

MORPHOLOGIC DYNAMICS OF ACNE VULGARIS

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Acne is a strictly follicular dermatosis occurring in sebaceous follicles.

The sebaceous follicles are most numerous on the face, and the V-shaped areas of the upper trunk. Their special features include a deep and cavernous infundibular canal and a tiny and inconspicuous pilary unit. The sebaceous lobules or acini are very large. The infundibular portion is divided into two sections. The terminal portion, for which the term acro-infundibulum has been coined, is exactly contiguous to the epidermis and keratinizes in the same fashion with a sturdy horny cell layer barrier. The lower portion is called the infra-infundibulum and makes up the major portion of the sebaceous follicle. It keratinizes, too, but produces only a thin and imperfect horny layer, whose cells soon slough. The corneocytes from this region seem to break open, are poorly defined and degenerate into detritus embedded in a matrix of sebum and bacteria.

SEBORRHEIC FILAMENTS

Seborrheic (or sebaceous) filaments are the white waxy worms that can be squeezed out of the sebaceous follicles, mainly from the face and the alae nasae. The seborrheic filaments may be the first transitional stage in the dynamic morphology of acne, but not every seborrheic filament will eventually change into a comedo. The filament is a cylindrical tube of 10–20 layers of keratinized material from the stratum corneum of the follicle enclosing a waxy mass of sebaceous lipids, enormous quantities of *Propionibacterium acnes* (*P. acnes*) and one centrally located hair.

MICROCOMEDONES

The true onset of the acne lesion starts when microcomedones begin to develop. Microcomedones are clinically invisible, but can be easily identified histologically as biopsy specimens from apparently normal skin in acne patients (Fig. 1). We have termed these

lesions the embryonic stage of acne. Histologically the follicular epithelium is hyperplastic and has a pronounced granular layer. Increasing amounts of horny cells are produced and retained. The microcomedo is heavily populated by *P. acnes*.

Acne can thus be defined as a disease of the infundibular canal of the sebaceous follicles (not of the sebaceous glands). The disease starts with hyperproliferation of corneocytes (as measured by 3H-thymidine and 3H-histidine incorporation techniques) and retention of this horny cell material. The most important factor in comedo formation is related to the for-



Fig. 1. Microcomedo. This lesion was clinically not visible. Early retention of corneocytes, abundant bacteria in cavities (or lacunae).

mation of the intercellular cement-like substance, which firmly glues the corneocytes together as compared to normal, uninvolved sebaceous follicles, where these cells are poorly defined, loose and incoherent.

CLOSED COMEDONES

The closed comedo is the first stage of acne in which the primary lesions of the disease are clinically visible (Fig. 2). They appear as tiny whitish nodules (whiteheads). Stretching the skin makes them more visible. Histologically they are very distinct. There is a cyst-like cavity which is filled with a compact globoid mass of corneocytes. The follicular epithelium thins and stretches out and the sebaceous acini regress in size. Above all, the orifice, which is found only in serial sections, is tiny. Bacterial colonization is heavy and channels or lacunae containing pure *P. acnes* colonies are characteristic. The pilary unit is intact and hairs are produced in regular hair cycles. Therefore, several hairs are often trapped in the comedonal kernel.

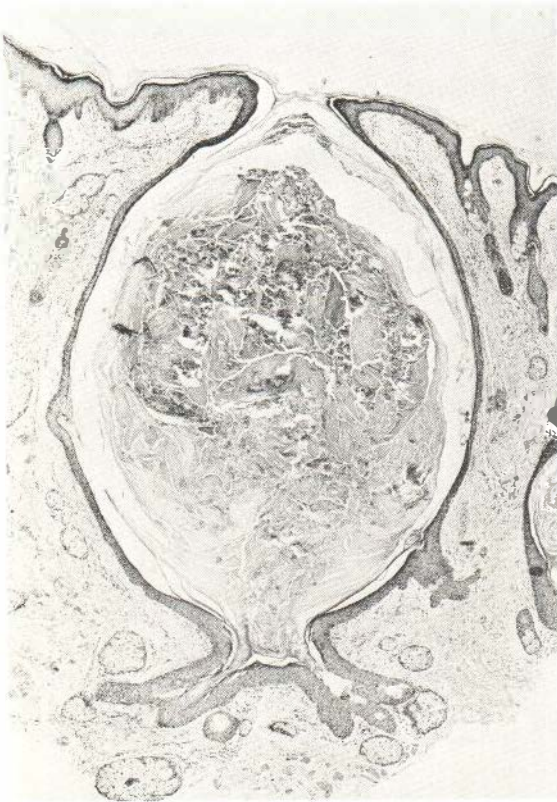


Fig. 2. Closed comedo. The wall is thin, the sebaceous glands regress in size, the cavity is filled with a cast of corneocytes, which contains many bacteria and retained hairs.

Closed comedones may either enlarge and turn into large open comedones, or may rupture, giving rise to inflammatory lesions like papules, pustules or nodules (Fig. 3).

OPEN COMEDONES

The next lesion is the classical lesion of acne, the open comedo. These are usually called blackheads. Histologically they are again quite typical. There are multiple concentric, often whorled, corneocyte layers along with increasing quantities of *P. acnes*. There is a thin atrophic comedonal wall, almost no sebaceous acini, and of course, a wide patulous opening. The pilary unit is still intact and up to 10 or 15 hairs are often trapped in the framework of corneocytes.

PIGMENT IN COMEDONES

The pigment which is clinically visible at the tip of open comedones, and which is also microscopically visible in closed ones, is melanin, not dirt or oxydized lipids (Fig. 4 and 5). Albino patients have unpigmented comedones, while heavily-pigmented races have extremely dark tipped comedones. Dr. C. Blair of England made this observation only eight years ago, thus ending a myth of many generations' duration. Melanin arises from melanocytes, which are distributed regularly along the basal layer of the acroinfundibulum but are not found below this level. The melanocytes transfer their melanin into keratinizing cells



Fig. 3. Dynamics of comedo formation. The giant closed comedo on the left is filled with a kernel of corneocytes. The remnants of the sebaceous acini are still visible. The epithelium at the bottom between the three acini is the former sebaceous duct, which is now part of the comedonal wall and keratinizes. The right side of the picture shows a normal sebaceous follicle with intact glands. The pilary units of both structures are not visible in this cut.



Fig. 4. Pigment in follicles and epidermis. Heavy melanin pigmentation in the interfollicular epidermis, the acro-infundibulum (but not the infra-infundibulum). Silver stain.

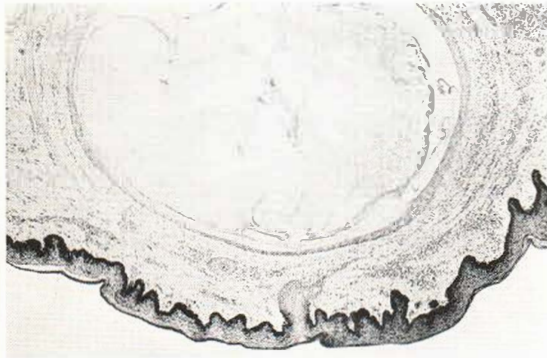


Fig. 5. Pigment in comedones. The closed comedo (the tiny orifice is not visible in this section) bears no melanin, the epidermis above is heavily pigmented. Silver stain.

which become tightly packed at the tip of a comedo. Several hundred and sometimes over a thousand melanin-containing adherent corneocytes form the apical portion of the comedo.

HAIRS IN COMEDONES

Coiled hairs are trapped in comedones. The age of a

single comedonal lesion can be closely estimated from the number of hairs, if the length of the hair cycle is known. Trapped hairs in comedones are harmless. However, once the comedo ruptures and the comedonal kernel is displaced far into the dermis, a reaction to the hair is often seen (Fig. 6, 7, 8). Hair, like horn,

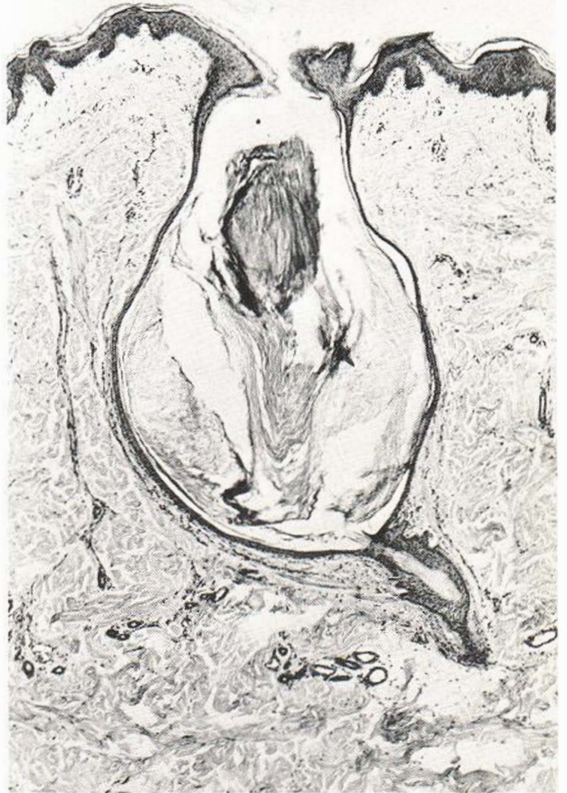


Fig. 6. Hairs in comedones. The pilary portion of this closed comedo (Halowax acne) is still actively producing a hair.

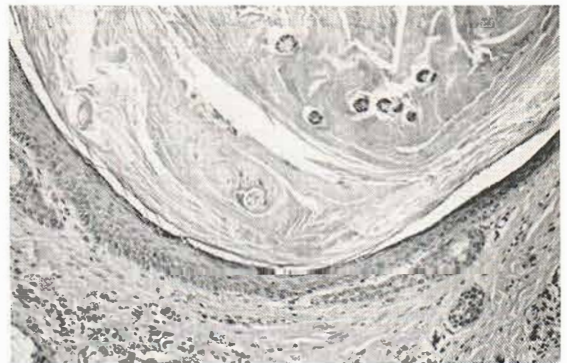


Fig. 7. Hairs in comedones. This tangential cut demonstrates the pilary unit, which merges from below into the closed comedo. There are fragments of hairs in the cavity, the horny cells have been lost during preparation.

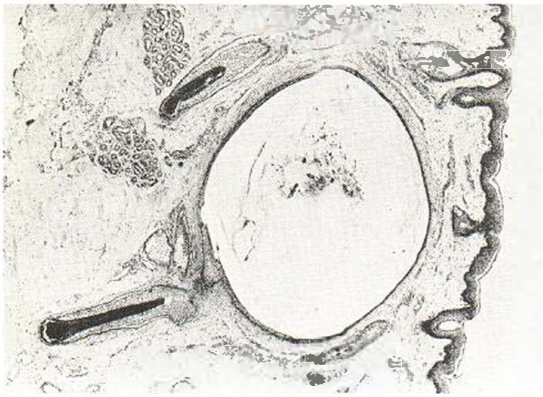


Fig. 8. Hairs in comedones. This old open comedo has multiple hairs, which are cross-sectioned at this lower portion of the lesion.

is not easily solubilized and can persist in the dermal tissue as a foreign body for a long time. Clinically papules and persistent nodules indicate that the resorption of hairs and corneocytes may take many weeks or even months.

SECONDARY COMEDONES

Microcomedones, closed comedones and open comedones are primary comedones.

Rupture and re-encapsulation of comedones creates secondary comedones. Rupture can be either very localized or involve massive destruction, after which the comedo may not survive. Cysts and polyporous comedones are secondary comedones.

CYSTS

The cyst is clinically a large cherry- to walnut-sized whitish, skin coloured rubbery nodule. It occurs mainly on the neck and less frequently in the face. Puncture or pressure releases a cheesy, crumbly, foul-smelling material. Histologically, cysts, like all secondary comedones, are asymmetrical in shape. The wall is usually thinned out and stretched. The sebaceous acini are either completely destroyed by multiple previous inflammatory episodes, or a tiny remnant composed of a few sebaceous cells indicate the previous size of the acini. Likewise the pilary unit is destroyed. The opening is present, but very small. The content of cysts is made up of loosely arranged corneocytes and, of course, many bacteria. The surrounding connective tissue is always scarred. Small pockets of inflammation are almost always present at a microscopic level but are not apparent clinically.

POLYPOROUS COMEDONES

These are also called fistulous comedones or double or triple comedones. Like cysts they are typical of acne conglobata. Groups of adjacent comedones and follicles are linked up by rupture and re-encapsulation. Irregular-shaped diverticular processes extend far into the dermis; the tunneled structure, comparable to a rabbit hole, opens at multiple sites onto the skin surface. The contents are made up of horny cell casts, remnants of hairs and *P. acnes*. The tips of the openings are usually heavily pigmented with melanin. Polyporous comedones are actually specialized scars.

DRAINING SINUSES

Among all inflammatory acne lesions the draining sinus is the most ferocious lesion. It is a variant of the acne nodule and a truly malevolent lesion. It is a huge tender lesion which periodically drains and crusts. Unfortunately, it is likely to develop on the face rather than the back. The follicular epithelium is not destroyed completely during the inflammatory breakdown but manages to survive. The remnants of the epithelial lining dissect through the necrotic tissue and create tunnels of hyperplastic epithelium. They form a complicated, bizarre labyrinth of galleries, which connect to the surface at various places. The lesion often extends linearly to form huge inflammatory ridges, which not infrequently may run for 5 to 10 cm across the cheek, along the nasolabial folds or along the mandibular line. Squeezing one side of the lesion leads to release of bloody purulent material at distant sites. There is a constant tug of war between the processes of rupture and repair. It may grow relentlessly for years, with intermittent periods of quiescence and activity with drainage. Keloidal linear finger-like and finger-long scars are sometimes the final outcome of this terrible lesion.

SCARS

Scars are one aspect of the polymorphic appearance of acne. There is an endless variety of scars including these that are flat, atrophic, elevated, hard, lumpy, keloidal, crateriform, pit-like, retiform, closed-comedo-like or polyporous. Inflammatory lesions of all sizes may leave scars of varying sizes. Scars are often made worse inadvertently by picking, squeezing, digging or expressing acne lesions or blemishes in the face that appear to be acne lesions to some patients.

Uncontrolled neurotic excoriations, most often found in the adolescent or adult female patient, lead to what is described by the French as *acné excoriée des jeunes filles*.

ACNE MALIGNA

Acne occurs in a wide spectrum from acne minor to acne major. At the very far end of the acne major spectrum is acne maligna. There are a few quite characteristic clinical forms presenting the uttermost end of the morphologic dynamics of acne.

Acne fulminans

One example is acne fulminans, or, as it is also called, acute febrile ulcerative conglobate acne with polyarthralgia. We have only seen this dramatic picture in young males with suppurative, highly inflamed raggedy ulcerations of the chest. The lesions are extremely tender and painful, and contain a gelatinous mush. The disease may be mistaken for leukemia, rheumatic fever or sepsis.

Acne tetrad

It took us some time to realize that there are strange varieties of acne, comparable to pustulosis palmaris and plantaris type Barber-Königsbeck as part of the

psoriasis spectrum. Dissecting cellulitis of the scalp with acne keloidalis nuchae-like scars, hidradenitis-suppurativa-like lesions in the armpits and groins, pilonidal sinus, and often but not always smouldering acne conglobata lesions such as hemorrhagic nodules, cysts, draining sinus and polyporous comedones are the part of this variety of acne. Tremendous ulcerations, tunnels and fistulae, which may dissect from the anal fold across the entire buttocks and down the groins are the worst expression of the disease.

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DISCUSSION

Cunliffe, Leeds: I would like to ask two questions. First, what evidence do you have to show that many of the closed comedones do in fact go on to open comedones? Second, how certain are you that what you see in your radioactive uptake studies is specific, rather than secondary to the phenomenon of stretching?

Plewig, Munich: It is easier for me to start with the second question. We always avoided inflamed lesions. We used comedones without acanthosis of the epithelium. Furthermore, we have found higher labeling indices in microcomedones which is further evidence that it is a real phenomenon and not an artifact.

Cunliffe, Leeds: What is the evidence that many of the closed comedones become open comedones?

Plewig, Munich: We made long term clinical observations in our patients. Individual lesions were marked by tattooing and we took serial photographs. Therefore we were able to map and chart individual lesions and follow them until they became open comedones. This point is a matter of dispute. Some individuals do not believe that it happens, but Albert Kligman believes that almost every comedone starts as a whitehead comedone and then develops into an open comedo. I share his opinion — many comedones start as small closed comedones and then become open comedones.

Leyden, Philadelphia: I would be interested to see where you stand today on one area that you did not discuss in detail. You mentioned the Odland body or the membrane coating granule. There is debate as to

whether or not the horny-cell impaction that occurs in the follicles are due to a decrease in these structures. On the other hand, there are those who feel that that has not really been shown and that maybe just the opposite is true, i.e. that the reason they are sticking together is that there are too many Odland bodies. Where do you and Helmut Wolff stand on this subject?

Plewig, Munich: It is not easy to answer this question because you need quantitative electron microscopic data. You would have to make serial sections and then count and map the Odland bodies. In normal follicles the Odland bodies of the keratinosomes are sparse at the mouth of the follicle. However, the number is greater in the infrainfundibulum. Nonetheless, in a developing lesion such as a microcomedo, the number of Odland bodies decreases again. That is our impression at the present moment, but I think this is still an open question that is worth further study.

Donsky, Toronto: We have felt that biopsy specimens of acne lesions on the face characteristically would show a granulation-type of reaction. In your discussion you have pointed out that you feel the sequence of events goes from a comedo to rupture into the tissue and then the development of granulation reaction. Is there any possibility that the sequence might involve first an inflammatory reaction around a comedo which then influences the development of the lesion, rather than each time being a sequential type of event?

Plewig, Munich: By definition, acne starts with retention of horny cells and then may become inflamed. The retention of cells may be minimal as in a microcomedo. There are special examples of acneiform eruptions, such as acne aestivalis (Mallorca acne) or steroid acne in which the initial lesion is inflammatory and in which the increased retention and production of horny cells is secondary. However, in acne vulgaris we have not seen any lesion that does not have an accumulation of horny cells first, followed subsequently by the inflammatory component. Remember, though, that inflammation may start very early and you may miss the horny component in the centre unless you study the biopsy specimens very carefully.

Lidén, Umeå: If you have removed a comedo how long does it take before you have a new one?

Plewig, Munich: We have studied the refilling time in comedones, either after expressing them or mechanically forcing them out (Plewig, G.: Follicular keratinization. *J Invest Dermatol* 1974; 62:308—15). We were surprised by two facts, first of all, when we express comedones and then take a biopsy immediately afterwards we have been surprised to find how much material has been left. You may think you remove the whole comedo but that is not true. Considerable material stays behind in many cases. Secondly, we have found that the time for a new comedo to form is very short. Comedones have redeveloped within four to six weeks and clinically the blackhead was visible. This supports the findings by autoradiography that cornocytes are produced at a very rapid rate.

Cunliffe, Leeds: I would agree with you Dr. Plewig that obviously rupture of the microcomedo is important, but I would appreciate comments as to whether there may not be an earlier development related to mediators of inflammation. We have been working with an immunofluorescent technique. Using these techniques for the examination of the very early lesion, at the microcomedo stage, there is evidence of the stimulation of the alternate pathway of complement in the relative absence of cellular infiltrate. The reaction is observed around the follicle and in the blood vessels. We also have observed that in the microcomedo site the early cellular infiltrate is mononuclear and not polymorphonuclear. Because we do not have adequate electron microscopic techniques we have been unable to distinguish between the lymphocytes and the monocytes, but since the acne bacillus, *P. acnes*, is probably identical with the organism, *P. parvum*, which stimulates monocytes, we feel that possibly some of these cells could be monocytic in origin. We know that the presence of monocytes and the presence of components of alternate pathway of complement are chemotactic. So our present working concept is that the conversion of a non-inflamed to an inflamed lesion of acne, is as follows: low molecular weight substances thus diffuse through the microcomedo and activate the alternate pathway-system. Monocytes also are attracted to the developing inflamed lesion. These in turn are chemotactic to the granulocytes which then break up in non-inflamed lesions, contributing to the inflammation.

Plewig, Munich: Yes. Some of this was discussed by Dr. Steve Tucker in the acne workshop at the last International Congress of Dermatology in Mexico City

in 1977. It is probably true that there are some areas of monocytic infiltration, but the question is what is normal. We did take biopsies from clinically normal areas of the face from patients with no history of acne. These specimens showed areas of monocytic infiltration. Facial and scalp skin have inflammatory cells which are lymphocytic and monocytic. In experimental studies, we injected surgical or hypodermic needles into the skin and comedones. In biopsy specimens taken two, four and six days later there was always a granulocytic reaction. Therefore under these conditions a different type of cellular infiltrate was seen. In summary then, there is no clear cut answer at present and this too is an open field to study.

Zachariae, Aarhus: You said that there is no sebum retention. Do you mean that there is no sebum retention in closed comedones?

Plewig, Munich: We have in our German language the term "Talgretentionszyste" which means: a cyst retaining sebum. There is no such lesion except for instance in steatocystoma multiplex — a lesion which contains huge amounts of sebum. Certainly some sebum is trapped in every acne lesion, but if you take frozen sections of open and closed comedones, you can see passage ways coursing up to the surface and there is no large accumulation of sebum. In fact, I have never seen a huge cavity of solid sebum in the many frozen sections of lesions that we have examined. It is also surprising to see large amounts of sebum in corneocytes when frozen sections are examined under electron microscopy. The lipid in the corneocytes represents epidermal lipid.

van Dijk, Amsterdam: Does acne in older people have anything to do with Favre-Racouchot's disease?

Plewig, Munich: Yes. There is a disease in the aged which according to the French is called: 'élastéidose cutanée nodulaire à kystes et à comédons Favre-Racouchot.' In a similar way comedones are induced by actinic rays, X-ray and ultraviolet light. The same phenomenon occurs around basal cell carcinomas treated with X-ray. This is not genuine acne vulgaris.

Shuster, Newcastle-upon-Tyne: I would very much agree with Dr. Cunliffe that you are probably looking at the rather late events and I would remind you of the interesting point that you rarely see inflammation arising around a blackhead. The main point I want to

bring up is related to the question of drainage of sebum. I accept, like you, that the evidence for retention is not good, but I do not accept that you have answered it. To exclude retention, you would have to show that the rate of production of sebum is no greater than that of its loss at the surface. To show that you have got intact canals travelling up to a small hole at the surface is not good enough. Unless you can show that the rate of production is precisely matched by the loss at the surface, important retention could occur. Maybe you have that evidence?

Plewig, Munich: No, I have no idea how one can study the rate of production in vivo in a single lesion and at the same time measure its output on the surface.

Shuster, Newcastle: I do not either, but until you can do that you will not have excluded significant retention.

Plewig, Munich: Nor can one then assume sebum retention. It is a pure assumption. Those who are in favour of it have to prove it.

Strauss, Iowa: I would agree with Dr. Plewig that we have no way of measuring what is happening at the gland level and comparing this to what we are measuring at the skin surface. However, I want to point out that we are talking about blocking the flow of an oily material and this is an impossibility. We have tried to block sebum flow for years, and it just cannot be done, any more than you can prevent oil from flowing between two metal surfaces unless you use gaskets. So I really feel strongly that the proof has to rest with those who doubt the current concept. This is based both on histology and just plain common sense of the flow mechanics of oily material.

Plewig, Munich: This may be a sophisticated problem, but it probably is not relevant to the pathogenesis of acne. One thing does come to my mind. If you look at the lesions of steatocystoma-multiplex where there are large cystic cavities and, indeed, huge amounts of lipid, the individual lesions hardly increase in size over many years. Yet, nothing comes to the surface and they do not drain because the solid cord does not permit sebum to come to the surface. Then, what happens to this sebum? Maybe if sebum is leaking through the epithelium and it is being reabsorbed again. This is another alternative.

Shuster, Newcastle: Demonstrating that some sebum comes up to the surface does not exclude the possibility of significant retention. And as for the argument that oil will find its own way to the surface . . . if that was true there would be no shafts and no oil-wells!

Rorsman, Lund: I would like to ask you a question related to the pigment in comedones. What is the melanin content of the whitehead?

Plewig, Munich: Melanin arises from melanocytes, as was beautifully demonstrated by Kaidbey and Kligman ("Pigmentation in comedones". *Arch Dermatol* 1974; 109:60—62). The melanocytes are confined to the epidermis and to the acroinfundibulum. They are rarely found in the infrainfundibulum, which forms the body of the comedo. Therefore, the melanin is coming only from the acroinfundibulum and is transferred into the corneocytes from the poral region. Closed comedones do show melanin pigment, but in a very small amount and only if you do a DOPA stain. In men there are few pigmented cystic lesions which are not related to acne. An example is the dilated pore of Winer which is a solitary trichoepithelioma which looks like a comedo. The melanocytes migrate throughout the entire lesion and may lead to the for-

mation of really pigmented lesions. One of the American colleagues, A.B. Ackerman, described one of these lesions as a vanilla-fudge cyst. Its contents is black and white on the inside. In acne melanocytes usually do not migrate to the lower portion of the follicle so only the tip is pigmented. In whiteheads, there is only minimal melanin pigment, enough to be detected by special histological stains in the tiny poral region, but not clinically.

Rorsman, Lund: Have you observed differences in the colour and in the type of melanosomes you observe in different types of skin pigmentation. For instance does a redhead have phæo-melanosomes in the corneocytes?

Plewig, Munich: We have only compared heavily pigmented African blacks or American blacks versus our European Caucasians. We did not study redheaded people. It is very easy to find and identify the pigment in individual corneocytes, even with light microscopy.

Rorsman, Lund: It is striking how dark the black-heads can be in a blond person.

Plewig, Munich: I agree.