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Activation of Factors XII (Hageman) and XI (PTA) by Skin Contact.* (31038)

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Blood coagulation can be initiated *in vitro* by contact with a foreign surface such as glass which activates Factors XII (Hageman) and XI (PTA)(1). Most known activating surfaces do not occur in the body and it is unknown whether similar reactions initiate *in vivo* coagulation. Recently stearic acid(2-6), uric acid(7) collagen and elastin(8) which are found *in vivo* have been shown to activate the Hageman and PTA factors. Evidence is presented below that blood contact with unbroken human skin results in accelerated clotting due to activation of the Hageman and PTA factors.

Materials and methods. Platelet-poor plasma was prepared without contact with glass or similar surfaces as previously described(6). Plasma deficient in Factors VIII, IX, XI or XII was obtained from patients with congenital deficiency of these factors. Celite exhausted plasma deficient only in Factors XII and XI was prepared by treating normal plasma with 20 mg celite per ml as previously described(6). Cephalin prepared as previously described(9) was used in a 1/100 dilution.

Coagulation was carried out in 10 × 75 mm glass tubes coated with siliclad (Clay-Adams). 0.1 volumes of plasma and cephalin were added to a silicone treated tube. The tube was inverted over an area of skin which had been carefully cleaned with ether, alcohol and then distilled water and the plasma-cephalin mixture was incubated in contact with the cutaneous surface for a variable time period. The tube was turned upright, 0.1 ml 0.025 M $CaCl_2$ was added and the tube re-inverted over the same cutaneous site so that the clotting mixture was again in contact with the skin surface. The time required to form a solid clot was measured from the time calcium was added. In the control experiments exactly the same procedure was carried out except that parafilm (Marathon, Wisconsin) was interposed between the clotting mixture and the skin surface during both the incubation and clotting periods. Each clotting time was recorded as the average of those obtained in 3 tubes.

Results. Incubation of normal plasma in contact with a cutaneous surface resulted in progressive shortening of the clotting time (Fig. 1). Most of the acceleration of clotting occurred during the first minute of incubation and after 5 minutes incubation an almost maximal effect was noted. Skin surfaces in various sites exerted different degrees of clot promoting activity—the palmar surface of the hands and the skin of the face were particularly active. Prior cleansing of the skin with distilled water, ether or alcohol did not appear to affect the clot-promoting activity. When plasma samples from patients with congeni-

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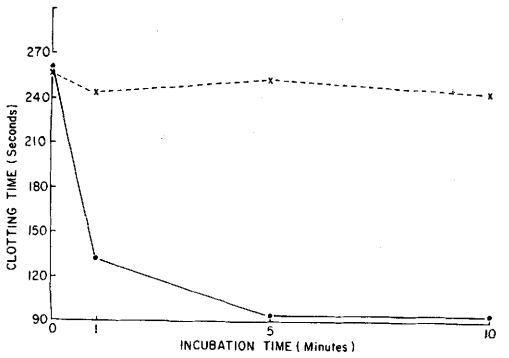

FIG. 1. Effect of incubation in contact with skin on clotting time of normal plasma. ●——● incubated in contact with cutaneous surface. x- - - -x incubated in contact with parafilm. Average of 6 experiments.

tal deficiency of different clotting factors were tested, the clotting of Factor VIII or IX deficient plasma was markedly accelerated, the clotting of Factor XII deficient plasma was only slightly accelerated and the clotting time of Factor XI deficient plasma was not shortened (Table I). The clotting time of plasma artificially rendered deficient in both Factor XI and XII activity (celite-20 exhausted plasma) was not affected by skin contact (Table I).

Discussion. The clot-promoting effect of skin contact on normal, Factor VIII or IX deficient plasma and the absence of coagulant effect on Factor XII or XI deficient plasma indicates that the clot-promoting effect is mediated by activation of Factors XII and XI. The skin surface may exert its effect by virtue of some surface physical property or through an excretion from its surface such as sebum which contains stearic acid(10), a known activator of Factors XII and XI.

The coagulation factor activating property of skin may well play a physiological role in the initiation of coagulation in blood exuding from surface wounds. The lack of defective hemostasis in congenitally Factor XII deficient patients casts doubt on the hemostatic importance of such coagulation(11). Study of the effect of denuded and traumatized skin on coagulation may lead to further understanding of the normal mechanism for initiating coagulation.

TABLE I. Effect of Skin Contact on Clotting Time of Plasma Samples Deficient in Different Clotting Factors.

Plasma sample	Clotting time (sec) after 10 min incubation in contact with: Parafilm	Skin
Normal*	242	93
Factor VIII deficient†	656	328
" IX " †	1042	482
" XI " †	343	360
" XII " †	414	363
Celite-20 exhausted (Factor XI and XII deficient) †	256	255

Clotting mixture in silicone treated tubes: .1 ml noncontact plasma, .1 ml cephalin (1/100), .1 ml $CaCl_2$ 0.025 M.

* Avg of 6 experiments.

† " " 3 " .

Summary. Incubation of non-contact normal plasma in contact with unbroken skin surfaces results in accelerated clotting of the plasma. The clot-promoting effect of skin contact is exerted by activation of Factors XII and XI.

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