

PROPOSAL OF FUTURE WORK ON PERCUTANEOUS ABSORPTION

For the past 5 years we have been involved in measuring percutaneous absorption of various chemicals in vitro and in vivo in human skin. We have been particularly interested in (1) the physical properties of agents in relation to absorption, (2) environmental factors influencing absorption, (3) the role of the horny layer as a barrier and as a reservoir for topically applied chemicals and (4) in the control of cutaneous biologic functions by topical application of pharmacodynamic agents. Our publications in the field are listed in the bibliography (1-16).

The areas we would like to study in the next few years are as follows:

- I. Effect of humidity and temperature on percutaneous absorption of different chemical agents.
- II. Effect of humidity and temperature on the reservoir functions of the horny layer for different compounds.
- III. Effect of sweating on percutaneous absorption and establishment of a reservoir in the horny layer (in vivo).
- IV. Comparison of penetration of C^{14} AHR-483 base and salt in human skin in vitro and comparison of penetration of the base and salt by in vivo methods.
- V. Detailed investigations into the effects of severe hydration of the horny layer in relation to reservoir properties and penetration. (There is early evidence that the heavily hydrated horny layer is far more permeable than the mildly hydrated horny layer. We want to study the gross and microscopic morphology as well as barrier function of the "soggy" horny layer as compared to the mildly hydrated horny layer.
- VI. Test the possible enhancing effects on penetration of the horny layer by chemical agents which are active on the keratinous structures; e.g. (a) molar urea, (b) sulfhydryl agents, (c) salicylic acid and by chemical agents which might bind water into the horny layer.

During the coming year we would like to specifically work with the AHR-483 salt and base to study the percutaneous absorption of radioactive (C^{14}) derivatives in vivo and in vitro using human skin. We also want to assay the comparative penetration of the base and salt on the basis of their ability to inhibit sweating. We feel that the minimum

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concentration to inhibit sweating can be found for both base and salt in a number of human subjects. The forearms of these subjects will be used for most of the in vivo testing of sweat responses. Also, recovery of labelled material from urine and blood following topical application will be tried. We feel that we would be most likely to succeed if we had a scintillation counter. This would allow us to use Tritium which would provide higher specific activity in the base and salt. Also, the scintillation counter would give us about a five-fold increase in sensitivity when working with C^{14} labelled agents. We now use a gas flow chamber, Nuclear-Chicago counter and scaler.

A surface counting technique would allow us to detect labelled base and salt in the horny layer. We will determine the length of time that the base and salt remain in the horny layer after different types of initial exposure where temperature, humidity and time factors will be varied. This retention of base and salt in the horny layer may play an important part in prolonged activity of the agent at the initial site of application.

The personnel, equipment and information to approach these problems has expanded over the past 3 years. We now have over 1200 feet of laboratory space and special as well as general instrumentation to attack these problems.

Dr. William Fritsch will work with us until July 1, 1964. Dr. Munro from St. John's Hospital in London will work with us on these problems from March 1964 to March 1965. Starting November 1963, we will have a person with a Ph.D. in biology to work with us 1/2 time, indefinitely. We will have one full time technician and one half time technician. The principal investigator will spend 25-30% of his time on this project.

BIBLIOGRAPHY

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B U D G E T

(December, 1963 - November 30, 1964)

PERSONNEL:

Full time technician	\$ 4,800.00
1/2 time technician	2,400.00
R. B. Stoughton - 25%	-0-
Wm. Fritsch - 50% (until July, 1964)	1,200.00
Dr. Dowling Munro - 50% (March, 1964 - Nov., 1964)	-0-
Fringe Benefits - 7.5%	630.00

PERMANENT EQUIPMENT:

Scintillation Counter	7,500.00
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CONSUMABLE SUPPLIES:

Radioactive Chemicals	800.00
Photographic Equipment	500.00
Glassware	500.00

HONORARIUMS:

2,000.00

TRAVEL:

600.00

Overhead - 39.5% of Salaries

3,566.85

TOTAL

\$24,696.85