DERMATOLOGICAL DRUG DEVELOPMENT - A REVIEW OF SOME IMPORTANT ISSUES

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INTRODUCTION

In this chapter, a view of the skin from a drug developer's perspective will be presented and a variety of issues pertinent to dermatological therapeutics will be discussed. The author is an experienced pharmaceutical physician who practises as a clinical dermatologist and is therefore well placed to provide a commentary on these subjects but will, naturally, be strongly influenced by his background.

It is logical to assume that the key end point of skin pharmacology and toxicology is to benefit mankind by making available new, effective and well tolerated medicinal agents for the treatment of skin diseases. In order to do this, we must carefully integrate fundamental knowledge concerning both healthy and diseased skin, approaching our task in an energetic, problem-oriented manner. It certainly requires the fusion of knowledge, direction and drive, accompanied by a slice of good fortune, to develop novel therapeutic agents for dermatology, which must be currently recognised as a "Cinderella specialty" competing for finite resources within the pharmaceutical industry against such giants as the cardiovascular system, the central nervous system and the gastrointestinal tract.

The theme of this NATO Advanced Study Institute "Skin Pharmacology and Toxicology - Recent Advances" begs for a fresh and innovative approach to be made. The starting point for this exercise is to carefully re-examine our perception of the skin. Following this, a critical look at the key structural and functional aspects of healthy skin should be combined with a deeper understanding of the clinical features and pathophysiological basis of the most important, or commonest, dermatoses. Dermatological dogma and "mythology", so often applied in the past with devastatingly negative and long-lasting effects on skin therapeutics, must no longer be permitted to act as stumbling blocks to genuine progress. The energies of the synthetic chemist and biotechnologist must be harnessed to produce novel agents worthy of advancement through the long and arduous drug development process. This effort requires team-work of the highest degree by professionals of varied disciplines. Recognition of the deleterious effects of skin
disease on both the soma and the psyche of those afflicted, coupled with an understanding of the massive scale of the problem in terms of the numbers affected, should act as a spur for our endeavours.

Of necessity, this review cannot be exhaustive and therefore the author has selected points for discussion which he considers of importance and which, in some cases, tend to be neglected.

OUR PERCEPTION OF THE SKIN

The skin is indeed a remarkable and many faceted organ. It is so exposed to the enquiring eye, a fact only too well recognised by those suffering from dermatological disorders, and yet so easily overlooked or taken for granted when in a normal condition. When one gazes, for example, at a naked figure one rarely recognises the skin as being an important and quite distinct entity. It is the sheer accessibility of this large and important organ that rendered it for years the subject of descriptive diagnoses and poorly structured therapeutic attempts. Yet it is this feature which should also make the skin so attractive to the drug developer. For it is the organ, par excellence, which is "treated" extensively both in health and disease. It offers unsurpassed scope for topically applied therapy, and yet is amenable to systemic medication. The scientific community is increasingly recognising the skin as an ideal organ for the in vitro and in vivo study of human tissue pharmacology (Camp and Greaves, 1987) with therapeutic implications, for example in the fields of inflammation, allergy, immunology and uncontrolled cellular proliferation, that go well beyond the specialty of dermatology. The pharmaceutical industry is beginning to awaken to facts long recognised by the cosmetic houses, i.e the skin represents a massive potential market-place which will handsomely reward genuine innovation, even of a modest degree.

In order to motivate those with the potential to create important new dermatological therapies, it is important that the skin is recognised by them as a dynamic and vital organ whose health is of fundamental importance to human well-being, and the study of which carries rewards, in terms of possibilities for ethical human experimentation and the development of knowledge, with implications well beyond the borders of the integument itself.

STRUCTURE AND FUNCTION

It would clearly be impractical, and undesirable, to attempt to present in this brief chapter a routine, comprehensive review of the structure and function of the skin. Excellent standard texts covering this subject already exist (Goldsmith, 1983; Jarrett, 1973-1986; Lever and Schaumburg-Lever, 1983; Rook et al., 1986a; Schaefer et al., 1982).

The functions of the skin are summarised in table 1.

I would like to focus my attention on certain aspects of barrier function, as this is of key importance in drug development and has pharmacokinetic implications for both topically and systemically administered drugs. The former is more often emphasised, but the latter is of importance when considering, in particular, anti-dermatophytic drugs (Shah, 1987) and other antimicrobial agents.