STUDIES OF THORIUM X APPLIED TO HUMAN SKIN

III. The Relative Effects of Alpha and Beta-Gamma Irradiation in the Production of Erythema*

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Many opinions have been voiced regarding the biologically effective radiation emanating from thorium X; and various theories have been postulated to account for the well-known erythema and pigmentation which follow the topical application of this radioactive material to the skin of man.

It has been long established that as thorium X disintegrates to reach thorium D (its stable form), it gives off alpha, beta and gamma radiation (Table I). Unlike radium, from which the alpha rays are filtered, all three types of radiation are present when thorium X is applied to human skin.

It has often been said that since alpha particles cannot pass through a thin piece of paper, they cannot penetrate the epidermis and therefore cannot be expected to be biologically effective. This leads to the conclusion that if any biologic effect is produced by thorium X, it must necessarily be due to the beta and/or gamma radiation. In contrast, it has been said that the amount of beta and gamma radiation given off by thorium X is insufficient to produce biologic effects, and therefore it must be the alpha emanations which are responsible for the gross and microscopic changes.

Lomholt (1) suggested that the histopathologic changes which he demonstrated 500 to 600 microns below the surface of human skin were due to thoron, the gaseous emanation from thorium X, diffusing through the tissue following topical application. Sulzberger (2) independently suggested that the vehicle carrying the thorium X might penetrate certain of the epidermal structures and thus deposit this radioactive material at various points below the surface. Our own investigations (3) (4) clearly demonstrated by the autoradiographic technic that thorium X in selected vehicles penetrates the human epidermis and its appendages when applied topically *in vivo*. In a recent article, Witten and Sulzberger (5) speculated on the mode of action of thorium X applied to human skin and suggested other mechanisms by which this radioactive material might produce biologic effects when applied to the skin surface in various vehicles.

None of these observations or speculations, however, provide any information

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concerning the *relative* biologic effects of the alpha radiation as contrasted with the beta-gamma radiation given off by thorium X. As early as 1923, Lomholt concluded by simple experimentation that if the alpha rays from thorium X were kept from the skin there was no gross evidence of biologic effect. This he accomplished by painting thorium X on the upper surface of a thin piece of gutta percha which was then applied to the skin and permitted to remain in place for several days. When the gutta percha was removed, no erythema was noted. Knowing that the alpha rays from the thorium X could not penetrate the gutta percha he concluded that the beta and gamma rays which did penetrate were insufficient to produce erythema. He was of the opinion, therefore, that the alpha particles were responsible for the biologic effects since an equal amount of thorium X in alcoholic solution applied directly to the skin's surface would produce a clinically-visible erythema.

In an attempt to shed more light on this controversial problem, we planned a series of experiments which we hoped would explain whether it was the alpha or beta-gamma rays (or a combination of these) emanating from thorium X which were responsible for the erythema. For this purpose special thin-window plaques were constructed into which thorium X solution could be pipetted (see Procedure). The plaques were constructed to seal in the thorium X and thus prevent the vehicle and the thorium X atoms from penetrating into the epidermis and its appendages.

Two forms of these thin-window plaques were made:

1) A thorium X "alpha" plaque*: with a window material thin enough to transmit essentially all of the alpha radiation (and, of course, the beta and gamma radiation).

2) A thorium X "beta-gamma" plaque*: with a window material of sufficient thickness to absorb the alpha particles but thin enough to transmit the beta and gamma radiation.

In each instance the plaques were loaded with a quantity of thorium X which if applied directly to the surface of the skin would regularly produce a distinct erythematous response.

PROCEDURE

Principles Involved in Design of Plaques

Thorium X decays through a series of radioactive daughter products to an isotope of stable lead. As it undergoes this decay, alpha, beta and gamma radiation is given off (Table I). As the alpha particles travel away from their parent atom they lose energy very rapidly, having a maximum range of about 10 mg/cm².** The beta particles lose their energy less rapidly than the alpha particles, with maximum ranges of about 1000 mg/cm². Thus when a plaque is covered with a material having a thickness of 10 mg/cm² all of the alpha particles are absorbed and none can reach the skin; it is then solely a "beta-gamma" plaque.

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* These names were given the two types of plaques solely for the purpose of this paper.

** Mg/cm² is used to express absorber thickness in mass per unit area. This permits for greater accuracy and eliminates the factor of density of the particular material used; e.g. 1 mm. water = 100 mg/cm², and 1 mg/cm² = 10μ.

Construction of Plaques

The first problem in the construction of suitable plaques was to find a window material thin enough to permit the desired radioactive particles to pass through, without allowing leakage of the thorium X. Polystyrene 10 mg/cm² thick proved to be a satisfactory window material for the "beta-gamma" plaques. However, for the "alpha" plaques it was necessary to have an even thinner film—approximately 1 to 2 mg/cm² thick. All plastic films less than 2 mg/cm² which were tried exhibited leakage. It was found, however, that mica could be split to the desired thickness, and if handled carefully to avoid cracking, would not leak.

The mica window was cut from a thick sheet of mica, which was then split to the desired thinness. Mica was split by first teasing the edge of the mica disk to separate the layers. The point of a fine needle was inserted a short distance to separate the layers, following which water was allowed to flow into the spaces between. The water, which was supplied by touching the needle with a wet brush tip, flows ahead of the needle, separating the

TABLE I

Thorium X Disintegration Series

NAME	SYMBOL	HALF-LIFE	ENERGY OF RADIATION IN MEV		
			Alpha	Beta	Gamma
Thorium X	$_{88}Ra^{224}$	3.64 days	5.68	—	—
Thoron	$_{86}Rn^{220}$	54.5 sec.	6.28	—	—
Thorium A	$_{84}Po^{216}$	.158 sec.	6.77	—	—
Thorium B	$_{82}Pb^{212}$	10.6 hrs.	—	0.36	—
Thorium C	$_{83}Bi^{212}$	60.5 min.	6.05	2.20	?
65% → Thorium C′	$_{84}Po^{212}$	3×10^{-7} sec.	8.77	—	—
35% → Thorium C″	$_{81}Tl^{208}$	3.1 min.	—	1.82	2.62
Thorium D	$_{82}Pb^{208}$	Stable	—	—	—

layers by capillarity, and preventing the needle from scratching the mica. With skill, a good grade of mica can be split to thicknesses of 1 to 2 mg/cm². It is possible to secure pieces as thin as ¾ mg/cm², though the pieces are fragile and the process very time consuming.

The second problem involved the choice of a proper cement for fixing the thin film to its support. The thin plastic films were destroyed quickly by cements containing a solvent and it was therefore necessary to use a polymerizing agent.* The thin mica windows were best cemented by a common commercial adhesive**, which shrinks on drying. This shrinkage was advantageous in that it pulled down the edges of the mica and helped prevent splitting.

The window material—plastic or mica—was mounted on a plastic ring, as shown in Figure 1. The ring is circular, ¾ inch in outside diameter, and 1 cm. in inside diameter. In order to cement the window material in place one of the flat surfaces of the ring was given a thin coat of the chosen adhesive. The circular piece of plastic or mica was then placed on the wet adhesive, and another thin coat of the same adhesive cement was applied to the surface of the film over its outer edge.

A plastic plug, machined from the same plastic as the ring, was made with a diameter a fraction less than 1 cm., thus making for a tight fit when inserted into the ring. An alcoholic solution of thorium X, was pipetted onto the end of the plastic plug and dried

* Bonding Agent R-313, Carl Biggs Co., Los Angeles 64, California.

** Duco Cement, DuPont.

under a heat lamp. This plug was inserted into the plastic ring carrying the thin film and the assembly was sealed by running cement (Duco) around the edge of the plug. After 30 minutes for setting of the cement, the plaque was ready for application to the skin.

The plaque just described (Figure 1) is the result of several modifications of the design first used.

Measurement of Output from Plaques

The plaques were measured in terms of the dose unit, the *rep* (roentgen-equivalent-physical). This unit, defined as the amount of ionizing radiation which gives 93 ergs to each gram of tissue, is the unit in which alpha and beta particles are measured, and corresponds to the *roentgen* for x-rays. One r of x-rays gives 93 ergs/gram of tissue. The calibration of the plaques consists in measuring the ionization in a small air volume at the surface of the plaque by means of a special ionization chamber called an "extrapolation chamber". This instrument measures the ionization in terms of esu/cc, and then calculation gives the dose rate in terms of rep. A detailed description of the instrument, its use, and the calculations involved are being published elsewhere (6).

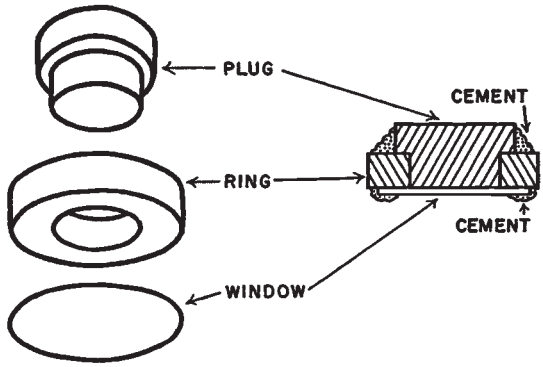

FIG. 1. Schematic drawing of thorium X plaque.

CLINICAL APPLICATION

The sealed plaques loaded with thorium X were applied to the anterior aspect of the forearm or to the antero-medial aspect of the upper arm of subjects selected among patients being treated at the Skin and Cancer Unit of the University Hospital. The plaques were firmly taped to an apparently normal skin area and allowed to remain in place for 48 hours. The subjects were instructed to keep this area dry.

The plaques were removed after 48 hours of continuous exposure and the areas were observed for visible biologic effects. Where pressure of the plaque or irritating effects of the adhesive tape were thought to be factors in the production of redness, the test sites were reread one to five days later. Any remaining clinically discernible redness was considered to be an erythema produced by the thorium X emanations.

Immediately after removal of the plaques the areas of skin which had been exposed were surveyed with a thin-windowed Geiger-Müller tube connected to an electronic scaling unit. The presence of any alpha or beta particles was readily recorded by this equipment. If leakage of the radioactive thorium X had occurred

any time during the test period it was thus detected. Sites with activity appreciably above the normal background, as determined by counting the normal unexposed, contralateral side of the body, were considered to be contaminated by a leaking plaque and the biologic reactions of these sites were therefore not considered as suitable for inclusion in this study.*

Early in the study only one plaque was applied to any one subject, but later both an "alpha" and "beta-gamma" plaque were tested on different sites at the same time.

RESULTS

During the course of the study a total of 140 plaques were applied to 96 subjects. Of these, 75 were "alpha" plaques and 65 were "beta-gamma" plaques. Sixty of the plaques leaked and the skin observations in these instances were necessarily discarded.

When the exposed sites were observed at the time the plaques were removed there was either no reaction or a minimal erythematous response. In no instance did the degree of erythema approximate the intense erythematous response that follows the direct application of an equal amount of alcoholic solution of thorium X to the skin.

Our observations were difficult to interpret until we were able to control the study by applying a "matched" pair of plaques on each subject. This consisted of loading an "alpha" and "beta-gamma" plaque with approximately equal amounts of thorium X and applying them simultaneously to adjacent areas of the skin. This procedure gave two skin areas which received similar beta-gamma doses** (from both the "alpha" plaque and the "beta-gamma" plaque); while only one of these areas received an alpha dose (solely from the "alpha" plaque).

Fourteen such pairs of plaques were applied and left in place for 48 hours. The "alpha" plaques produced erythema in 11 of the 14 cases. The "beta-gamma" plaques applied at the same time as the "alpha" plaques produced a questionable or barely discernible small macule of erythema in 9 cases and no reaction in 5. Pressure effects and irritation produced by the adhesive taping made it extremely difficult to interpret these poorly-developed erythemas.

The reactions were decidedly easier to read and interpret when the sites were reexamined one to five days later, after the effects of irritation had disappeared. Eleven of the subjects returned for follow-up examination. In seven of these the areas exposed to the "alpha" plaques presented a fairly well-defined erythema, some with pigmentation. This reaction conformed to the window area of the plaques. The remaining four subjects showed reaction involving more than one-half of the irradiated site. Three of the areas had an irregularly-shaped approxi-

* The specific criterion used was the following: plaques were considered as possibly having leaked if the increase in counting rate was 25 or more counts per minute above background. In our experience this increase above background could not be held responsible for the production of erythema.

** The beta-gamma output from each plaque was measured as previously described. The alpha output from the "alpha" plaque was also recorded.

mately 2–3 mm. macule of slightly greater reaction. These macules corresponded to a point of accumulation of thorium X, or "hot-spot", within the plaque. On reexamination the areas exposed to the "beta-gamma" plaques presented findings quite different than those for the alpha plaques; in only one instance did the "beta-gamma" plaques produce reaction which conformed to the size of the plaque window. In two other cases one could note a questionable erythematous response with pigmentation over approximately two-thirds of the irradiated sites. The barely discernible erythematous macules noted when the plaques were removed were slightly more apparent in the absence of the irritation effects in 5 cases. These small erythematous and pigmented macules were produced by "hot-spots" in the "beta-gamma" plaques and correspond to those seen with the "alpha" plaques.

DISCUSSION

When the evaluation of the relative biologic effectiveness of the alpha and beta-gamma components of thorium X was undertaken it was obvious that there would be differences between the experimental methods and the actual clinical use of the radioactive material.

It was anticipated that thorium X enclosed in a plaque, whether in an "alpha" or a "beta-gamma" transmitting plaque, would have a biologic effect on human skin *in vivo* quite different in degree from the effect produced by an equal quantity in alcoholic solution pipetted directly on the epidermal surface. This was evident from the very mild erythema produced by a plaque left in place for 48 hours, as contrasted to the very marked erythematous response produced by the same amount of thorium X solution pipetted directly on an equal area of skin surface. This difference is believed to be due to the actual penetration of the radioactive element, thorium X, into the epidermis and its appendages thus enhancing the biologic effect *many* times.

The study was further limited by the fact that it was impossible to separate thorium X alpha from the beta and gamma emanations and to pipette a solution of either one or the other onto the skin's surface. The most that could be done was to filter the alpha particles from the total alpha-beta-gamma spectrum and leave only the beta-gamma radiation. In order to achieve this the thorium X "alpha" and "beta-gamma" plaques were designed.

The results show that the "alpha" plaques produce an erythema conforming in area to the entire or to a major part of the active surface of the window, while the "beta-gamma" plaques applied at the same time to an adjacent site produce such a reaction in only rare instances and then in much less degree. It is concluded, therefore, that the visible biologic effects are due to the alpha particles emanating from the "alpha" plaques. This observation is of paramount interest in that it demonstrates for the first time that alpha particles bombarding human skin from the surface are capable of producing clinically visible biologic effects. This finding is contradictory to the many statements that appear in the literature which disclaim any biologic effect for alpha particles acting on the skin from the surface.

The small, irregular erythematous macules produced by both types of plaques are explained by the uneven distribution of thorium X within the plaque and accumulation at one site to form a "hot-spot". The beta-gamma output from these spots is sufficiently high to produce visible biologic effects.

Our studies indicate that the beta and gamma components of thorium X are capable of producing an erythematous response on human skin. The extent of our observations together with various difficulties encountered make it impossible to state the threshold erythema dose for this radiation. Based on the present study, however, it may be said that 1) the relative biologic effectiveness of the beta and gamma component of thorium X is many times less than that of the alpha component as judged from the degree of erythema and pigmentation produced, 2) it is evident that whatever the biologic effectiveness of the beta and gamma radiation the total dose present in the amount of thorium X customarily used on human skin is relatively small. This confirms forty years of clinical experience with thorium X, which have shown it to be incapable of producing serious sequelae and have demonstrated its wide margin of safety as used in the treatment of various dermatoses.

We believe that these inferences are justified in spite of the many uncontrollable factors in our studies. Among these factors are those producing variations in plaque output (differences in window thickness, unequal loading with thorium X, uneven distribution of thorium X inside the plaque), human variations in biologic response, and the difficulties of interpreting the subtler shades of erythema.

SUMMARY

The relative biologic effectiveness of the alpha and beta-gamma rays from thorium X was studied by utilizing specially prepared thin-window plaques applied to the skin of human subjects. These plaques were constructed to seal in the thorium X and thus prevent the vehicle and the thorium X atoms from penetrating into the epidermis and its appendages but at the same time permit the radiation to reach the skin. Two types of thin window plaques were used: 1) with a window material thin enough to transmit the alpha, beta and gamma radiation and 2) with a window material of sufficient thickness to absorb the alpha particles but thin enough to transmit the beta and gamma radiation.

Conclusions are drawn from the results obtained with 80 plaques applied to 58 subjects.

1. The degree of erythema produced by the plaques containing thorium X is small in contrast to the intense erythematous response that results from the direct application of an equal amount of alcoholic solution of thorium X to an equal area of skin.

This difference is believed to be due to the fact that when the thorium X solution is pipetted directly onto the skin the actual penetration of the radioactive element, thorium X, into the epidermis and its appendages, produces a major portion of the biologic effect.

2. Nevertheless, alpha particles bombarding the skin *from the surface* are capable of producing erythema and pigmentation.

3. The relative biologic effectiveness of the beta and gamma components of thorium X is many times *less* than that of the alpha component as judged by the degrees of erythema and pigmentation produced.

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DISCUSSION

DR. HERMANN PINKUS, Monroe, Michigan: We should congratulate Dr. Witten and his associates on the ingenious continuation of the fine work which he reported last year. I think these basic studies on thorium X were badly needed. It is good that somebody did them and did them in such a thorough and well planned way. The fact that the alpha rays of thorium X, when the thorium X itself cannot get on the skin but only the alpha particles, have a much smaller effect than otherwise, bears out what Dr. Witten has shown before, that thorium X actually penetrates into the epidermis if it is applied to the skin surface in the usual manner.

One point that I would like to inquire about is contained in a very short report in Nature of last October (Rottier, P. B. and Mullink, J. A. M.: Localization of erythemal processes caused by ultra-violet light in human tissues. Nature **170:** 574, 1952). These authors found that ultraviolet rays of 300 mμ produced erythema whether they act on the normal skin or on skin from which the horny layer had been stripped off with Scotch tape. But if they used the short ultraviolet rays of 250 mμ, then there was no effect on the stripped skin which had lost its horny layer. The authors concluded that most likely these short rays produce their primary effect on some substance in the keratin layer and that the erythema is produced secondarily by the chemically altered substance which diffuses down from the keratin layer. I wonder if this mechanism might have some application in the action of thorium X.

DR. VICTOR H. WITTEN (in closing): I wish to thank Dr. Pinkus for his discussion. It is possible that radiation, other than ultraviolet, which is incapable of penetrating any further than the epidermis can produce secondary changes. That

possibility also holds for thorium X, in which the greater part of the alpha radiation bombards the epidermis. Doctor Sulzberger and I in a recent article (Der Hautarzt, **11:** 521, 1952) speculated concerning the modes of action of thorium X applied to human skin. Among various other considerations we mention the possibility of secondary effects playing a role.

The range of the most energetic alpha particles in tissue is, at the most, 95 microns. The average thickness of the epidermis varies from 30 to 70 microns. Of course, it is much thicker in some places and thinner in other. If the alpha particles liberated from thorium X applied to the surface of the skin travel 95 microns they could well go into the papillary body and directly bombard the papillary tissue. In original work done many years ago and published in the Handbuch der Haut- und Geschlechtskrankheiten it was shown that the primary histopathologic changes produced by thorium X were in the papillary bodies. These facts permit the speculation that the alpha particles reach the papillary body and there produce biologic effects.