ON THE EFFECTS OF DEPILATORY ROENTGEN IRRADIATION AND OF CONCOMITANT ADMINISTRATION OF CORTISONE ON HAIR GROWTH IN MICE*†

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The present studies of the effect of potentially epilatory doses of x-rays on hair growth in mice and the influence of systemically administered cortisone on this effect were prompted by several considerations: 1) The methods for investigating the phases of the hair cycle have improved, and this has improved the opportunities for obtaining information on hair growth (1, 2). 2) The dosage of ionizing irradiation of the skin has gained precision. 3) Cortisone administration has been shown to impede hair growth (3–16).

In 1949 Chase reported that in black mice the response of the hair follicle to roentgen radiation depends on the phase of the hair cycle present at the time of the exposure (17, 18). He described the apparently somewhat paradoxical findings that the resting hair follicle of the mouse responded more readily with graying to the irradiation than did the growing follicle, but that the growing hair epilated sooner and at a smaller dosage. This latter observation was confirmed by Geary in Albino rats (19). Similarly, Koenigsbauer (20) obtained complete epilation by thallium only when the mice mice were 10 to 11 days old—at which age the hair cycle was in late anagen and club hairs were absent.

In a microscopic study of extracted human hair roots after depilatory exposure to x-rays, Van Scott and Reinertson also found the degenerative changes confined to the hair of growing follicles (21). On the other hand, Argyris who exposed mice to 3000 to 5000 r during either phase of the hair cycle did not observe any microscopic difference in the degree of damage to the skin between the animals exposed during the growing phase and those exposed during the resting phase (22). Only the latent period between exposure and hair loss—and the sequence of the sequelae (such as degeneration of the hair follicle, hair loss and wound formation) varied with the phase of the hair cycle which existed at the time of irradiation.

The lack in uniformity of these reports contributed to our interest in experiments to clarify some of the pertinent points.

In addition, our interest in any relationship between the effect of epilatory exposure to x-rays and hair cycle was reinforced by the observation made by different investigators (including ourselves (3–16)), that cortisone tends to arrest hair growth. The influence, therefore, of this steroid on the radiation effect was studied as well.

Experiments were devised in which

A. mice were exposed to roentgen radiation during the growing and resting phase, respectively, of the hair cycle and

B. mice were irradiated in the same manner while receiving cortisone injections.

METHOD AND MATERIALS

A total of 254 Swiss albino mice, laboratory bred from a strain received from Carworth Farm, New City, N. Y., were divided into two categories (A and B) and seven groups which were subjected to the following procedures:

A. Irradiation without Cortisone Administration

Group I—The skin of the interscapular area in 33 mice was irradiated with 500 r‡ during the growing phase of the 2nd hair generation.

Group II—23 mice were irradiated in analogous fashion with 500 r during the resting phase of the 2nd hair generation.

Group III—60 mice received 1000 r during the growing phase of the 2nd hair generation.

Group IV—55 mice received 1000 r during the resting phase of the 2nd hair generation.

B. Irradiation combined with Cortisone Administration

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‡ The radiation factors are given below.

TABLE A

Effect of Ionizing Radiation on Hair Growth of Mice

Group	Number of Mice	Radiation			Epilation of Growing Hair No. of Mice	Epilation of Club Hair No. of Mice	Growth of New Hair
		r Exposure	Phase of Hair Cycle				
			Growth	Rest			
I	33	500	×		33	0	Premature
II	23	500		×	—	0	Unchanged
III	60	1000	×		60	55	Premature in all Mice Stunted in half the Number
IV	55	1000		×	—	50	Delayed and stunted

TABLE B

Effect of Ionizing Radiation and Concomitant Cortisone Injections on Hair Growth of Mice

Group	Number of Mice	Radiation			Epilation of Growing Hair No. of Mice	Epilation of Club Hair No. of Mice	Growth of New Hair
		r Exposure	Phase of Hair Cycle				
			Growth	Rest			
V	20	500	×*	Cortisone induced Rest in 10 Mice	10	0	Premature in the 10 Mice epilated
VI	42	1000	×*	Cortisone induced Rest in 32 Mice	10	39	In the 10 Mice irradiated during (unchanged) Anagen: Premature and stunted. In the 32 Mice irradiated during (induced) Telogen: as in group IV.
VII	21	1000		×		20	Delayed and stunted

* Cortisone interfering with normal hair growth (3–16), the mice of Groups V and VI were exposed to irradiation at a time when the second hair generation was normally due to grow, *i.e.* when the mice were 33 to 35 days old.

Group V—20 mice were irradiated with 500 r during the growing phase* of the 2nd hair generation while receiving cortisone injections.

Group VI—42 mice were irradiated with 1000 r during the growing phase* of the 2nd hair generation while receiving cortisone injections.

Group VII—21 mice were irradiated with 1000 r during the resting phase of the 2nd hair generation while receiving cortisone injections.

Technic of Irradiation: X-ray exposure was carried out by applying 500 or 1000 r—100 KV, target skin distance 20 cm, HVL 0.9 mm Al—to a circular field, one cm in diameter, in the interscapular area. The mice were sedated by intraperitoneal injection of sodium pentothal, 0.05 mg/gm body weight, in 0.5 ml phsyiologic saline solution.

Identification of Phases of Hair Cycle: According to Borum's method (1), the phases of the hair cycle were identified by dyeing the fur of the mice black after the first hair cycle was terminated, i.e. at the age of 28 days. The growth of the 2nd hair generation above the skin surface became apparent from the emergence of undyed white hair on the surface of the skin; (on the day of this emergence the irradiations were performed which were scheduled for the period of follicular growth). The end of the growth period, i.e. the beginning of the resting phase was recognized from a uniform gray color which the fur assumed, once the white hair had reached its final length, and which did not become lighter any more thereafter.

The growing phase of the third hair generation was observed in the same manner as the growth of the second generation, after the fur had been dyed again during the resting phase of the second cycle.

* As cortisone was shown to interfere with normal hair growth (3–16), the mice of groups V and VI were exposed to irradiation at a time when the second hair generation was normally due to grow, i.e. when the mice were 33 to 35 days old.

Cortisone Administration: The mice of groups V, VI, and VII received subcutaneous injections of a cortisone acetate suspension (diluted with saline solution to 2 mg/ml) 5 times weekly for one week preceding and for one week following the irradiation. The individual doses varied from 0.3 to 0.5 mg cortisone, according to the weight of the animals.

Histological Examinations: The effects of 1000 r on the growing and the resting hair follicle, respectively, were studied histologically in 96 additional mice; 64 specimens were obtained from irradiated skin and 32 control specimens from corresponding skin areas in not irradiated mice of the same litters; the excisions were made at times varying between two days and two months after the day of irradiation. The specimens were cut serially.

RESULTS

A. Effects of Irradiation (without Cortisone Administration).

Group I—Thirty three mice were exposed to 500 r during follicular growth, *i.e.* on the day of appearance of the white hair of the 2nd hair generation above the skin surface.

This new hair was completely lost between the 4th and 7th day after the irradiation, whereas the club hair of the first hair generation—characterized by its black color—*remained.* The hair of the third generation, easily distinguished by its white color from the black club hair of the first pelage, appeared in the irradiated area two to three weeks after the loss of the growing hair. This third hair coat emerged in the irradiated area at least one week earlier—and in most of the mice two to three weeks earlier—than in the surrounding area. No changes of the skin proper were grossly visible.

Group II—Twenty three mice were exposed to 500 r during follicular rest, one week after the hair of the 2nd generation had ceased to grow.

No epilation occurred in the treated area. Grossly, the growth of the 3rd hair generation did not appear disturbed, nor did the skin show any appreciable macroscopic change.

Group III—Sixty mice were exposed to 1000 r during follicular growth.

In these, the growing hair epilated completely within one week after the irradiation and the hair of the subsequent (3rd) hair generation began to become visible 10 to 20 days earlier in the irradiated area than in the surrounding skin. In 32 of the 60 mice, however, *this growth was sparse and the new hair appeared abnormally thin and short.*

The fur had not regained its normal appearance three months following the irradiation.

In 55 mice of the group, *the club hair* was partly or completely *lost within 4 to 8 weeks* after irradiation.

The skin proper appeared grossly unchanged.

Group IV—Fifty five mice were exposed to 1000 r during follicular rest.

In 50 of the animals *the club hair* was either completely or nearly completely *shed within 4 to 6 weeks* after irradiation. The growth of the hair of the *3rd hair generation* was *delayed by at least 20 days* in the irradiated area; it was *extremely sparse, thin and short* and remained abnormal until the end of our observation period (three months). About 4 weeks after the irradiation, the irradiated skin of a considerable number of the mice showed macular areas which were abnormally smooth and distinctly shiny. These changes disappeared after 1 to 2 weeks.

B. Effects of Radiation and concomitant Cortisone Administration.

Group V—Twenty mice were exposed to 500 r at a time when follicular growth was normally due to occur; in addition, they received cortisone injections.

The steroid retarded the appearance of the 2nd hair generation in 10 of the 20 mice. In these 10, *neither epilation nor any other changes of the fur or skin were observed.* In the other 10 animals the results were the same as in the mice exposed during follicular growth without cortisone administration (Group I).

Group VI—Forty two mice were exposed to 1000 r and injected with cortisone at the time when follicular growth ordinarily occurs.

In 10 mice of the group cortisone failed to delay the growth of the 2nd hair generation. The exposure of the skin of these 10 animals caused damage comparable to that described for the mice irradiated with 1000 r during hair growth and not injected with cortisone (Group III).

In the other 32 animals of Group VI the appearance of the *second pelage* was considerably *delayed* and the growth of this hair generation was *very sparse* in the irradiated area: a few stubs only became visible, and these appeared 20 to 30 days

later than in the surrounding area where the hair growth had been delayed as well, though to a lesser degree—by cortisone.

The club hair, moreover, of the first pelage was lost.

Group VII—Twenty one mice were exposed to 1000 r during follicular rest and injected with cortisone.

The results were the same as in the mice exposed during the resting phase and not injected with the steroid (Group IV).

Microscopic Findings

a) Findings obtained after x-ray exposure during the growing phase (Group III).

The following three periods were distinguished which were primarily related to the different phases of the hair cycle observed:

1. 1–10 days after the irradiation. The growing phase—second pelage—under way at the time of irradiation was found terminated between the 8th and the 10th day after the x-ray exposure. This was normal, since the irradiation was applied on the 10th or 11th day of the growth period.

As early as on the first day after the exposure to x-rays—and throughout the growing phase a number of individual hair follicles showed disorganization of their deep subcutaneous portion (s. Fig. 1) These follicles had become twisted and tortuous, their sheaths appeared uneven and blurred. The sebaceous glands were unaltered.

Changes in the epidermis were limited to hyperchromasia and abnormal polarity of some cells, and a slight increase in the number of mitoses. Dermis and papillae appeared normal.

2. 10–15 days after irradiation. The hair follicles were in the resting phase.

It now was the epidermis where the most striking changes were seen. These changes were first apparent on the 13th day after the exposure to x-rays. There was thickening of the epidermis, hyperkeratosis, and loss of the normal undulation; the epidermal nuclei were large, irregular, and hyperchromatic.

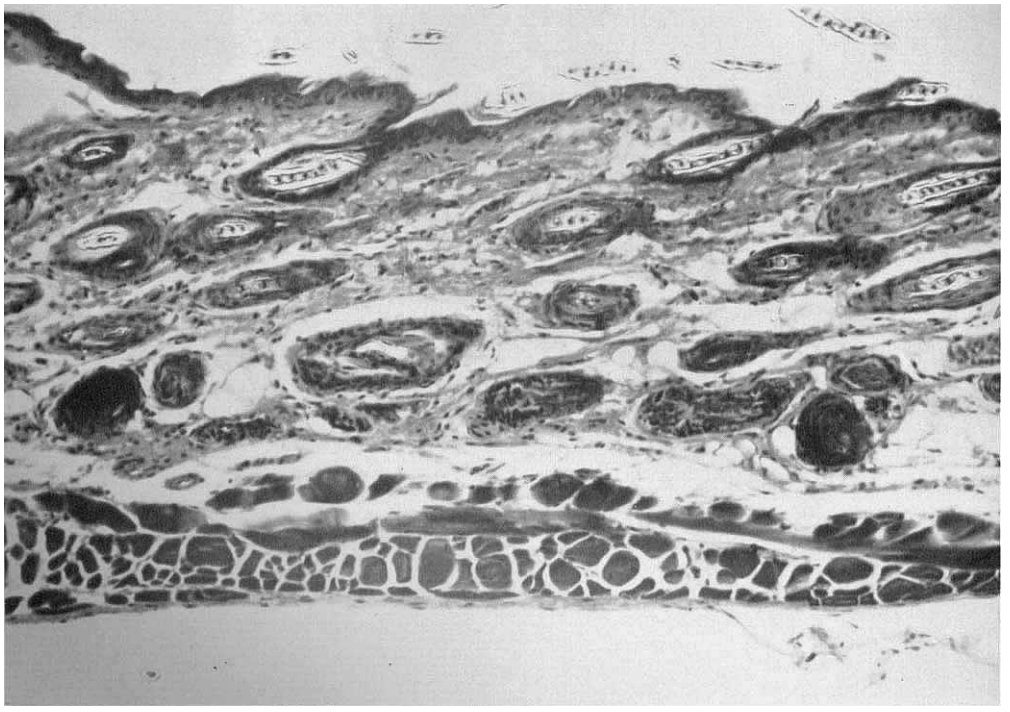

FIG. 1. Histologic Section to Days after Exposure of Skin to X-rays (1000 r) during Anagen*. Disorganization and abnormal Keratinization of growing Follicles. Hem.-Eos. × 82.

* The sequence of the photographs here presented is arranged according to the time interval between irradiation and biopsy excision, regardless of the phase of the hair cycle present at the time of irradiation, since most of the microscopic changes observed at comparable times after the irradiation were essentially quite similar, whether the exposure to x-rays occurred during anagen or during telogen.

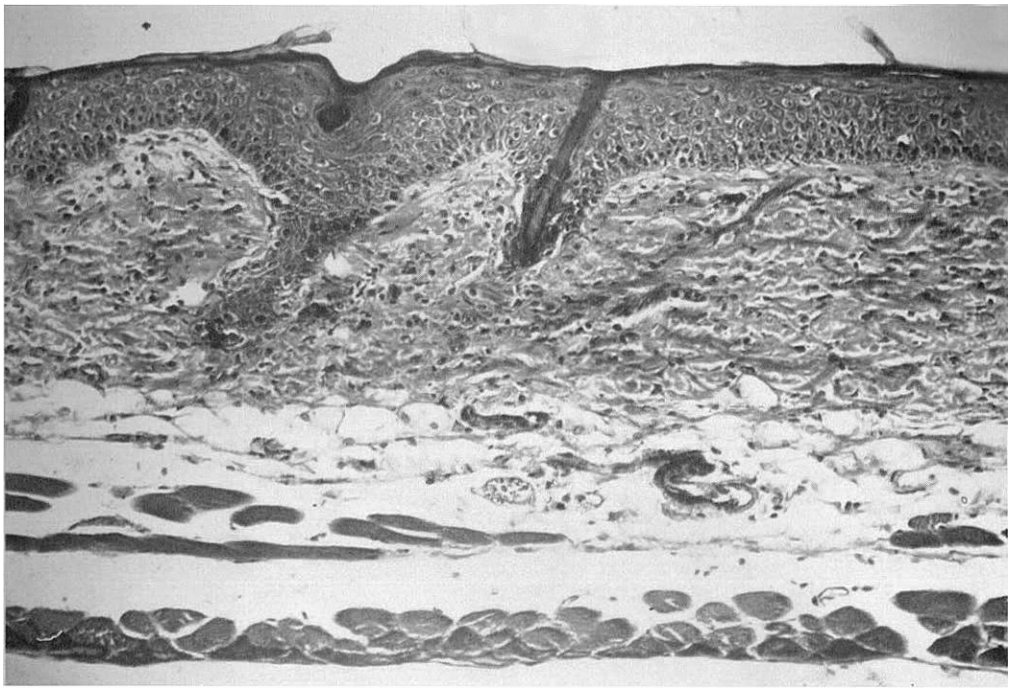

FIG. 2. 16 Days after Irradiation (1000 r) during Telogen*. Epidermal reaction. Next to a resting Follicle—containing a Hair—a solid epithelial intradermal Projection is seen, with a Papilla attached to its proximal End. Hem.-Eos. × 82.

* The sequence of the photographs here presented is arranged according to the time interval between irradiation and biopsy excision, regardless of the phase of the hair cycle present at the time of irradiation, since most of the microscopic changes observed at comparable times after the irradiation were essentially quite similar, whether the exposure to x-rays occurred during anagen or during telogen.

The infundibula and hair canals of a number of follicles were plugged with keratin; the hair sac was either thickened or abnormally thin. The sebaceous glands of some follicles were missing in such hyperkeratotic areas.

Epithelial columns proliferating from the epidermis down into the cutis were seen besides the inactive follicles. These cellular columns were either completely undifferentiated or partially keratinized. There were, furthermore, keratinized "pearls", lying within the cutis and connected with the epidermis by strings of epithelial cells.

In some specimens, the study of serial sections revealed the presence of a hair papilla located near the proximal end of some of the columnar epithelial proliferations, indicating that these strands actually were dedifferentiated—or incompletely differentiated—hair follicles (Fig. 2).-

3. 16th day after irradiation to end of observa tion (59th day). From the beginning of this period some of the follicles showed the features of growth (Fig. 3).

The epidermal changes in Group III continued to be visible for about 23 additional days during this third phase of observation.

While scattered follicles resumed growth activity from the 16th post-irradiation day, the remaining follicles stayed in the resting phase. A number of follicles, which varied from one specimen to another, showed a normal morphology both in the growing and in the resting stage. Others, however, showed drastic deformities (s. Fig. 4).

Some of the growing follicles were twisted, and in part displayed a tortuous, bizarre appearance and gigantic proportions of such degree that they assumed "monstrous" configurations. In other instances, the hairs were reduced practically to bundles of keratinous fragments situated in the sub-cutis.

Among the resting follicles, some showed an abnormally thick and hyperkeratotic—others an unusually thin hair sac, with irregularly arranged,

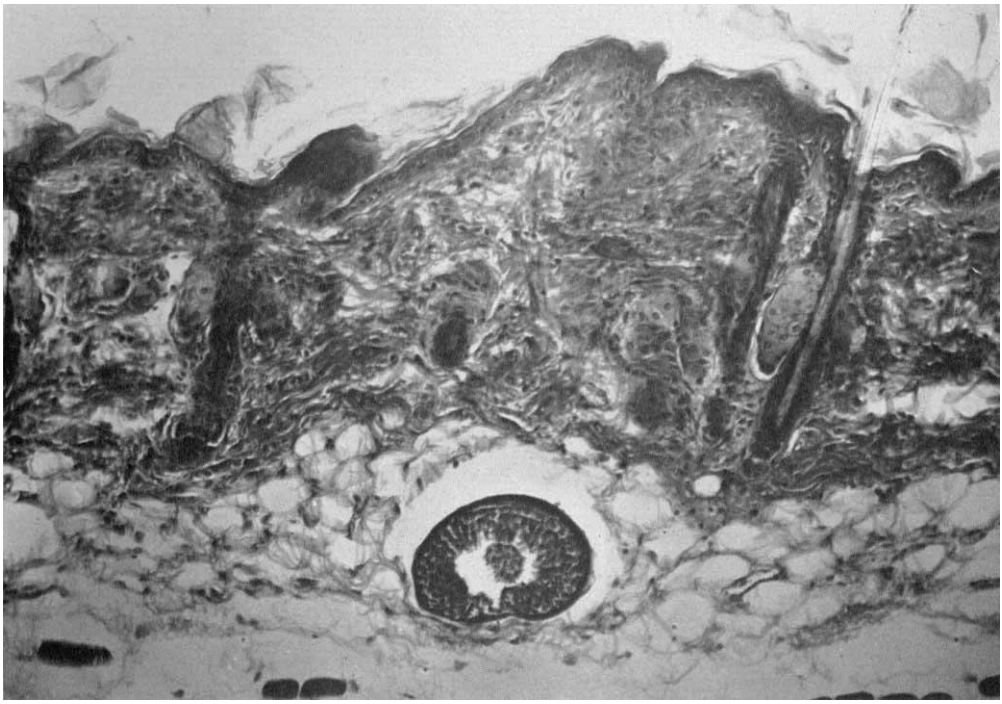

FIG. 3. 16 Days after Irradiation during Anagen. One Follicle shows growth Activity, while 4 other Follicles (with their Papillae attached) are at Rest. Epidermal Changes are exceptionally slight in this Instance. Hem.-Eos. × 82.

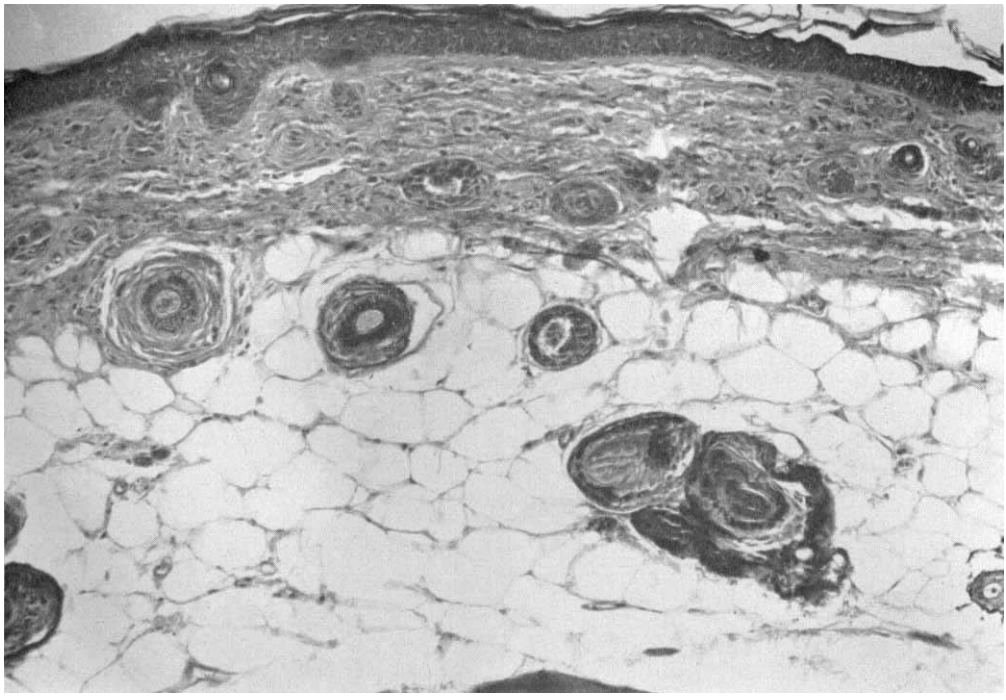

FIG 4. 19 Days after Irradiatinn during growing Phase. The characteristic epidermal Changes are seen, as well as Resumption of follicular Activity—and a disorganized "giant" Follicle. Hem.-Eos. × 82.

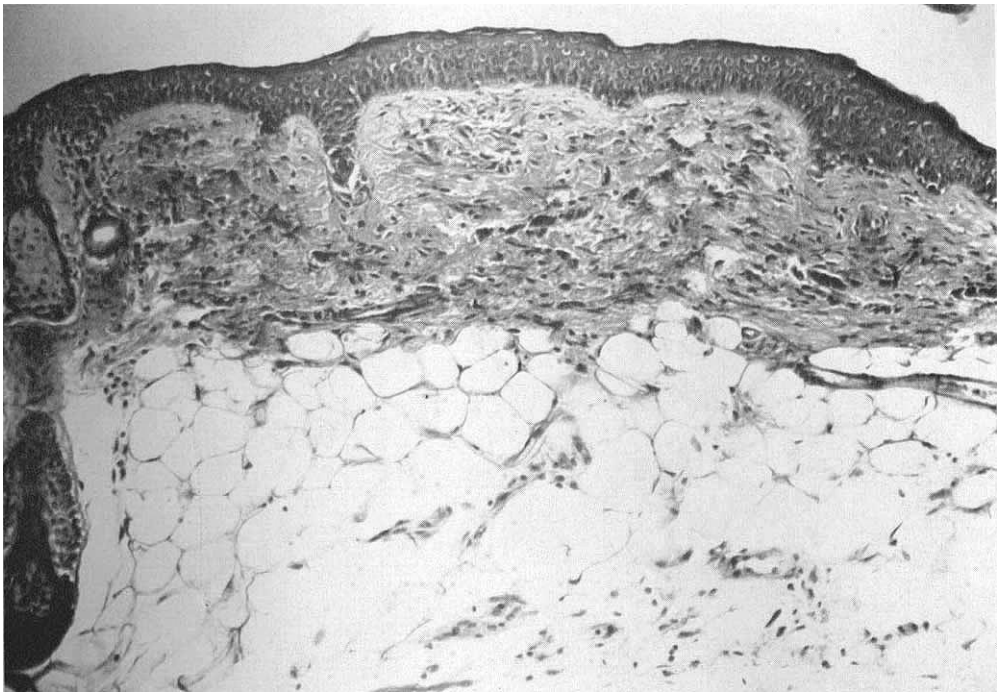

FIG. 5. 34 Days after Irradiation during Telogen. Note Persistence of epidermal Changes, a growing Follicle, a Scar-like Area with follicular Effacement—and a horny Cyst attached to the Surface Epidermis by a String of Cells. Hem.-Eos. × 82.

hyperchromatic epithelial nuclei. These sacs contained abnormally thin hair shafts.

The solid epithelial columns were still apparent, extending downward from the epidermis, and partly keratinized; and likewise the keratinized pearly formations were still seen in the cutis.

In certain areas, the follicles appeared to be diminished in number.

This variegated picture, showing areas of hyperplastic epidermal changes, seemingly normal resting follicles interspersed with apparently normal growing follicles, and numerous distorted follicles both in the growing and in the resting phase, was observed as late as on the 39th day after the irradiation. In some of the specimens abnormal follicles were found even on the 54th day following the exposure to x-rays.

b) Findings obtained after irradiation during the resting phase (Group IV).

Two periods were distinguished, according to the changes noted during different phases of the hair cycle:

1. 1 to 23 days after irradiation. The earliest changes were observed on the 10th day, while the follicles were still inactive. The changes were similar to those observed at the corresponding time after irradiation during follicular growth (Group III). Most apparent were epidermal acanthosis and hyperkeratosis, plugging of the follicular infundibula, and epithelial projections into the dermis. Occasionally attachment of a hair papilla to the proximal end of such a projection was demonstrable in the serial sections—again leaving no doubt that the columnar projections have resulted from transformation of hair follicles (Fig. 2).

2. 24 days after x-ray exposure to end of observation period (59th day) (Figs. 5–7). Hair follicular activity was noted in practically all specimens obtained from the 24th to the 34th day after the irradiation. The quota of active follicles, however, varied from one specimen to another, and they showed different stages of growth, rather than the pattern of a normal growth wave (s. Fig. 6). In many preparations the activity actually affected only individual follicles. Some of the growing follicles were abnormally twisted and tortuous; the outline of their sheaths was blurred. Occasional follicles were found in the process of disintegration and surrounded by foreign-body giant cells.

The degeneration of gowing follicles was as-

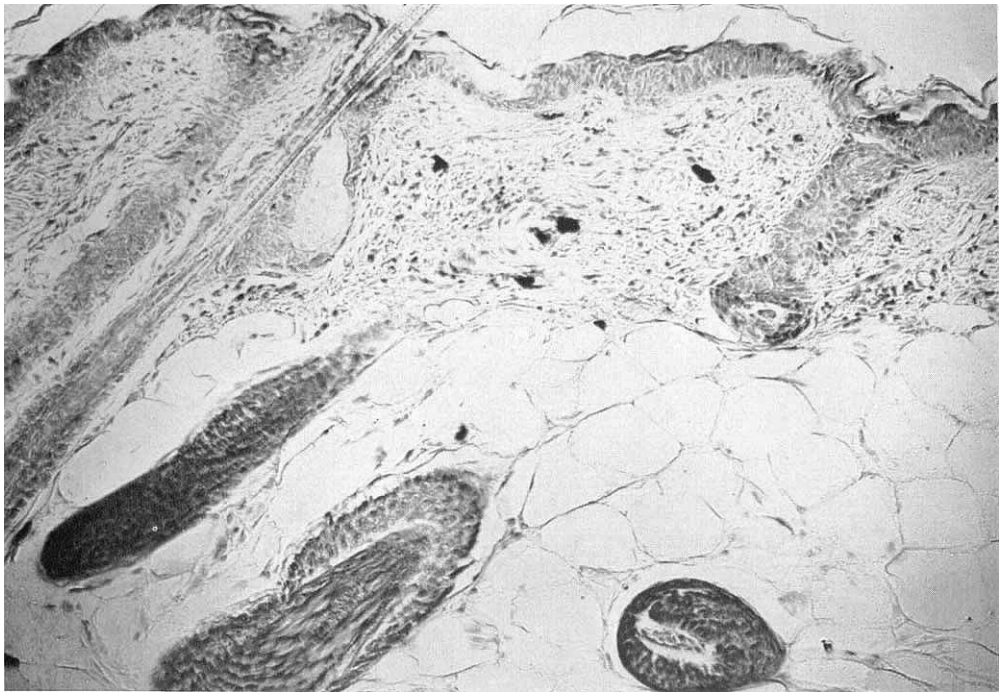

FIG. 6. 49 Days after Irradiation during Telogen. Epidermal changes persist. A Number of growing Follicles are present (one of which—with a Hair reaching above the Surface—is in Anagen VI). To the right, note massive epithelial Projection without Hair, beginning to resume growth Activity, as evidenced by epithelial Proliferation capping the Papilla. Tol. Blue × 82.

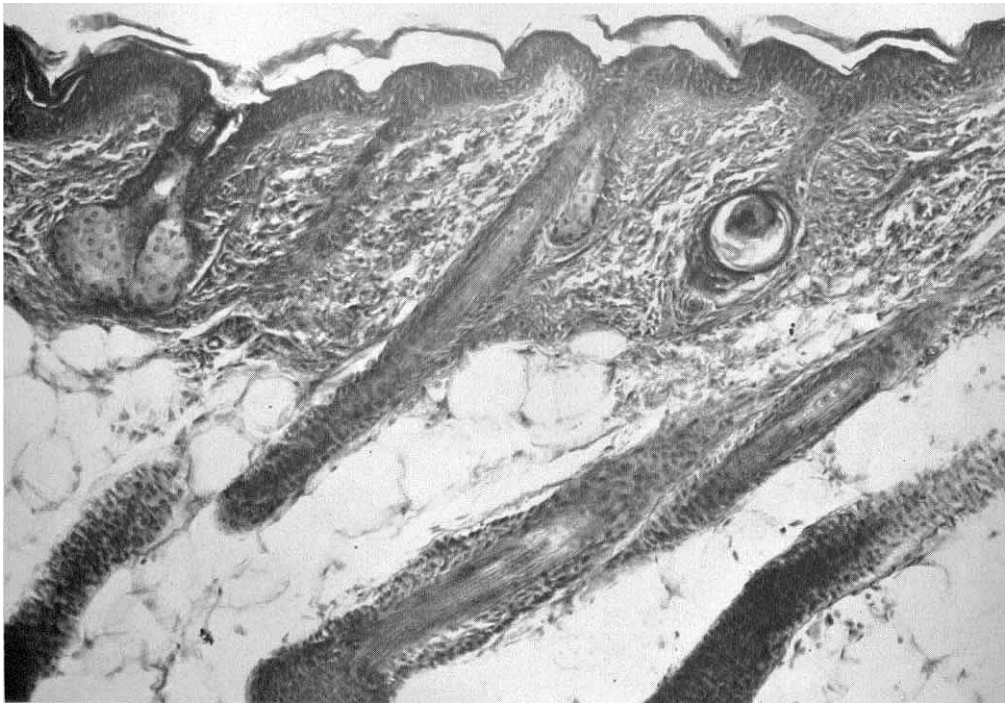

FIG. 7. 49 Days after Irradiation during Telogen. Epidermis still thickened. A number of growing Follicles are seen and a horny Cyst attached to the Surface by a Column of Epithelial Cells. The Papilla at deeper Part of cystic Formation reveals the latter's hair-follicular Origin. Hem.-Eos. × 82.

sociated with thickening of the epidermis proper. Also some horny cysts were present (s. Fig. 7).

In a few specimens the dermis had assumed a scar-like appearance, suggesting that the number of follicles was diminished (Fig. 5).

Some of the changes were still encountered at the end of our observation period, i.e. 59 days after the irradiation.

DISCUSSION

A. Effects of Irradiation without Cortisone Administration:

Gross Observations

When the described gross findings are subdivided into *immediate acute damage* produced by the irradiation to hair growth on one hand—and *late damage* on the other, the following conclusions are warranted:

Exposure to 500 r causes immediate interference with hair growth and epilation, when employed during anagen of the hair cycle; apart from premature growth of the succeeding hair generation—which is in accord with the findings of Geary (19)—no late effect is then apparent.

The same exposure applied during telogen appears ineffective.

Exposure to 1000 r during anagen produces similar immediate effects as does exposure to 500 r during this phase of the hair cycle. In addition, however, the same exposure is followed by distinct late effects, manifested by *stunted* growth of the *subsequent pelage*, and by shedding of the club hair of the preceding hair generation.

The same amount of x-rays applied during telogen, though not producing gross evidence of immediate damage, macroscopically causes even more severe late damage to the follicular apparatus than the exposure employed during the growing phase. This is apparent from the *delayed* and *still poorer growth* of the *subsequent hair generations* in the mice irradiated during the resting phase.

The distinction of immediate and late radiation effects on the hair follicular apparatus aids in explaining the reports of previous investigators (15–17, 18, 20–22), most of whom limited their studies to the early post-irradiation period.

Microscopic Observations

The three periods in the sequence of histologic findings observed upon irradiation with 1000 r during anagen can be correlated with the macroscopic findings: 1) acute degeneration of growing follicles accounts for the early epilation of anagen hair*; 2) the subsequent alterations of resting follicles and epidermis result in shedding of the club hair; 3) the *late degenerative alterations* involving also the *subsequent hair generation* cause the scanty, *poor*, and *unsynchronized* growth of the *next pelage.*

In agreement with the macroscopic observations, the microscopic changes found after the application of 1000 r during telogen are exclusively late changes. Again, the hyperkeratotic and other alterations of the epidermis and resting follicles lead to shedding of the telogen hair. Subsequent growth activity, occurring with delay and *in different follicles at very different times*, is associated with a multitude of follicular deformities—which all accounts for the *poor quality* of the *third hair generation.*

B. Effects of Radiation and Concomitant Cortisone Administration.

In agreement with previous experimental results obtained by several investigators (3–9, 14–16), as well as by our own group (10–12), the cortisone injections produced inhibition of hair growth in a considerable number of animals of groups V (exposed to 500 r during anagen) and VI (exposed to 1000 r during anagen). Consequently, the x-ray effects obtained in these animals are the same as those in the corresponding groups irradiated during telogen (groups II and IV, respectively). As cortisone remains without influence on the hair cycle when administered during follicular rest, it does not

* A number of the severely degenerating follicles may be expected to undergo atrophy, but this cannot possibly account for the epilation in general. Actually, most of the follicles examined during the first post-irradiation week continue to show the proximal part of the hair shaft and growth activity. This fact leads us to believe that the irradiation produces a zone of "dysplasia" or "constriction" (Van Scott (21, 23)) at the root of the anagen hair, which zone moves outward and at the time of epilation apparently is situated at a distal level in the follicle where the hair then tends to rupture upon the slightest mechanical insult, with surface baldness as the result. This type of defect would be similar to that observed by Van Scott et al. of some of the human hair roots examined after ionizing radiation (21), as well as to the effect he obtained from amethopterin administration (21, 23, 24). Preliminary observations made during microscopic examination of hair removed from some irradiated mice seem to support our assumption. Further pertinent studies are in progress.

modify the radiation effects on hair growth under such conditions (group VII).

CONCLUSIONS

The described experiments lead to the general conclusion that it is possible to epilate *growing* hair in mice by means of an x-ray dosage moderate enough to prevent damage to subsequent hair growth. *Resting* hair cannot be removed in this manner. Cortisone, interfering with hair follicular growth, can impair successful epilation of growing hair.

Further investigative work will be required to relate these findings to conditions in man, particularly regarding the possibility of sequelae of therapeutic x-ray epilation. Any means capable of deliberately inducing the growth phase of the human hair follicle might be of value in preventing persistent x-ray injury to the hair follicle (*e.g.* premature graying (18, 19, 25)), by allowing successful epilation with relatively small amounts of irradiation.

SUMMARY

1. Investigations were conducted of the effects of irradiation with 500 r and with 1000 r on the fur of Swiss albino mice, each dosage applied during hair follicular growth and during hair follicular rest, respectively. The same effects were studied in combination with concomitant cortisone injections.

2. The results observed may be subdivided into immediate and late effects. The immediate response was characterized by epilation of the growing hairs; the late response by shedding of the club hair and irregular, as well as poor growth of the subsequent hair generations.

3. a) Exposure to 500 r during anagen, i.e. the growth phase, produced the immediate response, i.e. epilation of the growing hair, with no discernible late damage.

b) Exposure to 1000 r during anagen produced epilation of the growing hair, followed by late effects, namely by shedding of the club hair and defective growth of the subsequent hair generations.

4. a) Exposure to 500 r during telogen or resting phase did not result in any gross changes.

b) Exposure to 1000 r during telogen failed to cause an immediate effect, but was followed later by loss of the club hair and subsequently by delayed, irregular, and very poor growth of the new hair.

5. The histologic findings obtained after irradiation with 1000 r during anagen and during telogen revealed bizarre degenerations of growing follicles, beginning on the 1st post-irradiation day, as evidence of the immediate response in mice exposed during anagen. Late manifestations were observed microscopically in both groups of animals, *i.e.*, resulting from irradiation in both phases of hair growth. There was thickening and hyperkeratosis of the epidermis and horny plugging of follicles at rest. Subsequently very irregular growth activity was noted, associated with degenerative alterations of growing follicles, which included transformation into undifferentiated epidermal cords.

6. In the two groups of mice—exposed to 500 r and to 1000 r—in which cortisone was injected at the time when hair follicular growth was due to occur, a substantial number of animals failed to show anagen hairs, in agreement with previous experimental results. In these animals the irradiation resulted in the same effects which were obtained in the corresponding groups irradiated during telogen, without cortisone administration. No modification of the radiation effects by cortisone was observed in the mice injected during telogen.

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