color factors of the guinea-pigs. *Proc. 7th Internat. Genet. Congr.* pp. 319-329.
- Wright, S., 1947 On the genetics of several types of silvering in the guinea pig. *Genetics* 32:115-141.
- Wright, S., 1949a Estimates of amounts of melanism in the hair of diverse genotypes of the guinea pigs from transformation of empirical grades. *Genetics* 34:245-271.
- Wright, S., 1949b On the genetics of hair direction in the guinea-pig. I. Variability in the patterns found in combinations of *R* and *M* loci. *J. Exp. Zool.* 112:303-323.
- Wright, S., 1949c On the genetics of hair direction in the guinea-pig. II. Evidence for a new dominant gene, *star*, and tests for linkage with eleven other loci. *J. Exp. Zool.* 112:325-340.

- Wright, S., 1950 On the genetics of hair direction in the guinea pig. III Interactions between the processes due to the loci *R* and *St*. *J. Exp. Zool.* 113:33-63.
- Wright, S., 1959a On the genetics of silvering in the guinea pig, with special reference to interaction and linkage. *Genetics* 44:387-405.
- Wright, S., 1959b Silvering (*st*) and diminution (*dm*) of coat colour of the guinea pig, and male sterility of the white or near-white combination of these. *Genetics* 44:563-590.
- Wright, S., 1959c A quantitative study of variations in intensity of coat colour of genotypes of the guinea pig at birth. *Genetics* 44:1001-1026.
- Wright, S., 1959d Qualitative differences among colors of the guinea pig due to diverse genotypes. *J. Exp. Zool.* 142:75-113.
- Wright, S., 1960a The genetics of vital characters in the guinea pig. *J. Cell Comp. Physiol.* 56 (Suppl. 1):123-151.
- Wright, S., 1960b The residual variability in intensity of coat colour at birth in a guinea pig colony. *Genetics* 45:583-612.
- Wright, S., 1960c Postnatal changes in the intensity of coat colour in diverse genotypes of the guinea pig. *Genetics* 45:1503-1529.
- Wright, S., 1963 Genic interaction. In *Methodology in Mammalian Genetics*, edited by W. J. Burdett, Holden Day, San Francisco.
- Wright, S. and Z. I. Braddock, 1949 Colorimetric determination of the amounts of melanism in the hair of diverse genotypes of the guinea pig. *Genetics* 34:223-244.
- Wright, S. and H. B. Chase, 1936 On the genetics of the spotted pattern of the guinea pig. *Genetics* 21:758-787.
- Wright, S. and O. N. Eaton, 1923 Factors which determine otocephaly in guinea pigs. *J. Agric. Res.* 26:161-181.
- Wright, S. and O. N. Eaton, 1929 The persistence of differentiation among inbred families of guinea pigs. *U.S. Dept. Agric. Tech. Bull.* 103:1-43.
- Wright, S. and P. A. Lewis, 1921 Factors in the resistance of guinea-pigs to tuberculosis, with special regard to inbreeding and heredity. *Am. Nat.* 55:20-50.
- Wright, S. and K. Wagner, 1934 Types of subnormal development of the head from inbred strains of guinea pigs and their bearing on the classification and interpretation of vertebrate monsters. *Am. J. Anat.* 54:383-447.