HIRSUTISM: A REVIEW OF THE GENETIC AND EXPERIMENTAL ASPECTS*

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INTRODUCTION

The genetic and environmental factors, which together are responsible for our lack or abundance of hair, are little understood. Especially noticeable is the paucity of knowledge about the regional variations in hair growth or the different sensitivities to pilary stimulation. Nevertheless, because of the easy applicability of investigational techniques and the availability of large amounts of experimental tissue, our knowledge of hair phenotypes and growth is considerable and significant.

Although disorders of the hair may have no practical or medical significance, involving little or no interference with the general physical condition, they are commonly important to the patient because of psychological factors. They may be an early warning of a serious underlying medical disorder, such as a congenital abnormality, or a clue to correct medical diagnosis. Explanations of disordered pilary metabolism could well provide the necessary insight whereby rational therapy could be applied to various diseases.

The ideal state of "hairiness" is not a characteristic of many men or women, nor can normal subjects be absolutely separated according to sex by their hair patterns. In fact, it is difficult to decide nowadays which is considered less esthetic in our society, too little or too much hair; but it is certain that as civilization changes do "ideal" amounts and distribution of hair. Although I will discuss hirsutism and alopecia separately, the distinction is arbitrary in a sense, since regional differences in end-organ sensitivities often result in hairiness in one area and hairlessness in another in response to similar pilary stimuli. If more than one disorder is present, the result is also a mixed picture. The treatment of these conditions will not be considered here.

In this paper, the term hirsutism is used in its traditional sense to denote only hypertrichosis. Some physicians, however, use the term to denote excessive growth of hair in a characteristic masculine fashion (Brooksbank, 1961; Wilkins et al., 1965). I have chosen not to do so because of the considerable overlap between normal men and women in the amounts and distribution of terminal hair. The overwhelming majority of women who consult physicians because of excessive hair on the trunk, extremities, or face are completely feminine by every other measurement and should not be considered masculine.

ENDOCRINE CONTROL OF HAIR GROWTH

Traditionally, lanugo and vellus hair, eye hair, and some hair on the extremities were not thought to be under hormonal control, whereas both axillary hair and lower pubic hair were pubertal events, similar in both sexes and related to adrenal androgens. The upper pubic hair, the beard, hair in the external auditory canals and nasal vestibula, and increased hairiness of the trunk and extremities were thought to be secondary sexual characteristics of the male (Danforth, 1939; Flesch, 1954; Porter and Lobitz, 1970). Major differences between the sexes are quantitative rather than qualitative; therefore classification becomes difficult. For example, hair on the scalp or extremities can be assigned to one of several categories, and certain variations are normal in familial and racial strains but abnormal in others; thus comparisons between individuals are often impossible. It is also likely that hair growth is never completely free of hormonal control.

Knowledge about the endocrine control of hair growth is deficient, but three points seem incontrovertible. (1) The androgens, particularly testosterone, are the principal stimuli for the growth of terminal hair. Their secretion by the gonads and the adrenals must be genetically determined by a variety of mechanisms; examples of abnormal androgen function are found in the heritable syndromes of congenital adrenal hyperplasia, familial multiple endocrine adenomas, and certain intersex problems. (2) The various responses of hair to androgenic stimulation are governed by genetically determined intrinsic qualities unique to a particular hairy region and especially to the individual follicle. New information that may explain this seeming paradox will be discussed later. (3) In most cases, aging is a prerequisite for the expression of the hair-stimulating effects of androgens (or for the loss of hair in the temporal and vertex regions of the scalp). However, aging is only a relative factor since hirsutism and baldness can develop rapidly in cases of precocious puberty or severe endocrinologic disease. Hairiness on the trunk and extremities frequently increases for several years after maximal levels of androgens have been attained in the plasma of normal men and women, an effect probably genetically influenced, though little information is available on this subject. Conversely, the loss of androgens as a result of castration or the removal of an androgen-secreting tumor rarely reverses hirsutism and common baldness rapidly; more commonly many months or years are required for normal patterns of hair growth to reassert themselves.

Baulieu (1970) pointed out that steroid hormones penetrate the cells which they affect, unlike peptide hormones which act at the level of the external membrane. Several studies have indicated that the potent androgen, dihydrotestos-
terone (DHT), which is the intracellular effector of testosterone action in the target tissue may reenter the blood from the tissue in which it is produced and cause androgenic effects on other tissues of the body. Larger amounts of DHT are more likely to originate from gonadal sources (Bardin and Mahoudeau, 1970; Bashirelahi and Villee, 1970). In prostatic cells, DHT was bound mostly in nuclei (Bruchovsky and Wilson, 1968). Although the reductase necessary for converting testosterone to DHT was found to be present in both nuclei and cytoplasm, only the latter contained the enzyme needed to reduce DHT to the relatively inactive androstanediol. Anderson and Liao (1968) proposed a specific receptor for DHT at its site of action from which it can be dislodged only with difficulty. Probably only a limited number of "androphilic receptors" (Hansson et al., 1971) are soluble protein macromolecules; at least in prostatic nuclei, the androphilic macromolecules are acidic proteins associated with nuclear chromatin. The function of the androgen-binding nuclear proteins is unknown, but they could affect gene transcription by inactivating repressor substances (Fang et al., 1969), an effect in agreement with the immediate activation of ribonucleic acid and protein synthesis by androgens (Williams-Ashman, 1965; Liao and Lin, 1967; Bashirelahi et al., 1969).

Recent studies indicate that normal human skin actively metabolizes androgenic hormones in vivo as well as in vitro (Wotiz et al., 1958; Baulieu, 1970; Faredin et al., 1970). Most of these studies provide substantial data on these effects in accessory sexual tissues, such as the prostate or seminal vesicles, but only a few studies have been done on the skin. Several hydroxysteroid dehydrogenases have been found in human skin (Baillie et al., 1966; Rongone, 1966), principally in the sebaceous glands, though steroid dehydrogenases also have been found in fibroblasts growing in tissue culture. In addition, androgenic steroids have been found in and on the surface of the skin and hair, and dehydroepiandrosterone can be metabolized by skin in vitro with the formation of testosterone as well as of other steroids (Cameron et al., 1966). In summarizing the literature on androgen metabolism in the skin, Strauss and Pochi (1969) pointed out that, although the specific site for such metabolism remains unknown, the sebaceous glands are implicated most clearly. Wilson and Walker (1969), however, found that even skin devoid of pilosebaceous structures had at least a limited ability to convert testosterone to DHT.

Human skin was shown by Faredin et al. (1970) to be an active metabolic site for androgenic steroids. They demonstrated that both normal and hirsute female skin synthesized testosterone, 5α-androstan-3,17-dione, and androsterone from [4-C14]androst-4-ene-3,17-dione and confirmed the latter compound as a precursor of testosterone and the presence of 17β-hydroxysteroid dehydrogenase in the skin as well. Bardin and Mahoudeau (1970) pointed out that increased clearance of testosterone by extrahepatic target tissues could explain the paradox of normal plasma testosterone levels occurring with increased rates of testosterone production in some virilized women.

In considering mechanisms whereby the increased stimulation of target tissues such as hair might be controlled genetically, I would also point to the possible role of the testosterone-binding β-globulin (TeBG), which binds testosterone in high affinity in some ways analogous to cortisol-binding globulin. Although the control of the metabolic clearance rate of steroids is not completely understood, several studies suggest that TeBG retards the metabolism of testosterone (Vermeulen et al., 1969; Bardin and Mahoudeau, 1970; Mercier-Bodard et al., 1970). According to Ito and Horton (1970), TeBG has a greater affinity for DHT than for testosterone. DHT arises principally from the ovarian secretions in the female and from the peripheral conversion of testosterone in the male. Thus, numerous factors influence the metabolic clearance rate of testosterone, including plasma globulin binding, the nuclear androphilic receptors, and the activity of steroid metabolizing enzymes in target tissues. The suggestion by Ismail and Loraine (1969) that hirsutism results from a lack of antiandrogenic substances has not been investigated.

Sansone and Reisner's (1971) report of significant regional variations in the ability of skin to convert testosterone to DHT confirms that variation in end-organ sensitivity. They observed that the conversion of DHT was 2 to 20 times greater in acne-bearing skin than in normal skin from a corresponding area and that normal facial skin showed more conversion than normal back skin. The rates of conversion to DHT were higher in male skin than in female skin from the same sites.

Human hair follicles have not been studied in this manner, but Takashima et al. (1970) published results on the in vitro metabolism of testosterone in the hair follicles of stump-tailed macaques, showing that the hair follicle itself is an actively metabolizing androgenic site and that scalp hair, both from bald and from nonbalding areas, is more active than back hair. The greatest activity was in the hair bulb, and anagen follicles were more active than telogen. Utilizing thin-layer chromatographic methods, they observed that the metabolism of testosterone was less active in follicles from the balding scalp than from the hairy scalp and that the production of its metabolites, mainly androstenedione, was much greater in the bald areas. Thus, they showed, for the first time, a biochemical difference between follicles in bald and hairy regions.

In an extension of this study, Adachi and Kano (1970) showed that in hair follicles of the human scalp adenylyl cyclase was greatly inhibited by DHT but not by testosterone. They proposed a molecular mechanism whereby DHT causes inhibition of
adenyl cyclase in the follicles, a decrease of the intracellular cyclic-AMP level, and consequent inhibition of energy production and protein synthesis in the hair. This inhibition causes premature termination of the growth cycles of terminal hairs and their transformation into vellus hairs.

These tentative insights into the mechanisms of hair growth still leave many questions unanswered. For example, what are the regional differences in the response to similar pilary stimulation? Nevertheless, an understanding of the enzymatic controls responsible for such differences in follicular metabolic activity appears to be within reach. An important avenue for the analysis of the genetic transmission of common baldness as well as of certain forms of hirsutism may have been provided.

**CLASSIFICATION OF HIRSUTISM**

From a clinical point of view, my previous classification of hirsutism (1969) is still reasonably satisfactory though a few alterations and additions have been made (Table). Genetic factors, though still undetermined, are operative in various degrees in almost every category. Even in drug-induced hirsutism, differences in individual susceptibilities are clearly evident.

**Racial and Familial Hirsutism**

*Normal distribution of hair.* Orientals, Eskimos, American Indians, and Negroes are much less hirsute than Caucasians. This is especially true of Orientals who rarely have facial or body hair except in the pubic and axillary regions and of American Indians who, in addition, rarely ever have common baldness in either sex. Lee and associates (1963) noted that East Asian Arctic Mongoloid women frequently have little or no pubic hair and Japanese women reportedly have much less axillary hair than white American women (Hamilton and Terada, 1963). At the other extreme, the Ainu, an aboriginal people who populate a northern Japanese island, are said to be the most hirsute (Cockayne, 1933). To my knowledge, detailed comparative studies of hirsutism and common baldness have not been carried out in non-Caucasoid women except by Hamilton (1958) who compared Japanese and white American women. Setty (1970, 1971) has also provided data of hair patterns in Caucasoid and Negroid men.

Despite the considerable diversity that exists among Caucasians, several major studies of hirsutism in healthy subjects have been reported. It is generally agreed that dark-haired, darkly pigmented Caucasians of either sex tend to be more hirsute than light-haired ones. I have found that persons of Mediterranean and Middle Eastern ancestry accept their hirsute tendencies as being inherited more readily than do others. Blond, fair-skinned, Nordic groups are less hairy; but descendents of Irish, English, Welsh, and Russian Jewish immigrants are frequently more hirsute than dark-skinned groups despite their light pigmentation and hair color (Danforth and Trotter, 1922; Schwartz, 1942; McKnight, 1964).

Detailed reports on English, Welsh, American, Danish, Dutch, and Indian women have indicated much diversity in the distribution of hair (Danforth and Trotter, 1922; Pedersen, 1942-1943; Beek, 1950; Shah, 1957; Thomas and Ferriman, 1957). These studies, suggested that terminal hair was commoner on the arms and legs of Welsh women than on those of Danish, American, and Indian women. On the other hand, the incidence of facial hair in Welsh women was similar to that in American women but higher than that in Swedish and Indian women. Beek (1950) analyzed the distribution and extent of hair in 1,000 healthy women in Holland, noting the incidence of hairiness by decades. He reemphasized that the incidence of hairiness is strongly age-related and that comparison of similar population groups is crucial. Among his more interesting results was the age-related increase in the number of women with moustache and beard hairs, from a relative zero incidence in the first two decades to approximately 90 percent incidence at age 65 and older. The incidence of hirsutism elsewhere was otherwise generally similar to that of Danish and American women.

McKnight's study (1964) of 400 women students at the University of Wales illustrates fully the difficulties of assigning medical significance to hirsutism. Eighty-four percent of these students had terminal hair on the lower part of the legs and 70 percent on the upper part of the arms and legs; 26 percent had terminal hair on the face, usually the moustache area, whereas 1 percent had hair on the chest or breasts; 35 percent had abdominal hair usually concentrated on the linea alba. The more severely hirsute were more likely to have terminal hair on the back, which involvement indicating the need for medical study. Only two women showed additional signs of masculinization and subsequently were found to have adrenal virilism; one additional patient was found to be a pseudohermaphrodite.

A familial tendency to hirsutism in white subjects is not an uncommon clinical observation (Hamilton, 1964). Hamilton et al. (1969) noted similar patterns and amounts of sternal and beard hairs in identical twins, but fraternal twins and siblings did not resemble their parents and differed as much from one another as from an unrelated control group. Lorenzo (1970) recently reported new evidence to support genetic etiology for familial hirsutism, probably based on a multifactorial pattern of inheritance. The familial incidence and distribution of hirsutism were ascertained in 90 subjects seen at the Endocrinology Clinic of the University of Michigan, in their first-degree relatives (mothers and sisters), and in a control group.
TABLE
Classification of hirsutism

I. In normal subjects
A. Intrinsic factors
   1. Racial and familial: generalized and localized forms including midphalangeal hair, hairy ears, and rare localized types
   2. Physiologic: premature pubarche, adolescent development, precocious sexual development, pregnancy, menopause, neural and emotional factors
   3. Idiopathic
B. Extrinsic factors
   1. Local trauma
   2. Drugs
      a. Without virilization
         Dilantin
         Diazoxide
         Hexachlorobenzene
         Corticosteroids; ACTH
      b. With potential virilization
         Progestogens
         Anabolic agents
         Androgen therapy
C. Hamartomas or nevi
   1. Pigmented nevi with hair, especially bathing-trunk type
   2. Nevus pilosus
   3. Pigmented hairy epidermal nevus (Becker)

II. In pathologic conditions
A. Endocrinologic disorders
   1. Ovarian origin
      a. Stein–Leventhal syndrome; familial hyperthecosis
      b. Virilizing ovarian tumors: arrhenoblastoma, granulosa theca-cell tumor, hilus-cell tumor, pseudomucinous cystadenoma, cystoadenocarcinoma, Brenner tumor
      c. Metastatic carcinoma to ovary (Krukenberg’s tumor)
   2. Pituitary origin
      a. Cushing’s syndrome
      b. Acromegaly
   3. Secretion of hormones by nonendocrine tumors
      a. Ectopic ACTH syndrome: mainly bronchogenic, thymic, and pancreatic carcinomas causing Cushing’s syndrome
      b. Multiple endocrine adenomatosis: Cushing’s syndrome and acromegaly
   4. Adrenal origin
      a. Syndromes of congenital adrenal hyperplasia
      b. Adult adenogenital syndrome
      c. Adrenal adenoma or carcinoma; adrenal rest tumors
   5. Intersex problems other than congenital adrenal hyperplasia
      a. Pure gonadal dysgenesis and Turner’s syndrome: with or without androgen-secreting tumors such as hilus-cell tumors or gonadoblastomas
      b. Male pseudohermaphroditism including incomplete testicular feminization and testicular masculinization–feminization syndromes
B. Congenital anomalies
   1. Hypertrichosis lanuginosa; idiopathic gingival fibromatosis and hypertrichosis
   2. Cornelia de Lange syndrome
   3. Congenital generalized lipodystrophy
   4. Leprechaunism
   5. Congenital hemihypertrophy
   6. Cowden’s syndrome
   7. Mucopolysaccharidoses
There were 20 women with associated ovarian dysfunction, 27 with adrenal cortical hyperfunction, and 43 grouped as "idiopathic" with no apparent endocrine abnormalities. The severity of the hirsutism could not be correlated with any diagnosis. The degree and extent of hairiness in the relatives were intermediate between those of the index cases and the controls. Because of the parallel association of hirsutism and androgenic equivalents which he identified as acne, common baldness, and clitoral hypertrophy, Lorenzo questioned the existence of a distinct idiopathic type of hirsutism. He proposed that the genetic control of all three entities was exerted at the hormonal level. I agree that in most cases the similarities among racial, familial, and idiopathic types of hirsutism are too great to permit their clinical recognition with reasonable certainty.

I know of no family pedigrees supporting an inherited pattern for the adult adrenogenital syndrome. However, the Stein–Leventhal syndrome does appear to have significant heritability. Cooper et al. (1968) investigated 18 families in which the Stein–Leventhal syndrome had appeared and concluded that the disorder was inherited, probably as an autosomal dominant characteristic. Support for this possibility is provided by the report of Givens et al. (1971) in which 41 members of two families were affected by a broad phenotypic spectrum of hirsutism and oligomenorrhea, thought to be transmitted as an autosomal dominant trait. The occurrence of hypogonadism in a few of the men and the greater frequency of the condition in the offspring of male family members suggest that this may be a separate rare entity.

Just as the amounts and distribution of terminal hair show considerable overlap between normal men and women, patterns of growth of pubic hair also vary greatly. Although horizontal patterns of growth are commoner in white American women and acuminate distribution is commoner in men, significant numbers of normal men and women have either type or intermediate types. Major racial differences have already been mentioned, as well as minor differences indicated by the report of Thomas and Ferriman (1957) who noted a lower incidence of an acuminate pattern and a higher incidence of the sagittal pattern among white English women than among white American women.

Dupertuis and associates (1945) and Beek (1950) confirmed the presence of a disperse type of pubic hair in which a heavy growth extends up the abdominal skin and occurs only in men, never in normal women. The only other types of hair distribution that are considered truly masculine are coarse ear hair reported by Hamilton (1947) in 75 percent of Caucasian men but not in women or eunuchs and by Beek (1950) in 59 percent of men 25 to 34 years of age but only in 1 percent of women of a similar age. Hamilton et al. (1969) also indicated coarse eternal hair to be a similar but less dependable sign of masculinization.

Localized forms of hypertrichosis. Most of the numerous observations on the heritability of localized areas of hypertrichosis deal with hair on the midphalangeal skin of the fingers. Danforth (1921) first suggested that the complete absence of hair at this site was due to a single recessive gene. Later, Bernstein (1949) postulated five different alleles to account for it. Reports of several affected children born to parents who lacked the trait indicated that the inheritance of mid-digital hair was not due to a single mendelian gene (Beckman and Böök, 1959).

Saldanha and Guinsburg (1961), who reviewed the literature and presented additional data of their own, noted that the trait is virtually absent among Eskimos and present in a frequency of 10 to 30 percent among Japanese, American Indian, and Negro subjects, and of 50 to 80 percent among Europeans. Similarities between this trait and the racial occurrence of hirsutism are immediately apparent; this type of hairiness is probably influenced by androgens (Garn, 1951). Of particular interest was the order of frequency of the affected fingers—fourth, third, fifth, and second; the action of different allelic genes is suggested. The inheritance of middle phalangeal hair has not yet been determined; although it may have some anthropologic importance, it is not an ideal subject for genetic investigation.

Hairy ears (hypertrichosis pinnae auris) are important only because genetic studies in Indian and Israeli pedigrees have indicated the likelihood of holandric or Y-linked inheritance (Slatis and Apelbaum, 1963; Dronamraju, 1964). Stern et al.
(1964) summarized the literature and presented data which, however, do not prove beyond a doubt that this characteristic is inherited. Its incidence among Israeli men was 25.8 percent; among two groups of Indian men from Madras and West Bengal, it was 70 percent and 30 percent, respectively. The trait, the severity of which varied widely, was never seen before puberty and usually did not reach full expression until much later in life. Unless the hairs are sufficiently coarse, there may be a question as to whether the trait is actually present. The true condition Includes only hair growing on or adjacent to the pinna of the ears and does not include hair growing on the lobule or in the external ear canal, another male trait that is related to androgen stimulation but is an unrelated phenomenon already discussed.

In each of the other striking observations of localized hypertrichosis, a mendelian inheritance has been suggested. Examples are hairy elbows (Brighton, 1970b) in an Amish kindred, inherited probably as an autosomal recessive trait, and hypertrichosis of the medial left eyebrow near the root of the nose in 9 members of three generations of a family observed by Ludwig and discussed by Cockayne (1933). Beek (1950) likewise reported symmetrical extensions of the eyebrows to the midline, equally common among men and women, in up to 22 percent of a Dutch population. Cockayne (1933) also reviewed briefly the details of various localized forms of hypertrichosis presumably related to dominant inheritance; evaluation of his data, however, is not possible. Persons were included who had excessive eyebrows and eyelashes and localized hypertrichosis of the forehead and neck. Mention should also be made of Trotter and Danforth's (1922) unlikely suggestion that hair in the moustache area is inherited by women as a dominant characteristic.

Physiologic Factors

This is an artificial category that cannot really be separated from the racial and familial factors since genetic mechanisms are significantly operative in all of them. Nevertheless, it provides a convenient focus for a discussion of some of the normal and important changes in adolescence and aging. The information about the genetics of these events is less conclusive.

Premature pubarche. This term refers to the unexplained development of pubic hair and, less commonly, axillary hair in children who show no other signs of sexual maturation. Commoner among girls than boys, it is seen in children as young as 4 or 5 years of age, the youngest affected patient reported being 5 weeks of age. Puberty follows normally in these children. Sigurjonsdottir and Hayles (1968b) reported 24 such cases; only one patient had organic disease of the central nervous system, which was attributable to neurofibromatosis. However, associated organic neural disease was noted in a third of the cases reported in the literature. Although no evidence suggests that premature pubarche in an otherwise healthy child heralds the onset of organic disease of the nervous system, it does occur rather commonly in children with severe organic brain disease.

The cause of the disorder is not known, but according to several postulates it reflects premature activity of the adrenal glands in the production of androgens and thus anticipates puberty, increased end-organ sensitivity of the pubic and axillary hair, or hypothalamic abnormality (Conly et al., 1967; Sigurjonsdottir and Hayles, 1968b). Familial occurrence of this condition is uncommon. Perloff and Nodine (1950) reported an affected brother and sister; of the 24 patients reported from the Mayo Clinic (Sigurjonsdottir and Hayles, 1968b), all but two were females and three had a family history of premature pubarche. A young woman with onset of the condition at 5 weeks of age and two brothers similarly affected experienced a normal adolescence and subsequently gave birth to two unaffected children. A second patient in the series reported the history of an affected paternal grandmother, and a third patient had a female first cousin said to be affected. None of these relatives, however, were examined by the authors. Thus, whereas well over 100 cases of this condition have been reported, only a few mention affected relatives. Adequate genetic studies have not been carried out, but there does seem to be a small degree of heritability.

Adolescent development. Puberty greatly stimulates the growth of hair, particularly of sexual hair. Adolescence begins with increased secretions of gonadotropic hormones by the anterior lobe of the pituitary gland concomitant with increased secretions of adrenal androgens in girls indicated by the development of sexual hair and increased urinary 17-ketosteroids. Wilkins et al. (1965) stated that puberty begins any time between the ages of 9 and 17 years, a little earlier in girls than in boys. Axillary hair begins to grow about 2 years after pubic hair (Hamilton, 1958) and reaches a maximum in the third decade. Adolescence is also the time of the greatest growth of terminal hair in other areas, especially on the extremities and the trunk in genetically predisposed women.

Little is known about the complex interaction of genetic and environmental factors that influence the onset of puberty. Where the environment is good, most of the variability in the age when menarche begins is due to genetic differences. In France the mean difference in menarcheal age for identical twins was 2 months compared with 8 months for nonidentical twins (Tisserand-Perrier, 1953). According to Motulsky and Epstein (1968), the time when menarche begins in mothers and daughters as well as in sisters shows a significant correlation and indicates control by multiple genes. Tanner (1962, 1969), who reviewed the literature on menarchal age, concluded that during the last 100 years menarche has been oc-
Occasionally, hirsutism in normal children. The evaluation of hirsutism in children can be rather complex, depending on the extent and severity of the involvement, and requires a total evaluation of the patients. This latter task is made even more difficult by the lack, except for Holzel’s study (1951), of systematic investigations of normal children; many more studies are needed. Small to moderate amounts of lanugo hair widely distributed in the newborn are not rare but usually disappear during the first year or two of life (Wilkins et al., 1965). Occasionally, the lanugo hair persists and forms terminal hair, most commonly in the lumbosacral region and longitudinally along the spinal column and on the extremities. Many of the generalizations about familial adult hirsutism can be made about the condition in children. Occasionally no etiologic factors will be found (Fig. 1A).

Pregnancy. Women in their first trimester of pregnancy commonly experience increased hairiness, especially on the face, extremities, and about the breasts (Bissell and Williams, 1945; Stoddard, 1945). In most cases the hypertrichosis is slight to moderate and disappears after or even before delivery. That predisposing genetic factors are significant was suggested by Bissell and Williams (1945), who reported transient hirsutism during the pregnancies of a woman and her daughter. An increase in adrenal androgens caused by increased stimulation of the adrenal glands during pregnancy has been postulated as the etiologic factor; however, the androgenic activity of progesterone is not thought to be responsible (Brooksbank, 1961).

Menopause. Beek’s study (1950) of women in the Netherlands confirmed the long-standing clinical finding that menopause heralds the onset of increased loss of hair in the pubes, axillae, chest, and extremities. In contrast, growth of hair on the chin and on the moustache area increases with age in postmenopausal women. Thomas and Ferriman (1957) corroborated these findings. Hamilton (1958) noted an abrupt decline in the growth of axillary hair coinciding with the menopause, which was accentuated in a study of Japanese women: in a group of women over 60, not a single axillary hair was found in 98 percent.

Although the decrease in axillary and pubic hair in older women can be explained by the decline in ovarian androgenic secretion, the paradoxical increase in facial hair cannot be attributed to increased adrenal androgens (Hamilton and Terada, 1963). Brooksbank (1961) summarized the various theories implicating an altered ratio of androgen to estrogen after the reduction of ovarian function. What role estrogens play in mitigating the effects of androgens on hair growth is largely unexplained; the fact remains that reasonably near physiologic concentrations of exogenous estrogens do not reverse the rapid rate of growth of sexual hair. Hamilton and Terada (1963) suggested that the seeming increase in facial hair after the menopause is actually coarsened hair produced by inherent changes within the follicles themselves which are age dependent but unrelated to hormonal stimulations. I am not aware of any recent familial studies on the extent and severity of postmenopausal moustache and chin hairs.

Neural and emotional factors. In previous reviews of the evidence for neural control of hair growth, I have concluded that there are no experimental or objective clinical observations to substantiate such control (1969). Quite the contrary, in most cases, hirsutism is usually related to hormonal mechanisms mediated through the hypothalamic-pituitary-adrenal-ovarian axis or is a fortuitous relationship. Emotional stress has been implicated as a factor in hirsutism. Bush and Mahesh (1959) emphasized the environmental aspects in their report of the rapid development of hirsutism in one of identical twins after severe emotional stress. When ACTH was given to both twins, the urinary excretion of 17-ketosteroids increased much more in the hirsute twin than in the nonhirsute twin. Meyer and Zerssen (1960) reported a high level of anxiety in hirsute women. Lloyd (1963) believes that intense and prolonged

Currying in European girls 3 to 4 months earlier per decade. Hong Kong Chinese girls and Cuban girls experience menarche the earliest. The Bundi of New Guinea are the only known group in which menarche is as late nowadays as it was in Europe a century ago.

Precocious sexual development. Such development accompanied by adult patterns of hair growth occurs more frequently in girls than in boys at exceedingly young ages. In a Danish population of about 4.5 million from 1938 to 1946, the incidence of constitutional or idiopathic precocious puberty was estimated by Thamdrup (1961) as 4 girls a year and 1 boy every other year.

In 80 to 90 percent of the cases of precocious puberty, no abnormality in the endocrine or nervous system is found. Infrequently associated pathologic disorders have included brain tumors, encephalitis, and ovarian and adrenal neoplasms (Seckel, 1946; Thamdrup, 1961; Sigurjonsdottir and Hayles, 1968a; Hung et al., 1971). In Thamdrup’s study among the patients with idiopathic precocious puberty, there was a distinct preponderance of close female relatives with unusually early pubertal development but no distinct pattern of inheritance. Wilkins et al. (1965) also noted a familial tendency to sexual precocity; in one family both sexes were affected. Jacobsen and Macklin (1952) reported four generations of a family in which 27 males but no females were affected. Precocious puberty in both a male and a female sibling with normal parents also has been reported (Ferrier, 1961). Sexual precocity in girls, accompanied by macular areas of hyperpigmentation of irregular outline, polyostotic fibrous dysplasia, and sometimes other endocrine abnormalities, is a rare nonfamilial disorder called Albright’s syndrome (Albright et al., 1938).

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emotional stress alters the patterns of secretion of adrenal steroids. Cortisol may augment the response to androgens, and epinephrine can increase the production of cortisol (Lloyd, 1968). Nevertheless, clinical observations of the relationship between hirsutism and psychologic stress are only rarely substantiated by adequate experimental data. As Lloyd (1963) pointed out, psychologically depressed patients may only be more conscious of excess hair.

Idiopathic Hirsutism

This term, which represents a poorly defined and heterogeneous category, is most commonly used to describe a type of hypertrichosis with android distribution that obviously excludes ovarian or adrenal lesions (Fig. 2). Usually it is accompanied by acne, irregular menses or amenorrhea, obesity, and even common baldness. This clinical syndrome blends so imperceptibly with the following three other main categories that it is often difficult to separate them with certainty: (1) the racial or familial type of hirsutism in which the menstrual cycle and fertility are completely normal, (2) the acquired adult adenogenital syndrome, and (3) the Stein-Leventhal syndrome. Except for Lorenzo’s study (1970), little information is available on the genetic influence of these conditions. I previously summarized the arguments (1969) for relating the idiopathic type to one or another type of hirsutism, but until more information and precise evaluation are available, this category should probably be maintained.

Extrinsic Influences on Hair Growth

Several investigators have suggested important environmental effects on hirsutism, especially in sun and wind on increased amounts of hair on sun-exposed areas, but this influence has never been proved (Castellani, 1938). Probably only severe and repeated cutaneous stimulation, like that reported in retarded patients who chew and bite their skin repeatedly (Ressmann and Butterworth, 1952), will cause localized hypertrichosis. Occupational types of localized hairiness of the shoulders and adjacent areas, like those of sack bearers (Csillag, 1921) and of porters carrying heavy loads on straps (Naus, 1961), have been reported. An excessive amount of hair has been noted about the peripheral areas of lichenified plaques (Ressmann and Butterworth, 1952) and hair neogenesis was postulated in stimulated acanthotic skin ( Muller, 1971). Several investigators (Becker and Obermayer, 1940; Ressmann and Butterworth, 1952; Flesch, 1954) have suggested that hyperemia of the skin increases the growth of hair, basing their hypothesis on the simultaneous occurrence of hirsutism and arteriovenous aneurysms in the same areas ( Allen, 1954). However, induced hyperemia of the skin had no therapeutic effect on alopecia, and hair is apparently not easily affected by external forces.

Drug-induced hirsutism, either a simple, generalized hypertrichosis or part of a virilizing syndrome, is an increasingly frequent complication of modern therapy (Fig. 3A). The types of drugs that cause this type of reaction vary considerably (Table). This complication should suggest major investigational avenues for study, but little progress has been made. The most interesting findings involve those forms of hirsutism caused by Dilantin (Bray, 1959; Livingston et al., 1955), diazoxide (Baker et al., 1967), and hexachlorobenzene (Turkish porphyria) (Cam and Nigogosyan, 1963), which are probably mediated by other influences than steroidal hormones. On the other hand, if steroid drugs capable of inducing virilization are administered, hirsutism is an expected complication. Progestogens, anabolic steroids, and testosterone and its derivatives are in this category. Genetic differences in individual susceptibility to the development of hirsutism and virilization are apparent in the variable doses of testosterone required to produce this effect. Some women are susceptible to exceedingly small doses of androgens (Hamblen, 1957), and brunettes are said to be more susceptible than blonds (Geist, 1941).

Hirsutism Associated With Nevi or Hamartomas

Severe hypertrichosis sometimes occurs in compound or dermal nevi, an association referred to as nevus pigmentosus et pilosus. A familial occurrence has been postulated for the inheritance of moles, with dominant transmission reported in some pedigrees (Denaro, 1944; McKusick, 1971). Moles are also a feature of Turner’s syndrome. Nevertheless, in most people, multifactorial inheritance is the more likely mechanism. When pigment cells are not present, as happens occasionally, such localized areas of hairiness in normal skin are called “nevus pilosus” (Fig. 1B). They occur most commonly on the back, especially in the lumbosacral region; occasionally they are associated with abnormalities of the spinal column.

Special mention should be made of the giant bathing trunk nevi that frequently have luxuriant growths of pigmented hair (Reed and Becker, 1964). Reed et al. (1965a) pointed out the dermatomal distribution, the asymmetry sharply delimited at the midline or the symmetry of the lesions, as well as occasional association with neurofibromatosis. Crowe and associates (1956) reported extensive bathing trunk nevi in three of their 223 patients with neurofibromatosis. Nevertheless, except for two possible cases involving a boy and his sister

Fig. 1. Hirsutism of unknown cause. A. In 7-year-old girl who had had dumbbell-type neuroblastoma resected from posterior mediastinum at 13 months of age, onset of hirsutism at 5 years. B. Nevus pilosis of right shoulder, present since infancy without change in 56-year-old man. C. Facial hirsutism in 54-year-old woman who had noted excessive hair growth 1 year before diagnosis of porphyria cutanea tarda.
(Cockayne, 1933), familial giant nevi have not been reported. Neurofibromatosis is transmitted as a mendelian autosomal dominant trait.

Copeman and Jones (1965) reported 24 cases, two of them women, with a distinctive type of hypertrichosis associated with nevus unius lateralis previously described by Becker (1949); the incidence of the lesions was estimated to be at least one in 4,000 patients. The lesions occurred most often on the upper part of the trunk and were considered a maldevelopment or hamartoma of the epidermis. Some areas were extensively involved, but epidermal thickening was not apparent in all cases.

Hirsutism Associated With Endocrinologic Disorders

The causes of hirsutism associated with known endocrinologic abnormalities are listed in the Table. It should be emphasized that these syndromes probably affect only 1 percent or less of patients with hypertrichosis (Fig. 3B and C). Known endocrinologic disease is more prevalent in extremely hirsute women, especially in those who show signs of defeminization or questionable virilization and constitute the largest number of patients referred to endocrinologic clinics (Deller et al., 1965). The main conditions with easily recognizable genetic aspects are the syndromes of congenital adrenal hyperplasia and other intersex disorders. Cooper et al. (1968) and Givens et al. (1971) suggest that the Stein-Leventhal syndrome be included in this category; but we need more information about the male members of such families before we can accept an autosomal dominant mode of inheritance.

Cushing’s syndrome and acromegaly. These conditions have been reported infrequently in the familial syndromes of multiple endocrine adenomas (Ballard et al., 1964; Steiner et al., 1968). Eight examples of acromegaly in affected members of two successive generations included four fathers and one or more affected sons (Koch and Tiwisina, 1959). Daughaday (1968) reported that hypertrichosis develops in 53 percent of patients with acromegaly and is usually detected early. Hirsutism in acromegaly has been related to excess pituitary trophic factors other than growth hormone. Late in the disease, loss of hair occurs when pituitary insufficiency develops. The incidence of...
HIRSUTISM IN CUSHING'S SYNDROME HAS BEEN ESTIMATED TO BE AS LOW AS 25 PERCENT AND AS HIGH AS 84 PERCENT (Soffer et al., 1961). FULL-BLOWN CUSHING'S SYNDROME IS EASY TO RECOGNIZE, AND HIRSUTISM IS NOT AN IMPORTANT DIAGNOSTIC SIGN SINCE OTHER CLINICAL FEATURES ARE SO PRONOUNCED. MILD FORMS OF THE DISEASE HAVE BEEN NOTED WITH OBESITY OF A NONDESCRIPT TYPE AND MILD HIRSUTISM (Goldzieher, 1964).

MENTION SHOULD BE MADE OF AN INCREASINGLY COMMON TYPE OF CUSHING'S SYNDROME ASSOCIATED WITH THE AUTONOMOUS PRODUCTION OF AN ACTH-LIKE SUBSTANCE BY NONENDOCRINE TUMORS. ALMOST 80 PERCENT OF THESE NEOPLASMS HAVE BEEN ONE OF THREE CELL TYPES—BRONCHOCARCINOMA, THYMUS CARCINOMA, AND PANCREATIC CARCINOMA (Liddle et al., 1965). A CURE OF CUSHING'S DISEASE WITH HIRSUTISM HAS BEEN REPORTED FOLLOWING REMOVAL OF AN ARGENTAFINOMA OF THE APPENDIX (Bernstein et al., 1970). UPTON AND AMATRUDA (1971) FOUND TUMOR PEPTIDES WITH CORTICOTROPIN-RELEASING FACTOR-LIKE ACTIVITY.


COMMON VIRILIZATION TYPE OF CONGENITAL ADRENAL HYPERPLASIA: Ninety-five percent of the cases of congenital adrenal hyperplasia are of this type, which is due to a deficiency of 21-hydroxylase that results in a block of C-21 hydroxylation of 17-hydroxyprogesterone. Of the two common forms, the milder, simple virilizing form constitutes two-thirds of the cases, and the virilizing, salt-losing form the other one-third. In the latter type, the production of aldosterone is decreased, and aldosterone antagonists accumulate and lead to severe wasting and addisonian crises. Degenhart and colleagues (1965) postulated that these forms were dependent upon different genetic defects; it is usually true that only one form or the other is seen in affected members of a kindred.


THE COMMON FORM OF CONGENITAL ADRENAL HYPERPLASIA AFFECTS BOTH SEXES EQUALLY AND IS INHERITED AS AN AUTOSOMAL RECESSIVE TRAIT. ITS INCIDENCE HAS BEEN ESTIMATED TO BE 1 IN 67,000 PERSONS IN MARYLAND AND 1 IN 5,000 IN SWITZERLAND, THE ESTIMATES OF THE FREQUENCY IN HETEROZYGOTES BEING 1 IN 128 AND 1 IN 35, RESPECTIVELY. USUALLY MORE FEMALES THAN MALES ARE REPORTED, SINCE THE CONDITION IS MORE EASILY OBSERVED AND DIAGNOSED IN FEMALES THAN IN MALES.

IN PATIENTS WITH THE SIMPLE, COMMON VIRILIZING FORMS, THE ONSET OF VIRILIZATION OCCURS AT DIFFERENT AGES IN DIFFERENT PEDIGREES; IN THE VIRILIZING AND SALT-LOSING FORMS, THE ONSET OF ELECTROLYTE LOSS BEGINS EITHER NEONATALLY OR LATER IN LIFE. SOTOS (1970) HAS POINTED OUT THAT SOME OF THE CASES OF WHAT SEEM TO BE MIXED FORMS OF CONGENITAL ADRENAL HYPERPLASIA ARE NOT EASILY EXPLAINED.

THERAPY FOR ALL FORMS OF CONGENITAL ADRENAL HYPERPLASIA IS USUALLY COMPLEX, DEPENDING ON THE EXTENT OF THE CORTIOL OR MINERALOCORTICOID DEFICIENCY. SURGICAL CORRECTION OF THE EXTERNAL GENITALIA IS SOMETIMES INDICATED; IN SUCH CASES, SPECIAL CONSIDERATION MUST BE GIVEN TO THE SEX OF REARING AND THE PSYCHOLOGIC ADJUSTMENT. SUCH THERAPEUTIC MEASURES ARE THERAPEUTICALLY DISCUSSED IN MOST STANDARD TEXTBOOKS ON ENDOCRINOLOGY (HUBBLE, 1969).


OTHER RARE GENETIC TYPES INCLUDE FORMS CAUSED BY DEFICIENCIES OF 3-β-HYDROXYSTEROID DEHYDROGENASE OR BY 17-HYDROXYLASE DEFICIENCY. COMPLETE DEFICIENCY OF THE FORMER RESULTS IN SEVERE LOSS OF SALT AND DEATH. FEMALES HAVE VARIABLE DEGREES OF VIRILIZATION OF THE EXTERNAL GENITALIA AND MALES HAVE DEFECTIVE VIRILIZATION OF THE EXTERNAL GENITALIA SINCE THE ENZYME DEFICIENCY IS ALSO PRESENT IN THE LEYDIG
cells of the testis. In such cases, virilization does not occur; instead sexual underdevelopment and a deficient synthesis of estrogens and androgens as well as of cortisol, plus excessive production of progesterone, 11-desoxycorticosterone, and corticosterone, are present. The biochemical error in the ovaries accounts for the defective production of estrogen. The inheritance of this form appears to be more complex, and there may be different genetic forms. Thus, a father and son have been reported to be involved; in another case, an X-linked recessive inheritance was thought to be implicated (McKusick, 1971; Sotos, 1970).

In lipid adrenal hyperplasia, the biosynthetic defect occurs between cholesterol and pregnenolone. Infants of both sexes have normal external genitalia since the production of estrogens and androgens is affected. All known subjects have lost salt, have had recurrent infections, and have died in infancy.

Intersex problems other than congenital adrenal hyperplasia. Five to 10 percent of patients with pure gonadal dysgenesis have had associated hirsutism or virilism, the causes of which were not always known. Recently Judd and associates (1970) demonstrated the production of testosterone by rudimentary gonadal streaks in a young woman with progressive hirsutism. Hirsutism and virilism have also been described in patients with Turner’s syndrome. In both conditions, explanations frequently have not been apparent; but in some cases androgen-secreting tumors, particularly hilus cell tumors and gonadoblastomas developing in the dysgenetic gonads, may have been responsible. In male pseudohermaphrodites reared as girls, hirsutism sometimes develops during adolescence as a functional consequence of testicular remnants, and a familial occurrence has been noted in some patients (McKusick, 1971). However, about a third of the patients with male pseudohermaphroditism, who are classified as having the complete form of testicular feminization and are frequently particularly feminine in appearance, do not have axillary or pubic hair; the remainders have sparse amounts of hair despite the normal concentration of plasma and urinary testosterone. Furthermore, testosterone does not cause an increased growth of hair in these patients. Karszmania and associates (1969) and Wilson and Walker (1969) suggested that the occurrence of decreased end-organ sensitivity involves a deficiency in the conversion of testosterone to dihydrotestosterone in the skin, but this has not been definitively confirmed. This form of testicular feminization is transmitted through apparently normal females and affects about half of their genetic sons. It is not known, however, whether this is an X-linked recessive or an autosomal dominant trait without effect in the female. It has also been suggested that the disorder results from a regulator gene abnormality.

Patients with the incomplete form of testicular feminization usually have ambiguous male external genitalia. Feminization is less adequate at puberty than in patients affected with the complete form. Some have scanty sexual hair, whereas others are hirsute. The inheritance is similar to that of the complete form, but whether it is a separate genetic entity is not clear (Sotos, 1970).

Patients with the testicular masculinization–feminization syndrome resemble those with the incomplete form of testicular feminization and are distinguishable mainly by the hereditary pattern, which suggests an autosomal recessive trait with consanguinity in the family background (Philip and Trolle, 1965; Sotos, 1970).

Hirsutism Associated With Congenital Anomalies

Many congenital syndromes, in which hirsutism is of variable significance, are included here. In some cases, such as hypertrichosis lanuginoso, Cornelia de Lange syndrome, congenital generalized lipodystrophy, and leprechaunism, hypertrichosis is a prominent feature; it has also been associated with congenital hemihypertrophy (Hurwitz and Klaus, 1971). Cowden’s syndrome, a rare disorder of which the genetics are not known, consists principally of congenital macrogingivae, large fibroadenomas of the breast which may become malignant, and papillomas of the mouth. According to Witkop (1971), hypertrichosis is sometimes a feature. In the mucopolysaccharidoses, the trisomy 18 (E) syndrome, and the Rubinstein–Taybi syndrome, hypertrichosis is of less clinical importance and will not be discussed further (Bartok et al., 1968; Smith, 1970). I have deleted Bloom’s syndrome from my previous list (1969) on the advice of German (personal communication), who has seen almost all the reported patients. The occurrence of hirsutism in the Seckel syndrome is also in doubt. Seckel (1960) reported that generalized hypertrichosis occurred in 4 of 15 patients who were bird-headed dwarfs, but no mention of this was made by other authors. On the contrary, McKusick et al. (1967) noted occasional alopecia in the Seckel syndrome. The various mechanisms leading to increased hairiness have not yet been explained. Undoubtedly other congenital anomalies will be added to the list, but confirmatory information on the relative frequency and importance of this characteristic is needed.

Hypertrichosis lanuginoso. In this extremely rare hereditary disorder of autosomal dominant inheritance, the generalized growth of lanugo hair persists (Cockayne, 1933; Flesch, 1954). The degree of hirsutism varies and the lanugo hair does not develop into terminal hair. Hirsutism may be present at birth or may not become apparent until as late as the seventh year. Dental abnormalities, especially anodontia and gingival fibromatosis, have been reported in several patients. Gorlin and Pindborg (1964) have referred to this condition as a syndrome of “idiopathic gingival fibromatosis and hypertrichosis.” The development of normal terminal hair in some patients seen by Gorlin and
Pindborg suggests different forms of the disorder since in the classic form terminal hair is said never to replace lanugo hair. This is best illustrated by Cockayne's (1933) separation of the condition affecting Julia Pastrana and her son into a separate syndrome termed by him "hypertrichosis terminalis" with Simian characteristics because of the terminal appearance of the hair, which was intensely pigmented, and of certain facial characteristics. In reviewing the literature from the 16th century to the present, Felgenhauer (1969) grouped all these cases into one syndrome, as did Beighton (1970a). Whether or not they are separate entities or constitute only variable expressions of an autosomal dominant trait remains to be seen.

Cornelia de Lange syndrome. Failure to grow, mental retardation, an abnormal distinctive cry, and a cluster of relatively minor congenital malformations are characteristic of this syndrome, which is of uncertain genetic etiology. Both autosomal recessive inheritance and a chromosomal aberration have been suggested (Jervis and Stimson, 1963; Hart et al., 1965; Schuster and Johnson, 1966; McKusick, 1971). Hirsutism is invariably present. The eyebrows are long, thick, and darkly pigmented and may meet in the midline and the eyelashes are long and delicate. The anterior hairline of the scalp is set low on the forehead. An increased growth of hair on the back is common, and occasionally other areas of the trunk and extremities are also hirsute.

Congenital generalized lipodystrophy (Berardinelli's or Seip's syndrome). The syndrome consists of congenital generalized lipodystrophy associated with accelerated somatic growth, acanthosis nigricans, diabetes mellitus, and a number of other abnormalities. There is hirsutism of the face, neck, arms, and legs and frequently a low anterior hairline. The hypertrichosis does not include pubic or axillary hair although enlargement of the phallus suggests an androgen effect. However, Gordon and colleagues (1971) have related this to the increased secretion of growth hormone or to the impaired peripheral breakdown of the hormone. Autosomal recessive inheritance is indicated; many cases have been of Portuguese-Spanish ancestry. Leprechaunism (Donohue and Uchida, 1954; Smith, 1970; Kaloustian et al., 1971) has been regarded as a possible variant of congenital generalized lipodystrophy. However, growth retardation and the leprechaun facies are completely different, and probably the syndromes are also different. Facial and body hirsutism similar to the Seip syndrome is sometimes seen, and the mode of inheritance is similar (Reed et al., 1965b).

Miscellaneous causes. A number of other conditions associated with hirsutism (Table) form an interesting group of disorders in which hypertrichosis is not easily explained. Special mention should be made of acquired hypertrichosis lanuginosa in adults (Lyell and Whittle, 1951; Fretzin, 1967) in which metastatic cancer was an associated finding. Hensley and Glynn (1969) reported such a case and reviewed 5 other similar cases in the literature, noting that epithelial malignancies (two of which were small cell anaplastic carcinomas of the bronchi) were reported in each case. No steroideal abnormalities in these patients have been reported to date, and the sexual hair is not affected. This syndrome of "malignant down," as Fretzin (1967) has called it, is completely different from the rare cases of hirsutism in women associated with metastatic carcinoma of the ovary (Krukenberg's tumor), which is sometimes associated with virilization or may result from the secretion of androgen by an ovarian stroma (Scully and Richardson, 1961; Ober et al., 1962).

Important also is the hirsutism associated with all the forms of porphyria, especially porphyria cutanea tarda (Fig. 1C), variegate porphyria, and congenital porphyria (Dean, 1963; Zeligman, 1963). However, the severest hirsutism was that of the so-called monkey children seen during the epidemic of porphyria in Turkey caused by the ingestion of hexachlorobenzene.

Hypothyroid children frequently have a noticeable unexplained increase in lightly pigmented fine hair on the trunk and extremities that is never seen with signs of virilism. Treatment with thyroid extract causes complete involution of the hair. The cause of the hirsutism or the reason for the susceptibility of children has not been explained, but increased conversion of testosterone to urinary metabolites with greater androgenic activity (Goldzieher, 1964) or alterations in the metabolic clearance rate of testosterone or in the testosterone-binding globulin are possibilities (Bardin and Mahoudeau, 1970).

COMMENTS

The management of a patient with hirsutism need not be complicated even though the associated disorders are numerous (Forbes, 1965; Muller, 1969). Endocrinologic abnormalities are seen in about 1 percent of the women who consult a physician about hypertrichosis but are commoner in severe degrees of hirsutism. New techniques will probably identify additional cases of abnormal endocrine function, like those shown by Bardin and Mahoudeau (1970) in some virilized women, who had increased testosterone-production rates but, paradoxically, normal plasma testosterone levels because of the increased clearance of hormone by extrahepatic tissues.

However, explanations for the extraordinary variability normally found in man and for the numerous cases of hypertrichosis that arise from nonendocrinologic causes will probably come from additional investigations of the end-organ responsiveness of the pilosebaceous structures themselves to androgenic stimulation. Studies in these areas have only just begun, but already tangible results can be seen in the reports of Bruchovsky and Wilson (1968), Adachi and Kano (1970), Faredin et
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al. (1970), Takashima et al. (1970), and Sansone and Reisner (1971), all having to do with variations in the end-organ responsiveness of pilosebaceous follicles in the skin.

New avenues of investigation of hair biology have been opened by Freedberg (1970), who reported a cell-free amino acid-incorporating system prepared from mammalian hair root cells that could provide important information about the regulatory mechanisms and biochemical pathways involved in the synthesis of hair protein. Should the system prove to be sufficiently active and reproducible, then hair bulbs should become a prime tissue where the abnormalities in several genetic and drug-induced disorders could be determined. Already available is a more direct application of plucked hair bulbs for the diagnosis of genetic disorders and the identification of heterozygotes reported by Silvers and associates (1971) in the Lesch-Nyhan syndrome. These workers showed the absence of hypoxanthine-guanine-phosphoribosyl-transferase by using hypoxanthine-C14 as substrate and measuring the conversion to radioactive nucleotide in affected patients and the mosaicism in hair follicles of obligate heterozygotes in which 25 percent of hair roots lacked the enzyme. These results, which are an additional confirmation of the Lyon hypothesis, strengthen the expectation that similar studies will confirm the usefulness of hair roots in the study of numerous genetic disorders.

Little is known about environmental influences on hair growth, but the possibilities of Freedberg’s model system (1970) as well as the use of follicle squash preparations for studies of cell kinetics and response to irradiation (Malkinson et al., 1971) suggest that much additional information will be forthcoming shortly. It has previously been shown that protein deprivation (Bradfield et al., 1967; Bradfield et al., 1968) causes significant atrophy of the hair root; such information has been used to survey protein malnutrition in a population group. The hair roots, therefore, are an important biologic tissue, easily available for investigation (Muller and Winkelmann, 1969), whose versatility has not been generally appreciated by the scientific community.

A number of fundamental clinical problems relating to hirsutism need to be resolved. What causes the hirsutism induced by Dilantin, diazoxide, or hexachlorobenzene? Why does hirsutism occur in patients with porphyria? Finally, and most importantly, why is hypertrichosis of the moustache and chin areas seen in many postmenopausal women in spite of declining levels of all sex hormones? Answers to these complex questions will no doubt be difficult, but they should provide abundant biologic information applicable to numerous medical problems.

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