GENETICS AND DERMATOLOGY
OR
IF I WERE TO REWRITE COCKAYNE'S *INHERITED ABNORMALITIES OF THE SKIN*[*]

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INTRODUCTION

At the outset I hasten to state for the benefit of all, especially representatives of publishing houses, that I have no intention of revising Cockayne's monograph, *Inherited Abnormalities of the Skin and Its Appendages* (1933). I do suggest that thinking about how one would organize a revision and what new concepts and information are now available is a useful way to approach the relationship between genetics and dermatology. (I use *dermatology* in the broadest etymologic sense as synonymous with the designation of this distinguished series of conferences, *The Biology of Skin*.)

Cockayne (1933, p. v) said he wrote his book for two purposes: (1) to inform dermatologists of genetics and to stimulate them to make more detailed family studies; (2) to inform geneticists of the opportunities for useful study afforded by skin disorders. These are indeed the two sides of the coin: the contribution of genetics to cutaneous biology, the contribution of cutaneous biology to genetics.

The approach we shall follow is basically historical: What was the state of genetics in dermatology in 1933 and how has it progressed in the last 38 years?

Edward Alfred Cockayne (1880–1956) (Fig. 1) was a physician who concentrated on diseases of children, particularly hereditary diseases. By avocation he was a respected entomologist and president of the Royal Entomological Society of London (1943–1945). A bachelor, Cockayne presumably had much time for the library work required to prepare his 1933 monograph, over 90 percent of which is a collation of pedigrees from the literature. He is said to have had many acquaintances and admirers but no close friends. Cockayne's name is eponymically immortalized in the Cockayne syndrome, an autosomal recessive disorder with dwarfism, photosensitivity, retinitis pigmentosa, deafness, and mental retardation as features, and in the Weber–Cockayne recurrent bullous eruption of the feet, a form of epidermolysis bullosa. He also wrote on the genetics of situs inversus viscerum (1938) and of the Laurence–Moon–Biedl syndrome (1935, Sorsby et al.,

1939) and described the Marfan (1935) and the Hunter syndrome (1936). Among the publications that seemed to have influenced him most was the *Mechanism of Mendelian Heredity* by Morgan, Sturtevant, Muller, and Bridges (1933). He also quoted from Baur, Fischer, and Lenz (1931).

Cockayne was educated at Charterhouse and at Balliol College, Oxford, taking "first-class honors" in the Natural Science School in 1903 and earning his B.M., B.Ch. in 1907, M.C.R.P. in 1909, D.M. in 1912, and F.R.C.P. in 1916. His entomologic work was genetic in nature. Prof. E. B. Ford in his *Ecological Genetics* (1964) described one of Cockayne's early contributions to entomology:

> Cockayne (1912–13) has suggested, no doubt correctly, that the two British races of the moth Bupalus pinarius, Selidosemidae, evolved in isolation during the last Ice Age. One of these belongs to the small Scandinavian form in which the pale areas of the male are white and the very distinct female is brownish. This is found throughout Scotland and northern England. The other, inhabiting central and southern England, is of the west European type, similar to that occurring in France and Germany. It is larger, the pale areas of the male are ochreous and the female has an orange tint. The two races meet about the latitude of Cheshire and Shropshire where they give rise to a belt of hybridization with considerable variability. This, however, is relatively narrow and in spite of it the populations remain distinct. It is probable therefore that *B. pinarius* is an interglacial relic in the north and a Holocene invader in the south, and that the two forms met at their present interface after the retreat of the ice. Their genetics are unfortunately unknown though the differences between them seem clearly polygenic.

Ford also cited some of Cockayne's unpublished findings of moth-collecting expeditions. Professor Ford writes me as follows:

> His knowledge of Lepidoptera in Great Britain was profound in the extreme. . . . He did a vast amount of genetic breeding-work and amassed a genetic collection of his bred material. This was of the most remarkable type which ought to but has not transformed

FIG. 1. Edward Alfred Cockayne (1880–1956).

entomological collections. That is to say, one would open the drawers of his cabinets and find the different broods of his bred material, and with them in the drawer the references to all relevant literature on the subject of the particular genetic quality which he was investigating. This collection, combined with appropriate material amassed by the second Lord Rothschild and with that amassed by Dr. Kettlewell, is in the Museum at Tring.

Cockayne (1933, p. 2) quoted some of his own entomologic work (published in 1928) to illustrate intermediate inheritance: "... if the two genes both produce an equal effect the children will be intermediate between the parents in respect of the character produced. An example ... is found in the scarlet tiger moth, *Callimorpha dominula*, in which the typical form has many white spots on the fore-wings and a broken black band on the bird-wings. Here the heterozygote lacks the central spot of the fore-wing, the others are much reduced in size, and the bands on the hind-wings are intermediate."

Cockayne began his preface as follows: "So far as I am aware, no attempt has been made to deal with the genetics of all the defects of any one part of the body in a single book." Since then, many have followed in Cockayne's footsteps, notably Butterworth and Gottron and Schnyder in the field of dermatology.[‡] After a chapter on the principles of genetics, Cockayne discussed the genetics of skin diseases. He showed many pedigrees but only *two* illustrations: the frontispiece, which is a picture of a girl with universal hypertrichosis, and an illustration (p. 183) of John Lambert, whose disorder (ichthyosis hystrix gravios) was thought to be X-linked until the report of Penrose and Stern (1958).

In assembling pedigrees from the literature, Cockayne was following the practice of several of

his countrymen including Adams (1756–1818) and Sedgwick in the preceding century; Edward Nettleship (1845–1913) and Charles Howard Usher (1865–1942), ophthalmologists, earlier in this century; and Julia Bell who came later. Furthermore he used the astrologic symbols of sex like other English geneticists rather than the squares and circles preferred on the continent and in this country. Frequent errors in page and volume numbers occur throughout the numerous references. Sometimes he cited an author, such as Siemens or Naegeli, without giving a specific reference. Cockayne may have presumed that such standard works were familiar to his readers but forgot that such omissions are disastrous for future generations and annoying even for Cockayne's contemporaries. His subject index seems adequate, but I would have liked an author index as well.

PRINCIPLES OF GENETICS

In any analysis of the role of genetic factors in the disorders of a particular organ system such as the skin, specific entities tend to fall into one of three categories according to the nature of the genetic determination: (1) chromosomal, (2) monogenic, and (3) multifactorial (or polygenic).

The chromosomal aberrations that have been recognized since 1959 are rather gross derangements which lead, in the case of autosomal chromosomes, to abnormalities in multiple organ systems. Most of these aberrations are not inherited in the usual sense; but since they involve the genetic material, they are one category of genetic disease.

Disorders are recognized as being determined primarily by a single locus (monogenic) by the fact that the laws of Mendel are satisfied in families. Data on the population distribution of the trait and its biochemistry are used to support the conclusion. Individual mendelian disorders are rare but, as we shall see later, there are so many of them that the aggregate represents a significant category of disease.

Many normal traits and common disorders, which fall into a multifactorial category, are determined by the collaboration of multiple genetic and exogenous factors, e.g., skin color and probably acne vulgaris, atopic eczema, and many others.

I will now discuss the understanding of these three areas as they are reflected in Cockayne's writings and the progress made since 1933.

The Chromosomes

Human chromosomes in mitosis were first pictured in 1882 by Walther Flemming (1843–1915), Professor of Anatomy at Kiel, who studied tumor cells. He introduced the terms *mitosis* (from Gk. "thread") and *chromatin* (from Gk. "color"), and Waldeyer first used the term *chromosome* in 1888 (Singer, 1949). Considerable advance in the un-

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[‡] Actually Waardenburg wrote a comprehensive treatise on genetic disorders of the eye in 1932.

derstanding of the behavior of the chromosomes in mitosis and meiosis had been made by 1896 when Edmund Beecher Wilson (1856-1939) published the first edition of his classic, *The Cell in Development and Inheritance*. The chromosomes were first proposed to be the bearers of genetic information independently by Sutton in this country and by Theodor Boveri (1862-1915) in Germany.

Walter Stanborough Sutton (1877-1916) was a Kansas farmboy. As a student at Kansas University, Sutton studied meiosis in the Kansas grasshopper under the direction of McClung. (It was not called meiosis because the term was not introduced until 1905. This word comes from the same root as the word *miosis*, reduction in the size of the pupil. It is fortunate that distinctive spellings have developed. *Meiosis* is also used in rhetoric for an understatement, the opposite of hyperbole.) Going to New York in the fall of 1901 to work with E. B. Wilson, Sutton was exposed to the new Mendelian theory through William Bateson's book, *Mendel's Principles of Heredity* (1902), and through a visit by Bateson to America in the same year. Sutton recognized the parallel behavior of Mendel's factors and of the chromosomes in meiosis. In an elegant paper (reprinted by Peters, 1959), he expounded the chromosome theory of inheritance (1903). Despite these auspicious early findings, Sutton did not complete his Ph.D. degree. Instead he went to the College of Physicians and Surgeons of Columbia University, graduating in 1907, trained in surgery at the Roosevelt Hospital in New York City, and practiced surgery in Kansas City until his untimely death from a ruptured appendix in 1916.

The chromosomal theory was quickly and almost universally accepted. The work of Bridges (1916), correlating anomalous X chromosomes with the anomalous transmission of X-linked genetic traits, helped to establish the theory. Bateson was one of the few long-time holdouts. The excitement of the first 12 years of this century, when Mendelism and its chromosomal explanation and the understanding of chromosome mapping through linkage came along, has been repeated during the past 12 years or so with similar excitement about the X chromosome and the Lyon hypothesis. Once again, a devil's advocate arose; this time Grüneberg (1967) held out against the new theory. Since 1953 molecular genetics has passed through an extraordinarily exciting period.

Cockayne (1933, p. 28) stated: "All recent workers are agreed that in the white, yellow, and black races of mankind there are 48 chromosomes in the somatic cells of the female, 46 autosomes forming 23 pairs and 2 sex chromosomes forming 1 pair, the X-chromosomes. von Winiwarter and Oguma think that the somatic number in the male is 47. . . . Painter, however, claims to have seen a small Y-chromosome, and thinks there are 46 autosomes in both sexes and a pair of sex-chromosomes, XX in the female, and XY in the male." The mistaken count of 48 chromosomes, made on the basis of meiotic studies, was due to the fact that precocious separation of the X and Y bivalent occurred; each was counted as a separate bivalent making 24 in all. Painter of the University of Texas pointed out in his 1923 paper that in some of his technically best preparations 23 bivalents were seen. Ferguson-Smith (1971) has recently suggested that the count of 47 in males may have resulted from the wide separation of the two portions of chromosome 9 on the two sides of a prominent secondary constriction on the long arm. Even after Tjio and Levan (1956) and Hamerton and Ford (1956), working on mitotic and meiotic material respectively, discovered the correct chromosome number, one worker (Kodani, 1957) still claimed that various numbers—46, 47, and 48—were found in man and represented a polymorphism.

That abnormalities in the number and structure of chromosomes are the basis of congenital defects (i.e., as one major category of genetic disease) was not mentioned by Cockayne, probably because in 1933 such defects had not been diagnosed in mammals. Blakeslee (1923) had analyzed the phenotypic effects of trisomy in each of the chromosomes of Oenothera. Not until 1934, however, were malformations in mammals linked to chromosomal abnormalities by Snell and his colleagues (1934), who worked in the mouse on radiation induced translocations (which were assumed on genetic grounds but not cytologically proved).

In the 1930s, several physicians speculated about the possibility of trisomy as the "cause" of mongolism. The earliest and clearest of these references were those of Waardenburg (1932) and Bleyer (1934). As Penrose (1961) pointed out, in 1932 P. J. Waardenberg, formerly of Arnhem, now of Oosterbeek, The Netherlands, had predicted a chromosomal aberration, and possibly a nondisjunction, in Down's syndrome. He wrote in *Das menschliche Auge und seine Erbanlagen* (p. 47) as follows (in translation):

I should like to suggest that cytologists investigate whether, in this specific case, it is not possible that there occurs in man an example of a chromosomal aberration. Why should this not also apply to human beings; and why should it then not be possible that, when this chromosomal aberration has no lethal effect, it should cause a remarkable anomaly of the constitution? Investigations should be undertaken to find out whether in mongolism we are perhaps dealing with "chromosomal deficiency" by "non-disjunction" or on the contrary, with a "chromosomal duplication."

In 1934, Adrien Bleyer (1878-1964), a St. Louis

pediatrician and long a student of Down's syndrome, independently suggested nondisjunction, writing as follows (reprinted by Montagu, 1961):

> It is thus probable that the problem of Mongolism may belong to the cytologist rather than to the common-clay clinician. . . . There may be an unequal migration of the chromosomes to the poles of the germ cell during the reduction period which will result in a cell progeny having a number of chromosomes unlike the number present in the parent. An example of this occurs in the evening primrose, *Enothera lamarkiana*. . . . The human cell is a forty-eight chromosome cell. Whether in the mongoloid imbecile one is dealing with forty-nine or forty-seven, with fifty or forty-six or with some other number of chromosomes must be left to the cytologist, in whose field the richest prizes in genetics now seem to lie.

Bleyer based his surmise on the multiplicity and generality of manifestations in Down's syndrome and the fact that to his knowledge all dizygotic twins were discordant and all monozygotic twins concordant.

Montagu (1961) called it "brilliant speculation." Bleyer (personal communication, 1961) considered it as merely a triumph of the clinical method, i.e., deductions drawn from close clinical study. Fifty or more other theories of mongolism, also based presumably on clinical observations and now proved to be erroneous, seem in many cases ludicrous. In practically all great medical discoveries, previous predictions or partial findings mark the progress toward definitive discovery. Pointing them out is often only a matter of interest and an illustration of the old axiom that "there is nothing new under the sun." Few of these earlier publications on Down's syndrome influenced the thinking at the time or played any role in the final discovery. One wonders if the "cause" of mongolism would have been discovered in the 1930s if the suggestions of Waardenberg, Bleyer, and others had been followed. Probably not, because the necessary techniques were not then known. In fact, as late as 1953 Mittwoch failed to demonstrate aneuploidy in a case of Down's syndrome.

The use of hypotonic solutions to spread the chromosomes, of colchicine to arrest dividing cells in metaphase, and of phytohemagglutinin to stimulate mitosis made possible the remarkable advances of the last 15 years. I would pay tribute to Dr. Edwin E. Osgood (1899–1970) of the University of Oregon who introduced phytohemagglutinin to separate white and red cells and thereby prepared the way for the discovery of its mitogenic effects by Nowell (1960). New techniques such as fluorochrome or Giemsa staining will, we hope, lead to equally important advances in the next 15 years. The new techniques should

enable us to detect the chromosomal basis of disorders now labeled "unknown etiopathogenesis." I am thinking, for example, of the Rubinstein syndrome, the Cornelia de Lange syndrome, Albright's polyostotic fibrous dysplasia, Ollier's enchondromatosis, and other distinctive congenital entities in which no chromosomal, Mendelian, or exogenous causation has thus far been detected. Tiny chromosome defects may be found even in some disorders that display a Mendelian pedigree pattern, e.g., some recessives or dominants with a complex phenotype that are private mutations, limited to only a single kindred.

Single Gene Mutations

Most of Cockayne's book is devoted to Mendelian disorders; his exposition of Mendelism is, I think, adequate. Some types of inheritance he discusses are today considered unlikely; for example, hologynic inheritance, Y-linked inheritance, and determination by two dominant genes ("double dominants" in his terminology, "double heterozygosity" in ours).

Cockayne (1933, p. 43) made the interesting observations that known recessives are relatively few in man compared with known dominants. In his table, the numbers in man are limited to dermatologic traits:

	Recessive	Dominant	Ratio
Drosophila	86	25	3.4 : 1
Man	20	80	1 : 4

Cockayne favored the view that this find was "due to the existence of many recessive characters of a pathological nature in man, some of which may be known but are not yet recognized as inherited abnormalities" and pointed out that this view is supported by the fact that in man X-linked recessives predominate over X-linked dominants.

Below is a count on autosomal traits considered confirmed in the latest edition of my *Mendelian Inheritance in Man* (1971), together with a similar count for the mouse assembled in 1967 by Dr. Margaret C. Green of the Jackson Laboratory.

	Recessive	Dominant	Ratio
Mouse	207	99	2.1 : 1
Man	365	415	1 : 1.1

Thus, the relative deficiency of recessives, though decreased, is still present.§ Since 1959, the number of known recessives has increased faster than

§ Another indication that many autosomal recessives remain to be described is the comparison of the X-linked recessives (about 75) and the number of autosomal recessives (about 365). Since the X chromosome is 6 percent as long as the total haploid autosome set, there should be about 1250 autosomal recessives.

TABLE I

Relative incidence of genetic disease

	Ver-schuer (1958)	McKusick's Mendelian Inheritance in Man		
		(1966)	(1968)	(1971)
Autosomal Dominant	285	269 (+568)	344 (+449)	415 (+528)
Autosomal Recessive	89	237 (+294)	280 (+349)	365 (+418)
X-Linked	38	68 (+51)	68 (+55)	86 (+64)
Totals	412	574 (+913) 1,487	692 (+853) 1,545	866 (+1010) 1,876

The numbers in parentheses refer to entries for which the mode of inheritance or the separateness from another entry is not considered proved.

the number of known dominants (Table 1), largely because of the burgeoning of biochemical genetics with its description of new inborn errors of metabolism. When an enzyme deficiency is demonstrated, a single case suffices to establish recessive inheritance if the parents are close relatives and if they both show an intermediate level of the relevant enzyme. In the case of the very rare disorder oroticaciduria, these criteria permitted confidence in the recessive mode of inheritance after only one patient had been observed (Fallon et al., 1964). Another approach which has contributed to the count of recessives is the study of inbred groups such as the Amish, in whom a dozen or more new recessives have been found. Judging from the findings in drosophila and in the mouse, most visible mutations, that is, those which produce changes in the phenotype that are detectable without special techniques, are recessive. In man, a recessive mutation can occur and never meet up with itself in a future generation, having been lost either by chance or because of detrimental effects even in the heterozygote. Inbreeding, as in drosophila and the mouse, is likely to bring the recessive gene more quickly to attention through the occurrence of homozygotes. In a minor way, inbred groups mimic the situation in the experimental species.

Furthermore, even if the gene does occur in the homozygous state in man, the disorder it produces may not be recognized as a distinct entity because it is a sporadic case. With small families the chances are excellent that only one affected child will be produced by parents both heterozygous for a recessive gene. Only in families of 6 or more children is there a better than 50% chance that more than one child will be affected. The large families usually found in inbred groups are an advantage in the detection of recessives. Finally, the "groupness" per se, i.e., the sociologic distinctness, increases the visibility of recessives. When even two distantly related cases of an unusual syndrome occur in members of an un-

usual group such as the Amish, recessive inheritance (McKusick et al., 1968) is suspected. Thalassemia major, which has been widely prevalent in the Mediterranean basin for centuries and probably millenia, was first clearly delineated, not in Rome, Athens, Padua, or Salerno, but in Detroit, Michigan, largely because of the ethnic distinctness of the minority group affected by the disorder. Among the recessive disorders that have been recognized by the inbreeding, large family size, and sociologic distinctness of the Amish are cartilage-hair hypoplasia (McKusick, 1965) and Cross's hypopigmentation–ocular–mental retardation syndrome (1967).

It is clear that unlike two other physicians, Cockayne was no mathematician. Apert introduced a method of correcting for bias of ascertainment in 1912, and Weinberg was a major contributor to the statistical basis of genetics, notably as codiscoverer of the Hardy–Weinberg Law. Cockayne (1933, p. 4), who appears to have understood the bias of ascertainment, stated that "Hogben gives one method of calculating the correction for this error and Haldane gives another." However, Cockayne used neither method to analyze the pedigree data he had collected on various disorders, and he frequently expressed dismay that the proportion of affected sibs was so much in excess of one-quarter (e.g., pseudoxanthoma elasticum).

As examples of X-linked recessive inheritance Cockayne cited one form of ichthyosis and anhidrotic ectodermal dysplasia; as an example of X-linked dominant inheritance, keratosis follicularis spinulosa cum ophiasi.

Although Cockayne considered sex influence, he did not discuss the difficulties of distinguishing X-linked recessive from male-limited autosomal dominant inheritance. Formally speaking, this is a problem in any condition—e.g., Duchenne muscular dystrophy or the Lesch–Nyhan syndrome —in which affected males do not reproduce; but the only conditions where the second alternative is plausible are those such as the testicular feminization syndrome. The defect, which consists of end-organ unresponsiveness to androgen, was first demonstrated by observations on the integument by my late senior colleague, Lawson Wilkins. He showed that affected persons, whose external genitalia and breast development are female but whose karyotype is that of a normal male, do not respond like normal females to the local application of androgen by the growth of sex hair. Testicular feminization is X-linked in the mouse and therefore in man since the X chromosome shows striking species-to-species homology. X-linked inheritance can be proved in several other ways (McKusick, 1964). If X-linked, one-third of the cases should be new mutants; if autosomal dominant, one-half should be new mutants. Another method is to observe the integument in heterozygous females. If the defect is X-linked and cell-limited, the Lyon phenomenon can be

observed; for example, patchy development of pubic and axillary hair and asymmetry of breast development in the testicular feminization syndrome. Some observations of this sort have been reported (Gayral et al., 1960). An in vitro study of the effects of androgen on hair bulbs might determine whether lyonization occurs.

One form of inheritance not recognized by Cockayne is X-linked dominant with lethality in the hemizygous male. To my knowledge, the first description in man‖ was by Widukind Lenz (1961) and concerned incontinentia pigmenti. Focal dermal hypoplasia (FDH) and type I orofaciodigital (OFD) syndrome also fall into this category. Only females are affected. An affected female transmits the disease to half her daughters. Her pregnancies produce a deficiency of males but an excess of abortions because of the loss of affected male fetuses. If a male has one of these conditions, the Klinefelter syndrome should be suspected and has been demonstrated for OFD (Wahrman et al., 1966). That the features of incontinentia pigmenti, focal dermal hypoplasia and perhaps of the OFD syndrome are spotty suggests that the Lyon phenomenon (*vide infra*) is operating.

Multifactorial Characters

Cockayne (1933, p. 44) rightly implicated polygenic inheritance as the basis of "normal" variations in the skin, particularly skin color. He made no attempt to evaluate pathologic characters on a multifactorial basis, however. His understanding of multifactorial inheritance was certainly much deeper than that of Karl Pearson (1857–1936) who in 1911 wrote as follows about albinism: "As we have seen in the course of this work albinism is a graded character, and we have every reason to believe that both in man and dogs separate grades are hereditary. . . . Mendelism is at present the mode—no other conception of heredity can even obtain a hearing. Yet one of the present writers at least believes that a reaction will shortly set in, and that the views of Galton will again come by their own."

Thus, Pearson was displaying his ardent antagonism to Bateson and Mendelism and his support for the inheritance theory of his predecessor, Francis Galton (1822–1911). (Pearson was likewise not influence by Garrod, who included albinism among the charter inborn errors of metabolism. In the same monograph on albinism, Pearson wrote: ". . . the ultimate difference between the normally pigmented individual and the albino will be found after all to be one of structure. It is easier to grasp the influence of a difference of genetic constitution on structure than on chemical process.")

In the first two decades of this century the controversy between the biometrics school represented by Pearson, Weldon, and others and the Mendelian school, led by Bateson, was vigorous. By 1933, however, the work of Nilsson-Ehle in Sweden, who used wheat, and of East in the United States, who used maize, had demonstrated the role of multiple genes in quantitative traits. Moreover, Davenport (1913) had collected data on skin color in racial hybrids, and R. A. Fisher (1890–1962) had published (1918) his classic paper showing that the blending inheritance of the biometricians is what one would expect if multiple genes, each behaving in a Mendelian manner, are involved. (Incidentally, his paper was turned down by *Biometrics* and other English journals controlled by the power structure. It was published in the *Journal of the Royal Society of Edinburgh*, but only after Fisher had paid 60 pounds in publishing costs, a stiff page charge even in today's currency. In this famous paper, Fisher introduced the term *variance*.)

Since 1933, the theories of multifactorial inheritance were applied to disease by Fraser Roberts and his colleagues. Roberts advised Pickering, who interpreted essential hypertension as the upper end of a continuous, multiple factor-determined distribution of blood pressure. This was one side of the Platt–Pickering controversy; the other was Platt's insistence on single-factor inheritance (McKusick 1960). Roberts's student, Cedric O. Carter (1969), has been a leader in applying a multifactorial hypothesis, with the additional feature of threshold, to common malformations.

The conclusion that multiple genes are involved in the causation of a particular trait should not discourage the search for individual genes and the biochemical characterization of their action. In man it is difficult to determine how many genes are involved in a given character. Analyzing the Herskovits data (1930) on skin color, Stern (1953, 1970) concluded that as few as 4, 5, or 6 loci are involved. Ainsworth Harrison also addresses himself to this problem in this issue. Studies of hypertensive rats, I am told, indicate that as few as three loci have the most effect on blood pressure level. Genetic heterogeneity must also be kept in mind. Some single genes are capable, largely alone, of producing a phenotype which more often than not is multifactorial. Thus, in rare cases, hypertension is due to pheochromocytomas inherited as simple autosomal dominant, and cleft lip and palate occur as an expression of a single dominant gene in the lip-pits syndrome.

BIOCHEMICAL GENETICS: THE PHYSICAL NATURE OF THE GENE AND THE MECHANISMS OF GENE ACTION

Cockayne's treatise is concerned almost exclusively with the transmission type of Mendelian genetics; biochemical genetics is notable by its absence. In part this reflects the embryonic state of the field in 1933, but surprisingly Cockayne

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‖ Notch in drosophila has this mode of inheritance (Hadorn, 1961, p. 147). The heterozygous female has notched wings but the hemizygous male and homozygous female do not survive beyond the embryonic or early larval stage.

made no mention of the work of his distinguished colleague Garrod# in relation to albinism, one of the four disorders discussed in the famous Croonian lecture (1908). Neither does he mention Garrod's theory of a block at one step in a series of metabolic reactions as a result of mutation-determined enzyme deficiency; and alkaptonuria, which certainly has cutaneous manifestations, was not mentioned although Cockayne described several extremely rare conditions whose inclusion is of doubtful value. Probably he was neither a chemist nor a mathematician.

Biochemical genetics has two somewhat arbitarily separated parts: (1) The chemistry of heredity means the physical nature of genes and the mechanisms by which the genetic message is read out and translated into a protein product. This brand of biochemical genetics is what is usually meant by the term *molecular genetics*. (2) The mechanism of gene action, particularly that whereby the mutant gene produces the abnormal phenotype, is what is meant by the term *physiological genetics*. This second variety includes immunogenetics and developmental genetics; the skin, of course, plays a central role in the former.

The Nature of the Gene

Cockayne (1933, p. 34) wrote: "The nature of the gene is a mystery and [is] likely to remain so, but in all probability it is a material body, and a mutation in a gene may be a change in its chemical constitution or physical state." Four years earlier Griffiths had demonstrated the phenomenon later termed *transformation*. In 1944, Avery, McLeod, and McCarty reported extensions of Griffith's work that strongly indicated that the gene is DNA; 20 years later, Watson and Crick (1953) discovered the structure of DNA; and 30 years later, the genetic code was well on the way to being deciphered by Nirenberg, Khorana, and others who did imaginative experiments with simple synthetic genes in cell-free systems. Cockayne showed little faith in the potentialities of science. His statement is internally inconsistent. If the gene is a material body subject to chemical or physical change in the process of mutation, why should its nature remain a mystery? Cockayne was displaying vitalism which, until rather recently, has been a prevalent view among biologists.

Herman J. Muller in 1921 had been much more insightful. In a paper on "variation due to change in the individual gene," he drew a parallel between the genes and d'Herelle bodies (bacteriophages) in "the most remarkable property of hereditary variation or mutability." He predicted

Cockayne was a junior colleague of Archibald Garrod. (1858–1936) at St. Bartholomew's Hospital and at the Great Ormond Street Hospital. Garrod left London in 1922 to become Osler's successor as Regius Professor of Medicine at Oxford. Little evidence of Garrod's influence is found in others of his contemporaries (Childs, 1970).

by implication how phages were to contribute to our understanding of the nature of the gene when he wrote: "We may be able to grind genes in a mortar and cook them in a beaker after all. Must we geneticists become bacteriologists, physiological chemists and physicists, simultaneously with being zoologists and botanists? Let us hope so!" A prominent zoologist, who chaired the session in which Muller had delivered the paper, reportedly remarked at the conclusion: "It's good to see you have a sense of humor, Muller."

The Nature of Mutation-Determined Abnormality

Before 1960, the trinitarian dogma of molecular genetics—the DNA–RNA–amino acid sequence of protein—was generally accepted. Some genes of special nature serve a regulatory function which at this point is not well understood in mammals. Better understood are the structural genes, so-called because they determine the primary structure, i.e. the amino acid sequence, of proteins. The gene-determined protein—or better, the polypeptide chain because one protein molecule can be formed from two or more distinct polypeptides each under separate genetic control—may be an enzyme. Mutation in the gene can lead either to a failure of the enzyme to be synthesized (eniotypy) or to the synthesis of a warped and functionally defective enzyme (allotypy) (Cinader et al., 1966). In either case, enzymatic deficiency can lead to an inborn error of metabolism. Since most enzyme systems have a confortable margin of safety, heterozygosity for the mutant gene is unlikely to have major effects on the phenotype. Only the homozygote shows abnormality. Thus, almost completely without exception, Garrodian inborn errors of metabolism are inherited as recessives.

In other cases, e.g., hemoglobin or a structural protein such as collagen, the gene-determined protein is nonenzymic. In such cases, as a result of changes in the physical properties of the protein, heterozygotes may show phenotypic abnormality even though only about half of the protein is of the mutant type. This is why we suspect a change in the amino acid sequence of collagen or an elastic fiber protein in some of the dominantly inherited disorders of connective tissue such as one or more of the Ehlers–Danlos syndromes. The dominant abnormalities of hair, such as monilethrix, might be expected to have amino acid substitutions in keratin. Indeed, in Clouston's ectodermal dysplasia, a structural defect of keratin may be present (Gold and Scriver, 1971).

Applied Cell Biology

In the last decade or so, a major technical advance in medical genetics that could not have been predicted by Cockayne and in which the skin has played an important role, has been the application of the cell-culture technique. Cultures of skin fibroblasts and of fetal cells from amniotic fluid have been substituted for the whole man in

the study of inborn errors of metabolism. Special techniques, especially those using cell hybridization, have provided a "substitute for sex," and have thus made possible the study of the formal genetics of man in the test tube. The usefulness of this technique in the study of inborn errors can be illustrated by homocystinuria and by the genetic mucopolysaccharidoses.

The enzyme defective in homocystinuria, cystathionine synthetase is not normally demonstrable in skin by direct assay.** Liver biopsy was necessary for the enzymatic diagnosis. However, Uhlendorf and Mudd (1968) found that fibroblasts cultivated from biopsies of skin do show enzyme activity and the homozygote shows virtually none. Hence, the diagnosis of homocystinuria is greatly facilitated. Fortunately, the same is true for most of the Garrodian inborn errors. The fact that the finding in skin fibroblasts is also reflected in the cells of the amniotic fluid makes the prenatal diagnosis of many of these disorders possible.

My *Mendelian Inheritance in Man* (1971) lists over 100 inborn errors of metabolism in which the specific enzyme deficiency has been identified. In many of these, fibroblasts have been studied. Exceptions to the rule that cultured fibroblasts show the relevant enzyme activity and that deficiency is demonstrable in the corresponding inborn error of metabolism include phenylketonuria, von Gierke's disease (glycogen storage disease I), and histidinemia. The last is a surprise because skin, specifically epithelial cells, shows histidase activity.

The fortunately wide repertoire of enzymatic activity of fibroblasts was not anticipated. Galactosemia was perhaps the first disorder to be adequately studied in fibroblasts by Wilma B. Bias and Herman Kalckar, and by Robert Krooth, working independently about 1960. In a symposium in 1962, Krooth (1964) listed cystathioninuria, oroticaciduria, essential fructosuria with hypoglycemia, and acatalasemia as inborn errors of metabolism then known to be "ubiquitous."

From the way radioactive sulfate is handled in cultured skin fibroblasts, Elizabeth Neufeld has demonstrated that the defect in the genetic mucopolysaccharidoses is a degradative one and has confirmed the conclusion drawn from electron microscopic studies that such conditions are lysosomal diseases. The degradative defect is corrected by mixing fibroblast cultures produced from different persons; by adding to the cultures of affected fibroblasts, medium in which normal fibroblasts have grown; or by adding partially purified urine protein to the same cultures. Neufeld's work demonstrates that in each of several

genetic mucopolysaccharidoses a diffusible protein, probably an enzyme, is deficient. These findings not only confirm the separateness of the several forms that have been delineated on other grounds but also suggest exciting therapeutic possibilities which are now under active investigation.

An interesting footnote is the finding that cross-correction does not occur between the Hurler syndrome and the disorder best delineated by Scheie, Hambrick and their colleagues (1962) and hence called the Scheie syndrome (MPS V in my nomenclature, 1966). These are clearly distinct disorders, one leading to death before age 10, the other compatible with a respectable life span and unimpaired intellect. A plausible explanation would appear to be allelism: although the genetic defect is at the same locus in the two disorders and involves the same enzyme, the alteration differs in the two conditions. One might compare them to the hemoglobins SS and CC.

A corollary is that some cases of genetic compounds are to be expected, e.g., patients with the Hurler gene on one chromosome and the Scheie gene on the homolog (a situation comparable to SC disease). The clinical features might be intermediate between MPS I and MPS V, and cross-correction would occur with neither. We (McKusick et al., 1972) have patients who fulfill these criteria.

These advances in somatic cell genetics during the 1960s would probably not have been possible without the study during the previous decade of the established human cell line derived from the patient, Henrietta Lacks. From her cervical carcinoma, the justly famous HeLa cell line was cultured in 1951 by Dr. George O. Gey (1899–1970) of Johns Hopkins (Jones et al., 1971). The list of scientists who have used the HeLa cell as the object of their study reads like a *Who's Who* of modern cell biology and the range of topics investigated is very broad. We (Jones et al., 1971) have recently restudied this famous case. Henrietta Lacks was a Negro woman who lived in the vicinity of the Johns Hopkins Hospital. In September, 1950, she had completed a normal pregnancy, her sixth. The carcinoma, which developed very rapidly thereafter, was so unusual in appearance and consistency that my colleague, Dr. Howard Jones, who saw her clinically on February 1, 1951, ordered a dark-field examination, which showed no spirochetes. At biopsy on February 9, 1951, the diagnosis was early carcinoma, but despite radium therapy the patient died in August, 1951, at the age of 31 years. The histopathology was originally reported to be epithelioid carcinoma, but a recent review of the sections shows telltale acini, which indicate an adenocarcinoma, an unusual variety for the cervical location. Perhaps this partly explains the unusual clinical and culture behavior of the tumor.

** The same is true of the enzymes deficient in most inborn errors of metabolism. An exception is histidinemia; histidase is normally present in skin (La Du, 1967).

Cockayne's treatise is defective in its discussion of what I consider three leading principles of clinical genetics: genetic heterogeneity, pleiotropism, and variability.

Genetic Heterogeneity

In the last few years, genetic heterogeneity has become a recurrent theme in medical genetics. Repeatedly, a disorder previously thought to represent a single entity has been found to involve two or more separate entities. Recognizing genetic heterogeneity in a particular phenotypic category profoundly affects genetic prognosis and genetic counseling, and search for the basic defect is aided by work on a group of cases in pure culture. Heterogeneity has been recognized in albinism, epidermolysis bullosa (Gedde-Dahl, 1971), the Ehlers–Danlos syndrome, ichthyosis, hyperkeratosis palmaris et plantaris, and intestinal polyposis (the Gardner syndrome, Peutz–Jeghers syndrome, etc.), to cite only a few examples of dermatologic interest.

It is not clear how the concept of genetic heterogeneity originated or who introduced the term. It was implicit in Johannsen's distinction between *phenotype* and *genotype* (terms he invented in 1909) and in his insistence on the corollary that the phenotype does not necessarily indicate the genotype. It is also implicit in Lenz's law: that in a disorder that is autosomal dominant in some families, autosomal recessive in others, and X-linked in yet others, the first form tends to be the mildest, the second the most severe, and the X-linked recessive intermediate. Stern (1949) explains genetic heterogeneity by comparing it to a stalled car. In all genetic disorders, the phenotype (the stalling) is the same, but the underlying cause (the genotype) differs.

Pleiotropism

This term refers to the multiple phenotypic effects of the primary action of a single gene. It is responsible for the many Mendelian syndromes (literally "running together") in medicine. Theoretically genetic linkage is not a satisfactory explanation since it cannot, because of crossing-over, cause the permanent association of traits in a population. Pleiotropism is important to clinical medicine because one of the pleiotropic effects of a single gene may be an external clue to grave internal derangements caused by the same gene. Pleiotropism is especially important to dermatology because many systemic genetic disorders have cutaneous features.

Since the word *pleiotropism* was apparently introduced by Hadorn in 1945, it was not used by Cockayne. But it is surprising not to find at least the concept discussed in detail in his book. The work "syndrome" is almost never used; eponyms are used sparingly, and then generally not combined with *syndrome*, e.g., Gaucher's disease, Darier's disease, Friedreich's ataxia, Quincke's edema, Catlin's mark. The only eponymic syndrome I could find was the Laurence–Moon–Biedl syndrome (p. 40). Most of the disease designations used by Cockayne are descriptive Latin ones. Continentals used eponyms more freely than the British. I think this is why *Morquio syndrome* and *Hurler syndrome* were generally used (Morquio and Hurler published in Continental journals) although the papers of Brailsford and Hunter were published simultaneously or earlier. The designation *Hunter syndrome* was first used in 1956. Cockayne discussed pseudoxanthoma elasticum without reference to its association with angioid streaks although 4 years earlier Ester Groenblad and James V. Strandberg, ophthalmologist and dermatologist respectively, had emphasized the syndromal association, and the original patient of Chauffard had demonstrated the combination (McKusick, 1966, p. 287).

In discussing the vague and to our retrospective view useless concepts *biotypes*, *atavism*, and *stigmata of degeneration*, Cockayne did mention the difficulties of distinguishing between linkage and multiple gene effects: "Some genes cause an abnormality of a different kind in another tissue, and the latter may be regarded as a stigma of degeneration. In actual practice it is difficult to distinguish these from cases of linkage. The late or noneruption of teeth in cleido-cranial dysostosis and the polydactyly associated with mental deficiency, obesity, and retinitis pigmentosa in the Lawrence [sic]–Moon–Biedl syndrome may be manifestations of the action of a single gene, dominant in the former and recessive in the latter case."

Under the heading of "Teeth Erupted at Birth" (p. 261), Cockayne wrote as follows:

> Anderson Murray describes a family in which hypertrophy of nails was inherited; the nails were smooth and very thick and were raised from the nail bed by a dark yellow horny mass. Of the seven members with this defect no fewer than six, who were marked with a cross in the pedigree, had incisor teeth erupted at birth. A similar if not identical defect of the nails is inherited as a dominant, so that it may be a case of linkage between the two mutant characters. Pires de Lima saw a baby boy with incisor teeth at birth and was told that his father, who had onychogryphosis, was also born with three erupted incisors apart from the defect of the nails.

Here Cockayne was clearly describing pachyonychia congenita, an autosomal dominant syndrome now well-known to have natal teeth as a

feature. Cockayne (1933, p. 203) discussed pachyonychia congenita separately, without reference to natal teeth.

Apparently Cockayne's predecessor, Jonathon Hutchinson (1828–1913), did appreciate the significance and diagnostic usefulness of syndromal association, although the pleiotropic effect of a single gene escaped him. Hutchinson wrote: "We must analyze, and seek to interpret partnership in disease." I introduced a clinical biography of Hutchinson, published in 1952, with this quotation because it epitomizes Hutchinson's approach and the approach of that breed of clinical geneticists we can call syndromologists to the study of disease. Parkes Weber (1862–1961) obviously had a grasp of syndromal association and probably has his name on more syndromes than any other single clinician in history: Sturge-Weber syndrome, Weber–Christian disease, Osler–Rendu–Weber syndrome, Klippel–Trenaunay–Weber syndrome (McKusick, 1963).

The concept of pleiotropism was applied to medicine by Hans Grüneberg, who in his *Animal Genetics and Medicine* (1947) showed how one can construct "pedigrees of causes," tracing all signs of a syndrome back to a unitary gene-determined derangement. Grüneberg's work was available to me when I applied the concept of pleiotropism to the syndrome of melanin spots and intestinal polyposis in my studies with Jeghers (1949). My *Heritable Disorders of Connective Tissue*, first published in 1956, may have done something to establish the syndrome concept in medicine. Robert Gorlin has achieved eminence as a syndromologist with his numerous original descriptions, many of which are collected in his monograph (with Pindborg), *Syndromes of the Head and Neck* (1964).

Cockayne (1933) discussed separately two traits now known to occur together as an autosomal dominant syndrome: distichiasis (p. 330ff) and hereditary lymphedema (p. 375ff). Since the syndromal association has been recognized only in the last few years, Cockayne's omission is forgivable.

Variability

The severity of a gene-determined pathologic trait can vary considerably from case to case. The major gene does not, of course, operate *in vacuo* but is influenced by the rest of the genes and by environmental factors. If genetic disorders, or for that matter disorders of any etiology, were invariable in their expression, then diagnosis would be child's play. Learning to interpret variation is a large part of learning medicine.

I can illustrate the variation of a single gene syndrome with the Marfan syndrome, an example justified in this presentation since it has skin changes, particularly striae distensae. Both of the brothers shown in Figure 2 have the Marfan syndrome, having inherited from their father the identical gene for this connective tissue defect.

But whereas the younger brother has the entire syndrome—ectopia lentis, striking skeletal features with extremely severe scoliosis, and mitral regurgitation—the older brother is tall and has a depressed sternum and some spinal curvature, but cardiac examination is negative and, of particular note, the eyes show no abnormality. In brothers, half the genes, on an average, are identical. The half of their genome that is different leaves plenty of room for different modifying influences on particular genes. In animals (for example, those shown by L. C. Dunn [1937] and others), a considerable change in the expression of the syndrome can occur when the gene responsible for a given syndrome is transferred onto a different genetic background. One feature of a syndrome can be so strongly modified that it is absent or has a low frequency on a particular background. That is the phenomenon observed in the older brother who failed to show one of the major features of the Marfan syndrome, ectopia lentis. In the Waardenburg syndrome, the deafness is sometimes present in one sib, absent in another (1951).

The degree of expression of a genetic trait, that is the severity of a pathologic genetic trait, is sometimes referred to as *expressivity*. If the expressivity is sufficiently low, we may fail to detect
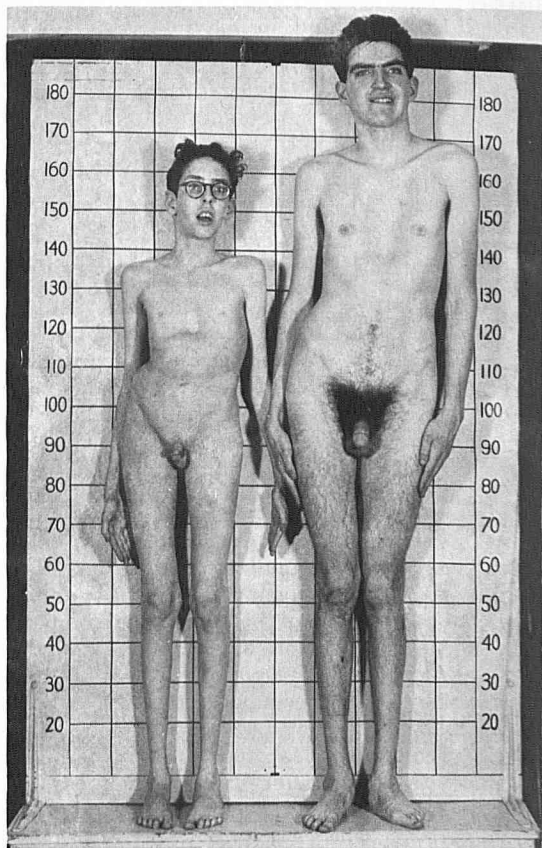

FIG. 2. Two brothers with the Marfan syndrome of disparate expressivity.

the trait which is then said to be nonpenetrant. The terms *expressivity* and *penetrance* were used by Timofeeff-Ressovsky about 1931 (Hadorn, 1955); but according to Stern (1960) they were coined by Oscar Vogt (1870–1959), a neuroanatomist, who founded the Kaiser Wilhelm Institut für Hirnforschung in Berlin-Buch and called Timofeeff-Ressovsky to it from the U.S.S.R. where he had trained and begun his scientific work.

THE DYNAMICS OF GENES IN POPULATIONS

As indicated or implied in the earlier discussion of pleiotropism, the implications of linkage†† for the association or rather the lack of association of traits at the level of a population was not clear to Cockayne. Cockayne (1933, p. 4), who expressed interest in the proportion of familial and sporadic cases, realized that the proportion among published cases is not representative although cases reported early in the nosography of a disease come closer to the true value. This interest of Cockayne's centered mainly on recessive disorders. A theory of population genetics not found in Cockayne is that of equilibrium between a new mutation adding genes to the gene pool and reduced fitness effectively extracting genes from the pool. The greater the impairment of fitness by a dominant trait, the larger the proportion of sporadic cases.

Cockayne was properly impressed with the usefulness of parental consanguinity as a clue to recessive inheritance. He did not mention, however, the inverse relationship, pointed out by Dahlberg in the 1920s, between the frequency of a recessive gene and the proportion of parents of affected persons who were first cousins. In 1935, in reviewing the few cases of the Hurler syndrome reported up to that time, he noted a lack of parental consanguinity, thought that recessive inheritance was unlikely and suggested "double recessive" inheritance, a most unlikely possibility in present view.

SELECTED GENETIC DISORDERS AS KNOWN TO COCKAYNE

Genetic Disorders of the Skin

Frequently certain genetic disorders have a scientific interest and importance out of proportion to their numerical frequency or at times to

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†† Cockayne (1933, p. 26) cited Davenport's demonstrations (1930) of hemophilia-colorblindness linkage. It was not until 1937 that Haldane and Bell made the first estimate of the interval separating two genetic loci in man, the same two X-linked loci, hemophilia and colorblindness. (See also Haldane and Smith, 1947.) They were tripped up by genetic heterogeneity. They failed to distinguish hemophilias A and B, both of which are X-linked but situated on quite far separated parts of the X chromosome. The hemophilia A locus is closely situated to the deutan and protan color vision loci; the hemophilia B is sufficiently far removed that free recombination occurs between the loci (review, McKusick, 1970).

their significance to the affected person. Let us see how some of the rare genetic disorders of the skin, favorites of researchers in recent years, fared in Cockayne's hands.

1. Fabry disease (Usage seems to have favored the eponym over diffuse angiokeratoma suggested by Wise [1962]. It is my contention that since the eponym is merely a convenient handle, the possessive form is inappropriate. Usually the man whose name is used was not the first to describe the disorder or to describe it in full detail.)

The angiokeratoma described by Cockayne (1933, p. 381) is a different disorder, related to chillblains. Cockayne (p. 116) referred to Archer's description in 1927 of two brothers with "multiple cavernous angiomata of the sweat ducts." Sibley had previously reported them in 1918. Parkes Weber (1927) recognized them as identical with the cases of "angiomatosis miliaris" reported by Steiner and Voerner (1909). All these cases are now known to have been Fabry disease. Wise et al. (1962), "aided by their uncommon surname and the London telephone directory," followed up on Archer's family. Cockayne made no mention of Fabry's paper published in 1898 (nor of later reports in 1916 and 1930) nor of the report by his countryman Anderson in 1898. Fabry disease, which has been proved to be an X-linked recessive, has been defined at the enzymatic level and treated with plasma infusions.

2. Nail-patella syndrome: This disorder is of genetic interest, having been the first rare dominant trait for which a genetic linkage was established (with the ABO blood group locus). This was the work of Dr. Renwick, (this issue). Cockayne (1933, p. 267) discussed the pre-1933 publications under the heading, "Anonychia and onychatrophy with absent or rudimentary patellae."

3. Bloom syndrome: This autosomal recessive disorder is of cytogenetic interest because of the high frequency of chromosome breaks (German, this issue). The definitive description by the clinician whose name is eponymically attached to the disorder came after 1933.

4. Xeroderma pigmentosum was the first disorder in which a defect of DNA repair was discovered (Cleaver, this issue). Cockayne (1933, p. 93ff) showed prophetic perceptiveness in classifying it among the metabolic errors. The association with mental retardation and neurologic abnormalities in a disorder that is probably distinct and goes by the name of de Sanctis-Cacchione syndrome was described later.

5. Angioneurotic edema of the familial type was well described in the last century by Quincke, Osler, and others. Cockayne (1933, p. 371ff) reviewed well the extensive recorded experience with this often fatal ailment. In the last decade, the nature of the basic defect—deficiency of the inhibitor of a complement component—has been defined and heterogeneity (different types) has been described.

6. Porphyria: Cockayne (1933, p. 103ff) described "porphyrinuria congenita," a recessive, as "hydroa vacciniforme of Bazin" and raised the question of a dominant form (p. 108). Pseudodominance from the marriage of heterozygotes and homozygotes probably explained some of these cases; others were probably one of the dominant forms of porphyria now known. An interesting group is that of *hydroa aestivale vacciniforme* without porphyrinuria. In some of these cases, especially in those families consistent with dominant inheritance, Cockayne may have been describing erythropoietic protoporphyria, but even today cases of hydroa aestivale without demonstrable disturbance of porphyrin metabolism and without known cause are observed.

Clinical "Odds and Ends"

Standing on the shoulders of clinical workers of the intervening 38 years gives me an unfair advantage, I realize, but it is of interest nonetheless to note deficiencies in Cockayne's clinical descriptions. Cockayne was extremely interested in the piebald trait and wrote at length about white forelock.‡‡ It is curious that he, like his predecessors, did not recognize the Waardenburg syndrome—white forelock, dystopia canthorum, and deafness—or the other syndromes of piebalding and deafness (Reed et al., 1967). Again this may have been due largely to his inability and that of most of his contemporaries to think in terms of pleiotropic syndromes. Cockayne cited (1933, p. 327) the family of Mende (1926), which was clearly affected by the Waardenburg syndrome, among the unclassified anomalies of pigmentation. His heading was "Hereditary Degenerative Deaf-mutism with Mongoloid Appearance and Anomalous Pigmentation."

Cockayne (1933, p. 318) described three interesting families who had what Brauer (1929) termed "hereditärer symmetrischer systematisierter Naevus aplasticus." Recently the disorder has been extensively restudied by McGeough and Reed (1972), who call it familial focal facial dermal dysplasia, and by Jensen (1971), who calls it congenital ectodermal dysplasia of the face.

Mosaics and Chimeras

Cockayne (1933, pp. 30, 388) displayed much interest in somatic mutation, some examples of which were by that time known in other animals. He reviewed four reports of its possible occurrence in man. Another possible case was reported by

Zlotnikoff (1945), and Figure 3 reproduces a water-color of an Indian boy drawn for Sir Jonathan Hutchinson (1828–1913) on a trip to India in 1903. Theoretically, a somatic mutation for neurofibromatosis might occur so that only a part of the skin is affected, or it might occur in a person heterozygous for albinism, producing albino patches and so on. But I know of no certain example of postzygotic somatic point mutation in man. Postzygotic chromosomal aberrations leading to mosaicism are, of course, well known and represent a form of somatic mutation.

The mention of mosaics brings us to a discussion of chimeras. The distinction between mosaic and chimera was, I think, first made by Billingham. The definitions given by Chu et al. (1964) seem valid and are currently accepted ones
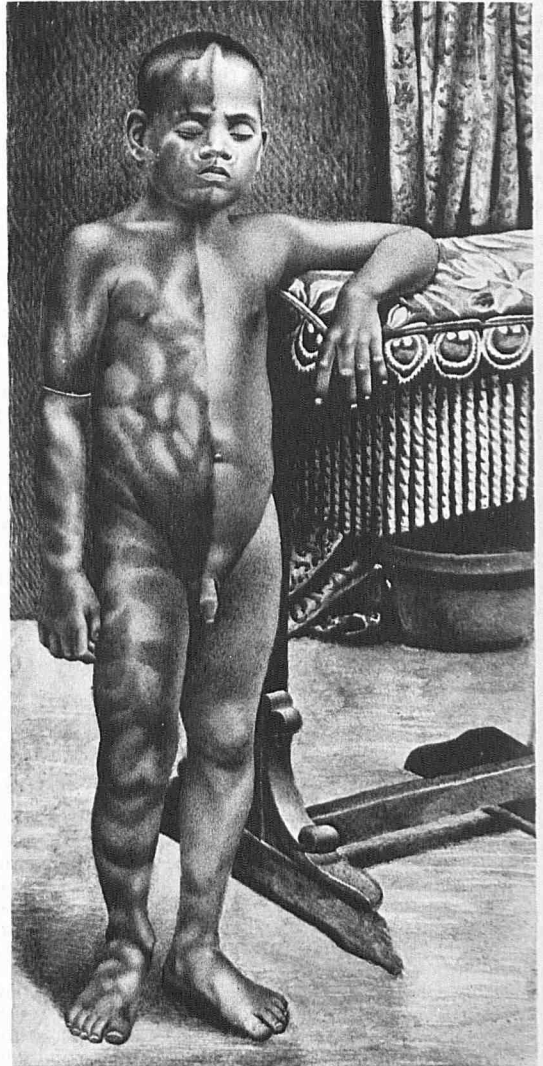

FIG. 3. A possible mosaic. From the Jonathan Hutchinson Collection, Welch Medical Library, Johns Hopkins University.

‡‡ Cockayne reported that the English family Whitelocke (Whitlock) owes its name to this trait (p. 56). Guppy (1890), naval surgeon and Fellow of the Royal Society of Edinburgh, stated that the family name occurred predominantly in Essex and Wiltshue. Perhaps the piebald trait exists among residents of those areas of England. It would be of interest to know whether piebaldism is present in anyone by the name of Whitlock listed in the London telephone directory!

useful for avoiding confusion. "A mosaic is an individual with cell populations of more than one genotype (e.g., karyotype) derived from a single zygotic genotype through mutational or zygotic events (e.g. somatic mutation, somatic crossing-over, mitotic loss, mitotic nondisjunction, etc.). A chimera is an individual with cell populations of more than one genotype arising through a mixture of different zygotic genotypes (e.g., transplantation, chorionic vascular anastomosis, double fertilization and subsequent participation of both meiotic products into one developing embryo, etc.)."

According to Benirschke's classification (1971), chimerism in man has three types: (1) blood chimeras, as in fraternal twins, caused by placental anastomoses and perhaps extending to germ cells; (2) transplacental chimerism, by which maternal cells populate the fetus; and (3) "whole-body chimerism" (Benirschke, 1971), which is in many ways the most interesting type, especially from a dermatologic point of view. Of the 11 cases of whole-body chimerism that have been recognized, all were detected principally because of hermaphroditism or at least ambiguity of the external genitalia. In most, karyotyping has shown two populations, one XX, the other XY. Further studies, particularly of blood groups and the typing of serum proteins such as haptoglobins, have also shown two populations of cells. In many of the patients, e.g., those of Corey et al. (1967), Zuelzer et al. (1964), and Race and Sanger (1968), a mottled pigmentary pattern of the skin was observed. Isosexual chimerism has been recognized in the mouse by unexpected genotypes in offspring (Russell and Woodiel, 1966). Isosexual whole-body chimeras should be as frequent in man as the heterosexual ones, but their detection will require a high level of awareness by dermatologists and the support that only sophisticated blood-grouping studies can supply.

Studies on the mechanism of these whole-body chimeras have centered on double fertilization. Early fusion of zygotes is an intriguing possibility that is rendered plausible by the work of Tarkofsky and of Mintz with what Mintz calls "allophenic mice."

COCKAYNE'S OTHER CONTRIBUTIONS TO MEDICAL GENETICS

Cockayne began writing on hereditary diseases about 1927. His first contributions included reports on familial factors in thyroid disease (1928) and on familial hypertrophic pyloric stenosis (1927–28, 1933, 1934, 1938). He reported cases of pyloric stenosis confirmed by Rammstedt pyloromyotomy operation (introduction in 1912) performed at the Great Ormond Street Hospital; undoubtedly these same cases were involved in a follow-up study reported by Carter (1961). Cockayne and Penrose (1943) tentatively suggested recessive inheritance of pyloric stenosis; Carter

found, however, that the data most satisfactorily fitted a multifactorial hypothesis.

In 1932 Cockayne reported a case of what we would term type II syndactyly, a dominant. Fingers III and IV were fused and the proximal phalanx of III was duplicated. The reported case was, however, sporadic; the parents were first cousins, but I doubt that this is relevant.

In 1933 Cockayne reported on congenital steatorrhoea at the urging of Sir Archibald Garrod, who had included this condition in the second edition of his *Inborn Errors of Metabolism* (1923). Presumably some of the cases of "congenital steatorrhea" were cystic fibrosis§§ because Cockayne commented on the high proportion of these patients who died of bronchopneumonia. Some may have been celiac disease. Cockayne's remark about the exceeding rarity of "congenital steatorrhea" may seem inconsistent with the reputation of cystic fibrosis as the most frequent chronic Mendelian disorder in children of northwestern European ancestry. But remember that in the prechemotherapeutic and preantibiotic era, death from the respiratory complications of this disease carried the infant or child off before the intestinal malabsorption had become a conspicuous feature; moreover, because of intestinal symptoms, cases were lost in the large numbers dying of the diarrheal diseases of infancy. Cystic fibrosis was not delineated until 1938, by Dorothy H. Andersen (1901–1963), pathologist at Babies Hospital, New York City, and large series of cases were not assembled until after World War II when sulfa drugs and penicillin were available. (The history of the early nosology of cystic fibrosis is recounted by Bodian [1952]). The Bloom syndrome, ataxia telangiectasia, Riley–Day dysautonomia, and the genetic immune deficiency disorders are postantibiotic diseases for similar reasons. Cockayne supported the recessive inheritance of "congenital steatorrhea," which is now firmly established for cystic fibrosis.

In 1935 Cockayne presented a case of "arachnodactyly with congenital heart disease," demonstrating his usual reluctance to use the eponym Marfan syndrome. The boy had a loud pansystolic murmur maximal at the apex with accompanying thrill. Cockayne thought there was probably interventricular septal defect, but mitral regurgitation from floppy valve is much more likely. The few cases of ventricular septal defect in patients with Marfan syndrome have probably been coincidental; mitral regurgitation, on the other hand, occurs in a high proportion of severely affected children.

Cockayne and his colleagues (Cockayne et al., 1935; Sorsby et al., 1939) wrote two long papers on the Laurence–Moon–Biedl syndrome. Again Cockayne opted for linkage rather than for pleio-

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§§ The condition termed cystic fibrosis of the pancreas by Anderson (1938) has gone by a number of other names; usage now favors simply "cystic fibrosis."

tropism (Sorsby et al., 1939): "It is suggested that the syndrome is determined by two recessive genes in the same chromosome, or that it is dependent on some chromosome error. . . ."

"Dwarfism with retinal atrophy and deafness," reported in 1936 and 1946, is now known as Cockayne's syndrome or better, in my opinion, the Cockayne syndrome. (Macdonald et al. [1960] seem to have been first to use this designation.) Although few cases have been described, it is clearly an autosomal recessive; the most extensively affected pedigree is that of Kloepfer and his associates (Paddison et al., 1963; Wise, 1962).

In 1935, Cockayne reported a 4½ year-old girl who clearly had the Hurler syndrome, and in 1936 he reported two brothers with the Hunter syndrome (MPS II), probably the first observed in England. He called the condition gargoylism, a term introduced by Ellis and his colleagues (1935). He recognized that his cases were similar to those reported by Hunter of Winnipeg in the same journal in 1917 and those reported by Davis and Currier (1934) as the Morquio syndrome. He also recognized their similarity to the cases of Helmholz and Harrington, the difference being the absence of corneal clouding. He stated that he had learned from Nonne (1925) that his twins were still alive at 23 and still mentally normal although sexually undeveloped. Thus, these were probably cases of the Maroteaux–Lamy syndrome (MPS VI). We have observed delayed sexual development in this disorder.

In 1936 Cockayne described a family with dominant inheritance of medullary retinal nerve fibers, so-called *Papilla leporina* (L. hare-like). In 1938 and again in 1947 he wrote about recurrent bullous eruption of the feet, a form of epidermolysis bullosa which carries the names of Weber (1926) and Cockayne. Cockayne had 3 families displaying autosomal dominant inheritance, or as he said in his 1938 article, "conditional dominant" (Levit's term) since like most rare heterozygous traits in man nothing of the phenotype of the homozygote is known. Where the homozygote has been observed, for example, in achondroplasia, it is usually much more severely affected (Hall, 1969). Weber's case (1926) may have been a distinct entity; it was sporadic and the parents were related. Genetic status was assigned this trait by the fact that Haldane (1942) reported on an extensively affected family. A large West Virginian family, descendants of one Zachariah Piles born in 1762, was reported by Cartledge and Myers (1943). The blistering in this disorder occurs only on the hands and feet, mainly in warm weather after an unusual amount of walking or after labor with hand tools. Readett (1961) claimed benefit from adrenocorticosteroid administration.

In 1938 Cockayne analyzed the genetics of *situs inversus viscerum.* In this publication, he displayed a better understanding of the bias of

TABLE II

Principles of medical genetics illustrated by dermatologic disorders

Phenocopies	The CRST syndrome (calcinosis, Raynaud phenomenon, sclerodactyly, telangiectasia) and hereditary hemorrhagic telangiectasia
	Phenolic dressings and alkaptonuria (both produce ochronosis)
	Atabrine and alkaptonuria
Diagnostic usefulness of pleiotropism	Gardner syndrome
Treatable genetic disease	Acrodermatitis enteropathica
	Fabry disease
Genetic heterogeneity	Polyposis
	Albinism
Genetic linkage	Nail-patella syndrome/ABO/adenylate kinase
Genetic drift and founder effect	Ellis–van Creveld syndrome (chondroectodermal dysplasia)
Biochemically elucidated defects	
Defect in repair of DNA after UV damage (deficiency of UV-specific endonuclease)	Xeroderma pigmentosum
Deficiency of C1 inhibitor	Angioneurotic edema
Ceramidetrihexosidase deficiency	Fabry disease
Dominant inheritance of structural protein defect	Clouston's ectodermal dysplasia
Recessive inheritance of Garrodian inborn error of metabolism (enzyme deficiency)	Homocystinuria
X-linked recessive	Ichthyosis
X-linked dominant	Keratosis follicularis spinulosa cum ophiasis
X-linked dominant lethal in hemizygous male	Orofaciodigital syndrome
	Focal dermal hypoplasia
	Incontinentia pigmenti
Lyon hypothesis	Anhidrotic ectodermal dysplasia
Ethnic or geographic concentration of recessives	Mal del Meleda
	Cartilage-hair syndrome
Chimerism	

ascertainment than he did in his 1933 monograph and concluded that the condition is inherited as an autosomal recessive. He mentioned the association with bronchiectasis pointed out by Kartagener, a Zurich internist, in 1933. Evidence for the recessive inheritance of the Kartagener syndrome is to me thoroughly convincing (McKusick, 1971). Clearly there is at least one form of *situs inversus viscerum* other than that of the Kartagener syndrome. Whether any of these are Mendelian is less certain.

SUMMARY

Since 1933 great strides have been made in an understanding of the basic mechanisms in genetic disorders of the skin. Furthermore, study of these disorders has contributed significantly to the understanding of the normal skin and in some instances to the genetics of man (Table II). The several contributions in this symposium will further document these statements. I see a bright future for genetics in dermatology and for dermatology in genetics, the two domains for which Cockayne wrote his book.

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