

Characterization of Contact Dermatitis and Atopy using Bioengineering Techniques. A Survey

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Bioengineering techniques useful in the characterization of contact dermatitis and atopy are surveyed, including non-invasive techniques for the measurement of skin colour, blood flow, skin surface temperature, skin surface contour, water barrier, and skin surface hydration. Ultrasound measurement of skin thickness and edema formation, and ultrasound cross-sectional imaging are also included. Structural and pathophysiological findings in the different types of dermatitis are outlined. *Weal or hive formation is covered additionally. Key words: Contact dermatitis, Atopy, Allergic, Irritant, Weal, Hive, Bioengineering methods, Inflammation, Erythema, Edema, Colour, Tristimulus analysis, Spectrometry, Laser Doppler blood flow, Transepidermal water loss, Hydration, Dryness, Conductance, Capacitance, Replica, Temperature, Ultrasound.*

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History and clinical examination are the main tools of the clinical dermatologist. Inspection of the skin is immediate, and the lateral extension and severity of a dermatitis are easily assessed. The disadvantage is that this method is essentially subjective. As a research tool it is open to bias and difficult to handle.

Punch biopsy and microscopy provide detailed information about the layers of the skin and their affliction with dermatitis, though a punch normally represents only a tiny fraction of the diseased skin, and processing and staining are a kind of desirable artefact. Even so, the result has a subjective element related to the pathologist's examination.

Information and knowledge is not simply a matter of high magnification and subtle detail. In the dermatological armamentarium there is an area between clinical evaluation and sophisticated techniques, where the non-invasive bioengineering methods may be appropriate. These provide:

- non-invasiveness and instant in vivo information;
- objective assessment (quantitation or imaging as a basis for computerized analysis);
- choice of body region and site of examination, with few limitations depending on technique;
- same site can be studied by different techniques, and follow-up examinations performed to study the spontaneous course or the effects of treatment, without interfering with the object being studied.

Prerequisites and planning of study by non-invasive technique

Various devices for non-invasive evaluation of the skin have become available. It is easy to place a probe on the skin and obtain a reading on a digital display. Generally speaking, variation and uncertainty are more likely to result from the way devices are used, rather than to deficiency in repeatability of the method. Before a study based on bioengineering methods is undertaken, the essentials of the method need to be known, and a number of questions asked:

- what information is expected?
- what is the most relevant variable to be measured, and which variables serve for description, comparison, support, or exclusion?
- what is the expected time course of variables, and when should the measurements be performed?
- are variables expected to develop linearly, or not?
- what are the ranges of variables in relation to the expected phenomenon or structure being studied, including inter- and intra-individual variation and dependence of anatomical site, sex and age?
- what function or structure is actually being tested?
- what is the measuring area and, if small, need more recordings be taken and averaged to overcome local site variation?
- are recordings with the equipment reproducible, and is the accuracy acceptable relative to variables being measured and their expected range?
- measuring standards and calibration procedures;
- environmental influences, including season, and need for special laboratory room facilities;
- needs for preconditioning of the individuals before testing;
- what precludes measurements from being performed?
- has the researcher or technician both the educational background and enough practical experience to conduct the study?

As in any other research field the results depend essentially on the ratio between signal and noise, where noise implies sources of variation, some predictable, others unknown. At the moment the success of studies based on non-invasive techniques depends mainly on the educational background of the researcher and appropriate planning, with emphasis on a strict control of predictable sources of variation.

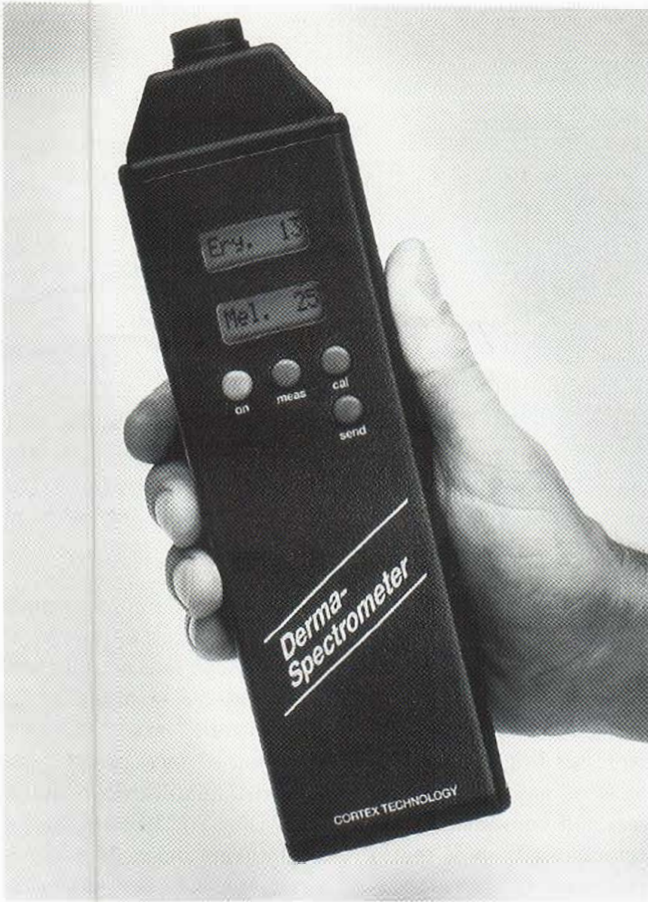


Fig. 1. A portable narrow band spectrometer (Derma-Spectrometer®, Cortex Technology, Hadsund, Denmark) for measurement of erythema index and melanin index.

Review of non-invasive techniques relevant to the study of contact dermatitis

Essentials about skin structure and function as a basis for bioengineering studies were reviewed in the past by Rothman and more recently by Goldsmith (1,2). Several monographs on bioengineering methods and their technical principles and applications have appeared (3,4,5,6,7). Recently, bioengineering and the patch test methods were summarized (8).

Several non-invasive techniques have been used in the past to study contact dermatitis, often using prototypes or laboratory equipment. Some techniques, such as polysulphide rubber replica, are simple and can be used directly, while others are complicated, and validation and commercialization are needed before they can attract general interest. The present introduction will deal mainly with techniques which are available and which can be practised in a variety of laboratories.

CHANGES OF THE SKIN SURFACE

Change of colour and of the topography of the skin surface are crucial to the visual assessment of contact dermatitis.

Skin colour, including erythema, can be measured by two different principles, i.e. by spectrophotometric scanning using

CIE system

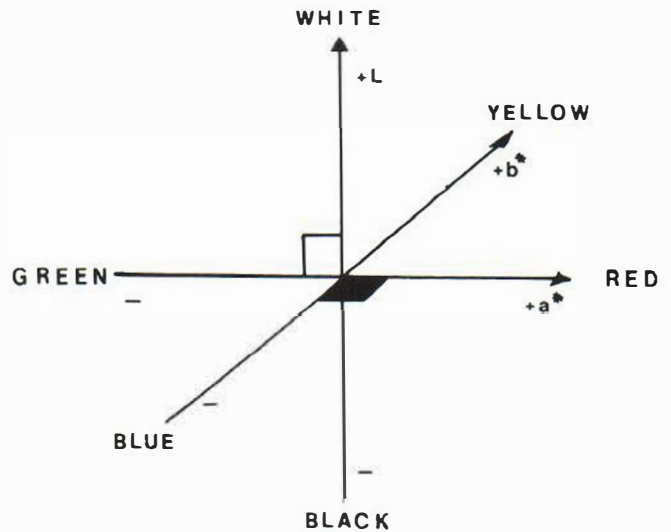


Fig. 2. The CIE (Commission International de l'Éclairage) colour system, which is essentially constructed to substitute for the human eye, i.e. taking the alinearity of colour perception into account. Each colour has its position in a three-dimensional coordinate system with two horizontal axes for colour, and a vertical axis for brightness.

wavelengths between 400 and 800 nm and measurement of absorbance and reflectance, or by tristimulus analysis of reflected flash light. Spectrophotometric scanning has proved of little practical use because the broad melanin absorption band overlaps the haemoglobin band, and since non-specific optical phenomena of the skin related to scaling and scattering influence recordings significantly. However, devices that measure the haemoglobin band specifically and express erythema as an index of haemoglobin relative to melanin have appeared (Fig. 1), and if technically of high precision may prove useful (9). The perception of colour by the human eye and brain has a range from 400 to 800 nm, and a maximum of sensitivity between 500 and 600 nm, corresponding to the colour of blood



Fig. 3. Minolta Croma Meter CR-200® (Minolta, Osaka, Japan) for tristimulus analysis of colour according to the CIE system. The apparatus may be set to express colour in other coordinate systems.

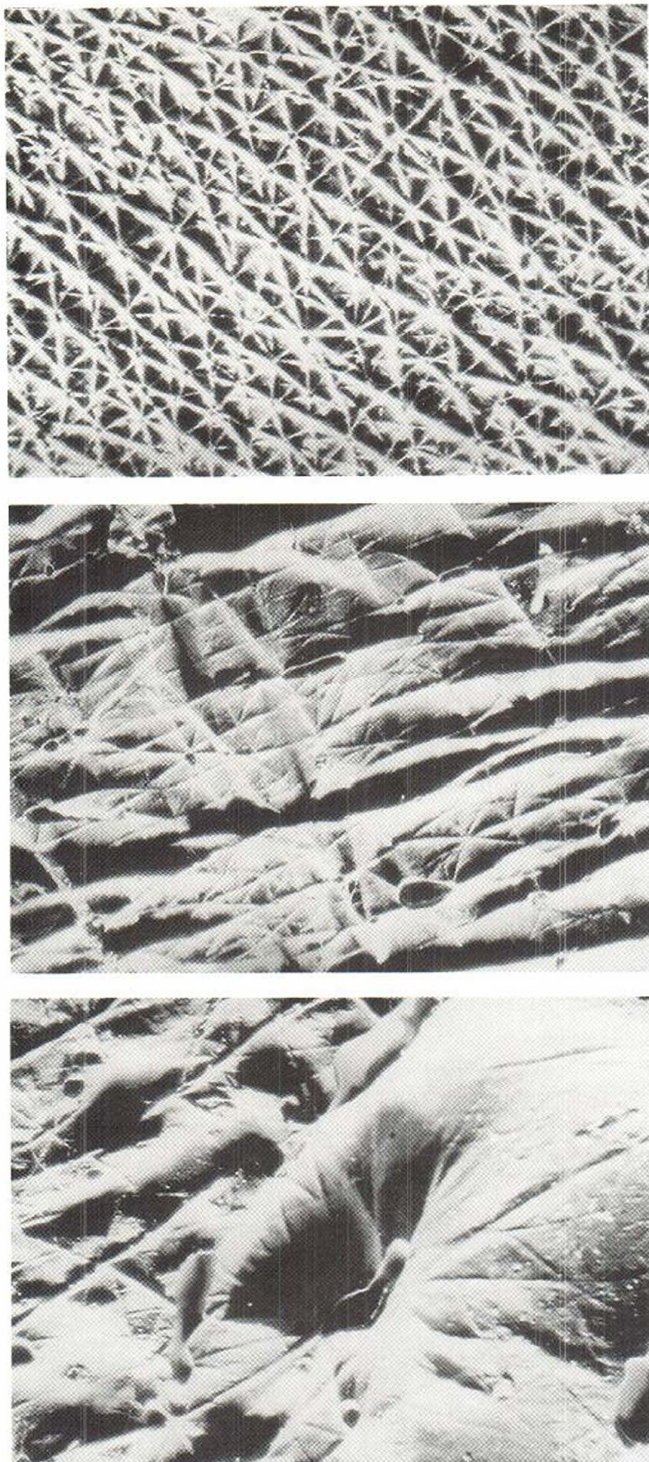


Fig. 4. Polysulphide rubber replica showing the surface contour of normal skin (up), irritant contact dermatitis after exposure to non-aqueous acid (middle), and an allergic patch test reaction (down). Shading is created by 30° incident light.



Fig. 5. Skin hydration measurer (conductance) described by Tagami and co-workers as a prototype for measurement of water absorption-desorption, Skicon-100® (IBS Ltd, Tokyo, Japan). The apparatus measures hydration superficially in the epidermis.

and hence of redness. Apparatus based on tristimulus analysis of reflected light and the CIE (Commission International d'Éclairage) takes this alinearity of the eye into account and expresses all colours in a three-dimensional system (Fig. 2) with green-red (a^*), yellow-blue (b^*) and L^* axes, where L^* expresses brightness (10). In erythema, a^* increases, L^* decreases, and b^* is unaltered (11). Tristimulus devices can be operated conveniently and quickly (Fig. 3). Recent studies (unpublished) show that a^* and erythema index by narrow-band spectrometry are closely correlated, in both normal skin as well and erythematous skin in psoriasis. With both methods, scales may obscure the redness, and erythema values will fall accordingly.

The skin surface contour, with scales, papules, vesicles, etc., can be studied by clinical photography and by various replica techniques (Fig. 4). The main difficulty with close-up photography is that the flash gun light, after diffusing within the skin, is reflected to the camera lens from different layers of the skin having different microstructures and under different angles of reflected flash light appearing from the same structure. Skin



Fig. 6. Skin hydration measurer (capacitance) developed to measure dryness of skin (Schwarzaupt, Cologne, Germany, more recently Courage and Khazaka GmbH, Cologne, Germany). The apparatus measures hydration more deeply in the epidermis.

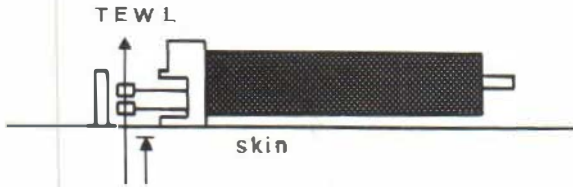


Fig. 7. Evaporimeter probe with a pair of sensors 3 and 6 mm above the skin surface, measuring temperature and humidity at two different levels in the water vapour boundary layer above the skin. The transepidermal water loss is calculated automatically. Registrations are very sensitive to air convection in the room and the probe chamber.

surface pictures become much sharper if the surface is coated, and transmission and scattering are eliminated. If by applying immersion oil, optical effects of the surface are eliminated, and dermal structures such as blood vessels can be observed. In clinical photography, film and the copy process are also subject to variations between batches, which has a significant effect on the finished photo (12). By using polysulphide rubber imprint material, 30° of incident light and a stereomicroscope, surface details can be clearly discerned, as the flexible rubber material is not transparent. Replicas can be stored, transported, and evaluated "blind" and in batches under laboratory conditions. Replicas can also be used as a basis for advanced quantification by the stylus method and by computerized image analysis (13). Recently a tape method was introduced, which is a development of the sticky slide technique for harvesting stratum corneum material. This may prove useful for both qualitative and quantitative evaluation of scaling and hyperkeratosis of dermatitic skin (14).

EPIDERMAL HYDRATION AND WATER BARRIER FUNCTION

Although invisible, the water barrier of the skin is very often damaged in dermatitis, with consequences for the biology of the epidermis and the clinical manifestations.

Skin surface hydration can be measured by electrical methods (15,16). The construction of the detector and the technical specifications determine which layer of the epidermis is to be measured. The contour of the skin and the size and shape of

the detector determine the electrical contact and influence the results. If the detector is small, more measurements will need to be taken and averaged in order to minimize local site variation. The conductance measurer described by Tagami and co-workers (Fig. 5) measures very superficially, while the Corneometer CM 420 (Fig. 6), based on electrical capacitance, measures more deeply in the epidermis (17,18). Recent studies have shown that the compartment of the epidermis capable of binding water is only small, and the diffusional equilibrium between stratum corneum and ambient air establishes itself quickly, i.e. within 10 min (19). Following occlusion, the biology of the epidermis changes, and equilibrium with ambient air takes longer, i.e. after 24 h of occlusion one hour or longer. Thus, when measuring skin surface hydration, the skin need to be uncovered for a time before recording, and also temperature and humidity of the laboratory room need to be kept within certain limits.

The transepidermal water loss (TEWL), expressing diffusional water loss through the skin, is a parameter of major importance in irritant reactions to detergents. Various closed-chamber methods were used in the past, but they were cumbersome and interfered with the spontaneous TEWL. The method described by Nilsson, using an open chamber, water vapour evaporation, and gradient estimation, is very often used nowadays (20,21). The water vapour pressure gradient is measured with sensors at two different levels above the skin surface (Figs. 7, 8), and the TEWL calculated (20,21). Appropriate preconditioning and a strict control of measuring conditions are essential if recordings are to be accurate. Sources of variation were recently reviewed, and guidelines were published by the standardization group of the European Contact Dermatitis Society (22). The water barrier of the skin is not like a filter or membrane within the skin; it is a gradient across the skin including a 10 mm layer of ambient air. Thus, the environment is itself part of the water barrier, and changes in temperature and humidity influence the passage of water from the skin, and also skin surface hydration. Eccrine sweating is in most body regions less important, except after physical activity when it can increase many fold. Environmental changes related to season also need consideration (23).

PARAMETERS OF INFLAMMATION

Vasodilatation and edema formation are the essential features of inflammation. While blood flow has been extensively studied, edema formation has been relatively ignored.

The skin surface temperature is more or less obsolete as a measure of inflammatory activity in contact dermatitis. In normal skin the temperature ranges within narrow limits. In dermatitis, vasodilatation tends to raise the temperature toward the core temperature, but evaporation, crustation and scaling tend to counteract temperature increase. Skin surface temperature can be measured by contact methods using cholesteric crystal sheets and by infrared non-touch methods (Fig. 9). The main use of contact thermography in contact dermatitis is to image lateral temperature gradients, which may provide detailed information about inflammation and crustation of patch test reactions (7,24,25), see Fig. 10A-D.



Fig. 8. Evaporimeter EPI® (ServoMed, Kinna, Sweden) for measurement of transepidermal water loss.



Fig. 9. Contact thermometer (Comark 2001®, Rustington, England, left) and infrared thermometer (Thermophil 203®, Ultrakust GmbH, Ruhmannsfelden, Germany) for measurement of skin surface temperature.

The *vasodilatation* of inflammation and the increase in blood flux are often measured by laser Doppler flowmetry (LDF) (6), see Fig. 11). A number of apparatuses are now available. The tone of the cutaneous vasculature is normally relatively contracted and it may be difficult to monitor vasoconstriction, such as blanching due to corticosteroids. In dermatitis, however, a 30-fold increase in flow may be seen. In advanced inflammation the edema may compress vessels, and the degree of inflammatory activity may be underestimated. Compared with other methods, LDF is both sensitive and discriminative. The vasculature and its tone is in a state of dynamic balance, and factors such as mental stress and noise instantly influence the blood flow. Thus, provision must be made for both preconditioning and measuring conditions.

The *edema* of inflammatory reactions may be measured by skin-fold calipers and by high-frequency ultrasound (Figs. 12, 13). Calipers inevitably compress the edema, and it is not clear which layer of the skin is included in the fold and being measured. When using ultrasound, high frequency and broad bandwidth are both needed. 20 MHz transducers have proved to be a good compromise between the needs of resolution and depth of the viewing field (Fig. 14). With A-mode scanners (Figs. 12, 14B) the thickness of dermatitic skin can be measured, and the increase in thickness representing edema formation calculated (26). With B-mode and C-mode scanners (Figs. 13, 14A-F) crosssectional imaging of the skin is possible (27). In vivo, distances, areas, volume, and structure can be determined by using computerized analysis. Ultrasound shows that inflammatory edema develops mainly in the papillary dermis, where it propagates and produces an echo-lucent band, which can be measured and monitored during the different stages of the inflammatory process. Information and training are needed in order to perform ultrasound examination, as in any other specialty.

Generally speaking, methods that determine static features such as structure and dimension are less susceptible to var-

iations in measuring conditions and are easier to standardize, in comparison with methods based on functions.

Allergic contact dermatitis

Erythema, infiltration, papules, and vesicles are the known manifestations of acute allergic contact dermatitis, read in routine patch testing. When using non-invasive technique, the same manifestations are quantified. In strong reactions, bullae, erosions and crusts may appear. Once elicited, it is our opinion that the sequence of events follow essentially the same course. In chronic disease hyperkeratosis and scaling are often prominent. Unlike the situation in irritant contact dermatitis, allergic reactions were not often studied with non-invasive techniques in the past.

Study of the *skin surface contour* by the polysulphide rubber replica technique shows that counts of papules and vesicles correlate with clinical readings, doubtful reactions can be divided into those with sporadic papules and those without, but an impression taken from the margin of the test chamber can be used instead (28). No studies on *skin colour* and allergic contact dermatitis have been published. Weak and moderate reactions can probably be ranked, but in strong reactions, changes in the physical character of the skin surface are likely to influence the optical properties and create variations. Epidermal *hydration* and *TEWL* must depend closely on the clinical stage of the dermatitis. In chronic dermatitis with scaling, conductance is decreased due to a reduced water-binding capacity, in contrast to TEWL, which is increased (29). The value of conductance measurements seems not to be so much the grading of early stage dermatitis but rather the determining of chronic disease and the documentation of healing. Decreased conductance and increased TEWL are very common in protracted dermatitis, irrespective of its origin. Nevertheless, increased TEWL is not a primary event in allergic reactions; rather, the water barrier becomes progressiv-

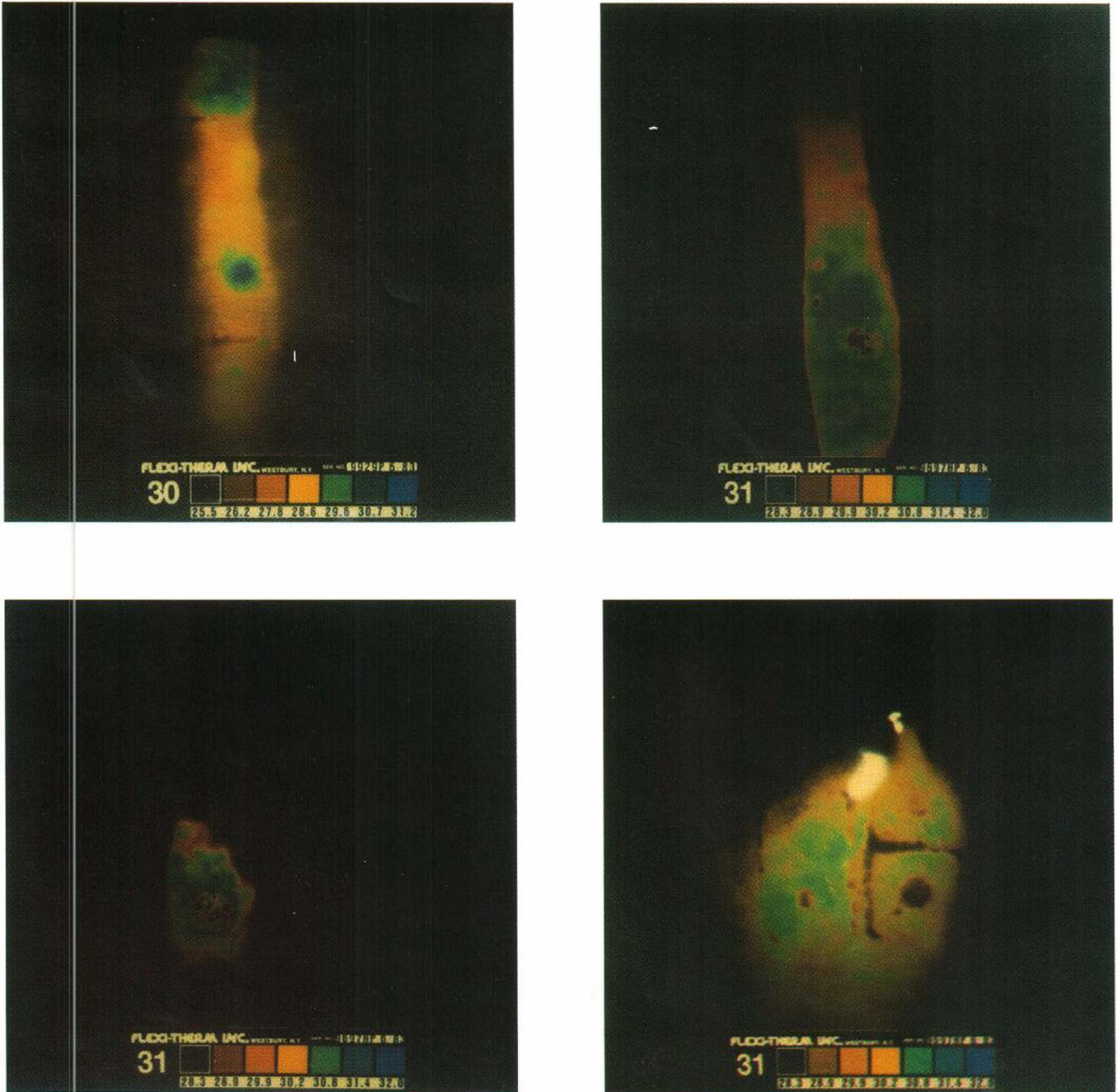


Fig. 10. Cholesteric film thermography for imaging of temperature gradients in the skin surface. Blue and green are warmer, and brown colder, mean 28.6°C ($25.5^{\circ}\text{--}31.2^{\circ}$). A sudden inflammatory reaction (allergic patch test reaction to nickel sulphate) is warm (A), but after 48 and 72 h the thermogram is irregular with cold areas due to crusts, despite ongoing inflammation (B and C). Irritant reactions (patch test sodium lauryl sulphate) are regular, discoid and cold (D).

ely damaged during the first days as the inflammation develops (30).

The surface temperature in acute allergic reactions is increased, though if vesicles and bullae leaving crusts occur the temperature pattern on the surface may be irregular (Fig. 10), with areas of decreased temperature corresponding to the crusted patches (24,25,31). Increased temperature may persist for a while after visible changes have disappeared (7).

Allergic reactions to nickel show increased blood flow as measured by LDF, and positive, doubtful and negative reac-

tions can be distinguished (32), though the positive reactions may be difficult to rank. Probably the inflammatory response has an initial stage dominated by vasodilatation, and a more advanced stage dominated by edema, which compresses the vasculature. Allergic patch test reactions and irritant reactions to sodium lauryl sulphate (SLS) show increases in blood flow at the same level (33).

Ultrasound measurement of skin thickness and the edema of allergic patch test reactions reveals progressive thickening of the skin as the clinical reaction intensifies (26,27,34). With

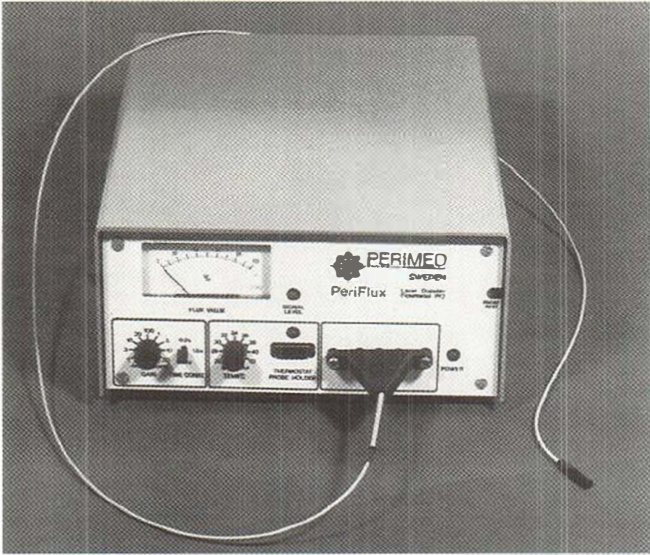


Fig. 11. PeriFlux® laser Doppler flowmeter (Perimed, Stockholm, Sweden). The measuring area is small, and multiple measurements with averaging are to be recommended when measuring cutaneous blood flow.

ultrasound, strong reactions can also be graded. The edema formation of allergic reactions is more severe than irritant reactions following SLS, matched with respect to strength of the reactions clinically (26). With ultrasound B-mode scanning, an echo-lucent band is seen in the papillary dermis immediately beneath the epidermis, representing a more advanced edema and swelling of the outer dermis (27), (see Fig. 14B). It is a general feature that inflammation in contact dermatitis afflicts mainly the papillary dermis, which is more easily distended under the influence of the edematous pressure than is the reticular part. Such changes cannot be evaluated by histological methods since the histological processing is highly intrusive to tissue water, which is extracted and replaced by lipophilic media before embedding in paraffin wax.

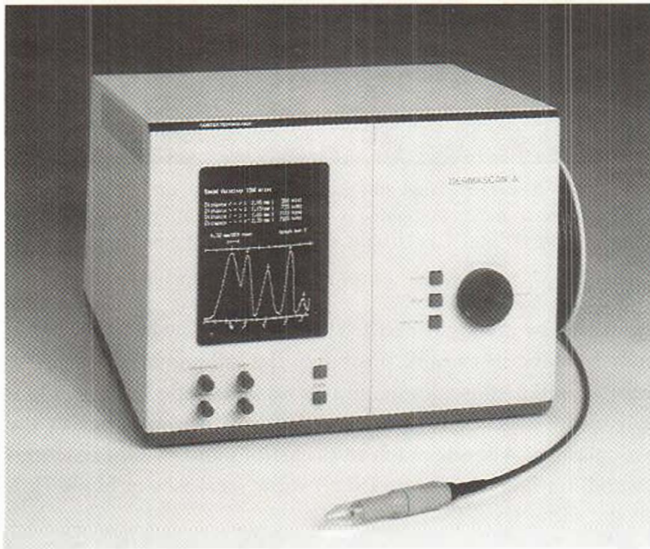


Fig. 12. 20 MHz ultrasound A-mode scanner (DermalScan A®, Cortex Technology, Hadsund, Denmark) for non-invasive measurement of skin thickness including the thickening due to edema formation.



Fig. 13. 20 MHz ultrasound A,B,C,M-mode scanner (DermalScan C®, Cortex Technology, Hadsund, Denmark) for cross-sectional imaging of skin and computerized image analysis. Images are shown in Fig. 14.

Irritant contact dermatitis

Irritant contact dermatitis is not a uniform entity of diseases, but each irritant exerts its special noxious effects on the skin, and each profession has its special battery of risk substances and mode of physical contact (35). Obviously, this creates disparity in the manifestations of irritancy and how it is best assessed. Moreover, reactions vary with age, body region, menstrual phase, skin complexion and skin type, including sensitivity to light, etc. Thus, control of a great number of variables is in principle a prerequisite.

A number of substances and test procedures have been evaluated in the past by Björnberg and more recently by Frosch (36,37). Monographs on irritant contact dermatitis and TEWL were published by van der Valk, by Pinnagoda and by Tupker (38,39,40). Irritancy and LDF was studied by de Boer (41), and Agner studied irritancy by various methods including replica, thermography, TEWL, LDF, colorimetry, high-frequency ultrasound and conductance (42).

The change in colour toward redness elicited by the irritant SLS is characterized by an increase in a*, a minor decrease in L*, and unchanged b* as measured according to the CIE system (11). Colorimeters based on the CIE system and tristimulus colour analysis are particularly suitable for a busy routine and for situations when preconditioning is difficult. Colorimetry appears accurate for the distinction of positive from

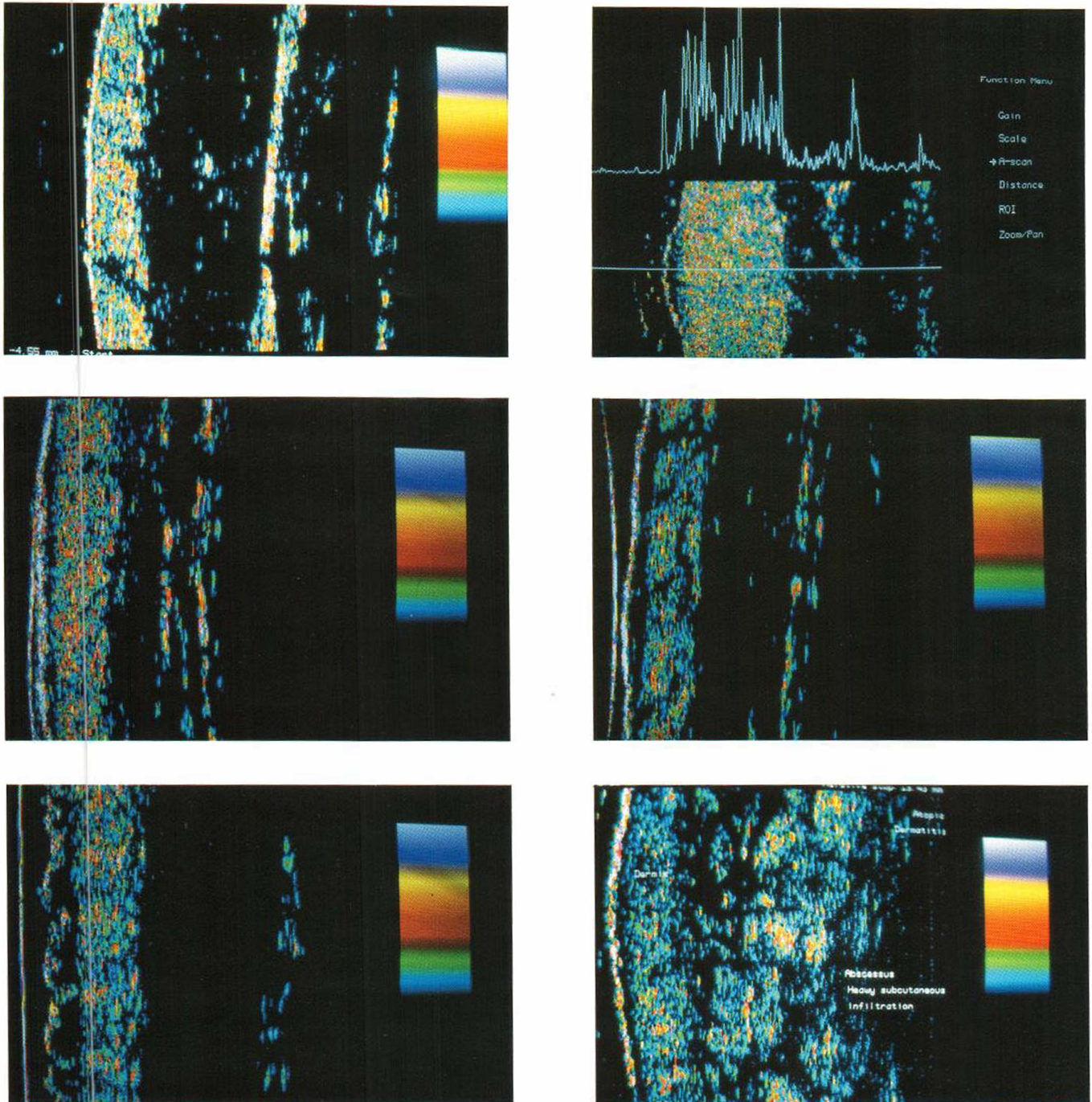


Fig. 14. High-frequency (20 MHz) ultrasound scanning of normal skin and conditions with dermatitis. A, normal skin rich in dermal echoes and with hair follicles. Subcutaneous fat is echo-lucent. The muscle fascia is seen below the fat. B, cross-sectional image (*lower half*) of allergic patch test reaction. An echo-lucent dermatitis band is seen beneath the epidermis. The A-mode scan is illustrated (*upper half*), and the selected scan line shown in the image. C, atopic dermatitis with an echo-lucent band in the subepidermal area resulting from inflammatory activity. D, atopic dermatitis with echo-lucent band with progression of the inflammatory activity along hair follicles and in a less regular distribution in the reticular dermis. E, atopic dermatitis with cross-section of skin with lichenification presenting a wrinkled skin surface. In the papillar dermis there is a broad echo-lucent band of inflammation, but the reticular dermis is straight and relatively uninvolved. The scan illustrates the relatively superficial character of lichenification, and the two-compartment pathological structure of dermatitic skin. F, atopic dermatitis with diffuse bacterial infection of the subcutaneous space, accumulation of clusters of fibrin seen as irregular patterns, but as yet, no accumulation in an abscess cavity.

negative reactions, though colorimetry is less precise for a more differentiated ranking of redness, depending on the irritant being studied (42,43). A main reason why grading of redness can prove difficult is that the vasodilatation of inflammation, as mentioned, does not run linearly but fades as

the edema progresses. Moreover, microanatomical changes in the skin surface during strong reactions influence the optical properties of the skin non-specifically, with consequences for the measurement of colour. In chronic dermatitis, hyperker-

atosis and scaling may obviously influence colorimeter measurements.

The *skin surface contour* changes (Fig. 4) according to the irritant and the time of the examination, as demonstrated by studies with the polysulphide rubber replica technique (44). Some irritants induce a papular pattern, others provoke a nonpapular pattern. Propanol, which is used as a vehicle for nonanoic acid, is itself irritant and modifies the skin relief.

The *skin surface hydration* of irritant contact dermatitis is the result of damage to the cutaneous water barrier induced by the irritant on the one hand, resulting in increased water vapour pressure in and over the stratum corneum, and the formation of crusts, hyperkeratosis, and scales on the other hand, resulting in reduced water-binding capacity and decreased stratum corneum hydration. Even in the acute stage of dermatitis, most irritants exert a noxious effect, giving a decrease in electrical conductance and capacitance, depending on the specific irritant and its ability to coagulate the skin surface, while increased hydration is only found in a few individuals and mainly following application of the detergent SLS (18). In chronic stage contact dermatitis the electrical measurements are decreased, almost without exception (29). Due to the variable structure and pathophysiology of acute irritant reactions, the electrical methods were not found very useful for the grading of irritancy (43).

Measurement of *TEWL and damage of the water barrier* has proved important for the characterization of irritant effects on skin elicited by detergents (38,39,40,42). Studies using mainly SLS as a model detergent have demonstrated that TEWL measurement is more accurate than other methods such as LDF, colorimetry and ultrasound for the grading of this irritant (39,40,42,43,45). Impairment of the water barrier and an increase in TEWL is found not just in the acute stage of dermatitis but also in chronic stages with hyperkeratosis and scaling (29). The problem with TEWL is that a number of prerequisites with respect to preconditioning and laboratory room conditions need be fulfilled in order for measurements to be accurate, as described by the standardization group (21). It must be stressed that different irritants have different effects on the skin, and experiences obtained with detergents cannot be uncritically extended to other substances (35,44,45). The use of TEWL to detect sensitive skin and predict the occupational risk of irritant contact dermatitis is described later.

Measurement of *skin surface temperature* is as previously mentioned not an accurate measure of inflammatory activity of irritant contact dermatitis. However, thermographic imaging (Fig. 10) of skin surface temperature gradients demonstrates that some reactions to irritants are "cold" due to the formation of a temperature insulating crustation, while others are "warm" (24,25,31). Different skin surface temperature patterns appear during the course of irritant reactions, and such patterns may be monitored using thermographic methods, and compared with allergic reactions.

Laser Doppler Flowmetry has been extensively used for the evaluation of irritant contact dermatitis (41,42,46). Experiments with SLS and LDF have demonstrated a dose-response relationship (41,42,43,45,46), and the method has proved valuable for the quantification of irritant reactions and the in-

flammatory component. In the evaluation of reactions elicited by SLS, LDF is, however, less accurate than TEWL and ultrasound measurement (43,45). As earlier, mentioned edema of strong reactions may compress the vasculature and restrict the blood flow. Also, skin surface changes such as vesicles, bullae, crusts, and hyperkeratosis and scaling may influence the optics of the skin and the laser signal. Using probes covering a small surface area only, averaging of three or more recordings is necessary to overcome local site variation in the cutaneous blood supply. The LDF registers the total blood flow, and recordings are easily influenced by measuring conditions such as talking, breathing, noise, mental stress. Thus, preconditioning and laboratory conditions need be carefully controlled.

High-frequency (20 Mhz) ultrasound measurement of skin thickening and edema formation has been used in different studies of SLS irritant reactions (26,27,42,43,45), and a dose-response relationship was demonstrated. For the evaluation of SLS reactions, where damage of the water barrier is prominent, ultrasound has an accuracy in between TEWL and LDF (43,45). In types of reactions with less pronounced damage to the water barrier, ultrasound is probably more accurate. Hitherto the cross-sectional ultrasound image of contact dermatitis has been relatively little studied. However, inflammatory edema of the skin does not expand the skin in a uniform way. Edema extends mainly in the softer and more pliable papillary dermis (Fig. 14B), and an echo-lucent band is seen by ultrasound (27). Ultrasound has the advantage that structures are studied and preconditioning and laboratory conditions are therefore not critical. The disadvantage is that training in this special technique is necessary.

Sensitive skin and hyperirritable skin

During a lifetime, almost every human experiences dermatitis on some occasion, and skin sensitivity represents a spectrum of reactivity. Frosch & Kligman defined a group of subjects on the basis of reactivity to SLS, who more constantly suffered from irritant contact dermatitis (47). Recent studies show that a skin type with high basal TEWL reacts more strongly to SLS, and this might be used to predict occupational risk (39,40,42,48), although prognostic and epidemiological studies are not available. Sensitive skin was also found more sensitive to light, by colorimetry more fair with a higher L^* , and thinner according to ultrasound, i.e. findings which may indicate a more profound structural and functional inferiority of sensitive skin including deviations in both the epidermis and the dermis (42,49). However, skin sensitivity is not simply constant, it also changes with age, menstrual cycle, season of the year, etc., i.e. factors that interfere and overlap and which may occasionally create the conditions for an irritant contact dermatitis to appear (23,50). All these variables need be taken into account whenever skin sensitivity is evaluated by non-invasive techniques and when determination of risk factors or dynamic testing by provocation with a standard noxious agent such as SLS is performed.

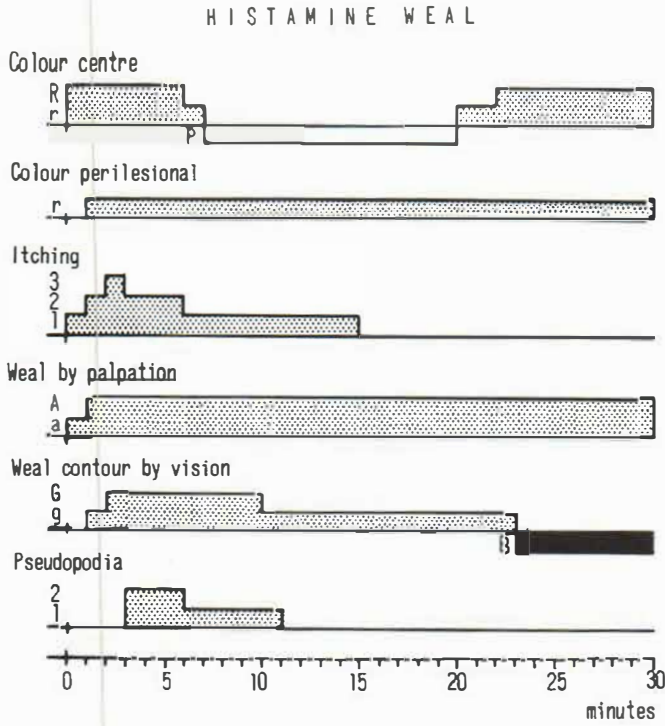


Fig. 15. Clinical signs and symptoms during weal formation after skin-prick with histamine 10 mg/ml. R, bright redness; r, slight redness; P, pale; itching 1/2/3: slight/moderate/intense; a, just appreciated; A, clearly appreciated; g, can be determined, G, very distinct; B, poorly defined; pseudopodia 1/2, can be observed/very distinct.

Atopic dermatitis

Patients with active hand dermatitis and young patients with active atopic dermatitis have hyperirritable skin and react more strongly to SLS in uninvolved skin, while the reactivity of uninvolved skin in chronic or healed eczema and in adult atopy and hand dermatitis is normal (51,52,53). Thus, whenever groups of patients are studied by non-invasive techniques, the groups need be clearly defined clinically, and the presence of active eczema somewhere is particularly important.

Even during improved phases, atopics show dryness or roughness of the skin with reduced conductance and capacitance, often associated with a defective water barrier and increased TEWL as in other conditions with dryness. Dry skin in atopic dermatitis was studied in detail by Y. Werner Linde, and is reviewed elsewhere in this supplement, including a review of studies on roughness and skin surface contour and studies on epidermal lipids.

Obviously, bioengineering methods such as colorimetry and LDF are also useful for the objective characterization of active dermatitis in atopics, although these methods were previously only sporadically used to quantify the inflammatory activity in this condition.

High frequency ultrasound imaging of the skin reveal a subepidermal echo-lucent band as in other conditions with inflammation and dermatitis (Fig. 14). This band is assumed to represent cellular infiltration and disturbance of the normally regularly ordered connective tissue fibre structure. In lichenification, only the superficial part of the skin is wrinkled or

folded, while the reticular dermis remains straight (Fig. 14). Thus, lichenification is structurally relatively superficial, determined essentially by the axes of joint motions, and with advanced dermatitis as a prerequisite. The dermis is really a two-compartment structure. The papillary dermis is more pliable and more easily distended under the influence of inflammation and the pressure of edema, while the structure of the reticular dermis is straight and more resistant. Thus, ultrasound examination demonstrates that the papillary dermis constitutes a special tissue space where the inflammation of dermatitic skin tends to accumulate and extend laterally.

Urticaria weals

Weals or hives are very dynamic lesions with rapid changes during the initial 30 min when a triple response develops (Figs. 15, 16). Thus, when measuring weals, the timing of the recordings needs to be precise and appropriate.

Weals have only sporadically been studied by non-invasive techniques. LDF reveals increases in blood flow in both the weal centre and the flare. Edema formation interferes with the vasculature, and measurements in the flare are more suitable to determine the strength of the reaction following histamine in different concentrations (54,55).

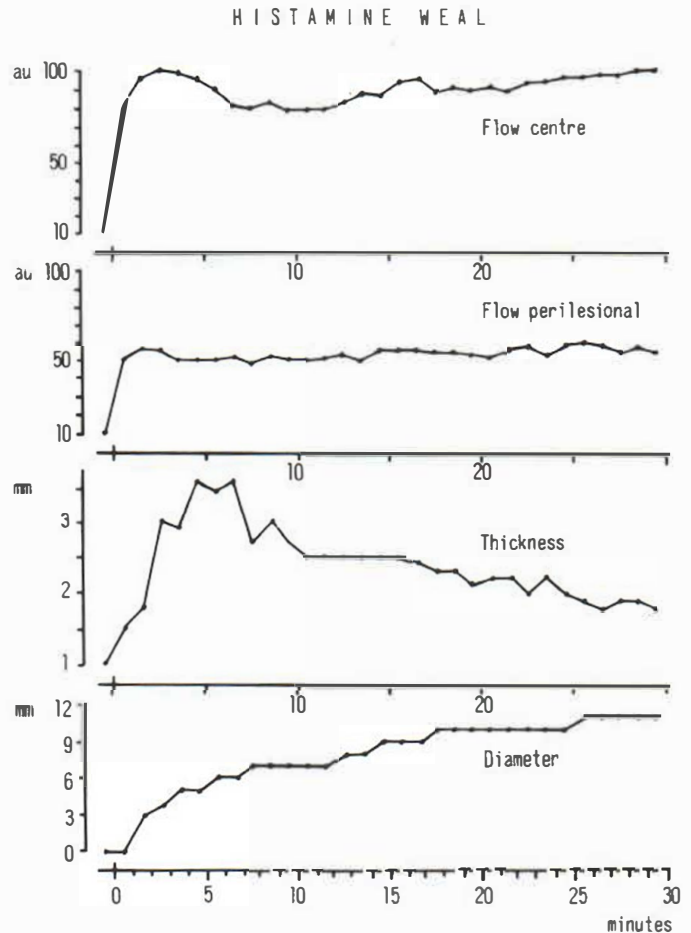


Fig. 16. Successive non-invasive recordings during weal formation after skin-prick with histamine 10 mg/ml. Blood flow determined by laser Doppler flowmetry; thickening by A-mode highfrequency ultrasound; diameter (mean) by a ruler.

Ultrasound examination of histamine weals shows that the weal is initially globoid, and on reaching a diameter of about 5 mm it extends laterally in the skin and becomes flatter (27,56). The thickness and volume of weals can be measured with ultrasound. Ultrasound cross-sectional imaging shows that edema of weal reactions propagates mainly laterally in the skin in the papillar dermis, which is more easily distended (27). At the same time this explains the formation of pseudopodia.

Dimethyl-sulphoxide (DMSO) weal reactions were studied by TEWL, conductance, ultrasound skin thickness and LDF measurements, and it was concluded that the methods are suited for quantification of responses – except for LDF, due to the influence of edema on the vasculature (57).

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