ACNE: POSSIBILITIES AND PROBABILITIES

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1. SEBORRHOEA

There are very few essential facts about adolescent acne. The first is that its severity is linearly and directly related to the sebum excretion rate. The second is that if you take normal people at all ages after puberty and adolescence the seborrhoea persists but not the acne. There are two broad conclusions from these observations: firstly, acne is related to seborrhoea; secondly, that although adolescent acne does not occur without seborrhoea, seborrhoea does not necessarily produce acne in later life.

Now let us take these key points more slowly:

(a) Acne correlates with seborrhoea

It could of course be argued that the association is fortuitous, that the acne is related to some other factor which happens to correlate with seborrhoea; correlation does not invariably mean cause. However, no other correlate has been found and when the seborrhoea is turned off by a compound which inhibits sebaceous lipogenesis or by an anti-androgen, the acne disappears. The evidence is therefore quite adequate to support a causal relationship between acne and an underlying seborrhoea. The reason this conclusion is still not generally accepted is two fold:

Firstly, the correlation between seborrhoea and severity of acne is a statistical one and there are many individuals in whom a high rate of ebum excretion does not correspond with a comparably severe grade of acne, and conversely. This argument always surprises me because biological variation of this sort is part of each and every attribute of life. For example the variation in number or organisms required to produce septicaemia when injected intravenously, like the individual scatter behind any LD or ED_{50}, does not invalidate the cause-effect relationship. You might as well use the enormous variation in the number of cigarettes smoked and incidence of carcinoma of the bronchus as evidence against a cigarette actiology. As I observed myself this morning in the queue for the men's room after the coffee break, the intensity of need in a small man like myself may be much greater volume for urine volume than in the big man who (I am sure unintentionally) crashed the queue and took the place ahead of me.

Another confusing factor concerns the relationship of cause to stage of disease. The relationship of seborrhoea and severity is apparent during development of the disease in adolescence and studies have often been bedevilled by an evolutionarily heterogeneous population some with early acne others with persistent or regressing disease. You might equally well attempt to refute Koch because the tubercule bacillus could not be isolated from the late fibrotic stage of the disease!

The second reason for the difficulty in accepting the obvious is due to a lack of understanding of the use of controls for experimental studies. "Controls" have unfortunately been confused with normal subjects. A control for an investigation into terminal cancer may be an individual in the last stages of a chronic infection or with inanition from starvation, depending on which aspect is under study. In brief a "control" subject is not necessarily a normal individual. In acne research unfortunately, controls have too often been individuals with and without acne. This is very often inappropriate because almost every one of us has had acne. It follows therefore that these "normal controls" are either the very very few abnormal individuals who do not get acne but are of the acne age group, or and far more commonly, individuals without acne because they are past the acne age group but who in fact had had acne in the past. Such individuals, for reasons which will be quite apparent, are quite inappropriate as controls for the question of seborrhoea. For these reasons, in most acne research, the topic under study is best compared as a progressive defect in relationship to severity. This is not invariably true of course, but it is in most cases, and in most cases it has not been done. This is one reason why so much of acne research is inadequate, and this is particularly true of studies which do not find a correlation between seborrhoea and acne.

In summary, the evidence is quite clear, at any rate as clear as can ever be expected in biological terms, that *adolescent acne is causally related to seborrhoea.*

(b) Post acne seborrhoea

Now let us return to the persistance of seborrhoea at a time when the acne disappears. This can be interpreted in several ways. (i) It can of course mean that the seborrhoea has nothing to do with the acne and that it was fortuitously related to grade of acne because of the relationship with some other factor in adolescence. This we can exclude for a number of reasons already discussed and most simply because of the curtailment of acne by drugs which reduce sebum production. (ii) It could also mean that a second factor with seborrhoea is required for the formation of acne. This is the two factor hypothesis to which we and others have contributed. It must be said however that it is by no means necessarily true, as we will be discussing below. However, the idea has generally been taken up because it fits so well with other current mythologies, namely the notion of a blocked duct whether primary or due to a secondary response to one of the sebum constituents, possibilities to which I return shortly. (iii) Finally and most attractively, seborrhoea alone would be an adequate explanation provided that the consequent acne itself induces some secondary or associated change such that the acne could not recur, e.g. a situation analogous to one of the many infections which produce permanent or near permanent immunity. I do not wish to labour the point but it should be quite clear that the two factor hypothesis is not a logical necessity, although it may yet turn out to be a biological fact.

(c) Cause of the seborrhoea of acne

Alas we have advanced little in our understanding of how the sebum excretion rate is maintained at the high level essential to adolescent acne. There are a number of factors and we still do not know which are the most important. The sebotrophic hormones are many and surprisingly varied. They are far better understood in rat than in man. In the rat the major sebotrophic hormones are androgens and the melanocyte stimulating hormone. Growth hormone is not specifically sebotrophic and prolactin is not sebotrophic at all. We have also shown that prolactin is not sebotrophic in man by lack of correlation between sebum excretion and prolactin and by the absence of the effect of bromoergocryptine on sebum excretion rate (and acne) although prolactin secretion is inhibited. Oestrogen has surprisingly little effect in reducing sebum secretion in the rat although there is good evidence that it is very effective in this respect in man. The action of thyroid hormone likewise differs in rat and in man, in that it operates throughout the hypo- to hyperthyroid range in the rat but operates only in the hypothyroid range in man. Androgens of various sorts are effective both in rat and in man and the androgens come from both adrenal and gonads. Our own work does not support the current view that it is the conversion of androgen (mostly testosterone) to dihydrotestosterone (DHT) as the critical step in the skin; indeed our evidence is that DHT is not the active material in human skin and that adrenal androgens are far more important than testosterone. Beliefs about the role of DHT have come about more by analogy with organs such as the prostate than by direct study of the skin.

The most important unknown factor in man concerns a powerful pituitary sebotrophic hormone which we have identified as a melanocyte stimulating hormone in the rat. Our evidence in man is that the hormone exists and is under inhibitory control. Its activity is particularly apparent in late pregnancy, suckling, after phenothiazines and in Parkinsonsism, and although it remains unidentified we still suspect that it belongs to the now increasing family of MSH peptides. Its identification will obviously be of importance because of its potential in the development of blocking agents; indeed we already have some evidence in the rat that partial blocking of this sebotrophic hormone can be brought about with certain "sub-MSH" peptide fractions.

There are two further important points about the inter-relationship of sebotrophic hormones. Firstly, we have shown that the action of MSH and androgen is synergistic (some prefer to call the action permissive; this is not correct and the difference is important pharmacologically). The easiest way to describe the difference between a synergistic and permissive act is as follows: when you go to bed with your girlfriend it is synergism, but when you go to bed with a prostitute it is permissive. We assume that as in the rat the sebotrophic hormone will synergise with androgen in man but we do not yet know whether this is the case. Secondly, a general point concerning the endocrine control of the sebaceous gland is that a number of sebotrophic hormones, and we have now shown this for androgen, MSH and progesterone, can either modulate or have their response modulated by changes in

the endocrine environment either in utero or in early life. Thus for example the response to progesterone can be made stimulatory or indeed inhibitory, depending on the endocrine state of the rat and the dose of the hormone. It should by now be apparent that the simplistic notion that the sebaceous glands are merely androgen controlled endocrine target organs greatly underestimates their physiology. Yet, it must be said that whilst working out their complex and multifactorial control has been enjoyable, it does not tell us how the seborrhoea of acne is maintained. My own belief is that on theoretical grounds alone it is unlikely to be due to an increase in a single hormone since virtually all the population contracts the condition, and since the control of sebaceous gland is multifactorial. I suspect that the seborrhoea represents a multifactorial summation of the individual's position on the normal distribution curve for each of the factors maintaining seborrhoea (endocrine, metabolic and structural). If this is correct there can be little point in further searches for increases in single hormones.

Androgens are of course major sebotrophic hormones and we find that just over half of a group of patients with acne respond to oral cyproterone acetate alone, and without topical or antibiotic therapy. Incidentally, it is quite clear that topical cyproterone acetate will not work even though adequate quantities get into the skin. Our own evidence suggests that this is because the action of cyproterone acetate is due to a metabolite of this drug formed other than in the skin. The identification and isolation of this metabolite would I believe provide a major new topical therapy.

2. BACTERIAL INFECTION

What beyond seborrhoea is the next hard fact about acne? Quite simply it is infection by the bacteria of acne (and almost certainly just the acne bacillus).

What can be said about the relationship of sebum excretion to the bacterial infection? The first and simple point is that the bacterial infection is secondary. Thus if sebum production is blocked by an inhibitor of sebaceous lipogenesis or by an anti-androgen the infection of acne will clear up without antibiotics in most (but not of course all) patients. However, the bacteria are essential because when adequate antibiotic is given to control the infection acne will also improve; while the sebum excretion rate is at its high level. There is much confusion about the role of the bacterial infection. Thus, it has been minimised in one study because lipase activity after tetracycline decreases before the number or organisms. This is a surprising misconception because after antibiotic administration, enzyme activity of all sorts decreases long before actual bacterial death, just as the creative activity of aging researchers departs long before its bodily vehicle. Attention has also been drawn to the lack of change of number of acne bacilli in the ducts after tetracycline. But this has nothing whatsoever to do with the output of organisms: you might as well deny the importance of a tap in controlling the rate of water flow because a cross section of the neck of the tap always contains the same volume of water! I have nothing further to say about the nature of bacterial infection and how it leads to inflammation other than to suggest to those dabbling in the field that it really requires a very very major study.

3. ALLEGED AND UNPROVEN FACTORS

The remainder of alleged contributing factors, all the poetic language and the glorious associated coloured photographic plates can be and indeed are best ignored. Thus, for example there is still no good evidence of functional blockage of the duct in adolescent acne. There is both keratin and lipids in the duct wall but it has not yet been shown that this actually blocks sebum excretion. Duct blockage undoubtedly occurs in some situations, e.g. after corticosteroid and cytostatic drugs in chloracne; it also occurs very superficially for example from hydrated keratin in hot moist climates, inducing tropical acne in those moving from milder climates; it is also a possible explanation on the premenstrual decrease in sebum excretion but as to whether duct blockage occurs as an integral part of adolescent acne has not been proved.

Although there is no hard evidence for such duct blockage, interestingly enough there are already a number of alleged explanations as to how it comes about! Of these an irritating lipid component is perhaps the favourite, particularly fatty acids. It is my view that the work on lipid composition of sebum reaching the skin surface has been the biggest single red herring in acne research and much time and money has been wasted on it. This is particularly true of fatty acids and lipases. The acne bacillus produces lipases and so inevitably there will be fatty acids in the sebum; by itself therefore their presence is meaningless and so is the fact that they produce inflammation when injected into the skin. The inflammation of acne is indeed interesting and singular, but I do not

think its nature will be solved by injecting a few blobs of infected sebum intracutaneously and if anyone still believes he is going to solve it by studies carried out between morning coffee and afternoon tea he should be firmly and not too gently discouraged.

Although the evidence demands that we should remember the prime factors of increased sebum secretion and bacterial colonisation, this is not to say that duct blockage cannot produce acne; on the contrary, there are situations where it clearly does. Nor is it to say that a constituent of sebum might not be inflammatory or promote keratinisation, but it is to say that we have no good evidence for these possibilities. Indeed it seems more probable that the changes which occur in the duct are due to the same sebotrophic hormonic stimulus acting on the duct and we have some preliminary but reasonbly firm evidence that this may be so from studies of lipogenesis using ^{14}C-glucose incorporation into lipids. However, this is for another time. The view of some that adolescent acne is primarily a disease of keratinisation of the ducts owes nothing to fact an as such needs of refutation. Analogy with corticosteroid acne is irrelevant.

4. PURPOSE AND CONSEQUENCE OF ACNE

I would like to end with two simple points about the purpose and consequence of acne. Firstly, the idea has been widely touted that acne and the human sebaceous glands serve no biological function other than providing a livelihood for dermatologists. I cannot agree. The close endocrine control of the sebaceous glands and the powerful depressing effect of acne both on self image and the views of others, and hence on social and sexual communication must mean that persistance of acne and/or the sebaceous glands serves a useful function. Whether this is in providing a substrate for the epidermis or augmentation of the phagocytic bodies and immune responses brought about by the acne bacillus itself or whether it serves as a sexual traffic light during puberty (when it signals red for stop) are all possibilities worthy of investigation. To my mind then, until proved to the contrary, we must assume that acne and/or the sebaceous glands have persisted because of an important evolutionary function.

Evolutionary arguments have of course to be seen in the context of the production and survival of offspring and the importance of acne in this respect can be seen from the work we have recently been doing on the influence of acne on self-image. If severity of acne is plotted against self-image (measured objectively from the patients' rating of a series of stylised visual images in response to specific questions). There are important male/female, age and duration differences as you might expect, but the overriding finding is that all patients show a progressive fall-off in their self-image which correlates perfectly with severity of the acne. For acne to persist in face of this grave deterioration of self-image must indicate the biological importance of the disease or the gland itself.

This could of course have considerable therapeutic implications. For one thing it proves a "misery index" which underlines the importance of treatment of the disease. However, if the disease itself rather than the seborrhoea is the biologically important factor, we may well have to look towards unwanted side-effects of treatment of a rather more social nature than we have been accustomed to look for in the past.

5. CONCLUSION

In summary, adolescent acne is a disease related to a multifactorial seborrhoea with consequent acne bacillus infection and clinico-pathological sequalae. Despite the increase in knowledge of the last 15 years I maintain now, as I did then, that we know quite enough about the two aetiological facets of acne to design really adequate treatments. I exclude work on agents designed to unblock ducts, because I do not yet know whether they are blocked and I would not know how to go about unblocking them even if they were. I suspect that both the traditional topical therapies and the newer ones such as retinoic acid are merely placebos. Likewise I would put an immediate moratorium on all studies of lipase inhibitors and other agents of dubious aetiological parenthood.

We know the sorts of hormones that control seborrhoea and a good deal about the lipogenic mechanisms within the sebaceous glands, certainly sufficient to produce drugs which will inhibit sebum production. Likewise we know the bacteria involved and which antimicrobials will control them. The problem remains as it has been for many years, the logical application of the techniques of the pharmaceutical industry to the production of drugs to reduce sebum production and to improve antibiotic control, probably by better delivery systems. Surely the production of a topical inhibitor of sebum production (whether as an anti-hormone or a blocker of sebaceous lipogenesis) and a locally effective antimicrobial agent is not beyond the wit of mankind?

DISCUSSION

Hagerman, Malmö: Professor Shuster has just given us a very personal view on the mechanism of acne. I would like to add a bit of my own. This theory is based on the minimal quantities of certain acnegens that are sufficient to elicit an obvious reaction. One example is the food colour amaranth (= E 123) as present in some vitamin dragées (see Table, page 18). This is a commonly used certified food colour, which does provoke acne lesions in many of my patients. If you wash off the colour used in the coating of the tablet they can tolerate it. I could elicit new active lesions after peroral doses of 0.62 mg. This may be compared to the well proven eliciting of asthma and urticaria after 1 mg of some other azo-colours, particularly tartrazine (= E 102).

Another example of acnegens are the antho-cyanin-group of red or orange pigments in most fruits and berries. Some patients will react with new active lesions after eating normal quantities of fruits such as strawberries or red apples. They can eat the same apples without any reaction after having peeled the apples. It is not known whether it is the pigments, the aromas or possibly both that are the offenders in this particular case. Anyhow, the eliciting dose is obviously very small, since it is located only in the peel. The citrus fruits, whose oils are well-known haptens in contact allergy, can also elicit acne lesions. It is, however, not known if the oils, the colours or both are the pertinent offenders. Many of the patients in my studies have also reacted to different spices and often with a markedly individual reaction pattern.

In my material, the usual time for the first visible reaction to appear was about 12 hours for the most superficial small lesions to about 48 hours for somewhat deeper ones. This reaction time could well tally with what is known for different types of allergic reactions. Baer & Witten (1960) observed wheals forming at the follicle openings within a few minutes after ingestion of chocolate, with acne papules appearing at these sites on the following day. Sulzberger & Baer observed exacerbations of lesions occurring as early as twenty minutes to as long as three days after ingestion of an eliciting food.

As to the pathomechanism, I would suggest the following theory. The tissue around the infundibulum is the target organ for the acnegen. Even a rather weak reaction around it would be sufficient to compress the follicular canal, which is very narrow here, and evoke a total obstruction of the sebum passage. This stage may possibly correspond to the "slight erythematous flare 5 to 10 mm in diameter in and around the developing lesion which may persist from one to three hours" according to Kahn & Cunliffe). Distention of the deeper part of the follicular wall and consecutive micro-injections into the surrounding tissue, would be the logical outcome. To the consequences of allergic reactions to food in the perifollicular tissue will then be added the effects of the extruded follicular content, which comprises primary irritants as well as allergenic substances. As to the nature of the reaction, Sulzberger & Baer considered that their reactions on food factors occurred in patients having "itching acne with urticarial swellings of their lesions". In my own material the chemical nature of low molecular, non-protein acnegens would tally best with a contact-type allergy. Juhlin's finding of a higher percentage of basophil cells in cantharidin-blister fluid from patients with severe acne seems to point in the same direction.

Cunliffe, Leeds: I want to put a question to Dr. Shuster. He claims that hyperkeratinization is not important in acne. I want to ask him how often he has seen inflammatory lesions arise in the complete absence of blockage of the pilosebaceous duct as assessed by clinical or histological examination?

Shuster, Newcastle-upon-Tyne: Quite clearly patients with acne have blackheads and excessive follicular keratinization, but that is not the point. Patients with tuberculosis tend to get the tuberculosis of the apex of the lung but what relevance is that to the course and treatment of tuberculosis? The question is whether the keratinization is a primary or secondary event? The question is whether the keratinization truly blocks the duct. I think the evidence, apart from existence of keratin in the duct as to whether this is of primary importance, is nil.

Zachariae, Aarhus: One very short question, do you use vitamin-A-acid therapy?

Shuster, Newcastle: No, I am not convinced that the results are different from a placebo.

Cunliffe, Leeds: I wonder whether Dr. Shuster has any evidence in man that the early environmental control of the individual will affect acne later on in life?

Shuster, Newcastle: We have no evidence on the influence of the early environment in humans and I think it is difficult to obtain. Ideally, you would need a prospective study. We have tried to find patients whose mothers' had been given hormones during pregnancy but we have not succeeded.