Recent Advances in Dermatology

Edited by **Arthur Rook**

NUMBER THREE

Recent Advances in Dermatology

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NUMBER THREE

Churchill Livingstone Edinburgh and London 1973

3rd edition 1973

International Standard Book Number
0 443 01008 0

Text set in 10/11 pt. Monotype Times New Roman, printed by letterpress, and bound in Great Britain at The Pitman Press, Bath

Preface

The first edition of *Recent Advances in Dermatology* was published in 1936. In it the single author, Dr. W. N. Goldsmith, set out to provide a comprehensive and lucid review of the advances in dermatology, both clinical and investigative, that had taken place since the end of the First World War, and he succeeded admirably.

For the second edition in 1954 Dr. Goldsmith was joined by Dr. F. F. Hellier and these two authors 'summarized and coordinated' the most important work published during the preceding eighteen years.

When I was invited to undertake this third edition of a book with so distinguished a record, I wondered whether in 1973 a book of this type was needed and indeed whether it would still be possible to provide, in a volume of reasonable size and price, a review as useful to dermatologists as the two previous editions had proved to be. The annual output of productive research in relation to the normal and diseased skin has increased so prodigiously during the past two decades that any general review of recent advances in dermatology would necessarily be so superficial as to be of little value. The published proceedings of symposia, yearly more numerous, make readily accessible the latest knowledge in most specialized fields of research. Monographs and review articles fill most of the remaining gaps. However the growing volume of accessible literature itself creates problems, particularly for the dermatologist in clinical practice or in training. For the very many for whom long hours in a well stocked library are not a practicable proposition there is a need for reviews which cover recent advances in laboratory and clinical dermatology in relation to the common diseases from one or more of which over 80% of our patients are suffering. The first criterion for the selection of a topic for this book was therefore that it was concerned with diseases which are frequently encountered or are of special importance in practice. The second criterion was that there had been important recent developments in our knowledge of such diseases.

Our contributors were asked to review the literature of the last ten years, but to do so critically and selectively in the light of personal experience. At several points some chapters overlap others. Where such areas of common ground have led only to repetition, the duplicated

paragraphs have been deleted from one of the chapters concerned. However in those cases in which the common ground has been the subject either of conflicting opinions or of differing but complementary points of view, the overlapping passages have been retained.

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Contents

Cutaneous Bacteriology

Howard I. Maibach, Richard R. Marples and David Taplin

During the last decade many advances have been made in the field of bacterial skin infections. Several texts have delved into specific areas in depth (i.e. M. J. Marples, 1965, and Maibach and Hildick-Smith, 1965). In this review we make no attempt to cover completely the area, but instead have emphasized those topics on which our personal experience permits us to make judgments.

CLASSIFICATION

There has been such change in classification of microorganisms on human skin that the dermatologist who has not followed the literature closely may find it difficult to comprehend current discussions on the matter. This summary attempts to provide the microbiologic background required for further reading in cutaneous infection.

Micrococcaceae and corynebacteria

Pillsbury and Kligman (1954) divided the normal flora into micrococci (staphylococci), corynebacteria, lipophilic fungi and anaerobic diphtheroids but indicated that this list was incomplete. M. J. Marples (1965) listed many species as included in the normal flora but emphasized the existing taxonomic confusion for the micrococci and the diphtheroids. Recent work has contributed to the understanding of these groups.

The micrococcaceae

Staphylococcus aureus has now been well characterized (Elek, 1959) and can be subdivided by bacteriophage typing for epidemiological purposes. The remaining members of the Micrococcaceae have received little attention until recent times. Early descriptions were based mainly on colour and the production of acid from lactose and mannite (McKee *et al*, 1939; Pillsbury and Rebell, 1952). Bergey (1957) reduced the number of *Staphylococcus* species to two, based on coagulase and mannitol fermentation. Several large studies (Shaw, Stitt and Cowan, 1951; Hill, 1959) even cast doubt on the validity of the two genera, *Staphylococcus* and *Micrococcus*. The realization that the mode of attack on glucose was

a basic difference between these genera (Evans *et al*, 1965) and the confirmation of the distinction by guanine cytosine proportions in DNA (Silvestri and Hill, 1965) and lysostaphin susceptibility (Klesius and Schuhardt, 1968) simplifies much of the confusion. Further subdivisions have been attempted (Cowan and Steel, 1965) but the most widely accepted subdivision has been that of Baird-Parker (1963, 1965). In this scheme, six types of *Staphylococcus* and eight types of *Micrococcus* are defined. This system has now been used for micrococci from the urinary tract (Mitchell, 1968), the skin (Noble, 1969), surgical implants (Holt, 1969) and acne lesions (Marples and Izumi, 1970; Izumi, Marples and Kligman, 1970). A modified system was used by Corse and Williams (1968).

Although recent opinion is that some of the types classified as *Micrococcus* are truly members of the genus *Staphylococcus* it seems better at this point to follow Baird-Parker's system rather than to use specific names. '*S. albus*' for instance is used specifically by McKee *et al* (1939) for white strains fermenting lactose and mannite, but is used loosely by other workers. The same name was given to certain strains by Corse and Williams (1968). *S. epidermidis*, as generally recognized, is equivalent to the S-II to S-V grouping in the Baird-Parker system. Marples and Izumi (1970) suggested that this name should be restricted to S-II and S-V. They evolved a simple system that should be of value to many dermatologic laboratories. Subtyping is accomplished by reducing Baird-Parker's scheme to a two-stage procedure. In this system, positive identification of the most common type, S-II, is accomplished rapidly and most groups can be tentatively identified. A second series of biochemical tests then confirm these tentative identifications and detect anomalous reactions. The catalase-positive cocci are divided into the two genera, *Staphylococcus* and *Micrococcus*, on the basis of fermentative (F) or oxidative (O) production of acid from glucose. The two genera are then subdivided using standardized methods. The first stage tests are listed in Table 1.

Table 1. First-stage Tests in Two-stage Classification of Cocci

	Staphylococcus						*Micrococcus*							
	I	II	III	IV	V	VI	1	2	3	4	5	6	7	8
F/O	F	F	F	F	F	F	O	O	O	O	O	O	−/−	−/−
Coagulase	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Phosphatase	+	+	+	−	−	−	−	−	−	−	−	+	−	−
VP	+	+	−	+	+	+	+	+	+	+	−	−	−	−
Lactose	+	+	V	−	+	V	−	+	V	+	+	+	−	−
Mannitol	+	−	−	−	−	+	−	−	+	+	+	+	−	−

On completion of the first stage tests, cocci falling into S-I (*Staphylococcus aureus*) and S-II with these reactions require no further tests. This accounts for more than half of the isolates from most adult skin areas. Remaining isolates are then retested for F/O, phosphatase, and MR/VP reactions, and also for urease, reduction of nitrate, hydrolysis of polysorbates, acid production from arabinose, glucose, maltose and sucrose, gelatinase, and effect on litmus milk. Apart from confirming the previous tentative identifications, lactose-positive M3 are separated from M4 on arabinose and lysis of polysorbates and lactose-negative S-II are detected (Izumi *et al*, 1970).

The corynebacteria

The determinative classification of these organisms, as found in Bergey (1957), is not practical for the separation of the diphtheroid species found on human skin. The organisms in this family include plant pathogens, animal pathogens, and mammalian commensals. Aerobic and anaerobic species are accepted in the same group. The aerobic species recovered from human skin were originally studied with the aim of distinguishing these morphologically similar strains from the epidemic pathogenic strains of *Corynebacterium diphtheriae* rather than of differentiation of species.

The occurrence of lipid-dependent and lipid-loving strains of aerobic diphtheroids was reported by Pollock, Wainwright and Manson (1949) who showed that five of 52 diphtheroid strains from the forearm did not grow unless supplied with oleic acid. A detailed analysis of the biochemical behaviour of this group has been published by R. F. Smith (1969). R. Marples (1969a) defined only two groups of lipophilic diphtheroids. The remaining aerobic diphtheroids do not show an absolute requirement for lipid but only a few species are clearly characterized. These organisms are very common in the axilla (Marples and Williamson, 1969).

C. minutissimum is the causative agent of erythrasma. Originally described as *Nocardia minutissima*, it was placed in the genus *Corynebacterium* by Sarkany and his co-workers (Sarkany, Taplin and Blank, 1961a, 1962) who redefined the species mainly on the production of porphyrin fluorescence in special media. Although not enough to define species, fluorescence does separate these organisms and some other biochemically distinct strains from the remaining aerobic diphtheroids. Crissey, Rebell and Laskas (1952) isolated and defined *C. tenuis* from cases of trichomycosis axillaris. Recently, three types of diphtheroids have been described from trichomycosis axillaris (McBride, Freeman and Knox, 1968), one of which resembles *C. minutissimum*, one which is lipophilic, and a third which matches *C. tenuis* in most respects. These latter organisms resemble some strains placed in Group 8 of Marples' classification (1969a) and some are clearly close to *Nocardia*.

Other lipophilic, but not lipid-dependent, strains which produce urease and form dry colonies are found in the axilla in moderate numbers. Marples (1969a) associated such strains with *C. xerosis* but this organism is reported to be urease-negative (Bergey, 1957). Further studies of isolates from the noses of children have yielded strains more closely resembling *C. xerosis*.

Several other varieties of aerobic diphtheroids are found on the skin but no accepted classification has been established. The difficulties of setting up a scheme lie in inadequate test systems for these strains and the necessity for lipid supplements for some strains. Reliance on nitrate reduction and carbohydrate acidification (Evans, 1968) or oxygen tension (Bouisset, Breuillaud and Michel, 1960) in the absence of good growth is bound to be unsatisfactory. A large study of dairy diphtheroids by Jayne-Williams and Skerman (1966) is important because of the similarities between their strains and those found on human skin and the recognition of lipid-dependent strains. Many older studies cannot be interpreted because much reliance was placed on serum-supplemented carbohydrate fermentation. Serum contains a variable and unpredictable amount of lipid.

For most studies a distinction between lipid-dependent and other diphtheroids is sufficient (Marples and Williamson, 1969) since lipophilic diphtheroids outnumber other aerobic diphtheroids manyfold, except in the toewebs and rarely in the axilla.

Marples (1969a) has systematically examined strains from various skin areas in man. He reported a relatively simple scheme that separated basic groups with emphasis placed on lipid requirement and hydrolysis, colonial morphology, the possession of urease, oxidase and lactase, and the production of fluorescent porphyrins. Table 2 is expanded from the original classification and represents data from 200 human skin strains.

We believe future work will show that considerable ecologic, physiologic, and pathogenetic differences exist between such strains, and that these differences may approach the significance of that seen with the staphylococci.

Classifications of this type are clearly a step forward.

Corynebacterium acnes

A bacillary form present in the deeper portions of acne lesions, particularly comedones, was described in detail by Unna (1896) from histopathological specimens. The same organism was cultured by Sabouraud in 1897 using stab culture in acid glycerine agar with a month's delay to permit the gelatin-negative cocci present to die out. This allowed the establishment of pure cultures of the 'bacille de seborrhee grasse'. He was unable to prepare streak cultures or induce experimental infections in animals. Gilchrist (1900), whose name is associated with the specific

Table 2(a). Biochemical Reactions of 200 Strains of Skin Diphtheroids: % Positive, () Tween 80 Only

	1	2	3*a*	3*b*	4*a*	4*b*	5*a*	5*b*	7
Oxidase	(+)	(53)	–	38	47	+	33	38	68
Phosphatase	(+)	(59)	+	+	+	36	44	62	+
Urease	–	+	+	–	–	+	–	–	–
NO_3	–	–	–	+	52	+	56	–	66
MR	(64)	–	67	63	–	–	–	–	45
Glucose	(61)	–	+	+	37	–	–	–	68
Maltose	–	–	71	(50)	–	–	–	–	45
Sucrose	(45)	–	–	50	26	–	–	–	64
Fluorescence	–	–	–	–	26	–	–	54	+
Tween 80 enhanced	++	++	71	50	26	–	33	–	–

(b). Growth on Lipoid Media: % Positive

Growth on	1	2	3*a*	3*b*	4*a*	4*b*	5*a*	5*b*	7
Tween 20	–	–	–	63	–	+	+	+	+
40	–	–	–	50	–	–	+	+	61
60	–	–	29	38	–	–	+	+	57
80	+	+	+	+	+	+	+	+	+
1288	+	+	+	+	+	+	+	+	+
1292	–	–	+	+	+	27	+	+	+
2127	–	–	–	–	–	–	+	+	–
Lytic Strains as % of Strains Growing									
20	+	+	+	40	50	33	+	–	+
40	+	–	+	50	–	–	+	–	63
60	+	–	+	33	–	–	+	–	72
80	+	31	–	50	58	–	44	–	26
1288	33	–	–	–	26	–	–	–	–
1292	–	–	–	–	47	–	67	–	59
2127	+	+	–	–	–	–	+	–	60

name, may have cultured another organism but clearly saw bacilli in smears of acne lesions.

Although Fleming (1909) had indicated that the bacillus of acne was a diphtheroid, it was first placed formally in the genus *Corynebacterium* by Eberson (1918) and passed into Bergey in 1923, as a diphtheroid in the genus *Corynebacterium*.

Douglas and Gunter (1946) transferred the organism to *Propionibacterium* on the basis of anaerobiosis and propionic fermentation, but listed optimum temperature, gelatinase, action on milk nitrate reduction,

lactate fermentation and habitat as major differences from other propionibacteria. They also demonstrated the presence of the organism on normal skin of the upper arm where it formed from 9 to 78% of the total flora, the remainder being nonpigmented cocci. Brzin (1964) studied 15 strains in detail and recognized indologenic and nonindologenic strains. Strains not producing indole were more saccharolytic. She also reported bacteriophage activity in *C. acnes*.

Recently, Puhvel (1968), and Ray and Kellum (1970) have described the acne bacillus in detail. Zierdt (Zierdt, Webster and Rude, 1968) considers that all the present-named species should be synonymized from Prevot's (1966) 12 species classification and be included in a new genus, *Sebobacillus* (personal communication, 1970). Moore and Cato (1963) prefer *Propionibacterium*. However, at least two types of anaerobic diphtheroids keep appearing. Reid and Joya (1969) state that *C. avidum* strains are not susceptible to the bacteriophage isolated by Zierdt, and Voss (1970) considered that two distinct types could be defined by biochemical, serological, and phage activity. He found a minority of strains to be gelatin- and indole-negative, to ferment trehalose, maltose, and sucrose, and to be resistant to Zierdt's bacteriophage. Questions of lysogenic strains have not yet been studied.

In summary, the main anaerobic diphtheroids found on human skin can still be classified as *Corynebacterium acnes*. Differences in lipolysis (Kellum, Strangfeld and Ray, 1970) or other tests are minor. It is, however, possible that *C. avidum* is distinguishable from *C. acnes* but further work is necessary to establish this beyond doubt and to determine the ecological niche filled by each species.

Other bacterial groups

Gram-negative rods are the organisms next most commonly encountered but these do not usually lead to difficulties in classification. The taxonomic problem of the non-nitrate-reducing species is real but recognition of this group is relatively simple (Taplin, Rebell and Zaias, 1963). The equivalence of *Bacterium anitratum*, B5W, *Herellea vaginicola*, and the similarity of these strains to *Moraxella wolfii* has been widely accepted (Cowan and Steel, 1965; Pickett and Manclark, 1965), but no one name has come into use.

Some other organisms are occasionally found which defy classification, including yellow strains which show S-R variation and morphological characteristics similar to *Arthrobacter*.

Other actinomycete-like bacteria, including *Nocardia* and *Actinomyces*, are sometimes found. Distinction from diphtheroids is often difficult.

Bacillus species are often present but are usually considered contaminants. Streptococci are rare on normal adult skin (Somerville, 1969a) but may be found on children and in exudative lesions at all ages. Other bacteria usually have been recognized by their pathogenic capability only.

BACTERIOLOGY OF ACNE VULGARIS

Around the beginning of the century early workers in acne vulgaris had no doubt that bacteria played a pathogenetic role in the disease. All agreed with some reservations that comedones were the result of infection with *Corynebacterium acnes* and Whitfield (1909), in a very modern-sounding statement of the mechanism, wrote 'acting as a mild irritant to the neck of the follicle [the acne bacillus] causes repeated attempts to be made by the epithelium to encyst it with the resultant acharacteristic onion-like formation'.

After the discovery of the acne bacillus on normal skin, the significance of the organism was mainly discounted and, with the recognition of *Staphylococcus aureus* as the important pathogen amongst the cocci, the other cocci were assumed to be 'non-pathogenic'. The literature is confusing in the period prior to the antibiotic era, mainly because little further study of actual lesions was carried out.

Smith and Waterworth (1961) studied 67 specimens from 39 patients using careful collection techniques. They found little difference between the bacteriology of different types of acne lesions. They obtained '*S. albus*' from 44, a coliform from one, and *C. acnes* from 57.

Kirschbaum and Kligman (1963) injected *C. acnes* into steatocystomata and concluded that the anaerobic diphtheroid could be pathogenic. Shehadeh and Kligman (1963) cultured 175 lesions finding both '*S. albus*' and *C. acnes* together in 128, *C. acnes* alone in 22, and '*S. albus*' alone in 20. They found other organisms only rarely including aerobic diphtheroids, *Aerobacter* and *E. coli*. One pustule yielded a few colonies of *S. aureus*. They concluded that the flora of acne lesions was a 'stable biad' of '*S. albus*' and *C. acnes*.

Similar results were reported by Smith and Mortimer (1967), who emphasized the importance of culturing material from inside acne lesions. Of 118 lesions, 52% yielded both organisms, 27% '*S. albus*' alone, and 14% *C. acnes* alone. *E. coli* was grown from pustules in two patients and *Candida albicans* in one boy on long-term prophylactic penicillin.

Ganor and Sacks (1969) compared comedones, relying greatly on examination of smears as well as cultures. They re-emphasized the finding of *Pityrosporum* in acne lesions and quote Yap as the first to see it in acne.

Recent surveys of pustules (Marples and Izumi, 1970) and comedones (Izumi *et al*, 1970) included a study of the coagulase-negative cocci, previously recorded as '*S. albus*', using the Baird-Parker classification. Staphylococcus type II was the most frequent type found. Quantitative studies of the comedones were also reported.

The infrequent but definite recovery of enterobacteria from acne pustules recurs throughout the literature. Fulton and his associates (Fulton *et al*, 1968) felt that a superinfection with enterobacteria could

take place under antibiotic therapy and named this syndrome 'Gram-negative folliculitis'. An increased frequency of enterobacterial carriage in the nose was found in acne patients receiving antibiotics (Marples *et al*, 1969b).

Immunological activity

Dating back to Fleming (1909), the concept of an immunological role of the bacteria in the pathogenesis and maintenance of acne vulgaris has been studied. Puhvel *et al* (Puhvel *et al*, 1964; Puhvel, Hoffman and Sternberg, 1966) have studied the immunological states of acne subjects over a period of years and suggest that high serum antibody titres, immediate and delayed hypersensitivity reactions to *C. acnes* or its purified products, do occur more often in acne patients than in controls. Similar studies using *Staphylococcus epidermidis* antigens were negative. Using fluorescent antibody to *C. acnes*, Imamura (Imamura *et al*, 1969) demonstrated antigen within macrophages as well as in the comedo. It is not clear whether immunological reactivity is directly concerned with the disease or is a secondary finding. Some suggestion of a generalized, diminished, delayed hypersensitivity is seen in acne conglobata (Izumi, personal communication, 1972).

Lipolytic activity

An indirect role for *C. acnes* in the pathogenesis of acne vulgaris, which has been postulated by Lynch (1940) and many other authorities, is concerned with the hydrolysis of the triglyceride secreted by the sebaceous gland. The ability of both cocci and *C. acnes* to liberate free fatty acids from lipids was first shown by Benians (1915) in a much overlooked paper. He demonstrated a rise in titratable acidity in an olive oil overlay to an equivalent of oleic acid. Nicolaides and Wells (1957) demonstrated the lack of hydrolyzed triglyceride in sebaceous cysts and Kellum (1967), using a microdissection technique, showed that free fatty acids were absent in sebaceous gland preparations. Yet surface lipid contains a variable but large proportion of free fatty acid (Downing, Strauss and Pochi, 1969). Bacteria have often been considered to be responsible for this lipolysis (Strauss and Kligman, 1960). By experimentally inhibiting natural populations of *C. acnes*, cocci and *Pityrosporum* in the living subject with antibiotics, Marples and his colleagues have shown that *C. acnes* is the most important source of lipolytic activity, *Pityrosporum* to have lipolytic activity and the cocci to be unrelated to lipolysis of surface lipid (Marples *et al*, 1970, 1971 and 1972).

Because of their greater irritancy (Kellum, 1970) and comedogenicity (Kligman and Katz, 1968; Kligman, Wheatley and Mills, 1970), the free fatty acids rather than the unhydrolyzed triglycerides are assumed to be of pathogenetic importance in acne vulgaris (Cunliffe and Shuster, 1969). Studies of antibiotic action and clinical interpretations support the view

that large amounts of free fatty acids in a genetically susceptible individual may lead to the production of comedones.

Less well documented are the theories of pathogenesis of acne vulgaris which postulate the diffusion of undetermined substances from the lesion, which may cause a local accumulation of polymorphonuclear leukocytes with resulting cell destruction. Such theories are implicit in several of the detailed taxonomic studies of isolation of *C. acnes* by Brzin (1964), Puhvel (1968), Ray and Kellum (1970), and Voss (1970).

There has been little interest in the significance of *C. acnes* bacteriophage in acne vulgaris, although the existence of these particles was noted by Brzin (1964) and put to taxonomic use by Zierdt (1968), and Voss (1970).

In summary, the historical view of the bacteriology of acne vulgaris is that the disease is not a specific infection, but that inception and continuance of lesions may be indirectly due to *C. acnes*, coagulase-negative micrococci, or *Pityrosporum*.

BACTERIAL ECOLOGY OF THE NOSE

The nose is a primary focus of multiplication and dissemination of micro-organisms onto the skin and into the air (White and Smith, 1963). While considerable literature has been published on the frequency of pathogenic staphylococci in the nares, the role of other micro-organisms has not been emphasized (Calia *et al*, 1969; Hallman, 1937; Williams, 1963). The close relationship of these micro-organisms may be a major factor in determining the nasal ecology of the skin. To elucidate these factors, Aly *et al* (1970) manipulated the nasal flora by administering cephalexin systemically. A quantitative and qualitative analysis of the composition and density of nasal flora was done.

Organisms found in the anterior nares were arranged into four major groups: (1) coagulase-positive gram-positive cocci; (2) coagulase-negative gram-positive cocci; (3) diphtheroid-lipophilic and non-lipophilic pleomorphic gram-positive rods; and (4) enterobacteria. The total count obtained before drug treatment was $5{\cdot}4 \times 10^6$ in staph carriers, and $3{\cdot}9 \times 10^6$ in non-carriers. It was observed that the lowest count of microorganisms was not during antibiotic treatment but three days after cessation of the drug. An inverse relationship between coagulase-negative cocci and lipophilic diphtheroids was seen in many individuals.

It has been shown (Williams, 1963) that the staph carrier rate is highest (>50–100%) in newborn infants and tends to decline gradually with age (Cunliffe, 1949; Rycroft and Williams, 1960). Little is known of factors that make one person a staph nasal carrier and another rarely a carrier. The use of the anterior nares to evaluate microbial drugs or to manipulate the normal flora is convenient (White and Smith, 1963; Aly *et al*, 1970; Marples, 1969c). Similarly, the antistaphylococcal enzyme,