ABSTRACTS OF PAPERS
GIVEN AT THE SYMPOSIUM ON
THE BIOLOGY OF HAIR GROWTH

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INTRODUCTION

WILLIAM MONTAGNA

From the point of view of biology, hair follicles are exciting organs. During the cycles of growth, which in different regions of the body last for days or years, they grow to the fullest extent of their inherent ability, and during the time of quiescence they are dormant. Numerous and inexplicable biological phenomena take place, including cyclical growth, differentiation and induction. These phenomena are demonstrated and repeated through each full cycle of growth of a hair generation. The purpose of this symposium is to bring together the various distinguished scientists who have studied the different aspects of the biological problems or hair growth. These range from considerations of growth to the synthesis and chemistry of the hair fibre. We have deliberately excluded the problems of alopecia and pathology; these problems must await future considerations, when we understand more fully the normal events in hair growth.

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The pilary system is a perfect microcosmic structure in which we find birth, development, ageing and death, activity and rest, colour formation and decoloration, greasiness and dryness, infection and sterilisation, hypertrophy and atrophy, benign tumours and malignant ones. Such a complexity of functions has attracted the attention of very different groups of scientists, and there is hardly any other field in which the groups of interested people is so heterogeneous as they are in the topic of hair growth.

"ANATOMY OF THE HAIR FOLLICLE"
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The hair follicles of various regions of the body have a basic similarity in structure ; modifications and deviations from this basic pattern serve to identify and differentiate the hair follicles of one region from those of another.

The hair follicles of the scalp are large, the roots of growing hairs extend deeply into the corium, and the sebaceous glands vary in size. Hair follicles occur singly or in groups ; each follicle remains as an individual unit within such a group until the level of the epidermis is reached, at which point the

follicles may merge into a common follicular pore. Hence, on the surface of the scalp multiple hairs may appear to emerge from a single follicle.

The hair follicles of the male beard are comparable in size to those of the scalp, but they tend to occur singly. A distinguishing feature of the follicle is a division of the lumen of the follicular neck into two distinct channels: through one channel traverses the shaft of the hair; the other directly connects the excretory duct of the sebaceous gland with the skin surface.

Approximately one-half of the hair follicles from the upper back are twin rooted. In such follicles two hair roots, each with its own sebaceous gland, are conjoined at the base of a common follicular neck. Hair shafts emerge to the surface through the common follicular neck and follicular pore.

Roots of mechanically extracted hairs may be identified as growing (anagen), involutional (catagen) or resting (telogen) by simple microscopic examination.

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"THE HISTOLOGY OF THE HUMAN HAIR FOLLICLE"
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The growing or proliferative part of a hair follicle is the matrix in the lower part of the bulb. This is composed of indifferent cells whose main function is to proliferate; the cells move up and synthesise keratin that forms the hair and the inner root sheath. The outer root sheath, once formed at the beginning of the hair growth cycle, remains fairly static. In the upper part of the bulb the indifferent cells that have arisen from the matrix become larger and begin to undergo their characteristic differentiation; the inner sheath is interlocked with the hair and must grow at the same rate as the hair. In the upper parts of the bulb, melanocytes synthesise melanin and feed it out to the cells that make up the cortex and medulla of the hair; the cuticle of the hair and the entire inner sheath remain non-pigmented. At the end of a hair growth cycle the follicle forms a club hair and the bulb is largely destroyed; a residual vestige of cells is left behind as the seed for the next generation of cells.

The quiescent hair follicle is totally different from an active follicle. It is much shorter than an active follicle, and consists of a sac of epidermal cells around the hair club; the sac remains in contact with the dermal papilla by a stalk of indifferent epidermal cells. The stalk of cells and the cells at the base of the epidermal sac comprise the hair germ from which re-grows a new hair follicle when activity sets in again.

Capillary networks are particularly rich around the lower part of active hair follicles. Tufts of capillaries penetrate the dermal papilla and connecting branches form a rich plexus around the entire bulb. In the upper two-thirds of the follicles vascularity is scant. The vascular pattern of

quiescent follicles is quite different. Since the bulb of the active follicles degenerates, the plexus of capillaries around it collapses in a bundle at the base of the dermal papilla. The papilla itself flows away from the tufts of capillaries and comes to rest immediately above it.

Just below the entrance of the sebaceous gland, hair follicles are surrounded by a collar of sensory nerves that record pressure stimuli. Oddly enough, these nerves are rich in cholinesterase, like the nerves of the parasympathetic nervous system. These sensory nerves are particularly in evidence around the nerves of the scalp.

"THE HISTOCHEMISTRY OF THE HAIR FOLLICLE"
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This paper presents a review of the histochemical findings in human hair follicles. Of the inorganic substances, calcium, magnesium, zinc, copper, sulphates, phosphates and iron have been investigated in quiescent and active hair follicles. The distribution of glycogen, PAS-positive but diastase resistant material and acid mucopolysaccharides in and around hair follicles is different during the different stages of hair growth. These substances are much more abundant in growing than in resting hair follicles. For the first time the histotopography of lipids, and especially that of phospholipids, unsaturated lipids and plasmal, has been reported fully in the different parts of the hair follicle. Amino acids, protein-bound sulphydryl groups and disulphide groups, as well as nucleic acids, have been studied during different stages of hair growth. The histochemical localisation of enzymes in the hair follicles is particularly important. Phosphorylase, succinic dehydrogenase, cytochrome oxidase, esterases, acid and alkaline phosphatases, 5-nucleotidase, glucose-6-phosphatase, cholinesterase, β-glucuronidase, amino-peptidase and carbonic-anhydrase have been studied and an attempt has been made to deduce their functional importance in relation to hair growth.

Histochemical studies of hair keratinisation are somewhat hampered by technical limitations of the methods used for the identification of keratin. The histochemical composition of trichlohyalin and of the keratinisation, the sigrificance of the nuclei in relation to keratinisation, and the fate of the nuclei during keratinisation are discussed.

"THE ELECTRON MICROSCOPY OF THE HAIR FOLLICLE"
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Thin sections of a variety of keratinised tissues, hair, skin, feathers, etc., show that a continuous structureless dermal-epidermal membrane (ca.

400 A. thick) separates the epidermis from the dermis. The basal layer of epidermal cells, usually somewhat columnar, are attached to the dermal-epidermal membrane, but their plasma membranes are separated from it by a less dense layer.

The epidermal (Malpighian) cells contain small mitochondria, agranular vesicles (Golgi type), and large numbers of dense ribonucleoprotein (RNP) particles which are not associated with the membranes to form an endo-plasmic reticulum such as occurs in protein secreting cells.

Fibrous keratin first appears as wispy bundles of fine filaments (100 A.) which in hair and feather rapidly aggregate to form definite fibrils lying parallel to the lengthening cells. In skin the filaments show a lesser tendency to form bundles and the orientation is more random. Frequently, the fibrils seem to sprout from the plate-like cell contacts (see later).

In the hair cortex the bundles of filaments grow in length and width and, above the bulb constriction, stain more readily with the osmium fixative. High resolution micrographs show that the stain is associated with a material between the original filaments. It is proposed, therefore, that fibrous keratin is a duplex structure consisting of a system of fine parallel α-filaments (ca. 60 A. diameter) cemented together with a material high in cystine and probably not fibrous (γ-component).

In the inner root sheath trichohyaline granules accumulate at first and later transform into fibrils. A similar change probably takes place in the keratohyaline of skin.

Epidermal tissues show several remarkable, specialised cell contacts. In skin, outer root sheath and feather, these take the form of localised plates comprising a thickened cell membrane and several layers of dense material within the cytoplasm "backing." Fibrils may sprout in tufts from the plates. At higher levels several layers of intercellular material appear between the "plates." A similar dilation of the membranes, with the interpolation of intercellular sheets, occurs generally in the hair and is most marked in the cuticle and inner sheath. These contacts may be associated with strengthening the formations.

" THE CHEMISTRY OF KERATINISATION"
A. GEDEON MATOLTSY

In the early stage of keratinisation, the formation of cytoplasmic fibrils appears to be a basic mechanism which later becomes associated with decomposition and elimination of certain cytoplasmic and nuclear elements. Although these are common properties of keratinising cells of both hair cortex and epidermis, the actual mechanism of keratinisation is different. In the differentiating cells of the hair cortex, the cytoplasmic fibrils gradually reach a high concentration and the cells practically consist of fibrils when the nuclear and cytoplasmic activities cease. A quite perfect elimination of

non-keratin constituents also takes place. In differentiating epidermal cells, cytoplasmic fibrillation does not seem to be a gradual process and the fibrils never seem to reach concentrations as high as in differentiating cells of the hair cortex. Elimination of nuclear and cytoplasmic non-keratin components is also less perfect.

Differences can be recognised in the chemical composition of the keratin which is formed in both hair cortex and in the epidermis. While hair keratin contains the basic amino acids : histidine, lsyine and arginine in a characteristic ratio of 1 : 3 : 10, this ratio is absent in epidermal keratin. The other amino acids also occur in differing quantities. It would appear that either the availability of amino acids might be different in the hair follicle and the epidermis, or that keratin synthesis proceeds according to different principles in these keratinising tissues.

<div align="center">"THE BIOSYNTHESIS OF FIBRES"</div>
<div align="center">E. H. MERCER</div>

The formation of many fibrous systems follows the following course : primary synthesis of a non-fibrous macromolecular precursor, the transformation of the precursor into a fibrous modification, the arrangement of these protofibrils into more organised structures and, in some cases, the hardening or tanning of the final formation.

Thin sections of a selection of fibre-forming cells, including silk-forming cells of the silkworm, collagen-forming fibroblasts of the skin of the rat, the cells forming the egg case of the cockroach, certain chitin-forming cells of insects, and mammalian epidermal cells, lead to the following tentative conclusions : protein fibre formation is associated with the presence of dense ribonucleoprotein (RNP) particles, as is also the case with cells forming soluble proteins ; chitin-forming cells have few dense RNP particles ; if the fibre-precursor is to be secreted from the cell the RNP particles are associated with reticulum ; if the protein fibrils merely accumulate within the cells the RNP particles lie in clusters freely in the cytoplasm. The secretion of the protein precursor may be effected through long, thin, finger-like protrusions of the cell membrane or, if synthesis is very rapid, large accumulations may separate in lumps at the cell edge.

The transformation of the non-fibrous precursor into protofibrils seems most often to be a kind of aggregation into linear or helical aggregates in which the original structure of the macromolecule is preserved. These protofibrils often separate spontaneously *in vitro* and may be photographed. The organisation of protofibrils into parallel arrays, networks, membranes, etc., is due to some added control mechanism, such as shear due to flow or the presence of already organised material. Keratin protofibrils form spontaneously and in hair seem to owe their orientation to a slight initial flow

in the deformed cells; this controls the direction of fibrils subsequently added.

"THE NATURE OF HAIR PIGMENT"

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The large variety of hair pigments has provided material on which naturalists, geneticists, and biochemists have been able to carry out comparative studies on the nature and control of pigmentation. Although superficial examination of hair would indicate a wide range of colour hues, microscopic examination has revealed only three types of pigmented granules, namely, black, brown and yellow.

The study of the nature of hair pigment has proved generally unrewarding because it has not yet been possible to isolate pure fractions for chemical characterisation. Many of the advances on the nature of hair pigment have been made using the synthetic approach following the action of enzymes in the hair bulb on chromogenic substrates. But ultimately it will be necessary to combine such a synthetic approach with chemical analysis of naturally occurring pigment.

Differences in hair colour are biochemical differences and the genetic pattern of hair colour indicates that brown and black pigment is under the same genetic control, whereas, yellow (pheomelanin) is under a different genetic control. Thus, two separate, but possibly interrelated, metabolic pathways of brown-black and yellow hair pigment are suggested.

Using a histochemical radioautographic technique and dl-tyrosine-2-C^{14} as a substrate, it has been shown that the hair bulbs of mice incorporate tyrosine into pigment cells. The activity of tyrosinase is related to the stage of the hair cycle. In the C-57 black mouse, tyrosinase activity is not detectable with the radioautographic technique during Anagen I and II, but appears weakly in Anagen III and gradually increases in amount during Anagen IV, V and VI. Tyrosinase activity is absent during the Telogen stage of the hair cycle. The factors that regulate the tyrosinase activity during the hair growth cycle are not known. It is possible, as suggested by Chase, that the cessation of tyrosinase activity just prior to catagen may be related to the development of an inhibitor.

The degree of incorporation of tyrosine-2-C^{14} indicated by silver deposit in the radioautographs is very strong in intense brown mice (a/a; b/b; C/C; D/D; P/P) and in brown mice with Maltese dilution where d/d replaces D/D. There is slightly less incorporation in both yellow mice ($A^y/_a$; B/B; C/C; D/D; P/P) and intense blacks (a/a; B/B; C/C; D/D; P/P) and decreased but detectable incorporation in black mice with pink-eyed dilution, p/p replacing P/P of the intense blacks. Albinos showed

no uptake of labelled tyrosine. The ability to oxidise tyrosine is thus found in both melanic and pheomelanic follicles, melanic animals showing a greater activity than pheomelanic.

It is quite clear at this time that black and brown melanin appear to be closely related chemically, and genetical evidence indicates that their modes of formation are closely similar. Pheomelanin differs chemically from melanin, and genetical evidence indicates a very distinct mode of formation for the two pigments. Tyrosinase is involved in the formation of both melanin and pheomelanin, and tyrosine can be considered to be the precursor of melanin. While tyrosine will act as a substrate for pheomelanic hair follicles *in vitro*, the pigment formed is abnormal, and there is little or no indication that tyrosine is the natural chromogen of pheomelanin; the oxidation of tyrosine by pheomelanic follicles may be involved only indirectly in pigment formation, and tyrosine (or its oxidation products) may not be the pigment precursor. The activity of the genes for pheomelanin production in the guinea pig or the mouse "turn on" the production of pheomelanin in a very definite way; no intermediates between melanin and pheomelanin appear to be formed. This clear-cut action of the genes presupposes a switch-mechanism, probably involving one enzymic step. The possible dual role of tyrosine and tryptophane intermediates in this switch-mechanism is suggested by the investigations of Butenandt, who showed that the formation of the red-yellow pigment, xanthomatin, depended on the conversion of dopa to dopa quinone in the presence of tyrosinase, and the non-enzymic oxidation of 3-hydroxykynurenin to xanthomatin by the dopa quinone which was reduced back to dopa. In some histochemical experiments using red human hair bulbs and hair follicles of intense yellow, e/e, guinea pigs, we have demonstrated that melanin formation is absent in pheomelanic human and guinea pig hair follicles following incubation in dopa and 3-hydroxykynurenin in a molar ratio of 1 : 4 for 20 hours. If the ratio of these substrates is 4 :1 (dopa : 3-hydroxykynurenin) no black pigment is formed in four hours, but after 20 hours (all the 3-hydroxykynurenin having been oxidised) black pigment is found to have been deposited. These results provide necessary but not sufficient evidence for an explanation of pheomelanin formation as the result of the oxidation of an o-aminophenol by dopa quinone produced by the oxidation action of tyrosinase on dopa. It is compatible with the observation that pheomelanic hair follicles contain tyrosinase, and it would explain the pigmentary switch-mechanism leading either to melanin or pheomelanin, this being the result of the absence or presence of o-amino-phenol. The critical enzyme operating the switch could be one bringing about hydroxylation of an aromatic amine. The yellowish-brown pigments formed by the oxidation condensation of o-aminophenols are soluble, as is pheomelanin, in dilute alkali. Although no systematic search for trypto-

phane intermediates has been made in hair, Rebell has recently isolated kynurenin from the yellowish hair of albino rats. In addition, we have observed that pheomelanic hair when illuminated with wave-lengths of 3,600 A. is fluorescent, and emits light varying from a dull orange to bright yellow. Yellow hair, the pheomelanic banding of agouti hair of mice, guinea pigs and golden hamsters and human red hair show this effect. The fluorescence of the mixture of 3-hydroxykynurenin and dopa in which hair follicles had been incubated was a dark orange colour resembling that of an alkaline extract of pheomelanic hair.

"THE BEHAVIOUR OF PIGMENT CELLS AND EPITHELIAL CELLS IN THE HAIR FOLLICLE"

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In the germ region of the regenerating hair follicle there are two centres of growth, one around the dermal papilla and giving rise to the bulb, the other producing the elongated lower external sheath. The first portion of the inner sheath forms from the early bulb and more is added as the bulb descends. The cells of the matrix, the lower bulb, are indeterminate in that they can be mechanically displaced and still give rise to the three layers of the inner sheath and the three regions of the hair shaft. Melanocyte stem cells reside in the upper bulb which is derived from the germ region capping the dermal papilla. The mature melanocyte has short dendrites, the cell body projects into the cavity of the dermal papilla and it delivers granules to be engulfed by the recipient hair cells. The club and surrounding capsule are formed at catagen from cells of the bulb matrix, but only after the dermal papilla has become partially rounded.

"THE ELECTRON MICROSCOPY OF THE MELANOCYTE"

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The examination of melanocytes from human hair bulbs with the electron microscope has allowed the mechanism of pigment granule formation to be studied.

A region near the nucleus of the melanocyte, corresponding to the Golgi region, contains numerous small vesicles ; these consist of an outer membrane with several concentric inner membranes. Melanin is deposited upon the vesicles, to form the completed pigment granules. These are then transferred to the cortical cells of the hair. Examination of albino hairs has shown that the complex membrane structures are synthesised by the melanocyte, but

do not become pigmented with melanin. Similar structures have also been found in the melanocyte of human skin.

"VASCULARITY AND PATTERNS OF GROWTH"

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The blood supply to skin and to hair has been reviewed and variations in the supply to different types of hairs and to hairs during the phases of growth have been studied, particularly in the rat and the rabbit. In the rat the monotrich has a rich supply from a dense network of capillaries around the lower half of the follicle and the dermal papilla contains capillaries ; awls have a less dense plexus of capillaries around the follicle and no papillary capillaries ; the smaller follicles do not possess individual plexuses, nor do they have vascularised papillæ.

In naturally occurring hair growth waves, as seen in the rat and the rabbit, the wave of hair growth is accompanied by a corresponding intensification of the blood supply which keeps step with the growth or recession of the follicle. These vascular changes have been studied in detail in the animals mentioned.

Artificially induced growth of hair by pulling and the associated vascular changes were studied in the rabbit and again a clear inter-relationship was established between hair growth and the vascularity. Local erythematous and œdematous phenomena occur in the skin following pulling.

Pulling single guard hairs in rabbits does not induce regrowth. There is a critical number of fibres (varying with conditions) which must be pulled before regrowth is started immediately. This shows that the act of pulling in itself is insufficient to cause immediate commencement of growth in a single follicle.

"MITOTIC ACTIVITY OF THE FOLLICLE"

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1. The distribution of mitotic activity in the growing follicle of the adult mouse is described. In the fully grown follicle such activity is confined to the matrix cells of the bulb.

2. Observations *in vitro*

    (a) It is shown that, for the development of active mitosis in a hair bulb, adequate supplies of oxygen and of some suitable carbohydrate substrate are essential. In the absence of either, the mitotic activity is powerfully inhibited.

    (b) Ideal carbohydrate substrates for the support of mitotic activity

are glucose, fructose, and pyruvate. The various Krebs cycle intermediates tested were not efficient in this respect.

(c) Any substance which is known to inhibit the process of glycolysis, of the Krebs cycle, or of the cytochrome system, also inhibits the mitotic activity of hair bulbs. The substance 2 : 4 dinitrophenol which is said to inhibit the process of energy transfer has the same effect.

(d) All the available evidence, therefore, points to the conclusion that the high mitotic activity of a hair bulb can only be maintained by a high level of energy production in the cells. Therefore, it must be expected that mitotically active hair bulbs will normally absorb large quantities of glucose and oxygen, and this is supported by the observations of Ryder (p. 8) on the rate and uptake of radioactive glucose.

3. Observations *in vivo*

(a) Unlike the surface epidermis the matrix cells of a rapidly growing hair follicle show no signs of any diurnal rhythm. No mitotic depression is seen after 6 hours of forced exercise.

(b) In starved mice the mitotic activity of the matrix cells does not become depressed until after about 36 hours when the animals are in a state of collapse, and at that time the addition of glucose is all that is needed to restore the mitotic activity to normal.

(c) In full shock induced by the removal of tourniquets or by the injection of ATP the mitotic activity of the matrix cells is almost completely inhibited, but in partial shock, mitotic activity is not greatly affected. In skin taken from fully shocked mice and incubated with glucose, mitotic activity returns to normal almost immediately.

"PHYSICAL FACTORS WHICH INFLUENCE THE GROWTH OF HAIR"
HERMAN B. CHASE

The production of hair might be increased in five ways : (1) initiation of a new growth in a quiescent follicle ; (2) delay or complete prevention of the quiescent state ; (3) transformation of a follicle into one having a longer growing and a shorter resting phase; (4) production of new follicles or multiple follicles ; (5) increase in the growth rate of a follicle. The first of these is the only practicable one ; many physical and chemical agents are effective and initiate a new growth of a quiescent follicle. Almost any agent which can cause sufficient damage to result in moderate epidermal hyperplasia is effective in initiating growth in a quiescent follicle. X-ray, at a dose of about 1,500 r in either the mouse or the rabbit, stimulates quiescent follicles to activity ; plucking of club hairs is the best known method and stimulates follicular activity at once.

X-rays cause a depilation of growing follicles sooner than that required

for resting follicles and at a lower dose.   In the mouse in which the same follicles may have a resting element with a club hair together with a growing element with a bulb, depilation by X-rays of each of these hairs is independent and characteristic.   This indicates that the effect is on the epithelium and not dependent on vascularity.

"EFFECTS OF IONISING RADIATION ON HAIR ROOTS OF THE HUMAN SCALP"
EUGENE J. VAN SCOTT

The direct effect of ionising radiation on hair follicles can be studied by microscopic examination of unstained roots of hairs extracted from the irradiated scalp.

Changes in the hair root are detectable as early as two days following irradiation and become progressively more manifest thereafter.   These changes are confined to growing hair follicles and consist of a characteristic progressive atrophy of the entire hair bulb, which begins in the matrix portion.   At the end of 10–14 days complete disintegration of the bulb occurs, leaving a severely tapered proximal tip of extracted hairs.   Such hairs fall out at the end of three weeks.   The roots of a proportionately few hairs recover during the first week, assume a structurally normal bulb, and continue to produce a hair ; the hair shaft has a smaller diameter in a demarcated zone which can be identified, as judged by its distance from the bulb, as that portion of hair shaft produced during the time of radiation.   Calculation of the percentage of growing hairs demonstrating morphological effects of irradiation may be done by examination of one hundred or more hairs manually extracted from areas of scalp exposed to different doses of radiation.   Such examinations, repeated at intervals during the week following irradiation, reveal that the percentage of hairs showing changes increases linearly in relation to both time and to the dose of irradiation to which the hair roots were exposed.

"CHANGES IN HAIR ROOTS OF THE HUMAN SCALP FOLLOWING THERAPY WITH A FOLIC ACID ANTAGONIST"
EUGENE J. VAN SCOTT

The loss of scalp hair following amethopterin (Methotrexate), unlike that due to either ionising radiation or systemic diseases, is due to a breakage of the hair shaft and not to a falling out "by the roots."

Microscopic examination of unstained roots of hairs pulled from the scalps of patients receiving therapeutic doses of amethopterin reveals a transient but reversible injury to the hair bulb.   There is a decrease in the diameter of the hair formed during the time of administration of the drug.

When the administration of the drug is stopped the bulb recovers completely and again produces a hair shaft of normal diameter. As a result, hairs from patients who have received amethopterin have zones of constrictions. The degree of constriction corresponds to the dose of drugs employed and may be so severe that the shaft breaks at this point when the hair is pulled or even when it is combed or casually manipulated.

"NUTRITIONAL FACTORS INFLUENCING THE GROWTH OF HAIR"
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The amount and quality of food governs the weight of wool a sheep grows, and a poor diet reduces the length and diameter of the wool fibres. The addition of both protein and carbohydrate to the diet increases wool production. Carbohydrate is needed to provide energy for protein utilisation, apart from releasing protein for wool growth. Carbohydrate is also essential for mitosis, and the importance of glycogen in the follicle has been amply demonstrated.

Cystine or methionine are essential for hair growth in many animals but sheep can readily synthesise cystine from sulphate. B vitamins are necessary agents for the growth of hair ; pantothenic acid seems to be associated with the utilisation of copper. Deficiency of copper causes loss of pigment, and in wool, a loss of crimp. Copper is thought to catalyse the oxidation of SH— to —S—S— groups but it has not been possible to detect copper in the follicle either histochemically or with the use of Cu^{-64}. It is doubtful, however, if any of the dietary deficiencies reported to cause impaired growth are really specific.

Loss of hair due to poor diet does not seem to be by the formation of "brush ends," but apart from the thinning of the fibre there is a reduction in breaking strength. A poor diet retards follicle development in young animals, but it is doubtful if there is a permanent effect.

The larger the papilla is, the more blood vessels it contains and the greater is the diameter of the fibre. Variations in diameter of the fibre seem to be associated with the number of vessels in the dermal papilla as well as variations in the density of the surrounding net of vessels. A large follicle has an extensive supply because it is large ; it is not this that makes it large.

Within a few minutes after the injection of cystine labelled with S^{-35}. radioactive particles appeared first immediately above the bulb, suggesting an entry at this level from the surrounding capillary net rather than through the papilla vessels. Soon after an injection of glucose labelled with C^{-14} the activity is in the bulb and not above it. There seems to be a rapid turnover of cystine in the body, but small amounts still enter the follicle up to 3 weeks afterwards after its injection.

"AGE, SEX AND GENETIC FACTORS IN THE REGULATION OF HAIR GROWTH IN MAN: A COMPARISON OF CAUCASIAN AND JAPANESE POPULATIONS"

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Techniques have been devised to provide repeatable quantitative measurements of hairs and their rate of growth in certain regions of the body. Using these methods, data have been obtained for each sex throughout the life span in Caucasian and Japanese populations. The standards constructed from these values can serve to assess some aspects of physiologic age, and to study endocrine status. They will also be valuable in gaining further understanding of the nature and interdependence of endocrine, ageing, genetic, environmental and other regulatory factors.

Beard growth, in Caucasian as compared with Japanese males, was found to be considerably greater and values reached a peak at an earlier age. This was shown by measurements of weight of hair grown per day, and was associated with higher values in Caucasians for area of skin with coarse hairs and for number of such hairs per sq. cm. of a standardised region of the cheek. In a large series of Japanese females no instance of facial hirsutism was found in contrast to the high incidence reported for Caucasian women. Males of both ethnic groups had similar values for the mean diameter of coarse hairs and of their component parts and for the percentage of grey hairs with advancing age.

Growth of axillary hair was also more pronounced in Caucasian than in Japanese males of comparable sex and age. The disparity between the two ethnic groups in values for axillary hair was even greater in females than in males.

These data for beard and axillary hair are in the same direction and extend previous reports of greater tendencies on the part of Caucasian males to develop coarse hairs on the external ears, to become bald and to develop acne.

As a rule some of the late sequelæ of sexual maturation were among those which tended to occur more frequently, and to progress further in Caucasians than in Japanese. This principle seems to apply to the areas with coarse hairs in the axilla and beard as well as to the severe forms of common baldness, and it may apply to acne.

Secondary sex characters and certain sex-differing pathologic states failed to develop in men who did not mature sexually. The degree to which maintenance of these conditions, once fully developed, depended upon gonadal secretions, differed among the items studied; these, listed in decreasing order of dependence, are the axillary hair, beard, and common baldness.

Under ordinary conditions these traits are dependent upon gonadal secretions for development, and in some instances for maintenance, but this

endocrine stimulation tends to act in a trigger-like fashion. The extent to which these states develop, and even the occurrence of certain sex-selective pathologic states, is regulated chiefly by inheritance and ageing. Studies of twins and members of large families, supplemented by comparisons of Caucasians and Japanese (including Japanese living in Tokyo, U.S., New York), delineate and emphasise the large measure of control exerted by genetic factors.

Endocrine indicators of the quantitative type employed in these studies are thus to be regarded as somewhat analogous to the comb in fowl, reflecting not only the nature and type of the existent endocrine stimulation but also the vitally important responsiveness both of target organs and the organism.

The inter-relations of endocrine, hereditary and ageing factors observed in studies of the beard seem relevant to growth of hairs in other regions such as eyebrow, nasal vestibule, external ear, and much of the body with the exceptions of scalp, axilla, and pubis.

The mean age-curves for axillary hair conform more closely than those for beard to the waning of gonadal secretions, as judged by titres of urinary androgens and ketosteroids.

Secondary sex characters merge almost indistinguishably with male-selecting pathologic states like common baldness and the severe forms of acne. There are suggestions that this spectrum may extend to some of the more lethal male-selecting pathologic states and to the shorter duration of life in males than in females in man and other species. It is of considerable interest, therefore, that in some aspects the modes of control of piliary secondary sex characters seem to be analogous, and may provide insight to those of certain sex-selecting pathologic states.

"HORMONAL FACTORS"

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Previous investigations on the effects of hormones on hair growth have been limited to observations on the spontaneous replacement of hair. The present studies provide information on the influences of hormones by comparing spontaneous replacement to growth initiated by plucking the hair from resting follicles in gonadectomised, adrenalectomised, hypophysectomised, thyroid hormone deficient, diabetic, and intact male and female black rats. The effects of various hormone preparations have also been observed in these experimental animals.

In the rat, spontaneous growth starts periodically in the belly skin and spreads dorsally as a wave ; in plucked areas the follicles grow simultaneously. Once a hair follicle becomes active, its cycle of growth is the same regardless of how activity is initiated. In the rat, growth of a hair normally requires

about 26 days, when growth ceases, and the follicle remains quiescent until activity is again initiated.

Male rats have coarse hair, and their moderately thick skin is covered with flakes of oxidised lipoid. The pelage of females is finer, the skin has no lipoid scales, and spontaneous growth waves tend to lag behind those of males. The cycle of growth in each follicle, however, is the same in both sexes. Sex differences disappear after gonadectomy ; the fur is intermediate in texture between that of males and females, and spontaneous growth resembles that of normal males. Re-growth after plucking is normal.

Daily treatment with estrogen retards the initiation and the rate of both spontaneous and induced hair growth in gonadectomised, adrenalectomised, hypophysectomised, or thyroid hormone deficient animals. These effects become masked by the accelerating effects of adrenalectomy or hypophysectomy. Estrogen induces the growth of fine, sparse hair in all animals except those which have been hypophysectomised. Thus, estrogen produces some of its effects on hair growth independent of the adrenal cortex. Daily treatment with androgen has no apparent effect on hair growth except that it promotes a coarse pelage in all except the hypophysectomised rat.

During pregnancy and lactation spontaneous replacement of hair is noticeably retarded. Hair growth, however, is transiently accelerated when the young are removed from the mother ; induced growth by plucking is normal in these animals. These effects are not duplicated when progesterone is given to intact females, but are partially simulated when luteotrophin is administered to females that have been nursing for a few days.

Adrenalectomy accelerates the initiation and the spread of spontaneous follicular activity, but has no effect on the rate or growth of the individual follicles ; induced growth is normal and the pelage is unaffected. Conversely, daily treatment with small doses of cortisone inhibits the spontaneous initiation of hair growth in the intact, gonadectomised, or adrenalectomised rats. Once growth has started, however, cortisone has no effect. There is no cumulative effect after long periods of treatment with cortisone, and the follicles do not become "refractory" to the hormone. Large doses of cortisone completely inhibit hair growth in intact rats, except in those follicles which had been plucked 4 or 6 days before the administration of the hormone. All hair growth is inhibited when propylthiouracil-treated or hypophysectomised animals are injected together with small doses of cortisone. In all of these cases growth commences as soon as the cortisone is discontinued. The precise mechanism by which cortisone affects the hair follicle is not known. Daily treatment with desoxycorticosterone has no effect on hair growth in intact or adrenalectomised rats.

Continuous treatment with adrenaline inhibits spontaneous hair growth in intact animals and delays the response to plucking, but once growth has

started it proceeds normally. Prolonged treatment with adrenaline produces a local inhibition of spontaneous or induced growth. Growth waves tend to by-pass the area of injection, and induced growth is locally retarded. The hairs which eventually grow near the sites of injection of adrenaline have no pigment. These effects are neither mediated nor potentiated by thyroid hormone. They are, however, partially linked to adrenocortical activity. Adrenalin inhibits hair growth more in cortisone-treated adrenalectomised rats than in adrenalectomised animals not receiving cortisone ; the effects are not due to the cortisone.

Spontaneous replacement is markedly retarded in alloxan-diabetic animals, but after an initial delay induced growth is normal. Phlorhizin treatment does not appear to affect hair growth despite a continued glycosuria and hypoglycemia. Insulin restores spontaneous replacment to normal in alloxan-diabetic animals and tends to enhance growth in intact animals despite the low level of glucose in the blood. Glucose-treated intact animals, on the other hand, display normal re-growth after plucking whereas spontaneous growth is often retarded. It seems likely, therefore, that insulin is more directly involved in hair growth than is glucose. Perhaps insulin regulates the utilisation of glucose from the blood during the early stages of growth in the hair follicles.

Continued intake of propylthiouracil that produces a deficiency in thyroid hormone inhibits the spontaneous waves of hair growth. Except for an initial delay, however, induced growth is normal in animals deficient in thyroid hormone. Injections of thyroxine accelerate spontaneous replacement of hair in propylthiouracil-treated rats and in normal animals ; the cycle of growth, however, remains normal regardless of how activity is initiated. Thyroxine and cortisone have antagonistic effects on hair growth, and one hormone can be used to offset the effects of the other. No such relationship is found between thyroxine and gonadal hormones.

Hypophysectomy accelerates the initiation and spread of spontaneous follicular activity, but has no effect on the rate of growth. The cycle of growth is normal after plucking, but the pelage is infantile. The administration of ACTH has an inhibitory effect on hair growth in intact, gonadectomised and hypophysectomised rats, but is without effect in adrenalectomised animals. ACTH retards the initiation of growth, but the actual rate of hair proliferation is not affected in either the clipped or plucked follicles. This inhibition of hair growth is obviously mediated through the adrenal cortex. The pituitary seems to exert a restraint on hair growth by means of the adrenal cortex. Hypophysectomy removes this restraint.

The influences of growth hormone on the hair follicle are still not completely clear. Implants of pituitary tissue or injections of growth hormone restore the pelage of hypophysectomised rats to an adult texture. Since the

hair remains infantile in hypophysectomised rats treated with gonadal hormones, it would appear that sex hormones modify the type of hair produced only if growth hormone is present. Aside from this effect, growth hormone has no obvious influence on hair growth.

"REGENERATION, WOUND HEALING AND 'DE NOVO' FORMATION"
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The many investigations which have been carried out on the healing of cutaneous lesions caused by a wide variety of injurious treatments—e.g. the topical application of carcinogens, freezing *in situ*, X-irradiation, burning or the excision of thin shavings—have provided evidence of the remarkable capacity of hair follicles to regenerate provided that the dermal papillæ survive and make contact with living epidermal cells again. Once the dermal papillæ have been destroyed, regeneration does not normally take place, however faithfully the fine fibrous architecture of the dermis, including the connective tissue follicle "sheaths," may have been preserved.

Recent studies on the healing of extensive wounds produced by excision of the full thickness of the skin from the sides of adult rabbits' chests have shown that if the process of wound contracture is arrested artificially, or fails to proceed to completion of its own accord, *de novo* formation of hair follicles takes place. The wound becomes first filled with granulation tissue which is resurfaced by epithelium that grows in from the margins. Within about 40–50 days this epithelialised scar tissue is transformed into a sort of *ad hoc* skin by the emergence of a dense crop of new medullated hairs. The new follicles possess well developed sebaceous glands but they lack arrector pili muscles and pigment, despite the fact that all the rabbits used belonged to pigmented breeds. The evidence suggests that these hairs are of completely new formation and have not originated from follicle remnants left behind in the wound bed.

Unequivocal evidence that completely new follicles can be formed in adult animals is forthcoming from our knowledge about the antlers of deer. These deciduous organs are shed in mid-winter and regenerated during early spring. They are completely covered by a layer of typical, hair-bearing, cervine skin—the so-called "velvet"—until they are fully grown and have reached maturity. The hairs in the velvet are pigmented and have well-developed sebaceous glands but, like the new hairs which appear in the wounds in rabbits' skin, they lack arrector pilorum muscles. Thus, the deer regenerates each year throughout life, a relatively large area of new skin complete with its complement of hair follicles. In the light of this evidence the rather rigid view of the older authorities that hair follicles can only be formed at birth or thereabouts can no longer be sustained.

"REGIONAL FREQUENCY DISTRIBUTION OF HAIR FOLLICLES AND SWEAT GLANDS IN THE SKIN OF MAN"

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There is a great individual and regional variation in the frequency distribution of hair follicles and sweat glands in the adult skin. The combined averages for cm² of fixed skin are 980 for the head, 270 for the trunk, 250 for the arm, 190 for the leg. In spite of gross difference; there is no significant sexual variation in the distribution of hair follicles in the face.

In the fœtus the density of the appendages is higher than in the adult ; the regional variation, however, is smaller and it increases during post-natal development. The differential rate of growth of the body surface is responsible for these regional variations in the adult. Initially, the density of distribution of the appendages appear to be similar over the entire body, but later the appendages become spaced farther apart in the trunk and extremities than they are in the head. The relative numbers of hair follicles to sweat ducts, however, vary from region to region even in the fœtus, and hairs are relatively more abundant in the head.

It is assumed, therefore, that hair follicles do not increase in number after they have been formed in the fœtus, and that their relative numbers appreciably decrease.