EFFECT OF RADIATION ON THE NAIL TISSUE

BY

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ABSTRACT

1. This article is concerned with the radiation effects on nail based upon macroscopic as well as histological investigations, and composes a series of studies on "Radiation Effect on Hard Tissues" in our Department of Radiology[6-11].

2. The nail plate is produced by the nail matrix and classified into two layers, the outer and the inner, of different stratification. The outer layer originates from the posterior half of the nail matrix and, on the other hand, the inner layer from the anterior half. The growth of nail plate is influenced by two factors, i.e., formation of nail plate at matrix and forward march of the plate induced by hyponychium.

3. The length of nail plate on mid-longitudinal section is 4.5 mm and length of nail bed is 2 to 3 mm on the same section.

4. Among the nail tissues the radiosensitivity is nail matrix, hyponychium and nail plate in order. In nail matrix, the posterior half is more sensitive than the anterior half.

5. The histological changes produced by a single 1000 R irradiation are slight, but ones in a single 3000 R irradiation are so severe that no recovery from the damage are observed. In a single 2000 R irradiation, the changes are severe but reversible.

6. The effect of irradiation to nail is lowered by fractionation.

7. The shedding of the nail due to irradiation, same as the histological change, is also more prominent in the higher dose and in less frequent fractionation.

8. The shedding of the nail is induced by combined processes such as the isolation of the nail plate from matrix, the separation of nail plate from the nail bed and the forward movement of the nail plate.

9. The recovery factor in nail is about same as one in the skin.

10. The growth of human nail is delayed by irradiation.

11. The radiosensitivity of nail is slightly lower than one of skin.

INTRODUCTION

The changes of the skin, including the nail, was apparently the first to be noticed among various biological effects of radiation on the human

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body following the discovery of X-rays in 1895, because man frequently estimated the quality of X-rays by the image of his own hand projected on the fluorescent screen at the early stage of the development of radiology. Even later, the changes of nail such as pigmentation, ridging, fragility, shedding and so on have been observed in the chronic radiation injury to the skin among the physicians, technicians and others[1–5].

The mechanism to produce such changes in the nail, however, has been little known till present. Thus, our investigation is directed to clarify the mechanism of nail changes produced by irradiation.

Method of Experiment

Our investigation was mainly based upon histological as well as macroscopic observations on nail of experimental animal, supplemented by clinical observations on human material.

1. Material

Female Wister rats, approximately 50 g in weight, were placed under the same and appropriate breeding condition. Nails of all toes of the hind legs of those animals were chosen to be investigated.

2. Method and Dose of Irradiation

The animal was anaesthetized by intraperitoneal administration of Pentobarbital Sodium (35 mg/kg of body weight) and the whole body except for the distal portion of the hind leg was covered by lead shield of 3 mm in thickness. The distal portion of hind leg placed on wax phantom was irradiated by the conventional radiotherapeutic apparatus (200 kVp, 18 mA, 0.24 Cu in HVL, 30 cm in FSD and 400 R per min. in dose rate). Irradiation was always carried out at approximately same time in the afternoon. According to the differences in method and dose of irradiation, the animal were divided into five group, as follows:

a) single irradiation of 1000 R
b) single irradiation of 2000 R
c) single irradiation of 3000 R
d) fractionated irradiation of a total dose of 2000 R (200 R daily for ten days).
e) fractionated irradiation of a total dose of 2000 R (400 R daily on every other day).

3. Methods of Observation

Gross appearance as well as histological changes of the nail following irradiation was observed. Amputated toe was placed in 10% Formalin solution, and embedded in celloidin after decalcification with nitric acid. The histological specimens sectioned approximately 20 μ in thickness were stained with Hematoxylin and Eosin or less frequently by Unna's method. The period of investigation was four weeks following the end of irradiation, since the newly formed nail plate at matrix reached the free edge of nail bed in four weeks in normal rat.

Results

1. Normal Nail Tissues of Rat

Figures 1 & 2 illustrate the normal nail tissues of rat. The portions profoundly affected by irradiation are nail plate, nail matrix and hyponychium.

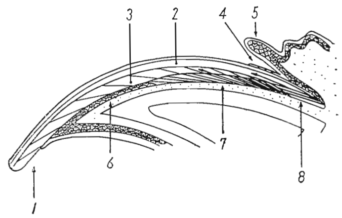

Fig. 1. Longitudinal section from a digid.
1. Free edge of nail plate
2. Nail plate (dorsal)
3. Nail plate (ventral)
4. Eponychium 5. Nail wall.
6. Hyponychium 7. Nail matrix
8. Nail matrix.

Fig. 2. Longitudinal section of normal digid (×15).

Nail plate is crescent in shape on longitudinal section and in inverted "U" shape on cross section. The nail plate opposite hyponychium is 0.27 to 0.33 mm in thickness, and gradually decreases in thickness toward both ends. The nail plate consists of two differently lamellated layers. Lamellae in the outer or dorsal layer run parallel with the surface of the nail plate, and ones in the inner or ventral layer run obliquely, as shown in Fig. 1.

The posterior half of nail bed is called nail matrix, which are composed of ten or more stratified layers of cells. Though cells are cylindrical in shape in the deep layers, they are gradually transformed to plygonal squamous cells and finally keratinized toward the outer surface. Mitotic activity is not infrequently encountered in cells of the basal layer of nail matrix, as shown in Fig. 3. It is interesting to notice that the dorsal keratinized layer of nail plate originates from cell columns in the posterior portion of nail matrix and the ventral layer originates from cell columns in anterior portion. The cell columns in the anterior portion of nail matrix are aligned in the same direction as lamellae in the ventral layer of nail plate.

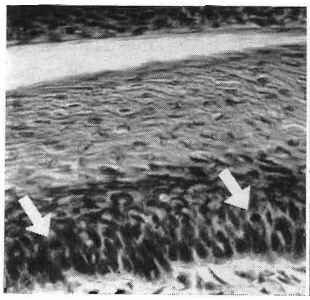

Fig. 3. Nail matrix (×200). Arrows indicate mitotic cells.

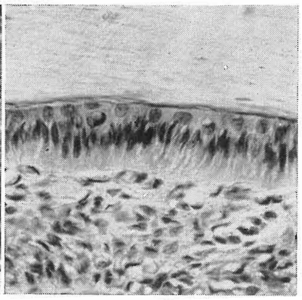

Fig. 4. Hyponychium (×200). Two layers of different cell-type.

Hyponychium is composed of two layers of different cell-type, high cylindrical cell in the inner layer and cuboid epithelial cell in the outer layer. There is no evidence of keratinization in the cuboid epithelial cell layer. The boundary between hyponychium and nail plate is quite distinct in rat (Fig. 4).

2. Growth and Length of Nail

The nail plate is produced by the nail matrix, and grows forward. The growth rate of nail in rat was determined by measurement of the forward march of a mark placed on the nail plate during a period of time, say one week, as shown in Fig. 5. The measurement of the growth rate was carried out in 34 toes resulting in 0.15 mm daily in average. This result indicates that the growth rate of nail in rat is somewhat faster than in man.

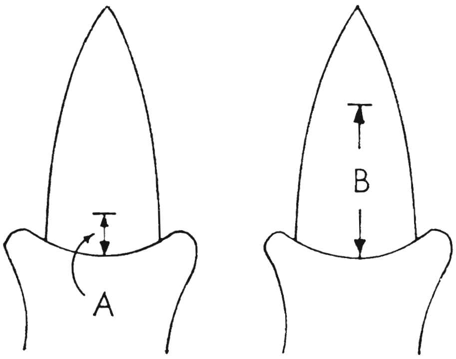

Fig. 5. Method of measurement.

$$\frac{B-A}{\text{Interval (days)}}=\text{Growth rate per day}$$

Since nail plate was 4 to 4.5 mm and hyponychium was 2 to 3 mm in length, it should take approximately 20–30 days until the newly formed nail reached at the tip of nail plate, and approximately 20 days until it reached the free edge of the nail plate.

3. Effect of Radiation on Nail Tissues

The histological changes produced by single or fractionated irradiation are summarized in Table 1.

Table 1. Histological changes in each group

Dose	Post-irradi. day	Nail matrix		Hyponychium	Nail plate	Connective tissues of nail bed
		No. of Mitosis	Other changes			
1000 R×1	1	−	−	−	−	−
	3	+	+	−	−	−
	5	++	+	−	−	−
	10	++	+	−	−	−
	14	++	−	−	−	−
	28	++	−	−	−	−
2000 R×1	1	−	−	−	−	−
	3	+	+	−	−	−
	5	+	++	+	−	−
	10	±	++	−	−	+
	14	+	++	+	+	++
	28	++	−	−	+	−
3000 R×1	1	−	+	−	−	+
	3	−	++	−	−	+
	5	+	++	−	+	+
	10	−	++	++	+	++
	14	−	++	++	++	++
200 R×10	1	±	+	−	+	+
	7	+	+	−	+	+
	14	++	−	±	−	+
	28	++	−	±	−	+
400 R×5	1	±	+	−	+	+
	7	+	+	±	+	+
	14	+	−	±	−	+
	23	++	−	±	−	+
Control	−	++	−	−	−	−

In 1000 R single irradiation, slight damage was observed in nail matrix in 1 or 10 days after irradiation but the damage completely disappeared in 28 days.

In 2000 R single irradiation, marked damage in nail matrix and subsequent inhibition in formation of nail plate were observed especially in 10 or 14 days after irradiation. However, nail was recovered from such damage in 28 days (Fig. 6c).

In 3000 R single irradiation, the damage in nail matrix was so profound that epithelium in the matrix disappeared and formation of nail plate was interrupted. In addition, paraungual tissues were also seriously damaged, and epilation, ulcer or even defect of soft tissues overlying bones subsequently ensued. Furthermore, signs of regeneration of nail tissues could not be elicited in this group of rats (Fig. 7).

In both groups of fractionated irradiation (200 R×10 & 400 R×5), on the other hand, the histological changes were as slight as ones in the group of 1000 R single irradiation.

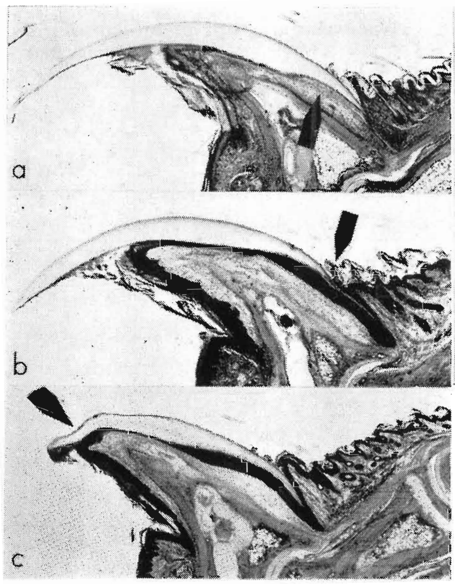

Fig. 6. a) 10 days after 2000 R single irradiation. (×15) Cells in nail matrix are replaced by connective tissues. b) 14 days after 2000 R single irradiation. (×15) Nail matrix is covered by newly formed nail plate. c) 28 days after 2000 R single irradiation. (×15) Marked recovery of nail matrix, leaving deformity at distal nail plate.

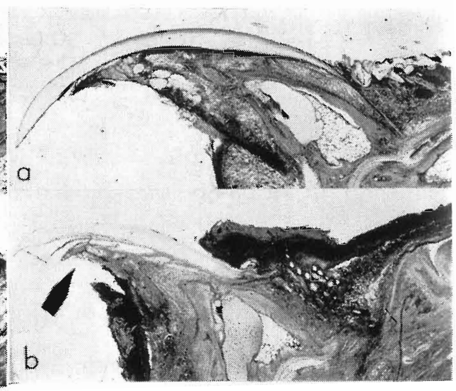

Fig. 7. a) 10 days after 3000 R single irradiation. (×15) Cells in nail matrix are replaced by connective tissues. b) 14 days after 3000 R single irradiation. (×15) Nail matrix and skin are seriously damaged, and nail plate is separated from nail bed.

4. Re-growth of the Nail following Extraction of Normal Nail Plate in Rat.

The process of re-growth of the nail following extraction of nail plate are demonstrated in Fig. 8.

The hyponychium usually lost its outer layer when nail plate was extracted but restored to its normal appearance in 3 days following extraction. Newly formed nail could be identified in the posterior portion of nail matrix at about same time when the hyponychium restored to its normal appearance. In 28 days the re-growth of the nail was complete.

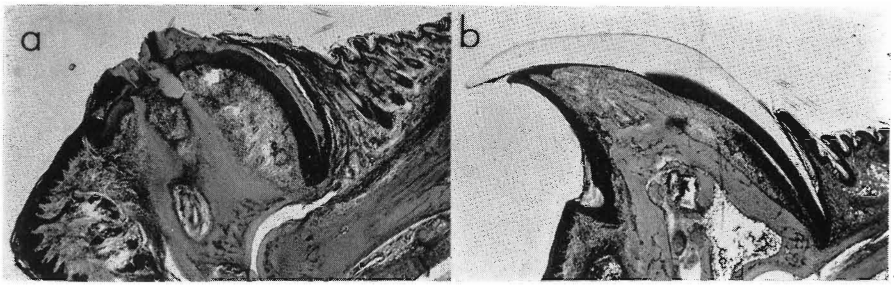

Fig. 8. a) 3 days after extraction of nail plate. (×15) Thin nail plate is seen on the nail matrix. b) 28 days after extraction of nail plate. (×15) Complete recovery.

5. Radiation Effect on Growth of Human Nail (Clinical experiences).

The growth rate of normal human nail was determined by measurement of forward march of a mark, placed on the nail, as shown in Fig. 9, resulting in 0.1 mm daily in average (Fig. 12).

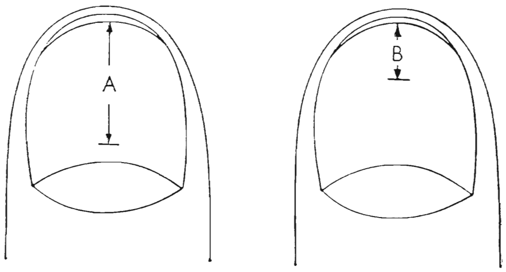

Fig. 9. Method of measurement.

$$\frac{A-B}{\text{Interval (days)}}=\text{Growth rate per day.}$$

The growth rate of irradiated nail was measured by the same method in three patients, and detail data are shown in Figs. 10 and 11. The growth of the nail was markedly impaired by irradiation in those three cases.

6. Shedding of Nail Plate following Irradiation (Macroscopic Observation).

"Shedding of the nail is defined as "fall off of nail plate" not caused by direct mechanical force, and is apparently the most evident among the macroscopic changes of the nail caused by irradiation. That is the reason why we investigated radiation effect on the nail from the viewpoint of shedding of the nail. There were two different methods of irradiation. The one was further subdivided into 5 groups, according to the difference in total dose of irradiation, i.e., 1000 R, 1500 R, 1750 R, 2000 R and 3000 R. The other was also subdivided into 7 groups, according to the difference in fractionation and total dose of irradiation, i.e., 200 R daily × 10, 400 R

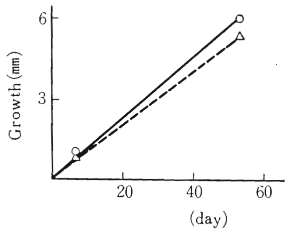

Fig. 10. Case 1. Index-finger nail.
△ Irradiated side.
○ Control.

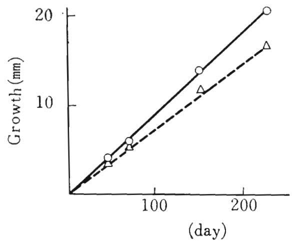

Fig. 11. Case 2. Index-finger nail.
△ Irradiated side.
○ Control.

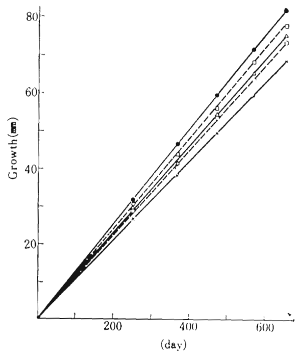

Fig. 12. Growth of nail (Adult).
●-● Thumb.
○-○ Index-finger.
□-□ Middle-finger.
△-△ Ring-finger.
×-× Little-finger.

every other day × 5, 430 R daily × 10, 680 R every other day × 5, 1000 R every third day × 2, 1250 R every third day × 2 and 1500 R every other day × 2.

Each group consisted of 8 rats and all toes of both hind legs of each rat were chosen as materials.

Shedding of the nail began to be observed approximately two weeks after the end of irradiation and gradually increased in number as time elapsed, reaching the maximum approximately 30 days after the end of irradiation in the majority of groups.

The relationship between the percentage of shedding and time is expressed by sigmoid curves, as shown in Fig. 13. Those curves are varied in differences in method of irradiation and dose. So far as the total dose is concerned, the curve is shifted toward left in the higher level and shifted toward right in lower level of dose.

So far as the number of fractionation is concerned, shedding of the nail develops at the earlier stage in the less frequently fractionated group.

To compare the radiation effect among all groups, there are two methods: the one is to compare the percentage of shedding of the nail on the 28th day from the start of irradiation and the other is to compare the number of day at 50 percent of shedding in each group.

Results of the two comparative studies are shown in Figs. 14 & 15 and it becomes clear that, at least, 1000 R was necessary to produce shedding of

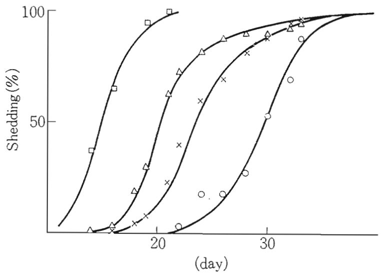

Fig. 13. Relation between percentage of shedding and post irradiated day in each single irradiation.
□ 3000 R, △ 2000 R, × 1750 R, ○ 1500 R.

the nail and approximately 1600 R was necessary to produce 50 percent of shedding.

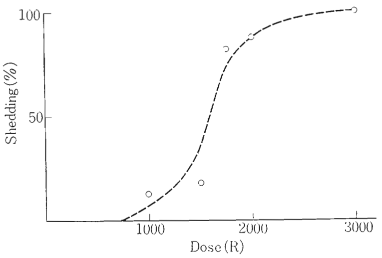

Fig. 14. Percentage of shedding observed 28 days after each single irradiation.

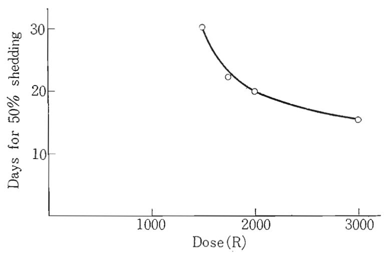

Fig. 15. Period to reach 50% shedding after single irradiation in each group.

Mechanism of Shedding of the Nail induced by Radiation.

There may be a few assumable mechanisms to explain the shedding of the nail secondary to irradiation.

a. Radiation injury to the nail matrix results in interruption of formation of nail plate, and the nail plate is subsequently isolated from the matrix whereas the forward movement of nail plate is maintained. The isolated nail plate from the matrix falls off when it moves forward beyond the free edge of nail bed. If so, it should approximately 14 to 20 days until the isolated nail plate would fall.

b. Radiation injury to both nail matrix and hyponychium results in the interruption of formation of nail plate as well as delay of the forward movement of the isolated nail plate. The isolated nail plate falls off as it is pushed forward beyond the foremost edge of nail bed by newly formed nail at matrix. If so, it should take longer period of time than in normal growth until the isolated nail plate would fall off. The larger dose of irradiation will produce the more profound delay-effect on shedding.

c. Radiation injury to nail bed, including matrix, results in total isolation as well as separation of the nail plate. If so, shedding would develop even soon after irradiation. The period till shedding should be the shorter in the larger dose of radiation.

d. Radiation injury to the nail bed, including matrix, results in partial separation of nail plate from the nail bed. In this case, the period till shedding should be apparently shortened by the partial separation of nail plate and the shorter in the larger dose of irradiation.

Among the above-mentioned, it is likely that the last three assumptions or their combinations play important role in shedding of nail secondary to irradiation. That is to say, irradiation to the nail in such dose as to produce the interruption of formation of nail plate in matrix may well be, at the same time, noxious to the function of hyponychium, it is hardly conceivable that hyponychium can be remained intact in such condition that the matrix is seriously damaged.

As shown in Fig. 13, the relation between percentage of shedding and period till shedding in each group is expressed by a sigmoid curve which is indicative that each group consists of nails of heterogeneous radiosensitivity. In practice, therefore, the period to reach 50 percent shedding following irradiation may be accepted not only as a useful single figure explanation of irradiation damage of nail for a group but also as an important indicator to compare the radiation damage to the nail among various groups of different doses and methods of irradiation. As shown in Fig. 15, the period till 50 percent shedding is shorter, the higher dose is irradiated to nail. It can be deduced from our experiment that dose below 1000 R produce neither interruption nor shedding of nail plate. After all, the shedding of nail is caused by damages to the nail matrix and hyponychium, and in other words, analogous to radiation injury to the epidermis.

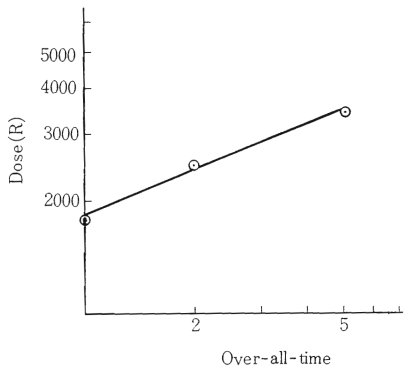

Fig. 16. Dose-time relationship of nail tissue.
$D=D_0 \cdot T^{0.33}$

The above conclusion is also supported by the fact that recovery index of the nail is about same as one in the skin (epidermis)[23,24], i.e., 0.33 (Fig. 16).

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