REVIEW

ENDOCRINE GENETICS OF THE ADRENAL GLAND

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INTRODUCTION

Genetic variation within a species can lead to phenotypic variation of two types, continuous (quantitative) and discontinuous (qualitative). Discontinuous variation permits the unambiguous assignment of individuals to alternative classes, even though there may be continuous variation within such classes. Frequently the different phenotypic classes are caused by differences at a single genetic locus, as in phenylketonuria or in haemophilia. When the observed variation is continuous genotypes can only be assigned unambiguously to individuals which have been progeny-tested. If the contribution of non-genetic (environmental) factors to the observed phenotypic variability is large (more than 50%) the variation may appear continuous, even though only one or two major genetic loci are involved. Even when environmental factors make a small contribution, variation in the observed character may be continuous if there are a large number of genes ('polygenes') involved. An apparently discontinuous distribution may result from a fundamentally continuous one if there is a threshold for the overt expression of the character (e.g. susceptibility to diabetes, Smith, Falconer & Duncan, 1972).

Sometimes genetic variation results in so extreme a phenotype that the result is pathological (e.g. adrenogenital virilism). In other cases all the alternative phenotypes appear healthy (e.g. bloodgroups) and natural populations are polymorphic. There is
no clear division between pathological mutations and genetic variation within the bounds of normality, just as the distinction between qualitative and quantitative variation can depend upon the way the character is defined (Spickett, Shire & Stewart, 1967).

Because of their clinical interest rare pathological variants have been much studied in man. In experimental animals more emphasis has been placed on the study of differences between normal individuals. In rodent colonies, animals with homologues of inherited human diseases usually die undiagnosed. The investigations on rodents and on man are thus complementary.

This review covers genetic variation affecting the adrenal cortex and medulla and their hormones. It is not concerned with details of differential diagnosis, therapy or genetic counselling, which have been recently dealt with in the book of Rimoin & Schimke (1971a, b) and the catalogue of McKusick (1971).

Detection of genetic variation

In man pedigrees form the basis of genetic investigations. Racial differences may also suggest the existence of genetic variation. Quantitative characters are usually investigated by means of correlations between relatives, including comparisons of mono- and di-zygotic twins. In animals the first evidence for genetic variation comes from the comparison of different strains or breeds which have been raised in a common environment. Discontinuous variation is confirmed by segregation of the character-differences in hybrid generations (F₂, backcrosses, etc.). Continuous variation typically results in a low variance for the F₁ hybrids and significantly higher variances for the F₂ and backcrosses. The relative size of the increases in variance allows the importance of genetic, as opposed to environmental, factors to be determined. The heritability of a character is one such metric frequently calculated. The genetic determinants of continuous variation can be further investigated by progeny-testing individual animals from the hybrid generations or from natural populations. If genetic variation affecting a character is present in a population, selective breeding can produce lines with extreme expressions of that character (e.g. high and low adrenal weight). The location of genes on particular chromosomes can be determined by following their associations with known marker-genes, or with particular chromosomal complements, such as the X chromosome in sex-linkage.

Variation in the adrenal cortex

Anatomical characters

There is much evidence for genetic variation affecting the weight of the adrenal glands. Elliot & Tuckett described, in 1906, differences in adrenal weight between two stocks of guinea-pigs. Eaton (1938) found that the adrenal weights of guinea-pigs of different strains raised under the same environmental conditions ranged from 65 mg/100 g body weight in strain B to 126 mg/100 g in strain 2. Watson (1907) noted that the adrenals of wild rats were much larger than those of laboratory rats. This has been confirmed (Hatai, 1914; Rogers & Richter, 1948; Nichols, 1950; M. Stockham, personal communication), even when the wild rats had been raised under laboratory conditions for eight generations (Donaldson, 1929). Differences between
laboratory strains (Wistar and Long–Evans) were shown by Freudenberger (1932). M. Stockham (personal communication) has found consistent differences in adrenal weight between a number of strains of rat. Relative adrenal weight in males ranged from 14 mg/100 g in Wistar rats to 22 mg/100 g in Lister rats of similar age. Keeler, Ridgway, Lipscomb & Fromm (1968) have shown a greater than threefold variation amongst five stocks of arctic foxes raised on the same ranch. In cattle there are several observations which suggest differences between breeds in the weight of the adrenals (Howes, Hentges & Warnick, 1960). In man there are racial differences in adrenal weight which may, in part, be due to genetic variation (Swinyard, 1940; Allbrook, 1956).

Table 1. The mean relative adrenal weights (mg/100 g body weight) of adult males in independent investigations of separate sub-lines of three inbred strains of mice

<table>
<thead>
<tr>
<th>Strain</th>
<th>C3H</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9·8</td>
<td>—</td>
<td>Chester Jones (1955)</td>
</tr>
<tr>
<td>9·9</td>
<td>10·8</td>
<td>Thiessen (1964)</td>
</tr>
<tr>
<td>—</td>
<td>11·3</td>
<td>Meckler &amp; Collins (1965)</td>
</tr>
<tr>
<td>—</td>
<td>11·8</td>
<td>Molne (1969a)</td>
</tr>
<tr>
<td>—</td>
<td>10·7</td>
<td>Doering et al. (1970)</td>
</tr>
<tr>
<td>10·1</td>
<td>—</td>
<td>Badr &amp; Spickett (1971)</td>
</tr>
<tr>
<td>10·1</td>
<td>13·2</td>
<td>Curé et al. (1971)</td>
</tr>
</tbody>
</table>

Marked and persistent differences in adrenal weight between genetically distinct strains have been best demonstrated in mice. The adrenal weights of at least 30 different strains have been compared in various combinations (Vicari & Little, 1945; Chester Jones, 1955; Thiessen, 1964; Badr & Spickett, 1965a; Meckler & Collins, 1965; Chirvan-Nia, 1967; Badr, Shire & Spickett, 1968; Badr, 1969; Badr & Spickett, 1971; Curé, Valatx & Delobel, 1971; Ciaranello, Barchas, Kessler & Barchas, 1972a). The dry weight of the adrenal also showed striking differences between strains (Chai & Dickie, 1966). The consistency of phenotype within strains can be seen from Table 1. Studies on the same sub-lines in different years show the differences between AC and C57BL (Molne, 1969a) and CBA and Peru strains (Badr et al. 1968; Shire & Stewart, 1972; Stewart, Fraser, Papaioannou & Tait, 1972) to be consistent and relatively constant. Relative adrenal weight varies almost threefold amongst unselected strains of mice, ranging in males from 10 mg/100 g in A mice to 29 mg/100 g in Peru mice (Stewart et al. 1972). In non-parous females the range is from 14·7 mg/100 g in C57L to 43·5 mg/100 g in C3H mice (Chirvan-Nia, 1967).

Badr (see Badr & Spickett, 1965a) started a successful experiment in which mice were bred for high and for low adrenal weight. After 26 generations of selection, followed by six generations of inbreeding, the male mice had mean adrenal weights of 34 and 13 mg/100 g. The corresponding values for females were 60 and 14 mg/100 g (J. G. M. Shire, unpublished observations). Successful selection provides good evidence that genetic variation underlies some at least of the observed strain differences. The significant responses in relative adrenal weight which accompanied selection for parameters of electrolyte metabolism in mice (Rapp, 1967; Stewart & Spickett, 1967) and in rats (Rapp, 1969a, b), for blood pressure (Rapp & Dahl, 1971) and emotional
reactivity (Feuer, 1969) in rats, and for growth rate in chickens (Farrington & Mellen, 1967) also indicated the existence of quantitative genetic variation affecting the adrenal gland.

Meckler & Collins (1965) showed, by a diallel analysis of four strains of mice, that both general and specific genetic combining abilities were significant. Badr & Spickett (1965a, 1971) crossed mice of the A and CBA strains and found that the genetically heterogeneous F₂ and backcross generations were very variable. Their data suggest that about 60% of the variation in adrenal weight in females was genetic in origin, as was 40% of the variation in males. Similar heritabilities for adrenal weight have been found in chickens (57%, Siegel & Siegel, 1960) and in pigs (60–65%, Wegner, 1971). The large adrenals of F₁ rats bred by crossing females of a laboratory strain with wild males (Donaldson, 1924; Rogers & Richter, 1948; M. Stockham, personal communication) also showed that there was a strong genetic component to the difference in adrenal weight between these populations of rats. In none of these cases has it yet proved possible to identify the individual genes causing the differences. However, it is known that single genes can have pleiotropic effects on adrenal weight. The ob (obese: Carstensen, Hellman & Larsson, 1961; Larsson, Hellman & Carstensen, 1962), lh (lethargic: Dung & Swigart, 1971) and Os (oligosyndactyly: Stewart & Stewart, 1969) mutations in the mouse all increased adrenal weight, nearly twofold in the first case.

Abnormal function of the adrenal glands can be associated with adrenal dysplasia. Inherited hypo- and hyperplasias in man and cattle are considered below. Massive hyperplasia of the adrenals, which may reach a weight of 25 mg, accompanied the onset of recessively inherited polydipsia in DE mice (Chai & Dickie, 1966).

Underlying the differences in adrenal weight are qualitative or quantitative differences in adrenal structure. In certain instances whole zones of the cortex may be missing. The X zone was effectively absent from mice with pituitary dwarfism, whether caused by the recessive dw (Deanesly, 1938; Bartels, 1941) or by the recessive df (Shire, 1967). The normal pattern of zonation was completely disrupted in certain cases of congenital adrenal hypoplasia (Weiss & Mellinger, 1970). The detailed appearance of the zona fasciculata is often distinctive for an individual strain (Shire, 1965a; Spickett et al. 1967). The zona glomerulosa differed between DBA/2 and C57BL/10 mice, the former being unusual in having a zone that was intensely sudanophilic (Doering, Shire, Kessler & Clayton, 1972).

Quantitative genetic variation affecting adrenal structure has been clearly demonstrated in mice. Howard (1938) examined six inbred strains and found that the proportion of the cortex occupied by the transient X zone ranged from 15% in DBA to 55% in the Danforth stock. Chirvan-Nia (1967) has also described significant strain differences in the width of this zone. Repeatable strain differences were found (Shire & Spickett, 1968a; Shire, 1970) in the volume of the permanent cortex and in the number of cells in it. Strain CBA adrenals had twice as many fascicular cells as did strain A adrenals. Strain differences were found in the volume of the fascicular cells, and in the absolute volume of the X zone in females (Shire & Spickett, 1968a). Two independent sets of hybrids between the A and CBA strains were bred and the difference in cortical volume was attributed to variation at one or, at most, two loci (Shire, 1970). Rapp (1967) has also shown significant differences in
cortical volume between lines of mice selected for high and low juxtaglomerular indices.

Peru mice differed from those of other strains in that the zona glomerulosa was very poorly developed (Shire & Spickett, 1967). This difference in the extent of the zone was due to variation at a single locus, Ezg (Shire, 1969). The allele homozygous in the Peru mice was recessive to the allele found in other strains and appeared to act by producing a high level of adrenocorticotropic hormone (ACTH) (Shire & Stewart, 1972). Treatment of Peru mice with dexamethasone resulted in the formation of a zone of normal width. The zona glomerulosa was also poorly developed in SF mice, but this had a different genetic cause (Shire & Spickett, 1967). Significant differences have been found between DBA/2 and C57BL/6 mice in nuclear volume in both the glomerular and fascicular zones (van Abeelen, van der Kroon & Bekkers, 1973).

Several quantitative studies (Meckler & Collins, 1965; Shire, 1965a; Chirvan-Nia, 1967; Ciaramello et al. 1972a) have shown not only that the left and right adrenals differed in size, but that the degree of asymmetry varied from strain to strain. The right adrenal was only half the size of the left in DBA/1 males but was similar to (CFW females) or somewhat larger than (C57BL/10 females) the left in other strains. A recessive gene (situs inversus viscerum) reverses the asymmetry in mice (Tihen, Charles & Sippel, 1948) and man (Cockayne, 1938). The position of the adrenal glands also varied from strain to strain. In CE mice the glands were within the renal capsule (Hummel, 1958) whilst in mice of the LR stock they often lay against the diaphragm (J. G. M. Shire, unpublished observations). In some strains (e.g. C57L, C58, A) the right adrenal lay so close to the vena cava that attempts at removal frequently damaged the vein, while in other strains, such as C3H, both adrenals could be removed easily (Hummel, 1958). The frequency of accessory nodules was also affected by genotype, C57L mice in particular having many (Vicari, 1943; Hummel, 1958; Jayne, 1963).

**Biochemical constitution**

In man there is a gene which, when homozygous, causes congenital lipid hyperplasia of the adrenals (O’Doherty, 1964; Camacho, Kowarski, Migeon & Brough, 1968; Degenhart, Visser, Boon & O’Doherty, 1972). The cells become laden with cholesterol (‘foam-cells’). The adrenal stores of 17-hydroxyprogesterone were raised in individuals homozygous for the gene causing deficient 21-hydroxylase activity (Bongiovanni, Eberlein, Goldman & New, 1967).

Vicari (1943) described differences in the sudanophilia of the cortex of young male mice of six strains. In four strains (C57, N, A, CE) only 2% of the cortex was sudanophilic, while in the DBA and C3H strains 32 and 13% of the cortex was sudanophilic. The distribution of the sudanophilic material was the same as for material giving positive histochemical reactions for cholesterol. Chemical analysis of the adrenals of older females (Vicari & Little, 1945) showed that the concentration of the cholesterol fraction in the adrenals was twice as high in C57 as it was in DBA mice. Chai & Dickie (1966) showed a 2½-fold variation in total lipid content when ten inbred strains of mice were examined. Arnesen (1955, 1956) found that the adrenals of adult male AKR mice were completely sudanophobic, and demonstrated that the difference
in sudanophilia between AKR and WLO mice was caused by variation at a single locus, ald. Mice homozygous for the recessive allele had adrenals replete with lipid before puberty, but at puberty the lipid was rapidly lost from the adrenal. Castration of adults caused a rapid reaccumulation of lipid. Vicari (1946) showed that the difference in sudanophilia between DBA and C57 increased after puberty. Doering and his colleagues (Doering, Kessler & Clayton, 1970; Doering et al. 1972) have shown that in DBA and AKR mice – both low-lipid strains – there was a deficiency of esterified cholesterol but not of free cholesterol. The adrenals from DBA and AC (a strain derived from AKR) mice had one-seventh of the concentration of esterified cholesterol found in adrenals from C57BL/10 mice. He also showed that depletion of the stores of cholesterol esters occurred at puberty in DBA mice and that it could be reversed by pre- or post-pubertal castration. Notwithstanding the apparently identical phenotypes of AKR and DBA mice, measurements on hybrid mice showed that the DBA phenotype was brought about by recessive variation at a locus, ald-2, different from the ald locus responsible in AKR mice (Doering, Shire, Kessler & Clayton, 1973). The lethargic locus, lh, may also affect the cholesterol stores (Dung, 1972).

The variation in stores of cholesterol esters within a single species of mouse is as great as the variation commonly found between species (Goodman, 1965). This, together with the finding of twofold differences in cholesterol concentration (fourfold per gland) between laboratory and wild rats (Nichols, 1950), suggests that variation in the chemical constitution of the adrenal glands may be widespread. Differences have been reported between the adrenals of selected strains of rats and mice in corticosterone content (Solem, 1967; Feuer, 1969), and between strains of mice in ascorbic acid concentration (Shire, 1968) and in the incorporation of [3H]uridine (Molne, 1969b).

Steroid production

In man there are a number of genetic variants that result in the inefficient functioning of particular enzymes involved in the biosynthesis of steroids. The enzymes affected are listed in Table 2, together with some of the pleiotropic effects of the mutants. The overall incidence of such enzyme defects is very low, the frequency of 21-hydroxylase defects having been estimated at between 1 in 40000 to 1 in 70000 in the U.S.A. (McKusick, 1971). Locally, however, a particular defect may occur at a much higher frequency, such as 1 in 5000 in the canton of Zürich in Switzerland and about 1 in 500 amongst the Yupik Eskimo of Alaska (Hirschfeld & Fleshman, 1969). In these two populations the frequencies of heterozygous carriers of the defects are about 3 % and over 10 % respectively.

Many of the defects depress the production of cortisol and thus lead to alterations in the feedback control of ACTH secretion. This in turn results in adrenal hyperplasia and in excessive stimulation of the metabolic steps preceding the block, and often also of those of subsidiary pathways. Intermediary substances and their metabolites often appear in plasma and in urine. Defects in 17-hydroxylase appear to result in the overstimulation of the corticosterone pathway (Mills, Wilson, Tait & Cooper, 1967; Bricaire, Luton, Laudat, Legrand, Turpin, Corvol & Lemmer, 1972). Deoxycorticosterone (DOC) accumulates in people with 11-hydroxylase defects (New & Seaman,
Table 2. Defects in adrenal enzyme function in man

<table>
<thead>
<tr>
<th>Enzymic activity</th>
<th>Inheritance*</th>
<th>Genetic heterogeneity</th>
<th>Partial defects</th>
<th>Urinary abnormalities†</th>
<th>Abnormal sex phenotype in:</th>
<th>Adrenal hyperplasia</th>
<th>Salt loss</th>
<th>Hypertension</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>20α-Hydroxylase</td>
<td>r</td>
<td>?</td>
<td>?</td>
<td>All steroids down</td>
<td>Male</td>
<td>Lipoid</td>
<td>+</td>
<td>–</td>
<td>Degenhart et al. (1972)</td>
</tr>
<tr>
<td>3β,Δ⁵-Dehydrogenase</td>
<td>r</td>
<td>?</td>
<td>+</td>
<td>Pregnenolone derivatives up</td>
<td>Male</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Parks et al. (1971)</td>
</tr>
<tr>
<td>21-Hydroxylase</td>
<td>r</td>
<td>+</td>
<td>+</td>
<td>Pregnanetriol up</td>
<td>Female</td>
<td>+</td>
<td>+ or –</td>
<td>–</td>
<td>Bongiovanni et al. (1967)</td>
</tr>
<tr>
<td>11β-Hydroxylase</td>
<td>r</td>
<td>+</td>
<td>+</td>
<td>THS up</td>
<td>Female</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Sizonenko et al. (1972)</td>
</tr>
<tr>
<td>17α-Hydroxylase</td>
<td>r or X</td>
<td>+</td>
<td>+</td>
<td>17-OH steroids down</td>
<td>Neither sex or both</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Biglieri et al. (1966)</td>
</tr>
<tr>
<td>17,20-Desmolase</td>
<td>r or X</td>
<td>DHA absent</td>
<td></td>
<td></td>
<td>Male</td>
<td>–</td>
<td></td>
<td></td>
<td>Zachmann, Völlmin, Hamilton &amp; Prader (1972)</td>
</tr>
<tr>
<td>18-Hydroxylase</td>
<td>r</td>
<td>?</td>
<td>?</td>
<td>TH180HB up; aldosterone down</td>
<td>Neither sex</td>
<td>+</td>
<td></td>
<td></td>
<td>Visser (1967)</td>
</tr>
<tr>
<td>18-Dehydrogenase</td>
<td>r or X</td>
<td>?</td>
<td>?</td>
<td></td>
<td>Neither sex</td>
<td>+</td>
<td></td>
<td></td>
<td>Ulick, Gautier, Vetter, Markello, Yaffe &amp; Lowe (1964)</td>
</tr>
</tbody>
</table>

* r = Autosomal recessive; X = X-linked recessive.
† DHA = dehydroepiandrosterone; THS = 5β-pregnane-3α,17α,21-triol; TH180HB = 5β-pregnane-3α,18,21-triol.
+ = present; – = absent; a blank indicates 'not known'; † = inconclusive evidence.
1970) and may be causally related to their hypertension. Diversion of corticosteroid precursors to androgen synthesis causes the virilization associated with the 11- and 21-defects (Bongiovanni et al. 1967; Visser, 1967). This might also underlie the apparent increased I.Q. of people affected by 21-defects (Lewis, Money & Epstein, 1968). Blocks which occur early in the pathway, such as the 20α- and 3β-hydroxy-Δ5-steroid dehydrogenase defects, lead to generalized deficiencies of steroids, the excessive production of precursors which are not hormonally active, and deficiencies in the male phenotype. The extra-adrenal consequences of the two mutations which affect reactions at C-18 in aldosterone biosynthesis are restricted to disturbances of electrolyte metabolism.

The enzyme deficiencies show considerable phenotypic and genetic heterogeneity (Table 2). In several instances partial rather than nearly complete blockage of a metabolic step has been reported [e.g. 3β,Δ5-dehydrogenase defect (Jänne, Perheentupa & Vihko, 1970; Zachmann, Völlmin, Mürset, Curtius & Prader, 1970; Parks, Bermudez, Anast, Bongiovanni & New, 1971); 11-defect (Sizonenko, Riondel, Kohlberg & Paunier, 1972); 18-dehydrogenase defect (David, Asnis & Drucker, 1972)]. In such cases the symptoms appear at a later age than would normally be expected (van’t Hoff & Bicknell, 1972; Santilli & Martin, 1972). Evidence for heterogeneity is most striking for the 17- and 21-defects. The 17-defect may be limited to the adrenal (New & Petersen, 1967; Miura, Yoshinaga, Goto, Katsushima, Maebashi, Demura, Iino, Demura & Torikai, 1968), or may involve adrenal gland and gonads, resulting in abnormalities of sexual phenotype (Biglieri, Herron & Brust, 1966; Mills et al. 1967; New, 1970; Bricaire et al. 1972). 21-Hydroxylase deficiency, which accounts for about 90% of congenital adrenal hyperplasia (Bongiovanni et al. 1967), may be accompanied by a syndrome of severe salt loss. This occurs in about 30% of cases. Within individual pedigrees the degree of electrolyte disturbance of affected people was relatively constant, which suggested that more than one genetic form of the enzyme defect existed. The salt-losing form was often associated with markedly reduced aldosterone secretion rates (Visser, 1967) whilst aldosterone production was frequently increased (e.g. 300 μg/day; Simopoulos, Marshall, Delea & Bartter, 1971; Dahl, Rivarola & Bergada, 1972) in the form with more normal electrolyte metabolism. This latter form of the 21-defect was generally less severe, since the adrenal hyperplasia was often sufficient to return the basal production rate of cortisol to normal (Beitins, Bayard, Kowarski & Migeon, 1972). Absence of salt loss was correlated with less severe genital abnormalities (Qazi & Thompson, 1972).

It is usually assumed that the genes responsible for the blockages of enzymic function are mutants at the structural loci that code for the amino-acid sequences of the enzyme molecules. Heterogeneity is attributed to different mutational events bringing about changes of greater or lesser severity in the structure of the enzyme and thus greater or lesser loss of catalytic activity. If this were so, heterozygotes would be expected to have enzymes of intermediate specific activities. In fact, at present there are no reliable means of distinguishing heterozygous carriers from normal homozygotes, although the possibility may exist for carriers of lipid hyperplasia (O’Doherty, 1964) and 21-defects (Hall, Smith, Harkness & Smart, 1970; Qazi, Hill & Thompson, 1971). The difficulties are not surprising in view of the negative feedback regulating cortisol production. All metrics of adrenal function used at present are
several stages removed from the measurement of activity of the individual enzymes of steroid biosynthesis. Studies in vitro are rare (Axelrod & Goldzieher, 1967; Degenhart et al. 1972). The enzymes carrying out the same reaction in different parts of the adrenal (e.g. in the z. fasciculata and z. glomerulosa) or in different steroidogenic tissues (e.g. adrenal and gonad) could have different amino-acid sequences and be coded for in different parts of the nuclear DNA. Similarly, if the same enzyme is present in different cell types, mutation might affect a control process specific to only one of the cell types. Such kinds of variation could account for significant production of aldosterone in some individuals with defects in 21-hydroxylation or 11-hydroxylation (Sizonenko et al. 1972). Similarly, the occurrence of some pregnane derivatives in cases of 3β,Δ5-dehydrogenase defect can be attributed to an intact hepatic enzyme (Parks et al. 1971). The changes in severity of this defect during development may also be different in adrenal and gonad (Parks et al. 1971). Until there are direct studies which show that individual enzymes from mutant adrenals differ from normal (e.g. in electrophoretic mobility, $K_m$, thermal stability, specific activity, antigenicity or amino-acid sequence), mutations at loci other than the structural loci are possible for some if not all of the severe variants of the different deficiencies. Such mutations can be classified as regulatory (altering rate of synthesis or degradation of enzyme), architectural (affecting incorporation of enzyme molecules into active sites in the cell, Paigen, 1971) or temporal (affecting the development of the tissue or the time of activation of regulatory systems, Paigen, 1971). In this context it is interesting that, in at least some families, the defect in 18-dehydrogenation was transient, disappearing after infancy (Rappoport, Dray, Legrand & Royer, 1968).

The two major forms of 21-defect might thus be different alleles at a single locus, mutations at structural loci for two different 21-dehydroxylases, or mutants affecting two different kinds of locus, one structural and one non-structural. Evidence on this point could come from the marriage of heterozygous carriers, one from a pedigree in which salt loss was present, the other from a family without abnormal electrolyte metabolism. The discovery that such a couple had had even a single affected child would resolve the genetic problem and should improve the genetic counselling which could be given to such parents in the future.

A further possible cause of heterogeneity in the enzyme-defect syndromes could well be the interaction of identical mutations with genetic variation affecting related aspects of adrenal function. Mutation α, when homozygous, might produce a more severe phenotype in people homozygous for the $b$ allele at a second locus, than it does in people heterozygous for the $B$ allele at the second locus. In the absence of the $a$ mutation, variation at the $B$ locus might well not lead to any state of disease, but rather to variation within the range of normal function. Such loci, which alter the penetrance or expression of mutant genes, are well known in the developmental genetics of experimental animals (Hadorn, 1961).

No mutations are known as yet in experimental animals which correspond to the enzyme blocks found in man. There are, however, qualitative differences in the pattern of corticosteroid synthesis. While it is generally agreed that corticosterone and 18-hydroxycorticosterone are the major products of the rat adrenal and that corticosterone is the chief product of the mouse adrenal, there is considerable
controversy about the production of other compounds by adrenals from these species (see Raman, Ertel & Ungar, 1964; Varon & Touchstone, 1964; Vinson & Chester Jones, 1964; Nandi, Bern, Biglieri & Pierprzyk, 1967; Vinson & Rankin, 1965; Young & Sweat, 1967). In particular the production of 17-hydroxylated steroids has been the subject of differing findings. Conflicting investigations differ not only in methodology, but also in the strains of animal used. The study by Nandi et al. (1967) is of great importance because, using a standard methodology, they found differences between four strains of mice in the occurrence of cortisol and 11β-hydroxyprogesterone (11-OHP). Similar genetic differences may underlie the production of 17-hydroxylated compounds by Wistar rats with adrenal regeneration hypertension (Brownell, Lee, Beck & Besch, 1963), but not by Long-Evans rats with adrenal regeneration hypertension (Laplante, Giroud & Stachenko, 1964).

The likelihood of some at least of these differences being due to genetic variation is enhanced by the finding of genetic differences in the relative proportion of different steroids formed by cortical tissue. Rapp (1969b) found differences, both in vitro and in vivo, between lines of rats selectively bred for high and low juxta-glomerular indices. The production of 11-OHP was relatively greater in the low line whilst aldosterone production was elevated in the high line. Rapp & Dahl (1971) have demonstrated a difference in the relative proportions of 18-hydroxydeoxycorticosterone (18-OHDOC) and corticosterone secreted into the adrenal vein in vivo and synthesized in vitro by the adrenals of rats selectively bred for high and low blood pressure. This difference was controlled by variation at a single locus (Rapp & Dahl, 1972). The heterozygotes were intermediate, 28% of the DOC being 18-hydroxylated. In the respective homozygotes 15 and 38% of the DOC was 18-hydroxylated. Both 18- and 11-hydroxylation occur in mitochondria, and the locus may control the relative proportions of the two processes by coding for a structural protein of the mitochondria. It may thus be an ‘architectural’ gene in the classification of Paigen (1971). Sixteen per cent of the difference in blood pressure between the selected lines of rats was due to the variation at this locus. The gene has been found segregating within the CD stock of Sprague-Dawley rats (Rapp & Dahl, 1972). It is interesting that Melby, Dale, Grekin, Gaunt & Wilson (1972) found excessive production of 18-OHDOC to be frequent in a clinical subgroup of patients with hypertension.

In mice, Badr (Badr & Spickett, 1965b; Badr, 1970) has shown that the ratio of synthesis of a compound identified as 11-deoxycortisol to that of corticosterone was affected by genetic variation. The ratio was high (1 to 1.5) in CBA and SF mice and low (0.4 to 0.6) in A mice. The difference between the A and CBA strains was determined by genetic variation at a single locus (Badr & Spickett, 1965b). The allele which was dominant produced a low ratio, by a mechanism which is unknown. In both rats and mice the ratio of major products can be altered genetically without affecting the total rate of production of C-21 steroids. Conversely, genetic variation exists which affects the overall rate of production of steroids without affecting the relative proportions of the component steroids. The ratios of steroids synthesized were similar in CBA and SF mice, but the total amounts formed per mg adrenal tissue were not (Badr, 1970).

Production rates of single compounds can thus show much variation. This is supported by indirect studies in man of secretion and excretion (e.g. Melby et al.
1972). Enzyme blocks in man also lead to alterations of steroid output, for not only may the production of certain compounds be reduced but production of other corticosteroids may be elevated. Such elevations may be due to the diversion of precursors or to pleiotropic effects of disturbed homeostasis. Genes causing adrenal hypoplasia (see below) cause obvious depressions of steroid output. More direct evidence comes from investigations of rodents, not only those described above, but also ones in which only a single hormone was measured. Differences in corticosterone production between inbred strains have been demonstrated by Nandi et al. (1967), Solem (1967) and Doering et al. (1972, 1973). The last two groups have shown marked (about twofold) differences in the rate of corticosterone production *in vitro* between mice of strains with *ald* phenotypes (CS, AC, DBA) and mice with lipid-replete adrenals (C57BL, WLO). No such differences were found in mice investigated before the onset of lipid depletion at puberty. The association between cholesterol ester stores and corticosterone output was further enhanced by the finding of intermediate precursor stores and intermediate corticosterone production in C57 × DBA F1 mice, and high stores and high output in castrated DBA mice. This study (Doering et al. 1973) also included measurements on backcross mice. For these mice the correlation broke down completely, implying that the variation affecting cholesterol ester stores and that affecting corticosterone output were caused by independent genes. Thus they could not both be pleiotropic effects of a single *ald*-like gene.

The absence of differences in steroid output between animals of different genotypes may, on occasion, be as revealing as the discovery of differences. A case in point was the finding of similar rates of aldosterone production in CBA and Peru mice (Stewart et al. 1972), which differed at the *Ezy* locus which affects the extent of the zona glomerulosa (see above).

Syndromes in man are known in which the rate of production of aldosterone is altered, even though no metabolic blocks are present in adrenal cells. In Bartter's syndrome, which is recessively inherited, increased aldosterone secretion was associated with hypokalaemic alkalosis and a defect in kidney function (Cannon, Leeming, Sommers, Winters & Laragh, 1968; Gardner, Lapey, Simopoulos & Bravo, 1970). There are two syndromes which may be caused by dominant mutations. In one of these an elevated production of aldosterone, which was suppressible by dexamethasone, was present (Salti, Stiefel, Ruse & Laidlaw, 1969; Gibbink, Gotlin, Biglieri & Katz, 1973). In the other (Liddle's syndrome) hypoaldosteronism was associated with a defect in kidney function (Liddle, Bledsoe & Coppage, 1964; Gardner et al. 1970).

*Corticosteroid degradation*

The chief sites of catabolism of corticosteroids are the liver and the adrenals. The first indications of genetic variation in the adrenal degradation of corticosteroids came from investigations of the urinary excretion of hydroxylated derivatives of cortisol by guinea-pigs. Inbred strains secreting high and low amounts of 2α- and 6β-hydroxylated cortisol were found (Nadel, Young & Hilgar, 1959). The differences between such strains were shown to be genetically determined, by variation at a small number of loci (Burstein, Bhavnani & Kimball, 1965). Studies on homogenates (Burstein, Bhavnani & Bauer, 1967) showed 2α- and 6β-hydroxylation to be nine and
seven times more active in the adrenals of strain 2 and 13 guinea-pigs than in those of the Hartley strain. In animals with active 2α-hydroxylation there were two apparent \( K_m \)'s for this enzyme activity, 10 \( \mu \text{mol/l} \) and 0.3 \( \text{mmol/l} \). Only a single \( K_m \), 10 \( \mu \text{mol/l} \), was found in animals with low excretion rates of cortisol metabolites.

Strain differences affecting steroid catabolism by adrenal tissue have also been found in mice (Maynard & Cameron, 1972). Incubations \textit{in vitro} showed that the metabolites of dehydroepiandrosterone (DHA) in LACA mice were ring \( A \) reduced steroids of the 5β series (e.g. aetiocholanolone) and 11β-hydroxyandrostenedione. Adrenal tissue from NH mice showed a markedly different pattern of DHA metabolism, the chief products being androstenedione, 5β-androstane-3,17-dione, aetiocholanolone and 5β-androstan-3β-ol-17-one.

Genetic variation affecting the catabolism of corticosteroids by the liver has also been found. The hepatic hydroxylation of cortisol was different in the two strains of guinea-pigs which differ in adrenal 2α- and 6β-hydroxylation. In contrast to the adrenal, in liver the difference in 6β-hydroxylation was small but that in 2α-hydroxylation was large; sevenfold (Burstein, 1968). The developmental patterns of the enzyme activities were also different in the two tissues. In the adrenal the two activities rose in parallel from birth to maturity. In the liver, hydroxylase activity reached a peak between 7 and 14 days after birth. This was much more marked for 6β-hydroxylation than for 2α-hydroxylation (Burstein, 1970). Although the overall difference between the strains was due to only a few loci, it is not known how many structural loci were involved or whether any regulated the rate of synthesis of the enzymes. Genetic variation affecting the inducibility of hepatic hydroxylases in mice is known (Nebert & Gielen, 1972).

The reductive catabolism of corticosterone \textit{in vivo} was greater in C57BL/10 mice than in DBA/2 mice (Lindberg, Shire, Doering, Kessler & Clayton, 1972). \textit{In vitro}, 3β,5α-tetrahydro compounds predominated in DBA mice. These two strains also differed in the extent to which corticosterone reduction (Lindberg \textit{et al.}, 1972) and cholesterol synthesis (Gaskin & Clayton, 1972) depended on exogenous sources of NADPH. Studies on six strains (Shire, Kessler & Clayton, 1972) suggested that only C57 strains (C57BL/6 and C57BL/10) were relatively independent of exogenous NADPH. Liver from BALB/c mice had a particularly low rate of steroid degradation. Threefold differences between selected lines of rats have been reported in the activity of steroid sulphatases in liver (Burstein & Zucker, 1967).

Direct evidence for genetic variation affecting steroid degradation in man is absent. Considerable constant differences do, however, exist between individuals. In a study of twenty normal males a ninefold variation in the excretion of 11-ketoaetiocholanolone and a 29-fold variation in that of 5α-androstane-3α,11β-diol-17-one were found (Dobriner, Kappas, Rhoads & Gallagher, 1953a, b; Sachar, Mason, Fishman, Hamburg & Handlon, 1965). Racial differences in the urinary excretion of 17-hydroxycorticosteroids have also been found (Politzer & Tucker, 1958; Simpson, 1965) and could, in part, be a reflection of genetic differences. The finding of particular patterns of urinary excretion of steroid metabolites associated with, and preceding, certain neoplastic diseases, also suggests the existence of genetic polymorphisms in steroid metabolism (Bulbrook, 1972; Rao, 1972).
Corticosteroid levels in plasma and their control

In any individual the concentration of a hormone in plasma is a reflexion of the balance between the rates of production and degradation. Since genetic variation affects both these processes, variation in plasma levels of corticosteroids, both at rest and after stress, are to be expected. Two- to threefold differences in the resting levels of plasma corticosterone have been reported between inbred strains of mice [A/J and C57BL/10J (Levine & Treiman, 1969); YS/ChWf and VY/Wf (Wolff & Flack, 1971); C57BL/6By and BALB/cBy (Eleftheriou & Bailey, 1972)]. The data of Wolff & Flack (1971) show an interesting genotype × background interaction. Substitution of a single dominant allele at the agouti locus had no effect on the plasma corticosterone levels of VY mice but did affect those of YS mice. Eleftheriou & Bailey (1972) measured F1 and backcross hybrids between BALB and C57, and also a number of recombinant inbred strains derived from these crosses. They found some mice amongst the backcross to BALB hybrids which had even higher plasma levels than those found in the BALB parental strain. They suggested that the difference between the strains was caused by differences at two interacting loci. In general their model fitted their observations well, but predicted that 25% of the backcross to BALB mice would have the BALB phenotype. The existence of such a class of mice is not obvious from their results. One of the factors which may have contributed to the high corticosterone levels was the low rate of corticosterone catabolism found in BALB mice (Shire et al. 1972). Feuer (1969) found that the resting plasma levels of corticosterone were lower in a line of rats selected for emotional reactivity than in a line selected for non-reactivity, even though the adrenal glands were heavier and contained larger stores of esterified cholesterol. Differences have also been found in the peripheral plasma levels of 18-OHDOC in rats (Rapp & Dahl, 1972) and in a substance identified as 11-deoxycortisol in mice (Badr, 1971). In both cases the plasma differences were associated with differences in steroid biosynthesis.

Evidence for comparable variation in levels in man is less strong, except when adrenal insufficiency or blocks in steroid biosynthesis were present. Plasma cortisol levels have been measured in a sample of twins by Maxwell, Boyle, Greig & Buchanan (1969) who found evidence for its genetic determination, at least in females. However, the timing and methodology of their sampling may have resulted in some of their samples not being truly representative of resting levels, which would have led to an increased environmental variance. Africans living in Zambia had higher plasma cortisol levels than Zambian residents of European or Asian ancestry (Briggs & Briggs, 1972). It is possible that part of these differences were genetic in origin. Pedigrees containing individuals with elevated plasma levels of aetiocholanolone, often associated with periodic or continuous fever, and sometimes suppressible by dexamethasone, have been reported (Bouronde & Doan, 1957; Driessen, Voûte & Vermeulen, 1968; Herman, Overholt & Hagler, 1969). Both dominant and recessive modes of inheritance have been described.

Although there is some evidence for consistent individual differences in the plasma levels of corticosteroids after stress in man (Hamburg & Kessler, 1967), most of the evidence has come from studies on rodents. Wragg & Speirs (1952) reported that seven strains of mice fell into two groups on the basis of their response to handling. Handling
produced marked and prolonged eosinopenia in C57BL/6, C57BR/cd and C57BR/a mice, but had only a slight, transient effect on mice of the 129, DBA/1, BALB/c and Street strains. Levine & Treiman (1969) were the first to demonstrate directly the existence of differences in the plasma corticosterone levels after stress. They showed that C57BL/10J and A/J mice showed large and prolonged elevations of plasma corticosterone, while in DBA/2J and AKR/J mice there was only a small rise of short duration. Chapman (1968) found that a slightly different test situation altered the relative rankings of the A and C57BL/6 strains. Doering et al. (1972), who measured the response to an injection of saline, found that C57BL/10J mice showed a greater response than DBA/2J mice. However, when ethanol was used as a stressor the response of C57BL/10 mice was less than that of DBA/2 mice (Kakihana, Noble & Butte, 1968). The intensity of the stress may have been different in the two strains in this case, as C57BL mice had a much greater preference for, and tolerance of, alcohol (McClearn, 1965).

The two strains, DBA and AKR, noted for small responses to stress, differed from a strain with a marked stress response, C57BL, in both the production and catabolism of corticosteroids (see above). To account for these observations the increased degradation in C57BL mice must have been more than compensated for by the increased adrenal output. The importance of differences in adrenal synthetic capacity is confirmed by the observations that the plasma corticosterone levels after stress were greater in castrated DBA mice than in control DBA mice, and that the effects of castration on C57BL/10 mice were slight (S. Blum, R. Kakihana, J. G. M. Shire & S. Kessler, in preparation). Such differences were not found before the onset of the adrenal differences at puberty. Solem (1967) found differences in the plasma corticosterone response to a standard dose of ACTH between adult CS and WLO mice. These strains, which differ at the ald-1 locus, were also not different when tested before puberty. The difference in adrenal synthetic capacity could not, however, account for the whole of the observed difference in stress response between C57BL/10 and DBA/2 animals. Doering et al. (1972) showed that the response to an injection of 100 mu. ACTH was greater in DBA than in C57BL mice, implying that the standard stress caused a smaller release of ACTH in DBA than it did in C57BL animals. The differences in adrenal biosynthetic capacity show autosomally linked, non-maternal inheritance (Arnesen, 1956; Doering et al. 1970, 1972, 1973). The differences in response to stress have a different pattern of inheritance. Treiman, Fulker & Levine (1970) found differences between reciprocal F1 males and interpreted this as evidence for maternal inheritance. Their data support X-linked inheritance equally well, but rule out autosomal inheritance.

Strain differences in plasma corticosterone levels following stress have been found in rats (M. A. Stockham, personal communication). After ether stress the mean peak plasma levels were 25 ± 1.2 µg/100 ml in Sprague–Dawley rats, 38 ± 1.1 µg/100 ml in Wistar rats and 59 ± 1.1 µg/100 ml in Lister rats. The times at which these peak values were reached also differed between the strains. A standard injection of ACTH raised plasma corticosterone levels to 30 ± 1.3 µg/100 ml in Wistar rats and to 50 ± 0.3 µg/100 ml in Lister rats. Woods (1957a, b) found that chronic stress increased adrenal weight, and acute stress lowered adrenal ascorbic acid levels, in Wistar but not in wild rats. Ten i.u. of ACTH depressed adrenal ascorbic acid levels significantly.

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in Wistar rats, whereas the wild rats required 20 to 40 i.u. to produce the same result. Hartley guinea-pigs showed a much greater rise in plasma corticosteroids after a standard dose of ACTH than did guinea-pigs of strains 2 and 13 (Nadel et al. 1959).

The biological consequences of the observed variation in plasma steroid levels will depend on the distribution of the hormones between the free and bound state. Pedigrees showing dominant, possibly sex-linked, inheritance of low levels of corticosteroid-binding globulin (CBG) have been published (De Moor, Meulepas, Hendrikkx, Heyns & Vandenschrieck, 1967; Lohrenz, Seal & Doe, 1967). A familial occurrence of elevated levels of CBG has also been reported (Lohrenz, Doe & Seal, 1968). M. A. Stockham (personal communication) has found significant strain differences in plasma corticosterone binding capacity in rats. Mean values were 34 ± 2 μg/100 ml for Wistar rats and 49 ± 5 μg/100 ml for Hooded rats.

Genetic variation also affects the renin–angiotensin system that regulates aldosterone levels. Both mice (Rapp, 1965) and rats (Rapp, 1969a) have been selectively bred for high and low granularity of the juxtaglomerular apparatus. Correlated responses were found in adrenal steroidogenesis and blood pressure (Rapp, 1967, 1969b). Bing & Poulsen (1971) studied five strains of mice and found a tenfold range in total renin content, which varied from 10 Haas–Goldblatt units in BALB to 1000 units in C/SSI mice. The effect of nephrectomy on plasma angiotensinogen levels also varied between the strains, the rise being relatively small in NZB and very large in DBA/2 mice.

**Normal and abnormal development**

The adrenals may fail to develop as a consequence of pituitary or hypothalamic deficiencies, as in anencephaly. Several such deficiencies which may be genetic in origin are known in man and are listed in Table 3. A recessively inherited absence of the pituitary has been found in Guernsey cattle (Kennedy, Kendrick & Stormont, 1957). The resultant adrenal aplasia leads to prolonged gestation of affected calves, implicating the adrenal cortex in the initiation of parturition in cattle. The 'small sella' syndrome in man appears to have an analogue in the recessive mutation found in Holstein-Friesians. The affected calves had small pituitaries, were hypoglycaemic, and developed adrenal insufficiency. Adrenal hypoplasia that spared the z. glomerulosa was present (Holm, Parker & Galligan, 1961).

In men cases have been reported of adrenal insufficiency secondary to the isolated deficiency of ACTH (Hung & Migeon, 1968). Most cases had normal pigmentation and showed normal responses to exogenous ACTH. Three cases have been described (Steinberg, Shechter & Segal, 1954) who were hyperpigmented, suggesting the possible production of an altered ACTH molecule which retained MSH activity but had lost its steroidogenic activity. Adrenal hypoplasia, associated with normal pituitary function, which results in adrenal insufficiency in infants, appears to exist in at least two forms (Weiss & Mellinger, 1970). In one, which seems to be X-linked, the adrenal glands are very small and disorganized. The production of aldosterone as well as that of glucocorticoids was very low (Sperling, Wolfsen & Fisher, 1973), and disturbances of electrolyte metabolism may be marked. In the other form, in which both males and females, including sibs, have been affected, the adrenals showed normal zonation but were greatly reduced in size. Addisonian crises may not occur
Table 3. Genetically determined adrenal insufficiency with early onset in man

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Adrenal cortex</th>
<th>Pituitary changes</th>
<th>ACTH levels</th>
<th>Other trophic hormones</th>
<th>Salt loss</th>
<th>Inheritance*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anencephaly</td>
<td></td>
<td>+</td>
<td>? Low</td>
<td>? Low</td>
<td></td>
<td>Mixed</td>
<td>Rimoin &amp; Schimke (1971a)</td>
</tr>
<tr>
<td>Empty sella syndrome</td>
<td></td>
<td>+</td>
<td>Low</td>
<td>Low</td>
<td></td>
<td>r</td>
<td>Steiner &amp; Boggs (1965)</td>
</tr>
<tr>
<td>Small sella syndrome</td>
<td></td>
<td>+</td>
<td>Low</td>
<td>Low</td>
<td></td>
<td>r</td>
<td>Ferrier &amp; Stone (1969)</td>
</tr>
<tr>
<td>Panhypopituitarism</td>
<td></td>
<td>?</td>
<td>?</td>
<td>Low</td>
<td></td>
<td>X</td>
<td>Schimke, Spaulding &amp; Hollowell (1971)</td>
</tr>
<tr>
<td>Isolated ACTH deficiency</td>
<td></td>
<td>-</td>
<td>Low</td>
<td>Normal</td>
<td></td>
<td>r</td>
<td>Hung &amp; Migeon (1968)</td>
</tr>
<tr>
<td>Unresponsiveness to ACTH</td>
<td></td>
<td></td>
<td>Very high</td>
<td>Normal</td>
<td></td>
<td>r or X</td>
<td>Franks &amp; Nance (1970)</td>
</tr>
<tr>
<td>Steroidogenic enzyme defects</td>
<td>Large</td>
<td>-</td>
<td>High</td>
<td>Normal</td>
<td>+ or -</td>
<td>r</td>
<td>See Table 2</td>
</tr>
</tbody>
</table>

* r = Autosomal recessive; X = X-linked recessive. + = present; = absent; a blank indicates ‘not known’; ? = inconclusive evidence.

ACTH = adrenocorticotrophic hormone.
until the first or second year of life, and salt loss is not an important feature. It is not known whether the primary site of the defects in adrenal hypoplasia lies in the adrenal cortex or in the functioning of the hypothalamus during organogenesis.

A syndrome of adrenal insufficiency due to adrenocortical unresponsiveness to ACTH has also been described in man (Franks & Nance, 1970). ACTH levels may be 10 to 20 times normal (Kershnar, Roe & Kogut, 1972), and the presence of hyperpigmentation showed that tissue responsiveness to MSH-like substances was unaffected. There are several lines of evidence which suggest that this syndrome is heterogeneous. The most usual histological finding has been of cortical degeneration sparing the z. glomerulosa. Hyperplastic, lipid-filled adrenals have also been reported (Keleh, Kaplan, Biglieri, Daniels, Epstein & Grumbach, 1972). Both autosomal and X-linked patterns of inheritance have been found (Franks & Nance, 1970; Keleh et al. 1972; Kershnar et al. 1972). The similarities in phenotype and age of onset suggest that, at least sometimes, recessively inherited adrenal hypoplasia I and hereditary ACTH insensitivity may be identical or subject to reciprocal misclassification. Recently Moshang, Rosenfield, Bongiovanni, Parks & Amrhein (1973) have described four sibs with signs of ACTH unresponsiveness. The two youngest were tested before and after they developed hyperpigmentation. At first they showed a positive 17-hydroxycortiocosteroid response to ACTH, but this disappeared after the onset of adrenal insufficiency. Thus ACTH unresponsiveness may be secondary to spontaneous degeneration of the cells of the z. fasciculata. Family B of Kelch et al. (1972) may have had a defect in ACTH response which affected steroidogenesis but not the stimulation of adrenal growth.

Adrenal insufficiency may also occur in association with adrenal hyperplasia in some of the inherited defects in enzyme activity. Other abnormalities of the adrenal in man which are expressed shortly after birth include adrenal insufficiency and calcification which occur as consequences of the deficiencies of lysosomal esterases in the two forms of Wolman's disease (Eto & Kitagawa, 1970; Lake & Patrick, 1970). Adrenal cytomegaly is a feature of the exomphalos—macroGLOSSIA—gigantism (Beckwith—Wiedemann) syndrome (Filippi & McKusick, 1970).

Addison's disease starting before the age of 20 showed a marked familial aggregation (Spinner, Blizzard & Childs, 1968). Some of these patients may represent variants of adrenal hypoplasia and adrenal unresponsiveness to ACTH, particularly as hypoaldosteronism was often absent. While the overall data fitted recessive inheritance, the excess of affected males implicates X-linked loci for some forms. One specific syndrome known to be X-linked is Addison—Schilder's disease, in which cerebral leucodystrophy and total degeneration of the adrenal cortex occur during childhood (Aguilar, O'Brien & Taber, 1967). The gene presumably affects some enzyme common to the metabolism of both brain and adrenal. A much less severe form of the syndrome, with onset between 30 and 40 years of age, appeared to be inherited as an autosomal recessive (Harris-Jones & Nixon, 1955; Penman, 1960). There was no excess of males amongst cases of isolated Addison's disease with onset after the age of 20 (Spinner et al. 1968). Addison's disease combined with hypothyroidism and diabetes mellitus (Schmitt's syndrome) affects adults and appeared to be recessively inherited. Differences between families in the age of onset suggested genetic heterogeneity (Spinner et al. 1968). Addison's disease combined with hypothyroidism and diabetes mellitus (Schmitt's syndrome)
parathyroidism and remarkable susceptibility to superficial moniliasis also showed a pattern of recessive autosomal inheritance.

Genetically determined abnormalities of adrenal development are not confined to man. The X-zone of mice, which differentiates postnatally, is absent from animals homozygous for \(dw\) or \(df\) (see p. 176). Adrenal hyperplasia and hyperactivity occurred in 'lethargic' (\(lh\)) mice around the time of weaning (Dung & Swigart, 1971). Strain differences in adrenal weight found in adult rats and mice were the consequences of different rates of adrenal development (Freudenberger, 1932; Badr et al. 1968). The adrenal lipid depletion phenotypes found in adult AKR and DBA mice became manifest at puberty. This developmental change can be induced by injections of testosterone and reversed or prevented by castration (Arnesen, 1956; Doering et al. 1973). Strain differences in the timing of developmental events affecting the X-zone have been found in male (Badr et al. 1968; Badr, 1969) and in female mice (Howard, 1938; Taylor & Waltman, 1940; Daughaday, 1941; Meckler & Collins, 1965; Shire, 1965b; Chirvan-Nia, 1967; Shire & Spickett, 1968b). Studies on F\(_1\) hybrids showed a genetic basis for the difference in the age at which X-zone involution occurred in DBA and C57BL mice (Daughaday, 1941; Meckler & Collins, 1965). The X-zone of A strain females was found to involute very early, shortly after puberty. This was shown to be due to the presence in this strain of a dominant allele, \(Ex\) (Shire & Spickett, 1968b), at a locus linked to the albino locus on chromosome 7 (Robinson, 1972). The recessive mutation nude, \(nu\), delayed the onset of X-zone degeneration in both sexes (Shire & Pantelouris, 1973) in addition to preventing differentiation of the thymus. Genetic variation can also affect the form of involution of the X-zone takes. Fatty degeneration occurred in the A, CBA, DBA and AKR strains (Howard, 1938; Arnesen, 1956; Meckler & Collins, 1965; Shire & Spickett, 1968b) while in C57BL and Peru mice the zone collapsed without lipids accumulating (Taylor & Waltman, 1940; Daughaday, 1941; Spickett et al. 1967). Collapse of the X-zone was found in strains which probably had high blood levels of ACTH (Shire & Stewart, 1972; Doering et al. 1972).

The occurrence of senescent changes in the adrenal is also dependent on genotype. Brown degeneration of the adrenal glands of mice showed marked differences between strains in its incidence and age of onset (for review see Dunn, 1970). These may have been due, in part, to strain differences in adrenal responsiveness to oestrogens (Westberg, Bern & Barnawell, 1957). Strain differences in the extent of connective tissue proliferation within the cortex of ageing mice have been described by Jayne (1963) and by Dunn (1970). When mice of the DE strain grew old their adrenals became greatly enlarged and filled with acellular material (Chai & Dickie, 1966).

In man multiple endocrine adenomatosis seems to have a dominant mode of inheritance (Aach & Kissane, 1969). Affected tissues include adrenals, pancreatic islets and parathyroids. Several cases of sibs with adrenocortical carcinoma have been reported and may have been caused by recessive mutations (Mahloudji, Ronaghy & Dutz, 1971). Adrenal carcinomas occurred in Osborne–Mendel rats at a frequency well above that recorded for other strains (Snell & Stewart, 1959). In mice, old females of the NH and BALB/c strain had a high incidence of adrenocortical carcinomas (Dunn, 1970). Pre-neoplastic changes were found in the adrenals of H-line mice which had a high frequency of testicular and mammary tumours in males (Furtado-Dias, 1959). Neonatal castration resulted in adrenal hyperplasia followed by neoplasia
in some strains of mice (BALB/c, CBA, CE, C3H, DBA, NH, Z) but not in others (A, C57BL, F, ICRC; Woolley, 1950). In crosses with the CE strain the hyperplastic response to castration behaved in a dominant fashion. Reciprocal transplantation experiments suggested that the specificity of the response lay in the cells of the cortex (Dunn, 1970). A number of these hyperplastic adrenals were biosynthetically active. They produced mainly oestrogens in DBA and CE mice, androgens in BALB mice, and both classes of hormone in CBA and C3H mice (Woolley, 1950; Dunn, 1970). The hyperplasia of the cortex was frequently associated with pituitary hypertrophy (Murthy, Brezak & Baez, 1970; Ranadive & Karande, 1970).

**Corticosteroid target organs**

**Kidney**

The diuretic response to electrolyte loads in CBA and Peru mice differed in ways which suggested that aldosterone was of much greater importance in CBA mice (Spickett et al. 1967; Stewart, 1969). Peru mice, unlike CBA mice, were unaffected by spironolactone (Stewart, 1969) which antagonizes the renal actions of aldosterone. Direct differences in renal sensitivity have been demonstrated (J. Stewart, personal communication). While some of the details of the renal mechanisms and their genetic controls have been elucidated (Stewart & Mowbray, 1972) it remains possible that Peru mice carry a genetic variant affecting the aldosterone receptor system described by Edelman (Funder, Feldman & Edelman, 1972).

Differences in target-organ requirements for mineralocorticoids are suggested by the reports of differences between stocks of guinea-pigs in their survival after adrenalectomy (Elliot & Tuckett, 1906), and the finding that adrenalectomy, even when accompanied by supplements of salt, was lethal for wild rats but not for Wistar rats (Richter, 1954). Sprague–Dawley, but not Long–Evans rats, developed hypertension after the administration of DOC (Hall, Ayachi & Hall, 1973).

**Liver**

Tyrosine aminotransferase (TAT) is one of several enzymes which can be induced by steroids, not only in vivo but also in vitro in cultured cells. Levisohn & Thompson (1972) have described a variant sub-line of an inducible hepatoma culture in which the basal levels of TAT were normal, but failed to respond to inducing steroids. The defect did not lie in steroid uptake but in a reduced level of specific corticosteroid-binding protein. Blake (1970) has described marked differences between strains of mice in the response of TAT levels to starvation. In C57BL/6 mice the levels were markedly elevated while in DBA/2J mice they were depressed below control levels.

**Gut**

Rat strains have been found to differ markedly in their susceptibility to the induction of gastric ulcers by restraint. Sprague–Dawley rats were relatively resistant whilst Wistar rats were very susceptible (Wilson, 1967). Sines (1959) increased the frequency of ulceration in a mixed population of Sprague–Dawley rats by selective breeding. Certain enzymes in the intestine can be induced by corticosteroids. One such enzyme, duodenal alkaline phosphatase, showed a threefold difference in activity between strains (Nayudu & Moog, 1967). SWR and AKR mice had high
levels and DBA and a Swiss line had low levels. Studies on hybrid mice showed that at least two interacting loci were involved.

**Immune system**

Corticosteroids affect the eosinophil count in blood. Basal eosinophil counts were very different in selected lines of rats, being elevated in a line selected for emotional reactivity (Feuer, 1969). Strain differences in resting levels have also been found in mice by Wragg & Speirs (1952). These workers also described differences in the dose of cortisone required to produce maximum eosinopenia in adrenalectomized mice. Six μg were sufficient for C57BL/6, C57BR/ed and C57BR/a mice but 24 to 96 μg were required for BALB/c, DBA/1, Street and 129 mice. Mouse lymphoma cells are normally sensitive to corticosteroids. Resistant lines have been selected in vitro in which cytoplasmic binding of the hormone, but neither nuclear binding nor its uptake by the cells, was reduced (Rosenau, Baxter, Rousseau & Tomkins, 1972).

**Foetus**

Strain differences have been reported in the susceptibility of mice to the induction of cleft palate by corticosteroids on day 11 of pregnancy (Levine, Yaffe & Back, 1968). The frequency was 100% in A mice and very low in CBA and C57 mice. Reciprocal transfers of blastocysts between susceptible and resistant strains have shown that susceptibility is determined by the foetus (Marsk, Theorell & Larsson, 1971). Studies on reciprocal backcrosses have shown that X-linked genes controlled sensitivity to cortisone-induced cleft palate, but not sensitivity to cortisone-induced resorption (Francis, 1973). Spontaneous cleft lip, which also showed strain differences, was not determined by X-linked genes (Bornstein, Trasler & Fraser, 1970).

The effects of corticosteroid injections given later in pregnancy also depended on genotype. Injection on day 15 repaired the eyelids-open-at-birth syndrome when this was caused by the \( lg^{Ml} \) mutation, but not when caused by the allelic \( lg, lg^{St} \) and \( lg^{Stein} \) mutations, or by the non-allelic \( Eo, oe \) and \( gp \) mutations (Ricardo & Miller, 1967). The foetal uptake of \(^{3}H\)corticosterone on day 17 was normal in the \( lg^{Ml} \) stock but three times higher in the \( lg^{Sn} \) stock, even though the anatomical abnormalities caused by both mutants can be repaired by cortisone therapy (Nguyen-Trong-Tuan, Rekdal & Burton, 1971). On day 18 the effects of dexamethasone injection on the net transfer of labelled glucose from mother to foetus showed marked strain differences (Wong & Burton, 1971). SMV mice showed the greatest inhibition, A/J less and C57BL/6 the least.

**Other systems**

Dexamethasone retarded the learning of a passive avoidance by A mice but had no effect on the performance of DBA/2 mice (Levine & Levin, 1970). Armany (1966) described a pedigree in which ocular hypertension induced by the topical application of dexamethasone showed an autosomal co-dominant mode of inheritance. Genetic differences have also been found amongst mice in the role of corticosteroids in the induction of enzymes in the adrenal medulla (see below).
**ADRENAL MEDULLA**

The volume of the adrenal medulla, corrected for differences in body weight, differed between inbred strains of mice by almost a factor of two when A/Cam and CBA/FaCam mice were compared (Shire & Spickett, 1968a). This difference was due to variation in at least two loci (Shire, 1970). One of these loci may have been pleiotropically related to the locus controlling the volume of the cortex. Pituitary dwarf mice, which lack both growth hormone and prolactin, had disproportionately large medullae and unusual corticomedullary proportions when compared with their normal sibs (Shire & Hambly, 1973). Swinyard (1940) and Allbrook (1956) have shown considerable phenotypic variation in medullary volume in man. Part of this may have reflected genetic differences between individuals.

![Diagram](image)

**Fig. 1. Diagrammatic representation of the pathway of biosynthesis of catecholamine hormones.**

The stores of adrenaline and noradrenaline in the medulla differed significantly between inbred strains (Ciaranello et al. 1972a). The concentration of adrenaline was twice as high in DBA/2 mice as it was in C57BL/10 mice. Adrenal catecholamine stores were elevated in mice homozygous for the dilute-lethal (d^3) mutation in comparison with their normal litter-mates (Doolittle & Rauch, 1965).

The pathway by which the catecholamines are synthesized is outlined in Fig. 1. Strain differences, threefold in one case, in the resting levels of three of the enzymes involved have been found in mice (Ciaranello et al. 1972a; Kessler, Ciaranello, Shire & Barchas, 1972). Tyrosine hydroxylase and dopamine β-hydroxylase activities differed between rats with genetically determined spontaneous hypertension and normal Wistar rats (Nagatsu, Nagatsu, Mizutani, Umezawa, Matsuzaki & Takeuchi, 1971). Phenylethanolamine N-methyltransferase (PNMT) levels may also differ between strains of rats (Ciaranello & Black, 1971). A diallel analysis of three strains of mice and their reciprocal F1 hybrids showed the genetic contribution to the observed differences to be very significant (Kessler et al. 1972). Maternal and sex-linked effects were absent.

The activities of all three enzymes in BALB/c mice of the J sub-line were found to be about double those in mice of the N sub-line. When the enzymes were considered separately, differences at a single co-dominant locus were found in each case (Ciaranello & Axelrod, 1973; Ciaranello, Shire & Axelrod, 1974). For all three enzymes variation in structure was ruled out by biochemical investigations, leaving the possibilities of either three independent regulatory genes or a single locus which regulated the concentrations of all three enzymes. The apparent co-segregation of the
alleles for the three activities favours the two sub-lines differing at a single locus which co-ordinately controls three of the four enzymes concerned in catecholamine biosynthesis (Ciaranello et al. 1974). The locus appeared to affect the steady-state levels of the enzymes by controlling their rate of degradation rather than their rate of synthesis, at least in the case of PNMT (Ciaranello & Axelrod, 1973).

The concentration of phenylethanolamine N-methyltransferase can be induced to rise. In rats this induction is slow and can be brought about by corticosteroids or by stimulation of the splanchnic nerve (Wurtman & Axelrod, 1966). In mouse induction was rapid, and differed markedly between strains, the rate of increase of enzyme activity being tenfold greater in DBA/2 than in CBA/J or C57BL/Ka strains (Ciaranello, Dornbusch & Barchas, 1972b). In CBA mice only glucocorticoids induced PNMT activity while in DBA/2 mice the enzyme was under both glucocorticoid and neural control. In C57BL/Ka mice induction could only be brought about by ACTH or by exposure to cold. Exogenous glucocorticoids were without effect and the effect of cold was prevented by hypophysectomy. In these mice ACTH may regulate medullary metabolism. The half-lives of induced PNMT activity ranged from 1 h in DBA/2 to 7 h in CBA mice.

The genetic variation in medullary structure and metabolism suggests the existence of genetically determined variations in the output of catecholamines by the adrenal medulla. Nadler & Hsia (1961) have shown that untreated patients with phenylketonuria had markedly lower levels of adrenaline and noradrenaline in both plasma and urine than did control patients. Mice homozygous for the dilute-lethal gene had higher urinary concentrations of catecholamines than their phenotypically normal sibs (Doolittle & Rauch, 1965).

The target organs of the catecholamines are also affected by genetic variation. Twofold differences between inbred strains of mice have been described in the uptake, turnover and endogenous pool size of noradrenaline in cardiac tissue (Page, Kessler & Vesell, 1970). Vasoconstrictor responses to noradrenaline were greater in arteries from rats with genetically determined spontaneous hypertension than in arteries from normotensive controls (McGregor & Smirk, 1968). Whilst investigating eosinopenia in mice, Wragg & Speirs (1952) noted differences between strains in the dose of adrenaline needed to eliminate non-specific effects.

Genetic differences are also known which affect the metabolism of catecholamines in the central nervous system (e.g. Sudak & Maas, 1964; Ciaranello et al. 1972a; Hunt & Johnson, 1972; Schreiber & Schlesinger, 1972).

The chief genetically determined abnormality of the adrenal medulla is phaeochromocytoma, in which massive quantities of catecholamines may be released into the bloodstream. The tumour has been reported to occur frequently in DBA/2 × CE F1 mice (Chai & Dickie, 1966). In man its inheritance is usually dominant. The various syndromes in which phaeochromocytoma occurs are summarized in Table 4 and are reviewed by Knudson & Strong (1972) and Melvin, Tashjian & Miller (1973). The several tissues involved in these syndromes may all have a common origin in the neural crest. Differences have been described between the tyrosine hydroxylase from phaeochromocytoma and that from normal adrenal glands (Nagatsu, Mizutani, Sudo & Nagatsu, 1972). Neuroblastoma, which appears to be recessively inherited, also occurs in the adrenal medulla (Griffin & Bolande, 1969).
Table 4. Occurrence of phaeochromocytoma in inherited diseases in man

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Phaeochromocytoma</th>
<th>Inheritance</th>
<th>Other features</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phaeochromocytoma with thyroid carcinoma</td>
<td>Bilateral</td>
<td>Dominant</td>
<td>Medullary thyroid carcinoma, excess calcitonin</td>
<td>Paloyan, Scanu, Straus, Pickleman &amp; Paloyan (1970)</td>
</tr>
<tr>
<td>Neuromata with endocrine tumours</td>
<td>Bilateral</td>
<td>Dominant</td>
<td>Medullary thyroid carcinoma, mucosal neuromata</td>
<td>Gorlin, Sedano, Vickers &amp; Červenka (1968)</td>
</tr>
<tr>
<td>Isolated phaeochromocytoma</td>
<td>Often multiple</td>
<td>Dominant</td>
<td>Non-familial († non-genetic) cases frequent</td>
<td>Knudson &amp; Strong (1972)</td>
</tr>
<tr>
<td>von Hippel–Lindau disease</td>
<td>Occasional</td>
<td>Dominant</td>
<td>Retinal angiomata, hemangioblastoma of cerebellum</td>
<td>Wise &amp; Gibson (1971)</td>
</tr>
</tbody>
</table>
THE SIGNIFICANCE OF GENETIC VARIATION

Individual diseases that are genetically determined are usually rare, except in certain isolated human populations and in certain stocks of domestic animals. All such diseases taken together represent a significant 'genetic load' on human society. Carriers of such diseases are much commoner than affected individuals. Genetic counselling, particularly if screening tests for carriers can be devised, can lead to lower frequencies of affected individuals in future generations. Few pathological variants are known which affect adrenal function in rodents. These animals, however, show much genetic variation within the range of normality, particularly continuous variation, even though often only a few of the most popular inbred strains have been studied. Comparable variation has rarely been looked for in man and other large mammals, though suggestive reports exist, e.g. phenotypic variation in the fluctuation of aldosterone secretion during the menstrual cycle (Katz & Romfh, 1972).

In systems which have been widely studied, such as the blood proteins, widespread genetic variation has been found in natural populations of men and other organisms (Lewontin & Hubby, 1966; Harris, 1969). Different populations of the same species usually show differences in the frequencies of the various phenotypes, in part as a consequence of adaptation to differing environments. Natural populations differ from inbred laboratory stocks as animals heterozygous at some or many loci are present in large numbers. The heterozygous F₁ animals bred by crossing inbred strains also differ from natural populations, for they are all identical whilst in natural populations only monozygotic litter-mates are identical. In an inbred strain a balanced physiology can be maintained even when the co-adapted genes, controlling for example the rates of production and degradation of steroids, are on different chromosomes. In natural populations co-adapted complexes are more likely to survive if the genes are linked on the same chromosome. The existence of balanced genotypes, and of several loci with apparently identical phenotypes (e.g. ald-1 and ald-2), provide for cryptic genetic variation. Unusual phenotypes may occur, through recombination, at low frequency, and be selected for when environmental conditions change (Thoday, 1953). Alternatively, cryptic variation in one environment may become overt phenotypic variation if the environment changes, e.g. by colonization of a new area, or by the introduction of a new drug.

USES AND ABUSES OF GENETIC VARIATION

The existence of genetic variation is sometimes blatantly ignored. In one publication commercially hypophysectomized rats of one strain were compared with intact controls of a different strain, and in another paper biosynthesis by adrenal neoplasms from one strain of mice was compared with control data from an unrelated strain. In both cases all the observed differences were attributed to hypophysectomy or to neoplasia. The neglect of genetic variation can also lead to other problems. An inbred strain may be chosen to minimize the effects of genetic variation in one type of experiment, and then the results generalized to apply to the rat, in all its laboratory strains and wild populations. Choice of different strains in different laboratories can lead to differing results, as in a study on the role of DOC in hypertension (Brown, Gaunt, Gisoldi & Smith, 1972), and hence to controversy. Similar problems can arise when
different lines of ‘Swiss albino’ mice or ‘Wistar’ rats have been used. Even with recognized inbred strains there may be important differences between sub-lines (q.v. medullary enzymes). Consistent differences (e.g. in intestinal serotonin, Thompson, 1967) have also been reported between rats of the same strain from different breeding sheds of a large commercial supplier.

The existence of genetic variation can be used to advantage in endocrinological experiments. The discovery of the forms that it takes may, of itself, be useful. For example, the widely differing inducers of phenylethanolamine N-methyltransferase found in different strains advanced ideas about the regulation of this enzyme activity in mice. The discovery of apparently identical phenotypes caused by different geno-loci (e.g. ald-1 and ald-2; dw and df) implies the existence of multiple steps in a seemingly unitary phenomenon. When a genetic difference has been found, its consequences for systems can be predicted. As those pleiotropic effects of the gene are found they can be used to build up a ‘pedigree of causes’ (Grüneberg, 1938). This starts with the chemical differences in DNA and protein and ends with the ultimate phenotypic manifestations of the gene. Such investigations can indicate unsuspected or unconfirmed interrelationships between endocrine systems. Knowledge of the pedigree of causes of pathological variants improves the chances of successful therapy, whose aim is to produce a phenocopy of a normal individual. Conversely, phenocopies of known mutations may result from environmental damage to developing individuals with normal, but susceptible, genotypes.

The combination of genetic variables with surgical and pharmacological manipulations has much to offer to experimental endocrinologists (Thoday, 1967). The controlled exploitation of such genotype–environment interaction underlies many of the experiments of molecular biology. The choice of genotypes for bioassays and for experimental material should be a deliberate one. Many animal models of human diseases exist. Insensitivity to a particular hormone may be a desired feature, and suitable variants are already known for some hormones (e.g. testosterone, Tf; Lyon & Hawkes, 1970). Alternatively, animals with maximum responsiveness may be required for a bioassay. These could come from selection experiments, or be chosen from a range of inbred strains. Where uniformity and repeatability are important, F1 hybrids with low phenotypic variance, produced by crossing a pair of carefully chosen strains, might be most useful. It is also possible to produce lines selected concurrently for several different characters (Thoday, 1967).

Genetic analysis can help to answer questions about causal relationships. Several symptoms are often recorded in association with each other. Do they form part of a unitary syndrome or are they associated solely by chance? This basic question can take several forms. A pair of inbred strains differ in two endocrine metrics; chance or pleiotropy? Are all the measured correlated responses to selection in a line selected for high blood pressure causally related to hypertension? Are the differences between two forms of a disease (e.g. defects in steroid 21-hydroxylation) due to differences in genetic background, or to independent mutations at the same or different loci? In experimental animals several methods can be used to answer this kind of question. The extension of the investigation to an additional strain may be useful, and has shown that the apparent correlation between brown degeneration of the adrenals and mammary cancer in mice was due to chance (Chester Jones, 1948). Crossing strains
or selected lines may produce reciprocal F₁ mice in which the original correlations no longer hold because the different genes have different dominance relations or linkages. If the correlation holds for F₁ hybrids it is important to breed segregating hybrid generations such as the F₂ and backcrosses. If the original correlation breaks down then two or more separable factors are involved. If the correlation still holds both characters are affected by the same gene, or by a pair of closely linked genes. The number of animals measured will determine how close two genes would have to be to account for the data. The breeding of segregating hybrid generations is particularly important when two inbred strains, one homozygous for a known variant, are compared. By such means the lipid depletion and leukaemia present in AKR mice have been shown to be causally unrelated (Arnesen, 1964). The AC and C57BL strains also differed at the ald-1 locus, and in the incorporation of [³H]uridine into, and in the level of glucose-6-phosphate-dehydrogenase activity in, the cortex (Molne, 1969b; Molne, Borrebaek & Walaas, 1969). Until F₃ or backcross mice have been studied it will not be known whether these associations were due to pleiotropy or to chance. Segregating generations also have the advantage of being closer than inbred strains to the genetic architecture of natural populations. In mice genetic analysis need no longer be restricted to characters which can be measured in individual animals. The development of clans of ‘recombinant-inbred’ strains allows characters to be investigated whose measurement requires pooling of tissue or data from several animals (Eleftheriou & Bailey, 1972). Genetic analysis in man follows fundamentally the same methods as those outlined above, except that the crosses are, perforce, uncontrolled.

Implications of genetic variation

Investigation of genetic variation within normality may enable the basis of some ‘constitutional’ differences in susceptibility to disease and in responsiveness to treatment to be understood, and individuals at risk to be identified. In addition to certain cancers, such diseases could include forms of hypertension, ulcers and inflammatory disease in which adrenal hormones are involved. The existence of genetic variation is important for pharmacologists, for the effectiveness of certain drugs may be very different in individuals of different genotypes. The same steroid may be safe in some people but have marked side-effects, such as ocular or vascular hypertension, in others. Similarly the introduction of a new therapy may differentiate dramatically, for better or for worse, between previously indistinguishable phenotypes.

As well as individuals with marked predisposition to endocrine disease there may well be people with particularly resistant genotypes and ‘better-than-average’ constitutions. Genetic variation in psychoendocrine aspects of adrenal function will be important but has been little studied (but see Hamburg & Kessler, 1967). In this context the reports of differences in learning behaviour in response to exogenous steroids (Levine & Levin, 1970) and the possible elevation of I.Q. in 21-hydroxylase deficiency (Lewis et al. 1968) are significant. Social factors and social change could greatly affect the incidence of overt stress-related disease in genetically polymorphic populations, whether of men or of rodents.
Endocrine genetics of adrenal gland

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Guinea-pigs.

Plasms.

Depletion.

Ganglioneurofibroma.

Suppressible dependent

Turcica.

Mice.

E.

H.

O.

R.

F.

B.

C.

J.

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**NOTE ADDED IN PROOF**