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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.

STUDIES ON BLISTERS PRODUCED BY FRICTION

I. RESULTS OF LINEAR RUBBING AND TWISTING TECHNIQUES

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Blisters produced by friction are distinctive forms of reactions which are practically confined to the human species. They are not found, as a rule, in lower animals. But these lesions of the human skin occur with such frequency that they constitute one of man's most common reactions to trauma. Practically everyone has at some time experienced discomfort from this commonplace skin lesion.

Under special circumstances, individuals can be disabled by friction blisters. Such blisters on the hands or feet, while usually merely an annoyance or cause of discomfort, will, under certain conditions and in particular occupations, cause various degrees of disability. They can even lead to serious consequences. Certain military activities rank high among those in which friction blisters and their sequelae can actually produce casualties.

Despite these facts, friction blisters have received little medical attention or scientific study. Notable exceptions are the precise investigations and detailed reports by Naylor (1, 2, 3) on the production of friction blisters under controlled conditions. Our present studies are mainly variations on and extensions of Naylor's fundamental work.

The paucity of scientific investigations on friction blistering stands in remarkable contrast to the abundance of studies and reports on clinical bullous dermatoses (*e.g.*, pemphigus, dermatitis herpetiformis, contact-type eczematous reactions, etc.) and on experimental blisters produced by heat, cold, ultraviolet rays, or chemicals such as cantharidin, croton oil, mustard gas, etc.

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Additional scientific information on the mechanism of friction blistering is needed. For quite apparent reasons, the many factors causing or contributing to clinical friction blisters cannot be precisely controlled nor readily analyzed under field conditions (*e.g.*, soldiers on a march or persons engaged in sports, etc.). Since the skins of laboratory animals do not respond like the skin of man and do not generally form blisters in response to friction, we adopted the following methods for the experimental production of friction blisters on the skin of volunteers.

MATERIALS AND METHODS

Linear Rubbing. By modifying rubbing instruments used by Goldblum and Piper (4) and by Naylor, (5) a special apparatus for linear to-and-fro rubbing was designed and constructed (Figure 1).

The instrument consists of a rubbing head to which various selected materials (leathers, cloth, plastics, etc.) can be firmly attached. The head can be moved over the surface of any chosen skin site at a chosen rate from 25 to 104 complete strokes per minute (counting each excursion and return to the original position as one stroke). The rubbing pressure against the skin can be determined by adding a known amount of weight from 215 to 1154 grams to the rubbing arm. Fluids, for example water or liquid emollients, can be accurately delivered to the rubbing interface by means of an attached perfusion pump. A strain gauge and a thermometer within the rubbing head permit continuous measurement of the frictional resistance and temperature. The temperature measured is that on the surface underneath the rubbing material where the thermometer is in place. Calculation of the frictional coefficient is obtained by the formula, $\mu = F/W$, where "F" is the frictional resistance at the surface, graphically recorded in gram units on a multichannel Oscillo-

† We are indebted to Dr. Irvin Levin of the Walter Reed Army Institute of Research for constructing the first of our linear rubbing machines, and to Mr. Emil Barish of the Research and Development Laboratory of the University of California, Medical Center, San Francisco, for constructing the second, and also for our most recent twist blistering apparatus.

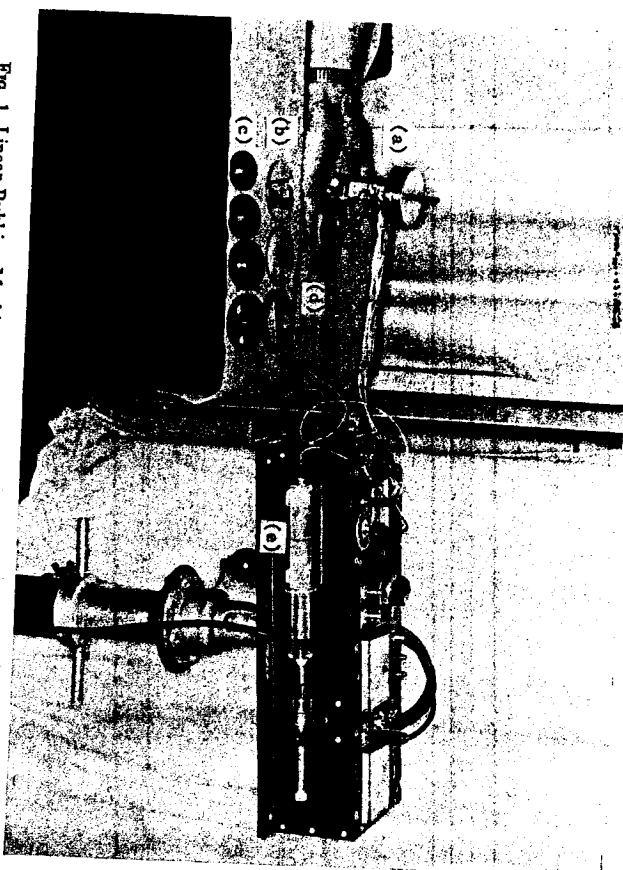


Fig. 1. Linear Rubbing Machine. (U.S. Army Photograph) a. Rubbing head with leather in place. b. Interchangeable rubbing-arm weight. c. Interchangeable gears for varying stroke weight. d. Roving probe thermometer. e. Perfusion syringe.

riter,* and "W" is the amount of weight in grams pressing downward on the skin.

Twist Rubbing. Friction blisters are readily produced on palmar skin using the eraser on an ordinary pencil. The pencil is held between an operator's palms of the operator, perpendicular to the skin surface with the flat end of the eraser pressed down firmly on the area to be rubbed. The pencil is briskly rotated in clockwise-counterclockwise directions with the arc of each twist being about 270°. Although this technique constituted a distinct advantage over linear rubbing for some of the studies which will be described, the factors are not as precisely measurable as with the linear rubbing machine.

Volunteers. All of our subjects were healthy male volunteers on active military duty with the U.S. Army at the Presidio of San Francisco and nearby installations, or (in one experiment) volunteers for studies carried out at the University of California, School of Medicine, San Francisco, California.

To date, 162 attempts at blister production have been made with the linear rubbing machine on 54 different volunteers.† Over 150 experimental friction blisters were produced.

*Texas Instruments, Inc., Houston, Texas.
† Few of the experiments were on Negroes and most of the subjects were Caucasians. Therefore, no attempt was made to ascertain possible differences in response between the Negro and Caucasian skin.

tion blisters on the palms have been made with the pencil eraser technique on 47 volunteers.

RESULTS

Relationship between the Amount of Friction, the Number of Strokes, the Duration of Rubbing (work), and the Biologic Response (Blister Formation)

In our experiments with the linear rubbing machine, when added moisture, speed, head pressure and rubbing materials were held constant, closely similar amounts were held constant, produced on corresponding areas on different individuals and on different symmetrically situated sites in the same individual. However, despite this equality in the level of friction, the time required to produce a blister on the palm varied in a very wide range. In some experiments a blister would be produced on the palm in three to four minutes, while in others 50 minutes or more of stroking with similar amounts of friction per unit of time failed to produce blistering.

(Rubbing was not continued beyond one hour even if no evidence of blister formation had appeared in that period).

Using the twisting eraser technic, blisters were often produced on the palm with only 30 seconds of friction and never required more than 3 minutes. This is to be compared with linear rubbing which never took less than 3 minutes of friction, and sometimes 50 or more minutes failed to produce blisters. Thus, on the palm, the prolonged rubbing time of our linear rubbing machine experiments was more apt to bring to light the variations in biologic response.

Further studies on the palm with higher frictional twist-force applied under controlled and measured conditions will be required to verify this variability. For this purpose, a new "twist" blistering apparatus was designed and constructed to produce skin-twist rubbing on two sites simultaneously with measurable and recordable degrees of friction (Figure 2). Studies with this instrument are now in progress.

Susceptibility of Different Skin Sites to Friction Blistering

Experiments with the linear rubbing machine and the twisting rubber eraser technic were carried out on the normal appearing skin of the back, buttocks, shins, forearms, upper arms, thighs, palms and soles of the volunteers. In fact, fluid-filled blisters were very difficult to produce on any of these areas except the palms and soles. Only rarely, and by chance, did we succeed in producing fluid-filled blisters on the back or on other "thin-skinned" areas with linear rubbing, and never with eraser twist. Further observations suggested the possible reason for this. On the less cornified and more fragile skin, it was not generally possible to give precisely the amount of frictional trauma required to produce the somewhat deeper epidermal damage which results in an intact blister without destroying or removing the superficial epidermal layers needed to form the blister roof. Therefore, no fluid-filled clinical blister could appear,

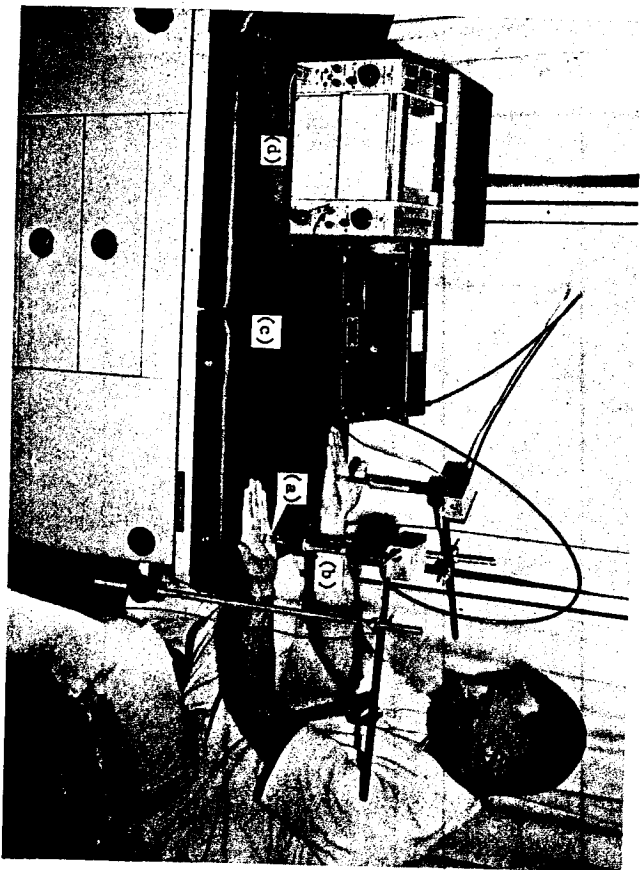


FIG. 2. "Twist" Rubbing Machine. This apparatus insures application of identical degrees of frictional trauma to two sites simultaneously. (U.S. Army Photograph) a. "Twist" rubbing head. b. Sleeve containing a calibrated spring. c. Motor control box. d. Two-channel recorder.

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but only an abrasion. In other words, on less cornified skin sites, frictional rubbing would either fall short of producing a clinical blister or would produce a "topless blister," i.e., an abrasion.

Our results on the palms were quite different. On these "tough" and thickly cornified sites, the superficial layers of the skin apparently resist the frictional trauma of rubbing so that this trauma does not destroy the superficial epidermal layers before the deeper process of blister formation can be initiated.

Blister Formation

The beginning of blister formation was often heralded by a stinging or burning sensation. While a few of the volunteers voiced no expression of discomfort, a sudden painful sensation was spontaneously reported by some. The earliest objective sign of beginning blister formation on palmar skin produced by either the linear rubbing or twist rubbing technic was the appearance of a pale, narrow collarette around the rubbed, reddened central area. With additional stroking, the pale zone gradually enlarged centrally until it occupied the greater part of the rubbed site and eventually became elevated over the underlying skin to form the blister top. The space thus formed in palmar skin of a subject in the erect position usually filled with fluid within one hour. The exact location of this cleavage and the causal and limiting factors in the accumulation of free fluid in the cleft will be described below.

Influence of Extrinsic Moisture on Skin Frictional Resistance

Figure 3 presents the graphic record of how various amounts of moisture at the interface in-

fluence the frictional forces produced by linear rubbing of the palmar skin with leather.

Using the linear rubbing machine with a stroke rate of 45 per minute, vertical load of 594 grams, and leather material (3 ounce), rubbing was started on the mid-palm with only the natural level of moisture on the skin surface. After 22 seconds for base-line stabilization, extraneous moisture in the form of tap water delivered from the attached perfusion pump was added at 0.04 ml per minute. Friction remained relatively stable at a constant level until the external moisture was added. As the wetness of the skin surface, of the leather rubbing material and of the interface between the two increased, the friction gradually increased to a maximal point. With continued stroking, the level of friction remained at this new, higher plateau for some time despite continued addition of water at an increased rate of 1.94 ml per minute. Finally, as the amount of fluid on the rubbing surfaces and between them became still greater, the level of friction dropped to a new lower plateau as shown in the tracing. In our experiments, frictional resistance of the very wet palm was still slightly more than for the same palm at the onset of rubbing.

There was considerable variability in this effect in different subjects. The level of friction did not always measurably increase with added moisture nor measurably decrease when the water which had been applied exceeded a given amount. Differences in the palmar sweat rates and in the amounts of natural moisture on the palms of different individuals during the experimental rubbing period may account for some of these variations.

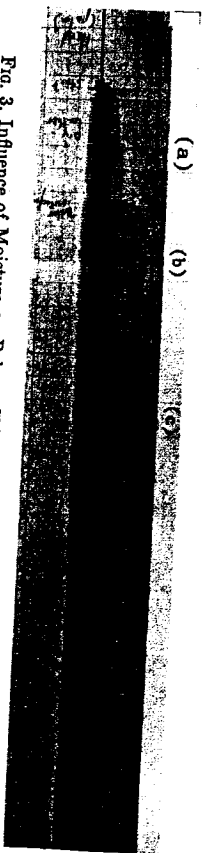


FIG. 3. Influence of Moisture on Palmar Skin Friction with Linear Rubbing. (U.S. Army Photograph) a. Skin frictional resistance with dry leather before addition of extraneous moisture (0.04 ml/min.) to the skin-leather interface. b. Water infusion rate increased to 1.94 ml/min. with flooding of the interface and consequent decrease in skin frictional resistance. Note: Chart tracing speed at 2 mm./sec. Each major division of the graph paper equals 10 mm.

Influence of Arterial Hydrostatic Pressure and Circulation on Fluid-Filling of Friction Blisters

The effect upon blister formation produced by occlusion of arterial circulation to the palm was studied on 10 volunteers.

A standard blood pressure cuff was applied at random to either the right or left upper arm. With the arterial circulation to one palm arrested by the inflated cuff, the blistering trauma was applied to the hypothenar eminence, using the twisting-eraser technique. Simultaneously, another operator produced a "control" blister by the same method at the corresponding site on the opposite palm with circulation unimpeded. Arterial occlusion to the "experimental" palm was maintained for 30 minutes.

At the beginning of the experiment and immediately

after cessation of the twist rubbing, both palms had a similar appearance, except for the cyanosis of the hand on the occluded side. Little difference in the rubbed areas was noted over the next 30 minutes during the period in which the arterial blood supply of one hand remained arrested. Even on the side without arterial occlusion, little filling of the blister occurred at this interval of time. The course of the blisters on the occluded and non-occluded sides differed significantly during the next few hours. At one hour after blistering trauma, free fluid was clearly evident in the blister compartment on the unoccluded side. In contrast, on the occluded side at this same time (30 minutes after release of the blood pressure cuff which had been in place for 30 minutes) the blister showed very little if any free fluid (Figure 4). This lag in

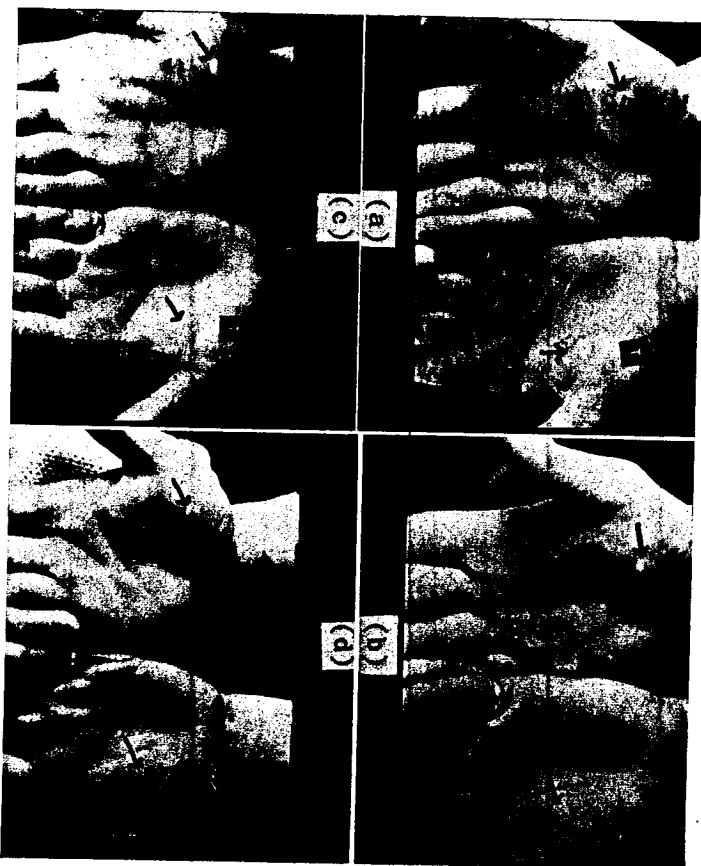


Fig. 4. The Effect of Arterial Occlusion on Blister Formation (U.S. Army Photograph) Arterial circulation to the left palm was arrested by an inflated blood pressure cuff on the left upper arm during twist blistering trauma and for 30 minutes thereafter. a. 5 minutes after blistering trauma (cuff in place). b. 31 minutes after blistering trauma (1 minute after release of cuff). c. 1 hour after blistering trauma (30 minutes after release of cuff). d. 4 hours after blistering trauma (3½ hours after release of cuff). Arrows point to blister-sites. Note the delay in blister filling on the occluded side in (a) and (b) and minimal filling in (c). In (d) at 4 hours, the blisters on both palms appear equal in size and fluid content.

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Fig. 5. Position assumed by the volunteer and held during the application of "twist" friction to both palms and for 1 hour thereafter.

filling was noticeable for a few hours; but by 4 hours the blisters on both palms appeared equal in size and in fluid content.

A second approach was to study the effect on blister formation produced by differences in the arterial hydrostatic pressure within the palm when the hand was held elevated above the head or kept in the dependent position. Four male volunteers were placed in the position shown in Figure 5.* A blister on the hypothenar eminence of each palm was produced simultaneously by two operators, using the twisting-eraser technique while the left palm was in the elevated position and the right palm held horizontally. On cessation of the twisting, the right hand was immediately lowered to dependency. The volunteers maintained this position (see Figure 5) for one hour after the blistering trauma.

*According to Rushmer⁷, the mean arterial pressure at the wrist with the palm held above the head is about 40 mm Hg, and the effective venous pressure is zero. With the palm in the dependent position, the arterial pressure at the wrist is about 125 mm Hg and the effective venous pressure is about 35 mm Hg.

Fluid-filling of the blister cavity on the palms which were kept elevated for one hour did not begin until the arms were lowered. In contrast, the blisters on the dependent palms contained free fluid within the first hour (see Figure 6) and became fully filled and tense within 2 hours. For 3 to 4 hours after the twist friction, filling of the blisters on the elevated palms lagged significantly behind the filling of those on the dependent palms. After 4 hours, however, the blisters on both palms were not noticeably different in their gross appearance.

While the original or primary damage produced by friction may be the same on sites with normal or reduced arterial blood pressure, the accumulation of blister fluid seems to be dependent upon a competent arterial pressure and an intact circulation.

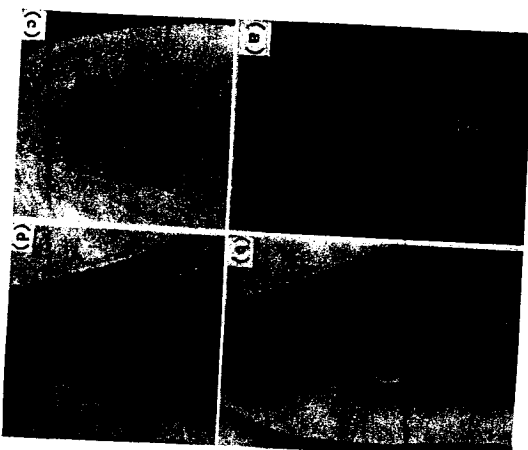


Fig. 6. Blister Filling on an Elevated Palm Compared to Blister Filling on a Dependent Palm (U.S. Army Photograph). As shown in Figure 5, the left palm was held above the head and the right palm dependent during and for 1 hour after blistering trauma. a. Elevated palm 1 hour after blistering trauma and just before the hand was lowered. b. Dependent palm 1 hour after blistering trauma. c. Elevated palm 5 hours after blistering trauma (4 hours after it had been lowered). d. Dependent palm 5 hours after blistering trauma. Note the delay in blister filling on the elevated palm at 1 hour in (a) as compared to the fluid-filled blister on the dependent palm at 1 hour in (b). At 5 hours, the filling of the blister on the elevated palm in (c) has "caught up" with that on the dependent palm in (d).



FIG. 7. Linear-Friction Blister on Skin of the Back. The cleavage occurs in the mid- or upper malpighian layer leaving intact the stratum granulosum and stratum corneum to compose the roof. (H&E, $\times 121$) (U.S. Army Photograph)

Histopathology of Friction Blisters on "Thin" and "Thick" Skin

Utilizing the twist rubbing technic, two experimental blisters were produced on the hypodermar eminence of each palm of three men and three women volunteers. Punch biopsy specimens (4 mm) were taken from the different test sites immediately after and one hour after the blistering trauma.* Using the linear rubbing technic on 54 male subjects, blisters which could be produced on the "thin" skin were excised at one hour. All specimens were fixed in formalin and prepared for light microscopy with hematoxylin and eosin stain. Figure 7 shows the microscopic appearance of a friction blister on the scapular area at one hour after linear rubbing, and Figure 8 of one on the palm immediately after twist-frictional trauma.

* These particular studies were carried out at the University of California School of Medicine, Division of Dermatology, San Francisco, under U.S. Army contract, No. DA-49193-MD-2912, by Dr. William L. Epstein, principal investigator.

In all instances, the histologic picture shows an intra-epidermal bulla involving the malpighian layer with necrotic and degenerated spinous cells. The blister cleft or cavity is always at the same level, with the blister roof composed of the stratum corneum, stratum granulosum, and a small segment of amorphous cellular debris. The basal cell layer below shows less damage and the stratum granulosum and stratum corneum above appear intact. The palmar blisters show remarkably little inflammatory reaction in the corium.

In collaboration with Dr. William L. Epstein, the histologic studies are continuing and will be reported in detail.

DISCUSSION

The present experiments in the controlled production of experimental friction blisters were undertaken because of the common occurrence and potential importance of clinical lesions of this type and the paucity of scientific studies on their formation.



FIG. 8. Twist-Friction Blister on Palm. Note that cleavage is at the same level as in Figure 7. (H&E, $\times 172$) (U.S. Army Photograph)

The amount of friction which is produced depends upon the nature of the surfaces which are juxtaposed, the pressure which is being exerted upon these surfaces, and other factors, notably the degree of moisture at the surfaces and at the interface between them.

Both Naylor (1, 2, 3) (*in vivo*) and Apple-wood and Barnet (6) (*in vitro*) experimentally demonstrated the substantial effects of various amounts of fluid lubricant on rubbing surfaces. Our studies corroborate their reports. Dryness or very low degrees of moisture tend to reduce the friction; intermediate degrees of moisture tend to increase the friction; and high degrees of moisture or complete wetness tend to decrease the friction. These findings are, of course, important in relation to the role of sweating, and the nature of the material which is worn next to the skin (more or less absorbent, more or less permeable, etc.).

When relatively high frictional forces are applied, individual variations in the work required to produce blisters tend to become inapparent.

However, when low frictional forces are applied to areas with a heavy stratum corneum, great variations in biologic response are seen to occur. That is, the amount of work which will produce blisters on one site, or one individual, or at one time may be entirely insufficient to produce blisters on other sites, or other individuals, or at other times. This variability of tissue response is unexplained and must be the subject of further study.

This result is somewhat in contrast to the results of Naylor, who found that essentially the same levels of friction per unit time in similar areas produced practically identical biologic effects. Naylor judged this by using "superficial abrasions" as an end-point in most of his experiments. It appears probable that the difference between Naylor's results and ours may be explained by differences in the experimental procedures. We believe that an important variable influencing the results may be the fact that Naylor used the anterior tibial surface of his subjects, while for reasons which will be described

below, we selectively rubbed the palmar surfaces. It is, therefore, possible that the sensitivity to friction of the skin over the tibia was such that histologic blisters or gross abrasions were produced so rapidly that any differences in the time and in the frictional work required were not easily discernible or measurable in Naylor's study. While on the much thicker and "tougher" palmar surfaces used in our studies, much more frictional work and additional time were required to produce gross clinical blisters and the differences in required time became apparent. This hypothetical explanation is supported by the fact that when, instead of the lesser force of our linear rubbing, we applied the much greater frictional force of the twisting eraser to the palmar surfaces, the individual differences in biologic response tended to be obscured. That is, blistering occurred not only rapidly but also after amounts of "frictional work" that seemed quite similar and varied but little from subject to subject, just like in Naylor's rubbings over the tibia.

Experimental friction blisters usually contain free fluid within 1 hour and are completely filled within 2 hours after blistering trauma. This course is altered when the arterial circulation is arrested during the blistering procedure and for 30 minutes thereafter, or arterial hydrostatic pressure materially reduced during the blistering trauma and for 1 hour thereafter. During both of these periods little or no free fluid accumulates in the blister cavity. Moreover, the usual time required for the complete filling of the blister with fluid is delayed by several hours. It apparently requires an intact arterial circulation and an adequate hemodynamic pressure for "free" fluid to accumulate in the area which has been damaged by the shearing forces.

The histologic picture of all the blisters examined has been uniform for both "thin" and "thick" skin in regard to the site in which the damage or cleavage within the epidermis occurs and the blister space forms. The roof over the space consists of stratum corneum, stratum granulosum, and a segment of traumatically degenerated stratum spinosum. It is in this cleft or damaged zone that the blister fluid accumulates to raise the blister top. On the palm, the cornium shows little inflammatory infiltrate.

Friction blisters occur readily and regularly only on areas which possess the following pre-

requisites: The first is a sufficiently firm attachment of the lower epidermis to the underlying tissue. This enables the frictional forces at the surface to be transmitted through the superficial layers of the epidermis (stratum corneum and granulosum) which are moved to-and-fro over the subjacent layers, and thus by shearing, create a zone of damage or cleavage. The second prerequisite is a sufficiently thick or resistant stratum corneum and granulosum to withstand the degrees of surface friction required to produce the deeper damage which causes blistering. Wherever the stratum corneum and granulosum are not capable of resisting these degrees of surface friction, an *abrasion* occurs instead of a blister. These prerequisites explain why friction blisters do not generally occur clinically where the "skin is loose" or the stratum corneum thin. That is why palmar and plantar skin and such sites as the heels blister most regularly in response to friction. They have both of the necessary requirements, i.e., a thick stratum corneum for the blister roof and tight adherence of the skin to underlying structures.

Experiments such as these, carried out with controllable degrees of friction, pressure, moisture, and other factors, permit the study of frictional blister formation in the endeavor to discover the reasons for individual, chronologic, and site-determined variations in susceptibility. They should eventually permit the study of different clothing materials and the varying conditions in the macro- and micro-environment in their relative tendencies to inhibit or promote blistering. Perhaps measures can then be discovered and applied to reduce the amount of discomfort and disability caused by friction blisters and their sequelae.

SUMMARY

1. Over 300 friction blisters have been produced experimentally on 117 volunteers.
2. The techniques employed for both linear rubbing and twist rubbing are described.
3. An improved linear rubbing apparatus was constructed. This permits the measurement of the factors involved in the production of frictional injury to the skin.
4. The influence of moisture on skin friction is confirmed. Intermediate degrees of moisture at the rubbing interface tend to increase skin fric-

tion, whereas extremes of dryness and wetness tend to decrease friction.

5. Friction blisters do not usually occur clinically on "thin" skin because it lacks the thick and resistant stratum corneum for the blister roof. Nor do they usually occur on "loose" skin, because it lacks the tight adherence of the skin to underlying structures necessary for shearing effects to be produced in the epidermis.

6. Histologic sections of a friction blister on "thin" and "thick" skin show an intra-epidermal bulla with necrosis and degeneration of the spinous cells. The blister roof consists of the stratum corneum, stratum granulosum, and some amorphous cellular debris.

7. Friction blister formation occurs in two stages: first, the production of an intra-epidermal cleft or space due to surface forces transmitted through a sufficiently resistant stratum corneum and granulosum to produce a shearing effect; and second, the influx of fluid into this

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8. During the period in which arterial circulation is arrested or the hemodynamic pressure to the part substantially reduced, little or no free fluid accumulates within the blister compartment.

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