STUDIES

IN THE MEASUREMENT, FORM AND INTERPRETATION

OF SOME ELECTRICAL PROPERTIES

OF NORMAL AND PATHOLOGICAL HUMAN SKIN

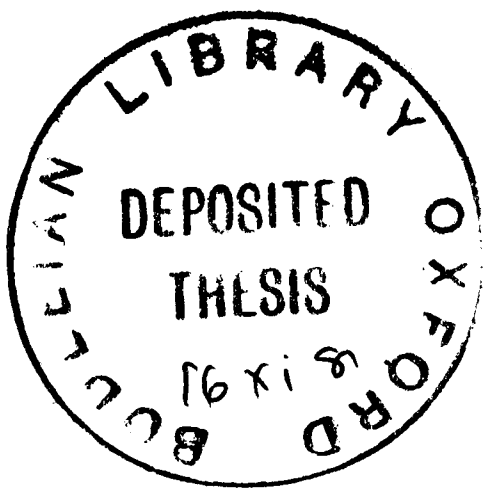
IN VIVO

A thesis submitted to the Faculty of Clinical Medicine

in the University of Oxford

for the degree of Doctor of Philosophy

Volume 1



David Charles Salter

Merton College

Easter 1981

STUDIES IN THE MEASUREMENT, FORM AND INTERPRETATION OF SOME ELECTRICAL PROPERTIES OF NORMAL AND PATHOLOGICAL HUMAN SKIN IN VIVO

David Charles Salter, Merton College, University of Oxford

Submitted for the degree of Doctor of Philosophy

Hilary Term, 1981

(Bound in three volumes containing xxiv + 669 pages)

ABSTRACT

During the past five years a study has been made of the electrical properties of human skin *in vivo* both experimentally and theoretically, seeking to make a coherent whole out of the very diverse phenomenology reported in the very scattered literature.

A Fourier transform method was used, employing novel electronic techniques and four non-invasive electrodes on the subject to separately determine the properties of the stratum corneum and the deeper tissues.

Both linear and non-linear, A.C. and D.C. properties were investigated in this way, and the wide perspective obtained has made it possible to re-interpret the findings of previous workers and so assemble a self-consistent model of nearly all the known electrical properties of human skin.

The main conclusions of this work are that:

(a) The small-signal A.C. impedance properties of skin are extremely well fitted by a minor arc of a circle on the complex impedance plane, and the depression of the centre of the circle below the equivalent series resistance axis is very significantly greater in psoriatic skin and in hyper-hydrated normal skin.

(b) This behaviour cannot be adequately interpreted by any extant physical model of skin, but can be adequately interpreted by considering the stratum corneum to be an inhomogeneous or amorphous semiconductor.

(c) The semiconductivity of human skin has been demonstrated both *in vitro* and *in vivo*, and was found to have activation enthalpies averaging 0.46 eV (10.63 kcal/mole).

(d) These insights into the mechanisms of electrical charge transport through skin may suggest new ways of characterizing the properties of skin using methods developed for the semiconductor industry.

(e) The results in the literature of "phoreography" should be re-interpreted, with much greater emphasis being placed on the properties of the skin appendages.

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ACKNOWLEDGEMENTS

The work described here seems to have lasted so long and to have involved so many people that this part of the thesis is one of the hardest of all to write. What is however sure is that I must and want to begin by expressing my indebtedness to Dr T. J. Ryan, Head of the Department of Dermatology at The Slade Hospital, Oxford, who nearly six years ago welcomed me into the Department, and agreed to supervise my research. However, I will be forever grateful that he chose to interpret this role as that of a "patron of the arts" rather than as that of a taskmaster, since this approach has proved to be exactly what best suited me and the nature of the work in hand. He has helped in innumerable ways, and I am very grateful.

Indeed, in many respects I am sad to have decided that now is the time to move on and leave the very agreeable colleagues and pleasant working environment I have enjoyed in the Department of Dermatology at The Slade Hospital. As I do so nevertheless, I would like also to record special thanks to other members of the Department, in particular Dr R. P. R. Dawber, Consultant Dermatologist, for clarifying to me various aspects of skin biology and clinical dermatology, Professor Graham Weddell, Emeritus Professor of Human Anatomy, for doing the same, and Chris Gummer, who took time from his own research to produce the majority of the photographic prints included in this thesis.

I would like to begin acknowledging the help received from outside the Department of Dermatology by thanking Professor T. J. Lewis of the Department of Electronic Engineering Science, University College of North Wales, Bangor, who, when I first met him at the 1978 Oxford conference of the Dielectrics Society, and at our subsequent meetings in this country and abroad, has been of as much help to me as have his various publications.

These publications can be seen from Chapter 11 to have been of very great help indeed, and to have contributed much of the basis of the theoretical work reported here. I am also very grateful to Professor Lewis for introducing me to his colleague Dr Ron Pethig, since I have greatly appreciated Ron's help through discussion, correspondence and latterly of course through his very comprehensive monograph "Dielectric and Electronic Properties of Biological Materials" (John Wiley, 1979).

Help with dielectric theory has also been received from various other experts, and I am very grateful to Trinity College Dublin for inviting me to spend a week working with Professor B. K. P. Scaife, whose clarity of thought I have admired and been indebted to many times. The U.S. National Academy of Sciences and the British Dielectrics Society made it possible for me to meet and profit from many hours of discussion with Professor R. H. Cole of Brown University in 1978, and I thank him (and others too) for going beyond the call of duty to help a fool who rushed in where angels feared to tread. I would also like to acknowledge helpful discussions about biological dielectrics with Professor H. Fröhlich, FRS, now of the University of Salford, and Professor J. B. Hasted of the University of London, and various discussions on theoretical solid-state physics with my long-time friend Dr W. G. Kleppmann, late of Merton College Oxford, and the Max Planck Institut für Festkörperforschung in Stuttgart, which I profited much from visiting at Willi's invitation.

Moving now to consider the help I have received with general biophysics, I want to express my indebtedness to Professor K. S. Cole, For.Mem.R.S., whose world-famous work undergirds the whole of this rather wide-ranging thesis, and whose publications have been quite literally fundamental to the subjects discussed later. I was therefore extremely honoured when "Kacy" invited me to stay in San Diego for four days as his guest in order that the

present work could be discussed and expedited. It was an unforgettable four days, and I will always be grateful to him and to his brother Professor R. H. Cole, who further helped me by acting as a telephone relay station between Oxford and California when we were arranging the visit.

I would also like to thank Professors Herman P. Schwan and Shiro Takashima of the University of Pennsylvania, Philadelphia, for helpful discussions and the opportunity to see and give a seminar in their Department, all of which I very much appreciated, given the fact of their own major contributions to the subjects dealt with later. I would also like to acknowledge the kind hospitality of Professor Otto Schanne of the University of Sherbrooke, Quebec, since I greatly welcomed the opportunity to visit Canada to lecture and discuss with him the relationship between the contents of his recent book on electrical impedance measurements in biology (Schanne and Ruiz P.-Ceretti, 1978), and our specifically dermatological investigations in Oxford.

As to the biophysics of skin, Dr R. J. Scheuplein spared time from his duties at the F.D.A. in Washington DC to discuss with me various aspects of what is known of the permeability of the skin. During the past six years I have also had many helpful talks both in England and France with Dr Edith Clar and Dr Michel Cambrai, and I hope that we will remain on speaking terms even after they become acquainted with the conclusions reached in this thesis !

I would also like to acknowledge helpful conversations with Dr R. E. Woodrough, late of St. Bartholomew's Hospital, University of London, who introduced me to the biophysics of the skin and whose years of work to produce a Ph.D. thesis I was sure I would never emulate, until Providence decided otherwise; Dr D. C. Fowles of the University of Iowa, who came to visit me, although I am sad to say that at the time I was insufficiently aware of the stature of his contributions to psychophysiology, and Professor P. H. Venables of the University of York, who kindly told Dr Fowles of my work, and who I later met in his Department in York.

In the matter of research into the effects of topical formulations on the skin, I am grateful for the collaboration of Henry Babol and Dr John Short of the Vick International R.& D. Labs lately at Slough, now at Egham, and for the more theoretically-oriented support given by Dr Michel Leduc of the associated Laboratoire Lachartre in Paris.

Advice concerning computing has been sought from, and willingly and helpfully given by, Tony Stark of the University Data Centre, The John Radcliffe Hospital, Oxford, and Tonia Cope and Frank Pettit of the University of Oxford Computing Teaching Centre. They have consequently helped to very considerably ease the labour involved in this thesis, and I am most grateful to them.

This work has been supported financially by Niagara Therapy Ltd., Vick International Ltd., and by my tenure of a Wellcome Foundation Postdoctoral Research Fellowship. Also, the expenses of a tour of North America in 1978 were met by awards from the J. R. Beard Travelling Fund of the Institution of Electrical Engineers (in England), the National Academy of Sciences (in the USA), and grants from the various Universities at which I gave lectures.

Finally, I would like to acknowledge the more general support given by various people too numerous to name, although I want to make an exception in the case of my long-suffering landlady Mrs Stewart, and last, but certainly not by any means least, my even longer-suffering parents. But for my parents this thesis would never have been written, but of course I am grateful to them for very much more than just that.

David Salter

Oxford, March 1981.

PART I: INTRODUCTION

Chapter 1. "PUTTING NUMBERS INTO DERMATOLOGY"

1.1 The need for measurements

Most people think of dermatology as a small medical backwater mainly concerned with vanity - face creams, dandruff and acne. Yet in fact at any one time there are a million sufferers from the very unpleasant skin disease psoriasis in the U.K. and Eire alone (cf. Rook, Wilkinson and Ebling, 1979, pp. 31-38), not to mention all those with the various forms of dermatitis which cause untold inconvenience and considerable unemployment; for example in 1970-1 seven million working days were lost in the British Isles because of skin conditions. Also, only those involved know that skin diseases can cause a great deal of emotional and related social disturbances over a very long period, and are sometimes fatal.

There is therefore a very considerable medical need to quantify the state of skin in vivo by some objective method - we need to "put numbers into dermatology". A suitable method should of course ideally be non-invasive, since this is not only preferable from the point of view of our patients, but also avoids injurying and thus altering, in the very act of measuring it, the biological system we are trying to characterize. We may also note that conversely, since non-invasive physiological monitoring is now an important aspect of clinical care, the behaviour of skin must be understood as the skin inevitably lies between the measuring system and that which it is required to monitor.

Medical applications of any such method could include non-invasively and objectively charting in vivo the course of a particular patients's skin disease and its healing, and the objective comparison of alternative skin treatments. For example, it might be possible to evaluate the benefits of skin moisturizers in the prophylaxis of primary irritant dermatitis in

industry. Indeed, perhaps such a method might also suggest a rapid, non-invasive industrial screening test for susceptibility to dermatitis, which is very much needed, just as much for the protection of the workers as for that of their employers.

Finally, we should remember that the need to characterize skin is felt not only by clinical dermatologists, but also by biologists, zoologists, toxicologists, occupational health specialists and those involved in the pharmaceutical, cosmetic and leather industries.

How then should the problem be tackled?

1.2 The electrical approach to skin characterization

The electrical approach, like most other ways of characterizing skin, has been in use for well over a century (see e.g. Rosendal, 1943; Dorscheid, 1960; Neumann and Blanton, 1970), although more often for physiological or biophysical investigations (Schanne and Ruiz P.-Ceretti, 1978) than for medical ones (Rothman, 1954; Edelberg, 1971). It was decided to join this electrical tradition rather than any other for five main reasons.

Firstly, physical properties can in general be more rapidly determined than chemical ones, and speed helps to make it possible to obtain final results while the patient is still in the clinical measurement room.

Secondly, electrical changes with skin structure and function are much larger than other physical changes when expressed as a percentage of the mean population value.

Thirdly, electrical properties can be determined non-invasively (though with difficulty).

Fourthly, electrical measurement technology is further developed than methods of quantifying other physical characteristics.

Fifthly, because the electrical properties of skin alter with cell permeability and thus with cell metabolism and function (e.g. Clar et al., 1976; Schanne and Ruiz P.-Ceretti, 1978), the accurate specification of its electrical properties is in itself as important as any other objective measurement that can be made under recognized physiological or pathological conditions, as was first argued by Cole and Curtis (1936). This point of view is of course supported by the adoption of the electrical approach in much now classic biophysical work (see e.g. Cole, 1972; Schanne and Ruiz P.-Ceretti, 1978)

There are therefore good reasons for investigating skin electrically, and very many people have taken this approach. Nevertheless, most of them seem to have come to different conclusions as to the meaning of their results. Even review articles have not yet adequately digested and reassembled the facts into a clear picture. This lack of coherence in the literature has arisen partly because of the variety of academic disciplines of the investigators, and partly because there are not a few difficulties in the electrical approach to skin characterization. These difficulties are invariably underestimated, usually because the electrical complexity of skin is generally underestimated. In fact the electrical properties of skin in vivo are extremely complicated, firstly by the many and varied living processes of the tissue, secondly by its gross stratification into epidermis and dermis, thirdly by the inhomogeneous nature and arrangement of the materials and structures which compose these layers, and fourthly by the exceptionally complicated and still largely unexplained electrical behaviour of such materials even in their pure form. Indeed, as we shall see, we enter the front line of theoretical solid-state physics research at this point! Of course the living processes of the tissue are also only partially understood, to clarify them being the main reason for investigating skin in the first place.

1.3 An apologia for this thesis

Perhaps in view of the difficulties we have considered it should not be surprising that the electrical characterization of skin in vivo has been greatly hindered by the unfamiliarity of skin biologists with the most appropriate technology and techniques, and by the unfamiliarity of physicists and engineers with skin biology. Very little work has been done since the promising start made with limited and cumbersome equipment before or just after the Second World War (Rein, 1929; Rothman, 1954), and, as a circumspective review of the literature easily shows, what little has been done has usually been far less careful than this early work, and indeed is often extremely suspect in methodology or biophysical interpretation due presumably to that general lack of interdisciplinary expertise or collaboration which has been mentioned above.

In consequence, a poor reputation has been acquired by this subject despite its acknowledged medical and economic importance. Therefore in the present work the mere collecting of further data takes second place to a concentrated attempt to improve the foundations of the subject, that is, deciding what measurements should be made and why, then how best to make them, and finally, having made them and examined the form of the electrical properties of skin derived from them, deciding from biological and physical considerations just how these properties may most reasonably be interpreted.

1.4 An introduction to the contents of the thesis

Following the introductory chapters 1 to 4 which try to set the conceptual scene, the first question to be considered is that of deciding what measurements should be made and why. This is dealt with in Part II, chapter 5,

with the aim of suggesting a methodology of measurement which can determine enough sufficiently fundamental physical indices to construct an adequate electrical basis for quantifying and thus comparing skin in vivo. The important though frequently neglected question of quite what constitutes an adequate basis with which to characterize the electrical properties of skin will also be dealt with, preceded by some introductory thoughts in chapter 4.

Having decided what we feel to be a theoretically sound methodology equal to the task of thoroughly re-exploring the electrical properties of skin in vivo, particular aspects of this methodology are worked out in detail in chapters 6, 7 and 8. These chapters include descriptions of the associated hardware designed and developed here over the past five years at a cost of some £25,000 (excluding the minicomputer). It should be stated immediately however that what has been learnt about skin using this powerful instrumentation would suggest that future equipment could be considerably simpler without severely reducing the value of the results obtained.

Part III contains two chapters, 9 and 10, describing some representative results obtained for normal skin and for pathological skin respectively. It could of course always be argued that very many more results than are presented here should be given in a thesis dealing with the electrical properties of skin, but it should be remembered that one has to set limits somewhere, and this is a suitable aspect to restrict in a thesis addressing itself primarily to the subjects of methodology of measurement and the interpretation of results, rather than to the amassing of yet more data before the data already collected has been adequately digested.

The question of what is the most probable biological and physical interpretation of the results has usually been only superficially considered in the past, and hypotheses have almost never been tested. Indeed, having

in chapters 4,9 and 10 examined in detail exactly what is the biophysical form of the electrical properties of skin, we will find in Part IV, chapters 11 and 12, that extant interpretations of these forms to not stand up to testing, in that when the interpretations are used as the basis of models of the electrical properties of skin, the behaviour of the models does not conform at all well to the results of clinical experiments. From Part IV however a more promising although less simple interpretation will emerge which actually does produce a model exhibiting electrical behaviour very much like that of real skin in vivo. Moreover, this interpretation is based upon the known physico-chemical properties of the materials composing skin.

Finally, Part V summarizes and consolidates the present work, and affords an opportunity to assess the ways in which the electrical properties of skin may be of medical interest in the future.

Chapter 2. SOME ASPECTS OF SKIN PHYSIOLOGY AND PATHOPHYSIOLOGY

2.1 Physiology

2.1.a An introduction to the skin

As the last Chapter sought to emphasize, this is a work involving aspects of many disciplines, and so in view of the shortness of life of author and reader, it should not be expected to serve as an introductory textbook for each of the disciplines it touches upon!

Consequently this Chapter may seem naive and oversimplified to those whose training is in skin biology and clinical dermatology, just as the next Chapter may to those whose training is in physics and electrical engineering. However, if one type of specialist is unfamiliar with the domain of the other, then perhaps these Chapters will prove to be useful. Many of the finer points will of course be dealt with later.

The first thing which should be noted is that the skin of man bears only slight similarities to that of the animals (Montagna and Parakkal, 1974, p. xii), and so the properties of animal skin are not necessarily reproduced in that of humans. The converse holds as well; for example, only human beings get the skin disease psoriasis.

In man, the skin is the heaviest organ of the body, representing about one-twelfth of the total body mass. Since its area in adults is about two square metres, depending of course on the size and shape of the individual, it is also one of the largest organs, exceeded in area only by the gut and the lungs. Moreover, it contains between 18% and 40% of the total water content of the body.

The functions of the skin include

(1) Protection against mechanical and chemical trauma

(2) Sensation of touch, pain and temperature

(3) Regulation of body temperature

(4) Provision of a barrier to the loss of body water

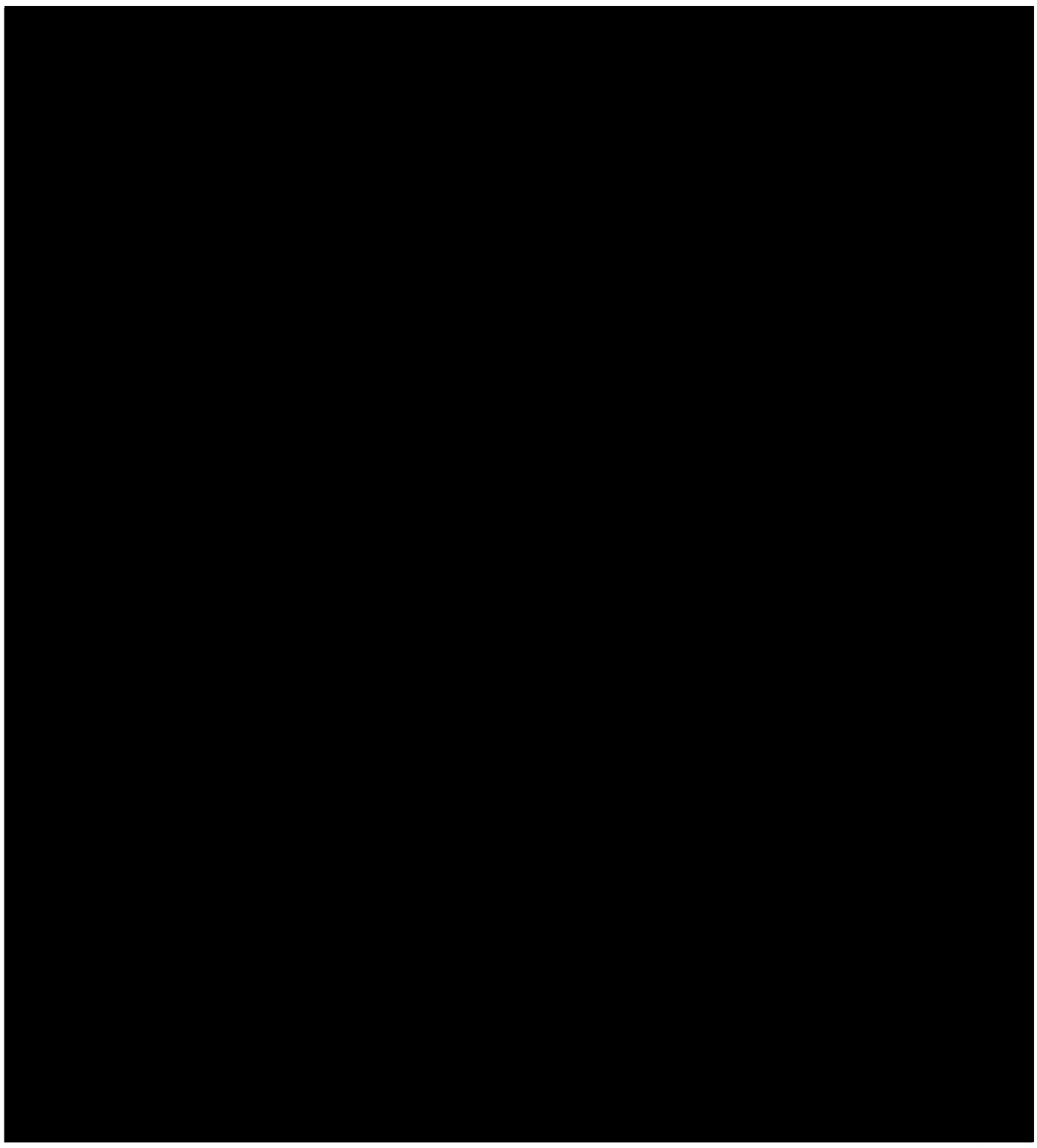

Fig. 2.1.b.I

and the complexity of the anatomical and physiological basis of these functions (see e.g. Jarrett, 1973-80, Vols. 1-6), indicates that skin is indeed a true organ, not just "a bag for the body".

2.1.b The layers of the skin

Like Gaul, all skin can be divided into three parts. These are known as the epidermis, the dermis, and the skin appendages. The outermost is the epidermis, underneath which comes the dermis, and the skin appendages pierce through both of these. Deeper still are various subcutaneous tissues which are not relevant to this thesis. All these are shown in Fig. 2.1.b.I, reproduced from Parrish (1975).

Leaving consideration of the skin appendages until later, it should be noted that there are very basic differences between the dermis and the epidermis.

The dermis is much thicker than the epidermis, and, being composed mainly of connective tissue, it provides most of the bulk, strength, elasticity and water-holding capacity of the skin. It is a semisolid mixture of fibres and water in a viscous material known as "ground substance". Ground substance consists largely of water and mucopolysaccharides (glycosaminoglycans), specially hyaluronic acid and various chondroitin sulphates. This material is usually in the form of a gel, but can be converted into a sol, a fact made use of by certain bacteria. Within the ground substance is a matrix of fibres of the proteins collagen and elastin. Collagen consists of molecules woven into triple helical structures which allow stretching and contraction while maintaining tensile strength. Elastin fibres, being highly elastic, presumably impart such qualities to the dermis as a whole. Together with this connective tissue, blood vessels, lymph

vessels (lymphatics) and nerves are also present in the dermis, but do not enter the epidermis. The boundary region is known as the papillary dermis, because it is from there that finger-like processes of dermis called papillae enter invaginations of the basement membrane of the epidermis, which the dermis nourishes via capillary loops in these papillae.

Above the basement membrane are the various cells of the epidermis, mostly organized into distinct layers, as shown in Fig. 2.1.b.II (reproduced



Fig. 2.1.b.II

from Parrish, 1975). The stratum which is deepest, and thus closest to the nourishing papillae, is a (usually) single layer of germinative cells, the stratum germinativum(also known as the basal cell layer, or, less frequently, the stratum basale). Physiologically these are stem cells, and reproduce themselves after some interval which is yet to be determined adequately (Wright, 1976; Salter, 1977; Wright and Salter, 1979), one daughter cell remaining in the stratum basale and the other being pushed upward into the stratum spinosum or prickle-cell layer, so called because of certain artefactual changes in the appearance of these cells caused by histological

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the inner, more firmly bound cell layers are sometimes known as the stratum conjunctum (or stratum corneum compactum).

Finally, we should note that the skin of the palmar and plantar surfaces is different in that there is an extra layer, the stratum lucidum, between the stratum granulosum and the stratum corneum. Also, the stratum corneum is thirty or more times thicker than at other skin sites, and yet is at least as permeable(Scheuplein, 1978, p. 1740).

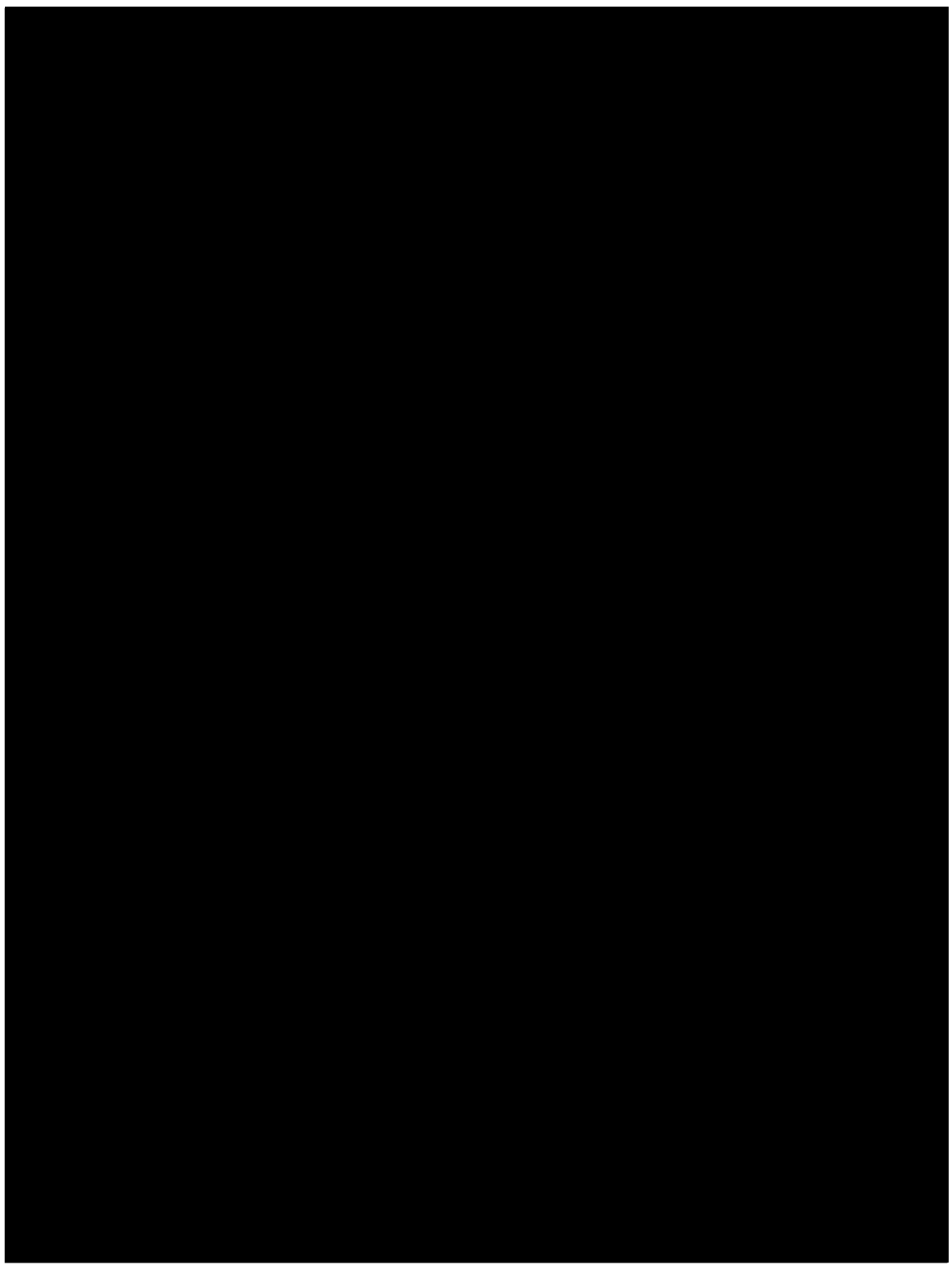


Fig. 2.1.c.I

2.1.c Skin appendages

There are in skin various multicellular structures, called the skin appendages, which are illustrated by Fig. 2.1.c.I (from Pillsbury and Heaton, 1980). They will however be described here only briefly, and in a rather partisan way which considers them primarily as "holes in the corneum", that is, shunts through the main permeability barrier of the skin.

The most important such shunt is the hair follicle. A hair follicle is basically an invagination of the epidermis down into the dermis, and usually contains a hair. The anatomy and physiology of the entire structure is however very complicated, and it is unreasonable to attempt to describe it here (see for example Jarrett, 1973-1980, Vol. 4). Hair follicles are found all over the body except for the palms, soles, dorsal aspect of the distal phalanges of the hands and feet, the penis, the labia minora and the lips.

Sebaceous glands are associated with hair follicles to the extent that the term "pilo-sebaceous unit" has been coined. Sebaceous glands produce sebum, consisting of fatty acids, cholesterol and various other substances, as a result of the breakdown of their cells. The cells are grouped into lobules which secrete the sebum into a common sebaceous duct emptying into the hair follicle at the level of the papillary dermis. The duct consists of a keratinous squamous epithelium continuous with the surface epidermis.

Another skin appendage associated with the hair follicle is the apocrine gland. In man it is found in the axillae, the ano-genital and peri-umbilical areas, the nipples and the areolae, together with modified forms in the external ear and the eyelids. Each gland has the form of a long tubule tangled into a bundle in the dermis, and its secretion, (which

is sufficiently unlike sweat to belie the term "apocrine sweat gland"), empties into the hair follicle through a long duct at the level of the papillary dermis. The secretion is produced under hormonal control, after puberty, at times of acute stress.

The second type of shunt through the corneum is the eccrine sweat gland, the main function of which is to secrete water onto the skin surface to aid thermoregulation by evaporative cooling. The sweat glands are distributed all over the body, with the exception of the mucous membranes. They have a coiled secretory portion (the glomerulus) in the dermis, leading into an initially coiled duct which straightens as it rises through the dermis, and finally assumes a helical form as it traverses the papillary dermis and the epidermis to emerge on the surface of the stratum corneum as a "sweat pore". Capillaries surround both the glomerulus and the dermal portion of the duct, and the glomerulus is innervated by sympathetic fibres of the autonomic nervous system which, strangely, are cholinergic. Sweating of the palms, soles, axillae and forehead is under the control of the premotor cortex of the brain, and as such occurs mainly in response to emotional stimuli. The sweat glands of other areas however are controlled by the hypothalamus, and their activity is mainly invoked for thermoregulatory purposes. For further discussion of the anatomy and physiology of the sweat glands, the detailed review by Hashimoto (1978) can be recommended.

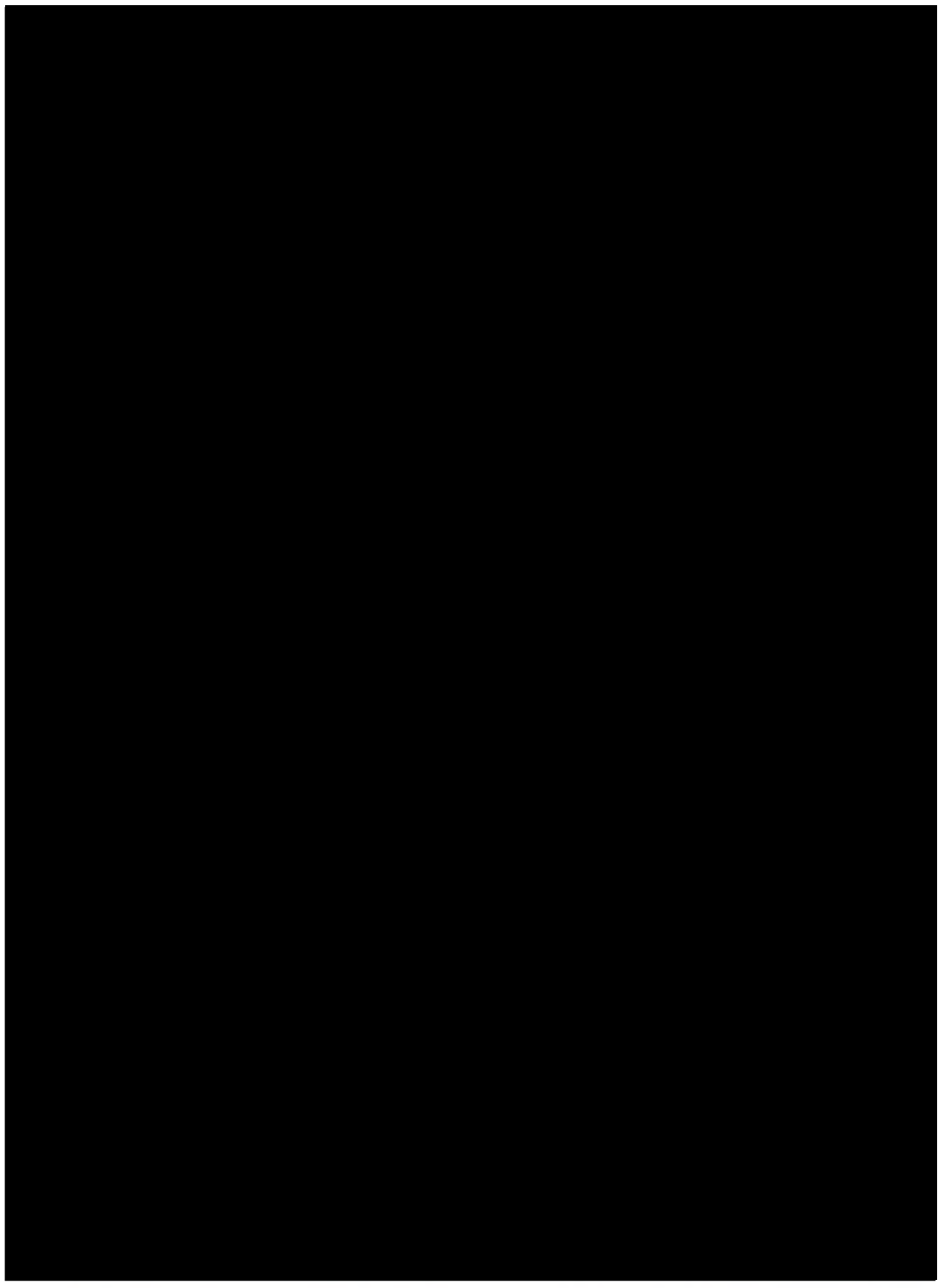


Fig. 2.1.d.I

2.1.d The electrical polarization of skin layers and appendages

If thin sections of the epidermis are stained with haematoxylin and eosin, a very distinct colour change is visible within them (see e.g. Fig. 2.1.d.I). The stratum granulosum and the other living layers are basophilic and stain blue, as has been discussed by Montagna (1962, pp. 50, 51). In contrast, however, the stratum corneum is acidophilic and stains pink, implying that it has a fixed negative charge at pH 7 (cf. Subsection 12.3.e).

This colour change is therefore a visible indication of an electrical potential difference between the stratum corneum compactum and the stratum granulosum. Indeed Edelberg has suggested (1977, p. 326) that this region is a reasonable site of origin for the epidermal contribution to the skin potential level, a concept which will be discussed in detail in Section 12.2.

There are also indications in favour of an electrical potential difference across the lumen of the sweat gland (cf. Section 12.2). Schulz et al. (1965) showed by microelectrode measurements that the lumen of the duct is about 40 mV negative with respect to the surrounding dermis, and Edelberg (1968) made similar measurements showing that the epidermis near the sweat pore is also negative with respect to the dermis, although less so than the duct.

Finally, an electrical potential difference between the hair follicle and the surrounding dermis has been discussed by Woodrough (1976), and although experimental evidence remains scanty, theory predicts that such a potential difference must usually be present.

2.1.e The innervation of the skin

The skin is innervated both by motor fibres of the autonomic nervous system and by sensory fibres of the central nervous system

Cholinergic autonomic fibres are motor to the eccrine sweat gland. Adrenergic autonomic fibres are motor to the arterioles, the arrector pilorum (hair erector) muscles, and probably also to the myopithelium of the apocrine gland, although there appears to be some doubt about this latter point (Sinclair, 1978, p. 487).

The afferent, sensory fibres innervating the skin conduct the impulses giving rise to the sensations of itch, pain, touch and temperature. The fibres are most generally unmyelinated and terminate as free nerve endings in the papillary dermis, and perhaps occasionally in the epidermis. Much more rarely, and indeed mainly in the palms and soles, the sensory fibres are myelinated and terminate in the various forms of "specialized nerve ending" such as Meissner corpuscles, Pacinian corpuscles, Krause end bulbs, Ruffini endings, Merkel discs and so on. For further discussion. the detailed treatment by Sinclair(1967. 1973) can be recommended. (A shorter review bearing on the subject, written bv myself, has been included in this thesis as Appendix G, since it is relevant to the topic of Subsection 10.4.c).

2.1.f The microcirculation of the skin

The vasculature of the skin is a network of vessels tending to form two plexuses which run parallel to the skin surface. Each plexus consists of arterioles and venules arranged in parallel. The one with the vessels of largest diameter is called the deep plexus, since it is in the lowest part of the dermis, and is linked by perpendicularly oriented communicating blood vessels to the superficial plexus, located in the upper part of the dermis. From this plexus, arcades of capillaries supply the papillae, each such "papillary loop" consisting of an ascending arterial limb and a descending venous one, together with a number of cross-connecting micro-vessels. Many capillaries also supply the skin appendages. The venous outflow of these venous capillaries empties into the postcapillary venules of the superficial plexus, and finally out of the skin into the small veins of the subcutaneous tissue. Further discussion of the rather complicated anatomy and physiology involved can be found in the detailed review by Ryan (1973).

Particularly in the hands, feet and ear lobes, arterio-venous anastamoses (or "A-V shunts") are present. These are specialized vessels connecting arterioles and venules, and are surrounded by muscle cells which act as sphincters. Such shunts enable blood flow to bypass the capillaries, which helps to avoid excessive cooling of the blood in acral skin. The sphincters of the shunts are under the control of the autonomic nervous system, which also controls the tone of the arterioles.

One of the main functions of the arterial vasculature is that of thermoregulation. Blood vessels in the skin help to maintain the various parts of the body at suitable temperatures. This action is controlled by the hypothalamus via the sympathetic nervous system, as we have noted already.

Another function of the dermal blood vessels is to distribute oxygen, water, nutrients and hormones to the skin, and to remove the unwanted products

of skin metabolism. The capillaries of the papillary dermis, intended of course to supply the epidermis. are very plentiful because the oxidative requirements of the epidermis are greater than those of the dermal connective tissue. Similarly, many capillaries supply the growing hair. The flux of blood through the dermis is however much greater than that required for such nutritive purposes because of the thermoregulative role it plays.

The dermal blood vessels are the target tissue element in inflammatory conditions of the skin (see e.g. Parish and Ryan, 1979), and the microcirculation of the upper dermis including the papillae is particularly involved when there is erythema.

There is also in the skin an elaborate network of lymphatic vessels (see e.g. Ryan, 1978), which parallels the vascular plexuses but which is independent of them. Lymphatics clear the tissues of the protein-containing capillary transudate ("lymph"), and return it to the venous system.



Fig. 2.1.g.I

2.1.g Trans-epidermal water loss and hydration levels in normal skin

Insofar as the dermis is "wet" and the air outside the skin is "dry", it might be expected that there would be a net outward movement of water, tending to equalize this difference. The flux of water is known as trans-epidermal water loss (or TEWL), and together with water desorption and invisible amounts of water loss through the sweat glands, it makes up what was referred to in the older literature as "insensible perspiration" (Grice, 1980).

Trans-epidermal water loss occurs by passive diffusion, and its rate therefore depends upon the water concentration difference between the dermis and the exterior, and the diffusion constants of the intervening skin layers. It is found however that the overwhelmingly dominant restriction upon the rate of diffusive transport resides in the stratum corneum, just as much to water inside the skin tending to diffuse out, as to substances outside the skin tending to diffuse in (see Kligman, 1964; Scheuplein, 1978; Grice, 1980).

The difficulty water experiences in diffusing through the corneum means that across this layer there is usually found to be a considerable gradient of water concentration (although not in general a linear one, because the corneum has a hydration-dependent diffusion constant). This gradient of water concentration is of very great importance for the effective functioning of the stratum corneum (see e.g. Idson, 1973), because some of the water is absorbed by the keratinocytes of the corneum, and constitutes usually 10% to 15% by weight (cf. Fig. 2.1.g.I, reproduced from Spencer et al., 1975). However, the actual amount is critical, because if it drops below about 10%, the corneum is unable to maintain adequate plasticity and cracks develop in it, destroying its barrier properties and allowing easy access to irritant substances. This cracking phenomenon is known as chapping, and occurs if the air in contact with the skin is very dry or if for some reason the water-holding capacity of the corneum keratinocytes is reduced.

Later sections will consider in detail the ways in which electrical measurements may be relevant to assessing the physiologically important quantity, the hydration of the corneum.

2.2 Pathophysiology

2.2.a Psoriasis

Psoriasis occurs only in humans. Nevertheless, it is one of the commonest skin diseases, afflicting between 1.5% and 2% of the population of the United Kingdom at any one time.

The disease may affect any part of the skin surface, including the nails. There are however certain "typical" sites, particularly the extensor aspects of the elbows and knees and the skin at the scalp and the sacral area.

The signs of psoriasis may be briefly described as well-defined erythematous plaques on the skin, covered with dry, silvery scales, the removal of which leaves a surface which is bleeding in a punctate fashion because of damage to capillaries (this is a principal diagnostic sign of psoriasis). The plaques are roughly but rarely exactly circular in outline, and vary in diameter from a few millimetres to a number of centimetres. There are also often signs in the nails, but these are not relevant to this thesis.

There are four common clinical types of psoriasis, but these are not to be regarded as anything more than fixed points in a spectrum of responses. The first is "acute (or guttate) psoriasis". This is typically provoked by an infection (e.g. tonsillitis), and affects all areas of the skin, although there are few changes in the nails. The lesions are small and drop-like ("guttate"). The second type is "chronic psoriasis". Here there is usually a family history of psoriasis, the lesions are large, they affect the "typical" sites, and nail changes are prominent. The third type is "arthropathic psoriasis". Although psoriasis and (sero-positive) rheumatoid arthritis may co-exist by chance there is a specific sero-negative poly-arthropathy which occurs in association with a psoriasis usually of the

chronic type. Finally, the fourth variety of psoriasis is "erythrodermic psoriasis". Here the entire skin is involved and presents a similar clinical impression to an exfoliative dermatitis.

Briefly, the pathophysiology of psoriasis involves dilation of the capillaries in the dermal papillae, and the infiltration first of the dermis and then of the epidermis by polymorphic white cells. Subsequently (Braun-Falco, 1976) the basal layer of the epidermis produces a greater number of progeny per unit time, the papillae become elongated and the capillaries tortuous and hypertrophied. The changes in the basal layer mean that the whole epidermis is replaced at much shorter time intervals, and because of this the keratinocytes pass through the stratum spinosum and stratum granulosum stages too quickly. Indeed the stratum granulosum is hardly if at all visible as such. The process of keratin synthesis and bonding, and the subsequent proteolytic digestion, both remain uncompleted. Consequently the cells of the stratum corneum still contain shrunken nuclei, mitochondria and other intracellular organelles, trapped in a matrix of imperfectly cross-linked keratins. This condition of the corneum is known as parakeratosis, because the processes of keratinization have not taken place normally. Such a parakeratotic corneum, even though it is usually thicker than usual ("hyperkeratosis"), is a much poorer permeability barrier, and this is reflected by the abnormally high values of TEWL through psoriatic lesions (Grice, 1980, p. 2147 ff; see also Fig. 10.3.a.I).

2.2.b Eczema and dermatitis

The terms "eczema" and "dermatitis" are synonymous, meaning simply an inflammation of the skin. However, the term eczema tends to be used if the cause of the inflammation remains unknown, whereas the term dermititis is used if the cause is an external irritant or allergen and has been or is likely to be discovered.

Eczema and dermititis are extremely common, affecting about 4% of the U.K. population at any one time and accounting for 10% to 20% of all referrals to dermatological outpatient clinics. Moreover, the conditions cause a major loss of time from work and a considerable degree of often chronic discomfort and disability for people of all ages.

It will however unfortunately be impossible here to describe eczema and dermatitis at all adequately; a textbook of dermatology should be consulted (e.g. Rook, Wilkinson and Ebling, 1979). The difficulty of providing a short yet adequate description arises from the fact that many factors can contribute to the aetiology and pathogenesis of eczema and dermatitis. When one factor plays a dominant role it tends to produce a recognizable clinical entity which can be labelled with a specific name. However, when several factors act together, a variety of clinical responses may result, and these can range from being clear-cut to ill-defined. Furthermore, all these responses present different clinical appearances at different stages and at different body sites, and they may last for any time interval between a few days and a lifetime.

The pathogenesis of eczema and dermatitis may however be briefly summarized as follows. While there may be invisible biochemical, pharmacological and immunological activity very early in the pathogenesis, the first visible change is a dilatation of the dermal capillaries, particularly those of the papillae, leading to an excessive leakage of plasma and

lymphocytes into the dermis. The excess fluid penetrates the basement membrane of the epidermis and diffuses between the cells of the stratum spinosum, increasing the intercellular distances and stretching the intercellular bonds (which are known as "desmosomes"). This is a histopathological condition called spongiosis. The spongiosis also enables the lymphocytes which have been exuded from the dermal capillaries to infiltrate the epidermis between the cells of the stratum spinosum. As the volume of fluid in the epidermis continues to increase, some of the desmosomes rupture and small cavities appear in the stratum spinosum. These microvesicles may contain lymphocytes or stratum spinosum cells which have become detached, and as the integrity of the stratum spinosum is further disrupted, so is that of the stratum granulosum. The excess fluid then begins to hyperhydrate the stratum corneum, and this begins to disintegrate. A raw area therefore develops on the surface of the skin, within which the dilated dermal capillaries, still oozing lymph, are clearly visible, producing the erythematous weeping lesion typical of acute eczema (or dermatitis). After the acute reaction has reached its peak, the loss of cells stimulates a reactive increase in the mitotic activity of the basal layers which in time leads to epidermal thickening ("lichenification"), and also to a parakeratotic stratum corneum, for the reasons we considered in the last subsection. (There is incidentally again an abnormally large TEWL.) These parakerototic corneocytes, together with the capillary exudate, form a crust over the new skin surface, and thus the lesion typical of subacute eczema or dermatitis. The condition can however persist into a chronic form, characterized by lichenification and often pruritis (itchiness) of the skin, together with parakeratosis, dryness and fissuring of the stratum corneum in particular.

2.2.c Skin cancers

The study of neoplastic conditions of the skin is a large subject, as can be seen from the full description given by Rook, Wilkinson and Ebling (1974). Consequently they will only briefly be considered here, insofar as they are relevant to later Chapters.

Basal cell carcinoma (BCC) is the commonest skin tumour, representing about 70% of cases. Only very unusual variants metastasize. As the name implies, it originates in the cells of the basal layer. These cells maintain their normal degree of mitotic activity, but there is no subsequent keratinization, and the permeability of the skin is therefore enormously increased because the stratum corneum is not formed.

In squamous cell carcinoma (SCC), epidermal cells invade the dermis, disrupting the basal layer and its basement membrane (the basal lamina). Keratinization occurs only in some parts of the lesion, producing what are known as "epithelial pearls" enclosed within it. The degree of malignancy can be determined by considering the ratio of differentiated to undifferentiated cells, and the extent of the invasion. A related condition is Bowen's disease, corresponding to an SCC which does not invade the basal layer. It does however produce regions of slight scaling within an erythematous and well-defined lesion.

Finally, malignant melanoma (MM) is a less common, but, as the name suggests, very malignant neoplasm occurring at the dermo-epidermal junction as a tumour of the melanocytes, cells which normally occupy positions in the basal layer and produce the pigment known as melanin.

Chapter 3. SOME RELEVANT ELECTRICAL CONCEPTS

3.1 Introduction

Just as the last Chapter was intended to provide a brief introduction to some relevant aspects of skin biology and clinical dermatology, so this Chapter is intended to give a brief introduction to some relevant aspects of physics and electrical engineering. I must again apologize to the specialists for the oversimplifications I know I have assumed, and again I hope that later Chapters will serve to suitably qualify and amplify the present one.

If however anyone finds even this Chapter to be too esoteric or condensed, a simple and detailed introduction to most of the concepts mentioned here can be obtained by consulting the following sequence of publications: Ball and Moore (1980), Edminister (1972), Hobbie (1978), Schwan (1957) and Wright (1979).

3.2 Ohm's Law

There are many phenomenological laws which say something like: "Effect is proportional to cause so long as the system on which the cause acts to produce the effect is not altered". Ohm's Law is one of these, and in its usual textbook form states that the electrical current flowing through a conductor is directly proportional to the difference of electrical potential maintained between its ends, so long as all physical conditions in the conductor, for example temperature, remain constant.

Writing current as I, and difference of electrical potential as voltage, V, it can be seen that Ohm's Law is describing the proportionality

$$I \propto V \qquad (3.2.1)$$

and this can be turned into an equation

$$I = G\,V \qquad (3.2.2)$$

by using a constant, G, known as "conductance". Ohm's Law can therefore be seen to predict that the conductance of a conductor is constant so long as the physical conditions obtaining within it remain constant. In the form (3.2.2) it is indeed analogous to Fick's first law of diffusion.

To relate this behaviour to more fundamental properties of the conductor, we have to consider the effect of shape and size, in order to define an index which describes electrical conduction in the material independently of whatever shape and size any particular piece of it may have. This index is known as "conductivity", σ, and as we would expect, the derivation of its value from measurements of G depends upon the shape and size of the piece of material the measurements were made on. The simplest case is that of a sheet or parallelepiped block of constant cross-sectional area A and uniform thickness d. For such a case we may write

$$\sigma = (d/A)\,G \qquad (3.2.3)$$

and then if we wish change (3.2.2) to

$$I = (A/d)\,\sigma\,V \qquad (3.2.4).$$

We may further interpret σ as

$$\sigma = n\,q\,\mu \qquad (3.2.5)$$

where n is the number of mobile electrical charge carriers in a unit volume of the material, q is the electrical charge on each carrier (all assumed to be identical), and μ is its diffusion (or drift) mobility.

Consequently (3.2.2) may again be rewritten, producing

$$I = (A/d)\,n\,q\,\mu\,V \qquad (3.2.6)$$

or, defining the "electric field" E by

$$E = V/d \qquad (3.2.7)$$

we may instead use

$$I = A\,n\,q\,\mu\,E \qquad (3.2.8).$$

Since it seems that very simple equations can be used to relate currents to particular voltages applied across the material, it follows that it is also possible to relate voltages to particular currents. To do this it is conventional to use an alternative form of Ohm's Law

$$V = R\,I \qquad (3.2.9)$$

where R is a constant called "resistance", and by comparing (3.2.9) with (3.2.2), it is possible to see that resistance must be equal to the reciprocal of conductance

$$R = 1/G \qquad (3.2.10).$$

3.3 Complex impedance, conductance and permittivity

A great deal of information can be derived about the material by investigating how the charge carriers in it respond to changes in the electric field applied to them. One way of carrying out such investigations is to apply a sinusoidal field, which of course repeatedly reverses direction. If identical parts of this sinusoidal wavetrain recur at time intervals Δt, then its "frequency" is defined by

$$f = 1/\Delta t \qquad (3.3.1)$$

and its "angular frequency", (unfortunately usually abbreviated to just "frequency"), by

$$\omega = 2\pi f \qquad (3.3.2)$$

Now, if such a sinusoidal field is applied to a material, it is in general found that the peaks of this field do not occur at the same time as the peaks of the current which flows in consequence. Nevertheless, we can characterize this behaviour by measuring both V', the potential difference across the material when the current is at its maximum, I_m, and also V", the voltage across the material when the current is (passing through) zero. We then define two quantities

$$R_s = V' / I_m \qquad (3.3.3)$$

and

$$X_s = V'' / I_m \qquad (3.3.4)$$

known respectively as the "equivalent series resistance" and the "equivalent series reactance". They both of course have the same units, and so can be employed as rectangular coordinates defining a vector Z on an Argand diagram known as the "complex impedance plane". (For an introduction to

the theory of complex numbers in this context see e.g. Edminister, 1972). The vector Z, the "complex impedance", can be written as

$$Z = R_s + jX_s \quad , \quad j = \sqrt{-1} \qquad (3.3.5)$$

the j only being present to indicate that the X_s component is at right-angles to the R_s component.

In general, both R_s and X_s may depend upon frequency, and consequently so may Z. On the other hand, R_s is always positive, whereas X_s may be either positive (inductive) or negative (capacitative). In the particular case of skin, it is negative. Consequently if we were to record on a graph of the complex impedance plane the information gained by making measurements using a sinusoid of frequency ω, the graph might look rather like Fig. 3.3.I,

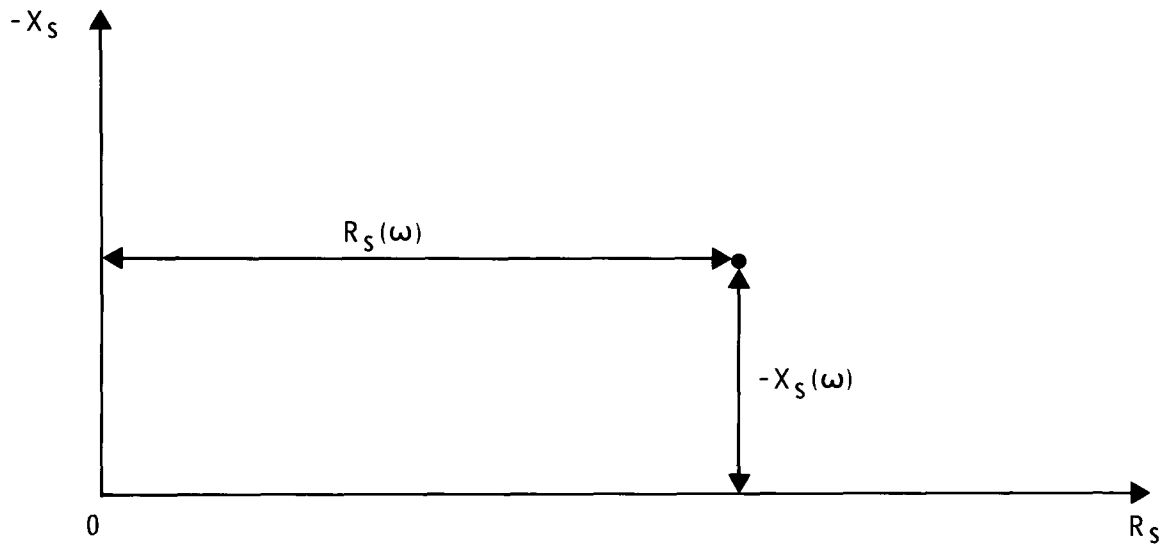


Fig. 3.3.I

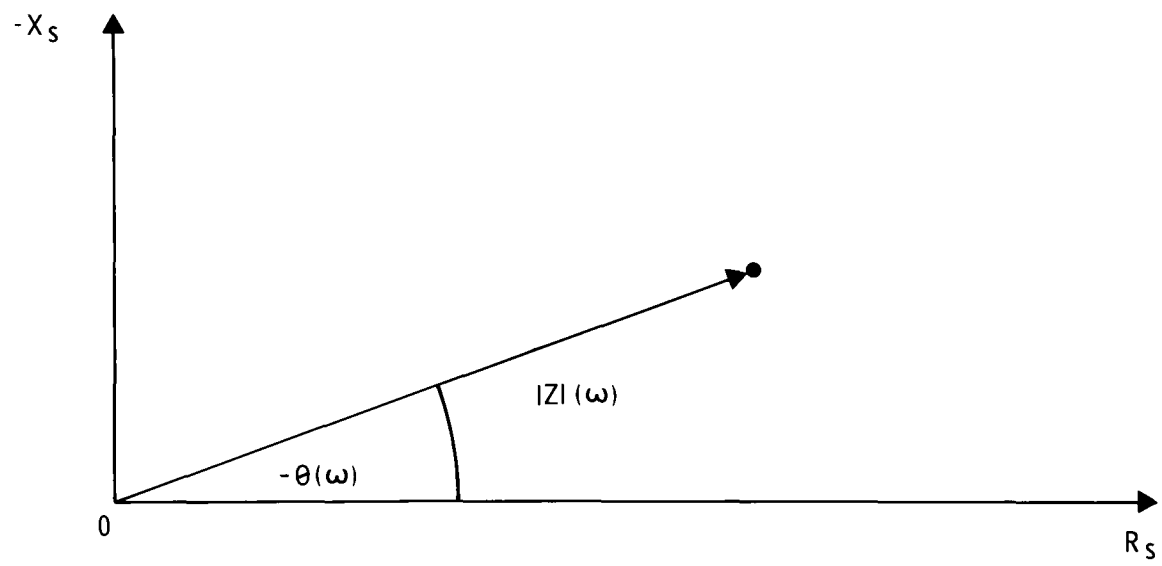


Fig. 3.3.II

which shows how the frequency-dependent coordinates R_s and X_s locate the point representing the complex impedance of the skin at that frequency.

We could alternatively express the position of such a point on the plane in terms of polar coordinates, as are shown in Fig. 3.3.II. To do this we define

$$|Z| = \sqrt{(R_s)^2 + (X_s)^2} \qquad (3.3.6)$$

which is a purely real quantity called the "impedance", or the "modulus of (complex) impedance", or the "impedance magnitude", and

$$\theta = \arctan (X_s/R_s) \qquad (3.3.7)$$

which is known as the "phase angle", equal to 2π (or 360°) times that fraction of Δt by which the peaks of voltage precede the peaks of current.

Having chosen one or other of these ways to locate the point on the complex impedance plane (it makes no difference which of the two ways is used), the benefits of this apparently rather complicated exercise can begin to be reaped, if we repeat the measurement procedure for sinusoids of many different frequencies, plot the respective complex impedance points onto the complex impedance plane, and then "join up the dots" (!) to reveal what is known as the complex impedance locus. Such a locus can be highly informative, as will be shown in later Chapters.

The locus which is obtained for skin looks rather like Fig. 3.3.III,

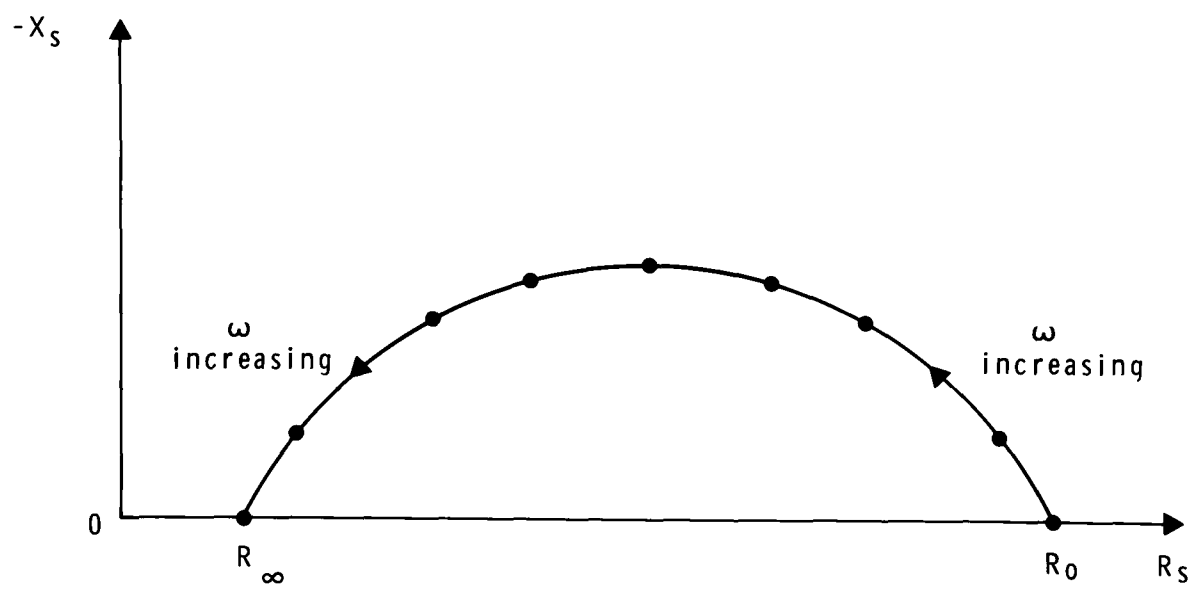


Fig. 3.3.III

and we see that in this case R_s tends to a limit, R_o, as frequency becomes very low, and to another limit, R_∞, as frequency becomes very high. Such limits do not however necessarily exist for other materials, because their complex impedance loci do not necessarily have a shape similar to the one shown in the Figure.

Now having seen that complex impedance is a generalization of the concept of resistance we met in Section 3.2, we may wish to generalize the concept of conductance in a corresponding way. This is easily done by writing a complex conductance G* as

$$G^* = G' + j\,G'' \qquad (3.3.8)$$

where G' is the "real" component and G" is the (algebraically) "imaginary" component. By analogy with (3.2.10) we may then set

$$G^* = 1 / Z \qquad (3.3.9)$$

and expanding this using (3.3.5) and (3.3.8) produces

$$G' = R_s / (R_s^2 + X_s^2) \qquad (3.3.10)$$

and

$$G'' = X_s / (R_s^2 + X_s^2) \qquad (3.3.11).$$

By calculating these components G' and G" from our values of R_s and X_s, we can use them as the rectangular coordinates of points on the complex conductance plane and thus reveal the complex conductance locus. If this is found to limit at very low and/or at very high frequencies then the symbols G_o and G_∞ are used to represent these limits.

By generalizing (3.2.3), we may now continue by defining a more fundamental property of the material, the complex conductivity

$$\sigma^* = \frac{d}{A}\, G^* \qquad (3.3.12)$$

and assuming $$\sigma^* = \sigma' + j\sigma'' \qquad (3.3.13)$$

we then have

$$\sigma' = \frac{d}{A} G' \qquad (3.3.14)$$

and $$\sigma'' = \frac{d}{A} G'' \qquad (3.3.15)$$

Calculating these components enables the complex conductivity locus to be drawn. If this has low and/or high frequency limits, they are represented by σ_o and σ_∞ respectively.

Finally, we may define a quantity known as the complex permittivity. This is

$$\varepsilon^* = \varepsilon_o \varepsilon_r^* = \sigma^* / j\omega \qquad (3.3.16)$$

Where ε_o is the permittivity of free space, 8.8543×10^{-12} Farads/metre, and ε_r^* is a complex relative permittivity (or complex relative dielectric constant), which has no units. It follows from (3.3.16) that

$$\varepsilon^* = \varepsilon' - j\,\varepsilon'' \qquad (3.3.17)$$

where $$\varepsilon' = \sigma'' / \omega \qquad (3.3.18)$$

and $$\varepsilon'' = \sigma' / \omega \qquad (3.3.19).$$

Using these equations the complex permittivity locus may also be derived, and this too we will find to be highly informative in succeeding Chapters. Whatever low and/or high frequency limits this locus may have are labelled $\varepsilon_o\ \varepsilon_s$ and $\varepsilon_o\ \varepsilon_\infty$ the symbol ε_s representing a "static" field value multiplied by the constant ε_o defined above.

3.4 Linearity and time-variance

In this thesis we shall be concerned to distinguish which electrical properties of the skin can be considered to be "linear", and under what conditions. In order to clarify this statement, suppose we think of skin as a "system", producing an "output" in response to an "input". An example of this would be the discussion in Sections 3.2 and 3.3, in which we were considering applying to skin an electric field (the input), and observing the flow of current which takes place in consequence (the output). Then from the definition of linearity used in the theory of systems (see e.g. Faulkner, 1969), we can say that a linear system is one whose output, due to a sum of (sets of) inputs, is the sum of the outputs which result when each (set of) input(s) acts separately. Such a linear system is said to satisfy the "principle of superposition". For example, for a linear electrical resistance, if a current $i_1(t)$ results from the application of a voltage $V_1(t)$, and $i_2(t)$ results from the application of $V_2(t)$, then $i_1(t) + i_2(t)$ will result from the application of $V_1(t) + V_2(t)$. Thus a resistance which obeys Ohm's Law is linear.

A second point relevant to the description of skin as a "system" is the following. It is usually assumed in the literature and in this thesis that during the course of making measurements on skin, its properties do not change. Such an assumption is equivalent to considering skin to be a "time-invariant" system, although as might be expected, this is only an acceptable approximation over short time intervals. In general, we must assume skin to be a "time-varying" system, the properties of which do indeed depend upon the time (and sometimes also upon the duration) of the measurement, and this is of course a good thing, since it provides additional physiological information.

3.5 Equivalent circuits

As the name suggests, an equivalent circuit is an electrical circuit which has the same, or an acceptable approximation to the same, electrical behaviour as the system it is intended to model. Alternatively, it is sometimes a circuit whose electrical behaviour is an analogue of some other type of behaviour of the system it is intended to model.

The term "equivalent circuit" is in practice also used to refer to just a diagram of an equivalent circuit as defined above. This is a very succinct way of conveying information about system behaviour to electrical engineers and others trained to interpret such diagrams, just as chemists can readily deduce information about the behaviour of chemicals from appropriate formulae and structural diagrams.

3.6 Relaxation times

If a system responds to an impulse or step-function perturbation of state with a response which is exponentially dependent upon elapsed time, then the time taken for about 63% of the response to be completed is known as the "relaxation time" of that system to a perturbation of that state.

It might alternatively be said that if following such a perturbation the rate of change of the response with time is proportional to the magnitude of the response at that time, then the reciprocal of the constant of proportionality is known as the "relaxation time", and the change takes place as an exponential function of time.

The concept of relaxation tims is much used in the design of equivalent circuits. In this context a relaxation time is often called a "time constant" of the circuit, and its magnitude is usually determined by some capacitance multiplied by some resistance, or by some inductance divided by some resistance (see e.g. Edminister, 1972, Ch. 16).

3.7 Distributions of relaxation times

It follows from the definitions given in Section 3.6, that if a system responds to an impulse or step-function perturbation of state with a response which is not exponentially dependent upon time, than to the extent that the the system may be approximated as linear and time-invariant, its response may be described in terms of the sum of responses resulting from the existence of a number of different relaxation times in the system, present according to some probability distribution. Such a probability distribution is known as a "distribution of relaxation times", often abbreviated to DRT. The mere possibility of such a description does not however provide sufficient proof of the actual physical existence of a particular distribution of relaxation times (see Daniel, 1967, p. 76).

The most thorough introduction I know of to the majority of the extant forms of DRT can be obtained from a discussion of them in the context of dielectric relaxation by Böttcher and Bordewijk (1978, Chs. 8 and 9).

3.8 Polarization impedance

The polarization impedance Z_p is an electrical circuit element of constant phase-angle originally employed to describe the impedance behaviour of electrode/electrolyte interfaces, although in fact the phenomena represented by it occur very much more generally, with or without a monotonic spatial gradient of electrical properties. It is indeed widely used in the general theory of dielectric and mechanical as well as semiconductive relaxation processes. Discussion of its biological significance usually begins by citing Fricke's paper of 1932 because this was the first presentation by a biophysicist of simple equations describing the electrical behaviour represented by the polarization impedance. People do not seem to have

realized, however, that these "classic" equations of the biological literature are not only wrong, but are also almost identical with equations available for many years due to the truly classic work of Hopkinson on dielectrics (Hopkinson and Wilson, 1897). The dielectric phenomenology of Hopkinson was rediscovered empirically by Philippson (1921) during studies of the impedance characteristics of biological materials, since fundamental physics representable by a polarization impedance often lies at the heart of relaxation processes in both inorganic and organic substances. Probably then it is Hopkinson, Philippson, and those who followed them (see Section 11.2) who really deserve the credit for the application of polarization impedance concepts to biology, and in view of the importance and general relevance of these concepts the most basic associated equations are given here for reference. This is unfortunately all too necessary because the very useful work of authorities such as Cole (1972) and Geddes (1972) has been spoilt by mixing up symbols in such equations. Moreover, since neither these authors nor Schwan (1968) have corrected Fricke's simple theoretical analysis, this too will be done here.

The constant phase-angle of the polarization impedance does not necessarily equal $\pi/4$, the ideal diffusional Warburg case (Cole, 1972, p. 181; Geddes, 1972). Thus more generally, if the subscript p indicates a frequency-dependent polarization element, the polarization impedance Z_p can be described by

$$Z_p = R_1 (j\omega\tau)^{-\alpha}, \tag{3.8.1}$$

which resolves into the equivalent series components

$$Z_p = R_{s1}(\omega\tau)^{-\alpha} + jX_{s1}(\omega\tau)^{-\alpha} = R_{sp} + jX_{sp}, \tag{3.8.2}$$

where α is a constant over a wide frequency range at a value between 0 and 1, the Warburg case having $\alpha = 0.5$, and the subscripts of 1 refer to the value at $\omega\tau = 1$ (cf. Cole, 1934). Then

$$R_{sp} = \frac{V_1}{I_1} (\omega\tau)^{-\alpha} \cos (\alpha\pi/2) \qquad (3.8.3)$$

and

$$- X_{sp} = \frac{V_1}{I_1} (\omega\tau)^{-\alpha} \sin (\alpha\pi/2) = \frac{1}{\omega C_{sp}}, \qquad (3.8.4)$$

where

$$C_{sp} = \frac{I_1}{V_1} \omega^{(\alpha-1)} \tau^{\alpha} \operatorname{cosec} (\alpha\pi/2) \qquad (3.8.5).$$

Thus a graph of log C_{sp} against log ω or log ($f = \omega/2\pi$) will have a slope of ($\alpha - 1$), or ($- m$). Similarly a graph of log R_{sp}, or log ($- X_{sp}$) against log f will be of slope ($-\alpha$), as will a graph of log $|Z_p|$ since

$$|Z_p| = (R_{sp}^2 + X_{sp}^2)^{\frac{1}{2}} = \frac{V_1}{I_1} (\omega\tau)^{-\alpha} = R_1 (\omega\tau)^{-\alpha} \qquad (3.8.6).$$

Such graphs are used, for example, by Geddes (1972) for electrodes, and for normal human skin by Barnett (1938).

The phase angle ϕ of Z_p is given by

$$\phi = \arctan (X_{sp}/R_{sp}) = -\alpha\pi/2 = -(1-m)\pi/2 \qquad (3.8.7),$$

this being the complement of the angle derived by Fricke (1932), to conform to modern convention, and negative due to the capacitative quality of X_{sp}. The most important attribute of ϕ is its frequency-independent value of between zero and $-\pi/2$, those for an ideal resistor and an ideal capacitor respectively.

In his paper of 1932, Fricke posited that at the time t_o an impulse of current $i\delta t_o$ passed across a metal/electrolyte interface. He then used a Duhamel superposition integral to infer that if the potential difference

across the interface caused by this transfer of charge decayed with the elapsed time $(t-t_o) = \Delta t$ according to $V(\Delta t) = V_o/(\Delta t)^m$, the polarization impedance would obey relationships of the form (3.8.3) to (3.8.7), which were confirmed by his and previous experiments. Unfortunately, however, Fricke did not point out that what he was calling a counter-EMF actually has the dimensions of a reciprocal capacitance, so that, in fact, his superposition integral for an impressed current $i = i_o \cos \omega t$ should really be

$$E = \int_{-\infty}^{t} \frac{i_o}{C(t-t_o)} \cos \omega t_o \, dt_o \qquad (3.8.7)$$

where $C(\Delta t) = 1/V(\Delta t)$. Using this with (3.8.9) exactly generates the relations (3.8.3) to (3.8.7), and shows that to correct the unphysical units of Fricke's succeeding expressions for R_{sp}, X_{sp} and C_{sp} we must take care to specify correctly the quantity which he called V_o. Now modern linear systems theory (Macdonald and Brachman, 1956; Faulkner, 1969; Wylie, 1975) shows that the "system transfer function" contains complete information about the system and hence specifies it completely. Consequently the polarization impedance (3.8.1), which is the reciprocal of the frequency response function and thus very directly related to the system transfer function, must be a property of the system that is invariant with respect to the form of the stimulation. Then, in particular, it is readily shown by the use of the well-known Fourier transform pair

$$F\left[(j\omega)^{-x}\right] = \frac{(\Delta t)^{x-1}}{\Gamma(x)} \qquad (3.8.8)$$

or its Laplace equivalent that by taking (3.8.1) as our starting-point the change of voltage with time after a unit impulse of current must be of the form

$$V(\Delta t) = \frac{V_1}{I_1 \tau} \frac{1}{\Gamma(\alpha)} (\Delta t/\tau)^{\alpha-1} = \frac{V_1}{I_1 \tau} \frac{1}{\Gamma(1-m)} (\Delta t/\tau)^{-m}, \quad (3.8.9)$$

which is in units of Farads^{-1} since it represents the voltage produced per applied unit quantity of charge. There is a danger in using something like Fricke's V_o because a different group of constants is involved for each type of stimulation of the system; for example, upon a unit step function of current at $t = 0$

$$V(\Delta t) = \frac{V_1}{I_1} \frac{1}{\Gamma(1-\alpha)} (\Delta t/\tau)^{\alpha} = \frac{V_1}{I_1} \frac{1}{\Gamma(2-m)} (\Delta t/\tau)^{1-m}, \quad (3.8.10)$$

which has units of ohms since it is the voltage produced per unit applied current. A similar result was given correctly by Cole in 1934 but confused again in his book of 1972 (p. 42).

It is, however, the more modern procedure to specify the system by means of its "indicial admittance", the current decay function after the application of a unit step of voltage at $t = 0$. For a bare polarization impedance this decay of current per unit of applied voltage is

$$(\Delta t) = \frac{I_1}{V_1} \Gamma(1 + \alpha) (\Delta t/\tau)^{-\alpha} = \frac{I_1}{V_1} \Gamma(2 - m) (\Delta t/\tau)^{m-1} \quad (3.8.11)$$

in admittance units. It is often associated with the name of Hopkinson, who early used a similar equation (Hopkinson and Wilson, 1897;Taylor, 1957; Daniel, 1967, pp. 83-86.

Finally, it should be noted that to obey the physical requirement of having not only a finite initial charge in the system as Δt tends to zero, but also a finite total charge transfer as Δt tends to infinity, the observed power-law decay of current resulting from step-potential stimulation has to have a knee between regions obeying different exponents. This does not imply two consecutive mechanisms (Salter, 1978a),but only that in real

physical materials the polarization impedance cannot be the only element in the equivalent circuit; one must add an ideal capacitance in series and another in parallel (Cole and Cole, 1941, 1942) when considering materials which are dominantly dielectric, or an ideal resistance in parallel and another in series when considering materials which are inhomogeneous conductors or semiconductors (e.g. Jonscher, 1975). Recalling that the relaxation characteristics of materials which obey the principle of superposition can always be modelled using an equivalent circuit with a distribution of relaxation times (DRT), and that for this reason concepts and algebra can be taken from one phenomenology and applied in another, we infer that if the DRT is of the Cole-Cole form (Cole and Cole, 1941), a polarization impedance can be used to simplify the representation of the equivalent circuit, regardless of whether the relaxation is dielectric, mechanical or semiconductive. It is all the more useful phenomenologically because even DRTs quite far removed from the Cole-Cole form can produce similar behaviour over a limited range of frequencies. I once tried to interpret the polarization impedance more thermodynamically by using the Cole-Cole energy criterion (Salter, 1978a) much invoked by Jonscher (e.g. 1978), but unfortunately the criterion has no physically simple equivalent in the time domain in which physical events actually happen (see Appendix H of this thesis, or Salter, 1978c). Indeed, for the case of dielectric relaxation, it has since proved possible to show analytically that screening *per se* is not sufficient to generate DRT-like behaviour. Jonscher's group too has abandoned the idea, and has reverted to a theory based upon something like DRTs, as we shall review in subsection 11.3.b.

3.9 Conductors, semiconductors, dielectrics and band theory

The response of materials to applied electric fields may be broadly classified in terms of their "direct-current (D.C.) conductivity", which can be calculated from (3.2.8) if I is the time-independent current produced in response to a constant applied field E.

If this conductivity is greater than about 10^3 ohm^{-1}/metre (Siemens/metre), the material is classed as a "conductor". From equation (3.2.5) it can be seen that the large D.C. conductivity of a conductor must result from a large value of the product of the number of mobile electric charges per unit volume, n, and the mobility of each charge, μ. Generally, in conductors such as metals, n is very large, and so the product $n\mu$ is large even though μ is in fact quite small.

Materials classed as "semiconductors" have D.C. conductivities in the range 10^3 S/m down to about 10^{-5} S/m. They may have a very wide range of carrier density n, and a similarly wide range of μ. Silicon and germanium provide examples of semiconductors.

Finally, materials are classed as "insulators", also called "dielectrics", if their D.C. conductivity is below about 10^{-5} S/m. They have a low conductivity because most of their charge carriers are restricted to moving within a small region of the material, and those carriers which may be able to move further within the material, although they have reasonable mobilities, are too few per unit volume to produce a moderate conductivity. Some examples of materials usually classed as dielectrics would be mica, glass and oil.

Now semiconductors are rather special in that the volume density of charge carriers free to move a long distance, ("free" carriers), n, depends very sensitively upon temperature. Such large alterations of n do not occur in either conductors or dielectrics. Conductors tend to be rather full of free carriers, making it difficult to get any more in, and because

there are so many, the removal of a few hardly makes any difference either. In dielectrics, it is very difficult to produce any more free carriers, and those that may be produced usually only stay free for very short periods of time.

The dependence upon temperature of σ_o, the D.C. conductivity of a semiconductor, can often be approximated by a simple "thermally-activated" or Arrhenius form

$$\sigma_o = \sigma_{HT} \exp(-\Delta E/kT) \qquad (3.9.1)$$

where σ_{HT} is some limiting high-temperature conductivity, ΔE is an "activation energy", or more strictly an activation enthalpy (see e.g. Kauzmann, 1942; Lewis, 1977), k is Boltzmann's constant and T is the absolute temperature. This dependence, (3.9.1), may serve as a hint that electrical conduction relies upon charge carriers being given by the thermal vibrations of the material (i.e. the kinetic energy of the atoms or molecules of its structure) enough energy to "pay back" their binding energy, escape from the site of their restriction of movement, and become able to travel freely through the material, contributing to its conductivity. However, only that fraction of carriers which are not trapped again at some site while moving between one electrode and the other can contribute to the D.C. conductivity (3.9.1).

As we will consider in very much greater detail in Chapter 11, these concepts indicate that there may be a common physical mechanism underlying the behaviour of at least some representatives of the classes conductor, semiconductor and dielectric; namely, that of charge carriers moving from binding-site to binding-site (these also sometimes being called "traps" or "localized states"), or even right through the material, by means of making energy exchanges with the thermal vibrations ("phonons") of that material.

In the case of conductors and crystalline semiconductors, some of these ideas have been available for many years as part of the so-called "band theory"

of electrical conduction in solids. Very simply, this suggests that when the atoms or molecules of a material are arranged in an ordered structure (such as a crystal), then electrons and holes (a "hole" being a lack of an electron), will find it specially easy to propagate their way through the material by entering spatially and energetically extended energy states known as "bands". Since electrons and holes are respectively carriers of negative and positive electric change, the band theory predicts how large D.C. conductivities may arise in such instances, and also gives an insight into why certain materials may be classed as "conductors", and others as "high-mobility crystalline semiconductors". (This necessarily shortened description of the band theory is however as woefully inadequate as calling the skin a bag for the body would have been in Chapter 2; a fuller yet still elementary introduction can be found in Wright, 1979, and a discussion adequate for most purposes in Kittel, 1976.)

Much more recently it has been realized that long-range order is not a necessary precondition for the applicability of band theory concepts (for a brief description see e.g. Smith, 1978, p. 485 ff, or Pethig, 1979, pp. 270-273, and for a fuller but less recent treatment see Mott and Davis, 1971). This realization has resulted from, and further encouraged, an increasing interest in the properties of "amorphous" materials whose electrical properties are those of the class of semiconductors. One of the main theoretical concepts involved in this extension of band theory is that in non-crystalline solids, charge carriers tend to be trapped by localized states distributed in energy within so-called "bandtails", these having energies intermediate between those of the bands which allow extended transport. Since a range of different activation energies may then be required to escape from a bandtail, depending on the "depth" of the particular localized state a charge carrier is occupying "below" the "conduction" band, there exists the possibility that such materials will display

a distribution of relaxation times, as we shall consider further in Chapter 11.

Finally, Lewis (1977) has drawn attention to the fact that these concepts, and especially that of bandtails, indicate that at least some materials classed as dielectrics are likely to be physically equivalent to semiconductors of low carrier density and restricted carrier mobility. There are very interesting corollaries to this conclusion, and in consequence some aspects of his monograph will be reviewed in detail in subsection 11.8.a.

Chapter 4. AN INTRODUCTION TO THE OBSERVED ELECTRICAL PROPERTIES OF SKIN

4.1 Introduction

There is a very extensive literature concerned with the electrical properties of human skin. Here, for example, is a list of some of the better publications of which a substantial part has been a review of various electrical properties of the skin: Rein (1929), Rosendal (1943, 1944, 1945), Rothman (1954), Lawler, Davis and Griffith (1960), Dorscheid (1960), Keller (1963), Tregear (1966), Pfister and Schulz (1966), Edelberg (1967), Venables and Martin (1967), Edelberg (1971), Fowles (1974), Woodrough (1976) and Edelberg (1977). Some other particularly relevant papers are: Rein (1926a, b, c and d), Gerstner and Gerbstädt (1949), Kryspin (1965), Yamamoto and Yamamoto (1976a) and those reviewed in Section 11.2.

Unfortunately however there appears to have been far too little digestion and systematization of information about the electrical properties of skin within this literature, as may be appreciated by reading it. Moreover, I am not aware of any publications which have dealt with the whole range of electrical properties of skin we will be considering in this thesis. (The closest approach was that of Tregear, 1966.) Consequently this Chapter attempts to provide a brief overview of all these properties, using information which in most cases has been available for many years, but which no-one seems to have distilled into a reasonable compass before. This Chapter, and Chapters 11 and 12, are indeed the result of six years of reading and systematizing the literature in German, English and French, and I hope they will save other people from needing to undertake a comparable amount of labour.

The two main Sections of this Chapter, 4.2 and 4.3, are intended to serve as introductions to the very much more detailed discussions presented in Chapters 9, 10, 11 and 12.

Section 4.2 and Chapter 11 will deal with those electrical properties of skin which are "linear and possibly only slowly time-variant". Firstly, with regard to linearity, this means those properties which obey the principle of superposition (see Section 3.4) in that to observe them requires an electrical perturbation of the state of the skin, and the magnitude of the electrical response produced is directly proportional to the magnitude of the perturbation. Secondly, assuming that these properties are possibly only slowly time-variant means that they need not, and are assumed not to, change during the course of an experiment, but only over longer time intervals. This for our purposes is equivalent to assuming them to be time-invariant, and we may therefore make use of interpretations involving distributions of relaxation times (Section 3.7).

Unfortunately, however, most, and perhaps all, electrical properties of skin ought really to be described as "non-linear and not necessarily slowly time-variant". Consequently Section 4.3 and Chapter 12 take this approach, yet since some properties are very non-linear but not rapidly time-variant, others are only a little non-linear but very rapidly time-variant, and others still are both highly non-linear and highly time-variant, it seemed most reasonable to me to extend the work of Gerstner and Gerbstädt (1949) and classify all these properties in terms of the phenomena which can be observed at different applied voltages. (Voltages are usually discussed in the literature rather than electric fields because of the uncertainty about the effective thickness of the skin.) Consequently the general classification of the electrical properties of skin presented in Section 4.3 and Chapter 12 will begin by describing the phenomena observed at zero applied voltage, and then continue by describing those observed at progressively higher applied voltages.

The Chapter then concludes by making use of the overview of the electrical properties of skin in a discussion of some of the deficiencies

in the electrical characterizations of the skin which have been made in the past, thus preparing the ground for the next Chapter, in which we will consider the design of a methodology for making new measurements to improve this characterization.

4.2 Linear and possibly only slowly time-variant properties

Certain electrical properties of skin are approximately linear, provided that no more than a few hundred millivolts are applied across the skin during its characterization.

If measurements of equivalent series resistance, R_s, and equivalent series reactance, X_s, are made using voltage magnitudes of this order (or indeed larger ones), then when plotted on the complex impedance plane they lie on a locus having the form of a minor arc of a circle, such as is shown drawn through the dots of Fig.4.2.I.

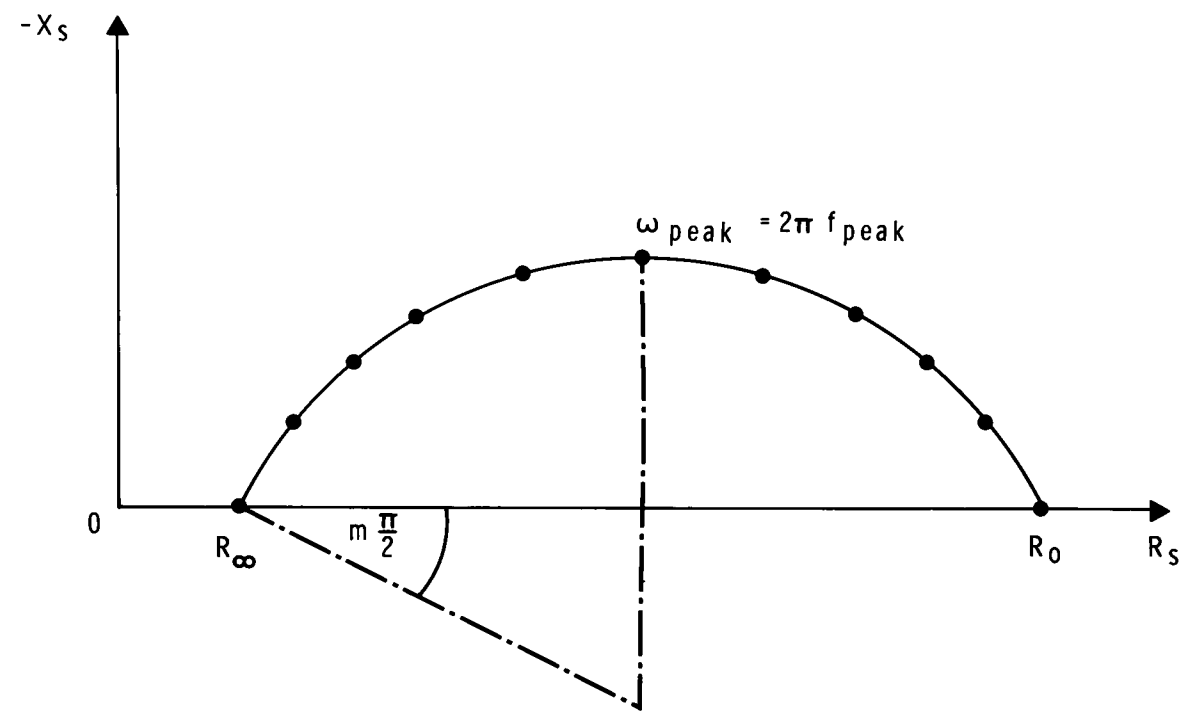


Fig.4.2.I

The locus has a high-frequency intercept R_∞, and a low-frequency intercept R_o, the D.C. resistance of the skin. The departure of the centre of the arc from the resistance axis is expressed in terms of the angle $m\pi/2$, in turn defining the parameter m, which has a value between zero and one.

Following the same reasoning and making the same tests as were used by Cole and Cole (1941, p.346) to analyse complex permittivity data, it can

be concluded that the (linear) complex impedance of skin is very well described by the Cole equation shown in Fig. 4.2.II. This empirical

$$Z = R_\infty + \frac{R_0 - R_\infty}{1 + (j\omega\tau_p)^{1-m}}$$

$$\tau_p = 1/\omega_p = 1/(2\pi f_p)$$

Fig. 4.2.II

equation was proposed by Cole in 1940 to describe the complex impedance of certain biological tissues, and it has been widely employed since. (Its labelling by Schwan, 1957, Brown and Kastella, 1965, and Khallafalla et al., 1971, is however less consistent with other relevant literature than is the form used here.) The quantity τ_p is a time-constant, and m is a dimensionless numerical constant as we have already implied above.

The relationships

$$j^x = \exp[jx(\pi/2)] \qquad (4.2.1)$$

and

$$\exp(jy) = \cos(y) + j\sin(y) \qquad (4.2.2)$$

enable the Cole equation to be rationalized and separated into its equivalent series components

$$R_s = R_\infty + \frac{(R_o - R_\infty)\ \{1 + \sin\ [m(\pi/2)]\ (\omega\tau_p)^{1-m}\}}{1 + 2\ \sin\ [m(\pi/2)](\omega\tau_p)^{1-m} + (\omega\tau_p)^{2(1-m)}} \qquad (4.2.3)$$

$$-X_s = \frac{(R_o - R_\infty)\ \{\cos\ [m(\pi/2)]\ (\omega\tau_p)^{1-m}\}}{1 + 2\ \sin\ [m(\pi/2)]\ (\omega\tau_p)^{1-m} + (\omega\tau_p)^{2(1-m)}} \qquad (4.2.4)$$

and these and the corresponding values of $|Z|$ and θ, namely

$$|Z| = \left[R_\infty^{\,2} + \frac{(R_o-R_\infty)\{(R_o-R_\infty) + 2R_\infty\ (1+\sin[m(\pi/2)](\omega\tau_p)^{1-m})\}}{1 + 2\ \sin\ [m(\pi/2)](\omega\tau_p)^{1-m} + (\omega\tau_p)^{2(1-m)}}\right]^{\frac{1}{2}} \qquad (4.2.5)$$

$$-\theta = \arctan\ (A/B)$$

$$A = (R_o-R_\infty)\ \{\cos[m(\pi/2)]\ (\omega\tau_p)^{1-m}\}$$

$$B = R_\infty\ \{1 + 2\ \sin\ [m(\pi/2)]\ (\omega\tau_p)^{1-m} + (\omega\tau_p)^{2(1-m)}\}$$

$$+ (R_o-R_\infty)\ \{1 + \sin\ [m(\pi/2)]\ (\omega\tau_p)^{1-m}\} \qquad (4.2.6)$$

are sufficiently complicated to reveal the many published multi-subject or multi-patient measurements of R_s, X_s, $|Z|$ or θ at a single frequency ω as being fundamentally ambiguous, since they could be produced by many different values of the fundamental quantities R_∞, R_o, τ_p and m. It is therefore a waste of time to try to draw conclusions about the state of the skin, as indicated by its linear electrical properties, from anything other than a

plot of the full complex impedance locus, or some other diagram containing enough information to determine the values of R_∞, R_o, τ_p and m uniquely.

The complex impedance described by the Cole equation corresponds to that of either one of the irreducible equivalent circuits shown in Fig. 4.2.III (see also Section 11.2). Each boxed element is a polarization impedance (Section 3.9). The inclusion of a polarization impedance in an equivalent circuit



Fig. 4.2.III

usually implies that there exists in the material a number of different relaxation times present according to some probability distribution (Section 3.7), although in fact it need not (see Appendix H). The distribution of relaxation times in skin, implied whenever its Z locus has a non-zero value of m, may arise within each and every cell membrane (Cole and Jahn, 1937; Cole, 1940; Schwan, 1957; Cole, 1968), or as a result of grosser structural inhomogeneity, one possibility being a change with depth in the electrical properties of the stratum corneum (Barnett, 1938; Tregear, 1966;

Yamamoto and Yamamoto, 1976b), or perhaps in both ways. A detailed investigation of the problem is presented in Chapter 11.

Having derived the value of τ_p from the Z locus using

$$\tau_p = 1/\omega_{peak} \qquad (4.2.7)$$

it is possible to derive values for the time constants

$$\tau_A = ((R_o-R_\infty)/R_{1A})^{\alpha}.\tau_p \qquad (4.2.8)$$

and

$$\tau_B = (R_o^2/(R_{1B}(R_o-R_\infty)))^{\alpha}.\tau_p \qquad (4.2.9)$$

using

$$\alpha = 1-m \qquad (4.2.10)$$

and values of R_{1A} and R_{1B} chosen on some external basis. Such a choice is necessary because there is no way involving changes in frequency (or in time) of uniquely separating the contributions of R_1 and τ to each polarization impedance; they form part of a complex constant against which frequency acts. For example, Tregear (1966, p.65) called this constant k and denoted the complex impedance of the boxed element by

$$\tau_p = kf^{m-1} \qquad (4.2.11)$$

so

$$k = R_1 (2\pi j\tau)^{m-1} \qquad (4.2.12)$$

Consequently k should have units of resistance x $(\text{time})^{m-1}$. Although k

can be determined quite easily, R_1 and τ cannot be extracted uniquely from within it. It is therefore necessary to make some assumptions about the relationship of R_1 to R_o and R_∞ if the associated value of τ is to be derived from the Z locus using (4.2.7) and either (4.2.8) or (4.2.9).

Most of the literature uses circuit A with the arbitrary choice

$$R_{1A} = (R_o - R_\infty) \qquad (4.2.13)$$

just because this arbitrary value conveniently gives $\tau_A = \tau_p$. However, the use of circuit B may perhaps provide more physical insight, and if on theoretical grounds the time constant τ_B is expected to be of the Debye form

$$\tau_B = (\varepsilon_s - \varepsilon_\infty) / (\sigma_\infty - \sigma_o) = \tau_D \qquad (4.2.14)$$

then it is most convenient (though still arbitrary) to set

$$R_{1B} = 1/(\sigma_\infty - \sigma_o) = R_o R_\infty / (R_o - R_\infty) \qquad (4.2.15)$$

whereupon using (4.2.9), the Cole equation may be rewritten as

$$Z = R_\infty + \frac{(R_o - R_\infty)}{1 + (R_o/R_\infty)\ (j\omega\tau_D)^{1-m}} \qquad (4.2.16)$$

However, the arbitrary nature of these substitutions is an indication of the need for an adequate theory with which to interpret the fact that the complex impedence of skin obeys the Cole equation.

Chapter 11 will attempt to provide such a theory, based on the idea that skin is a semiconductor. Certainly measurements of R_o as a function of temperature indicate that skin has an activated D.C. conductivity (see subsection 9.2.c). Furthermore, the Cole equation corresponds to complex conductivities of the form

$$\sigma^* = \sigma_o + \frac{\sigma_o \left[1 + (\sigma_o/\sigma_\infty)\right] (j\omega\tau_p)^{1-m}}{1 + (\sigma_o/\sigma_\infty) (j\omega\tau_p)^{1-m}} \qquad (4.2.17)$$

and in the case of skin the approximation $(R_\infty/R_o)\to 0$ is quite reasonable, implying that $(\sigma_o/\sigma_\infty)\to 0$ and that over a wide range of frequency the complex conductivity of skin is approximately given by

$$\sigma^* \simeq \sigma_o + \sigma_o (j\omega\tau_p)^{\alpha} , \quad (1>\alpha>0) \qquad (4.2.18)$$

a behaviour typical of many semiconductive materials.

4.3 Non-linear and not necessarily slowly time-variant properties

4.3.a At zero and all larger magnitudes of applied voltage

As soon as an area of skin is covered by an electrode, an electrolyte solution, or both, there begins a very slow (and ever slowing) increase in the conductance of that skin with a time constant of the order of ten minutes. The progress of this slow increase in conductance is however affected by the time-course of the magnitude and polarity of whatever electric field is applied.

This behaviour has been reported by Rein (1926b, Figs 4-7), Rosendal (1943, pps. 137, 138), Blank and Finesinger (1946, pps. 552-556), Edelberg and Burch (1962, Fig.2), Khallafalla et al. (1971, Fig.7), Geddes and Steinberg (1973), and various others.

4.3.b at zero applied voltage

If no electric field is applied to the skin it is only possible to observe the difference in electrical potential between a skin site of interest and some reference site, which may for example be another skin area. The measured potential will however depend upon the electrical conductance of the skin (see Section 12.3), and will therefore be altered by the effects described in the last subsection.

4.3.c at very small applied voltages

When continuously monitored for periods of less than a few minutes, and/or if the trend described in subsection 4.3.a has equilibrated, the prevailing skin conductance is not noticeably dependent upon the applied voltage magnitude, the applied voltage polarity or the duration of voltage application, and its properties approximate to being linear, as described in Section 4.2.

This behaviour has been reported by Rosendal (1944, p.201), Gerstner and Gerbstädt (1949), who called it "region a", Edelberg (1967, pps. 18, 19) and Cambrai et al. (1979, Fig.1), amongst others, for applied voltages less than 0.1V (Rosendal, 1944), less than 0.8V (Gerstner and Gerbstädt, 1949), less than 0.25V (Kryspin, 1965) or less than 0.5V (Edelberg, 1967).

4.3.d at small applied voltages

Above a certain voltage threshold of magnitude dependent upon the polarity of the probe electrode compared with that of the fixed charge of the stratum corneum, skin conductance increases with increase in the applied voltage magnitude, independent of the applied voltage polarity. This phenomenon is "time independent" in the sense that the time-course of the increase in conductance produced in response to a sudden increase in applied voltage magnitude is too rapid to be observed.

This behaviour has been reported by Gerstner and Gerbstädt (1949) who called it "region b", Kryspin (1963) who called it "time-independent non-linearity", and for rat skin by Cambrai and Do Linh (1974, Figs. 4 and 5).

The appropriate voltage range is at least 0.25V (Kryspin, 1965), at least 0.5V (Cambrai et al.,1979), or at least 0.8V (Gerstner and Gerbstädt, 1949)

4.3.e at medium applied voltages

Above a certain voltage threshold of larger magnitude again dependent upon the polarity of the probe electrode compared with that of the fixed charge of the corneum, skin conductance increases or decreases with time depending on the polarity of the probe electrode compared with that of the fixed charge of the corneum. These perturbations of conductance are reversible, and the applied voltage magnitude determines their maximum amplitude and the time-constant governing the approach to equilibrium. The time constant of this ambivalent process is of the order of tens of seconds, which is much shorter than that governing the slow monotonic increase in conductance described in subsection 4.3.a.

This behaviour has been reported by Gildemeister and Kaufhold (1920, pps.156, 157), Ebbecke (1922, pps. 320, 321), Rein (1926b, Figs. 4-7), Rosendal (1943, Figs. 4-6), Rosendal (1944, Figs.2-5), Gerstner and Gerbstädt (1949), who called it "region c", Kryspin (1965) who called it "true-dependent non-linearity", and various others.

The appropriate voltage range is less than or equal to 2V (Rosendal, 1943), greater than 3V (Gerstner and Gerbstädt, 1949), or at least 0.52V (Kryspin, 1965).

4.3.f at large applied voltages

If the current density flowing through the skin exceeds a certain threshold value, then after a short latent period of a few seconds, the conductance of that skin increases very abruptly and substantially, increasing still further with increase in the magnitude and/or the duration of application of the applied voltage. The threshold value of current density depends on the polarity of the electrode compared with the polarity of the fixed charge of the stratum corneum, and also upon the pH of the contact electrolyte. The occurrence of this "electrical breakdown" is associated with a local inflammatory response of a severity depending on the current density employed and the duration of its flowing. Sensations of itching, burning or pain, local hyperaemia or even whealing may all be induced.

This behaviour has been reported by Ebbecke (1923, p.202), Rein (1926c), Rosendal (1943, e.g. Fig.3), and various others. The critical current density usually occurs at applied voltages of the order of several volts.

4.4 Some limitations of past characterizations of the electrical properties of skin

Having briefly described the phenomenology of the electrical properties of skin, it is now possible to point out some limitations of various previous investigations in this field, and thus to justify the work reported in this thesis.

One limitation which is particularly frustrating to those with dermatological interests is that very few instigators have attempted to define the properties of a single skin region in vivo. The techniques employed have usually produced results appertaining to a number of different skin regions measured together, it being very difficult to separate them (see Chapter 6).

Another limitation is that most investigators seem to have been unaware of, or have not adequately allowed for, the effects of electrode gel or contact electrolyte on the properties of the skin, effects which unfortunately are very important (see subsection 4.3.a and Section 12.2).

Concerning the linear electrical properties of skin, many investigators seem not to have realised that these are described by the Cole equation, and consequently have been content to use measurement techniques which are only very poorly suited to characterizing the linear electrical properties of skin in terms of the parameters of this equation. Many people have for example applied square waves to the skin (e.g. Lykken, 1971), yet an impedance obeying the Cole equation, as skin is known to do, has a very complicated response to a square wave, as can be seen from the work of Poon and Choy (1978). The complicated nature of this response means that it is difficult to identify the best-fitting values of τ_p and of m. Some investigators have however chosen to ignore the existence of a non-zero value of m, thus treating the polarization impedance as a pure capacitor, a shocking

approximation, since the value of m is of considerable physiological interest, as will be shown in Chapters 10 and 11. For example Burton et al. (1979) made this approximation in a paper on the Bode analysis of skin impedance which seems to have profoundly misunderstood the work of K.S. Cole, and such laxity has since misled others into emulating it, (e.g. Reichmanis et al., 1978; Jackson et al., 1980).

There is also an unfortunate number of papers in the literature which are almost useless because their authors did not realise that measurements made at only one frequency are fundamentally ambiguous (as is pointed out in Section 4.2 and subsection 10.1.b).

Moving on to consider the non-linear electrical properties of skin, it seems that many investigators did not realize that there were such things, or that such properties might affect their results. Moreover, even those authors who did recognise that the electrical properties of skin are in general non-linear, nonetheless usually appeared to be unaware of the complexity of the phenomenology (compare e.g. Stephens, 1963, with the contents of Section 4.3).

Another limitation of quite a few characterizations of the electrical properties of skin has been the carrying out of an inadequate number of experiments before proceeding to publish the conclusions, this hasty approach being particularly regrettable in papers which have subsequently been widely quoted. For example, Plutchick and Hirsch (1963) made measurements on only two subjects, and for the particularly interesting work of Yamamoto and Yamamoto (1976a, 1976b), there seems to have been only one.

Finally, one may easily find a large number of papers so awful that it is not worthwhile to attempt to criticise them. They are naive methodologically, or dermatologically, or in both ways, and many have been written by people who seem anxious to provide apparently objective evidence in favour of strange philosophies or cults. It would be a disservice to

further publicise such papers, and it is sad that they have tended to bring the subject of skin electrophysiology into disrepute.

In view of these limitations of past characterizations of the electrical properties of skin, the making of new measurements will now be considered.

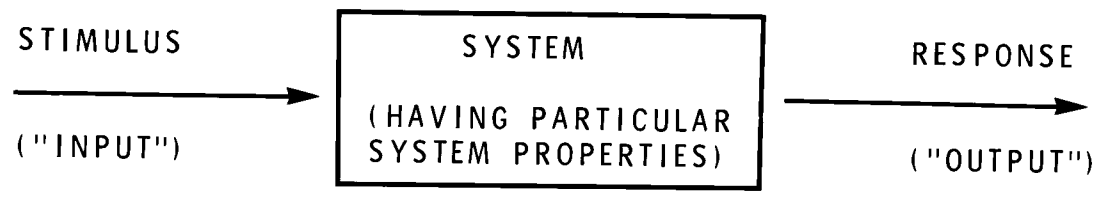
PART II: MAKING NEW MEASUREMENTS

Chapter 5. A GENERAL APPROACH TO THE MEASUREMENT OF THE ELECTRICAL PROPERTIES OF SKIN IN VIVO

5.1 Skin as a "Black Box"

We are presented with skin as a biological "system", a "black box", the properties of which we want to define. This sort of problem is very common in physical science and technology (see e.g. Faulkner, 1969), and the accepted ways of solving it are slowly finding their way into biology (see e.g. Grodins, 1963; Marmarelis and Marmarelis, 1978).

In general, we define the properties of a system by what it does when it is given a particular form of stimulation (Figure 5.1.I). This applies in biology too: kick a dog and you will observe behaviour which may be termed "dog-like" (and may be painful!).



The response of a system to a known stimulus defines the properties of that system.

Fig. 5.1.I

Usually however we only investigate simpler systems and use simpler and more precisely regulated inputs to do so. Also for simplicity, we are going to assume for the time being that during the course of a typical experiment the system in which we are interested, skin, does not significantly change its properties, and may thus be approximated as a "time-invariant system". Those versed in the theory of systems will as we continue be able to note other assumptions which in the interests of space and clarity are not mentioned explicitly here.

Indeed, we are going to refer very loosely to the output divided by the input as the "generalized impedance" of the system. Thus in particular, when the system is investigated by applying an electrical input and measuring the electrical output, one is of course characterizing its electrical properties, and these are (all) embodied in the "generalised electrical impedance", which we will denote by "Z".

We have already decided to characterize the properties of the system in which we are interested, skin, electrically, and it is because of the very complicated nature of the electrical behaviour of skin that we need the *entirely general* and perhaps rather unfamiliar way of describing it which will be developed in this thesis. Less fundamental approaches are unable to inter-relate the multifarious aspects of this complicated electrical behaviour and so in the past the literature has been "compartmentalized" into descriptions of the alternating-current properties of skin, its direct-current current/voltage characteristic curve, the skin potential level and so on. All these however appear quite directly from the formalism we will develop in this Chapter and hence they can be commonly represented by it. *We can therefore finally overcome the artificial compartmentalization of the literature.*

5.2 System characterization in the time domain and in the frequency domain

5.2.a Introduction

The characterization of systems is neither a small subject nor a simple one, and so it is suggested that the general review by Marmarelis and Marmarelis (1978) be consulted to amplify and correct the simplistic statements with which we must be content here.

Generally speaking, however, the choice between methods of system characterization depends upon the choice of the form of the input to the system. Here we may consider only simple forms of input, and these can be divided into two basic types.

The first type of input produces an abrupt disturbance of the system, and classical forms of such a disturbance are the impulse, delta or spike function, the step function and the ramp function (see e.g. Grodins, 1963 p.29). Impressing such an input upon the system, and relating the system output to the input, is what we mean by characterizing a system in the time domain. The whole procedure is also known as "transient analysis".

The second type of input does not produce an abrupt disturbance of the system. The classical form of this input is that of a sine wave at a particular frequency. Relating the system output to such an input, and repeating the process for very many input frequencies, is what we mean by characterizing a system in the frequency domain. The procedure is also known as frequency analysis.

We must note however that although these two approaches to system characterization give equivalent information about system properties when the system is linear, this is NOT necessarily so when the system is non-linear. Therefore we must choose between them.

5.2.b Time-domain methods

The time-domain approach to system characterization is very popular, and even if we restrict ourselves to time-domain methods which might after some modifications be applicable to characterizing the electrical properties of skin, there is still an appreciable number of recent and relevant papers. These include the publications of Farber and Ho (1969) on characterizing electrical networks, Pilla (1970) on electrode kinetics, and Bottelberghs (1978) on solid electrolytes. Moving closer to the field of interest of this thesis, there is the work of Singh et al., (1979) on characterizing the dielectric properties of body tissues in vivo using techniques developed from Hyde (1970), and the work of Kent (1980) on characterizing the dielectric properties of fish muscle in the frequency range 20Hz to 10kHz.

I know however of only two papers which apply a time-domain approach to the particular case of the characterization of the electrical properties of human skin, and the horribly simplistic publication by Reichmanis et al. (1978) contrasts sharply with the excellent paper by Poon and Choy (1978). (Comparing one with the other will show that these comments are not undeserved!)

5.2.c Why we chose a frequency-domain method

There appears to be some doubt as to whether or not frequency-domain methods are better or worse than time-domain methods. Marmarelis and Marmarelis (1978, p.72) say that frequency-domain methods are generally better, and particularly so in helping to diminish the effect of "noise". Bottelberghs (1978, p.152) however says the reverse, thus favouring time-domain methods. Poon and Choy (1978, p.639), considering the particular case of measurements on human skin, agree that the time-domain approach may be better, but only marginally so.

We however decided upon a frequency-domain approach, and did so for three main reasons.

Firstly, we wanted to ensure the ready comparability of our results with those of the majority of previous investigators. They had made measurements in the frequency domain, and if we did not do likewise, attempting to transform our results over from the time-domain would be at worst suspicious, given the known non-linearity of skin, and at best highly inconvenient and probably inaccurate.

The second reason was to maximise mathematical simplicity, since as Marmarelis and Marmarelis note (1978, p.75), the integral equations relating input and output in the time-domain become algebraic equations in the frequency domain. This is especially useful in determining and describing the particular form of the linear electrical properties of human skin; compare the time-domain equivalent of the Cole equation obtained by Poon and Choy (1978) with the Cole equation itself (Fig. 4.2.II), or, for analogous algebra, compare Cole and Cole (1941) with Cole and Cole (1942).

The third reason is that, as Marmarelis and Marmarelis again note, (1978, p.75), the frequency domain permits a neater description of the properties of composite systems, even if the system is non-linear. Skin, of course, is a non-linear and certainly composite system, as we shall review in detail in Chapter 12.

Having however opted to investigate a composite non-linear system in the frequency domain, it is then necessary to develop a suitable mathematical approach.

5.3 The frequency-domain characterization of electrical impedances

5.3.a The generalized electrical impedance to sinusoidal stimulation

Let us now see how the "generalized electrical impedance" discussed in Section 5.1 can be described by a set of electrical properties which may be divided into two subsets composed of "linear" properties and "non-linear" properties respectively. Later, Chapter 8 will show in more detail how these two subsets define quantities already familiar in various compartments of the literature of skin electrophysiology.

Suppose a current "I" is passed through whatever generalized electrical impedance is being considered. Then there will in general be, whether or not there was before, a difference of electrical potential across the impedance. Suppose we then arrange to measure this voltage, "V", and to monitor it as the "output" from the system.

Now it is desirable that the electrical input to the system should have some simple form, because, if it were complicated, the system would be likely to behave in a complicated way in response to it. Because we have opted to work in the frequency domain, we therefore choose the input current to be a pure sine wave. Then from the relationship we discussed in Section 5.1

$$\text{output} = \text{input} \times [\text{generalized impedance}] \qquad (5.3.a.1)$$

we expect

$$V_{output} = I_{input} \times [\text{generalized electrical impedance}] \qquad (5.3.a.2)$$

and in particular

$$V(t) = B \sin\left(2\pi \frac{t}{T_o}\right) \times [\text{generalized electrical impedance}] \qquad (5.3.a.3)$$

if the input current has a peak-to-peak amplitude B and repeats after a time interval T_o. Indeed, because the input is periodic we can expect the output V(t) to be periodic too, with the same period T_o. It may well not be a pure

sine wave however. Consequently its departure from the form of a pure sine wave can be used to characterize the generalized electrical impedance, which acts upon the pure sine wave to produce this departure (cf. Cherry and Rivlin, 1941). Thus by rigorously characterizing V(t) we can rigorously characterize the generalized electrical impedance.

Now a standard and rigorous way of characterizing a periodic waveform of absolutely any shape, so long as it obeys the Dirichlet conditions in having only a finite number of finite discontinuities within its repetition period T_o, is to represent it as a constant plus the sum of various simple waves of particular frequencies, integer multiples (harmonics) of $f = 1/T_o$ in fact. This "expansion in a Fourier series" looks like

$$V(t) = C + a_1 \cos(2\pi\frac{t}{T_o}) + b_1 \sin(2\pi\frac{t}{T_o}) + a_2 \cos(4\pi\frac{t}{T_o}) + b_2 \sin(4\pi\frac{t}{T_o}) + \ldots \quad (5.3.a.4)$$

$$\text{or} \quad V(t) = C + \sum_{n=1}^{n=\infty} [a_n \cos(n2\pi\frac{t}{T_o}) + b_n \sin(n2\pi\frac{t}{T_o})] \quad (5.3.a.5)$$

Thus (5.3.a.3) becomes

$$V(t) = B \sin(2\pi\frac{t}{T_o})\left[\frac{C}{B \sin(2\pi\frac{t}{T_o})} + \frac{a_1\cos(2\pi\frac{t}{T_o})}{B \sin(2\pi\frac{t}{T_o})} + \frac{b_1\sin(2\pi\frac{t}{T_o})}{B \sin(2\pi\frac{t}{T_o})} + \frac{a_2\cos(4\pi\frac{t}{T_o})}{B \sin(2\pi\frac{t}{T_o})} + \frac{b_2\sin(4\pi\frac{t}{T_o})}{B \sin(2\pi\frac{t}{T_c})} + \ldots\right] \quad (5.3.a.6)$$

and using $j = \sqrt{-1}$ the generalized electrical impedance can be written as

$$Z = \underbrace{\frac{b_1}{B} + j\frac{a_1}{B}}_{\text{"linear" properties}} + \underbrace{\frac{C + a_2\cos(4\pi\frac{t}{T_o}) + b_2\sin(4\pi\frac{t}{T_o}) + \ldots\ldots}{B \sin(2\pi\frac{t}{T_o})}}_{\text{"non-linear" properties}} \quad (5.3.a.7)$$

We will assume temporarily that effects due to the "linear" properties are in some sense directly proportional to the magnitude of the input and thus obey the principle of superposition. Such obedience is the criterion for "linearity" in a system (see Section 3.4 or Faulkner, 1969). The coefficients of order greater than one (a_2, b_2, a_3, b_3 ...) characterize what is usually called non-linear distortion and the constant C is classed with these non-linear terms because any asymmetry of response (with respect to the sign of the stimulus) reflects non-linear properties which, if present, will cause partial rectification and contribute to the value of C which is observed. The remainder of the observed value of C is made up from the average output for zero input, and this is also a non-linear property of the system.

Since we know the form of the input stimulation, the generalized electrical impedance can therefore be completely described using the so-called Euler coefficients C, a_1, b_1, a_2, b_2 ... and <u>if we can determine these we will have completely specified the properties of the system</u>, which may for example be skin. All we need to do to determine the Euler coefficients is to measure V(t) for a time period T_o and then as is well known (see e.g. Wylie, 1975, Section 6.2)

$$C = \frac{1}{T_o}\int_0^{T_o} V(t)\ dt \qquad (5.3.a.8)$$

$$a_n(V) = \frac{2}{T_o}\int_0^{T_o} V(t)\ \cos\left(n2\pi\frac{t}{T_o}\right)dt \qquad n = 1, 2, 3 \ldots \qquad (5.3.a.9)$$

$$b_n(V) = \frac{2}{T_o}\int_0^{T_o} V(t)\ \sin\left(n2\pi\frac{t}{T_o}\right)dt \qquad n = 1, 2, 3 \ldots \qquad (5.3.a.10)$$

Actually, because we have to sample the value of V(t) at certain times, these integrals degenerate into weighted summations, as we shall see in a moment. Also, although a_n for n = 0 is not really defined, if we calculate it from (5.3.a.9) we find $a_o = 2C$. Thus (5.3.a.8) is often abandoned and C written and calculated as $\frac{1}{2}a_o$.

5.3.b Measuring the Euler coefficients

In practical applications such as ours, the input waveform has only a finite length in time and the Fourier series (5.3.a.5) tends towards the Fourier transform ("F.T."). (For this reason, the equipment described in Chapter 7 was called a Fourier Transform Impedance Analyser.) Also, since we are compelled to sample the waveform and thus do not know it in its entirety, the formulation of the discrete Fourier transform must be applied (Brigham, 1974). Certain important constraints ((1) to (4), op. cit. p.102) must be adhered to, but then if a total of N samples of the waveform are taken at equally-spaced time intervals T such that $NT = T_o$ and the kth sample is taken at time $t = kT$, we can write (5.3.a.9) and (5.3.a.10) as

$$a_n = \frac{2}{N} \sum_{k=o}^{k=N-1} V(kT) \cos\left(n2\pi\frac{k}{N}\right) \qquad (5.3.b.1)$$

$$b_n = \frac{2}{N} \sum_{k=o}^{k=N-1} V(kT) \sin\left(n2\pi\frac{k}{N}\right) \qquad (5.3.b.2)$$

$$\text{and in particular} \quad C = \tfrac{1}{2}a_o = \frac{1}{N} \sum_{k=o}^{k=N-1} V(kT) = \frac{\text{sum of sample values}}{\text{number of samples}} \qquad (5.3.b.3)$$

which is obviously the mean value of the function V(t).

Now if we do not want to be restricted to sampling, storing and processing only one repetition period ("truncation interval") T_o, but rather wish to deal with c complete cycles of the waveform in a redefined truncation interval $T_c = 1/f_c$, then what is really the fundamental frequency f in this wavetrain will appear as the cth harmonic of the redefined wavetrain frequency f_c. Thus to obtain the nth harmonic coefficients of the true fundamental frequency f, we have to calculate instead of the right-hand sides of (5.3.b.1) and 5.3.b.2) the quantities

$$a_n = \frac{2}{N_c} \sum_{k=o}^{k=N_c-1} V(kT) \cos\left(nc2\pi\frac{k}{N_c}\right) \qquad (5.3.b.4)$$

$$\text{and } b_n = \frac{2}{N_c} \sum_{k=o}^{k=N_c-1} V(kT) \sin\left(nc2\pi\frac{k}{N_c}\right) \qquad (5.3.b.5)$$

where N_c is the total number of samples taken in the full truncation interval $T_c = cT_o$.

5.3.c Linear properties as a subset of the not necessarily linear properties

We have seen that the properties of a generalized electrical impedance must in general be considered to be not necessarily linear, indeed that was the reason for our introducing the concept of a generalised electrical impedance in the first place. This (infinite) set of not necessarily linear properties, which describes the generalized electrical impedance completely, may if desired by separated into two subsets of properties which may be termed "linear" and "non-linear" respectively. We in fact made such a separation in equation (5.3.a.7).

Now the "linear" properties defined by equation (5.3.a.7) correspond to the "describing function" of Marmarelis and Marmarelis (1978, eqn.3.151) in that b_1 and a_1 may well depend upon B unless B is sufficiently small. Only when they are independent of B can they be considered to be truly linear properties. Fortunately, in the case of skin, a range of B does exist in which the "linear" properties are indeed truly linear (see subsection 4.3.c and Section 12.4).

This subset of the not necessarily linear properties

$$Z = \frac{b_1}{B} + j\frac{a_1}{B} \qquad (5.3.c.1)$$

is probably more familiar when rewritten as the complex electrical impedance

$$Z = R_s + jX_s \qquad (5.3.c.2)$$

which the generalized electrical impedance reduces to if the Euler coefficients of order other than 1 can be neglected. However, insofar as R_s and X_s depend upon B, it is undesirable to neglect these coefficients.

In the case of skin, the electrical properties are usually significantly non-linear (as we shall see in detail in Chapter 12), and consequently the complex electrical impedance is only a sufficient description of the electrical

properties of skin so long as it remains independent of input amplitude. To be safe, we should therefore measure and assess the whole set of not necessarily linear properties, thus treating the skin as a generalized electrical impedance, and only disregard the non-linear properties in cases in which they are proved to be insignificant. This is the approach taken in this thesis.

The next three Chapters will describe ways of measuring the generalized electrical impedance of particular skin regions in vivo.

Chapter 6. MULTIPLE ELECTRODE METHODS

6.1 Some properties of electrodes

Having considered how best to characterize electrical impedances, we must now discuss how to make the necessary measurements. Let us begin by considering the properties of the electrodes we must use to apply an electric field across the material whose electrical properties we are trying to determine. It is necessary to consider these electrode properties in order to distinguish them from the properties of the material being characterized.

The electrical properties of "biomedical" electrodes have been thoroughly examined by Geddes and Baker (1968), Schwan (1968), Geddes (1972), Hill (1973), and Grings (1974). The electrode/electrolyte interface upon which these characteristics depend has been well described by Greatbatch (1974) and by Albery (1975). Therefore only some relevant practical aspects need be summarized here.

The electrode/electrolyte charge distribution determines the electrical impedance of the interface, the half-cell potential difference across it, and the rather large capacitance associated with it due to the very small separation of the planes of opposite charge. This "double-layer" capacitance increases with area increase upon surface roughening, for example by platinization, and with the reduction of charge separation when temperature or electrolyte concentration is increased. Hence following for example Epelboin et al. (1974) and Albery (1975), the interface can be represented over some frequency range by a lumped-component equivalent circuit in which a pure resistance is in series with a parallel combination of the half-cell voltage, the double-layer capacitance and the so-called Faradaic leakage pathway (cf. Baker, 1971), the latter being a polarization impedance whose α value is not necessarily equal to 0.5, the Warburg case, (N.b. Geddes' (1972) "α" is really what everyone else calls "m", including Fricke (1932) and Section 3.8 above.) This approximate equivalent circuit

produces impedance locus plots like the Sluyters diagrams of Albery (1975, Figs. 3.34 and 3.35), but cannot represent the more complicated phenomena occurring at very low frequency and D.C. (cf. Bockris and Matthews, 1966), for which different equivalent circuits become necessary. These still involve polarization impedances.

If the interfacial current density is increased beyond a certain frequency-dependent threshold value, the equivalent series capacitance rapidly increases with current density and the equivalent series resistance rapidly decreases with current density, as of course does the impedance, from (3.3.6) and (3.8.4). These supra-threshold changes are relatively greater, that is more sensitive to changes in current density, the lower is the frequency, since the threshold reduces to zero as frequency reduces to zero (Schwan, 1968). Another complication is that above the threshold the equivalent series resistance and reactance no longer obey a "simple" power-law frequency dependence. Thus as little current as possible should be passed through the interface to avoid its non-linear current-dependent properties above the threshold with their consequent distortion of the waveform - an effect which has often in the past been attributed to non-linear properties of the biological material under test. The final complication, as might have been expected, is that the "threshold" is not really a threshold at all, but rather a gradual transition into increasingly non-linear behaviour.

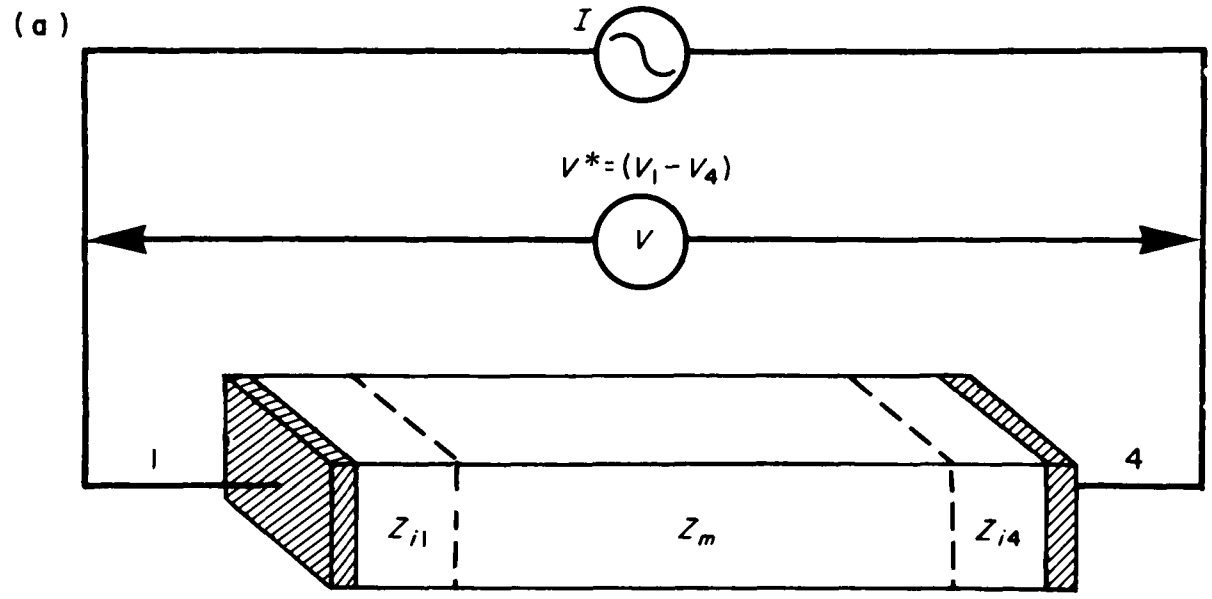
Inhomogeneity of polarization impedance over the surface of a potential sensing electrode will have a potentiometric action, placing the electrode at a potential level different to that which it ought to register (Schwan, 1968, Fig.14c). The problem can be minimised by the use of a fluid bridge between a relatively large electrode surface and a relatively small region whose potential is of interest (op. cit. Fig.15). Such a bridging column also protects the interfacial double layer from mechanical disturbance,

helping to maintain constant the electrical properties of the electrode, and thus avoiding "movement artefact" (Greatbatch, 1974).

Finally it should be noted that although the platinized platinum electrode is inferior to the silver/silver chloride electrode for D.C. work, it is superior for A.C. studies, being unsurpassed in its low polarization impedance (Schwan, 1968).

6.2 Basic principles of multi-electrode methods

Suppose that we have an isolated, macroscopically homogeneous block of the material of interest, and a system, represented by a voltmeter, with which we can determine the complex voltage V* existing between any two points in the circuit involved in passing a current I through the material via two electrodes to be labelled 1 and 4. We further suppose that the voltage-measuring system has such a high input impedance that it draws a negligible measuring current, and thus drops a negligible potential across each voltage-sensing contact, the impedance of these contacts thereby becoming of no interest. Then denoting the (complex) impedance of a current electrode/material interface by Z_i, and the impedance of the material itself by Z_m, various arrangements are possible (Figures 6.2.I; 6.2.II and 6.2.III).



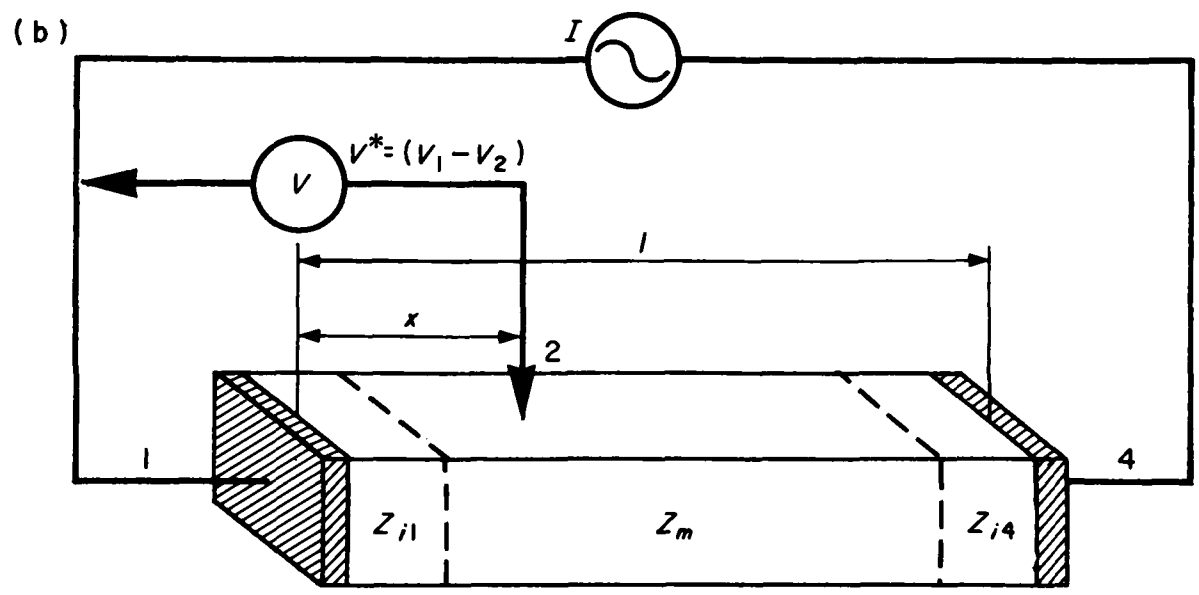
Two-electrode (i.e. "two-terminal") impedance measurement.

Fig. 6.2.I

Fig. 6.2.I illustrates the two-electrode method, for which

$$Z = \frac{V^*}{I} = \frac{V_1 - V_4}{I} = Z_{14} = Z_{i1} + Z_m + Z_{i4} \qquad (6.2.1)$$

showing that the inferred characteristics of Z_m may be seriously in error if the inclusion of the two interface impedances in Z is not allowed for. Unfortunately a great deal of work in the literature is subject to criticism on this account (Schwan, 1968). A better approach was used for example by Fatt (1964), who removed Z_m and determined the reduced Z under the same conditions of frequency and current-density etc. (cf. Section 6.1). Alternatively, such a reduced system may be provided continuously by a separate reference circuit employing electrodes and experimental conditions as similar as possible to those being used in the test circuit (cf. subsection 7.5.a). Such an electrode circuit involves only the two electrodes face-to-face, and hence the difference between the impedances of this and the test circuit is that of Z_m alone. Some other methods of deducing the properties of Z_m alone have been described by Schwan (1968).



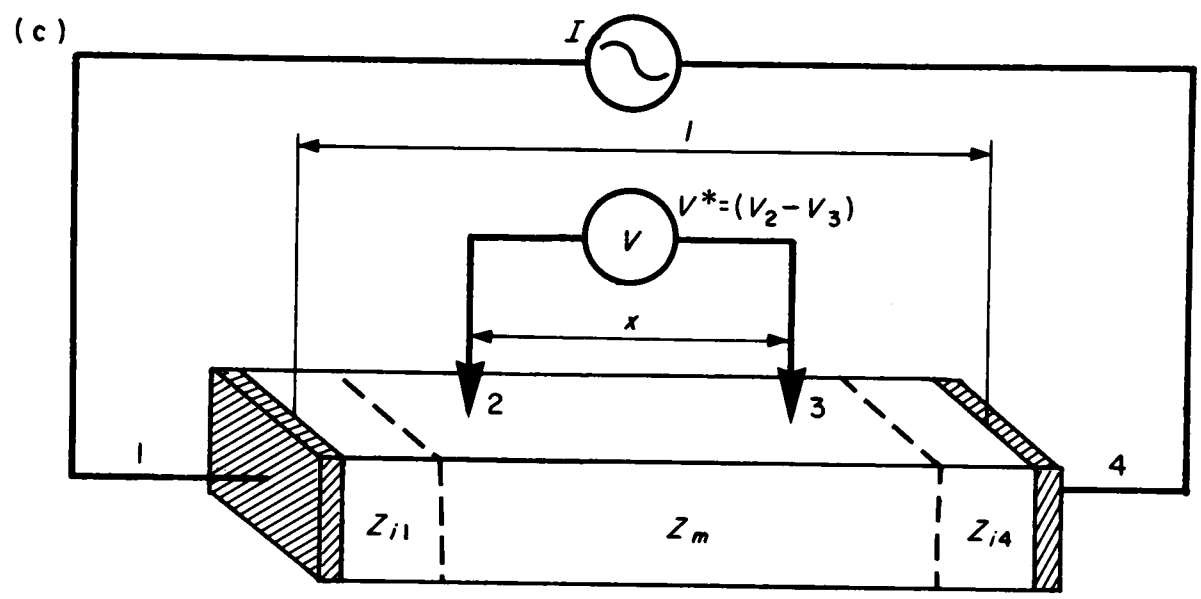
Three-electrode impedance measurement.

Fig. 6.2.II

Study of a single interface can be undertaken with the three-electrode method of Fig. 6.2.II, for which

$$Z = \frac{V^*}{I} = \frac{V_1 - V_2}{I} = Z_{12} \simeq Z_{i1} \quad \text{when } x << l \qquad (6.2.2)$$

and l is the sample length.



Four-electrode impedance measurement.

Fig. 6.2.III

Similarly, study of the bulk material alone is possible using the four-electrode method of Fig.6.2.III, since this has

$$Z = \frac{V^*}{I} = \frac{V_2 - V_3}{I} = Z_{23} \simeq \frac{x}{l} Z_m \qquad (6.2.3)$$

which is independent of current-electrode impedances. The concept was first applied by Bouty in 1884 (cf.Barnett, 1938; Geddes and Baker, 1968).

6.3 Clinical implementations of multi-electrode methods

6.3.a Advantages and disadvantages of each method

Biological impedance determinations, particularly in vivo, are as would be expected very much more complicated than similar investigations of a simple block of material. Useful general reviews have been produced for example by Schwan (1963, 1968), Geddes and Baker (1968) and Hill (1973), while Tregear (1966a) has discussed two- and three-electrode methods as applied for investigating the impedance of skin. The gross differentiation of skin into two layers, epidermis and dermis, certainly complicates such investigations if they are to be made non-invasively at audio and sub-audio frequencies, as is usually the case.

More generally applicable complications arise from

(a) electrode interface potentials, inhomogeneities and non-linearities (Section 6.1);

(b) biological potentials and endogenous currents (cf. Section 12.2);

(c) lack of geometrical constraints (cf. Geddes and Baker, 1968; Baker, 1971), and

(d) unwanted admittances due to electrode geometry (Schwan, 1963; see also subsection 6.3.d), or to surface leakages (subsection 6.3.d).



Fig. 6.3.a.I

The action of unwanted admittances is clear from Fig.6.3.a.I, which is a clinical version of Fig.6.2.I, approximating the various distributed impedances by lumped elements, although in fact a cable-theory type of treatment would be more rigorous. Clinically, we have to consider the shunting effect of Z_s, the impedance of the surface layer of sebum, sweat, electrode jelly leakages and so on (cf. Edelberg, 1977). The measured impedance is

$$Z_{14} = Z_{i1} + \frac{Z_s.(Z_{e1} + Z_d + Z_{e4})}{Z_s + Z_{e1} + Z_d + Z_{e4}} + Z_{i4} \qquad (6.3.a.1)$$

and it is only if the unwanted surface admittance tends to zero that the simple situation described by (6.2.1) obtains, that is

$$Z_{14} = Z_{i1} + (Z_{e1} + Z_d + Z_{e4}) + Z_{i4} \qquad (6.3.a.2)$$

Now, by using for example a reference electrode circuit (Section 6.2) we can determine the sum of the interface impedances contributing to (6.3.a.2) and subtract both away, but we are still unable to separately determine either the impedances of the two regions of epidermis Z_{e1} and Z_{e4} or the impedance of the intervening dermis and deeper tissues, Z_d or Z_{d14}. Early investigators of skin impedance were content to ignore Z_d, considering that at audio and sub-audio frequencies it was much smaller than the epidermal impedances and that thus their results were effectively due to properties of the epidermis alone. This approximation however obviously attributes to the epidermis properties changed from their true value by the vectorial addition of the deep impedance, and the error is all the more serious at high frequencies (cf. Vransky and Emanuilov, 1966), or if the impedance of the epidermis is unusually small, as it can easily be in some types of pathological skin. Moreover, a two-electrode method is further restricted by its inability to distinguish between the epidermal properties at the two sites contacted.



Fig. 6.3.a.II

Barnett (1938) applied earlier work to solve the latter problem, and help with the former, by using a three-electrode arrangement as in Fig.6.3.a.II (cf. Fig. 6.2.II) to isolate the impedance of a single region of epidermis. The dermal and deep-tissue impedance Z_d does not contribute significantly in this arrangement so long as electrode 2 is close to electrode 1, but Barnett found that the results then depended critically upon electrode shapes and separations, presumably because of potential-averaging over electrode surfaces and (Fig.6.3.a.II) the effect of the unwanted impedance Z_{112}, the inter-electrode leakage capacitance, and the surface leakages Z_{s12} and Z_{s24}, which also depend upon such geometrical factors. While these impedances remain finite, some current will flow through Z_{i2} and Z_{e2}, producing a potential offset and thus an error in V*. (Barnett does not seem to have taken account of this, nor of the relatively small changes in Z_d associated with small changes of electrode separation, although he did realize that the localized

impedance which this method measures includes one electrode interface (Z_{il}) as well as the epidermal impedance Z_{el} of interest, and so it is still necessary to determine Z_{il} and subtract away its effects.) The error in V* caused by closeness of electrodes can only be reduced by separating them more, but then Z_{dl2} begins to affect the properties attributed to the epidermis and we have the original two-electrode problem again - unless we have determined Z_{dl2} independently.



Fig. 6.3.a.III

The four-electrode method of Fig. 6.3.a.III (cf. Fig. 6.2.III) can be employed to determine in isolation the dermal and deep-tissue impedance Z_{d23}, which is usually used to estimate either the whole value of Z_d or proportions of it such as Z_{dl2}. The impedance Z_d is of course the prime focus of attention during clinical impedance plethysmographic investigations of tissues and organs other than the epidermis (e.g. Geddes and Baker, 1968; Baker, 1971; Hill, 1973). The potential drop V* measured with this method is usually assumed to result entirely from the flow of the current I through

Z_{d23}, which it would then determine. However, V* is an incorrect registration of the true potential drop across Z_{d23} insofar as current flows through Z_{i2}, Z_{e2}, Z_{i3} and Z_{e3} into Z_{il2}, Z_{sl2}, Z_{s23}, Z_{l34} and Z_{s34} while these latter remain effectively finite, for example because of inadequate electrode separations. Errors in V* can also arise of course in any of these multi-electrode techniques if the voltage-measuring system lacks the requisite very high input impedance and common-mode rejection ratio (a function of the amplifier input impedance and the difference in voltage-sensing contact impedances - Hill, 1973; Gatzke, 1974).

6.3.b A new multi-electrode technique

There does seem to be a way out of the methodological mire we found ourselves in in the last subsection. By combining the strengths of the various techniques we considered there, their weaknesses can be made to cancel out, and we become able for the first time to derive independently the impedances of the epidermis alone at two sites, Z_{e1} and Z_{e4}, and to distinguish each from that of the intervening dermis and deeper tissues, Z_d, which in fact is also determined, as are the current-carrying electrode/electrolyte interface impedances too.

To do all this we propose some usually reasonable simplifying assumptions:

(1) That by adequately separating the (four) test electrodes, potential-averaging effects are minimised, and surface current leakage and inter-electrode capacitative admittance become negligible at the frequencies used. Consequently in Fig. 6.3.a.III we assume that

$$Z_{s12} \simeq Z_{s23} \simeq Z_{s34} \simeq \infty \qquad (6.3.b.1)$$

and $$Z_{l12} \simeq Z_{l23} \simeq Z_{l34} \simeq \infty \qquad (6.3.b.2)$$

(2) That by spacing these electrodes appropriately we can so arrange that

$$Z_{d12} \simeq Z_{d23} \simeq Z_{d34} \simeq \frac{1}{3} Z_d \ , \ (Z_d = Z_{d14}) \qquad (6.3.b.3)$$

(3) That the current-carrying electrode/electrolyte interface impedances Z_{i1} and Z_{i4} have approximately the same value, Z_i, and that their sum can be estimated to sufficient accuracy using a reference circuit consisting of two electrodes 1a and 4a arranged face-to-face with no biological material interrupting the bridging electrolyte, and

operating under the same conditions of current density, temperature etc. as those two of the four test electrodes (placed on the skin to be investigated) which are carrying current.

These three assumptions reduce the network of Fig. 6.3.a.III to the very much simpler one shown here as Fig. 6.3.b.I. The two middle electrodes, 2 and 3, do not carry current but merely sense electrical potential.



Fig. 6.3.b.I

It can be seen that if we measure the potential at each of the six electrodes 1, 2, 3, 4, 1a and 4a for an impressed current I, we can calculate from the measurements

$$Z_{14} = \frac{V_1 - V_4}{I} = 2Z_i + Z_{e1} + Z_d + Z_{e4} \qquad (6.3.b.4)$$

$$Z_{24} = \frac{V_2 - V_4}{I} = \frac{2}{3} Z_d + Z_{e4} + Z_i \qquad (6.3.b.5)$$

$$Z_{34} = \frac{V_3 - V_4}{I} = \frac{1}{3} Z_d + Z_{e4} + Z_i \qquad (6.3.b.6)$$

and by assumption (3)

$$Z_{14a} = \frac{V_{1a} - V_{4a}}{I} = 2Z_i \qquad (6.3.b.7)$$

which immediately provide us with Z_i and the quantities we are interested in for physiological reasons

$$Z_{e1} = Z_{14} - 2Z_{24} + Z_{34} - \tfrac{1}{2}Z_{14a} \qquad (6.3.b.8)$$

$$Z_{e4} = -Z_{24} + 2Z_{34} - \tfrac{1}{2}Z_{14a} \qquad (6.3.b.9)$$

$$\text{and} \quad Z_d = 3\,[Z_{24} - Z_{34}]\ (= 3Z_{23}) \qquad (6.3.b.10)$$

So far as I know, no-one seems to have unravelled epidermal, dermal and electrode impedances before; previous multi-electrode investigations of skin have left one or more mixed up with the others (cf. Section 7.1). Even the methodology advocated by Kinnen (1965) averages the properties of two adjacent epidermal sites, and this is not usually acceptable (Vránsky and Emanuilov, 1965) so a better methodology is still needed (as was admitted by Kinnen, 1966). This is what we have sought to develop here. The present six-electrode technique is indeed able to fully separate all of these impedances continuously, and appears to be the simplest method able to do so.

The next step is therefore to combine this new technique with the discrete Fourier transform method of harmonic analysis which we met in Section 5.2. The impedances Z_{e1}, Z_{e4} and Z_d can then be characterized quite generally as to their non-linear as well as their linear properties.

6.3.c The harmonic implementation of the new technique

From Fig. 6.3.b.I it can also be seen that

$$(V_1 - V_4) = 2V_i + V_{e1} + V_d + V_{e4} \qquad (6.3.c.1)$$

$$(V_2 - V_4) = \frac{2}{3}V_d + V_{e4} + V_i \qquad (6.3.c.2)$$

$$(V_3 - V_4) = \frac{1}{3}V_d + V_{e4} + V_i \qquad (6.3.c.3)$$

and of course by assumption (3)

$$(V_{1a} - V_{4a}) = 2V_i \qquad (6.3.c.4)$$

where V_{e1} for example is the potential drop across the "generalised electrical impedance" Z_{e1} associated with the input current I_{in}.

To simplify notation let us now denote the result of the operation of forming an Euler coefficient from V(t) by E(V). It should be recognised from equations (5.3.a.8), (5.3.a.9) and (5.3.a.10) that any such operation is linear, since as is well known

$$\int_a^b [f(x) + g(x)]\, dx = \int_a^b f(x)\,dx + \int_a^b g(x)\,dx \qquad (6.3.c.5)$$

so long as f(x) and g(x) are integrable functions of x in the range a to b.

Thus for example (5.3.a.9) can be written

$$a_n(V_1+V_2) = \frac{2}{T_o}\int_o^{T_o} [V_1(t)\cos(n2\pi\frac{t}{T_o}) + V_2(t)\cos(n2\pi\frac{t}{T_o})]\, dt$$

$$= \frac{2}{T_o}\int_o^{T_o} V_1(t)\cos(n2\pi\frac{t}{T_o})\, dt + \frac{2}{T_o}\int_o^{T_o} V_2(t)\cos(n2\pi\frac{t}{T_o})\, dt$$

$$= a_n(V_1) + a_n(V_2) \qquad (6.3.c.6)$$

Consequently it can easily be shown from (6.3.c.1) that

$$E(V_1-V_4) = E\,(2V_i + V_{e1} + V_d + V_{e4})$$

$$= 2E(V_i) + E(V_{e1}) + E(V_d) + E(V_{e4}) \qquad (6.3.c.7)$$

and similarly

$$E(V_2-V_4) = \tfrac{2}{3}E(V_d) + E(V_{e4}) + E(V_i) \qquad (6.3.c.8)$$

$$E(V_3-V_4) = \tfrac{1}{3}E(V_d) + E(V_{e4}) + E(V_i) \qquad (6.3.c.9)$$

$$E(V_{1a}-V_{4a}) = 2E(V_i) \qquad (6.3.c.10)$$

whether E is taken to mean $\frac{1}{2}a_o$ (=C), a_1, b_1, a_2, b_2 or some even higher order Euler coefficient throughout this system of equations.

It follows as before in the last subsection that

$$E(V_{e1}) = E(V_1-V_4) - 2E(V_2-V_4) + E(V_3-V_4) - \tfrac{1}{2}E(V_{1a}-V_{4a}) \qquad (6.3.c.11)$$

$$E(V_{e4}) = -E(V_2-V_4) + 2E(V_3-V_4) - \tfrac{1}{2}E(V_{1a}-V_{4a}) \qquad (6.3.c.12)$$

$$E(V_d) = 3[E(V_2-V_4) - E(V_3-V_4)] \qquad (6.3.c.13)$$

and

$$E(V_i) = \tfrac{1}{2}E(V_{1a}-V_{4a}) \qquad (6.3.c.14)$$

where again E can be taken to represent any particular Euler coefficient throughout. Equations (6.3.c.11) to (6.3.c.14) can of course be further simplified but for engineering reasons they are used in the form given.

It may now be seen how E(V) for each particular region of physiological interest, equations (6.3.c.11) to (6.3.c.13), can be obtained simply by making voltage measurements and applying one of the operations (5.3.a.8) to (5.3.a.10), or rather (5.3.b.1) to (5.3.b.3), to derive the individual Euler coefficient required. Applying different operations to the *same*

(recorded) set of voltage measurements enables *all* the Euler coefficients of that region to be derived, and since we may also measure the form of the electrical input, we can therefore obtain from (5.3.a.7) a complete characterization of the electrical properties of the region concerned, because we find we have derived its generalized electrical impedance, as required.

So then, equations (6.3.c.11) to (6.3.c.14) make it possible to separate and completely describe the electrical properties, both linear and non-linear, of two epidermal sites, the region of deeper tissue between them, and the current-carrying electrodes, at a particular frequency and peak-to-peak amplitude of input current. This is extremely useful, and, so far as I know, such a separate and complete description has not been achieved before.

Finally, however, we should note that even using this method, what we have been calling "epidermal" properties here are in fact very probably dominated by the properties of the stratum corneum. Thus the correspondence between "electrical epidermis" and "anatomical epidermis" is not as straightforward as one might wish, but then this is of course a non-invasive technique and such techniques commonly suffer from similar problems. On balance, however, these inconveniences to the investigator do not outweigh the advantages to the patient.

6.3.d The general four-electrode case

If the approximations of the previous Section are untenable for some reason, we have to compute an approach to the solution iteratively by a full network node voltage analysis. Now Schwan (1963) has considered the avoidance of stray-field effects in vitro that are analogous to the Z_i of Fig. 6.3.a.III, but in vivo determinations of skin impedance may also be affected by the surface components Z_s, which he did not treat. Thus consider here a simple model which can be used to calculate the effects of both types of unwanted admittance, if we find that we cannot subtract them off by any experimental means. We discuss unwanted admittances since these can be raised slightly from zero in a clearer way than unwanted impedances could be reduced slightly from infinity, and to avoid making the model considerably more cumbersome it includes only those potentials which result from the applied current.



Fig. 6.3.d.I

The general network of Fig. 6.3.a.III is re-drawn as Fig. 6.3.d.I with V_1 to V_4 representing the potentials available for measurement at the electrodes, and V_a to V_s representing potentials at various nodes in the network measured from the level of V_4, the reference node. Then in terms of this reference

$$V_1 = V_a + V_4 \tag{6.3.d.1}$$

$$V_2 = \frac{Y_3V_a + Y_6V_c}{Y_3 + Y_6} + V_4 \tag{6.3.d.2}$$

$$V_3 = \frac{Y_{10}V_e + Y_{12}V_4}{Y_{10} + Y_{12}} \tag{6.3.d.3}$$

and the reference level V_4 will be taken as zero. Then by the usual methods of node voltage analysis the matrix form of Ohm's Law (Y)(V) = (I) in this case involves a complex admittance matrix (Y) of order 7x7. The column matrix (V) gives the potentials at the seven nodes, and the driving current is represented by a column matrix (I) of which only the first element exists, the input current I.

Then by requiring conservation of current at each node. Ohm's Law produces

$$\begin{pmatrix} A & H & J & O & O & O & O \\ H & B & K & L & O & O & O \\ J & K & C & M & N & O & O \\ O & L & M & D & O & P & O \\ O & O & N & O & E & R & S \\ O & O & O & P & R & F & T \\ O & O & O & O & S & T & G \end{pmatrix} \begin{pmatrix} V_a \\ V_b \\ V_c \\ V_d \\ V_e \\ V_f \\ V_g \end{pmatrix} = \begin{pmatrix} I \\ O \\ O \\ O \\ O \\ O \\ O \end{pmatrix} \tag{6.3.d.4}$$

in which

$$A = Y_0 + Y_1 + \frac{Y_3 \cdot Y_6}{Y_3 + Y_6} \qquad K = -Y_4$$

$$B = Y_1 + Y_4 + \frac{Y_2 \cdot Y_5}{Y_2 + Y_5} \qquad L = -\frac{Y_2 \cdot Y_5}{Y_2 + Y_5}$$

$$C = Y_4 + Y_7 + Y_8 + \frac{Y_3 \cdot Y_6}{Y_3 + Y_6} \qquad M = -Y_7$$

$$D = Y_7 + Y_9 + \frac{Y_2 \cdot Y_5}{Y_2 + Y_5} \qquad N = -Y_8$$

$$E = Y_8 + Y_{11} + Y_{13} + \frac{Y_{10} \cdot Y_{12}}{Y_{10} + Y_{12}} \qquad O = \text{zero}$$

$$F = Y_9 + Y_{11} + \frac{Y_{14} \cdot Y_{16}}{Y_{14} + Y_{16}} \qquad P = -Y_9$$

$$G = Y_{13} + Y_{15} + \frac{Y_{14} \cdot Y_{16}}{Y_{14} + Y_{16}} \qquad R = -Y_{11}$$

$$H = -Y_1 \qquad S = -Y_{13}$$

$$J = -\frac{Y_3 \cdot Y_6}{Y_3 + Y_6} \qquad \text{and} \qquad T = -\frac{Y_{14} \cdot Y_{16}}{Y_{14} + Y_{16}}$$

Solving for the node voltages we find that

$$V_a = I\left(\frac{\Delta_{11}}{\det Y}\right), \quad V_b = I\left(\frac{\Delta_{12}}{\det Y}\right), \ \ldots\ldots \ V_g = I\left(\frac{\Delta_{17}}{\det Y}\right) \qquad (6.3.d.5)$$

where Δ_{lm} is the cofactor of the element Y_{lm} of (Y), and det Y is the determinant of Y.

Despite the simplicity of the model it is still sufficiently unwieldy to require the use of a computer to produce numerical results, since for example

$$\Delta_{13} = [D(HK - BJ) + L(LJ - HM)][E(FG - T^2) - R(RG - ST) + S(RT - SF)]$$
$$- P^2(HK - BJ)(EG - S^2) + HNLP(RG - ST) \qquad (6.3.d.6)$$

and $$\det Y = A\,\Delta_{11} - H\,\Delta_{12} + J\,\Delta_{13} \qquad (6.3.d.7).$$

Chapter 7. THE OXFORD-PLESSEY MICROSYSTEMS FOURIER TRANSFORM IMPEDANCE ANALYSER

7.1 The development of the methodology

Conventional methods of automated impedance analysis by means of presently available gain-phase meters are increasingly inaccurate as input frequency increases and as the attenuation across the test impedance becomes greater. Furthermore, conventional gain-phase analysis is completely incapable of determining constant offsets and harmonic distortion, and its measurements of equivalent series resistance and reactance are less accurate than Fourier transform methods can in principle provide. Indeed we have seen already that the considerable power of Fourier techniques lies in the fact that they give not only accuracy, but also, by the very nature of the mathematics, *all* the interesting indices required to rigorously characterize an impedance. In other words, they deal with and quantify even non-linear behaviour, an ability perhaps especially important in biomedical and electrochemical investigations. Thus in view of their value, we will briefly note here several systems reported in the literature which have included some of the methodology discussed in earlier Sections.

It would seem that the main development of Fourier transform impedance analysis has been by Professor Otto Schmitt's group at the University of Minnesota (Almasi and Schmitt, 1974). The Ph.D. thesis of a research student of Schmitt's showed that in 1966 the equipment being used there was still rather basic, involving measurement of Lissajous figures, but in 1971 the same student described much improved apparatus on-line to a computer (Khalafalla et al., 1971) which used a discrete Fourier transform (DFT) method over a frequency range of 10 Hz to 1 kHz to determine harmonics 0, 1 and 2 using N_c = 64 samples in the wavetrain; the number of cycles in this wavetrain is not mentioned. A reference electrode circuit and a controlled sinusoidal input current was used of I_{in} = 20 microamps (p-p ?),

producing a current density at the two rectangular German 'silver' plate electrodes of 2.8 μA cm^{-2} . It should be noted however that only two electrodes were used since this reproduces the errors criticized by Barnett in 1938. (The much-quoted 1947 work by Gougerot is also subject to criticism on this account.) Furthermore, although a lot of the paper is taken up with discussion of a tissue-equivalent circuit, this should be ignored because it relies upon the use of a frequency-dependent resistor (cf. Rothschild, 1946, p.87) giving

$$Z = R_\infty + \frac{R_o - R_\infty}{1 + j^{1-m}(\omega\tau_p)} \qquad (7.1.1)$$

which is not even the same as their own equation (3), which should itself be the same as the Cole equation (Sections 4.2 and 9.5):

$$Z = R_\infty + \frac{R_o - R_\infty}{1 + (j\omega\tau_p)^{1-m}} \qquad (7.1.2)$$

The equation they are in effect using, (7.1.1) is incorrect because it does not predict the observed (see Section 9.5) ω dependence of Z along the Z locus (cf. Cole and Cole, 1941) and unphysically splits the operator (jω). On this last ground alone integral transform arguments (Macdonald and Brachman, 1956) show that such an equivalent circuit can only be a crude approximation.

In 1974 Almasi and Schmitt showed that the equipment had again been improved; display of results was now by video monitor, the input current could be chosen to be up to 3 mA, and calculation also produced the third harmonic. The frequency range had been shifted to investigate much lower frequencies, down to 0.005 Hz though at the expense of reducing the high-frequency limit to 500 Hz. The measurement procedure now took only 8 samples over only one cycle, in order to obtain rapid results from even extremely low frequencies. Taking only 8 samples however must have considerably

reduced the accuracy of the results of the DFT, since this accuracy is related to the total number of samples N_c taken from the wavetrain. In other words, the accuracy depends upon integrating possible noise to zero by the use of many samples. Applying three electrodes in y-delta circuit transformation was implemented to distinguish the impedance contribution 'under' each respective electrode (also done by Thiele and Malten, 1973) but this when more closely inspected can be seen to include the electrode interface impedance modified by the inter-electrode and surface admittances, and the impedance of an unspecified amount of dermis as well as the impedance of some of the epidermis. Hence circuit transformation methods are not very useful, since they cannot separate all these contributions uniquely to determine which one if any is altering; multiple electrode techniques such as those described in Chapter 6 are required. Almasi and Schmitt were indeed at the time of writing (1973) extending the system to take four electrodes and also to provide the input sinusoid by means of digital synthesis.

Bell, Coster and Smith (1975) have described the in vitro impedance analysis of cells using related apparatus not employing a DFT procedure, but rather a least-squares fit to a pure sinewave. This of course throws away all harmonic information and the constant offset term, which apparently was of no interest either. However, the system does have some features in common with those discussed before in that it uses a controlled current and stores the data of 35 frequencies in 8k of memory with 252 samples per cycle at low frequencies (< 100 Hz) and 12 samples per cycle at 'high' frequencies (>> 100 Hz). The number of cycles and total number of samples at each frequency is not specified, but it would seem that N_c decreased with increase in frequency and the accuracy of the results is indeed stated to be frequency-dependent, which would be a consequence. The frequency range was 0.1 Hz to 1 kHz, being extended to 20 kHz.

As yet however there do not seem to have been any reports of an implementation of the DFT method without the use of moderately large and expensive computer installations. Yet in fact the arithmetic involved in the method is trivial, such that with the advent of rapid microprocessors a desktop DFT impedance analyser is perfectly feasible and its production has been long overdue. Plessey Microsystems Ltd. therefore engineered such a system around their MIPROC-16 microcomputer following a design report (Salter, 1976, unpublished) containing information similar to that of Chapter 6, a performance specification and a schematic diagram of a suggested system hardware layout.

The finally resulting F.T. Impedance Analyser is a mere 19" wide by 10" high by 12" deep (483 x 254 x 305 mm) and should represent the 'state-of-the-art' in impedance characterization at the time of its construction (1978). It has frequency-independent accuracy since it takes a constant 1024 samples from the wavetrain of the selected frequency, and this seems to be the first time that such frequency-independent accuracy has been used. Its frequency range is 0.1 Hz to 100 kHz, comfortably beyond previous systems; it uses a selectable controlled-current stimulation; it has a reference electrode circuit and four other electrodes with which to characterize mutual as well as transfer impedances. Moreover, the constant offset and harmonics 1 - 4 are determined for each monitored node of the network and can be selected for display either by L.E.Ds on the front panel or via a video monitor screen as part of a remote-control system of teletype or minicomputer with which the Analyser can be interfaced. Such a mini-computer can very rapidly command, calculate and display a complete impedance locus plot together with a mathematical analysis of it, as will be discussed in detail in Chapter 8.

Figures 7.1.I to 7.1.IV afford some general views of the Analyser.

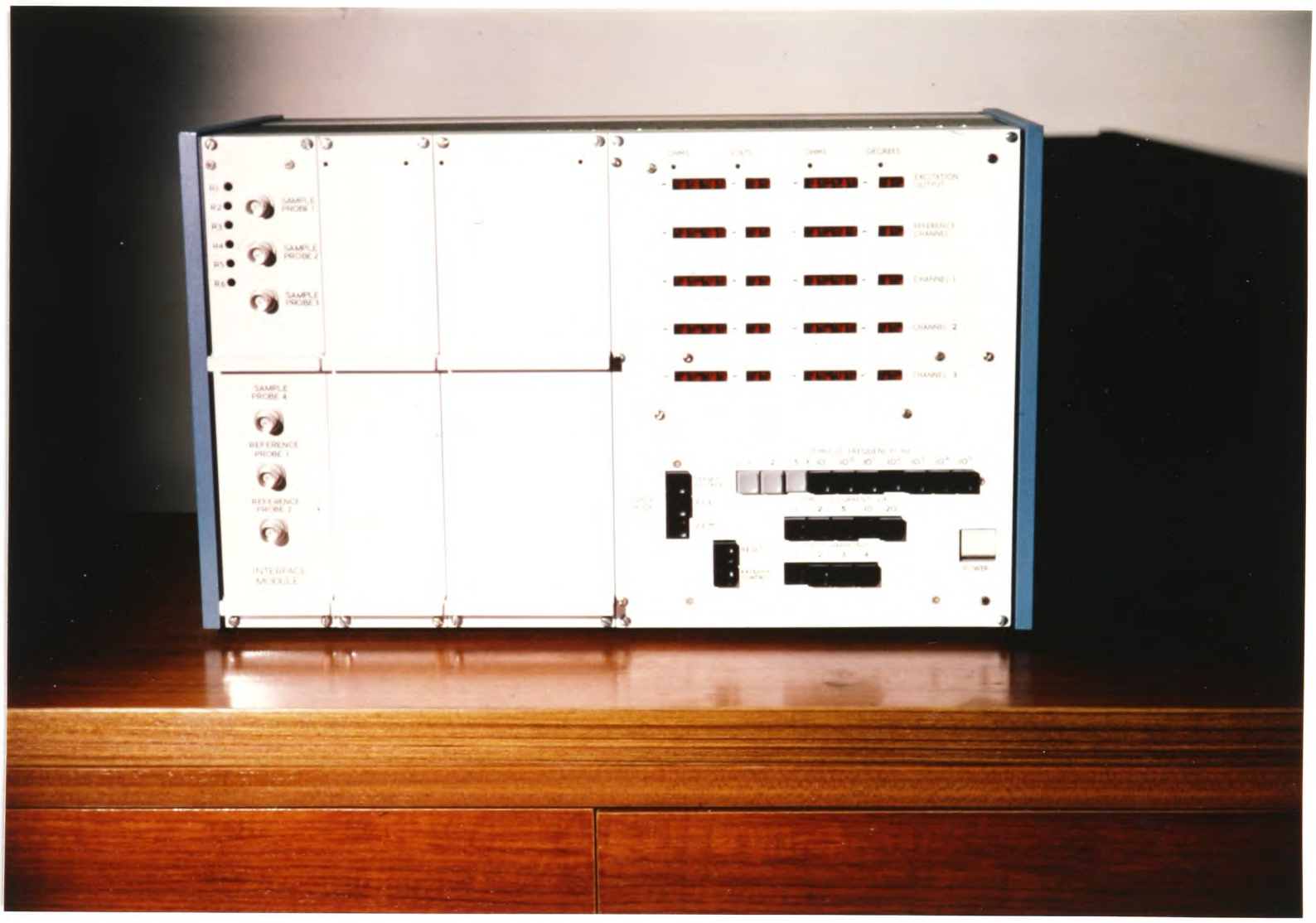


Fig. 7.1.I The Analyser seen from the front.

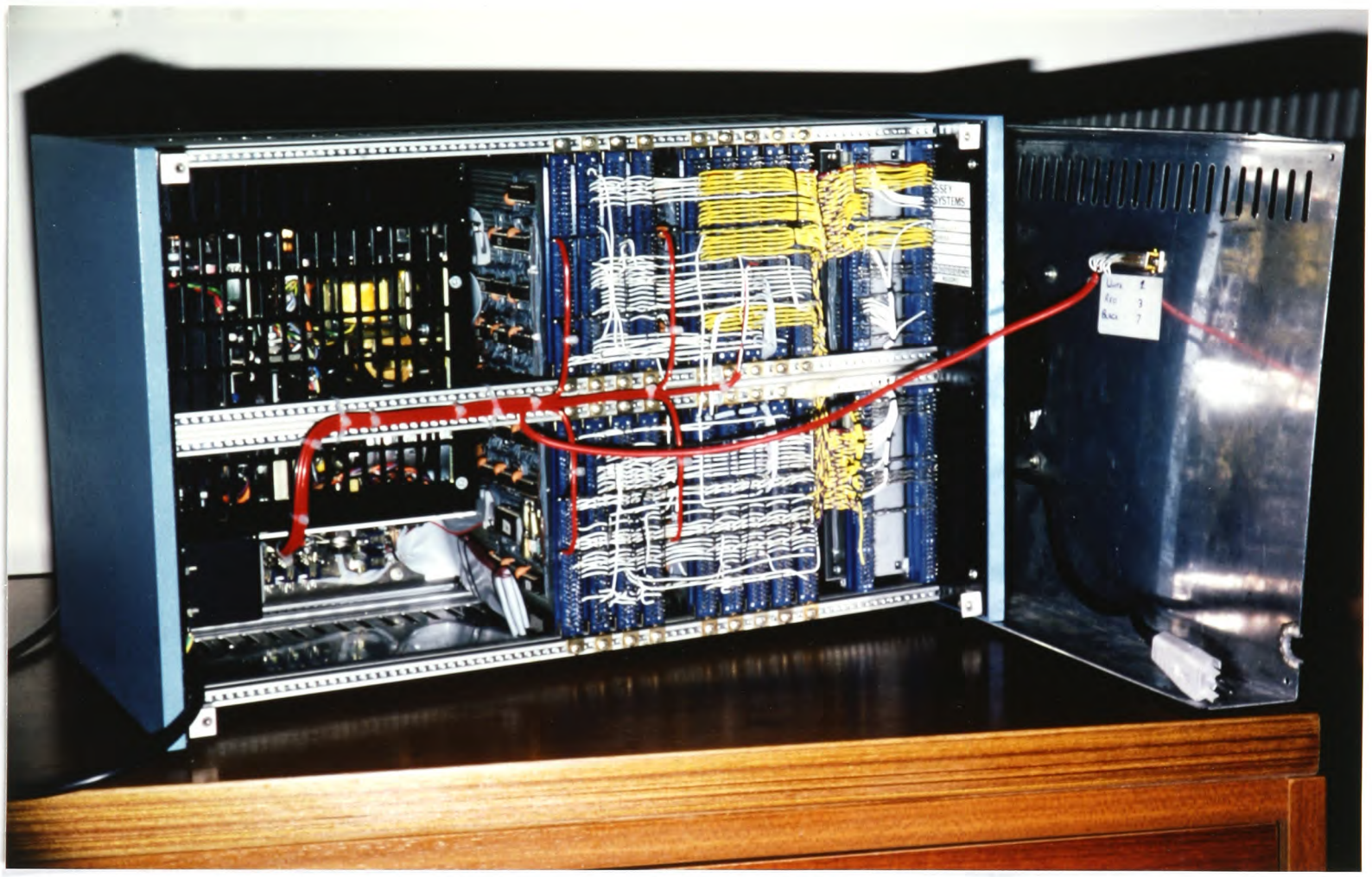


Fig. 7.1.II The Analyser seen from the rear.



Fig. 7.1.III The boards housing the digital sections of the circuitry.

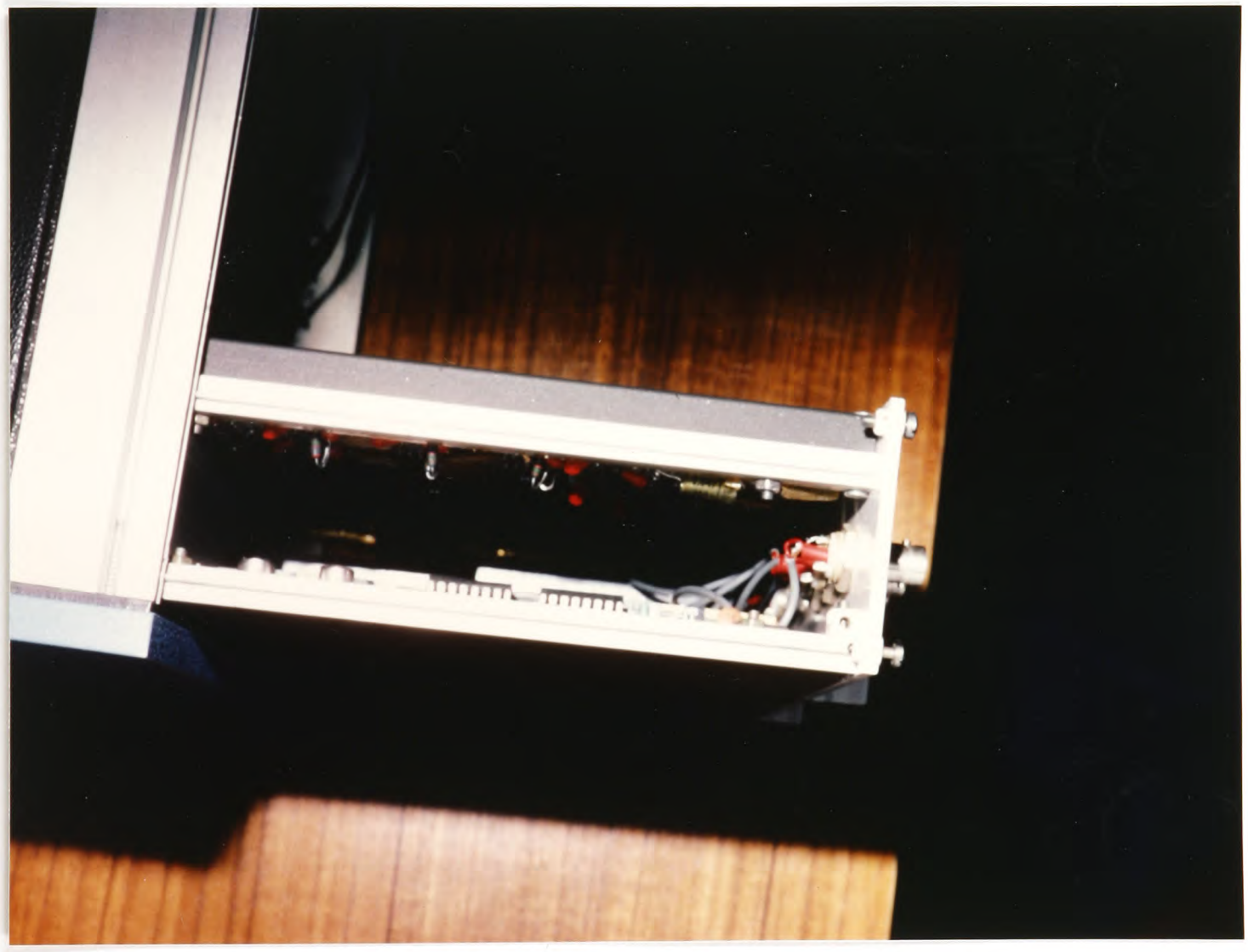
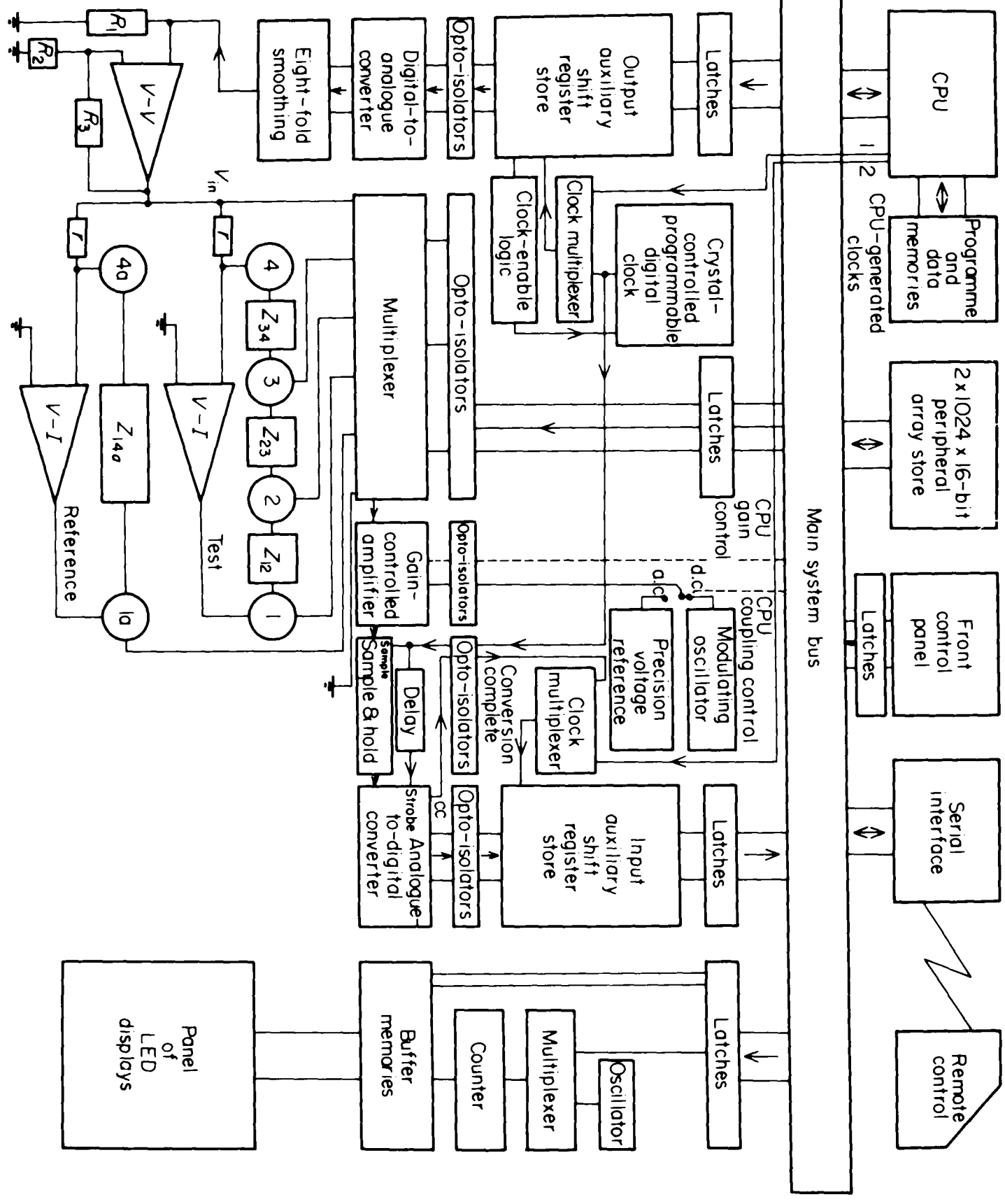


Fig. 7.1.IV A vertical view of the boards housing the analogue sections of the circuitry.



A schematic diagram of the Fourier Transform Impedance Analyser.

Fig. 7.2.I

7.2 The hardware configuration

Figure 7.2.I shows the complete instrument to consist of eight basic modules:

(a) the system microcomputer, comprised of the CPU and its associated program and data memories,

(b) the front control panel,

(c) the serial interface for operation by remote control,

(d) the peripheral array store,

(e) the excitation frequency generator,

(f) the analogue section including the electrodes and the patient,

(g) the network node-sampling and data digitization subsystem, and

(h) the L.E.D. display subsystem.

The microcomputer is the Plessey Microsystems MIPROC-16, which when I was designing the Analyser (1976) was claimed to be the fastest available. It is a bipolar processor having an instruction cycle time set in this application at 450 ns, most instructions requiring only one cycle when working with 16-bit operands.

7.3 The front panel and the serial interface

Functions may be selected on the front panel as follows:

(a) "Reset", which begins a complete measurement re-run employing the experimental conditions already selected using other front-panel buttons;

(b) "Select Excitation Frequency", from a choice of 0.1, 1, 10, 100 Hz, 1, 10, or 100 kHz, multiplied by 1x, 2x or 5x to cover the six-decade range 10^{-1} to 10^{5} Hz, the settings of 200 and 500 kHz defaulting to 100 kHz;

(c) "Select Mode Displayed", being either the constant bias offsets and nothing, the resistances and reactances or the impedances and phases;

(d) "Select Harmonic Displayed", which if the constant offsets have not been chosen via (c) will provide either the conventional first harmonic values R_s and X_s or the 2nd, 3rd or 4th harmonic descriptors, or the polar equivalents;

(e) "Select Excitation Current" from the reasonable biomedical options of 1, 2, 5, 10 or 20 microamps peak-to-peak, and

(f) "Remote Control" which connects the RS232 serial data interface as a two-way link for the transfer of instructions and results between the Analyser, which uses a 16-bit parallel word format, and some external interrogating unit such as a teletype or computer terminal employing a serial word format.

7.4 The excitation frequency generator

This has a frequency accuracy better than 0.3% and a repeatability better than 0.1%. To produce the frequency required, two associated stored variables are extracted from the CPU data memory; the constant controlling the digital clock frequency and the number of cycles "c" to be included in the output stimulus wavetrain. The clock constant is preloaded into a 16-bit counter being fed by a 10 MHz crystal-controlled oscillator; the larger the constant the sooner the counter overflows and since the constant is thereupon loaded back in, the overflow signal will repeat, at a frequency to be used as that of a programmable digital clock. The CPU then uses a 256-step stored quadrant of sine wave to synthesize a full-scale output sinusoid of the required number of cycles, and this is stored in one half of the peripheral array store, the other half being occupied by a cosinusoidal wavetrain synthesized at the same time and used as the quadrature reference. The sinusoidal data is then multiplied by a scaling factor to correspond with the current selected, rounded to ten bits and stored sample by sample in the 1024 x 11-bit output shift register beside an eleventh bit which equals one, except in the case of the last sample which has a zero, the 'stop-clock bit'. The use of a logic gate thus enables the last sample to be recognised by means of this label. The programmable digital clock frequency is then used to clock out the scaled output wave-train sample by sample via an opto-isolator bank to the digital-to-analogue-convertor (DAC), until the last sample is recognised. Previous systems using digital wavetrain synthesis for accuracy have inevitably excited the test network with energy at frequencies other than that of the fundamental sinusoid, and thus the information gleaned from the resulting DFT was the more misleading and inaccurate the poorer the resolution in constructing the initial wavetrain. For example, the steppiness obviously reduces the accuracy of the phase analysis. However, in the Analyser, the purity of the input

wavetrain is considerably enhanced using an eightfold smoothing by means of linear interpolation.

7.5 The analogue section : applying multi-electrode methods

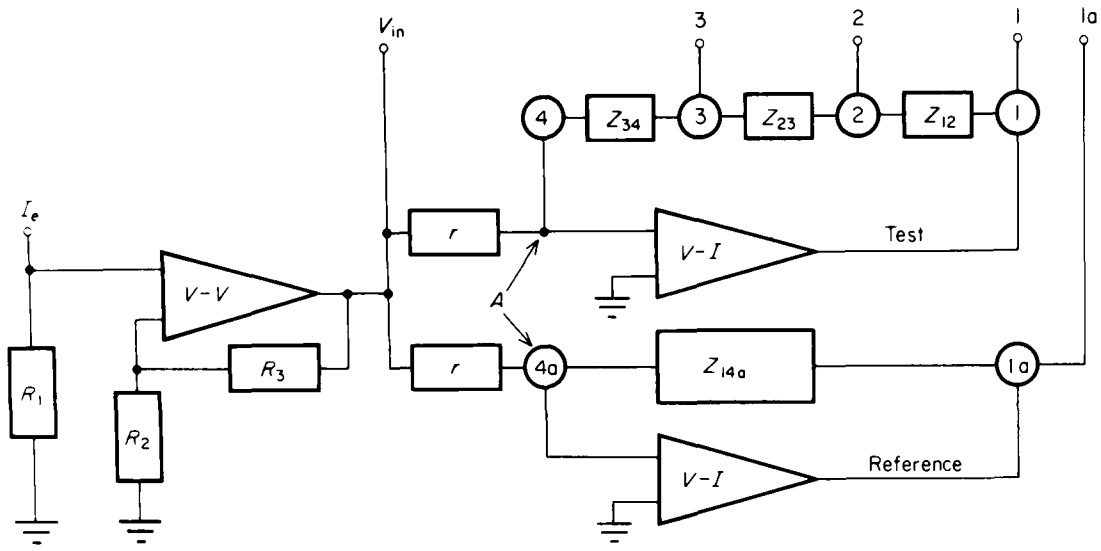
7.5.a Circuitry

In designing the circuitry which will be most directly in contact with the patient our first technical consideration must be whether to control the stimulation in terms of voltage or current. Edelberg (1967) has given a good general discussion of the relative merits and demerits of "constant voltage" and "constant current" (i.e. controlled voltage or controlled current) circuits for measuring the electrical properties of skin. There are physiological reasons for preferring controlled voltage, as we shall see in Chapter 12 (see also Section 4.3), but there are rather more technical problems in its use (cf. Edelberg, 1967, p.23 ff), and an overwhelming reason for using controlled current, namely the confidence and safety of the patient. Only when using controlled current can both patient and clinical investigator be assured that this current will not exceed a safe value even if the impedance encountered in unexpectly low. It is certainly reassuring to the patient to hear a statement for example that the currents involved will not even light a torch-bulb.

For this reason, the circuitry of the Analyser was designed to employ a controlled current approach.

We have discussed the strategy of measurement in Chapter 6; the network to be analysed is excited with a known current at a known frequency, and equipment used to sample the voltage produced by this current at various chosen nodes of the network. Then knowing the amplitude and phase of the input current together with the amplitude and phase of the voltage at the sampled node points determines the characteristics of the network impedance elements between the nodes monitored.

Figure 7.5.a.I shows the Analyser circuitry which implements the multi-electrode methodology described in subsections 6.2.b and 6.3.c.



The current feedback loops of the test and reference circuits, with the terminals (electrodes) at which they are monitored.

Fig. 7.5.a.I

Two voltage-to-current (V-I) converters can be seen, the uppermost being the one involved in passing a known current through the test network, in our case the skin of the patient. The circles enclosing numbers represent the respective electrodes discussed in subsection 6.3.b. Now the V-I converters are essentially differential amplifiers which strive to maintain the points marked "A" at earth potential; these points are therefore called "virtual earths". If a sinusoidal current I_{in} negotiates each input resistor r down to the virtual earth point A because of an applied sinusoidal voltage V_{in}, each V-I converter will pass that same current I_{in} through its feedback loop to keep its virtual earth at earth potential. So by adjusting V_{in} we can control the current $I_{in} = V_{in}/r$ flowing through the chain of impedances Z_{12}, Z_{23} and Z_{34} in which we are interested, i.e. the patient; the arrangement is rather like that of Figure 6.3.b.I. If for example we monitor at point 1 (Fig. 7.5.a.I) the

voltage V_1 which is being required to obtain this necessary current I_{in} through the chain of impedances, we see that since

$$Z_{14} = Z_{12}+Z_{23}+Z_{34} = \frac{b_1[V_1-(V_4\simeq 0)]+ ja_1[V_1-(V_4\simeq 0)]}{b_1(I_{in})} \simeq \frac{b_1(V_1)+ ja_1(V_1)}{b_1(V_{in})} \cdot r \qquad (7.5.a.1)$$

(cf. subsections 6.3.b and 6.3.c) we have in effect determined the sum of the impedances in the feedback loop, rather like determining the sum of the three impedances in (6.2.1) with the arrangement of Fig. 6.2.I. In the general case of course V_1 will be out of phase with V_{in} when the impedance chain has reactive properties.

Sampling the voltage amplitude and phase at further points along the chain imparts the ability to determine "what impedance is where" and thus to split the chain of impedances into its constituent network elements. By also sampling the voltage at points 2 and 3 we are no longer monitoring the potential of just the current-carrying electrodes 1 and 4, and so (cf. Fig. 6.2.III) we can analyse mutual impedances as well as transfer impedances.

The second V-I converter is used for the purpose suggested in Section 6.2, that is, determine the electrical characteristics of the electrode/jelly/electrode system alone, so that this contribution can be subtracted from the total results to obtain the pure characteristics of the patient's skin. Since both feedback loops have I_{in} passing through them, the reference electrode circuit operates at the same current density as the test electrode circuit. Other experimental conditions of the circuits should of course also be kept as closely similar as possible.

It is desirable that the resistors r be precision components of fixed value if we are to monitor I_{in} by voltage-sampling, but then to obtain a

variable I_{in} we must provide a variable V_{in}. Such an adjustable sinusoidal input voltage can be supplied via an amplifier, for example the V-V converter shown, the gain of which is set by its feedback resistors R_2 and R_3. Varying the amplitude of the amplifier input excitation voltage $I_e R_1$, or varying the amplifier gain, or both, can then provide the required means of altering the voltage V_{in}.

7.5.b The electrodes used

On the basis of the information contained in the published reviews mentioned in Section 6.1, it was considered best to employ the Ag/AgCl type of electrode together with an electrode/skin contact gel based on NaCl or KCl (discussion of the contact gel we used will be deferred to the next subsection). Such choices were further supported by the comments of Edelberg and Burch (1962), and Venables and Martin (1967, p.67).

The next consideration was the size of the electrodes. Blank and Finesinger (1946) found that the measured D.C. resistance of a skin site depends upon the area of the electrode used to measure it, but not in the linear way expected. Pasquali (1967) observed a similar effect when working at 100 kHz. Mitchell and Venables (1980) have reviewed the evidence again and carried out further experiments to demonstrate the non-linearity. I think however that the sizes of electrodes these investigators used were much too large to attribute the non-linear dependence to "spreading resistance" effects (e.g. Jeans, 1925, Section 394), and so the interpretation of this phenomenon remains unclear (but cf. Edelberg, 1967, p.20 ff). The existence of this non-linearity means that there are only pragmatic criteria for choosing a standard electrode size. Venables and Martin (1967, p.68) point out that large electrodes are to be preferred because any seepage of contact gel around them is relatively less important in changing the effective area than for small electrodes. Indeed for very small electrodes this can be a very important problem, and source of time-dependence of the results. Very large electrodes are however not very convenient, and do not permit the specific investigation of small skin areas or lesions. Therefore to avoid the disadvantages of very large and of very small electrodes, an area of 1 cm^2 was decided upon as a standard.

As to the construction and attachment of the electrodes, we decided upon "top-hat" or "chamber" electrodes as Edelberg calls them (1967, p.11),

which consist of a circular flange which can be stuck to the skin, sealing a chamber in which is the Ag/AgCl electrode immersed in contact gel. Such a method of electrode attachment standardizes the electrode pressure at almost zero, which is advantageous in the light of Gerstner and Gerbstädt's report (1949, p.114) that when electrode pressure exceeds 100 gm/cm^2, the electrical impedance of the skin site is pressure dependent.

These various considerations led us to use "Searle Bioscience" E.C.G. electrodes, consisting of an Ag/AgCl dish in a recessed plastic chamber of area exactly 1 cm^2, attached to a circular plastic flance which is attachable to the skin by a thin adhesive ring, usually covered by a protective paper ring. A suitable amount of gel can be placed into the chamber and removing the protective paper ring before attaching the electrode to the skin also removes excess gel.

Finally, we must consider the separation of the electrodes on the skin. In contrast to the findings of Barnett (1938), Edelberg (1967, pps. 13, 14) has shown that the effects of changing the electrode separation are negligible for separations of greater than a couple of millimetres when using poorly conducting contact gels. We therefore felt quite confident in using separations of, on average, three centimetres centre to centre.

7.5.c The electrode gel used

For reasons which will be discussed in detail in subsection 9.3.b, we developed our own electrode gel using a carboxyvinyl polymer ("Carbopol 940") base of 4% w/w, dispersed in IMS with 0.29% NaCl (or KCl; there appear to be no detectable differences) and water in the range 5% to 10% w/w.

The acidic pH of these gels (pH2 - pH3) was not found to be irritant to the human skin we tested in vivo, and indeed it served to ensure that the fixed charge of the stratum corneum was positive in the case of all our subjects (see subsection 12.2.e).

7.6 The network node-sampling and data digitization subsystem

The input multiplexer switch has six channels connected to the points shown in Fig. 7.2.I and thus monitors the input waveform as well as its consequences. The earth reference is provided to determine the offset introduced by the analogue circuitry itself. The gain-controlled amplifier which these switched inputs continue to is a rather sophisticated circuit (Robinson, 1978) having a gain variable between 10 and 100,000 while being capable of amplifying low-level signals at frequencies up to 100 kHz. Both A.C. and D.C. coupling must be used to measure the alternating and static components of node voltage (the latter perhaps twenty times the former) without limiting the dynamic range of the A.C. signal. Conventional solutions to the D.C. coupling of a high-gain amplifier were not possible in this case since, due to the large bandwidth required, chopper stabilization methods were not practical and temperature fluctuations would have rendered preset trimming techniques useless. Thus since the system is only sensitive to time independent constant offsets, the fundamental excitation frequency and its harmonics, a double frequency-modulation was employed.

The gain of the complete amplifier is of the form $g = A_1/(1+A_1A_2)$ where A_1 is the CPU-switched gain of an op-amp chain and A_2 the frequency-dependent gain of two long time constant integrators in the feedback loop around this chain. At D.C. the compensating ability of the integrators is maximum, as is their gain A_2, and a typical value of g would be 10^{-4}. At high frequencies A_2 tends to zero and g tends to A_1, 10^5 for example. D.C. information is obtained despite this A.C. coupling by modulating the incoming signal both before and after the amplifier with a low-distortion sinewave of high frequency (such that $A_2 \rightarrow 0$) bearing no harmonic relationship to the excitation frequency. Since $\sin^2 x = \frac{1}{2}(1 - \cos 2X)$, the resultant signal amplitude has a term independent of the modulating frequency just as if the signal had been passed through a D.C.-coupled amplifier of reasonable

gain $g \simeq A_1$, plus of course an irrelevant high-frequency spectrum which has been chosen not to affect the harmonic results in any way. Hence a large D.C. offset, accurately measured by this means, will not limit the accuracy of the A.C. measurements, obtained by replacing the modulation with a precision constant voltage applied to the voltage-controlled multipliers within the amplifier module.

The amplifier supplies an ultra-high-speed sample-and-hold (S&H) module feeding a 1μS 10-bit analogue-to-digital converter (ADC). The S&H samples the amplified signal in synchronism with the output of a step in the sinewave from the DAC, maintaining the possibility of dealing with a known, required and integer number of cycles in the input shift register store. Such an integer number of cycles avoids 'leakage' (see e.g. Brigham, 1974) and resultant leftover errors upon carrying out the summations of the DFT procedure. The known number of cycles also gives the number "c" of (5.3.b.4) and (5.3.b.5), enabling the DFT procedure to deal with only those harmonics which are relevant, and not for example those introduced by the sampling procedure itself. This arithmetically eliminates input filtering problems. The ADC is strobed by the S&H pulse after a delay equal to the acquisition time of the S&H. The "conversion complete" signal from the ADC is then used to clock the 1024 x 10-bit input shift register store. It can also be clocked directly by the CPU.

Much use has been made of optically-coupled data links, "opto-isolators", between the digital sections of the Analyser and the analogue parts, which contact the "network under test" - the patient. As an obvious safety precaution, separate power supplies for this isolated analogue section are provided using (isolated) D.C.-to-D.C. converters.

7.7 The L.E.D. display subsystem

The display subsystem includes five independent channels of multiplexed seven-segment displays, each channel consisting of two sections which can be used to show either the constant offset and nothing, the equivalent series resistance and reactance at some harmonic from 1 to 4, or the corresponding values of impedance and phase. Information is presented by each section as a four-figure mantissa and a two-figure exponent beside a polarity display. The five channels monitor the input stimulation waveform, test electrodes 1, 2 and 3 of Fig. 7.2.I and the reference electrode 1a. Thus for example if the constant offsets are selected the channel displays will operate on their left-hand sides only, and show

$$(1)\quad I_O = \tfrac{1}{2}\, a_o \left[I_{in} = \frac{V_{in}}{r} \right] \quad \text{(this should be checked to be acceptably close to zero)}$$

$$(2)\quad V_{O1a} = \tfrac{1}{2}\, a_o \left[V_{1a} - (V_{4a} \simeq O) \right]$$

$$(3)\quad V_{O1} = \tfrac{1}{2}\, a_o \left[V_1 - (V_4 \simeq O) \right]$$

$$(4)\quad V_{O2} = \tfrac{1}{2}\, a_o \left[V_2 - (V_4 \simeq O) \right]$$

$$(5)\quad V_{O3} = \tfrac{1}{2}\, a_o \left[V_3 - (V_4 \simeq O) \right] \qquad (7.7.1)$$

If resistance and reactance or impedance and phase are selected instead, then for each particular input frequency $f = \omega/2\pi$ we use the formulae of Section 5.3 to slowly build up points around the Z locus of Fig. 4.2.I, and for example channel 5 referring to electrode 3 of Fig.7.2.I would display Z_{34} pertaining to the harmonic chosen, resolved into

$$R_{s34}(\text{nth harmonic}) = \frac{b_n[V_3-(V_4\simeq O)]}{b_1(I_{in})} = \frac{b_n[V_3-(V_4\simeq O)]}{b_1(V_{in})} \cdot r \qquad (7.7.2)$$

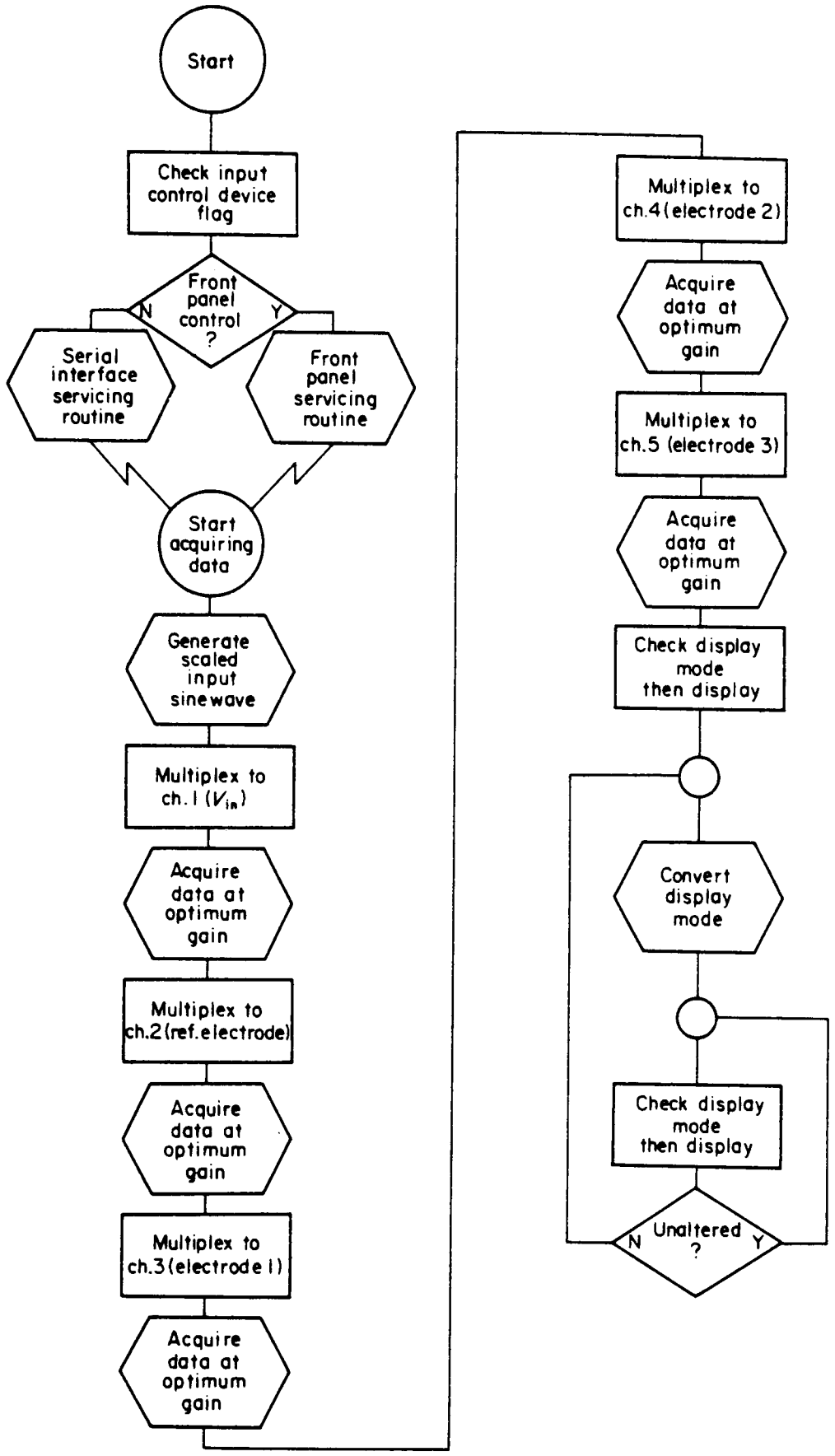
on the left display (cf. eqn. 7.5.a.1), and

$$X_{s34}(\text{nth harmonic}) = \frac{a_n[V_3-(V_4\simeq O)]}{b_1(I_{in})} = \frac{a_n[V_3-(V_4\simeq O)]}{b_1(V_{in})} \cdot r \qquad (7.7.3)$$

on the right, or by selecting another switch the corresponding values of $|Z|_{34}$ (nth harmonic) and Θ_{34} (nth harmonic) using (4.1.2) and (4.1.3). The values for n = 1 are those discussed in Sections 4.2 and 8.3, and are those to be used in building up a Z locus; higher harmonics can be employed to derive the particular way in which the voltage-current characteristic of the biological material under test departs from Ohmic (linear) behaviour. This is relevant to biophysical and physiological studies, as will be discussed in Chapter 12.

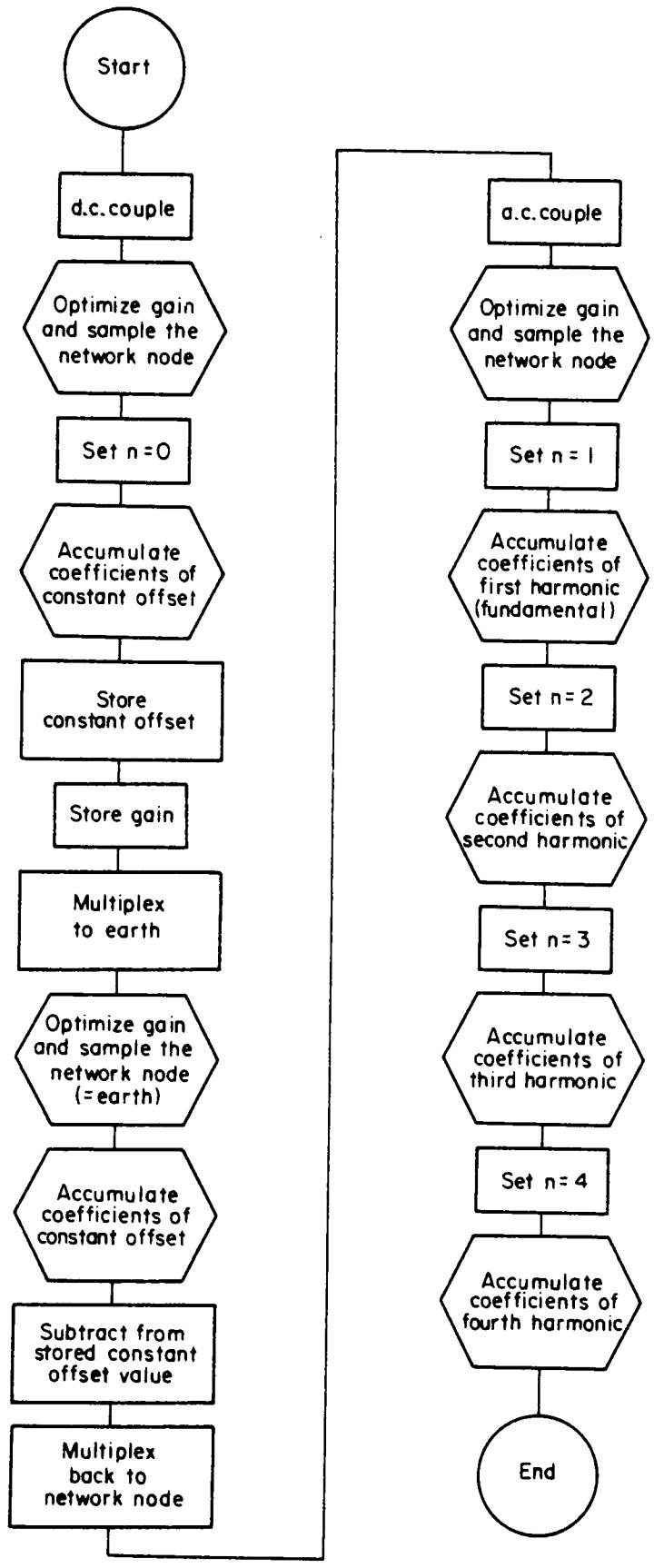
7.8 The software configuration

The software has been restricted to less than 4096 instructions, and its main basis is illustrated in Figs. 7.8.I, 7.8.II and 7.8.III. Fig. 7.8.I shows that having decided where control instructions should be coming from, a subroutine is invoked to generate the scaled input sinewave. The Analyser then stimulates the test and reference networks with this sinewave while sampling the voltage produced at the particular node selected by the multiplexer. This is done with both D.C. and A.C. coupling at separately optimized gains under the direction of the subroutine of Fig. 7.8.II, the procedure relying on the smaller routine of Fig. 7.8.III. The subroutine of Fig. 7.8.II thus produces from the data of the selected electrode channel five pairs of numbers, the resolved in-phase and quadrature components (harmonic coefficients) for harmonics 0, 1, 2, 3 and 4, the subroutine which accumulates these coefficients implementing (5.3.b.4) and (5.3.b.6), and at least one of these ten numbers, the b_o term, should be zero. Having dealt with one multiplexer setting in this way, the procedure is repeated with the next until all five channels have been examined and their data acquired. Then having checked what information has been selected for display, the Analyser calculates the requisite indices and displays them in the chosen mode.



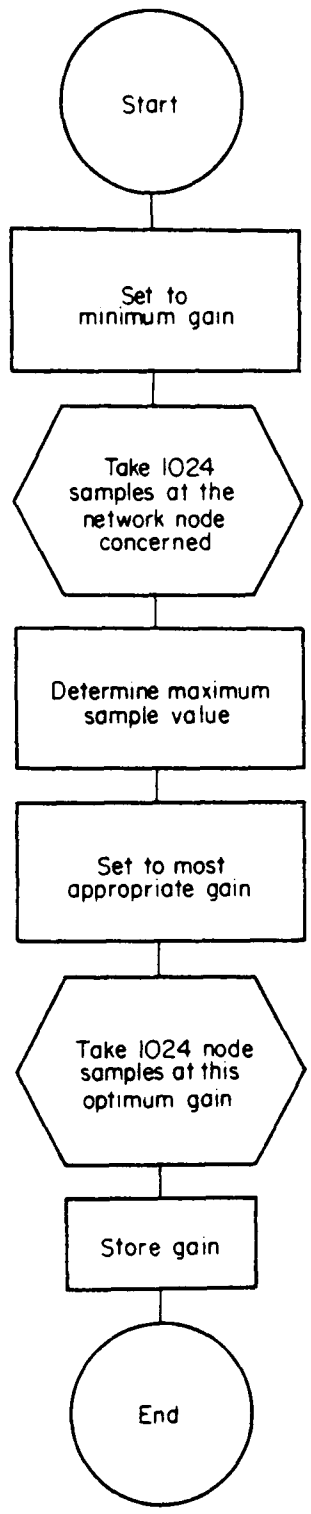
A schematic diagram of the software controlling the operational procedures.

Fig. 7.8.1



The subroutine to acquire data at optimum gain.

Fig. 7.8.II



The subroutine to optimize gain and sample a network node.

Fig. 7.8.III

Chapter 8. PROCEDURES FOR ACQUIRING AND ANALYSING CLINICAL DATA

8.1 The MINC-11 minicomputer system and the hard-copy unit

Although the Analyser is capable of fulfilling all its functions without external assistance other than intelligent operation of the front panel controls by the clinical investigator, I always envisaged that it would eventually be connected to a dedicated minicomputer system. This has a number of advantages.

Firstly, the expertise required of the clinical investigator can to some extent be built into the programs of the computer, and the computer can then control the clinical measurement procedure with minimal instruction from the human operator, who can be left to get on with the more important task of talking with the patient.

Secondly, after a measurement run at a particular frequency of input current, the computer is capable of electronically noting the results obtained by the Analyser, and this is a great deal quicker than an operator having to write down 45 six-digit numbers from the front panel displays before the next frequency can be measured. (If only an approximate skin characterization is being made it is sufficient to copy fewer numbers, but the principle remains the same.)

Thirdly, avoiding the need to write down the results by hand means that the entire sequence of clinical measurements, involving measurements at many frequencies, can be completed very much more quickly, and thus there will be less likelihood of the skin having changed its properties during this time, for example by the absorption of electrode gel, or through the alteration of sweat-gland activity. Consequently the characterization of the properties of the skin will be more accurate.

To gain these advantages, a minicomputer system was purchased and interfaced to the Analyser as had always been planned.

The minicomputer system is the so-called MINC-11 manufactured by the Digital Equipment Corporation. "MINC" is an acronym for Modular Instrument Computer, designed as a small system to control and acquire data from laboratory equipment of various types, and to display the processed results on the screen of the associated VT105 VDU (visual display unit). In our particular application we did not require any "laboratory modules" which are intended to configure the system for the measurement or control tasks it is to be dedicated to; in our case the Analyser fulfilled all the necessary functions and the computer program merely had to tell the Analyser what to do when, and then input and store the results presented to it by the Analyser at its serial interface (see Section 7.3).

Mechanically the system is in two main parts, the CPU which is housed on a trolley and the VDU to which it is linked by an extending cable.

The system uses "MINC BASIC", a variant of the BASIC programming language and consequently very much easier to "de-bug" than languages of the FORTRAN family. The VDU is capable of displaying a number of type sizes and shades, and also graphics.

To complete the system, a Tektronix 4632 Hard-Copy Unit was purchased. This connects to the VDU by coaxial video cable, and, when the appropriate button is pressed on it, makes a photocopy of whatever is displayed on the VDU screen at the time.

8.2 Acquiring and recording clinical data

8.2.a Preparation of the subject and arrangement of the equipment

Measurements were made in a room with controllable air temperature and humidity, but not before the subject had been (usually) seated close to the equipment for a minimum equilibration period of twenty minutes with the relevant areas of skin exposed.

At the beginning of this equilibration period, four electrodes of the type described in subsection 7.5.b were attached to the skin sites of interest, and electrical contact was ensured by the use of electrode gel as described in subsection 7.5.c. The electrodes were equally spaced apart (cf. subsection 6.3.b) with a separation of at least 1 cm. and usually more.

Finally, the temperature of skin areas as close as possible to these four skin sites was measured using a Yellow Springs Instrument Co. "Telethermometer" model 43TA equipped with a type 408 "Banjo" thermistor probe of time-constant 0.6s and 1 cm in diameter. The ambient relative humidity of the room was also noted from a small hygrometer.

Figure 8.2.a.I shows measurements being made on a dorsal forearm. Four electrodes are visible attached to the arm and the connecting leads run to the Analyser just behind it. Above the Analyser is a simple X-Y oscilloscope (Telequipment type D10llR) arranged to monitor the output of the Analyser by means of Lissajous figures. To the right of the Analyser is the VDU and its keyboard. Above the VDU is the thermistor bridge temperature monitor together with various other items used in the clinical measurement procedure such as electrode gel, spare electrodes and so on. Finally, to the right of the VDU is a water bath in which the reference electrodes la and 4a may be held at the appropriate skin temperature.

Figure 8.2.a.II shows the MINC-11 minicomputer on its trolley. The subject sits in a chair between the computer and the rest of the system described above. Finally, the hard-copy unit mentioned in Section 8.1

is situated on the other side of the room (Figure 8.2.a.III) and connected to the Analyser by a coaxial video cable.



Fig. 8.2.a.I Measurements being made on a dorsal forearm.



Fig. 8.2.a.II The MINC minicomputer on its trolley.

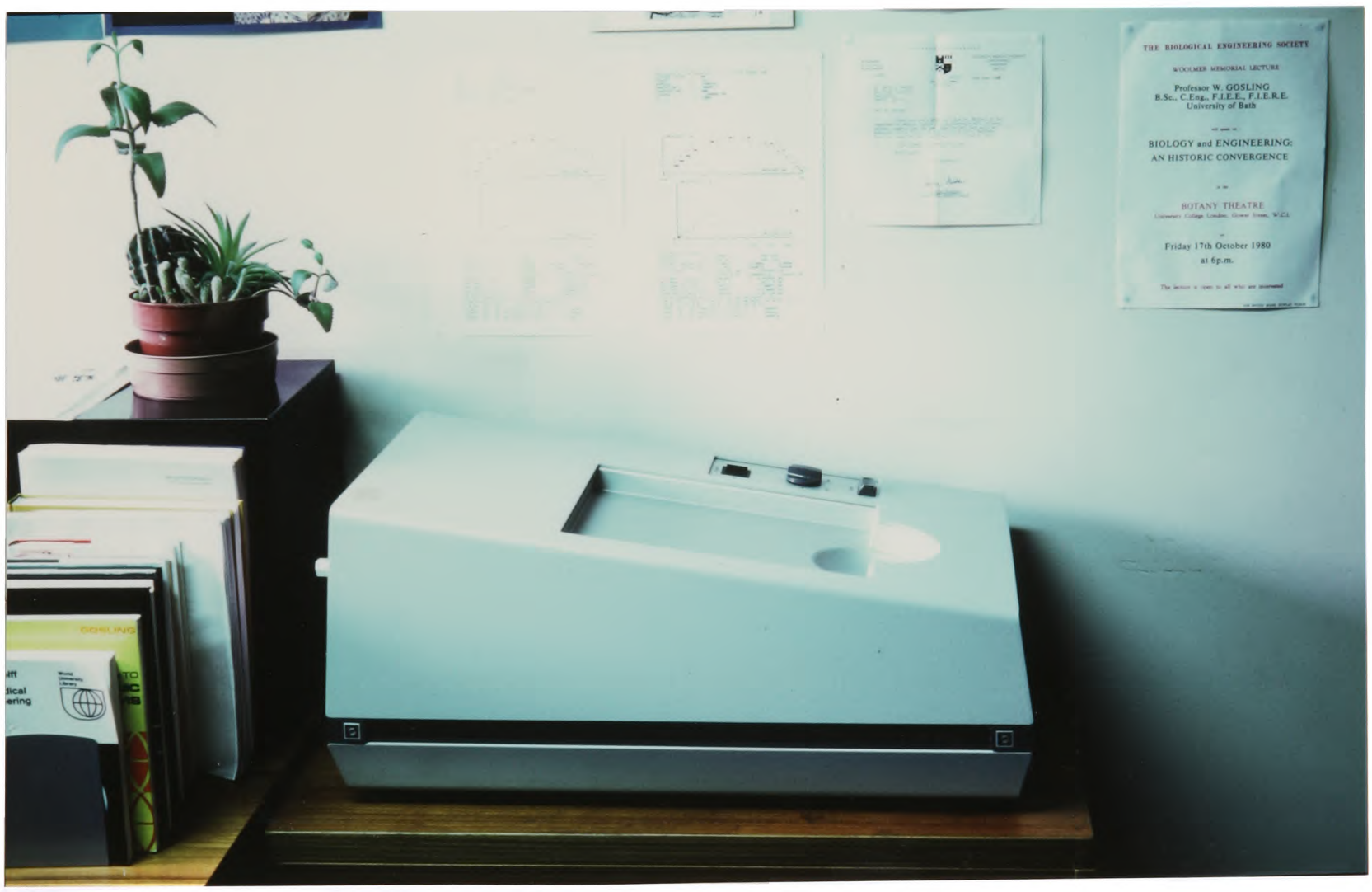


Fig. 8.2.a.III The video hard-copy unit.

8.2.b Making measurements without computer assistance

When the Analyser is used under direct control from its front panel, the clinical investigator firstly ensures that the "EXTERNAL CONTROL" button is not engaged, then selects an input current amplitude and frequency using the appropriate buttons (cf. Section 7.3) and finally pushes the "RESET" button. After a delay of a few seconds, the exact number depending on the frequency selected, the Analyser displays the results obtained, and these appear in the form described in Section 7.7. The clinical investigator must then record these by hand before instructing the Analyser to make measurements at another amplitude or frequency of input current.

Measurements made at a single frequency are enough to determine the voltage/current characteristic curve of the three regions of skin mentioned in subsection 6.3.b, at least for the current range $-\frac{1}{2}I_{in}$ to $+\frac{1}{2}I_{in}$ where I_{in} is the selected peak-to-peak input current.

However, to characterize the linear properties of skin by means of a complex impedance locus (cf. Section 4.2 and Section 8.3 to follow), measurements must be made at at least three different frequencies, and preferably more. The Analyser is capable of measuring up to nineteen.

When the sequence of measurements is completed, the data must then be analysed with the aid of the MINC minicomputer, or some other computer. Consequently I am very grateful to have been allowed the full use of the CTL 8050 computer at the John Radcliffe Hospital, Headington, since it is possible using this main hospital computer and its associated Hewlett-Packard graph plotter to generate very much more attractive charts of processed results than the MINC VDU and the hard-copy unit are capable of producing. For this reason the results presented in this thesis have been drawn by the graph plotter at the John Radcliffe, and not the VDU of the MINC in my room at The Slade.

8.2.c Making measurements with computer assistance

When measurements are made with the Analyser under computer control, the clinical investigator does not need to push front-panel buttons to select new frequencies, and even better, there is no need to record data by hand since the computer records them electronically via the serial data interface of the Analyser (cf. Section 7.3).

Use is made of two programs called TEST and PROC. After starting up the computer system in the usual way described in its instruction manuals, and having switched the Analyser on, the operator types "OLD" and then "TEST" on the VDU keyboard to recall and load the program TEST. The operator then types "RUN" to start the program, and from then on receives instructions from the program itself.

Program TEST instructs the operator to supply the computer with data pertaining to the subject and the experimental conditions, including the input current amplitude and the current frequencies it is required to obtain measurements with. It, of course, records these data.

The program next transmits to the Analyser the input current amplitude required, and then for each of the set of N required frequencies F(z), z = 1, 2, ... N,

(a) transmits to the Analyser the frequency required and the "GO" command,

(b) waits and then receives back the consequent character strings of (coded) results, and

(c) records F(z) and the associated character strings in the file HEXDAT at a location dependent upon Z.

This completes program TEST, and it signals its completion by causing the VDU to produce a short audible tone, and also by printing on the VDU screen "the requested sequence of measurements has now been completed".

(The contents of the file HEXDAT may if desired be inspected by using the ancillary program HEXDAT. The operator types "OLD", then "HEXDAT", and finally "RUN". On the VDU screen a sequence of data then appears. Firstly, the details of the subject and the experimental conditions, and then a succession of N blocks of results, one for each measurement frequency used. Each block is arranged in a tabular form with labels in English, but numerical results in a code known as hexadecimal twos-complement fractional binary notation.)

At this point the clinical investigation may be ended, since the measurements which have been made are recorded on a floppy disk in the minicomputer system, and these measurements may be processed later. Meanwhile, new floppy disks may be inserted and other subjects investigated if desired.

When however the measurements finally are processed, this may be done using program PROC. The operator types "OLD", "PROC" and "RUN". The program is then enacted.

For values of Z from 1 up to N, it

(a) takes from the file HEXDAT a block of characters defined by Z

(b) operates upon the block to strip it of unnecessary characters (such as labels) and decode the remainder into ordinary (decimal) numbers, and

(c) stores the translated block in the file RAWDAT at a location dependent upon Z.

For values of Z from 1 up to N the program then continues by

(a) taking from RAWDAT a block of numbers defined by Z

(b) operating upon this block to self-calibrate the measurements, and then to calculate from them the Euler coefficients corresponding to the impedances of interest (Z_{in}, Z_{ei}, Z_{e4}, Z_d and Z_i - see Section 5.3, and subsections 6.3.b and 6.3.c). Finally,

(c) the program records F(Z) and the corresponding Euler coefficients in the files IINDAT, VE1DAT, VE4DAT, VDDAT and VIDAT at locations dependent upon Z.

This completes program PROC, which, together with programs TEST and HEXDAT, may be inspected in Appendix A.

The further processing and analysis of the data will be described in the next two Sections, dealing with linear and non-linear electrical properties respectively.

8.3 Characterizing the linear electrical properties of skin

We have seen in Section 5.3 the way in which it is possible to define the electrical properties of a material in terms of its "generalized electrical impedance", and in subsections 6.3.b and 6.3.c we considered a way of deriving the generalized electrical impedance for particular skin regions in vivo. The problem before us now is that of extracting the linear electrical properties from within these regional generalized electrical impedances, and then of reducing the linear properties we extract to rather more basic biophysical indices.

Now we saw that the linear electrical properties of a generalised electrical impedance are described by expressions such as (5.3.c.1) or (5.3.c.2), which are merely descriptions of a complex number. Consequently, as we considered in Section 3.3, R_s and X_s can be used as the rectangular coordinates of a point on the "(complex) impedance plane", an Argand diagram, and will in general produce a locus on this plane as the point moves with changes in the stimulating frequency. This complex impedance locus completely specifies the linear electrical properties of a material. Consequently it is often employed in the analysis of the properties of "black boxes", and has acquired the special name of "Nyquist diagram" (see e.g. Grodins, 1963).

Let us therefore now apply this approach and become able to specify the linear electrical properties of epidermis, dermis or electrodes by constructing their respective complex impedance loci.

Suppose we take as an example the epidermis under electrode 4. Then considering only its properties which are linear, its equivalent series resistance at the frequency of the input current is found by setting $E = b_1$ in (6.3.c.12) to give

$$R_s(\omega)_{e4} = \frac{b_1(V_{e4})}{b_1(I_{in})}$$

$$= \frac{-b_1(V_2-V_4) + 2b_1(V_3-V_4) - \tfrac{1}{2}b_1(V_{1a}-V_{4a})}{b_1(I_{in})} \qquad (8.3.1)$$

The Euler coefficients such as $b_1(V_3-V_4)$ in this equation are derivable from the information available via the serial interface of the Analyser (see subsection 8.2.c and Appendix A), and so is $b_1(I_{in})$ representing the amplitude of the pure sine wave input current, which should of course equal the nominal peak-to-peak current value I_{pp} selected for the test. The voltage amplitude and waveform producing this current input is nevertheless measured by the Analyser just as carefully as it measures the voltage amplitudes and waveforms produced across the skin impedances as a consequence of this input (cf. Sections 7.5 and 7.6), in order that the results may be self-calibrated during the subsequent data processing.

Similarly, the equivalent series reactance of the epidermis under electrode 4 is

$$X_s(\omega)_{e4} = \frac{a_1(V_{e4})}{b_1(I_{in})}$$

$$= \frac{-a_1(V_2-V_4) + 2a_1(V_3-V_4) - \tfrac{1}{2}a_1(V_{1a}-V_{4a})}{b_1(I_{in})} \qquad (8.3.2)$$

Since a_1 terms are in quadrature with b_1 terms, whether of voltage or current, the reactance $X_s(\omega)$ for skin is in fact negative, i.e. capacitative.

Now, by calculating pairs of coordinates (8.3.1) and (8.3.2) from the blocks of Analyser data obtained at a number of different frequencies, a complex impedance locus can be built up just as we saw in Section 4.2, and for epidermis this locus is in fact a minor arc of a circle, as is illustrated in Fig. 8.3.I.

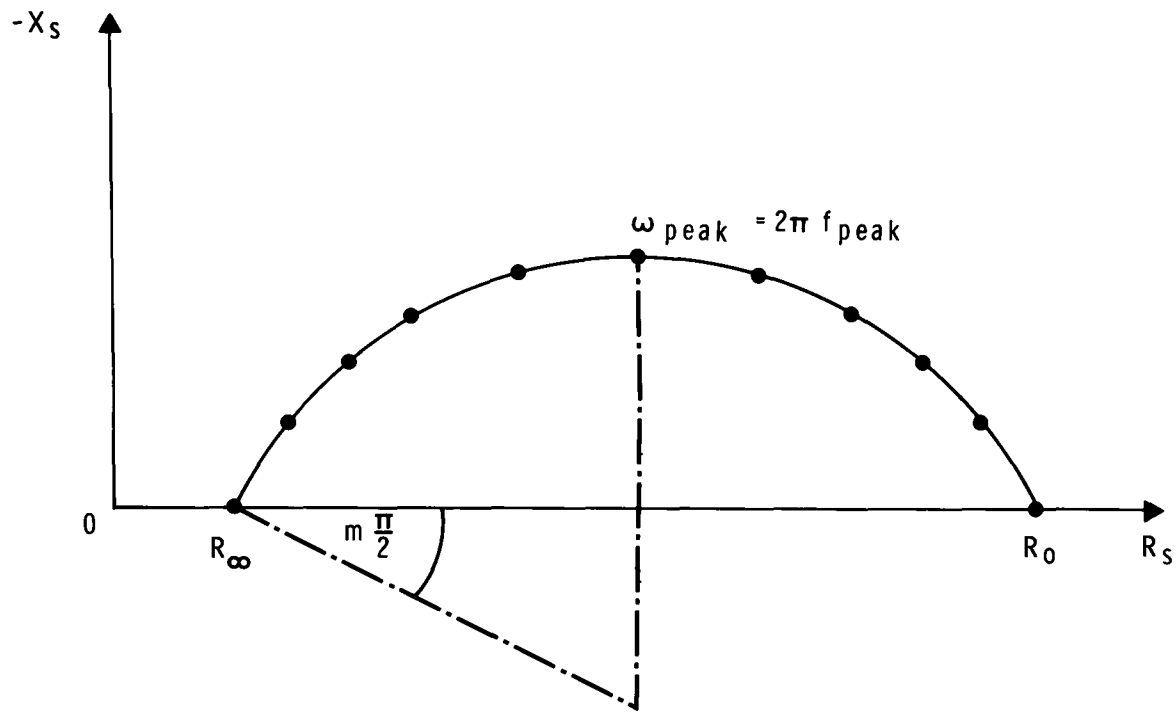


Fig. 8.3.I

This form of complex impedance locus can be completely specified in terms of only four basic quantities R_o, R_∞, τ_p and m if we write the Cole equation (cf. Sections 4.2, 9.5 and 11.2)

$$Z = R_\infty + \frac{R_o - R_\infty}{1 + (j\omega\tau_p)^{1-m}} \qquad (8.3.3)$$

where

$$\tau_p = 1/\omega_p = 1/(2\pi f_p) \qquad (8.3.4)$$

Consequently the linear electrical properties of an epidermal site can also be completely specified in terms of these four basic quantities, and can if desired be normalized to unit dimensions given the electrode area and the mean thickness of the epidermis (or better, the stratum corneum) at the site concerned.

It should however be emphasized again, that, as we pointed out in Section 4.2, ALL FOUR of these basic quantities must be derived in order to obtain an adequate basis for quantifying and comparing the linear electrical properties of skin. Unfortunately most of the literature has not recognised this and so has wasted everybody's time by only providing essentially ambiguous results.

The biophysical interpretation of the four basic quantities, and of the fact that the complex impedance of epidermis obeys the Cole equation, will be deferred until Chapter 11 where these questions will be dealt with in detail.

Here we will continue by considering how the data pairs derived from equations such as (8.3.1) and (8.3.2) can be further analysed so as to extract the maximum amount of information from them. This too however is such an extensive subject that the details have been relegated to a large and necessarily mathematical Appendix, Appendix B, so that here we need only consider the concepts involved.

The data analysis procedures described in detail in Appendix B are implemented by the program RESULTS, written for the main hospital computer in BASIC. This program, followed by another called CLINPLOT, produces on an associated graph plotter charts of analysed results which look very much nicer than photocopies of the MINC VDU screen, and so it is such charts which have been included in this thesis.

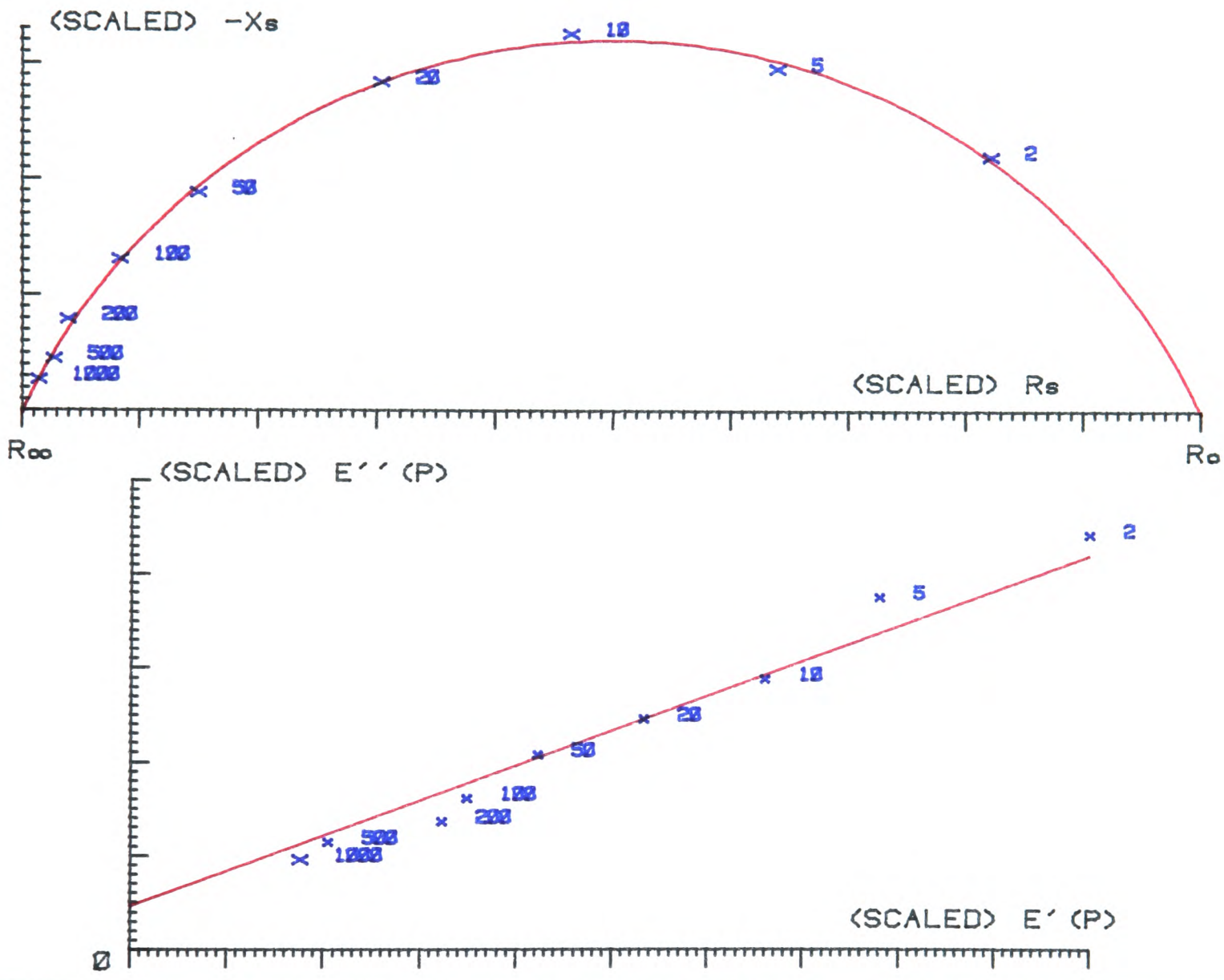
Let us consider such a chart, Fig. 8.3.II, produced by the versions of the programs RESULTS and CLINPLOT which may be inspected in Appendix C.

At the top is a list of the experimental conditions under which the measurements were obtained.

Below this section is the analysis of the results, in this case in fact pertaining to an epidermal site under what was electrode 4 on the left dorsal forearm of the subject, whose skin was normal. From the first entry in the

NAME	=	ANDREW STOCKLEY
AGE	=	24
DATE	=	24TH APRIL 1979
TIME	=	12.30 P.M.
BODY SITE	=	LEFT DORSAL FOREARM
SKIN TEMP.	=	27 C
AMBIENT R.H.	=	65 %
P-P CURRENT	=	1 MICROAMP

Fig. 8.3.II



			+PSE	+/-SE	-PSE
NO. OF DATA PAIRS	=	9			
R(ZERO)	=	1.77687E+06		19988.3	
R(INFINITY)	=	3928.48		19988.3	
F(PEAK) [USING M1]	=	8.71285	.351669	.338026	
F(PEAK) [USING M2]	=	8.71189	.127356	.125521	
E'' [E'=Ø]	=	6.37744E-10		5.19608E-10	
'U'	=	2.67288E-08	2.14552E-09	1.98610E-09	
M1 FROM Z LOCUS	=	.271517		1.23605E-02	
M2 FROM V/U PLOT	=	.273539		4.68930E-03	
M3 FROM E* LOCUS	=	.228417		.013115	
M4 FROM LN E'' PLOT	=	.247617		1.69077E-02	
& WEIGHTED MEAN M	=	.267567		8.08483E-03	

SINCE COMPARING M1 WITH M2, M3 AND M4 RESPECTIVELY,
THE SIGNIFICANCE OF THE DIFFERENCE BETWEEN THE MEANS IS
Ø.1Ø < P Ø.1Ø < P AND Ø.1Ø < P

COEFF. DET. OF (UNWEIGHTED) Z ARC FIT	=	.999441
COEFF. DET. OF (WEIGHTED) V/U PLOT	=	.999708
COEFF. DET. OF (WEIGHTED) E* LINE FIT	=	.836542

lower non-graphical section of the chart, we see that 9 resistance and reactance data pairs were used. The procedures of Subappendix B.1 were applied to these data pairs with the result that R_o and its standard error, R_∞ and its standard error, and an estimate of m called M1, together with its standard error, were estimated to have the values shown on the basis of the least-squares-best-fit minor arc of a circle.

A suitably scaled graph of the result of this procedure is plotted in the upper half of the chart. The range (in ohms) from the estimate of R_∞ to the estimate of R_o is assumed to fit exactly into a fixed line divided into ten units and a hundred sub-units, the (scaled) equivalent series resistance (R_s) axis. An equivalent series negative reactance ($-X_s$) axis is then plotted to the same scale beginning either at zero on the R_s axis if R_∞ is negative, or at R_∞ if R_∞ is positive. The experimental (R, X) data pairs are then plotted at the appropriate points on this graph as blue crosses, with the frequency (in Hertz) at which they were obtained plotted immediately to the right. Finally note that the red curve is the least-squares-best-fitted minor arc of a circle.

This fitted arc determines the estimates of R_∞, R_o and the M1 estimate of m (there are other ways of estimating m as we shall see in a moment). The estimates of R_∞ and R_o are then employed in the procedures detailed in subappendix B2 to produce two estimates of f_p, the frequency of maximum (negative) reactance. Estimating f_p involves a weighted least-squares fit of the data on the so-called Cole-Cole (v/u plot. The weights are chosen in order to favour the points with the largest reactance, for reasons explained in subappendix B.2. The fit of data on the (v/u) plot also provides another estimate of m, this being called M2. If we use this value in the procedure for estimating f_p, we obtain what I have called F(PEAK) [USING M2] on the chart, but if we assume M1 obtained from the Z locus arc fit to be correct instead, and constrain the f_p estimation procedure accordingly,

we of course obtain a different final result, which the chart also prints. These estimation procedures rely however upon non-linear transformations of variables, and so the +/- standard error, when put through the reverse transformation, comes out as two unequal quantities I have called "pseudo standard errors". Subappendix B2 gives a reference to a description of the rather cumbersome alternative to this procedure, namely iteration.

The program continues the analysis by using the estimate of R_o to calculate from the (R, X) data pairs the associated "processed" complex permittivity locus, ε^*_p, "processed" such that the effects of D.C. conductivity are subtracted off (see subappendix B.3). Such a clarified permittivity locus is very helpful in deciding whether or not certain biophysical hypotheses which have been put forward to interpret the linear electrical properties of epidermis are reasonable or not (cf. Section 11.6).

This locus is found to be a straight line to within experimental error, and from the Cole equation (8.3.3) there is reason to expect the angle between such a line and the axis of real permittivity ε'_p to be $m\pi/2$. Consequently a (weighted) least squares fit of a straight line to the locus is able to provide a third estimate of m called M3. The weights are chosen to favour those points obtained at frequences near f_p, since these come from the relatively more accurate data as we have mentioned above. The weights favour more highly however those points obtained at frequencies greater than f_p. Any inaccuracy in the estimate of R_o has a relatively greater effect on the derivation of the processed permittivity components at lower frequencies as R_s approaches R_o, and these less accurate points should have smaller weights. The lesser accuracy means that a greater scatter of "experimental" points about the fitted straight line is to be expected for frequencies below f_p, so such a scatter can be ignored unless it clearly shows an apparent trend.

The chart of results includes a graph of the processed permittivity locus, scaled arbitrarily but equally on each axis, and with data points and fitted line plotted in a similar way to that used for the Z locus. (The particular fitted line of Fig. 8.3.II is not one of the best; the weighting procedure has mindlessly taken too much notice of the fact that random errors happen to have aligned the points for 50, 20 and 10 Hz along a line of rather smaller inclination than would probably be drawn by hand. The poor fit is reflected in the atypically low value of M3 with its atypically high standard error, and by the low coefficient of determination at the bottom of the chart. However, the weighting procedure was designed to, and does, produce good results in most cases - compare for example Figures 9.3.b.II and 9.3.c.I - III.)

An estimated intercept of the fitted line on the ε''_p axis is also given on the chart, and this value multiplied by cot(M3.π/2) is related to the estimated value of ε_∞ by appropriate scaling factors depending on the electrode area and the corneum thickness. (Fig. 8.3.II is again a poor example, for the reasons above. Compare Figs. 9.2.b.II and Figs. 9.3.a.I - III which are more typical.)

As is mentioned in subappendix B4, an algebraic description of a straight line ε''_p locus may be derived from theoretical considerations, and it is possible using this algebraic description to obtain a further estimate of m, M4, by plotting the logarithm of ε''_p against the logarithm of frequency, and then performing a linear regression on the plotted points. It is also possible to calculate the value of a quantity "U" which gives all the information which has not yet been, but still can be, extracted about the polarization impedance in the equivalent circuit of the Cole equation. This too is discussed in subappendix B.4.

Now, if we assume that the Cole equation is a perfectly accurate description of the linear electrical properties of skin, and we also assume

that R_∞ is negligible in comparison with R_o, then all four estimates of m, M1 to M4, should not be significantly different from each other according to a t-test. Such a t-test is carried out according to subappendix B.5 and the results are printed on the chart. Such differences as exist have always been found to be insignificant at the 5% level, although sometimes significant at the 10% level. Since however a large amount of numerical fitting has been carried out in the analysis preceding this test, I think that differences at the 10% level may be ignored and our two assumptions justified. Consequently a weighted mean estimate of m is calculated from the estimates M1 to M4 and their standard errors (see subappendix B.5).

Finally, the wisdom of fitting a minor arc of a circle to the data on the Z plane, a straight line to the data in the log (v/u) against log f plane, and a straight line to the data on the ε^*_p plane, is tested by calculating the respective coefficients of determination according to the methods outlined in subappendix B.6. (The closer the values approach unity, the better is the goodness-of-fit.)

8.4 Characterizing the non-linear electrical properties of skin

From (5.3.a.2) it can be seen that by taking data obtained at one particular stimulating frequency and plotting the voltage measured against the current applied, we are producing a graph the slope of which is the generalized electrical impedance at that particular frequency. When non-linear electrical properties are negligible, the impedance at this frequency reduces to just a (complex) constant, as given by (5.3.c.2). Thus the slope of the graph will be constant, i.e. the graph will be a straight line, if the electrical properties of the system are solely linear. Consequently, then, non-linear properties at a particular frequency will show up as non-linearity in this graph of voltage measured against current applied, and such non-linearity as is found in the curve when it is constructed may if desired be interpreted in terms of an electrical charge gradient, as is done in the case of current / voltage characteristic curves of semiconductor junction diodes. Here however we plot voltage against current rather than vice versa, merely because for us current was the "cause" and voltage the "effect", but of course these graphs contain the same information as current/ voltage characteristic curves, and may be used as such if turned through 90°.

Let us now consider how to construct a voltage/current characteristic curve for "isolated epidermis" in vivo. Because an adequately separative electrode technique (such as that of subsection 6.3.b) has not been applied before, it has not previously been possible to make the necessary measurements for the construction of such a curve without injuring the subject. As a further advantage, the method to be described produces results pertaining to a single stimulating frequency, whereas ramp methods of deriving characteristic curves do not, and may produce rather misleading results in consequence (Salter, 1975, unpublished work). The present method is more fundamental and therefore potentially better.

We may in fact use the voltage / current characteristic curves we obtain to DEFINE the non-linear properties of "isolated epidermis" in vivo. After a measurement procedure at a single frequency the Analyser will have collected enough data to define in this way, quite independently, the non-linear properties of epidermal site 1, of epidermal site 4, of the deep tissue between sites 1 and 4, and of the current-carrying electrodes. Although both epidermal voltage/current characteristic curves would need to be completed and displayed when comparing the two epidermal sites in the same subject, here the methods of data processing will be demonstrated by taking just one case, that of epidermal site 4, just as we did in the last subsection. This has a purpose, as we shall see later.

Firstly, we compute $a_n(V_{e4})$ and $b_n(V_{e4})$ using (6.3.c.12). The Euler coefficients on the right hand side of (6.3.c.12) will have been calculated and stored in the Analyser following its electrode voltage sampling procedure, and the Analyser is designed to allow them to be extracted via the serial interface. However, since in fact the Analyser only calculates and stores the various coefficients for n = 0, 1, 2, 3, and 4, we can only derive from (6.3.c.12) the epidermal coefficients up to $n_{max} = 4$ when reconstructing the epidermal voltage output waveform, which is the next step. We compute a single period of this output waveform by using

$$V_{out} = V_{e4}(f) = V_{e4}(\frac{k}{N}.2\pi)$$

$$= \tfrac{1}{2}a_o(V_{e4})$$

$$+ \sum_{n=1}^{n=n_{max}} [a_n(V_{e4}) \cos (n2\pi\frac{k}{N}) + b_n(V_{e4}) \sin (n2\pi\frac{k}{N})]$$

$k = 1, 2, 3 \ldots N;$ $\quad N =$ some large number (8.4.1)

The units of this reconstruction are of course volts, as they are of the $a_n(V_{e4})$ and the $b_n(V_{e4})$.

Now a sine wave having the same period as $V_{e4}(t)$ is $\sin(2\pi k/N)$. This can be used to represent the input current, by writing

$$I_{in} = I_{e4}(t) = \tfrac{1}{2}I_{pp} \sin(2\pi\frac{k}{N}) \qquad (8.4.2)$$

which for k = 1, 2, 3 ... N is the cycle of input current associated with the cycle of output voltage $V_{e4}(t)$ in (8.4.1), I_{pp} being the selected peak-to-peak current value.

We can now produce a graph of input current against output voltage for epidermal site 4, i.e. its voltage/current charasteristic curve, by choosing N to be some suitably large number (e.g. 100), and incrementing through values of k from 1 to N, calculating I_{in} from (8.4.2) and plotting it as the x - coordinate (input), and calculating V_{out} from (8.4.1) and plotting it as the y - coordinate (output), at each value of k. Then by the time that k = N, a complete Lissajous figure will have been constructed, probably looking rather like a hoop, and indeed a bent hoop if the generalized impedance the current passes through is at all non-linear. To see the loop "edge-on", and thus obtain a more easily interpretable voltage/current characteristic curve, we must correct for any phase difference between input and output waveforms by using

$$I_{in}(\text{phase corrected}) = \tfrac{1}{2}I_{pp} \sin\left[2\pi\frac{k}{N} - \arctan\frac{a_1(V_{e4})}{b_1(V_{e4})}\right] \qquad (8.4.3)$$

instead of (8.4.2) in the calculation of the x - coordinate, the arctan term being the phase difference between the actual input waveform (8.4.2) and the dominant harmonic component of the output waveform (8.4.1). Incrementing the values of k up to N will now construct a classical "characteristic" curve, such as the schematic one shown in Fig. 8.4.I.

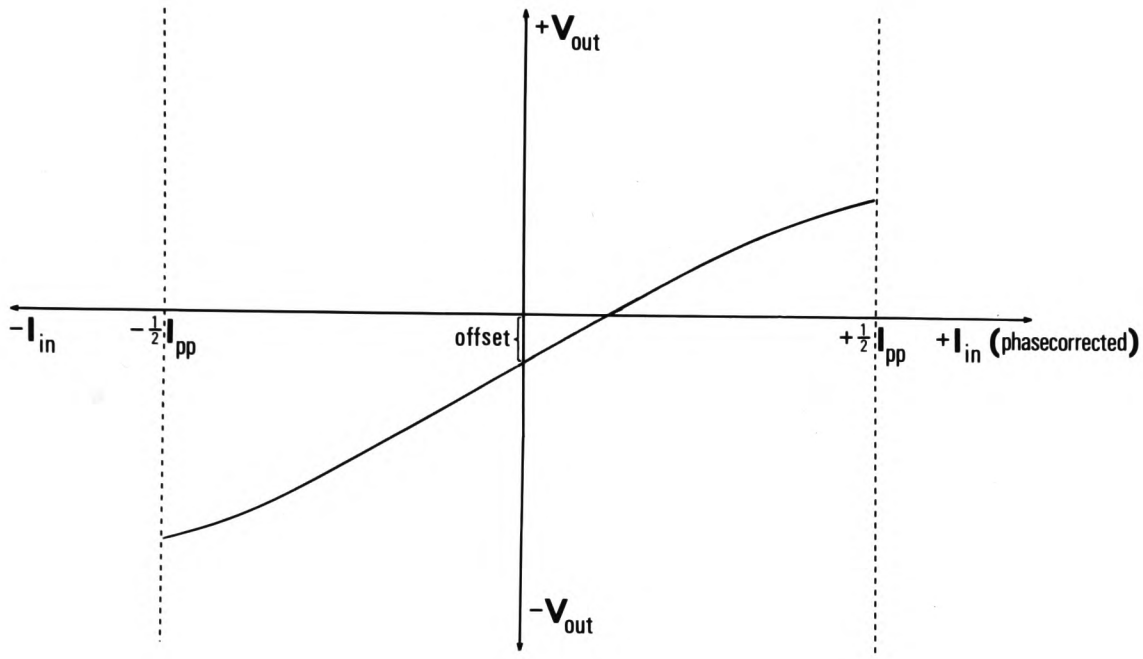


Fig. 8.4.I

For purposes of standardization, and in order to observe the maximum amount of non-linearity in this curve, it should be constructed from measurements made at a frequency low enough to ensure that the linear electrical impedance tends to R_o. A suitable frequency can be estimated from a complex impedance plot such as we considered in the last subsection.

Any voltage offset of the curve from the origin at $I_{in} = 0$ indicates the presence of a generator of e.m.f. in series with the impedance being characterized. Thus for our present example the offset (which is not necessarily the same as C in (5.3.b.3), a simple voltage average in conditions of non-zero current), enables the skin potential level at site 4 to be derived, the offset being the potential of the surface of the corneum at site 4 with respect to the underlying dermis, plus the site 4 electrode interfacial e.m.f. which can be subtracted off. This approach avoids the

difficulties of trying to apply equation (61) of Salter (1979). The skin potential level is of course of considerable physiological interest (cf. Section 12.3), and a review of its dermatological relevance has been given by Woodrough (1976).

To produce charts of voltage / current characteristic curves which are more presentable than would be possible using the MINC VDU, I wrote a program called VICHAR and a series of graph plotting programs for use with the main hospital computer. These programs, which are described in Appendix D, produced Figure 8.4.II, which is included here as an actual example of a voltage/current characteristic curve.

Fig. 8.4.II represents the linear and non-linear properties at 2Hz of that same epidermal site 4, the linear properties of which were fully characterized in Fig. 8.3.II.

The chart is drawn such that the V/I characteristic curve is centred in the enclosing frame, and the (scaled) voltage and current axes move about within the frame to define the points on the curve. The values of the ends of these axes are given in the legend at the bottom right hand corner of the chart, and a small cross is printed immediately to the right of the point k = 1 to indicate the amount of phase-correction.

Note that the characteristic appears to be curved across its full extent, although when the applied current is such as to produce a voltage across this epidermal site of a magnitude less than about 1 volt, the characteristic curve may well be linear to within experimental error. I still stand by my published statement of disbelief in a truly linear region (Salter, 1981), but I have included a discussion of it in Section 4.3 and Chapters 11 and 12, because under certain circumstances the non-linearity time-variance of the skin may be approximated as negligible if one is prepared to be less than maximally rigorous.

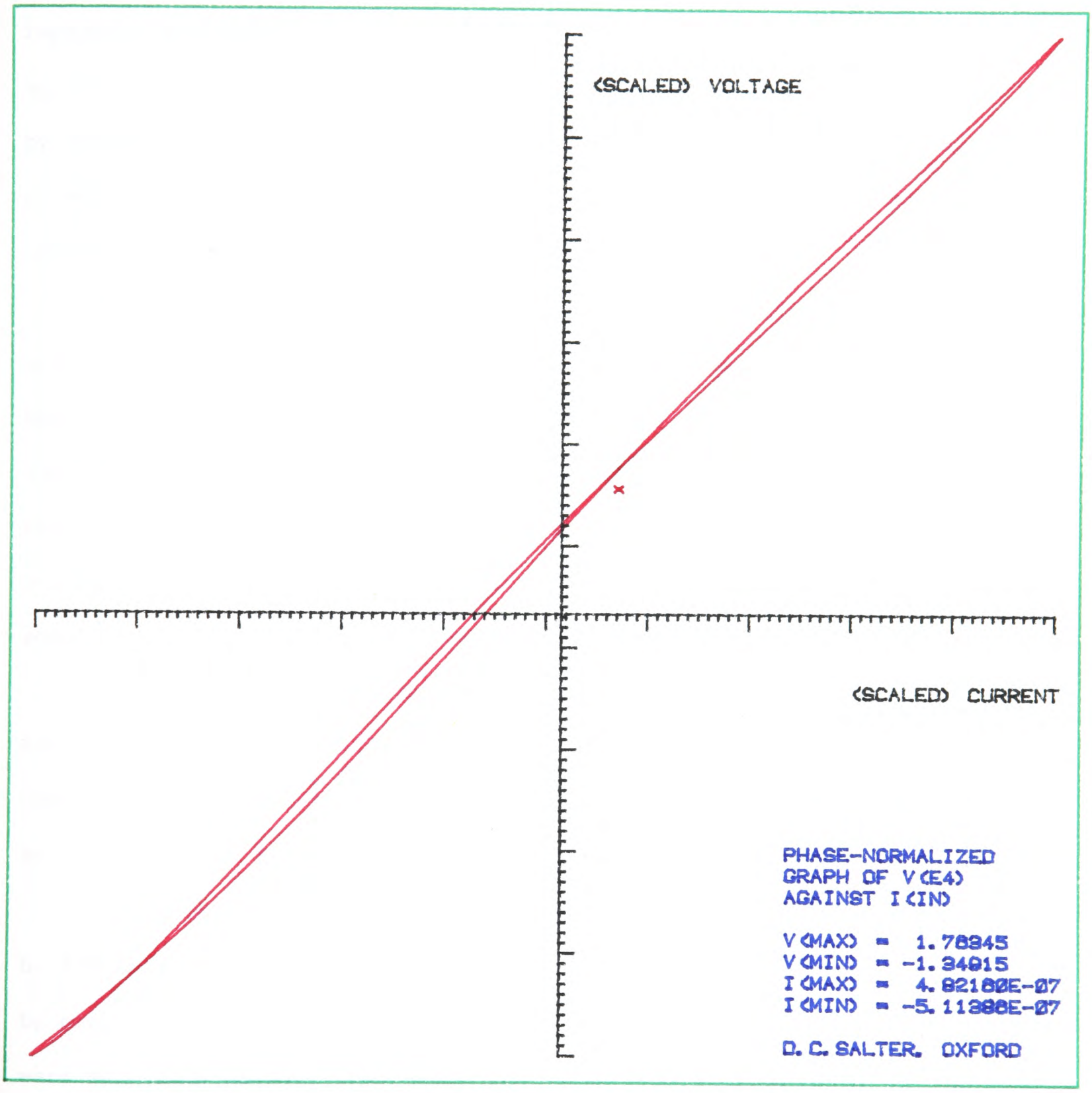

(SCALED) VOLTAGE
(SCALED) CURRENT
PHASE-NORMALIZED
GRAPH OF V(E4)
AGAINST I(IN)
V(MAX) = 1.78345
V(MIN) = -1.34915
I(MAX) = 4.82180E-07
I(MIN) = -5.11388E-07
D. C. SALTER, OXFORD

Fig. 8.4.II

8.5 Problems with the Analyser

As I have acknowledged before (Salter 1979), but without mentioning what unfortunately must be apologized for here, the Fourier Transform Impedance Analyser was sponsored by Vick International Ltd., and built for us by Plessey Microsystems Ltd. on the basis of a design report written by myself in August 1976. The outline specification and quotation we accepted were dated October 1976 and delivery was stated to be 20 - 24 weeks from receipt of the order (see Appendix E).

Due to a number of factors at Plessey which it would be less than gracious to mention, the Analyser was not however delivered to The Slade Hospital until 30th August 1978. What had been estimated to be a six-month job had therefore taken nearly two years, and despite many consultations with me and even my spending many days actually at the Plessey factory, a number of engineering compromises, some of which we were aware of but most of which we were not, became incorporated into the equipment.

Shortly after the Analyser was delivered, I was appointed to a Postdoctoral Research Fellowship in the Department of Pathology at another Oxford hospital (The Radcliffe Infirmary), and this severely restricted my opportunities for testing the Analyser.

I soon observed however that the current output wavetrains produced by the Analyser could sometimes (and, amazingly, only sometimes) be felt by people with normal skin, even though the current densities concerned were very much smaller than those for which such effects might be expected. I complained to Plessey that this would probably cause difficulties in the use of the Analyser with patients having abnormal skin which might therefore be more sensitive, but I do not now remember how I was persuaded to attempt to live with this problem. We soon discovered another as well - there was an unexpected and unpredictable fault in the data display subroutines (cf. Appendix D).

Meanwhile, a considerable administrative delay at Vick International meant that we only received the MINC minicomputer in December 1979, and without a link to a computer there had been little point in using the Analyser. By January 1980, I had however assembled the computer from the kit form in which it arrived, learnt to program it, and attempted to interface it to the Analyser, but only to find that the Analyser would not interface with it properly. After a day of effort by a representative of Plessey and a representative from Digital, the manufacturers of MINC, I myself finally traced the fault to a missing earth wire in the Analyser - another fault due to Plessey.

Programming then proceeded smoothly, until I discovered that when the results of the Analyser's measurements were read by the computer via the serial interface, they only made sense if the Analyser had been measuring a purely resistive network (cf. Appendix A). After making the obvious checks, no simple fault had been discovered, and everyone remained baffled.

Vick International then decided to call in an outside opinion to investigate where the blame for all these faults might lie, and maybe to suggest ways to cure them. The experts chosen were from the German medical electronics consultancy Lauer GmbH, which, I understand, has included the U.S. space agency NASA among its clients.

I am glad to say that these German engineers exonerated me, but sad to say that they found a large number of faults in the construction and operation of the Analyser which are briefly described and illustrated in a shortened version of their technical report (Appendix E). These were considered to be attributable to Plessey.

Vick International reported the conclusions to Plessey, but because the period of warranty on the Analyser had long since expired, negotiations had to take place regarding the likely cost in terms of time and money of rectifying these faults. Eventually Vick was told that to correct the

data available via the serial interface, together with increasing the speed of data transfer (which was a modification we wanted undertaken), would cost about £1,500 and take perhaps a month, whereas to do this *AND* attempt to get rid of what we now knew to be large spikes and other undesirable phenomena in the output wavetrains, would cost between £6,000 and £10,000 and take perhaps six months. Whether or not this latter proposal was intended to be discouraging, in the event it certainly was, and Vick opted for the cheaper and only partial repair.

However, in the meantime the Analyser had broken down with a new fault due simply I assume to wear and tear over its two years of intermittent use without computer assistance. This breakdown paralysed it.

When Plessey had to add to the old estimate the cost of repairing the breakdown, an estimate was mentioned of £2,300 and about three months' work. This however was the straw which broke the camel's back, and Vick, instead of going ahead with the repair, decided not to do so, but instead to consider legal action against Plessey to attempt to recoup some of their losses.

Due to the non-repair it was therefore not possible to complete program PROC and the other programs which would have reproduced on the MINC VDU the same type of charts as are produced (rather more attractively in fact) on the main hospital computer graph plotter by the programs discussed in Appendices C and D. Nevertheless, this Chapter has I hope shown that it has been possible to vindicate the original methodological approach of the Analyser, even though using it was always more difficult than it need have been.

PART III: SOME REPRESENTATIVE RESULTS

Chapter 9. FINDINGS IN NORMAL SKIN

9.1 Introduction

The electronic problems discussed in Section 8.5 made it very difficult (though certainly not impossible) to use the Analyser in the more sophisticated tasks for which it had been designed, and consequently these were undertaken relatively infrequently. Most of our clinical investigations were in fact of just the linear electrical properties of skin, and employed the Analyser with a simple configuration of two test electrodes on the subject and two reference electrodes connected face-to-face by Carbopol gel (see subsection 7.5.c). The reference channel showed that the impedance of the electrodes and gel was usually very small (being almost purely resistive over the frequency range 2Hz - 20kHz with an equivalent series resistance averaging 500 ohms at a current of 20 microamps), and the deep tissue impedance was comparable (cf. Barnett, 1938; Gerstner and Gerbstädt, 1949; Yamamoto and Yamamoto, 1976a). Therefore considering the magnitude of the impedance Z_{14} over the frequency range we were using, the electrode and deep tissue impedances could be neglected without significant loss of accuracy. (This approximation would not however have been acceptable had use been made of larger electrodes and more conductive electrode gels, such as many previous investigators employed. The criticisms made by Barnett (1938) would then have applied to our work too.)

This Chapter considers the variability of the electrical properties of normal skin, since unless the bounds of normality are defined, it is not possible to distinguish abnormality. The Sections which follow are intended to briefly review the results in the literature and, where appropriate, to integrate them with our own findings.

9.2 The inherent electrical variability of normal skin

9.2.a with body site

The variability of the electrical properties of skin is very large, and the variation with body site is the largest factor contributing to this. Consequently, this factor is very well known and has been investigated by many people, usually however rather perfunctorily. They have investigated the variation between sites in a single subject, and also the variation between a single site in several subjects.

Rosendal (1943, p.135; 1944, p.187) for example, showed that the variation between sites in a single subject could easily exceed a factor of 100 in the case of R_o, and he attributed this finding to variations in the properties of the stratum corneum at the sites concerned. It is interesting to observe how closely such results are indeed correlated with regional variations in stratum corneum thickness and permeability (discussed for example by Scheuplein, 1978, Ch.56).

Rosendal (1943, p.135; 1944, p.187) also investigated a few sites in a number of subjects, but the much more extensive data given by Edelberg (1967, Table 1.1) clearly show that the corneum is not the only determinant of R_o, and that an increased surface density of skin appendages tends to increase the D.C. conductance, as expected.

Some statistical aspects of such measurements have been considered by Richter (1969), who investigated the distribution of R_o values in 110 men and 100 women between the ages of 7 and 82, on the forehead, the back of the hand, and the thorax directly below the middle of the clavicle, for both sides of the body. He found bimodal distributions, whereas Grings (1953), working with only 33 subjects, had found unimodal distributions.

We have not attempted to investigate statistical distributions, but an enormous variation of Cole equation parameters with body site has been observed, and a lesser one between similar sites on different subjects,

all for the same conditions of room (not skin) temperature and relative humidity. On dorsal forearms, our most frequently measured site, the maximum and minimum values of R_o derived for a single epidermal site were 1.4×10^6 and 1.85×10^9 ohms, with τ_p values of 2.27×10^{-2} and 1.33×10^{-3} seconds respectively. On this scale, R_∞ was indistinguishable from zero. The parameter m also varies considerably from site to site in the same subject, and also between subjects, usually lying in the range 0.15 to 0.4.

There is much discussion in the literature of the "phase angle" θ and its value at a single frequency as a function of body site, pathology, age, sex and so on (e.g. Barnett, 1938; Gougerot, 1947; Rothman, 1954). I have pointed out elsewhere though (Salter, 1979, Section 4.2; and this thesis, Section 4.2) that if the Cole equation is obeyed, such measurements are extremely difficult to interpret, because θ at a single frequency can vary with so many factors (see equation (4.2.6)). A plot of θ over many decades of frequency is however rather more useful, but less so (subsection 10.1.b) than for example the Z locus plot, from which the parameters of the Cole equation can all be obtained. These parameters are much more fundamental than the phase angle, and that is why we are working in terms of the Z locus and the Cole equation in this thesis.

9.2.b with time

The variation in the electrical properties of skin with time may obviously be the result of a large number of factors which it would be impossible to consider adequately here. Let us then merely consider the magnitude of the variation and not its causes. Even this topic may be split for convenience into three headings: short-term variation, diurnal variation, and longer-term variation including seasonal changes.

Short-term variations of the order of seconds or minutes are reviewed in appropriate detail in Sections 12.2, 12.3 and 12.6.

Diurnal variations have been discussed by Rosendal (1943, p.135; 1944, p.186) and he found that on average there was a day-to-day change by about a factor of 6 in the value of R_o on the volar forearm. Regelsberger (e.g. 1952) examined daily rhythms in much more detail, and his work is reviewed by Dorscheid (1960, pps. 17 ff). Amongst many other observations, he found that R_o was greater in the morning than in the evening, and also increased following the intake of food or drink, or during a period of expectation of such intake. In experiments upon myself (1974, unpublished) I found that peaks of conductance and skin temperature were present at around 12.30 p.m. and 4.30 p.m., the peak-to-trough difference being about 35% for conductance and 6 K for temperature. I think that the shunting of blood away from the dermis to the intestinal tract is not in itself important because R_o is hardly dependent on the resistivity of deep tissues at all. Rather, I think the effect arises from duirnal variations in trans-epidermal water loss associated with changes in metabolic rate. As metabolic rate rises, so does TEWL, the hydration of the corneum, and also its electrical conductance (Appendix G, p.15).

More recently I have measured a marked pair of sites on my left dorsal forearm under exactly the same conditions on two consecutive days. The experiment was repeated a number of times and typical results are shown

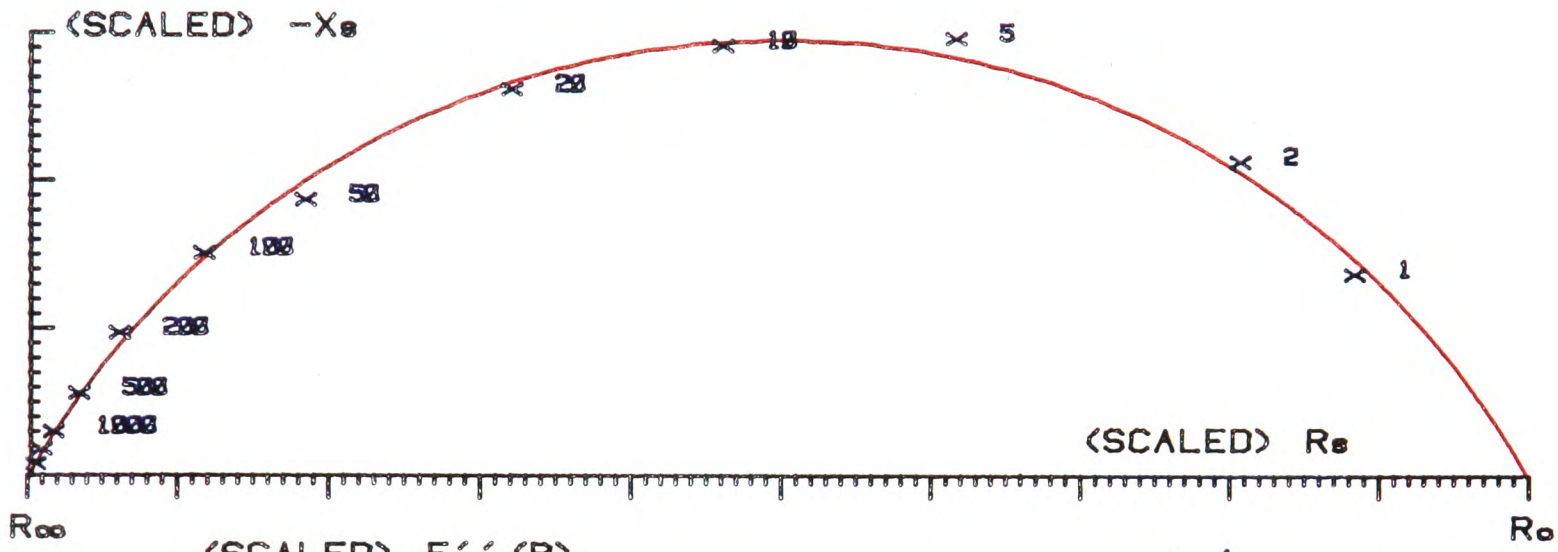
in Fig. 9.2.b.I for Day 1 and Fig. 9.2.b.II for Day 2. We see a decrease in R_o by about a factor of 6 (cf. Rosendal's finding mentioned above), a slightly larger change in f_p, and a relatively small change of about 20% in m. The estimates of R_∞ however have too large a standard error to make comparison of these values worthwhile. (Note incidently that as R_o decreases, m increases. This is not invariably found, but does at least correspond to the case of increasing the hydration of the corneum, as we shall see later in subsection 9.3.c and in Section 11.9.)

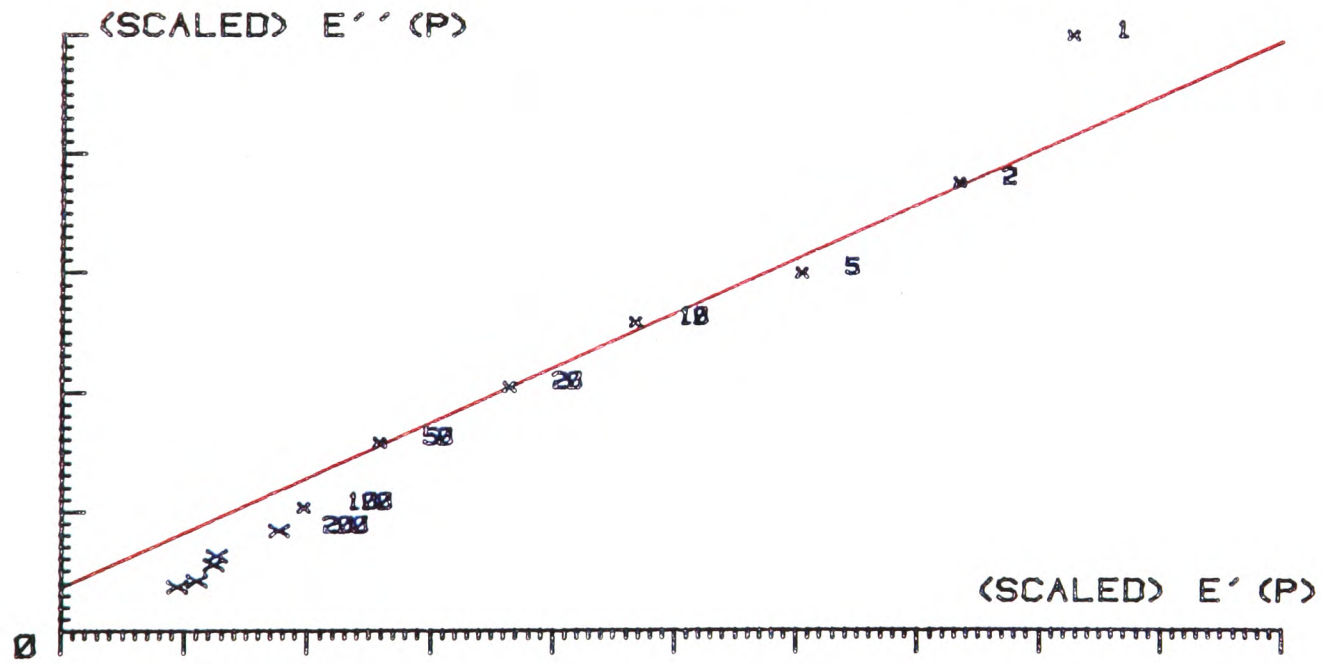
Now let us consider longer-term and seasonal changes. One's first thought may be of the menstrual cycle, and indeed Ipser (1969) observed a change in R_o connected with this cycle, although he also claims that there is a rather less evident monthly cycle in men too, which remains unexplained.

Barnett (1940) measured epidermal impedance at 11 kHz by a three-electrode method with an electrode area of 6 cm^2, and found there was a maximum in summer. This conclusion however contrasts with that of Lawler et al (1960) who could not detect any seasonal variation in skin impedance at 4 kHz measured with a two-electrode technique having an electrode area of π cm^2. However, I suspect that any seasonal (as other) changes will in fact affect R_o by a much greater percentage than R_∞, and so they will be more easily detected at lower frequencies (cf. the Rosendal/Gildemeister controversy: Rosendal, 1943, pps.131, 132). Certainly Ipser (1969), who was using D.C., was able to detect a minimum of R_o in January, and a maximum in the summer, tending to agree with Barnett.

NAME	=	DAVID SALTER
AGE	=	25
DATE	=	7TH FEBRUARY 1978
TIME	=	3.20 P.M.
BODY SITE	=	LEFT DORSAL FOREARM
SKIN TEMP.	=	27 C
AMBIENT R.H.	=	63 %
P-P CURRENT	=	5 MICROAMPS

Fig. 9.2.b.I





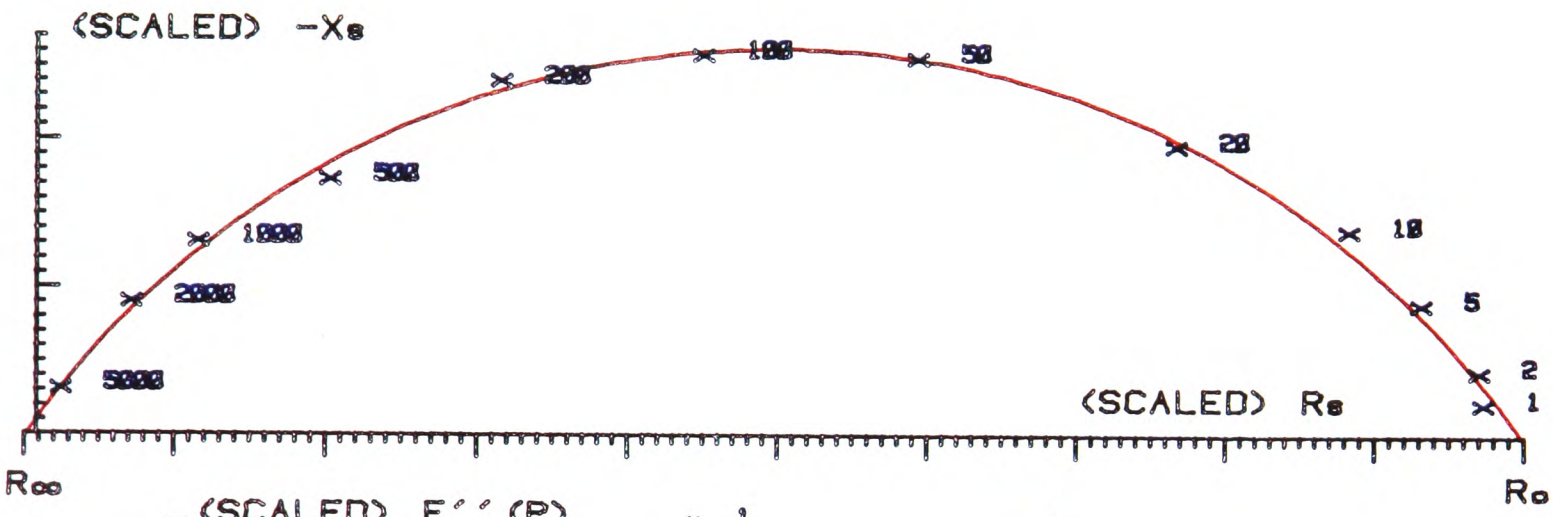
		+PSE	+/-SE	-PSE
NO. OF DATA PAIRS	=	12		
R(ZERO)	=	421944	5804.62	
R(INFINITY)	=	-664.187	5804.62	
F(PEAK) [USING M1]	=	8.39843	1.04096	.926161
F(PEAK) [USING M2]	=	8.38391	.225019	.219137
E'' [E'=0]	=	2.97294E-09	7.87875E-10	
'U'	=	1.32957E-07	1.06721E-08	9.87909E-09
M1 FROM Z LOCUS	=	.316152	1.48833E-02	
M2 FROM V/U PLOT	=	.338401	7.85229E-03	
M3 FROM E* LOCUS	=	.274085	5.63811E-03	
M4 FROM LN E'' PLOT	=	.320414	1.66418E-02	
& WEIGHTED MEAN M	=	.299179	1.68779E-02	

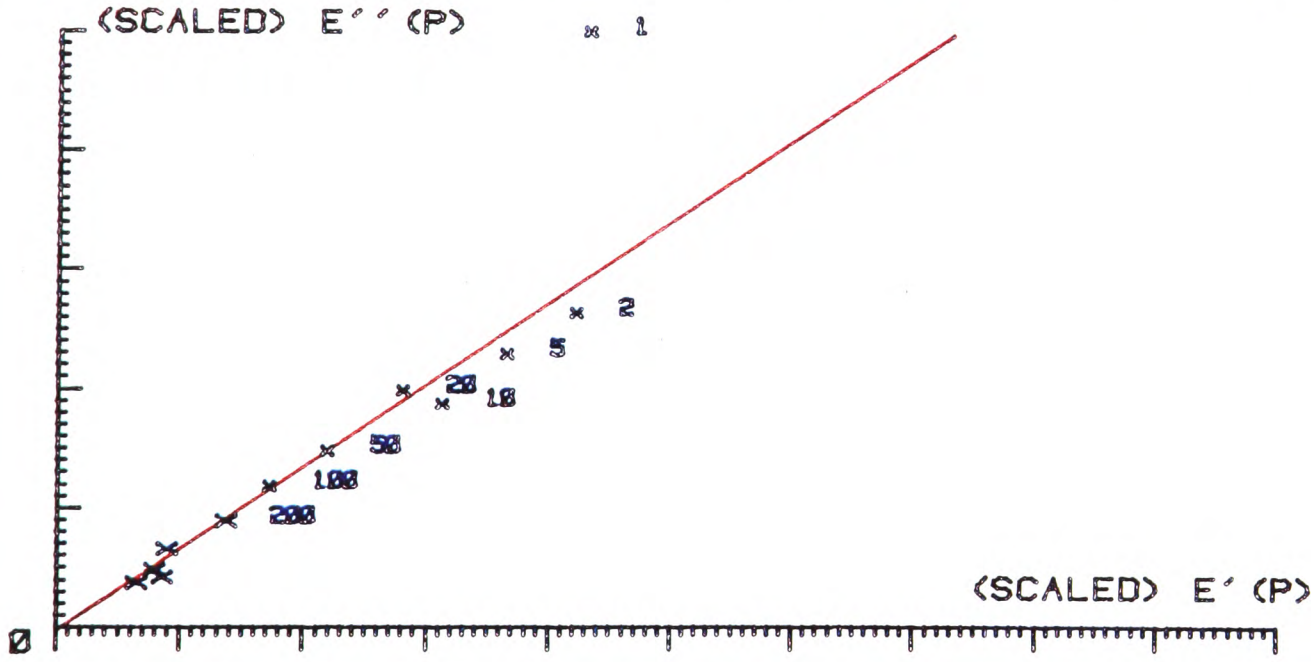
SINCE COMPARING M1 WITH M2, M3 AND M4 RESPECTIVELY,
THE SIGNIFICANCE OF THE DIFFERENCE BETWEEN THE MEANS IS
0.10 < P 0.10 < P AND 0.10 < P

COEFF. DET. OF (UNWEIGHTED) Z ARC FIT	=	.999159
COEFF. DET. OF (WEIGHTED) V/U PLOT	=	.998593
COEFF. DET. OF (WEIGHTED) E* LINE FIT	=	.9748

NAME	=	DAVID SALTER
AGE	=	25
DATE	=	8TH FEBRUARY 1978
TIME	=	3.00 P.M.
BODY SITE	=	LEFT DORSAL FOREARM
SKIN TEMP.	=	28 C
AMBIENT R.H.	=	63 %
P-P CURRENT	=	5 MICROAMPS

Fig. 9.2.b.II





			+PSE	+/-SE	-PSE
NO. OF DATA PAIRS	=	12			
R(ZERO)	=	72092.4		1121.58	
R(INFINITY)	=	-553.55		1121.58	
F(PEAK) [USING M1]	=	78.3823	28.5034		20.9023
F(PEAK) [USING M2]	=	78.5961	3.64027		3.47914
E'' [E'=0]	=	-3.23316E-10		5.70021E-10	
'U'	=	2.30838E-07	1.44502E-08		1.35989E-08
M1 FROM Z LOCUS	=	.380089		1.55443E-02	
M2 FROM V/U PLOT	=	.349183		6.62444E-03	
M3 FROM E* LOCUS	=	.383382		8.45561E-03	
M4 FROM LN E'' PLOT	=	.375912		8.83680E-03	
& WEIGHTED MEAN M	=	.36884		8.88143E-03	

SINCE COMPARING M1 WITH M2, M3 AND M4 RESPECTIVELY,
THE SIGNIFICANCE OF THE DIFFERENCE BETWEEN THE MEANS IS
0.05 < P <= 0.10 0.10 < P AND 0.10 < P

COEFF. DET. OF (UNWEIGHTED) Z ARC FIT	=	.999609
COEFF. DET. OF (WEIGHTED) V/U PLOT	=	.998965
COEFF. DET. OF (WEIGHTED) E* LINE FIT	=	.983156

9.2.c with skin temperature

A change in skin temperature will affect the electrical properties of that skin in at least two ways. Firstly, there are likely to be physiological alterations in sweat gland activity which will in turn affect the degree of appendageal shunting of the impedance of the epidermis. Secondly, there will be purely physical effects in that activation energies for diffusion will be acquired more or less frequently. Let us consider these physiological and physical aspects in succession.

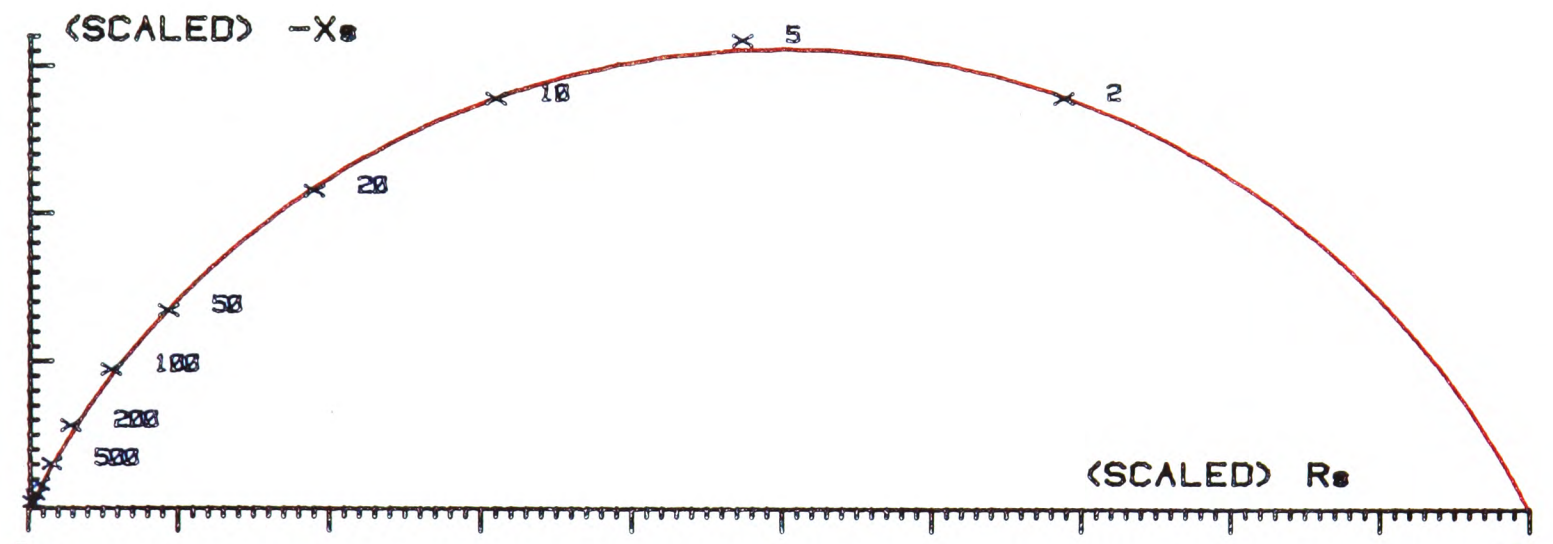
Smith (1937) was an early investigator of the effect of temperature upon the electrical properties of skin, and claimed that he found them to be unchanged by the facilitation of sweating. He admitted, however, to allowing the process of subject relaxation to intrude, and relaxation is well known to have the effect of raising the skin resistance level.

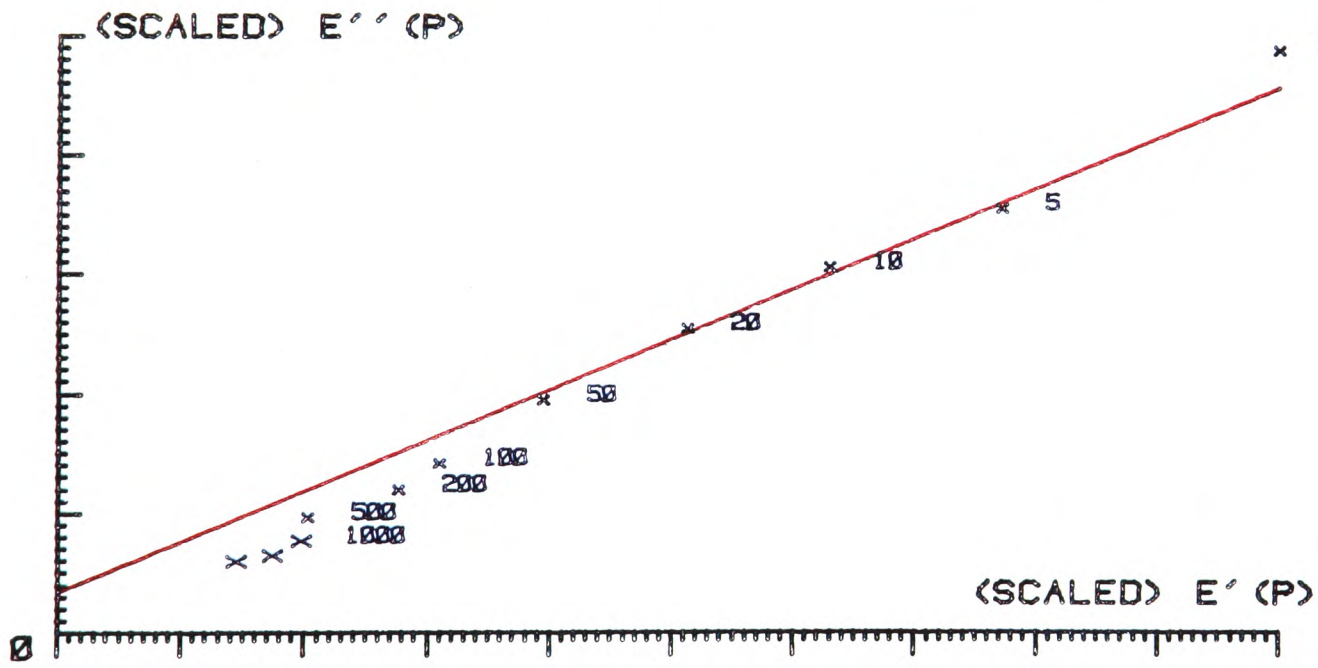
The lack of change observed by Smith seemed so unlikely to me on both physiological and physical grounds that I conducted some simple experiments to disprove it, and to ascertain the electrical effect of temperature change upon the parameters of the Cole equation.

Some typical results are shown in Figures 9.2.c.I and 9.2.c.II; in the first case I was in a room temperature cold enough to ensure that sweating was minimal, whereas in the second case I was subjectively hot and objectively sweating. We can see that the increase in skin temperature and the onset of sweating has produced a considerable reduction in R_o and a corresponding increase in f_p, BUT THE VALUE OF M IS NOT SIGNIFICANTLY CHANGED. I consider this to be very important, since we may infer that the magnitude of m depends upon the state of the corneum, not the appendages. If indeed it has had any effect at all, the very slight percentage change represented by an increase of 10 degrees on an initial (Absolute) temperature value of about 295 degrees has only produced a very slight reduction in the value of m, and this in fact is in very good agreement with the theoretical

NAME	=	DAVID SALTER
AGE	=	25
DATE	=	22ND FEBRUARY 1979
TIME	=	11.ØØ A.M.
BODY SITE	=	LEFT DORSAL FOREARM
SKIN TEMP.	=	22 C
AMBIENT R.H.	=	63 %
P-P CURRENT	=	5 MICROAMPS

Fig. 9.2.c.I





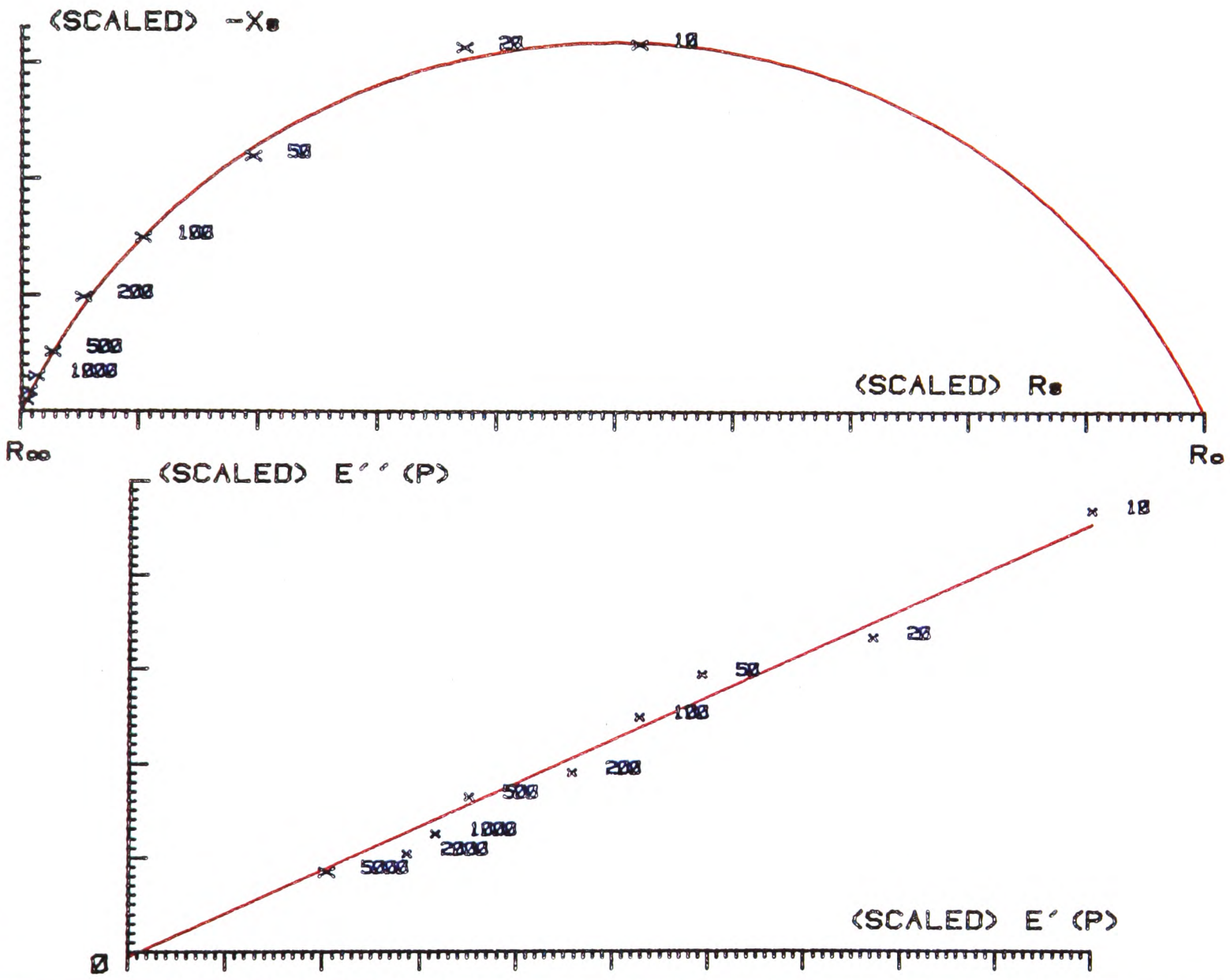
		+PSE	+/-SE	-PSE
NO. OF DATA PAIRS	=	11		
R(ZERO)	=	820395	7150.81	
R(INFINITY)	=	-801.66	7150.81	
F(PEAK) [USING M1]	=	4.47862	.151636	.146669
F(PEAK) [USING M2]	=	4.47695	2.29588E-02	2.28424E-02
E'' [E'=Ø]	=	1.73208E-09	7.68614E-10	
'U'	=	9.86971E-08	3.95971E-09	3.80697E-09
M1 FROM Z LOCUS	=	.284973	8.78820E-03	
M2 FROM V/U PLOT	=	.287948	2.20368E-03	
M3 FROM E* LOCUS	=	.254898	5.17988E-03	
M4 FROM LN E'' PLOT	=	.255073	9.84854E-03	
& WEIGHTED MEAN M	=	.281909	7.27008E-03	

SINCE COMPARING M1 WITH M2, M3 AND M4 RESPECTIVELY,
THE SIGNIFICANCE OF THE DIFFERENCE BETWEEN THE MEANS IS
Ø.1Ø < P Ø.1Ø < P AND Ø.Ø5 < P <= Ø.1Ø

COEFF. DET. OF (UNWEIGHTED) Z ARC FIT	=	.999349
COEFF. DET. OF (WEIGHTED) V/U PLOT	=	.999914
COEFF. DET. OF (WEIGHTED) E* LINE FIT	=	.974836

NAME	=	DAVID SALTER
AGE	=	25
DATE	=	22ND FEBRUARY 1979
TIME	=	12.10 P.M.
BODY SITE	=	LEFT DORSAL FOREARM
SKIN TEMP.	=	32 C
AMBIENT R.H.	=	56 %
P-P CURRENT	=	2 MICROAMPS

Fig. 9.2.c.II



			+PSE	+/-SE	-PSE
NO. OF DATA PAIRS	=	9			
R(ZERO)	=	430936		12111.7	
R(INFINITY)	=	-389.515		12111.7	
F(PEAK) [USING M1]	=	11.2086	4.09882		3.00129
F(PEAK) [USING M2]	=	11.0106	.606087		.574465
E'' [E'=0]	=	-1.40762E-10		1.10963E-09	
'U'	=	9.07845E-08	2.13826E-08		1.73064E-08
M1 FROM Z LOCUS	=	.274147		2.68283E-02	
M2 FROM V/U PLOT	=	.377315		1.30932E-02	
M3 FROM E* LOCUS	=	.274842		1.03756E-02	
M4 FROM LN E'' PLOT	=	.288918		4.34408E-02	
& WEIGHTED MEAN M	=	.310299		2.79485E-02	

SINCE COMPARING M1 WITH M2, M3 AND M4 RESPECTIVELY,
THE SIGNIFICANCE OF THE DIFFERENCE BETWEEN THE MEANS IS
0.002 < P <= 0.01 0.10 < P AND 0.10 < P

COEFF. DET. OF (UNWEIGHTED) Z ARC FIT	=	.993691
COEFF. DET. OF (WEIGHTED) V/U PLOT	=	.996915
COEFF. DET. OF (WEIGHTED) E* LINE FIT	=	.942815

interpretation of m discussed in Section 11.9.

(Note that the anomalous estimate of M2 arises due to the fact that the weighting procedure used to fit a line on the log (v/u) against log f plane, as described in subappendix B.2, is heavily weighted in favour of the usually more accurate data points occurring near f_p, the frequency of maximum reactance magnitude. In the particular case of Fig. 9.2.c.II, the "rogue" point at 20 Hz has therefore had an undeservedly large corrupting effect which has not, for this locus, been adequately corrected by enough data points obtained at frequencies less than f_p. Consequently the estimate of M2, and of the significance of its difference from M1, should not (for this particular set of results) be considered to be reliable.)

The reduction of R_o with increase in skin temperature should naturally lead us on to think of purely physical effects too, and in particular the question of whether or not skin acts as a semiconductor in having a definite activation energy for D.C. conduction. (A semiconductor may be defined as a material which has a negative temperature coefficient of resistance and a thermally activated conductivity - see e.g. Smith, 1978.)

Now, Maulsby and Edelberg (1960) were so far as I know the first to investigate carefully and quantitatively the dependence of the D.C. resistance R_o upon skin (surface) temperature in vivo. They fitted their data approximately by straight lines on graphs of log R_o against skin temperature in ^oC, which was interesting, but not physically interpretable in any simple way. However, their data can be represented just as well by straight lines on graphs of ln R_o against 1/(skin temperature + 273.15^oK) in $(^oK)^{-1}$, since if B is the skin temperature and A is 273.15^oK

$$\frac{1}{A+B} \simeq \frac{1}{A} - \frac{1}{A^2} \cdot B \quad \text{by Maclaurin expansion as } B \ll A \qquad (9.2.c.1)$$

From such graphs it is indeed possible to derive an effective activation energy, although of course the biological interpretation of such an entity is debatable.

For the Maulsby and Edelberg (1960) Figure 1 line representing data obtained on a single subject, I derived the following Table:

Table 9.2.c.A

R_o (Ω)	skin temp. ^oC	Calculated R_o (Ω)
7,000	38.3	7,066.2
8,000	34.8	7,985.6
9,000	31.65	8,936.4
10,000	28.8	9,913.9
11,000	25.95	11,020
12,000	23.6	12,043
13,000	21.5	13,052

in which the calculated results were obtained by a least-squares fit to

$$R_o = R_{\infty T} \cdot \exp\left[\frac{\Delta E}{kT}\right] \qquad (9.2.c.2)$$

giving

$R_{\infty T}$ = resistance at infinite temperature = 0.149625 Ω

ΔE = 0.28885 eV = 6.6589kcal/mole = 27.874 kJ/mole (9.2.c.3)

k = Boltzmann's Constant = 8.6171×10^{-5} eV/^oK

and T = skin temperature + 273.15^oK

The Maulsby and Edelberg Figure 2 line representing data obtained on seven subjects was processed in a similar manner and yielded

ΔE = 0.23665 eV = 5.4555 kcal/mole = 22.837 kJ/mole (9.2.c.4)

The prefactor $R_{\infty T}$ was however meaningless in this second case because of previous inter-subject normalization of the data.

The work of Maulsby and Edelberg, which, as we have seen, indicates that skin is a semiconductor in vivo, has been extended to the in vitro case by

Allenby et al. (1969), producing results which are very interesting because an in vitro methodology ensures that they are not affected by physiological changes in the sweat glands.

Allenby et al. found that the activation energy of skin impedance at 1.5 Hz (this impedance therefore being very close to R_o) was

$$\Delta E = 14.6 \text{ kcal/mole} = 0.633 \text{ eV} \qquad (9.2.c.5)$$

This value is remarkably similar to that for the diffusion of water molecules through skin, 15.4 kcal/mole (0.668 eV; cf Scheuplein and Morgan, 1967, who quote 15 kcal/mole, 0.651 eV), and far higher than that for ionic conduction in free water (3.6 kcal/mole, 0.156 eV) and for the self-diffusion of free water (4.7 kcal/mole, 0.204 eV according to Scheuplein and Morgan, 5.3 kcal/mole, 0.230 eV according to Allenby et al.). Comparing these last values with (9.2.c.3) and (9.2.c.4) suggests to me that perhaps the effects observed by Maulsby and Edelberg were predominantly due to the diffusion of ions through the fluid in the ducts of the sweat glands. However, according to the work of Spencer et al. (1975, Fig.3), they also correspond to the enthalpy of water absorption/desorption in the stratum corneum at relative humidities of about 70% and 75% respectively, and thus they may well represent the properties of the corneum after all.

We may summarise this subsection with three conclusions.

Firstly, sweat gland activity does not significantly affect the magnitude of m. We may therefore infer that m is an indication of the state of the corneum, not the appendages.

Secondly, sweat gland activity does however reduce R_o and raise f_p, as expected, because conductance shunts are being opened up around the epidermal impedance.

Thirdly, skin behaves as a semiconductor both in vivo and in vitro. The fact that it does so in vitro too implies that the presence of this effect is independent of sweat gland activity.

9.2.d with ambient humidity

For ambient relative humidities greater than about 40%. we expect that as relative humidity (RH) increases, trans-epidermal water loss (TEWL) will decrease (Grice, 1980, p.2123 ff). Then the average water content of the corneum will increase and R_o can be expected to decrease (see subsection 11.9.d), causing (considering circuit theory and the circuits reviewed in Section 4.2), a corresponding increase in f_p. Finally, we expect both from observations (subsection 9.3.c) and theory (subsection 11.9.h) that as corneum hydration increases, there will be an increase in m.

These effects however are not likely to be large unless the change in RH is also large. In fact Smith (1937) was unable to detect any influence of humidity on electrical properties, although this is as ridiculous a result as his other conclusion we reviewed in the last subsection. Wenger (1962, Table 5.2) reported low negative correlations between palmar skin conductance and ambient RH, which led Venables and Martin (1967, p.72) to state that the influence of RH was not likely to be important enough to warrant the construction of humidity-controlled measuring environments.

Edith Clar and her co-workers did however bother to make investigations of the electrical properties of skin in humidity-controlled environments. Their work will be reviewed in more detail in subsection 11.6.a, and suffice it to say here that although no very firm conclusions should be drawn from their results because they used a rather inaccurate method of data analysis, it does at least seem that they showed that m increases as RH increases, as expected. Examining the results in Table IV of Clar, Her and Sturelle (1975) with the knowledge, by comparing (11.6.a.2) with (11.6.a.3), that Clar's parameter α is the same as our (1-m), we see that for the volar forearms of five subjects, m was on average 0.634 at 86% RH, decreasing to 0.608 as RH was decreased to 66%.

9.2.e with age

Despite Edelberg's call for more measurements (Edelberg, 1971), the influence of age upon the electrical properties of skin has not yet been adequately investigated. For example, the work of Gerstner (1948) on the influence of age upon skin impedance at only one non-zero frequency is quite inadequate (see subsection 10.1.b). However, from guesses based upon what is known of the influence of age upon the epidermis and skin appendages (see e.g. Freeman,1971), I expect the influence of age to be small, at least after puberty.

Richter (1969) has at least made a start on the problem by investigating the magnitude of D.C. conductance ($1/R_o$) on the forehead, para-sternal thorax and dorsum of hand of 110 men and 100 women between the ages of 7 and 82. The correlation coefficients between age and D.C. conductance were 0.1, 0.03 and 0.13 respectively. The higher correlation in the dorsum of the hand agrees with the statement by Edelberg (1971, p.543) that this is one of the few skin sites at which the epidermis changes with age.

9.2.f with sex

Lawler et al. (1960), investigating the impedance of skin at 4 kHz using a two-electrode method and electrodes of πcm^2, were unable to detect any significant difference in impedance between the sexes. However, as I mentioned in subsection 9.3.b, it is likely that sex will affect R_o much more than R_∞ and so differences in impedance would be the more easily detectable the lower the frequency used.

We have already noted that Ipser (1969) working with D.C., found variations in R_o which correlated well with the menstrual cycle. I myself have observed sudden reductions in R_o at the onset of menopausal "hot flushes" in subjects.

Rein (1929, p.75) reported that in D.C. experiments using N/100 KCl on the volar forearm, he had found R_o to be higher in men than in women, and especially so for anodic current. This electrical difference between the sexes was however only detectable on average, and not necessarily for each individual. If R_o tends to be less in women, this from equation (12.6.d.3) means that what the older German literature calls the "polarizability" (Polarisierbarkeit) will also be less in women, as indeed Rothman records (1954, p.12).

These D.C. findings of Rein agree with those obtained at 200 Hz by Gerstner (1948, pps. 130, 138).

9.3 Iatrogenic changes

9.3.a The reproducibility of the results

The reproducibility of the results depends upon the reproducibility of the measuring procedure and the constancy of state of the thing being measured.

In our case, the reproducibility of the measuring procedure is almost perfect. I carried out measurements using the Analyser on a test network of a 10 kohm resistor in series with a parallel combination of a 47 khom resistor and a 47 nF capacitor, and the standard error boxes were only about 500 ohms square along the R_S and X_S axes, representing a reproducibility of about 2% on average.

Unfortunately however skin itself changes with a number of factors as we are in the course of reviewing, and so measurements made on it are not very reproducible. However, at least with our particular methodology of measurement, it seems that the observed variability is overwhelmingly a physiological one, in the sense that it is giving us information about the skin, and not about the Analyser.

9.3.b The effect of electrode gel composition

One of the main restrictions upon assessing the electrical properties of skin, and upon obtaining reproducibility of results, is the fact that electrode gel used to make electrical contact between electrodes and skin tends to diffuse into the skin and alter its electrical properties. This effect is actually required of commercially available ECG-type gels, and for this reason they should be avoided in the electrical characterization of skin. Even if no gel is used, insensible perspiration builds up under the electrode, even if it has the form of a mesh, and the impedance of the skin reduces with time as the corneum becomes more hydrated. All these effects are reviewed in more detail in Section 12.2.

What we need is an electrically conductive gel between the electrodes and the epidermis which does not alter the hydration or any other electrically relevant properties of the skin it is placed on. To produce such a gel is probably impossible, given the variability of the properties of skin which the gel must not alter. We may begin the attempt however by seeking to minimise the effects of gel upon skin.

Now Edelberg (1968) stated that normal atmospheric vapour pressures at the skin surface can be simulated by using various mixtures of polyethylene glycol (PEG) and 0.1M NaCl. The idea was that gels with a greater or lesser water and electrolyte content could be made, and one particular composition would match the water and electrolyte content of the outer stratum corneum. Gels with more water and electrolyte than this would tend to make the impedance of the skin reduce with time as the water and electrolytes diffused into the skin, and conversely gels with less water and electrolyte than the optimum would tend to make the impedance of the skin increase with time. Henry Babol of Vick International and myself have in fact collaborated in many such experiments in order to determine by interpolation an (average) optimum water content for electrode gels.

Clar et al.(1975) noted that Edelberg PEG mixtures had a very high resistivity and moreover showed relaxation phenomena above only 5 kHz, thus limiting investigations of the electrical properties of skin to quite low frequencies. They suggested adding NaCl up to 0.9% by weight, making the mixture more conductive and shifting the relaxation to above 100 kHz. Compositions of the gel were given for various values of air temperature and relative humidity. However, the temperature used in such calculations would be better taken as skin surface temperature than as ambient air temperature, and similar considerations apply to relative humidity.

I reported before (Salter, 1979, p.54) that for a while we employed a Clar-type gel with a composition chosen for 28°C and 65% relative humidity, modified by the use of a fraction of higher molecular weight PEG to make the application of the gel more convenient and less messy. Helping to maintain a well defined electrode area is very important because, as is well known (e.g. Blank and Finesinger, 1946), skin impedance determinations can alter with electrode area, current density, junction composition and applied pressure if the electrode is in direct contact with the skin, (Gerstner and Gerbstädt, 1949). We found however that PEG gels tended to "melt" when in contact with the skin and were very messy. Moreover, they do not eliminate the hydration problem, but only reduce it; whatever the in vitro results may show, during in vivo investigations there is still an initial neo-exponential fall in impedance with time after electrode application even though this is admittedly much smaller and more rapid than that found with less appropriate electrode gels. Perhaps the effect is something to do with the skin appendages (contrast Tregear, 1965 with Woodrough, 1976), and certainly Clar et al. (1975) report the same disappointing findings in vivo.

More recently we abandoned the PEG gels and moved, after many (unpublished) experiments involving measurements at 25 Hz, to "Carbopol" gels such as are described in subsection 7.5.c. These have much more

stable and convenient mechanical properties.

However, due probably to random mismatching of the water content of the chosen gel and the skin it is applied to, even these Carbopol gels usually cause a (small) change in impedance with time, and although our experiments are continuing, I feel that such effects may be something we are going to have to live with. Indeed I even went to Washington to talk about the problem with Dr R.J. Scheuplein, probably the world expert on diffusion processes in human skin, and he was not able to offer much hope of solving it.

The problem is well recognised in the literature. For example, Rein (1929) and Rosendal (1943, 1944, 1945) showed that the pH and the concentration and size of the ions in the contact electrolyte affects both the linear and the non-linear electrical properties of skin. These findings are considered in more detail in subsections 12.2.e and 12.6.f respectively. We may note here with respect to electrolyte concentration however the statement by Gerstner and Gerbstädt (1949, p.115) that NaCl solutions stronger than 1% increase the capacitance of the skin, i.e. $-X_s$ is reduced. I think however that this merely results from the fall in R_o with time which we were considering above. Such a fall would also decrease R_s by an amount depending on the frequency used, and the fact that at 200 Hz R_s was not found to alter significantly is by no means a disproof of the hypothesis.

9.3.c The effect of applying moisturizing substances

If we define "moisturizing substances" to be those which tend to increase the water content of the stratum corneum, the simplest such substance can be seen to be water itself.

Yamamoto and Yamamoto (1977) determined the parameters of the Cole equation as a function of time after two unprepared skin sites of 9 cm^2 on different forearms were brought into contact and thus occluded. Electrical contact was made with these sites by large indifferent electrodes formed by placing the right foot of each of the two subjects into saline up to the ankle. The results, shown in their Fig.4 and abstracted here as Table 9.3.c.A, showed that R_o decreased with time as the occluded skin became more hydrated due to the blocking of TEWL, and at the same time THE PARAMETER M INCREASED. This is a most important finding, since as we shall consider in Chapter 11, it immediately casts serious doubts upon current interpretations of why skin obeys the Cole equation.

Yamamoto and Yamamoto (1977, Table 1) also obtained similar results

Table 9.3.c.A Data taken from Yamamoto and Yamamoto (1977, Fig. 4)

Time (minutes)	m	R_o (kΩ)
15	0.166	520
20	0.2	440
30	0.288	276
40	0.305	240
60	(0.333)*	168
80	0.35	133

* corrected by interpolation: 0.3 was the value given by Yamamoto and Yamamoto.

during experiments in which saturated saline, or Beckman electrode paste, was allowed to soak into the skin.

Now the Yamamoto paper is rather obscurantist and sometimes conceptually misleading, for example in talking of the "Cole-Cole" circular arc (which is a terminology used for the complex permittivity plane, not the complex impedance plane - see Section 11.3.a), but it seems reasonable to conclude from these results and those of Clar et al (1975) discussed in subsection 9.2.d, that as the hydration of the corneum increases, R_o decreases, f_p increases and m increases. The inverse relationship between R_o and f_p is mainly due to investigating the phenomenology on the complex impedance plane, and is not very important. Changes in R_o and m however are much less interrelated, and therefore present more valuable information.

It is pertinent to note that these findings of the Yamamotos are supported by some observations of Rosendal. As long ago as 1945, he found (Rosendal, 1945, p.42 ff) that a dry "membrane" of pulverised stratum corneum proteins behaved as described by the Cole equation with m approximately equal to zero, but that as the membrane hydration increased, so did m. Such behaviour is in fact a feature of proteins generally. His report that hydration increased the capacitative conductivity however probably only means that R_o was decreased as we would expect, which would in turn reduce $-X_s$ and R_s at each particular measuring frequency.

Considering these findings, the question arose as to what might be the effect produced by commercially available moisturizing substances, and experiments were begun on "Oil of Ulay". This is an oil-in-water emulsion containing 86 ± 3% of water, with the rest mainly lipidic in nature, including fatty alcohols, Vaseline oil and cholesterol. A typical experiment will now be discussed.

The subject was seated in a room at 23°C and 63% r.h. and two pairs of contralateral sites were marked out on the dorsal surfaces of the forearms.

Our usual electrodes (subsection 7.5.b) and gel (subsection 7.5.c) were applied and the subject was allowed to equilibrate from 12 noon to 3 p.m., lunch not being taken because of the effect this is known to have upon skin impedance (subsection 9.3.b).

At 3 p.m. the electrical properties of the left arm sites were measured ("Test before" results), and immediately afterwards, at 3.10 p.m., the properties of the right arm sites ("Control before" results).

At 3.20 p.m. both pairs of electrodes were removed and both pairs of sites were lightly cleaned with soap and water, then gently dried using absorbent paper tissue. This procedure was intended to remove electrode gel. A thin layer of Oil of Ulay was then applied to the test (left arm) sites and allowed to begin to dry for twenty minutes. After this time, BOTH pairs of sites (test sites on the left arm and control sites on the right arm) were again gently washed and dried (to remove Oil of Ulay from the test sites while affecting both arms equally), and new electrodes and new gel applied. The electrical properties of the control sites were again measured at 3.45 p.m. and those of the test sites at 3.55 p.m. These results were labelled "after".

The data was processed in the usual way and the results are shown here as Figures 9.3.c.I to IV representing "Test before", "Control before", "Test after" and "Control after" respectively.

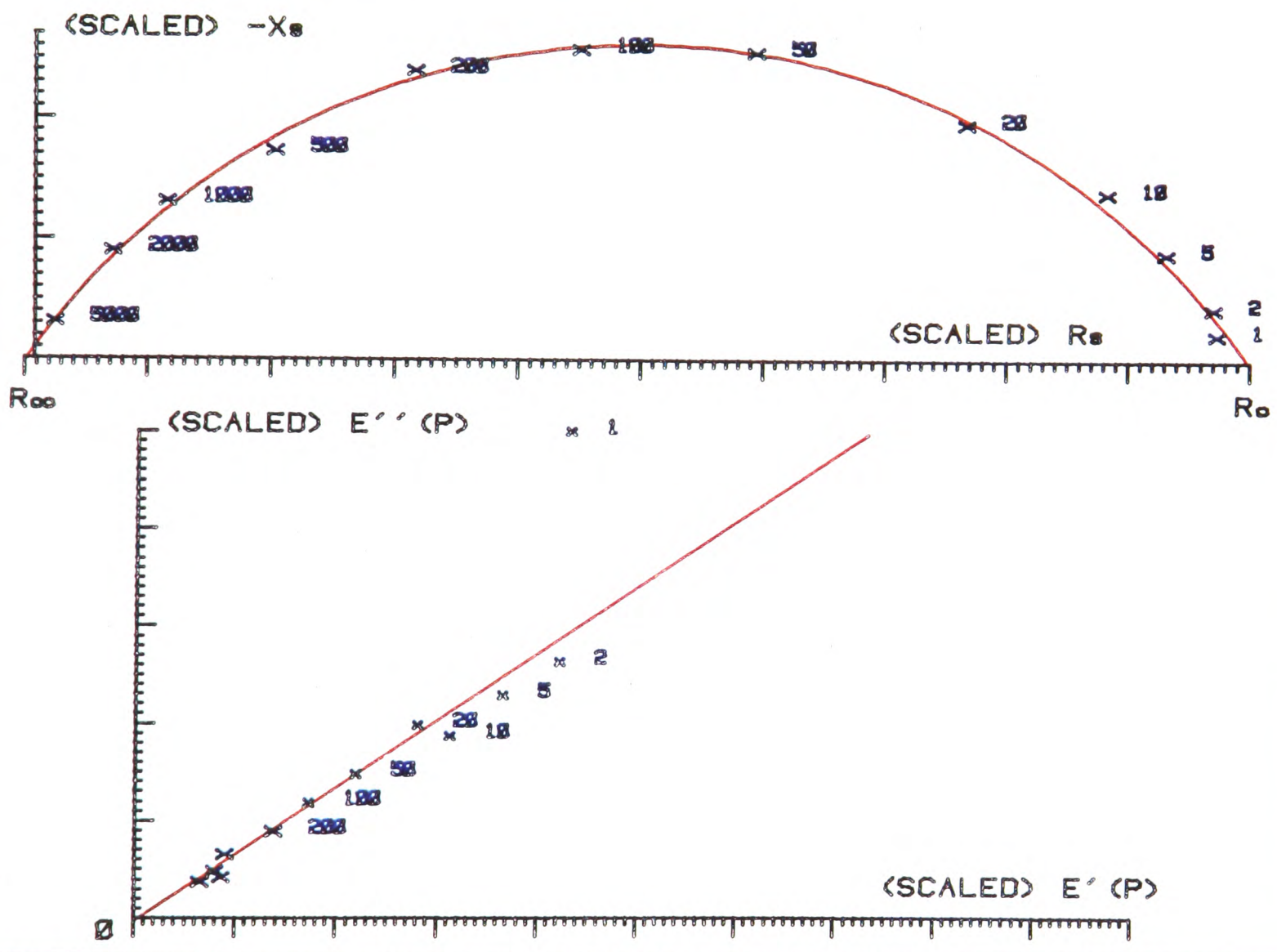
We see that at the control sites, R_o increased by about 32% during the experiment, and m decreased by about 16%. From the work of the Yamamotos and others we might therefore conclude that the gel tended to dehydrate the skin of the subject. This is a quite reasonable possibility since we use a gel with a water content which is only optimal on average, and therefore not necessarily optimal for a particular subject at a particular time.

However, at the test sites R_o decreased by about 18% during the experiment, so presumably the occluding and hydrating effect of the Oil of Ulay was sufficient to overwhelm the dehydrating effect of the electrode gel. We might therefore have expected m to increase accordingly, and the fact that it did not, but remained constant to within experimental error, may be due to the fact that there are lipid components in Ulay. The theory developed in Section 11.9 suggests that if the local dielectric permittivity in the corneum increases, then so does m. Thus when the corneum absorbs water, which has a very high relative permittivity of about 80, m increases accordingly, just as the Yamamotos found. However, when skin has the opportunity to absorb lipids (which it does more avidly than it would polar substances such as water - see e.g. Scheuplein, 1978), the local permittivity will tend to decrease, and m will decrease too. Thus when the corneum absorbs Ulay, having both a polar fraction and a lipid fraction, the effect on m will depend upon whether or not the local permittivity is increased or decreased, or, on balance, not significantly affected.

NAME	=	DAVID SALTER
AGE	=	25
DATE	=	8TH FEBRUARY 1978
TIME	=	3.00 P.M.
BODY SITE	=	LEFT DORSAL FOREARM
SKIN TEMP.	=	28 C
AMBIENT R.H.	=	63 %
P-P CURRENT	=	5 MICROAMPS

Fig. 9.3.c.I

"Test before" results



			+PSE	+/-SE	-PSE
NO. OF DATA PAIRS	=	12			
R(ZERO)	=	72092.4		1121.58	
R(INFINITY)	=	-553.55		1121.58	
F(PEAK) [USING M1]	=	78.3823	28.5034		20.9023
F(PEAK) [USING M2]	=	78.5981	3.84027		3.47914
E'' [E'=0]	=	-3.23316E-10		5.70021E-10	
'U'	=	2.30839E-07	1.44502E-08		1.35989E-08
M1 FROM Z LOCUS	=	.380089		1.55443E-02	
M2 FROM V/U PLOT	=	.349183		6.62444E-03	
M3 FROM E* LOCUS	=	.383382		8.45561E-03	
M4 FROM LN E'' PLOT	=	.375912		8.83680E-03	
& WEIGHTED MEAN M	=	.38684		8.88143E-03	

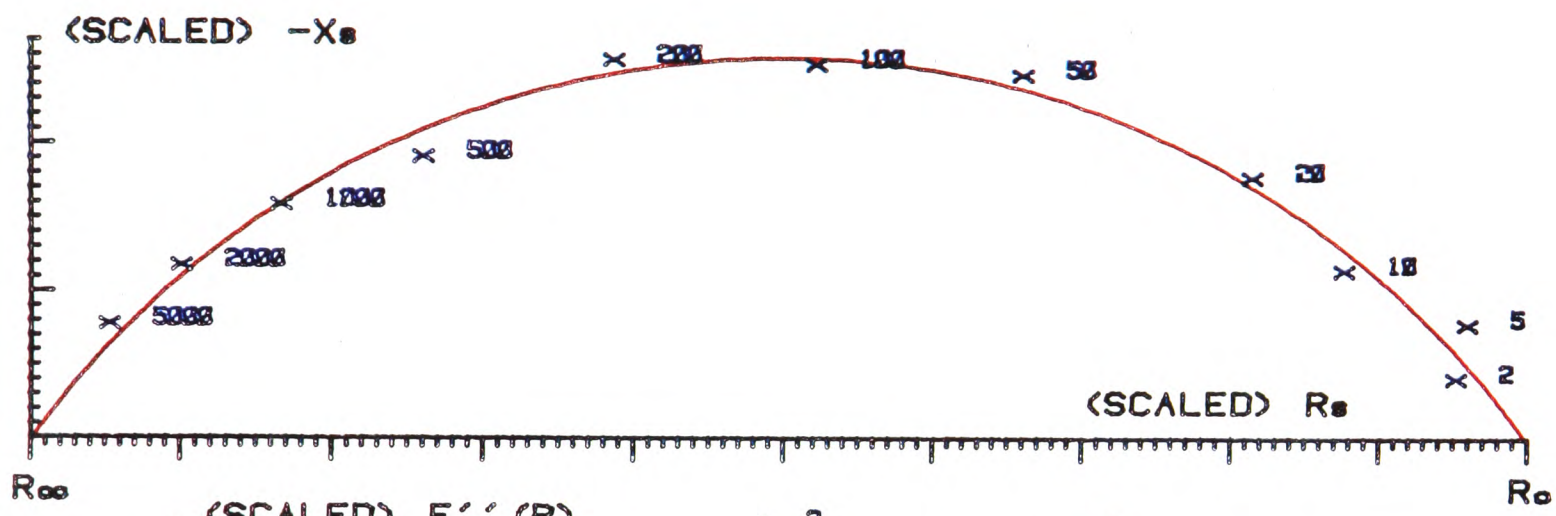
SINCE COMPARING M1 WITH M2, M3 AND M4 RESPECTIVELY,
THE SIGNIFICANCE OF THE DIFFERENCE BETWEEN THE MEANS IS
0.05 < P <= 0.10 0.10 < P AND 0.10 < P

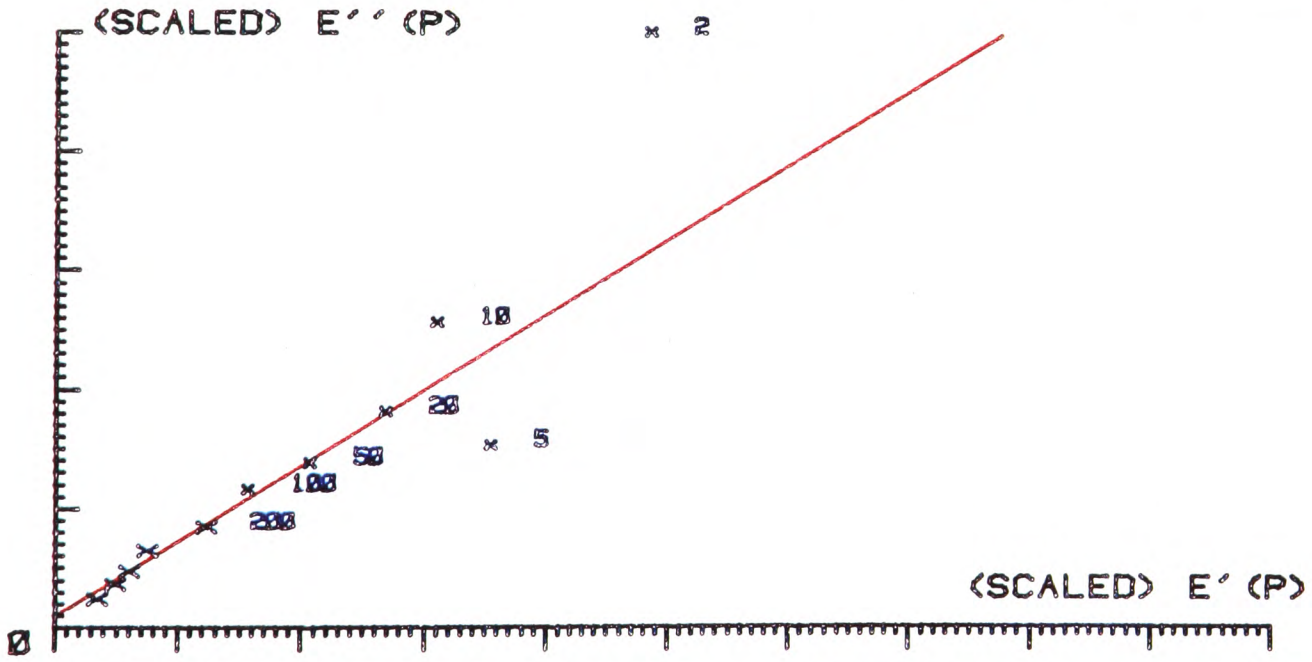
COEFF. DET. OF (UNWEIGHTED) Z ARC FIT	=	.999609
COEFF. DET. OF (WEIGHTED) V/U PLOT	=	.998965
COEFF. DET. OF (WEIGHTED) E* LINE FIT	=	.983156

NAME	=	DAVID SALTER
AGE	=	25
DATE	=	8TH FEBRUARY 1978
TIME	=	3.10 P.M.
BODY SITE	=	RIGHT DORSAL FOREARM
SKIN TEMP.	=	26.5 C
AMBIENT R.H.	=	63 %
P-P CURRENT	=	5 MICROAMPS

Fig. 9.3.c.II

"Control before" results





		+PSE	+/-SE	-PSE
NO. OF DATA PAIRS	=	11		
R(ZERO)	=	37210.9	1299.37	
R(INFINITY)	=	250.367	1299.37	
F(PEAK) [USING M1]	=	112.783	16.2291	14.1875
F(PEAK) [USING M2]	=	112.782	8.64806	8.03215
E'' [E'=0]	=	2.10713E-09	1.14519E-09	
'U'	=	3.60253E-07	4.18872E-08	3.75242E-08
M1 FROM Z LOCUS	=	.387174	3.49591E-02	
M2 FROM V/U PLOT	=	.38364	9.58048E-03	
M3 FROM E* LOCUS	=	.358649	1.27688E-02	
M4 FROM LN E'' PLOT	=	.378265	1.51451E-02	
& WEIGHTED MEAN M	=	.375812	6.25460E-03	

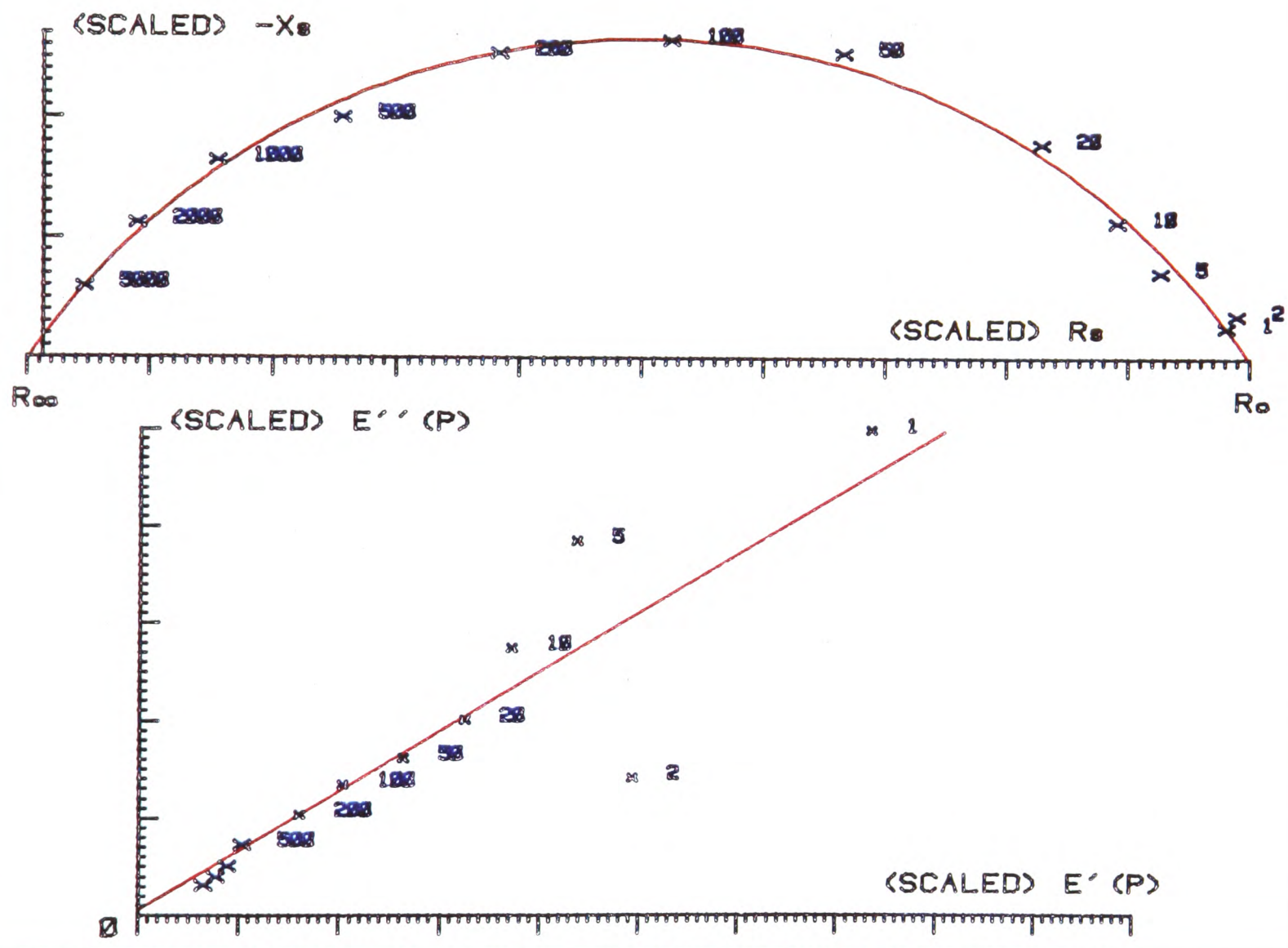
SINCE COMPARING M1 WITH M2, M3 AND M4 RESPECTIVELY,
THE SIGNIFICANCE OF THE DIFFERENCE BETWEEN THE MEANS IS
0.10 < P 0.10 < P AND 0.10 < P

COEFF. DET. OF (UNWEIGHTED) Z ARC FIT	=	.998538
COEFF. DET. OF (WEIGHTED) V/U PLOT	=	.99783
COEFF. DET. OF (WEIGHTED) E* LINE FIT	=	.957382

NAME	=	DAVID SALTER
AGE	=	25
DATE	=	8TH FEBRUARY 1978
TIME	=	3.55 P.M.
BODY SITE	=	LEFT DORSAL FOREARM
SKIN TEMP.	=	27.5 C
AMBIENT R.H.	=	63 %
P-P CURRENT	=	5 MICROAMPS

Fig. 9.3.c.III

"Test after" results



			+PSE	+/-SE	-PSE
NO. OF DATA PAIRS	=	12			
R(ZERO)	=	59762.8		1335.26	
R(INFINITY)	=	-799.266		1335.26	
F(PEAK) [USING M1]	=	111.987	11.0924		10.0927
F(PEAK) [USING M2]	=	111.987	9.04862		8.37044
E'' [E'=0]	=	7.01403E-10		5.69404E-10	
'U'	=	2.30986E-07	2.21645E-08		2.02239E-08
M1 FROM Z LOCUS	=	.3727		2.23638E-02	
M2 FROM V/U PLOT	=	.371655		1.02877E-02	
M3 FROM E* LOCUS	=	.349039		9.34817E-03	
M4 FROM LN E'' PLOT	=	.39222		1.26489E-02	
& WEIGHTED MEAN M	=	.367257		9.52677E-03	

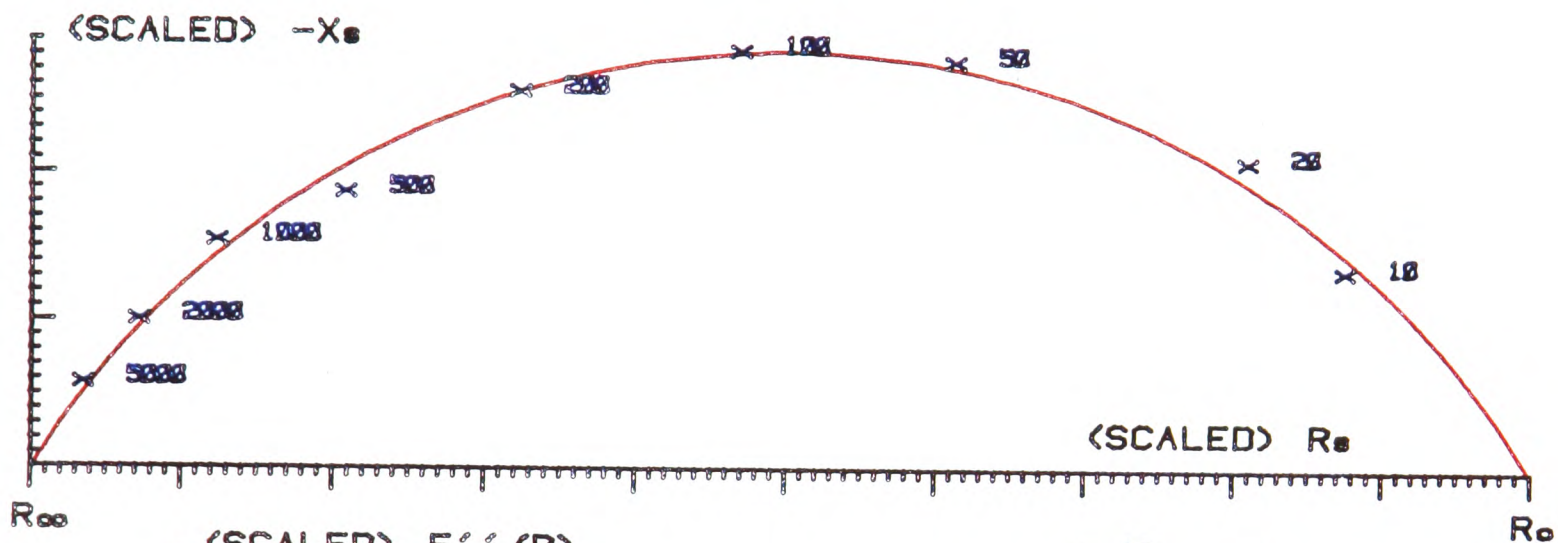
SINCE COMPARING M1 WITH M2, M3 AND M4 RESPECTIVELY,
THE SIGNIFICANCE OF THE DIFFERENCE BETWEEN THE MEANS IS
0.10 < P 0.10 < P AND 0.10 < P

COEFF. DET. OF (UNWEIGHTED) Z ARC FIT	=	.999132
COEFF. DET. OF (WEIGHTED) V/U PLOT	=	.997326
COEFF. DET. OF (WEIGHTED) E* LINE FIT	=	.971612

NAME	=	DAVID SALTER
AGE	=	25
DATE	=	8TH FEBRUARY 1978
TIME	=	3.45 P.M.
BODY SITE	=	RIGHT DORSAL FOREARM
SKIN TEMP.	=	27.5 C
AMBIENT R.H.	=	63 %
P-P CURRENT	=	5 MICROAMPS

Fig. 9.3.c.IV

"Control after" results



		+PSE	+/-SE	-PSE
NO. OF DATA PAIRS	=	9		
R(ZERO)	=	49389.2	1331.13	
R(INFINITY)	=	406.199	1331.13	
F(PEAK) [USING M1]	=	88.1893	18.1008	14.9592
F(PEAK) [USING M2]	=	88.1241	7.84805	7.19085
E'' [E'=Ø]	=	2.38310E-09	5.67738E-10	
'U'	=	2.62881E-07	3.09677E-08	2.77041E-08
M1 FROM Z LOCUS	=	.33921	2.92658E-02	
M2 FROM V/U PLOT	=	.350438	1.25132E-02	
M3 FROM E* LOCUS	=	.305081	5.52478E-03	
M4 FROM LN E'' PLOT	=	.342323	1.59852E-02	
& WEIGHTED MEAN M	=	.315833	1.05684E-02	

SINCE COMPARING M1 WITH M2, M3 AND M4 RESPECTIVELY,
THE SIGNIFICANCE OF THE DIFFERENCE BETWEEN THE MEANS IS
Ø.1Ø < P Ø.1Ø < P AND Ø.1Ø < P

COEFF. DET. OF (UNWEIGHTED) Z ARC FIT	=	.998863
COEFF. DET. OF (WEIGHTED) V/U PLOT	=	.997409
COEFF. DET. OF (WEIGHTED) E* LINE FIT	=	.988471

9.3.d The effect of stripping the stratum corneum

It has been demonstrated by many investigators that the effect of puncturing the corneum, abrading it away or stripping off its layers with adhesive tape is to progressively reduce and eventually abolish the distinctive linear electrical impedance properties of the skin, and also some of its non-linear electrical properties (presumably because of the dermal microcirculatory and sweat gland responses which are initiated). For proof of this one should consult for example the publications of Lewis and Zotterman (1926-27), Hill and Taylor (1937), Rosendal (1943, 1944, 1945), Gerstner and Gerbstädt (1949), Pfister and Schulz (1966), and Yamamoto and Yamamoto (1976a).

These publications have increasingly clearly shown that the polarization impedance in the equivalent circuit of skin (Sections 4.2 and 11.1) resides exclusively in the stratum corneum. Without the stratum corneum, the impedance of skin is almost independent of frequency (Gerstner and Gerbstädt, 1949, p.117; Yamamoto and Yamamoto, 1976a, p.152).

This in turn means that the parameter m relates exclusively to the condition of the stratum corneum. This is very useful indeed. It means that we can monitor the condition of the stratum corneum without injuring the skin in any way, and by using the method described in subsections 6.3.b and 6.3.c we can be quite sure which area of corneum our results relate to.

Yamamoto and Yamamoto (1976a) carried out the interesting experiment of measuring the linear electrical properties of skin sites in vivo after successive strippings with adhesive tape to slowly remove almost all the stratum corneum. By analysing the differences between these successive measurements they were able to infer the properties of the keratinocyte layers which had adhered to the tape, and to relate these to depth within the corneum (see also Yamamoto and Yamamoto, 1976b). Their results, which are considered in some detail in Chapter 11, showed that even very thin

sections of the corneum, perhaps even only one cell layer thick, obeyed the Cole equation, and WITH A NON-ZERO VALUE OF M. This is another finding which casts serious doubt upon the current interpretations of why linear properties of skin obey the Cole equation.

Finally, we may note that Lawler et al. (1960) found that stripping the skin increased its equivalent PARALLEL capacitance. This was deduced from a decrease in equivalent parallel (negative) reactance, which from Section 4.2 can be seen to have the form

$$- X_p = R \sin (\alpha \frac{\pi}{2}) (\omega\tau)^{-\alpha}, R_\infty << R_o \qquad (9.3.d.1)$$

and since the constant R will decrease as the corneum concerned becomes more hydrated, the finding that $-X_p$ decreases with depth can be interpreted much more easily than Lawler et al,(1960) would suggest. I think the findings of Yamamoto and Yamamoto (1976b) on the increase of equivalent parallel relative permittivity with depth can be easily interpreted in a similar way as being due to the increase in corneum hydration with depth.

9.4 The dependence of the results upon the amplitude of the input current density

When using the Analyser, effects were observed such as would be expected on the basis of the literature introduced in Section 4.3 and which will be reviewed in detail in Chapter 12. This literature discusses the (very complicated) way in which the electrical properties of skin alter as a function of the applied voltage. As the peak-to-peak current requested from the Analyser altered, it would of course alter the voltage it applied across the skin in such a way as to produce the requested current, and this procedure would therefore tend to produce a dependence of the results obtained upon the input current, or for some effects, the input current density (cf. Section 12.7).

In general, and thinking for the present in terms of the Cole equation and the complex impedance plane, the derived value of R_o tends to diminish as the magnitude of the applied voltage increases. This implies the existence of non-linear distortion, which, as Gougerot and Marstal (1959, p.991) pointed out when considering the same problem, can be seen as the distortion of Lissajous figures. The methods of Section 8.4 indeed actually exploit this fact to characterize the non-linearity, and thinking in terms of this V/I characteristic curve, we may say that in general the slope of the V/I curve is less at greater voltage magnitudes.

In this way it is easily possible to see that the voltage-dependent A.C. properties reported by Gildemeister and by Malov and Rschevkin (reviewed by Gerstner and Gerbstädt, 1949, pps. 113, 114), the voltage-dependent behaviour reported by Grings (1953, Fig.2), and that reported even more sketchily by other people, is all a consequence of the phenomenology introduced in Section 4.3, and reviewed in detail in Chapter 12.

9.5 An examination of the pertinence of the Cole equation

For a particular amplitude of sinusoidal stimulation, the complex electrical impedance of skin has usually been assumed to obey the Cole equation (Cole, 1940, p.117).

$$Z = R_\infty + \frac{R_o - R_\infty}{1 + (j\omega\tau_p)^{1-m}}, \quad o < m < 1 \qquad (9.5.1)$$

We ourselves made this assumption in Section 4.2. Equation (9.5.1) implies that the apparent distribution of relaxation times in skin is of the Cole-Cole form (Cole and Cole, 1941). However, it should perhaps be noted here that (9.5.1) does NOT describe a Cole-Cole dielectric, since although the algebra of the Cole-Cole complex permittivity equation is analogous, it does not transform into (9.5.1).

Now, Schwan (1957, p.157) has pointed out that it may be very difficult to distinguish different types of distribution of relaxation time just from the loci they produce on the complex impedance plane, and this is indeed true if measurements are not made over a sufficiently large range of frequency. Schanne and Ruiz P.-Ceretti (1978, p.323) however seem to have taken Schwan's statement to mean that the accuracy of experimental measurement of the Z locus is USUALLY insufficient to determine whether or not they really do fall on a minor arc of a circle (and thus require a Cole-Cole DRT to describe them), or just a curve rather like a minor arc, in which case some other DRT would be required to represent them.

In the case of skin, I do not think such pessimism is appropriate, but rather believe that the accuracy obtainable is great enough to distinguish whether we really are dealing with a Cole-Cole DRT or not. The question is however still being discussed in the literature. For example, Yamamoto and Yamamoto (1976a), some of whose results were reviewed in Section 9.3.d,

implied that thin sections of the corneum obeyed the Cole equation, but only rather approximately. Their work seems however to have been based upon the decomposition of only a single impedance locus shown in their Figure 1, and this single locus happened unfortunately to be left-skewed due, I assume, to inadequacies in the measurement technique. Certainly, neither I nor anyone else whose work I know of have ever observed such a skewed complex impedance locus for human skin. The Yamamotos did in fact eventually ignore these deviations and conclude (p.157) that the various layers of the corneum do after all obey the Cole equation. But some seeds of doubt may still have been sown, and the subsequent test of the pertinence of the Cole equation to skin applied by Poon and Choy (1978, Fig. 7b) was inadequate because it covered less than two decades of frequency.

Therefore I decided that the pertinence to skin of the Cole equation and the Cole-Cole DRT, should be thoroughly tested, and vindicated or disproved once and for all.

Of the commonly encountered DRTs, the one closest to the Cole-Cole is the log-normal distribution discussed by Yager (1936). Cole and Cole (1941) themselves said it was hard to distinguish between the two, and this fact is further illustrated by the papers of Kauzmann (1942) and Branin and Smyth (1952). I therefore thought that if our data could be shown to fit the Cole-Cole form better than the best-fit log-normal, the pertinence of the Cole equation would be proved, and we would then only (!) have to interpret what it means biophysically.

Now, plotting results on the Cole-Cole log (v/u) against log ω (or log f) plane (Cole and Cole, 1941, or see subappendix B2) provides a critical test of whether or not the data can be described by a Cole-Cole DRT, such as we expect if skin really does obey the Cole equation. The test is particularly sensitive at frequencies well away from f_p, which are those for which distortions of the Z locus may be overlooked. A Cole-Cole DRT produces a straight

Table 9.5.A

VALUES OF THE COLE-COLE CHORD RATIO (V/U) CALCULATED DIRECTLY FROM THE TABLES GIVEN BY YAGER (1936).

(Those values marked with an asterisk have been slightly corrected graphically)

$\ln(\omega\tau_p)$ or $\ln(f/f_p)$	(f/f_p)	b = 0.15	b = 0.25	b = 0.35	b = 0.5	b = 0.8	b = 1.0	b = 2.0	b = ∞ ("Debye")
- 6.0	2.48×10^{-3}	1.3629×10^{-1}	4.1254×10^{-2}	1.5846×10^{-2}	4.9614×10^{-3}	3.6602×10^{-3}	3.1801×10^{-3}	2.6300×10^{-3}	2.4800×10^{-3}
- 5.0	6.74×10^{-3}	1.9572×10^{-1}	7.6957×10^{-2}	3.6795×10^{-2}	1.3405×10^{-2}	9.9541×10^{-3}	8.6515×10^{-3}	7.1005×10^{-3}	6.7403×10^{-3}
- 4.0	1.83×10^{-2}	2.7592×10^{-1}	1.3742×10^{-1}	7.9644×10^{-2}	3.5603×10^{-2}	2.6967×10^{-2}	2.3493×10^{-2}	1.9509×10^{-2}	1.8306×10^{-2}
- 3.0	4.98×10^{-2}	$*3.8665\times10^{-1}$	$*2.3425\times10^{-1}$	$*1.6342\times10^{-1}$	$*9.4948\times10^{-2}$	7.3501×10^{-2}	6.4600×10^{-2}	5.3192×10^{-2}	4.9923×10^{-2}
- 2.5	8.21×10^{-2}	4.4934×10^{-1}	$*3.0227\times10^{-1}$	2.2165×10^{-1}	1.4545×10^{-1}	1.2199×10^{-1}	$*1.0855\times10^{-1}$	8.6742×10^{-2}	8.1951×10^{-2}
- 2.0	1.35×10^{-1}	5.3188×10^{-1}	3.8870×10^{-1}	3.0329×10^{-1}	2.1630×10^{-1}	1.8615×10^{-1}	1.6988×10^{-1}	1.4602×10^{-1}	1.3492×10^{-1}
- 1.5	2.23×10^{-1}	6.2383×10^{-1}	$*4.9728\times10^{-1}$	4.1737×10^{-1}	$*3.2240\times10^{-1}$	2.8760×10^{-1}	2.6949×10^{-1}	2.4180×10^{-1}	2.2293×10^{-1}
- 1.0	3.68×10^{-1}	7.2421×10^{-1}	6.2145×10^{-1}	5.6658×10^{-1}	$*4.8108\times10^{-1}$	4.4359×10^{-1}	4.1951×10^{-1}	3.8262×10^{-1}	3.6768×10^{-1}
- 0.5	6.07×10^{-1}	8.5362×10^{-1}	$*7.9541\times10^{-1}$	7.4827×10^{-1}	$*6.8630\times10^{-1}$	6.6528×10^{-1}	6.5220×10^{-1}	6.1976×10^{-1}	$*6.0635\times10^{-1}$
0	1.00	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
0.5	1.65	1.1715	*1.2572	1.3364	*1.4570	1.5031	1.5333	1.6135	*1.6492
1.0	2.72	1.3808	1.6091	1.7650	*2.0786	2.2543	2.3837	2.6136	2.7197
1.5	4.48	1.6030	*2.0109	2.3959	*3.1017	3.4770	3.7106	4.1357	4.4858
2.0	7.39	1.8801	2.5727	3.2971	4.6231	5.3719	5.8864	6.8485	7.4119
2.5	1.22×10^{1}	2.2255	*3.3083	4.5116	6.8753	8.1971	*9.2122	1.1528×10^{1}	1.2202×10^{1}
3.0	2.01×10^{1}	*2.5863	*4.2688	*6.1192	$*1.0532\times10^{1}$	1.3605×10^{1}	1.5480×10^{1}	1.8800×10^{1}	2.0031×10^{1}
4.0	5.46×10^{1}	3.6243	7.2768	1.2556×10^{1}	2.8088×10^{1}	3.7083×10^{1}	4.2567×10^{1}	5.1257×10^{1}	5.4626×10^{1}
5.0	1.48×10^{2}	5.1094	1.2994×10^{1}	2.7178×10^{1}	7.4598×10^{1}	1.0046×10^{2}	1.1559×10^{2}	1.4084×10^{2}	1.4836×10^{2}
6.0	4.03×10^{2}	7.3372	2.4240×10^{1}	6.3106×10^{1}	2.0156×10^{2}	2.7321×10^{2}	3.1446×10^{2}	3.8022×10^{2}	4.0322×10^{2}

line of slope (1-m) on this (v/u) plot, whereas any other distribution will produce a curve.

Table 9.5.B

f Hz	R_s ohms	$-X_s$ ohms	(v/u)	(f/f_p)
1,000	28,400	49,390	31.681	114.81
500	50,960	81,900	18.294	57.405
200	73,710	141,330	10.841	22.962
100	151,620	234,640	5.9222	11.481
50	267,260	334,740	3.6308	5.7405
20	541,240	506,030	1.8088	2.2962
10	824,600	579,600	1.1095	1.1481
5	1,134,700	526,610	0.6657	0.5741
2	1,458,100	394,030	0.3364	0.2296

From the Tables given by Yager (1936), I calculated the values of (v/u) at the various values of (f/f_p) and log-normal distribution parameter b which Yager had treated. These results were checked graphically and curvilinear interpolative corrections performed where necessary. This produced Table 9.5.A. Eighteen large-scale graphs of (v/u) against b for the eighteen (f/f_p) ratios dealt with by Yager were then employed as follows.

Let the procedure be illustrated by an example, using the example data we used before in Sections 8.3 and 8.4. This set of data is listed in Table 9.5.B. Using the values of R_o and R_∞ determined from this set of data by least squares following the methods of subappendix B.1 (see Fig. 8.3.II), values of the chord ratio (v/u) were obtained following the methods of subappendix B.2. Having from these latter methods also obtained

the frequency of maximum reactance, f_p, the frequency scale was normalized by this value in order to facilitate comparison with the log-normal DRT models. A graph of log (v/u) against log (f/f_p) was then plotted.

From this graph, the value of (v/u) at the particular values of (f/f_p) considered by Yager (1936) were then estimated (Table 9.5.C), and from the

Table 9.5.C

(f/f_p)	Est. (v/u)	b_{app}	(v/u) for $\bar{b}$=0.535
(148) 54.6	18	0.44	(62) 23
20.1	8.8	0.51	9.18
12.2	6.1	0.51	6.29
7.39	4.2	0.51	4.30
4.48	2.95	0.54	2.935
2.72	2.08	0.61	1.995
1.65	1.44	0.55	1.433
0.607	0.69	0.58	0.697
0.368	0.49	0.56	0.498

graphs of the appropriate frequency ratios prepared from the work of Yager, the value of the distribution parameter b corresponding to this value of v/u was read off ($b_{apparent}$). These values of b_{app} were then averaged and a mean value $\bar{b}$ obtained. (This procedure is better than merely equating the depressions of the locus peaks predicted by different distributions, which does not minimise the distortions from circular arc behaviour at values of (f/f_p) much greater or much less than 1. The present procedure treats the extremes of the Z locus as just as important as the peak.) Using this mean value $\bar{b}$, values of (v/u) were obtained from the graphs

pertaining to the frequency ratios considered by Yager, and these defined the "best-fit" (v/u) locus assuming a log-normal DRT. This locus was then superimposed on the original data.

The results of this analysis are shown in Fig. 9.5.I, showing that over the whole range of frequencies, the example data are very well represented by a straight line of slope (1-m) where the m is in fact M1 obtained from the Z locus arc, exactly as expected for a Cole-Cole DRT. The corresponding inappropriatness of even the best-fit log-normal distribution is also apparent, and especially so the higher the frequency.

For every set of our experimental data for which an analysis like the above was carried out, it was invariably found that the data points traced out a locus more linear than the best-fit log-normal prediction, and often considerably so.

We may therefore conclude that the apparent distribution of relaxation times in skin is very accurately of the Cole-Cole form. An alternative way of saying the same thing is to say that the Cole equation (9.5.1) is obeyed very accurately indeed. This is important because no extant theory of the linear electrical properties of skin predicts a complex impedance sufficiently close to the form of the Cole equation, and Chapter 11 will consider this fact in greater detail.

Finally, we may note that the use of the Cole equation and the equivalent circuit models of it (Section 4.2) is further justified by the fact that the locus of complex permittivity with the effect of D.C. conductance subtracted off (Section 8.3 and subappendix B.3), is to within experimental error usually a straight line intercepting the origin. This behaviour is most clearly shown in Figs. 9.2.b.II and 9.3.c.I - III, and is exactly what would be expected from the Cole equation with R_∞/R_o tending to zero.

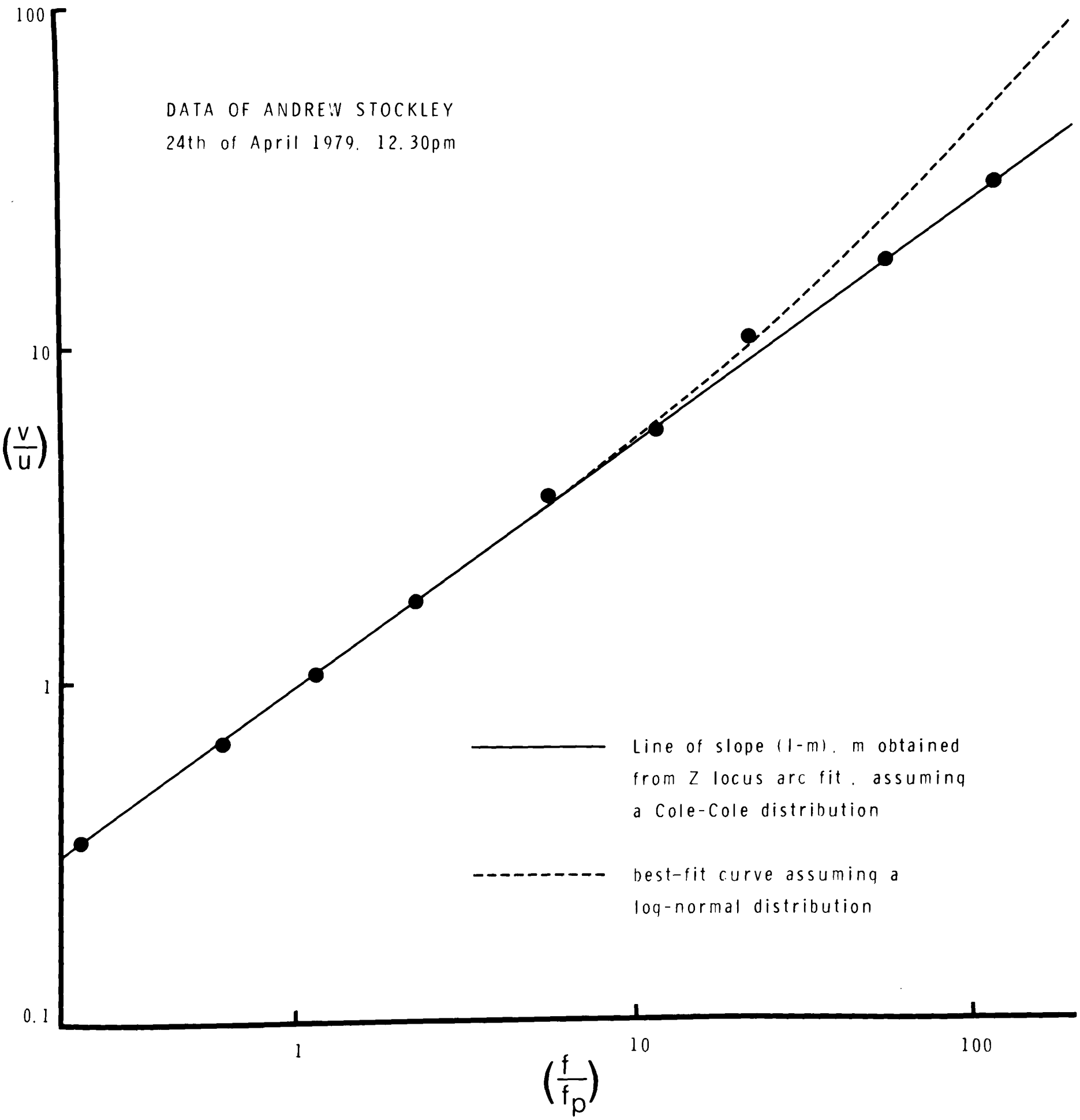


Fig. 9.5.I A test of the pertinence of the Cole equation.

Chapter 10. FINDINGS IN ABNORMAL SKIN

10.1 Introductory remarks

10.1.a The scope of this Chapter

The electrical properties of abnormal, that is injured or otherwise altered skin, are of interest because if they are sufficiently different from the electrical properties of normal skin, we can use them as non-invasive and objective indices of what a dermatologist would classify as abnormality. The need for such indices was discussed in Chapter 1.

However, the faults in the operation of the Analyser which were discussed in Section 8.5 led us to postpone investigating subjects with abnormal skin, i.e. patients, until such time as these faults should be corrected by Plessey. We did this to avoid inconveniencing our patients. We did not of course know that the correction of the faults would be postponed indefinitely.

Consequently, this Chapter presents a critical view of the electrical properties of abnormal human skin as they have already been reported in the literature, criticism being possible in the light of our experience of measurements made on normal skin.

10.1.b Linear properties: the fundamental ambiguity of most of the findings reported in the literature

In this subsection, I want to stress the importance of gathering and reporting data in an adequate way.

In Section 9.5 we saw that the linear electrical properties of skin very accurately obey the equation

$$Z = R_\infty + \frac{R_o - R_\infty}{1 + (j\omega\tau_p)^{1-m}} \qquad (10.1.b.1)$$

although unfortunately only a minority of investigators of the electrical properties of skin seem to have realised the fact.

From this obedience follows the very important consequence that the linear electrical properties of skin under given experimental conditions can be completely described by quoting just the four values R_∞, R_o, τ_p (or f_p) and m. Conversely it also follows that the linear electrical properties of skin have NOT been completely described UNLESS these four values HAVE been quoted, or at least can still be derived from the results presented.

Unfortunately however in most of the literature authors have not provided either the four values directly, or processed results from which they can still be derived uniquely. It therefore follows that MOST OF THE CLINICAL FINDINGS IN THE LITERATURE ARE FUNDAMENTALLY AMBIGUOUS. This does not seem to have been realized before.

Let us illustrate this criticism with some particular examples. From equation (10.1.b.1) or (4.2.3) to (4.2.6) which follow from it, it can be seen that R_s, X_s, $|Z|$ and θ depend not only on ω but also on (at least) R_∞, R_o, τ_p and m. Consequently if measurements of equivalent series resistance R_s, equivalent series reactance X_s (or capacitance $C_s = -1/\omega X_s$),

impedance magnitude $|Z|$ or phase angle θ, are obtained at only one frequency, then they are little better than worthless, since they are insufficient to determine the fundamental parameters R_∞, R_o, τ_p and m. If these remain undetermined, any observed changes in the electrical properties of the skin cannot be traced unambiguously to alterations in one or more of the fundamental parameters.

Very many, indeed perhaps most, of the papers reporting investigations of the linear electrical properties of skin have employed only one stimulating frequency. Consequently the interpretation of the results reported must be approached with very great care, or false inferences are very likely to be drawn.

It should also be noted in passing that despite my already having drawn attention to the above methodological dangers (Salter, 1979, p.27) some people who refer to my publication in their own have nevertheless gone ahead and developed for commercial production an instrument incorporating their fruitless methodology. It makes measurements of skin phase angle at one frequency and purports thereby to quantify skin hydration (Jackson et al., 1980). However, the value of phase angle obtained will depend upon all four parameters R_∞, R_o, τ_p and m, and these certainly do not only alter with hydration (see Section 9.2). If we are to make measurements of hydration it is therefore necessary to define the most hydration-dependent locus in (R_∞, R_o, τ_p and m) space and then observe skin move along it. Without such a level of sophistication, a change in skin hydration cannot necessarily be distinguished from, for example, a change in sweat-gland activity or in skin temperature. Perhaps in consequence of this the relationship between phase angle and skin water content obtained by Jackson et al. (their Fig.8) is a rather unconvincing scattergram.

When we move on to consider papers reporting measurements made at more than one frequency, the situation is not necessarily better. For example,

the most extensively quoted investigation of the linear electrical properties of pathological skin is that by Gougerot (1947). His work has indeed been quoted extensively by Rothman (1954) and Edelberg (1971), but neither has pointed out that his graphs of tan Θ against ω are fundamentally ambiguous. Let us see how this ambiguity arises.

If we are using polar coordinates (as Gougerot chose to), we are describing Z in terms of its magnitude, $|Z|$, and its phase angle, Θ, by

$$Z(j\omega) = |Z(\omega)| \exp [j\theta(\omega)] \qquad (10.1.b.2)$$

Then following for example Faulkner (1969), p.64 ff) we may write

$$\Theta(\omega) = \frac{2\omega}{\pi} \int_0^\infty \frac{\ln |Z(\nu)| \, d\nu}{(\nu^2 - \omega^2)} \qquad (10.1.b.3)$$

(cf. Cole, 1972, p.21), and

$$\ln|Z(\omega)| = \ln |Z(o)| - \frac{2(\omega^2)}{\pi} \int_0^\infty \frac{\Theta(\nu)\, d\nu}{\nu(\nu^2-\omega^2)} \qquad (10.1.b.4)$$

From equation (10.1.b.3) it can be seen that if we know $|Z(\omega)|$ over a large enough (ideally infinite) range of frequency, we can derive the corresponding $\Theta(\omega)$, and thus from (10.1.b.2) the complex impedance which we could plot on a complex impedance locus to derive R_∞, R_o, τ_p and m. Thus graphs of $|Z(\omega)|$ against ω (or f) are as capable of fully defining the linear electrical properties of skin as are plots of the complex impedance locus on the complex impedance plane.

However, from (10.1.b.4) it can be seen that the converse is not true; even if we have a complete knowledge of $\Theta(\omega)$ as a function of frequency, it is still not possible to uniquely determine $|Z(\omega)|$ and thus obtain the

coordinates of the impedance on the complex impedance locus, because $Z(o)$, i.e. R_o, remains undetermined. Consequently Gougerot, in plotting his results as graphs of $\tan\theta$ against frequency, irretrievably threw away the information from which R_o and R_∞ could be derived, and R_o at least is a very important quantity for describing the condition of the skin, as we saw in the last Chapter.

In summary, then, we may say that the way in which data are gathered and reported is very important, and must be adequate to define the parameters R_∞, R_o, τ_p and m of the Cole equation if the time and nervous energy of those involved in making the measurements and reading about them is not to be largely wasted.

10.1.c Non-linear properties

There are, as we have seen already in Section 4.3, various electrical properties of skin which are not described by the Cole equation but which can nevertheless be employed to characterize the state of normal or abnormal skin.

The most popular such index is the "skin potential", or skin potential level (SPL), being the potential difference between an epidermal site of interest and a reference site which has been scarified, or is otherwise equivalent to the dermis. Such measurements have recently been reviewed at length, and with particular reference to pathological skin, by Woodrough (1976). Consequently rather less than their fair share of attention will be paid to them in this thesis. The various phenomological properties of the skin potential in pathological skin will however be touched upon in this Chapter, and in Section 12.3 the phenomenology will be reviewed in detail.

The other main approach to the non-linear electrical characterization of skin is by means of its voltage/current (or current/voltage) characteristic curve, and the practice of measuring and drawing such curves has become known as "phoreography". This technique and the results obtained by using it on pathological skin will be reviewed together in Section 12.5, where we will attempt to interpret what it all may mean.

10.1.d The concept of the "polarization" of the skin

Much of the earlier literature describes the electrical properties of abnormal skin in terms of its "polarization" (German "Polarisation", cf. Rein, 1929). This is not however the same as dielectric polarization, and we will review the concepts in detail in subsection 12.6.d, since they still affect the literature very much. For example, Melczer (1976) has recently produced a review of the electrical properties of skin cancers which conceptually belongs to the German literature of the twenties. He writes in terms of "polarizability", presumably to correspond with the "Polarisierbankeit" of this literature.

Until the more complete treatment later we may assume however that discussion of "polarization" or "polarizability" values may be related to the quantities we have met before by the expressions

$$\text{Polarization} = V_{app}\left[1 - \frac{R_\infty}{R_o}\right] \qquad (10.1.d.1)$$

where V_{app} is the applied voltage, and

$$\text{Polarizability} = \left[1 - \frac{R_\infty}{R_o}\right] \qquad (10.1.d.2)$$

10.1.e A note concerning skin appendages

Skin appendages act as shunts across the impedance of the skin, and increased activity of the sweat glands will decrease R_o (cf. subsection 9.2.c). This has been known since at least as long ago as 1888, when Vigoureux found a high skin resistance on the anaesthetic and/or paralyzed side of hemiplegics and "hysterics". Alterations in sweat gland activity also alter skin potential, as we will see later (Section 12.3).

Therefore it is pertinent to note, as did Edelberg (1971, p.545) that "the emotional consequences of skin disfigurement may cause emotional reactions which change sympathetic (sudomotor) activity and hence skin resistance and potential". In other words, there are complicating factors from higher centres which affect the electrical properties of abnormal skin.

It might be useful at this point to explain Gildemeister's observation (1928, p.110) that the equivalent series capacitance C_s of the skin is altered during anaesthesia. We know that

$$C_s = \frac{1}{j\omega X_s} \qquad (10.1.e.1)$$

and from the Cole equation it follows that (at constant m), anything which decreases R_o will also decrease the magnitude of X_s at all frequencies, and consequently from (10.1.e.1) increase C_s accordingly.

In fact most, if not all, of the apparent changes in "skin capacitance" discussed in the literature are very likely to have been due to changes in R_o, which again emphasizes the desirability of using the complex impedance locus, or the parameters of the Cole equation, to report experimental results.

10.2 Skin injury

10.2.a The electrical effects of mechanical injury and scarring

As might be deduced from subsections 9.3.d and 10.1.e, puncturing stratum corneum reduces R_o and thus the impedance of the skin very considerably, possibly to the value of the deep tissue impedance if the "hole" is big enough. This type of experiment dates back to Lewis and Zotterman (1926-27).

The effects of such an injury upon skin potential have been reviewed by Edelberg (1971, p. 544, 545), and agree with what would be expected on the basis of the interpretative models discussed in Section 12.3.

If a scar subsequently forms, the work of Rein (cf. 1929, p.84) showed that there is a diminution in the electro-osmotic and other phenomena reviewed in detail in Section 12.6, an effect which I believe can be explained by the reduction in the number of skin appendages.

10.2.b The electrical effects of non-mechanical injury: UV-erythema

Keller and Rein (1928) found that the erythema produced by irradiating the skin with ultraviolet light (of unspecified wavelength) was associated with a reduction in skin polarization. From equation (10.1.d.1) it can be seen that this was most likely due to a decrease in the D.C. resistance R_o, which would agree with the comments made by Keller and Rein who felt, quite rightly, that damage had been caused to membranes, making them more permeable.

The results obtained by Cambrai et al. (1979, p.207 ff) support this conclusion. They used electrical indices to monitor the photochemotherapy of psoriasis by 8-methoxypsoralen and PUVA, and their work will be more fully discussed in Section 12.5. Here we will just note that their results imply that after irradiation there is a temporary reduction in R_o and an increase in m, and that these effects could well result from a temporary increase in the hydration of the stratum corneum, with or without an increased permeability of the skin appendages.

10.3 Pathological skin

10.3.a Psoriasis

Keller and Rein (1928) noted a reduction in polarization in psoriatic skin, which I expect (from equation 10.1.d.1) to be due to a reduced D.C. resistance R_o.

In 1947 Gougerot made electrical measurements in psoriatic skin but reported them in a fundamentally ambiguous way as we have noted already (subsection 10.1.b). All that can be concluded, (rather less than Rothman, 1954, and subsequent reviews have implied), is the following.

Compared with the skin of normal subjects, active lesions of psoriatics have an increased f_p, (probably because R_o is decreased), and an increased value of m. This can be deduced from Gougerot's Figure 8 because the Cole equation implies that

$$\tan\theta = \frac{X_s}{R_s} = \frac{(R_o - R_\infty)\ \cos(m\frac{\pi}{2})\ (\omega\tau_p)^{1-m}}{R_\infty[1+2\sin(m\frac{\pi}{2})(\omega\tau_p)^{1-m}+(\omega\tau_p)^{2(1-m)}]+(R_o-R_\infty)[1+\sin(m\frac{\pi}{2})(\omega\tau_p)^{1-m}]} \qquad (10.3.a.1)$$

so for very low frequencies

$$\tan\theta \simeq k_1\,\omega^{(1-m)},\ \omega << \tau_p \qquad (10.3.a.2)$$

and for very high frequencies

$$\tan\theta \simeq k_2\omega^{-(1-m)},\ \omega >> \tau_p \qquad (10.3.a.3)$$

where k_1 and k_2 are constants.

By similar reasoning the uninvolved skin of psoriatics ("peau apparement saine"), by comparison with that of normal subjects, appears to have a rather lower value of m, and perhaps a lower value of f_p (possibly due to a higher value of R_o).

These deductions are partially confirmed by examining Fig. 4 of Clar et al. (1976) in the light of the Cole equation. These investigators claim to have found two distinct groups of psoriatic patient. For "Type I" the lesion has much the same electrical properties as the uninvolved skin. For "Type II", the impedance of the lesion is much reduced compared with that of the uninvolved skin, and the m value is substantially increased. Probably "Type II" corresponds to the findings of Gougerot, and since only three patients were found to have "Type I" responses, perhaps the existence of this form should be more firmly established.

Fortunately Clar et al. (1976) published (means of) skin impedance data obtained at 5 Hz and 1 kHz, therefore assuming R_∞ to be zero gave three points on the complex impedance plane through which a minor arc of a circle could be fitted. The results were approximately

Table 10.3.a.A Processed results of Clar et al.(1976, Table 1)

	Active psoriatic lesions (9 patients)	Adjacent uninvolved skin (9 patients)
R_o =	4.95 kΩ	2.18 MΩ
m =	0.4289	0.1789

These results are very interesting in that I believe they fully confirm the deductions made above from the results of Gougerot. In active psoriatic lesions it seems that R_o is reduced, and m increased, compared with values I would consider typical for the skin of normal subjects. Conversely, the uninvolved skin adjacent to psoriatic lesions seems to have a larger than usual value of R_o and probably a smaller than usual value of m.

Later, in subsection 12.5.c, further work of the same group of investigators is reviewed (Cambrai et al., 1979) and similar results are obtained from processing this extra data (see Table 12.5.c.A).



Fig.10.3.a.I

I think that the reduced R_o and increased m in active psoriatic lesions is an indication of an increased hydration of the stratum corneum (cf. subsection 9.3.c), resulting from the known increase in TEWL (see Fig. 10.3.a.I, reproduced from Grice 1980, p.2153). Grice however has stated (1980, p.2148) that the apparently normal, uninvolved skin adjacent to psoriatic plaques has normal rates of TEWL, a finding which can be reconciled either with the present "hydration interpretation", or with Gorgerot's results on the uninvolved skin of psoriatics, but not with both. However, since the adjacent skin will not have normal values of TEWL if it has recently been part of a lesion (cf. Grice, 1980, p.2148), perhaps the "uninvolved" skin Gorgerot measured was like this.

10.3.b Eczema and dermatitis

As with psoriasis, so with eczema, Keller and Rein (1928) recorded a diminution in the polarization of the skin, again I expect due to a reduction in R_o.

Gougerot (1947) also made electrical measurements on eczematous skin, finding that R_o was "very low" (p.109), suggested too by the high f_p values of his Figure 7. This lowering of R_o may perhaps have been due to the appearance of small fissures through the corneum. He also found that the tan θ curves were rather flattened, as in psoriatic skin, and implying as we saw in the last subsection that m is increased above its average value for the skin of normal subjects. It is particularly interesting to note that the abnormal electrical properties did not become normal as the skin apparently reverted to what would be classed as normal by the usual clinical criteria.

Our "hydration hypothesis" based upon TEWL may again be applicable to eczematous skin, and in this case the comments of Grice (1980, p.2152) tend to give it more support. She notes not only that TEWL is greatly increased in active eczematous lesions (cf. Fig. 10.3.a.I), but also that the skin appears to be normal before the TEWL returns to (close to) normal. This may explain the findings of Gougerot. Even in the apparently normal skin of patients with eczema there is somewhat increased TEWL.

Richter and Heidelbach (1970) investigated the value of making measurements of R_o as an indication of reaction in cases of allergic contact dermatitis, but concluded that such measurements would not be particularly valuable.

10.3.c Skin cancers

Woodrough (1976) measured the skin potential level at the sites of suspected basal cell carcinomas. The mean value of the results was significantly different from the mean value of the results obtained in benign inflammatory lesions, but the variances of both populations were so large that the overlap made the technique useless for diagnosing an individual patient.

Melczer and Kiss (1977) report however that for basal cell carcinomas, squamous cell carcinoma and malignant melanoma, results of significant diagnostic use can be obtained if the D.C. resistance R_o is measured instead, and Woodrough 1977) seemed happy to agree with this. The publications of Melczer however unfortunately continue to propagate extremely antiquated and sometimes thoroughly disproved concepts (see e.g. subsection 10.1.d) and for this reason his review article (1976) cannot be recommended.

10.4 Skin affected by pathological changes elsewhere

10.4.a Thyroid dysfunction

In 1888 Vigoureux described low skin resistances (R_o) in cases of exopthalmic goitre, and since then a number of investigators have sought to relate thyroid disorders with the electrical properties of the skin.

Exopthalmic goitre is also known as Graves's disease in the English literature, Morbus Basedow in the German literature, and more simply as thyrotoxicosis or hyperthyroidism. The stratum corneum of patients with this condition tends to be rather damp and sweaty, and the epidermis is thinner than usual (see e.g. Beeson and McDermott, 1975, p.1711).

Gildemeister (1928, p.110) says that the capacitance of such skin is raised above normal, but I think this can be explained simply by a reduction in R_o (see subsection 10.1.e) due to the increased sweat gland activity. Certainly Barnett (1937, 1939) found that there was a lowered VHF impedance in the skin of thyrotoxic patients but that the VHF phase angle was not significantly different, and these findings fit such a "perspiration model" quite well (compare the sweating/not sweating results of subsection 9.2.c). They also fit his own model based on the known thinning of the epidermis, but the fact that he found the same results in mentally-disturbed patients with no known thinning of the epidermis (Barnett, 1940), I think tends to support my model in preference to his; it is much more reasonable to postulate a chronic increase in sweat gland activity in mentally-disturbed patients than it is to postulate a thinning of the epidermis.

When the functioning of the thyroid is inadequate, i.e. in hypothyroidism (Myxoedema), the opposite electrical effects are observed. Gildemeister (1928, p.110) noted a reduction in skin capacitance, which I think is probably due to a raised value of R_o. Certainly the stratum corneum tends to be dry and rather scaly, and perspiration is much reduced.

10.4.b Cancer

Gerstner and Gerbstädt (1949) investigated the skin impedance at 200 Hz in various cases of carcinomas of organs other than the skin, but such measurements made at a single frequency which is neither low enough to approximate to D.C., nor high enough to avoid the effects of R_o variation due to sweat gland activity, are unfortunately almost useless (cf. subsection 10.1.b).

The measurement of R_o has however been shown to be of some use in establishing a diagnosis of lung cancer (Anon.,1966) and this type of association will be considered in the next subsection.

10.4.c Viscero-cutaneous reflexes in general

In the 1890s, Dr, later Sir Henry, Head discovered that localized changes in the skin could give valuable information about diseases in particular internal organs.

It was soon discovered that these "viscero-cutaneous reflex phenomena" were associated with changes in the electrical properties of the skin (see e.g. Regelsberger, 1950), and an enormous field of investigation was opened up, most of the work for some reason being done in the German-speaking countries.

This initial enthusiasm has by now been shown to be somewhat over-optimistic (Bauch, 1966), but nevertheless viscero-cutaneous reflexes are a very important phenomenon and a very important reason for monitoring the electrical properties of the skin. Unfortunately they also seem to be very complicated, and consequently rather than try to review the subject again here, I have merely included, as Appendix G, a rather long paper I wrote on the neurological background and some of the electrical effects which can be observed. (The paper was however written four years ago and I am now embarrassed by the naivety of various parts of it.)