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DEPARTMENT OF DERMATOLOGY

SYRACUSE 2-4300  
EXTENSION 481

March 8, 1965

Lt. Col. N. G. Bottiglieri, MC.,  
Chief, Clinical Research Division,  
Directorate of Medical Research,  
U. S. Army Arsenal, Building 3120,  
Edgewood, Maryland

Dear Colonel Bottiglieri:

I should like to sketch out a program of basic work which I feel will greatly enhance our understanding of the agencies which influence the skin's behavior, particularly with reference to increasing or decreasing the rate of penetration of substances through it. As you know, there is general awareness of the insufficiency of our fundamental knowledge about skin physiology. I think it essential that we undertake systematic studies which do not have immediate practical objectives in view.

I would like to advise that the Army's interest in cutaneous permeability is fully shared by myself and others who recognize the pre-eminent importance of this topic. Perhaps, you do not know that I work rather closely with Dr. Robert Scheuplein of Harvard University who already has an Army contract on this subject. Indeed, we are in the process of preparing several papers together.

The subject upon which I would like to focus now is one that has been studiously neglected, viz., irritation. Curiously enough, our basic knowledge of skin allergy is rather advanced, whereas, practically nothing of real depth is known about the much commoner problem of irritancy. I will simply list the areas that I feel will be most rewarding for study:

1. Methods for quantitating the effect of irritants.

Irritants vary in toxicity and some means must be found to measure the degree of irritation in a reproducible and simple fashion. Standard conventional patch tests are far too variable. We shall model our efforts along the lines used by classical toxicology: i. e., the calculation of the

March 8, 1965

Lt. Col. N. G. Bottiglieri, MC.,

dose which will cause a cutaneous reaction in 50% of the subjects. This may be done with one exposure for potent irritants but may require a number of exposures for milder ones. Even so elementary a matter as to how to judge irritancy constitutes a problem. We know, for instance, that the skin may be considerably damaged histologically without visible clinical manifestations. Redness, the usual sign of inflammation, is unsatisfactory in negroes. More sensitive methods are required. We will evaluate electrical surface conductivity, impedance, water permeance, skin temperature, exfoliative cytology and histochemistry. ✓

## 2. Factors affecting the skin's reaction to irritants.

A suitable quantitative method will enable one to examine the influence of a variety of environmental and endogenous factors which affect the skin's reactivity. These certainly include temperature, humidity, previous irritation, skin lipids, diet, sweating, washing, emotions, etc. ✓

We shall select for study agents which damage the skin in quite different ways; for instance, cantharidin blisters, croton oil pustules, detergents, acids and bases, solvents, amines, proteolytic enzymes, etc.

## 3. Skin hardening or accommodation.

We have considerable preliminary evidence that the skin has a mechanism for acquiring a resistance to substances which are toxic to it. Once hardened, the skin is remarkably indifferent to not only irritants but to allergens and physiologic agents. Nothing is known about the mechanism. This conceivably could be due to a change in permeability but our preliminary findings do not support this. It is remarkable how nearly normal the skin may become after being deeply inflamed by the repeated application of some toxic agent. We are prepared to explore this in depth, including sophisticated histochemical techniques, and general physiologic study of accommodated skin.

4. It is our intention to shape our work so that it has areas of contact with Army interests; we are experimenting with the topical effects of anti-cholinergic agents. The local anhidrosis produced by these provides a convenient end point for estimating the rate of penetration. It will certainly be important to learn what local or systemic factors modify the rate of penetration of

March 8, 1965

Lt. Col. N. G. Bottiglieri, MC.,

these substances into skin. Here again, past work has been too limited and too project oriented. With more fundamental knowledge, we should come to understand how the skin can be made either less permeable or more permeable to such agents.

I want to reassure you that the skin program will always be a subordinate part of the Army investment. I would estimate that the annual cost will not exceed \$35,000.00. I am well aware of your concern and will guarantee that the tail will not wag the dog. Henceforth, we shall begin to submit bills for volunteers participating in work relating to the above subjects.

I have one last request, viz., that you endorse the hiring of one biologist who will be exclusively concerned with the skin project. He will be stationed at Holmesburg and will be engaged full time to pursue the above cutaneous researches. I include this person's salary in my \$35,000.00 estimate.

I deeply appreciated the chance to talk with you and your associates. I can assure you that you are going to see some serious changes in our setup in the coming months.

With every good wish, I remain

Sincerely yours,

  
Albert M. Klugman, M. D.

AMK/a