Neurohormonal Regulation of the Hair Cycles in Rats and Mice

ALBERTO B. HOUSSAY, CARLOS E. EPPER AND JORGE H. PAZO

Centro de Endocrinologia, Ministerio de Asistencia Social y Salud Pública, Godoy Cruz 1221, and Comisión Nacional de la Energia Atómica, Buenos Aires, Argentina

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I. INTRODUCTION

Hair growth in rats and mice is cyclic, each hair follicle having alternate periods of growth and rest (Dry 1926; Butcher 1934, 1951; Chase 1954). Furthermore, the hair follicles develop their activity gradually in waves of hair growth, defined by Chase and Eaton (1959) as "the orderly progression in time and in space in which the follicles begin their growth phase".

Diverse endocrine factors act upon the hair follicles and alter growth, texture, or pigmentation of the hair (Emmens 1942; Ralli and Graef 1945; Baker 1951; Hundley and Ing 1951; Houssay 1953*a*; Mohn 1958; Davis 1963; Ebling and Johnson 1964). They also frequently modify the hair growth waves, accelerating or delaying the rate, or producing irregular or widespread growth (Butcher 1937; Dieke 1948; Baker 1951; Houssay 1953*a*, 1962).

This paper aims to demonstrate how hormonal factors can modify the initiation and progression of the hair growth waves in rats and mice and to present experimental evidence suggesting a neuro-hormonal control of these growth waves.

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II. Materials and Methods

All experiments were performed in C_3H/Ep mice or in rats. The C_3H/Ep mice belonged to the subline of the inbred strain of mice bred under the direction of Dr. Carlos E. Epper at the Comisión Nacional de la Energia Atómica, Buenos Aires. The rats belonged to the Animal Colony of the Centro de Endocrinologia. The animals were selected in such a way that litter-mates were equally distributed in the different groups of the same experiment.

Every animal was clipped at the beginning of every experiment with an electric clipper number 0000, over an area extending along the back from the neck to the base of the tail.

The clipped area was observed two or three times a week throughout the experiment and the percentage of the denuded area covered by hair was estimated each time using the following method. The contours of the denuded surfaces were drawn on transparent paper of uniform thickness. The areas defined by the contours were then cut out and weighed on a Mettler H 5 balance. The weight of the cut-out from the freshly clipped area (0-day cut-outs) was compared with the other later cut-outs obtained from measurements in the same animal, using the following formula: Hair growth in denuded area (%)

$$100 - \frac{\text{Weight of the cut-out} \times 100}{\text{Weight of the 0-day cut-out}}$$

In these experiments only spontaneous replacement of hair was observed. The method of plucking the hair was not employed to start the anagen phase in the resting follicles, since this effect is also obtained, without producing damage to the hair follicles, by certain endocrine procedures such as gonadectomy in male C_3H/Ep mice (Houssay and Higgins 1949*a*; Houssay 1953*a*).

III. Hair Growth Waves in Intact Rats and Mice

Spontaneous hair growth in the intact rats and mice used in these studies is similar to that reported by other authors (Dry 1926; Butcher 1934, 1951; Haddow *et al.* 1945; Dieke 1948; Durward and Rudall 1949; Borum 1954; Johnson 1958*a*; Mohn 1958; Chase and Eaton 1959). The period of growth lasts 21 days in C_3H/Ep mice and it is divided, according to the histological appearance, into several phases: (a) anagens I, II, III, IV, V and VI, (b) a period of regression or the catagen phase follows which lasts 7 days, whereupon (c) the rest period or telogen phase begins. The telogen phase lasts a variable period of time which increases in each hair cycle.

The first generation of hair which occurs in prepubertal animals rapidly covers the skin with a continuous coat of hair which develops from the back to the abdomen and extremities. Growth is not simultaneous but it extends so rapidly that it can hardly be considered a growth wave.

The classical growth wave is produced in the other hair generations.

The waves originate in a limited part of denuded skin as transverse and symmetric bands where the hair follicles are in the same state of activity. These bands move slowly backwards, or sometimes forwards and to the sides, and gradually cover the remaining skin. As they pass a region, that region goes into a resting period.

In pigmented animals, such as C$_3$H mice, these bands can be seen after clipping the animals by the dark pigmentation of the skin that precedes hair eruption. This is due to hairs in anagen phase IV to VI. In this way, the movement of the hair growth waves can be easily observed in the animal with denuded skin. Thus, each complete coat of hair is produced by a hair wave which slowly and gradually covers the entire skin surface of the animal in an orderly and symmetric manner. As the animal grows older it is covered more slowly by hair waves and the telogen phase becomes longer.

IV. Principal Alterations of Hair Growth Waves

Varied nutritive, hormonal, or traumatic factors can modify the normal rhythm of hair growth waves (Butcher 1940; Dieke 1948; Baker 1951; Houssay 1953*a*; Chase 1954, 1958; Ryder 1958). The most common alterations are those of acceleration or delay in the speed of the hair wave, irregular hair growth, and diffuse hair growth.

The stimulating factors of the hair cycle produce waves that rapidly cover the skin surface of the animal. There is no acceleration in the rate of growth of individual hairs, but a denuded zone is more rapidly covered with hair. Typical examples are many adrenalectomized rats and mice.

If the stimulating factors of the hair cycle are even more intense, diffuse hair growth is produced. An example of this is seen in castrated mice. Immediately after surgery all the hair follicles in telogen phase are stimulated so that the animal is covered in 21 days by a new coat of diffuse hair.

The inhibitory factors of the hair cycle produce hair waves which slowly cover the surface of the animal. Examples of this are found after the administration of excessive doses of oestrogens or in thyroid insufficiency. When inhibition is greater, the orderly pattern of the waves disappears and hair growth is irregular. Growth centres which advance very slowly also appear. Greater inhibition almost completely retards hair growth or the progression of the hair wave.

V. Diffuse Hair Growth

A. *Its Production after Castration, Adrenalectomy, or Hypophysectomy*

Diffuse hair growth is the most striking alteration of the normal hair rhythm. It is produced by the following endocrine conditions: gonadectomy in the mouse (Houssay and Higgins 1949*a*, 1949*b*; Houssay 1953*a*), adrenalectomy in the rat and mouse (Butcher 1937; Ralli and Graef 1943; Baker 1951; Houssay and Higgins 1951; Houssay 1953*a*), and hypophysectomy in the rat and mouse (Houssay 1954; Houssay *et al.* 1955; Mohn

1958; Davis 1963; Ebling and Johnson 1964). Surgery results in an immediate stimulation of the resting hair follicles, so that the animal is covered with a new coat of diffuse hair in 21 days.

If all the hair follicles of the denuded area are in the telogen phase at the time of surgery, the hair will grow in a diffuse manner. When pigmented breeds of rats and mice are used, the skin becomes dark after 15 days, and in 21 days the new hair coat is as long as in unshaved animals. When there is an area of active hair follicles present in the denuded area, visible as a dark band in the pigmented animals, these follicles continue their normal growth, and end it before the appearance of the diffuse wave. Thus, a part of the shaved area is covered by the already active wave but the remaining surface, which was in telogen phase at the moment of surgery, is covered by the diffuse growth.

In summary, immediately after surgery, the hair follicles are stimulated and produce diffuse hair growth. The follicle bands in anagen phase continue their normal growth which terminates before the diffuse growth. In either case, 21 days after surgery, the animal is covered by a new coat of hair. When the diffuse wave terminates, the cyclic rhythm reappears in slow waves in further hair generations in these animals.

The diffuse hair growth follows the same pattern and takes the same time to cover the denuded surface of the animal with hair, when it is produced by any of the already mentioned operations or combinations of them. Thus, for example, in mice the diffuse wave is exactly the same if produced by castration in males or females, by adrenalectomy, by hypophysectomy, or by any combination of these operations (Houssay 1953*a*, 1962). In rats it is exactly the same if produced by adrenalectomy, by hypophysectomy, or by adrenalectomy-hypophysectomy (Houssay *et al.* 1955). Castration does not produce diffuse growth in the rat (Houssay 1953*a*) with the exception of one strain studied by Letti (1959).

After castration or hypophysectomy all animals show diffuse growth if they belong to certain strains. When rapid hair waves are seen instead of diffuse growth, autopsy specimens will show that surgery was incomplete. Thus the presence of diffuse hair growth 15-20 days after surgery is an excellent proof of complete hypophysectomy.

We have not found any exception to the production of diffuse hair growth after castration in thousands of male C_3H/Ep mice. It is also found in other strains of mice such as C57, CBA, C, and Ce (Houssay and Higgins 1949*a*, 1949*b*).

The diffuse hair wave after hypophysectomy is not produced in at least one strain of rats in Buenos Aires and apparently in the strains used by some other authors (Snow and Whitehead 1935; Dieke 1948).

B. *Influence of the Accessory Adrenals upon the Diffuse Hair Wave*

After adrenalectomy, a 100% appearance of diffuse hair growth was never obtained in our rats or mice. Twenty to 30% of our rats and 50% of the C_3H/Ep mice showed accelerated hair waves, whereas in the remaining animals diffuse hair growth appeared after removal of the adrenals

Accessory adrenals were assumed to be the cause of this difference and therefore the following experiments were undertaken to check this hypothesis.

When the adrenalectomized mice were killed, a careful dissection and removal of the perirenal and the intrascrotal fat was performed. These tissues were stretched on cardboard and submerged in 10% formalin, where they remained for at least 48 hours. The tissue was then dehydrated in increasing concentrations of alcohol and stained with galocyanine. The stained preparation was submerged in benzol in order to dissolve most of the fat tissues.

These preparations were then studied under a surgical microscope (Zeiss) and all the stained tissues were removed and embedded in paraffin for histological study. After staining with haematoxylin–eosin the diagnosis of accessory adrenals was made under the microscope.

Correlating the findings from autopsy specimens with the *in vivo* observations upon hair growth, we observed that mice with accessory adrenals showed accelerated hair waves after adrenalectomy whereas those without accessory adrenals showed diffuse waves.

These results demonstrate that the gonads, adrenals, and the hypophysis have an inhibitory action on the hair cycle. Elimination of any of these three factors in the mouse and of the latter two in the rat remove inhibitory influences, so an immediate stimulation of the hair follicles is obtained. The fact that when the diffuse hair wave terminates the cyclic wave rhythm is restored can be explained by a local adaptation, or by an increase in the inhibitory action of other endocrine glands, for example, the adrenals in the case of castrated mice.

C. *Inhibitory Action of Steroid Hormones*

Many gonadal or adrenal steroid hormones have an inhibitory effect on hair growth. This has been demonstrated with oestrogens (Zondek 1936; Emmens 1942; Forbes 1942; Hooker and Pfeiffer 1945; Houssay and Higgins 1949*b*; Johnson 1958*b*), androgens (Houssay and Higgins 1949*b*; Houssay 1953*a*; Light and Tornaben 1953*a*, 1953*b*; Johnson 1958*b*; Houssay *et al.* 1959), and glucocorticoids (Baker and Whitaker 1948; Whitaker and Baker 1948, 1951; Houssay 1953*a*; Andreasen 1958; Fukuyama and Baker 1958; Mohn 1958; Whiteley 1958; Houssay *et al.* 1959).

Small physiologic doses of these hormones impede diffuse growth caused by gonadectomy (Houssay 1953*a*; Houssay and Higgins 1949*b*; Johnson 1958*b*), or by hypophysectomy (Houssay *et al.* 1959). Small doses of glucocorticoids inhibit diffuse hair growth in castrated mice (Houssay 1953*a*), whereas large doses of oestrogens or androgens are required to inhibit hair growth produced by adrenalectomy (Baker and Whitaker 1949; Houssay *et al.* 1959). If the adrenalectomized animal receives sub threshold doses of glucocorticoids, the diffuse hair growth produced by adrenalectomy can be inhibited with small doses of oestrogens or androgens (Ingle and Baker 1951; Houssay *et al.* 1959).

Large or pharmacological doses of oestrogens (Zondek 1936; Emmens 1942; Forbes 1942; Hooker and Pfeiffer 1943; Houssay 1953*b*), androgens (Houssay *et al.* 1959; Houssay and Higgins 1949*b*; Light and Tornaben 1953*a*, 1953*b*), or glucocorticoids (Baker and Whitaker 1948; Whitaker and Baker 1948, 1951*a*; Houssay 1953*a*; Mohn 1958), inhibit hair growth in normal, castrated, adrenalectomized, or hypophysectomized rats and mice, and hair waves are slow. The administration of higher doses brings about irregular growth or almost complete cessation of hair growth or even falling out of the hair. The adrenal mineralocorticoids such as desoxicorticosterone also have some inhibitory action on hair growth (Ralli and Graef 1945; Houssay and Higgins 1949*b*; Whitaker 1949; Whitaker and Baker 1951*b*).

We can infer that the physiologically inhibitory action of the gonads and adrenals on the hair cycle is due to their respective steroid hormones, androgens, oestrogens, and glucocorticoids.

D. *Inhibitory Action of Pituitary Hormones*

Hypophysectomy produces diffuse hair growth immediately following surgery in rats and mice (Houssay 1954; Houssay *et al.* 1955; Davis 1963). Hair growth in waves is restored in the next generation of hair (Houssay *et al.* 1955).

The diffuse hair growth produced by hypophysectomy is inhibited by the administration of chorionic gonadotrophins, pituitary gonadotrophins, or adrenocorticotrophin, but not by growth hormone (Houssay *et al.* 1955). Adrenocorticotrophin also inhibits the hair waves of the normal and gonadectomized rats (Moon 1937; Baker *et al.* 1948; Johnson 1958*b*).

These observations suggest that the principal action of the hypophysis on the hair cycle is an inhibitory one through its influence upon the gonads and adrenals.

VI. Effects of the Thyroid Upon Hair Waves

Thyroidectomy in rats and mice slightly decreases the rate of growth of hair and slows down the hair waves. There is a long delay in the covering of the denuded skin surfaces and often the process remains unfinished (Chang 1926; Chang and Feng 1929; Emmens 1942; Dieke 1948; Houssay *et al.* 1960*a*).

In mice which were radiothyroidectomized 20 days before castration there was no diffuse hair growth, but a hair growth wave covered the skin at about the same speed as in control intact animals (Houssay *et al.* 1960*a*). That is to say, the stimulation of castration accelerates the speed of hair growth waves from the low rate observed in hypothyroid animals to the higher one in control animals (Fig. 1). Therapeutic substitution with l-thyroxine administered from the moment of castration restores diffuse hair growth in castrated-thyroidectomized animals (Houssay *et al.* 1960*a*).

There is also an antagonism between the action of the thyroid and the adrenals on the hair cycle (Butcher 1941; Zeckwer 1953; Mohn 1958;

Houssay *et al.* 1960*b*). While some workers state that adrenalectomy accelerates the development of the diffuse wave more in intact rats than in thyroidectomized rats (Zeckwer 1953; Mohn 1958), others find the same amount of acceleration in thyroidectomized and intact rats (Butcher 1941).

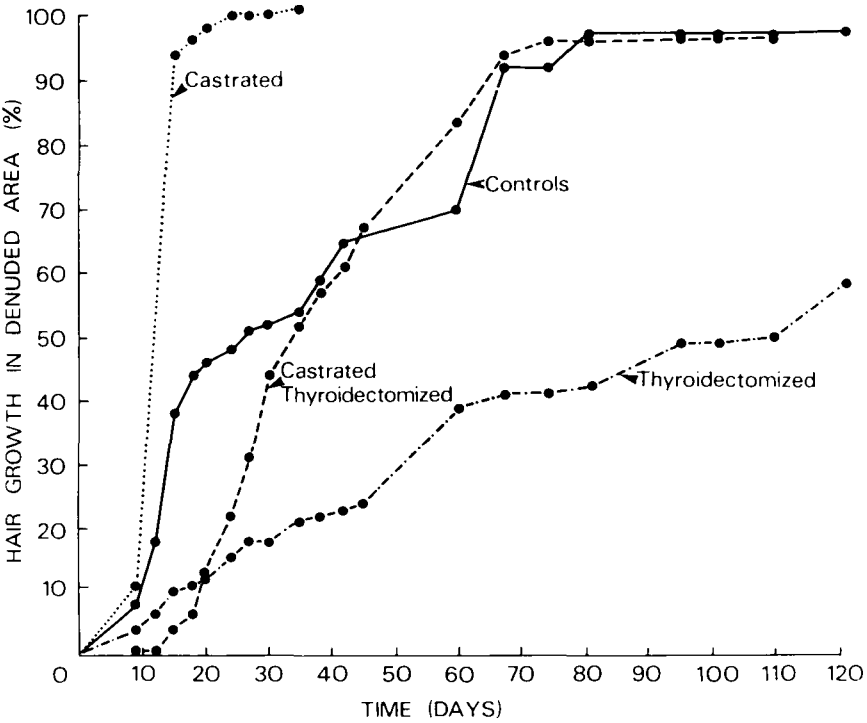

Fig. 1.—Antagonism between the effects of thyroidectomy and castration upon the hair waves in mice.

In our experiments, radiothyroidectomy carried out 20 days before adrenalectomy causes a slight delay in, but does not impede, diffuse hair growth in adrenalectomized C_3H/Ep mice *without* accessory adrenals. On the other hand it markedly decreases the speed of hair waves in the adrenalectomized mice *with* accessory adrenals (Fig. 2). As the difference between both groups depends on the presence and functional capacity of the accessory adrenals, we assume that a minimal level of circulating glucocorticoid hormones is required for the inhibitory effect of radiothyroidectomy (Houssay *et al.* 1960*b*).

The administration of thyroid hormones restores normal hair growth waves in thyroidectomized non-castrated rats and mice (Chang 1926; Chang and Feng 1929) and the diffuse hair growth in thyroidectomized-castrated mice (Houssay *et al.* 1960*a*). This demonstrates that thyroid hormones have a physiologically stimulating action on hair growth.

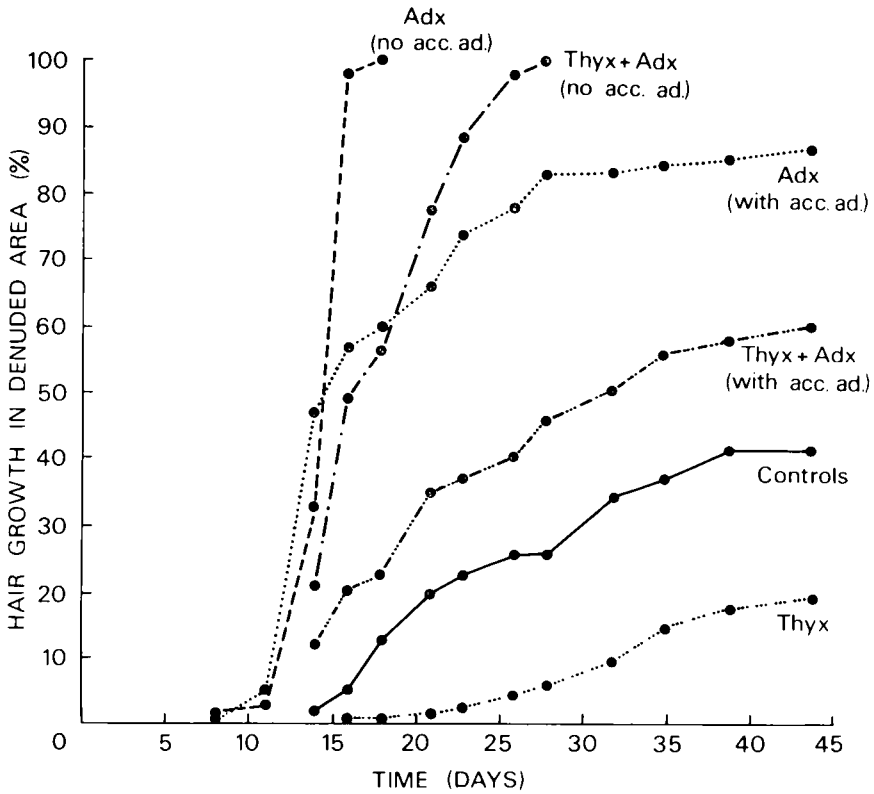

Fig. 2.—Antagonism between the effects of thyroidectomy and adrenalectomy upon the hair waves in C_3H/Ep mice. Role of the accessory adrenals.

Large doses of thyroid hormones may accelerate hair waves in normal rats and mice (Chang 1926; Butcher 1937, 1940; Kozam 1952; Davis 1963; Ebling and Johnson 1964) although excessive doses may inhibit them (Chang 1926; Baker 1951).

The hypophysis also has a stimulating effect on the hair cycle by means of its action on the thyroid. It is not known whether thyroid insufficiency is responsible for the slower hair waves appearing after the diffuse wave in hypophysectomized animals.

VII. Influence of the Nervous System Upon the Hair Waves

The nervous system also intervenes in the regulation of the hair cycle. The work of Covián and Antunes-Rodrigues (1960) demonstrates the existence of very slow hair waves in hemidearchicorticated rats. The inhibitory action is produced by means of the characteristic gonad stimulation, as shown by its suppression through castration.

Considering that the hair growth waves are probably maintained by a

balance between stimulating and inhibitory factors and that hypophysectomy produces a disappearance of the inhibitory factors and stimulation of hair growth in all the resting follicles, we can assume that humoral extrahypophyseal factors are balanced with inhibitory hypophyseal factors. The work of Eser and Tuzunkam (1958) in C57 mice appears to demonstrate a stimulating action of the hypothalamo–posterohypophyseal hormones, but we have been unable to confirm their results in our C_3H/Ep mice.

Lesions of the central nervous system were made 3 or 4 days before castration in C57 male mice in order to see where lesions must be placed to prevent the diffuse hair wave of castrated mice; the electrodes were placed by means of a stereotaxic instrument (Baltimore Instrument Company). A special forceps with ear plugs was devised to hold the head of the mouse. The co-ordinates used to place the lesions are described in Table 1. In each instance the lesions were produced by an electric current of one mA for 5 seconds.

Only mice with lesion 2 showed inhibition of the diffuse hair wave. Histological study showed that this lesion was located in the olfactory cortex, in the anterior and internal part of the tuberculum olfactorium, and the tractus diagonalis was partially compromised. The other lesions did not inhibit the diffuse hair wave.

TABLE 1

EFFECT OF LESIONS OF THE CENTRAL NERVOUS SYSTEM UPON THE DIFFUSE HAIR WAVE INDUCED BY GONADECTOMY IN MALE C57 MICE

Animals			Co-ordinates of the Lesion (mm)			Diffuse Hair Wave
	Number					
Group	Initial	Final	Antero-posterior	Vertical	Lateral	
1	8	5	5.5	3.5	0.5	yes
2	10	4	5.0	3.5	0.5	inhibition
3	9	2	4.5	4.0	0.5	yes
4	10	7	4.0	4.0	0.5	yes
5	9	4	3.5	4.0	0.5	yes
6	5	5	no lesion			yes

These results prompted us to study the effects of surgical resection of the olfactory bulb and related structures upon the hair growth. The operations were performed by suction after perforating the anterior portion of the frontal bone with a dental burr. Twenty C_3H/Ep male mice were clipped and distributed in three groups: (a) 9 mice with bilateral resection, (b) 7 mice with unilateral resection, and (c) non-operated control mice. All animals were castrated three days after the operation.

The diffuse hair wave induced by castration appeared in all the control mice and in all those with unilateral removal of the olfactory bulbs and related structures. The hair growth was retarded in 2 out of the 5 surviving mice with bilateral removal of these structures.

Histological study showed that in the 2 mice with and the 3 mice without hair growth inhibition both olfactory bulbs had been completely removed. Damage in the anterior part of the tuberculum olfactorium was evident in the mice with hair growth inhibition.

VIII. Neurohormonal Regulation of the Waves of Hair Growth

The determining factors in the initiation and advance of hair growth waves are not well known. Chase has suggested that the growth cycle is caused by the rise and fall in the activity of an "inhibitor" (Chase 1955; Chase and Eaton 1959). Other workers have used the same arguments in favour of the existence of a "stimulator" (Davis 1962). Our suggestion has been that the regulation of the hair waves may be explained by a balance between stimulating and inhibitory factors (Houssay 1962).

From the material presented above it can be appreciated that hormones may be stimulants or inhibitors and modify the initiation, advance, and characteristics of the hair wave. They may also impede hair follicles from entering the anagen phase in certain areas and at certain moments.

The inhibitory hormonal factors appear to be of pituitary origin and to act by means of the adrenals and gonads. The adrenal glucocorticoids appear to be the principal inhibitory factors. The stimulating hormonal factors are in part hypophyseal and in part extrahypophyseal. Part of the stimulating action of the pituitary is produced by means of the thyroid. The central nervous system would act in these regulatory mechanisms partly through its action on the pituitary and also through extrahypophyseal effects. The balance of the stimulating and inhibitory factors, according to our hypothesis, is shown schematically in Figure 3.

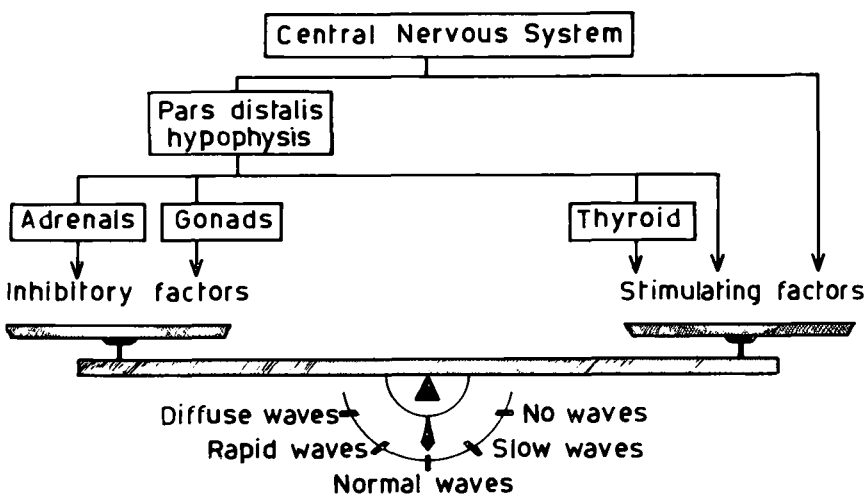

Fig. 3.—Schematic representation of neurohormonal factors regulating the initiation and progression of the hair waves.

It is known that hormones do not create processes but regulate metabolic mechanisms, especially the enzymatic systems of the tissues. So it is possible that hair growth waves might be controlled by local metabolic processes of the skin modified by hormonal actions.

So far, we have not been able to decide if the initiation and advance of the hair waves is solely due to local metabolic factors of the skin, or whether it is regulated by higher mechanisms, probably located in the nervous system, which would regularly alter the balance between the stimulating and inhibitory factors.

This should be taken merely as a hypothesis, based on the facts presented in this paper. Further experimentation will be necessary to ratify or rectify its different parts.

IX. Summary

An interesting alteration of the normal cyclic rhythm of hair growth was obtained in male or female adult mice by gonadectomy, adrenalectomy, or hypophysectomy, and in adult rats by adrenalectomy or hypophysectomy. All the hair follicles in telogen are immediately stimulated by the operation and the animal becomes covered by a diffuse coat of hair. This type of hair growth has been called a diffuse hair wave and was found in 100% of adult animals of sensitive strains after castration or hypophysectomy. It also appeared in 100% of the adrenalectomized animals when accessory adrenals were not detected in autopsy specimens.

The diffuse hair wave induced by castration or adrenalectomy was inhibited by oestrogens, androgens, or glucocorticoids. The diffuse hair wave induced by hypophysectomy was inhibited by any of these hormones and also by adrenocorticotrophin or by pituitary or chorionic gonadotrophins.

Thyroidectomy inhibited the diffuse hair wave induced by castration and the animals showed apparently normal hair waves. The administration of thyroid hormones was necessary to produce diffuse waves after castration in thyroidectomized animals. Thyroidectomy did not affect the diffuse hair wave produced by adrenalectomy provided accessory adrenals were not present. However, when accessory adrenals were found, thyroidectomy decreased the speed of the hair waves of the adrenalectomized animals.

Lesions of the central nervous system were performed 3 or 4 days before castration in C57 male mice. Some animals with lesions of the olfactory cortex showed inhibition of the diffuse hair wave.

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