

Estimation of the general incidence of specific lanolin allergy

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Synopsis—The literature pertaining to LANOLIN HYPERSENSITIVITY is critically reviewed with reference to relevant definitions, exposure to lanolin, limitations of test methods, inherent exaggeration of test results, AUTOXIDATION, multiple sensitivities, selection of test subjects and the distinction between secondary and specific lanolin ALLERGY. Using recent data relating to 8.25×10^8 population in three European countries the incidence of specific lanolin allergy amongst the general population is calculated to be no more than 9.7 per 10^6 and probably considerably less.

Scope. The object of this work is not to review an exhaustive list of all known literature on the subject, since several summaries and commentaries have already been given (1), (2), (3). It is to study the more representative, extensive and significant publications and to draw from this detailed evidence a valid conclusion about the general incidence of specific lanolin allergy. This has not previously been attempted.

INTRODUCTION

Cases of allergy or hypersensitivity to lanolin have been recorded over a period of approximately 50 years. Although the absolute incidence of this hypersensitivity does not appear to be increasing (2), over the last decade particularly the subject has become more prominent in the medical and scientific press, yet the vast majority of this work has been concerned not with the general public but with relatively small groups of patients attending skin hospitals, including patients having severe symptoms such

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as leg ulcers and therefore abnormal sensitivity. Such work cannot be equated to the overall general situation.

Since lanolin is a widely used ingredient, not only of products applied to the skin such as cosmetics and ointment bases, but also of many other common household commodities, it is important to establish as far as possible the incidence of hypersensitivity, or more particularly of primary specific allergy, to the substance amongst the general population.

Hardly any substance at all can be said to be completely non-allergenic. Even foods such as milk, eggs, fish and fruit, also common metals such as nickel used in coinage and clothing attachments, provoke a small but real incidence of allergy. Clearly, if every substance which was known to have elicited even a single case of allergy over its whole history were to be regarded as suspect, there would be little left for people to eat, drink or wear. For any substance in common use, therefore, the incidence of allergy to that substance should be weighed against its benefits to the whole community to decide whether the incidence is acceptable or not.

The benefits of lanolin as a unique combination of emollient for the skin and W/O emulsifier have been proven beyond doubt by subjective evidence of the practical results of its use over a period of centuries (1), and by its inclusion in most national pharmacopoeiae for many decades. Lanolin is more readily miscible with sebum and more penetrating than petroleum jelly (2), and a very versatile and useful carrier with good release properties for certain medicaments (4), (5). It is widely used in industrial hand protectives ('barrier creams') (6), and has been specifically recommended for this purpose (7) to prevent the development of dry skin with consequent increased risk of developing dermatitis. Other important applications of lanolin are instanced later, and it can be seen, therefore, that we are dealing with a substance which is of considerable value both to medicine and also to the community as a whole.

DEFINITIONS

It is necessary to define the term 'lanolin' since some publications on the subject of allergy have referred to 'lanolin derivatives' without being specific (8), (9), (10). To assume identical dermatological behaviour by lanolin and all its chemically modified derivatives is clearly wrong in the absence of proof. Indeed, several workers have established distinct differences in allergic incidence between various derivatives (11), (12).

Lanolin, in the common usage of the term, should more correctly be referred to as 'Anhydrous lanolin', synonyms being Wool Fat, Wool Wax or the Latin name *Adeps Lanae*. It originates as a natural, unique type of wax secreted by sebaceous glands in the skin of sheep, and its refining involves the removal of adventitious and natural impurities without significantly affecting the essential substance. In composition it is predominantly a complex mixture of esters of high molecular weight alcohols and fatty acids (13), and these esters can be hydrolysed to yield separate alcoholic and acidic fractions both of which are themselves complex mixtures. The alcoholic fraction, like the parent lanolin, is widely used in products for skin care again under a variety of names: Wool Alcohols, Wool Wax Alcohols, Lanolin Alcohols, *Alcoholia Lanae*, and so on.

EXPOSURE TO LANOLIN

Previous authors have noted that small amounts of unrefined wool wax can be present in wool clothing, since the wool textile industry deliberately aims to leave a small residue of the wax in wool in order to retain its softness to the touch. For example, the standard allowance in the industry for the residual grease (wool wax) content of dry-combed wool tops supplied to spinners is 0.634%, as high as the lanolin content of many cosmetics. Most people may thus be expected to be in frequent and prolonged contact with wool wax, irrespective of whether they use lanolin-containing products on their skin or not. A few cases of allergic sensitization to wool have been recorded in the literature (8), (14), (15), in one of these a cure was claimed following a desensitizing treatment with an extract of wool.

In addition to wool and preparations intended for use on the skin, many other commodities also contain lanolin, wool wax or lanolin alcohols, a few examples being shoe polishes, floor waxes, paper, printing ink, man-made textile finishes, fur dressings and leather dressings (16). Thus, most members of the public in developed countries may be expected to be in frequent contact with lanolin or wool wax from one source or another, and this very extensive exposure must be considered in arriving at any estimate of allergic incidence in general.

LIMITATIONS OF TEST METHODS

The results of investigations so far published contain uncertainties and

exaggerations inherent in the stringent test methods which have been forced on investigators by the difficulty of the problem. The underlying difficulty is that the allergic response to lanolin is so weak that results from even the 100% substance are unreliable, (9), (10), (17), (18), (19), whilst diluting lanolin with an inert vehicle further increases the chance of false negative results (12).

Attempting to circumvent these difficulties, many workers, especially the more recent, have employed two modified types of test, now designated (a) and (b):

(a) In the first modification an addition of 2–5% of salicylic acid or 2% of resorcin, to quote but two examples, is made to lanolin in order to act as a keratolytic and increase the penetration of any allergens through the epidermis. The weakness of this method is that salicylic acid can itself, as is well documented, provoke an allergic response or even primary irritation. Hence sometimes, but not always, the precaution has been taken of testing subjects both with the lanolin mixture and with salicylic acid in petroleum jelly, only cases of positive reaction to the former with negative reaction to the latter having been regarded as significant. This qualification is inadequate, however, since it is known that a mixture of substances, each innocuous on its own, may exhibit synergism or in some other way induce a false positive result (20). For example the occurrence of false positive results from lanolin with added keratolytic was experienced and reported by Cronin (19), whilst the method has been criticized also by Thune (2) and by Fisher (8). Bonnevie (21) queried whether his positive reaction to 5% salicylic acid in lanolin was perhaps a secondary irritation from salicylic acid. Present opinion is almost unanimous that a test modification of this type invokes a large degree of exaggeration, and this point is discussed later in more detail.

(b) As a second modification, tests are made not with lanolin itself but with a solution of lanolin alcohols in petroleum jelly, usually at 30% concentration although some workers have used 6% ('eucerin') or intermediate levels. In all cases this method has elicited an increased incidence of positive reactions compared to the use of 100% lanolin, and again there is a fundamental weakness since the method assumes a similarity in dermatological effect between esters on the one hand and alcohols on the other, whereas there is a distinct chemical difference between the two. Moreover, due to the relatively severe processing conditions needed to hydrolyse lanolin esters, it is possible that commercial lanolin alcohols contain degradation

products not present in the original lanolin. It is thus not certain that a positive reaction to lanolin alcohols proves sensitization to lanolin.

INHERENT EXAGGERATION OF TEST RESULTS

Even if both (a) and (b) modifications are employed in the same test series, since each has its own uncertainties the results must still be inconclusive and much of the recently published work can only be regarded as presenting an exaggerated picture of the situation. Different opinions on the extent of exaggeration have been given, but according to Epstein (22) the addition of salicylic acid to lanolin or to eucerin can yield positive results of which half or more are false. Epstein also considers that patch testing with 30% of lanolin alcohols in petroleum jelly produces a significant number of false-positive irritant reactions, and would regard only positive reactions to 20% and 10% concentrations as 'clear cut indicators of lanolin allergy'. This is a helpful qualification but does not resolve fully the known uncertainties. Differences in dermatological effect between lanolin and lanolin alcohols have, in fact, been established by de Beukelaar (23) and by Bandmann and Reichenberger (24). There are a number of quantitative comparisons of the incidence of positive reactions from lanolin alcohols and lanolin respectively. Thus Reichenberger (25) found diluted lanolin alcohols to elicit fifteen times as many reactions as lanolin, whilst Wereide (9) found 7.5 times as many when both test substances contained 5% of salicylic acid. Thune (2) found 10 times as many with added salicylic acid, and 3.2 times without. An increase by a factor of 3.7 was reported by Hjorth and Trolle-Lassen (10), a factor of 2.5 by Baer, Serr and Weissenbach-Vial (31) and a factor of 5.5 by Epstein (22). When a keratolytic was added to lanolin, Thune (2) demonstrated increases in the incidence of positive reactions by factors of 2.5 and 2.6, and he attributed this exaggeration to false positive reactions whilst also believing that even 2% of added salicylic acid caused too many false positives and that salicylic acid in petroleum jelly used as a control could yield false negatives since the jelly is not as penetrating as lanolin. Again on adding a keratolytic, Hjorth and Trolle-Lassen (10) found a factorial increase in incidence of 2.8, and Epstein (22) a factor of 3.0. Fisher (8) emphasized that tests for lanolin sensitivity should be carried out with 100 per cent lanolin alone, since admixture with keratolytic, emulsifier or anything which increased penetration into the skin could cause false positive results.

Although these weaknesses and criticisms of both test modifications are severe, it must be recognized that such powerful methods have been used by investigators because of the difficulty of diagnosing hypersensitivity to a weak allergen, and may well be a help, if not essential, in making the first critical diagnosis of a troublesome case.

Autoxidation

The pattern of allergic response to lanolin is irregular. It can vary between age groups and sexes (10), and between different localities (27), (28). Some samples of lanolin or lanolin alcohols have elicited positive reactions, whilst others have not. The possibility of this difference in behaviour being due to the presence or absence of autoxidation by-products has been investigated and significant evidence found to the effect that not only did autoxidation of lanolin alcohols markedly increase the incidence of allergy, but also that the addition of certain antioxidants to lanolin depressed the level of incidence (10). Schwarzfeld (26) referred to the possibility of autoxidation degradation products being responsible for allergic reaction to lanolin, and for a similar reason Reichenberger (25) recommended testing with both fresh and aged eucerin.

As a result of research into their effects (29), (30), the addition of approved antioxidants to lanolin is now permitted by a number of pharmacopoeiae, an addition to Wool Alcohols being mandatory in the BP since 1968. For this reason one might expect the general incidence of allergic hypersensitivity to lanolin and lanolin alcohols, whatever this incidence is, to be favourably influenced.

CROSS-SENSITIZATION AND MULTIPLE SENSITIVITY

Efforts have been made to relate allergy to lanolin with concomitant allergy to other substances such as long chain fatty alcohols, isopropyl myristate, Lanette Wax and glyceryl monostearate (10), (12). No specific or constant relationship could be established, but many cases of multiple sensitivity were found. For example, Magnusson *et al.* (27) tested six groups of patients at different hospitals and listed the percentage within each group of positive reactions to a total of 24 different substances. The column totals varied from 11% to 158%, indicating a considerable degree of multiple sensitivity. In the work of Fregert *et al.* (28), the percentages total 78.5% but this was the proportion of 4825 patients out of whom only 40% gave a

positive reaction on patch testing with anything. Out of all 1930 positive reactors, therefore, the total percentage of reactions amounts to 196.25%, thus each reactor was sensitive, on the average, to 1.96 substances. Baer *et al.* (31) found the average number of sensitivities per patient, out of 743 in total, to be 4.37 for weak reaction and 2.72 for strong reaction. Cases of this type are not necessarily indicative of true cross-sensitization, of course, but are at least to be regarded as polyvalent sensitivity. Hjorth and Trolle-Lassen (10) found that sensitization to lanolin rarely went alone and that similar symptoms could be provoked by, for example, parabens, or neomycin which are far removed in chemical structure from lanolin. They also reported that some forms of dermatitis, particularly varicose eczema of the leg, were more likely than others to be associated with hypersensitivity to lanolin, and that most patients had a long history of eczema before lanolin sensitivity was diagnosed. Some of these findings were corroborated by Wereide (9) whilst Cronin (19) reported that lanolin hypersensitivity could be an aggravating factor rather than a primary condition. In other words, the sensitivity was grafted on to an already existing pattern of dermatitis which did not entirely disappear when contact with lanolin was discontinued. Epstein (22) also referred to multiple sensitivities, whilst Stolze (35) dealt in detail with this matter and made a regression analysis showing how the average number of sensitivities per case increased with duration of case history, from 1.6 sensitivities at zero duration to 6.0 at 37 years.

On the same theme, a large-scale co-operative European study by Fregert *et al.* (28) found that, out of a total 4825 patients at skin clinics in seven different countries, whereas 115 showed a positive reaction to lanolin alcohols, 35 of these were simultaneously sensitive to neomycin, 24 to wood tar, 22 to colophony, and so on (private communication to the author). Hence, a reported case of hypersensitivity to lanolin or lanolin alcohols does not automatically mean that either substance was the primary or initiating allergen.

Approaching the problem from the opposite direction, tests for allergy to lanolin carried out on normal, apparently healthy skins have not elicited a single report of positive reaction. Sulzberger and Lazar (11) tested three normal subjects, Sulzberger, Warshaw and Hermann (12) tested 120, Newcombe (1) reported on 50 and Norholm-Pederson and Sylvest (32) tested 111, results on all 284 being negative. Even when using an enhanced 'maximization test', in which sodium lauryl sulphate is used to make the skin more sensitive to test substances, Kligman (33) failed to elicit any hypersensitivity to lanolin in 25 human subjects, whilst Magnusson and

Kligman (34), using the same method with a parallel Landsteiner-Draize test on guinea pigs, obtained zero scores throughout. As confirmation of these results, the present author has not personally known of a single case of hypersensitivity to lanolin or wool wax amongst employees engaged in lanolin refining, crude wool wax recovery, or woolsorting, where people are in constant and liberal contact with the substances, out of a total of at least 3000 over a period of 28 years.

Primary specific lanolin allergy and secondary hypersensitivity

Attempting to identify a specific allergen in lanolin, various workers have tested patients known to be hypersensitive to lanolin with certain individual, known constituents of the substance. The absolute purity of the samples used was not, however, reported and the test results were mixed. Thus, Ellis (36) investigated the effect of cholesterol from two sources and obtained positive results to both, on several patients. Sulzberger and Lazar (11), also Sulzberger, Warshaw and Herrmann (12) found mostly negative reactions to two lanosterol samples of different purity and also to cholesterol from two sources (lanolin and cattle spinal cord), only one positive reaction (to lanosterol) being reported. Everall and Truter (37) worked with crude cholesterol, lanosterol, cholestanol and cholesta-3,5-dien-7-one, only the crude cholesterol yielding positive reactions. After purification of this cholesterol reactions were negative, and it does seem unlikely that cholesterol could be the allergen since it is a normal and essential constituent of the human body. Everall and Truter isolated a small quantity of the impurity from the crude cholesterol and found it to give a positive skin response, but no specific chemical identification was made.

In the present state of knowledge, no single chemical entity has been certainly identified as the principal allergen of lanolin, but it is now well established in the cited literature that certain sufferers from dermatitis, particularly where some types of eczema such as eczema of long duration, varicose eczema and ulcus cruris are concerned, become polyvalently hypersensitive to a number of chemically unrelated substances, one of which may be lanolin. Although in some of these cases a primary, specific lanolin allergy may be the original cause, in many others lanolin will not be the actual initiating allergen, if a single specific allergen does indeed exist. Since some patients may develop a hypersensitivity to lanolin as a secondary result of some entirely different primary cause, it is important in estimating the incidence of specific lanolin allergy to discount those cases, even though diagnosis of the lanolin hypersensitivity, along with

any other concomitant hypersensitivity, might be necessary for the successful treatment of such patients. This fundamental distinction has been lacking in almost all the published literature, and so the true picture of the lanolin allergy situation has inevitably been distorted. Moreover, when an investigation has included not the whole patient list of a skin clinic or hospital but only a selection from the list, then a second source of doubt arises. Baer *et al.* (31) made a particular point of the fact that a distorted picture can be drawn from results based on a deliberate selection of suitable subjects for testing. Bearing these distorting factors in mind, the gross incidence of lanolin/lanolin alcohol sensitivity amongst patients at skin hospitals may be derived by starting with the tabular summary given by Peter, Schröpl and Franzwa (3) and, to be cautious, discount all results prior to 1957 inclusive, since lanolin allergy was then not being as diligently sought as it is today, and may therefore have been less frequently diagnosed. A weighted average of the lanolin and lanolin alcohol hypersensitivity incidence out of a total of 22 523 subjects gives the figure of 1.70% and it should be remembered that not only were these patients at skin hospitals, but that they also included such highly non-representative results as those of Reichenberger (25) who tested exclusively patients with *ulcus cruris*, only one-third of whom did not show hypersensitivity to some substances, and those of Stolze (35) who employed exceptionally potent test media. These figures, although atypical, have not been excluded from the ensuing calculations in order that the latter should tend to err on the high side rather than otherwise.

A second basis for calculation is the extensive European study (28), where 115 out of 4825 patients showed a positive reaction to lanolin alcohols (note: not lanolin, which was not tested). The proportion of positive reactions here was 2.38% and this may be combined, again as a weighted average, with the previous percentage to give a mean gross incidence of positive reactions out of 27 348 patients of 1.82%. The term 'gross' implies that the figure has been arrived at without discounting any of the known exaggerating factors. That is to say, the figure relates to all skin patients whether or not they were specially selected, and no matter whether they were tested with lanolin, lanolin alcohols, eucerin or mixtures of these with keratolytics. This gross incidence of 1.82% ignoring its inherent exaggeration, seems modest and relatively insignificant amongst the patients in relation to the great usefulness and convenience of lanolin and lanolin alcohols in ointment bases used for treating the other 98.18% or more of dermatitis patients.

Estimation of the incidence of primary lanolin allergy

The gross incidence of lanolin allergy amongst patients at skin clinics is a very different matter compared to the primary specific allergy amongst the general population. The literature yielded no data from which the latter could be reliably derived, but information supplied to the author privately by certain of the participants in the Joint European Study (28) can provide the basis for approximate calculations relating to three of the eight countries concerned in that study. The necessary information was not available from the other five countries.

The data supplied comprised two statistics: (i) the approximate number of the general population served by a particular hospital; and (ii) the average number of new cases per year diagnosed as hypersensitive to lanolin alcohols.

Thus, for Wycombe General Hospital the population from which patch test patients are drawn is estimated to be 225 000 \pm 25 000. The contact clinic at Sahlgrenska Hospital, Gothenburg serves approximately 350 000 population. At the University of Lund Department of Dermatology in Malmo the population served is estimated at one million, but this is shared by three other clinics. Assuming equal shares this is equivalent to 250 000 per clinic.

These data are summarized in *Table I*, a striking feature of which is the close agreement of the figures in the last column where the maximum deviation from the average is 6.5%. This average represents the gross incidence and must now be subjected to two correcting stages. The first stage is to allow for the exaggerating factor inherent in the use of lanolin alcohols in place of lanolin. This factor has been reported as being from a minimum of 2.5 (31) through 5.5 (22) to 15 (25) for lanolin alcohols without added keratolytic.

Table I. Gross incidence of lanolin alcohol allergy at three European skin clinics

Clinic	General population served	Average no. of new cases of lanolin alcohol hypersensitivity per year	
		Numerically	Per million population served
Gothenburg	350 000	24	68.6
Lund	250 000	15.4	61.6
Wycombe	225 000	15	66.7
Total or average	825 000	54.4	65.9

The second stage correction is to distinguish between secondary lanolin hypersensitivity and primary lanolin allergy of which lanolin is the initial and sole cause. The only distinctive criterion for primary lanolin allergy is, surely, when the symptoms disappear completely on cessation of contact with lanolin not only in skin care products but also with wool wax in clothing or other commodities. Schwarzfeld (26) noted that some types of eczema can be aggravated or sustained by contact with wool wax in clothes, and Sulzberger and Lazar (11) made a similar postulation. It is possible, however, to derive from the literature an approximate ratio between secondary and primary hypersensitivity in certain groups of patients. Thus Wereide (9) referred to 'several' specific hypersensitivities out of a total of 270. A quantitative proportion was given by Hjorth and Trolle-Lassen (10), namely 17 out of 50. Another by Reichenberger (25) who found 28 out of 97; by Stolze (35), 11 monovalent reactions out of 52; Epstein (22), 1 out of 5, and by Hjorth (17) who, in a small selection of patients, found a much higher figure of 19 out of 25. Including even the latter figure a weighted average of these quantitative results yields 33.18% as the proportion of lanolin hypersensitivities which are monovalent and specific.

Applying this second correction to the minimum and maximum first stage factors of 2.5 and 15 we obtain overall correction factors of 7.53 and 45.21 respectively which, applied as divisors to the average gross incidence of 65.9, yields a range of primary specific lanolin allergy amongst the general population of 1.46 to 8.75 per million.

Residual errors

The foregoing range takes no account of the fact that some patients may be treated by general practitioners without being referred to skin clinics. A compensating error is the deliberate inclusion of exaggerated figures in the stage two correction.

Finally, there is an error inherent in estimating the population area served by a hospital. If we assume this to be $\pm 11.1\%$ as in the case of Wycombe, the corrected range of incidence extends from 1.3 to 9.7 which can be expressed as 5.5 ± 4.2 per 10^6 . Thus, the general incidence of specific lanolin may be said to be, at the most, 9.7 per 10^6 without making any deduction for test material which could have been autoxidized, distinguishing between lanolin from different manufacturers, or eliminating test results from subjects with abnormal skin conditions. The likelihood is that the true figure is considerably less than this calculated upper limit.

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REFERENCES

- (1) Newcomb, E. A. Lanolin Allergy. *J. Soc. Cosmet. Chem.* **17** 149 (1966).
- (2) Thune, P. Allergy to Wool Fat. *Acta Dermatol Venereol.* **49** 282 (1969).
- (3) Peter, G., Schröpl, F. and Franzwa, H. Experimentelle Untersuchungen über die allergene Wirkung von Wollwachsalkoholen. *Hautarzt.* **20** 450 (1969).
- (4) Lower, E. S. Lanolin—I. *Man. Chem. Man. Perf.* **15** 13 (1944).
- (5) de Kay, H. G. The release of medication from an emulsified ointment base. *Amer. Perfum. Cosmet.* **77** (Sec. I) 109 (1962).
- (6) Bandmann, H.-J. and Dohn, W. *Die Epicutantestung.* 179 (1967) (Verlag J. F. Bergmann, Munich).
- (7) Schwartz, L. *The prevention of occupational skin diseases.* 20, 23, 28 (1955) (Ass. Amer. Soap Glyc. Prod. Inc., USA).
- (8) Fisher, A. A. *Contact dermatitis.* 179, 215 (1967) (Lea and Febiger, Philadelphia, USA).
- (9) Wereide, K. Contact allergy to wool-fat (lanolin). *Acta Dermatol-Venereol.* **45** 15 (1965).
- (10) Hjorth, N. and Trolle-Lassen, C. Skin reactions to ointment bases. *Trans. St. John's Hosp. Dermatol. Soc., London.* **49** 127 (1963).
- (11) Sulzberger, M. B. and Lazar, M. P. A study of the allergenic constituents of lanolin (wool fat). *J. Invest. Dermatol.* **15** 453 (1950).
- (12) Sulzberger, M. B., Warshaw, T. and Herrmann, F. Studies of hypersensitivity to lanolin. *J. Invest. Dermatol.* **20** 33 (1953).
- (13) Truter, E. V. *Wool wax* 31-60 (1956) (Cleaver-Hune Press Ltd, London).
- (14) Lord, L. W. Cutaneous sensitization to wool. *Arch. Dermatol. Syph.* **26** 707 (1932).
- (15) Hertslet, L. E. A case of dermatitis due to wool. *S. African Med. J.* **8** 182 (1934).
- (16) Gillespie, D. T. C. Wool wax. A review of its properties, recovery and utilisation. *J. Text. Inst.* **39** P45 (1948).
- (17) Hjorth, N. Routine patch tests. *Trans. St. John's Hosp. Dermatol. Soc., London.* **49** 99 (1963).
- (18) Cronin, E. *Contact dermatitis from cosmetics.* Soc. Cosmet. Chem. Gt Brit. Symposium. Eastbourne, Nov. 15th, 1966.
- (19) Idem. Lanolin dermatitis. *Brit. J. Dermatol.* **78** 167 (1966).
- (20) Rieger, M. M. and Battista, G. W. Some experiences in the safety testing of cosmetics. *J. Soc. Cosmet. Chem.* **15** 161 (1964).
- (21) Bonnevie, P. *Aetiologie und Pathogenese der Ekzemkrankheiten.* 354 (1939). (Nyt Nordisk Forlag, Arnold Busck, Copenhagen).
- (22) Epstein, E. The detection of lanolin allergy. *Arch. Dermatol.* **106** 678 (1972).
- (23) de Beukelaar, L. Allergic reactions to wool fat alcohols. *Dermatologica.* **136** 434 (1968).
- (24) Bandmann, H. J. and Reichenberger, M. Beobachtungen und Untersuchungen zur Frage der durch Eucerin bedingten seltenen Allergie. *Hautarzt.* **8** 11 (1957).
- (25) Reichenberger, M. Zur Epikutan Sensibilisierung bei Ulcus cruris-Kranken. *Arch. Klin. Exp. Dermatol.* **223** 56 (1965).
- (26) Schwarzfeld, H. K. Sensitivity to ointments containing wool fat. *U.S. Armed Forces Med. J.* **3** 1371 (1952).

- (27) Magnusson, B., Blohm, S-G., Fregert, S., Hjorth, N., Höding, G., Pirilä, V. and Skog, E. Routine patch testing, IV. *Acta Dermatol. Venereol.* **48** 110 (1968).
- (28) Fregert, S., Hjorth, N., Magnusson, B., Bandmann, H.-J., Calman, C. D., Cronin, E., Malten, K., Meneghini, C. L., Pirilä, V. and Wilkinson, D. S. Epidemiology of contact dermatitis. *Trans. St. John's Hosp. Dermatol. Soc.* **55** 17 (1969).
- (29) Clark, E. W. and Kitchen, G. F. A note on autoxidation and its inhibition in wool alcohols B.P. *J. Pharm. Pharmacol.* **12** 233 (1960).
- (30) Idem. Autoxidation and its inhibition in anhydrous lanolin. *J. Pharm. Pharmacol.* **13** 172 (1961).
- (31) Baer, R. L., Serr, F. and Weissenbach-Vial, C. Studies on allergic sensitization to certain topical therapeutic agents. *Arch. Dermatol.* **71** 19 (1955).
- (32) Nørholm-Pederson, A. and Sylvest, E. Über die Häufigkeit des Auftretens von Allergien bei Benutzung einer bekannten Hautcreme auf einer dermato-venereologischen Krankenabteilung. *Dermatologica.* **104** 424 (1952).
- (33) Kligman, A. M. The identification of contact allergens by human assay, III. *J. Invest. Dermatol.* **47** 392 (1966).
- (34) Magnusson, B. and Kligman, A. M. The identification of contact allergens by animal assay. The guinea-pig maximisation test. *J. Invest. Dermatol.* **52** 269 (1969).
- (35) Stolze, R. Dermatitis Medicamentosa in eczema of the leg. *Acta Dermatol-Venereol.* **46** 54 (1966).
- (36) Ellis, F. A. Allergic contact dermatitis due to wool fat and cholesterol. *Arch. Dermatol. Syph.* **56** 801 (1947).
- (37) Everall, J. and Truter, E. V. Cutaneous hypersensitivity to lanolin: investigation of one case. *J. Invest. Dermatol.* **22** 493 (1954).