Morphogenesis and Malformation of the Skin

Editor
Richard J. Blandau

March of Dimes
Birth Defects Foundation

Birth Defects: Original Article Series
Volume XVII • Number 2 • 1981

Alan R. Liss, Inc.

March of Dimes Birth Defects Foundation
Birth Defects: Original Article Series, Volume XVII, Number 2, 1981

MORPHOGENESIS AND MALFORMATION OF THE SKIN

Sixth International Workshop on Morphogenesis and Malformation
held at Lake Wilderness, Washington, September 18–20, 1980
Sponsored by
March of Dimes Birth Defects Foundation

Editor: **Richard J. Blandau, PhD, MD,** Department of Biological Structure, University of Washington, School of Medicine, Seattle

Associate Editor: **Natalie W. Paul,** March of Dimes Birth Defects Foundation

Assistant Editor: **Florence Dickman,** March of Dimes Birth Defects Foundation

ALAN R. LISS, INC., NEW YORK

To enhance medical communication in the birth defects field, the March of Dimes Birth Defects Foundation publishes the *Birth Defects Compendium (Second Edition),* an *Original Article Series, Syndrome Identification,* a *Reprint Series,* and provides a series of films and related brochures.

Further information can be obtained from:
March of Dimes Birth Defects Foundation
Medical Education Division
1275 Mamaroneck Avenue
White Plains, New York 10605

Published by:
Alan R. Liss, Inc.
150 Fifth Avenue
New York, New York 10011

Views expressed in articles published are the authors', and are not to be attributed to the March of Dimes Birth Defects Foundation or its editors unless expressly so stated.

Library of Congress Cataloging in Publication Data
Main entry under title:

Morphogenesis and malformation of the skin.

(Birth defects original article series; v. 17, no. 2)
Bibliography: p.
Includes Index.
1. Skin – Abnormalities – Congresses. 2. Skin – Growth – Congresses. 3. Cutaneous manifestations of general diseases – Congresses. 4. Pediatric dermatology – Congresses. I. Blandau, Richard Julius, 1912- II. Paul, Natalie W. III. Series. RG626.B63 vol. 17, no. 2 [RL31] 616'.043s 81-8302
ISBN 0-8451-1042-X [616.5'043] AACR2

The **March of Dimes Birth Defects Foundation** is dedicated to the goal of preventing birth defects and ameliorating their consequences for patients, families, and society.

As part of our efforts to achieve these goals, we sponsor, or participate in, a variety of scientific meetings where all questions relating to birth defects are freely discussed. Through our professional education program we speed the dissemination of information by publishing the proceedings of these and other meetings. From time to time, we also reprint pertinent journal articles to help achieve our goal. Now and then, in the course of these articles or discussions, individual viewpoints may be expressed which go beyond the purely scientific and into controversial matters. It should be noted, therefore, that personal viewpoints about such matters will not be censored but this does not constitute an endorsement of them by the **March of Dimes Birth Defects Foundation.**

Contributors

Gregory S. Barsh, BS, Department of Pathology, University of Washington, School of Medicine, Seattle, WA 98195 [**147**]

Eugene A. Bauer, MD, Division of Dermatology, Washington University School of Medicine, St. Louis, MO 63110 [**173**]

Richard J. Blandau, PhD, MD, Department of Biological Structure, University of Washington, School of Medicine, Seattle, WA 98195 [**xi**]

Robert A. Briggaman, MD, Department of Dermatology, University of North Carolina, School of Medicine, Chapel Hill, NC 27514 [**39**]

Melodie M. Buxman, MD, Department of Dermatology, University of Oregon, Health Sciences Center, Portland, OR 97201 [**205**]

Peter H. Byers, MD, Departments of Pathology and Medicine, University of Washington, School of Medicine, Seattle, WA 98195 [**147**]

D. Martin Carter, MD, PhD, Department of Dermatology, Yale University, School of Medicine, New Haven, CT 06510 [**117**]

Beverly A. Dale, PhD, Departments of Periodontics and Medicine (Dermatology), University of Washington, School of Medicine, Seattle, WA 98195 [**257**]

John M. Dwyer, MD, PhD, Department of Medicine, Yale University, School of Medicine, New Haven, CT 06510 [**93**]

Barbara A. Gilchrest, MD, Harvard Medical School, Beth Israel Hospital, Boston, MA 02215 [**227**]

Judith G. Hall, MD, Department of Medical Genetics, The Children's Orthopedic Hospital and University of Washington, School of Medicine, Seattle, WA 98195 [**243**]

Karen A. Holbrook, PhD, Departments of Biological Structure and Medicine (Dermatology), University of Washington, School of Medicine, Seattle, WA 98195 [**9,147**]

The bold face number in brackets following each contributor's name indicates the opening page number of that author's paper.

James R. Miller, PhD, Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada V6T 1W 5 [67]

William Montagna, PhD, Director, Oregon Regional Primate Research Center, Beaverton, OR 97006 [1]

George F. Odland, MD, Departments of Medicine and Biological Structure, University of Washington, School of Medicine, Seattle, WA 98195 [257]

Frank Parker, MD, Department of Dermatology, University of Oregon, Health Sciences Center, Portland, OR 97201 [79]

Vincent M. Riccardi, MD, Department of Medicine, Baylor College of Medicine, Houston, TX 77030 [129]

Larry J. Shapiro, MD, Department of Pediatrics, Division of Medical Genetics, Harbor-UCLA Medical Center, Torrance, CA 90509 [191]

*__David W. Smith,__ MD, Dysmorphology Unit, Department of Pediatrics, University of Washington, School of Medicine, Seattle, WA 98195 [61]

Lynne T. Smith, MS, Department of Biological Structure, University of Washington, School of Medicine, Seattle, WA 98195 [9]

Virginia P. Sybert, MD, Departments of Pediatrics and Medicine, University of Washington, School of Medicine, Seattle, WA 98195 [257]

*Deceased.

Preface

The scientific program of this workshop demarcates a path leading from the basic aspects of the morphology of skin to and through the complexities of some of the congenital abnormalities that are urgent and often confusing problems to the physician.

The primary value of a workshop such as this is not only the opportunity the laboratory scientists and physicians have to explore a subject in depth but also, and perhaps of greater importance, to direct attention to the significant gaps that remain in our knowledge of the basic etiology of so many of these distressing aberrations. If the report of this workshop awakens more interest for basic research in young dermatologists and helps to strengthen and expand the enthusiasm of those who are themselves in investigative dermatology, the labor of those who participated will be richly compensated.

Richard J. Blandau, PhD, MD

Contents

The Consequences of Having a Naked Skin

William Montagna, PhD

Most of the disorders, congenital or otherwise, that afflict human skin do so because, first, human beings refuse to practice eugenics and prefer to practice dermatology, and second, human skin is a highly complex organ different from that of all other mammals. Many of these differences reflect the fact that human skin has lost its fur cover. Regardless of racial and individual differences, human skin bears millions of hairs; most of them are so small as to be nearly invisible and the skin thus appears bare. And yet hairs generally grow vigorously and prominently on men's faces; on the limbs and trunks of some people; and particularly on the scalp, axillae, mons, and anogenital areas of both sexes.

Islands of long hairs surrounded by naked expanses can be readily observed and have probably piqued human curiosity from time immemorial. The biologists of antiquity conceived the idea that hairs were the product of dense gases released from the body by intrinsic heat; as these fuliginous gases escaped through the pores of the skin, they condensed and their growth was maintained by the continued condensation of gases behind them. Galen (130 to 200 A.D.) believed that hair grew long on the chin and head because the "exhalation" from the body humors rose to the head and Nature made use of its thicker residues to nourish the hair. Galen wrote that since men had much more of these residues than women and their bodies were warmer than women's, Nature had devised for men two ways to evacuate these residues: from the hairs of the scalp and from the hairs of the chin. Even Morgagni, in the 18th century, with obvious modifications, clung to the gaseous origin of hair. Early biologists also believed that the different colors of hair were due to differences in the nature of the excreted body gases and, therefore, to the types of humors of the organism.

Birth Defects: Original Article Series, Volume XVII, Number 2, pages 1–7

Most of the long hairs on the human body, except perhaps those of the scalp, serve no discernible function, and since they are sustained by androgens, their main purpose is ornamental and epigamic, that is, they serve to attract attention for sexual stimulation. Lacking adequate protection from hair, human skin has undergone adaptive structural changes that give it strength, resilience, and a highly developed sensibility.

Since all nonhuman primates are covered with fur, their skin adaptations differ only slightly, if at all, from those of other furred animals. Like the latter, nonhuman primates from birth onward are protected from the environment, and their skin, thus protected, does not have to adapt to the environment. It follows that all the major changes that have taken place in man have occurred concurrently with the loss of hair cover; hence, they are truly geared to the environment.

Miniaturization of the hair over much of man's body marks his major divergence from the other primates; all of the other adaptations are in some way related to this fact. These changes coincided with man's attainment of an erect bipedal posture and locomotion at least 3 million years ago and must be interwoven with and related to the total biologic needs of an erect body. In other words, the loss of body hair must have accompanied bipedality *pari passu*. The connection is logical. Man is a large animal whose body mass must be balanced vertically to prevent its toppling over, and his orientation in space is maintained by the continuous action of interrelated postural reflexes that, supported by two pillars, are harder at work than those in quadrupeds, which are supported by four. Even when a human being is standing still, sitting, squatting, or lying prone, most of the skeletal muscles of the trunk, limbs, and head must maintain a degree of tone by working synergistically lest the body collapse. Therefore, except during unconsciousness, much of the human muscle mass is continuously using energy and generating heat that must be eliminated. And it is for this very task that man's skin has been primarily tailored. Dissipation of heat is the function that most conspicuously distinguishes human skin from that of all other animals.

The loss of hair cover and the acquisition of an elaborate vascular system and sweat glands eminently accommodated this need but left the body exposed to environmental hazards. As early man wandered geographically, he encountered a number of problems. The fortunate coincidence of dark skin pigmentation in all human races that live in the tropics made possible an existence in sunny climates, but pigment that readily absorbs excessive ultraviolet light also absorbs infrared, which makes the body hot. A dark skin, then, is only a partial solution to a blazing, hot sun. What really equips human beings for survival is an intelligence that dictates not just when to come in out of the sun, but also how to make clothes to protect the body against the sun—or the cold. A fatty skin enables the inhabitants of near-arctic regions to live comfortably in environments that would be deadly to less well-adapted peo-

ple. Darwin wrote in his notebooks that when he arrived in Tierra del Fuego and stood with others on the deck of the Beagle, shivering in spite of heavy clothes and overcoats, naked Fuegians welcomed them in canoes. And, as it is not pigment alone that saves man from the sun's murderous rays, so it is not fat alone that protects the body against the cold; in each case an entire array of physiologic adaptations is involved.

Nakedness has left the large human animal unprotected and totally visible, even at a distance. Primitive man, therefore, needed to be less visible to predators and prey. Fortunately, a naked skin is easy to paint, and all known aboriginal peoples in the world, though often removed from each other by impassable barriers, have developed the custom of painting their bodies in a variety of ways and for a variety of purposes. Fragmentary evidence indicates that even early man practiced body painting to imitate the color patterns of other animals and to make himself terrifying in combat and more attractive in social encounters. Perchance by accident, early man discovered that the body paints that contaminated his wounds left permanent colored marks when the wounds healed. Some such event must have given birth to the universal practice of tattooing, an art that was practiced by the Egyptians 4,000 years ago and perhaps by earlier cultures as long ago as 8,000 years.

Today, as in ancient times, tattooing is often decorative, rarely useful, but always a badge of distinction. Like many other human motives, the reasons for one's wanting to be tattooed are not always evident, but whatever they may be, and they have changed along with social customs, tattoos would not exist if human beings possessed a furry skin. Tattooing is practiced by all known extant human societies, primitive or advanced. In recent times, the art has attained its highest achievements in England and in the Far East. People have themselves tattooed for the same reasons they paint their bodies—to gain identity, to express amorous or religious zeal, to mollify malignant spirits, to cover ugly scars, to become formidable to enemies, or simply for the sake of ornamentation. Since the most intricate tattoos are often hidden by clothes, their owners probably enjoy the secrets that their clothes hide. Tattoos are best imprinted on smooth and well-padded skin covered with nearly invisible hairs. Thus, the most florid designs and colors are to be found on the skin of oriental people and on the skin of women. Egyptian figurines of dancing girls of more than 3,000 years ago show decorative tattoos around the necks, wrists, and ankles.

Primitive Old World people also discovered that infected wounds produced proud flesh when they healed. Deliberate scarification, or the willful induction of keloid by rubbing inert substances into wounds, is widely practiced by primitive people, especially women.

Nakedness exposes all body contours, for example, women's breasts. Of female mammals, only women have large breasts when they are not lactating; these must be sexual attractors, and their visual effect is heightened by their

lack of surrounding long fur. Nakedness also accentuates the effect of the odd tufts of hair that grow here and there on the human body. A coat of fur would obviate the special visual cues we receive from pubic and axillary hair, beard, mustache, and eyebrows. Furthermore, man's deep concern with sexuality is probably related to nakedness and his highly developed cutaneous sensibility.

Most of the heightened sensibility of man's skin is directly related to the increased innervation of the hair follicles. Although the hair follicles of all mammals are equipped with some sensory nerve endings, only their vibrissae, or sinus hair follicles, are truly copiously innervated. In human skin, however, all follicles, large and small, have a superlative innervation, comparable to that of the vibrissae of other mammals. Even though man lacks true vibrissae, his skin is supplied with their functional equivalents everywhere. Equipped with Meissner corpuscles and other sensory receptors on the fingers, and heightened sensory receptors around the hair follicles over the rest of the body, man is a touching, stroking animal. This acute cutaneous sensory system could develop only with the acquisition of a large brain that could accommodate all the signals coming to it and that could determine instantly which course of action to pursue. Thus, nakedness and increased modalities of sensibility are necessary and related adjuncts of the gestalt of the evolving human skin.

Man may have diminished this sensibility somewhat when he donned clothes, but he managed to protect himself from his environment. I believe that the necessity of wearing clothes has played a key role in helping man devise cultures, mores, and social order. Human beings have used clothes to protect their bodies, to be sure, but they have also used them for disguises to assume the many roles that their fertile minds have fancied. Clothes also pique the curiosity and increase the desire for sexual contact. Thus, clothes have shaped human conduct. What if—denuded of external crutches—we were left to face the world naked? Would heads of state and schoolmasters still hold their heads high if their flabby bodies were exposed? Naked, would Napoleon, Hitler, Mussolini, Idi Amin, Pope John Paul II, and Carrie Nation have been as convincing and self-assured? What would kings and presidents, generals and sergeants stripped of their uniforms, medals, and ribbons have to do to command the obedience accorded them in full attire? And what about *me* and *my* crutches? If I had to face my colleagues in staff meetings or an employee I was firing in my office, without the embellishment of clothing and with my aging body exposed to them, could I continue to exercise what authority I have or think I have?

Clothes play a much more important role than mere protection from a hostile environment. They conceal liabilities and accentuate assets. As external symbols, clothes and cosmetics have played a singularly important role in human history. Ancient warriors adorned their helmets with flagrant displays of

horsehair and feathers. African and Indian warriors painted themselves in bewildering colors and wore frightening masks. Plumed hats and huge furred busbies adorned the heads of swashbuckling musketeers and grenadiers, respectively. No self-respecting Elizabethan blade would have appeared in public without his padded stockings, high-heeled boots, and codpiece. And modern man also has his concealments and adornments; some threaten to become as garish as those of his predecessors.

A grenadier I knew in London some years ago was an agreeable, mild-mannered young man. With *the* uniform on, he looked terrifying and was haughty and unapproachable. In the early days of the Fascisti, when I was young, I refused to become a Babilla or young Fascist. One evening at the theater, a friend from infancy thought I was defying his authority when, in full Fascist regalia, he and some of his companions arbitrarily decided to keep order. He slapped my face with such authority that I did not retaliate. After this devastating blow to my dignity and our friendship, I waited outside the theater to even the score. But before I could try to strangle him (my intent), he held out his hand saying: "Now look here, Guglielmo, we can be friends, but when I am in uniform you must respect me." Years later, when I performed in an orchestra, dressed in tails and white tie, the full impact of that young lout's remark struck me because so attired I regarded myself as a different person. What a transformation a few yards of textile can achieve! I wonder if we would be holding this seminar with straight faces if we were not dressed.

The subject of nakedness leads inevitably to the phenomenon of baldness, which has always intrigued man. It was Hippocrates (circa 460 to circa 360 B.C.), the alleged founder of Greek medicine, who first observed that eunuchs did not become bald. Aristotle (shown as balding in extant effigies) proposed that baldness resulted from a greasy and hot scalp. He observed that of all the animals he knew only human beings went noticeably bald, that no one went bald before the time of sexual activity, and that those who were naturally prone to intercourse always went bald. Aristotle believed that hair was nurtured by "oil and viscous secretions," which in libidinous men were dissipated so rapidly that baldness occurred. Women, apparently, did not go bald because "their nature" was similar to that of children, and like children, they were incapable of "producing seminal secretion." Eunuchs, who did not go bald because of "their transition to the female state," did not attain body hair, and if they had body hair at the time of castration, they lost it. Similarly, women had no body hair, but grew pubic hair. To Aristotle the situation in eunuchs could be explained in terms of a change from the male to the female state.

Apparently, human beings have always regarded scalp hair as the crown of their own beauty and baldness as an affront and a mischief. And yet the biol-

ogic aspect of baldness is at once exciting and perplexing since in both sexes scalp hair, at least through the adolescent years, grows longer than that on any other part of the body. To understand baldness, we must first realize that except for the types of hairs they bear, the scalp and forehead are structurally indistinguishable. It is the hairline that defines and accentuates the two, but, as daily experience shows, this is a vague demarcation, never fixed, forever retreating. If allowed to, scalp hair follicles can grow uninterruptedly for 12 or more years and produce hairs of such length that they are a liability. Hair and beard five or more feet in length are calamitous: they can be tripped over or become mixed in food and libations and entangled in environmental obstacles. But we have hands that turn this handicap into an ornament. In most nonhuman primates, head hairs are generally only slightly longer than those elsewhere on the body. Only in a few species are the crown hairs longer than those over the rest of the body.

On the human scalp, hair grows vigorously and densely during the early years, then gradually thins after the age of 30 in many men. But the belief that baldness represents a reduction in the number of hair follicles is wrong; baldness is a gradual, systematic involution of follicles until they are as small as those found during fetal life and produce nearly invisible hair.

The process of balding begins in all human beings during late gestation. Until the 7th month, the hair on the forehead of the human fetus is as long as that elsewhere on the head, and scalp and forehead are continuous. During the 7th and 8th month the follicles on the forehead either remain small or gradually involute, whereas those over the rest of the scalp continue to grow so that by birth the forehead appears naked. After birth, the hairs of the upper forehead continue to diminish until a clear hairline has been established. But the process continues, in most cases imperceptibly, throughout life; it becomes obvious in those with pronounced pattern baldness. In balding, the follicles on the frontal and parietal scalp involute just as those on the forehead did during late gestation and the early postnatal years. In cases of widespread baldness, the upper occipital scalp also becomes involved; except in extremely old men, the lower occipital and temporal areas rarely become bald. Since this disparity in topographic involvement reflects ordained biologic properties that are found in the scalps of all human beings, there is no scientific justification for regarding baldness as a defect.

Since we are cajoled and harangued daily about the indispensability of head hair to our beauty, we are likely to refute the truth, which is: 1) that baldness is a natural tendency of the scalp follicles to diminish as the individual matures, and 2) that human "capillary ornament" is fated to be replaced by the ornamental phase of the future, total baldness. Whether we like it or not, our species is becoming progressively more hairless and more bald; in

time we may become entirely so. It would be futile to challenge this statement since none of us will be able to observe this evolution.

Human beings have no monopoly on baldness. A few other primates routinely and predictably become bald. Male and female uakaris, stump-tailed macaques, orangutans, most chimpanzees, and some gorillas show varying degrees of alopecia in their mature years; the biologic phenomenon that brings about their alopecia is exactly the same as that in human beings.

We don't really know the extent to which man shares other dermatologic characteristics with his fellow animals. The only time cutaneous problems in other animals concern us is when they afflict domestic animals, in particular, fur- and wool-bearing ones and pets. Veterinary dermatologists are at a disadvantage when confronted with the cutaneous diseases of domestic pets, which are conundrums; many are probably the result of inbreeding. Among nonhuman primates we often see poor fur and idiopathic epilation, even in apparently healthy animals. There is also the case of the ruffed lemur *(Lemur variegatus)*, which has two color phases: black and white and red and white. In captivity, the two varieties breed readily, but the offspring are often nearly hairless. And, speaking of hairlessness, this genetic defect may occur in human beings as well as in a number of other animals. Hairless rats, mice, and rabbits have been successfully bred for laboratory purposes: little more than the genetic aspects of their hairlessness, which are straightforward, have been studied. Hairless chihuahuas have been bred since before the Aztec civilization, and yet there is not even a single good paper on the anatomy of chihuahua skin. Partial hairlessness is common in poodles. Since breeders cull such pups, nothing is known about the defect.

We do not know which congenital skin disorders are uniquely human because comparative dermatology is in its infancy and will remain so as long as we keep on ignoring the skin of other animals. Even the anatomy of the skin of most feral mammals remains unknown, and what we know shows great species differences. Skin disorders have concerned the animal breeder only when they have threatened his business. When only an occasional horse or cow has psoriasis or exfoliating dermatitis, it is expedient to shoot it. A feral animal with a debilitating dermatitis perishes, either on its own accord or by the hand of man.

Withal, however, congenital skin disorders are well established only in our species because of our belief in the sanctity of life and the reproductive rights of every individual, even one with skin like an alligator's; we thus ensure the perpetuity of such diseases.