Research into Psoriasis—The Last Decade

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Psoriasis is an infuriating disease. It is an arrogantly trivial disorder placqued on to a systemically unimportant organ. Yet it affects 1–2% of the population,⁶² some of whom are so badly afflicted that life is reduced to a biological chore. This is the frustration: the psoriatic without his spots is totally fit. So that, in terms of personal happiness and social usefulness, research into psoriasis has more to achieve than many of the spectacular endeavours of contemporary medical science. All of us in dermatology have been heartened in recent years by the beginnings of a real attempt to understand this disease. In this review I do not intend to cover all of the many recent findings; I propose to indicate the more important factual developments which have occurred in the last decade, and certain general concepts and future lines of research which the present suggests.

What sort of disease is psoriasis? All the recent work takes us back again and again to the skin itself. There is absolutely no evidence that psoriasis is an epiphenomenon of a systemic disorder (in particular, the “idea” that psoriasis has a significant psychosomatic component scarcely merits these 15 words). Nor indeed is there convincing evidence that the psoriatic process affects organs other than the skin. There is an associated arthropathy—a “seronegative” rheumatoid type of arthritis with certain territorial predilections—but this is not psoriasis of the joints. Again, there are certain systemic and metabolic disturbances in patients with psoriasis, but these are a consequence of the rash; they are not psoriasis of inner organs. Psoriasis remains therefore a disease of the skin itself* and with this now reasonably well established we can return to the question of what sort of disease it is.

Histological Studies

Conventional histology, ultramicroscopy, histochemistry, and autoradiography have consolidated our views on the dynamic morphology of the condition.

The histopathology is well known⁶³—the greatly thickened epidermis, split up by a dermis containing dilated capillaries and which reaches unusually close to the surface. It has been suggested that it is from these dermal high spots that leucocytes emigrate into the epidermis where they form micro-abscesses.⁶⁴ There is no granular layer—the layer in which the epidermal cells are normally transmogrified into keratinocytes—and the normal keratinocytes are replaced by parakeratotic cells, which are poorly keratinized keratinocytes containing nuclear remnants. Ultrastructurally there is a paucity of tonofibrils—presumptively fibrous prekeratins—and those which do occur are poorly orientated; there are few desmosomes, the specialized cohesive areas between epidermal cells; and there is an increase in the number of cellular organelles.⁶⁵ Scanning electron microscopy shows abnormal “pores” and “villi”, unconnected desmosomes, and an increased intracellular space.⁶⁶ Small cytoplasmic processes protrude into the dermis from the basal cells⁶⁷—an abnormality seen in other diseases with an increased

epidermal turnover, and indeed in the regenerating limbs of amphibia. Other abnormalities, such as the extracellular position of epidermal cell membrane-coating granules,⁶⁸ are not understood. Many of the fundamental histochemical studies have been done by Braun-Falco's group,⁶⁹ and the most important histochemical findings in the lesions are those associated with increased energy production, possibly associated with a change from an oxidative to a glycolytic pathway.⁷⁰ These changes are probably related to the increased mitotic activity of the epidermis because they are more obvious over areas where the mitotic activity is highest. Other significant histochemical abnormalities are those related to the absent granular zone and disordered keratinization.^{71 72}

Increased Metabolic Activity

As would be expected from the histological and histochemical findings there is much biochemical evidence of increased metabolic activity with increased oxygen consumption in the plaques.⁷³ K. M. Halprin and A. Okawia studied carbohydrate metabolism in the lesions and in normal looking skin between the lesions.⁷⁴ They found no enzyme deletions or gross reduction, and therefore rejected the idea of a specific enzyme defect in an important metabolic pathway. What they did find led them to the important general conclusion that “the reorganization of cellular metabolism necessary to sustain the increased rate of proliferation in the psoriatic plaque, occurs not by increasing the concentration of one or few key enzymatic steps but by increasing each of the enzymes responsible for a whole series of reactions . . .” Almost all the biochemical, and many of the histochemical studies point in the same direction; a general increase in metabolism within the plaques and no specific biochemical defect.

The histological suspicion of increased mitotic activity in the epidermis has now been confirmed in a number of ways. S. Rothberg and his colleagues showed the rapid passage of 14-C glycine through the epidermis,⁷⁵ but the most satisfying of the earlier analyses was that of E. J. van Scott and T. M. Eckel,⁷⁶ who showed the speed-up of epidermal turnover by histiometric methods. The advances which followed owe themselves to the method of local injection of isotopes intradermally and subsequent analysis either by autoradiography^{77 78} or by scintillation counting.⁷⁹ These and other studies show that in the psoriatic plaques epidermal turnover is about 10 times faster than in the skin of normal people. This rapid turnover occurs in both germinative cell layer and the granular layers.^{77 79} It is well known from conventional histology that there are many more suprabasal mitotic cells in psoriatic than in normal skin. I find it an intriguing paradox that the increase shown autoradiographically⁸⁰ is not as great as the increase shown by conventional histology. Could this mean that the duration of mitosis is less in suprabasal than in basal cells in psoriasis?

Abnormal Keratinization

There have been a good many studies, particularly histochemical, of the abnormal keratinization in psoriasis^{67 71 72} and its relationship to the depleted granular cell layer. One early study showed a change in the x-ray diffraction pattern of the keratin, suggesting an abnormal aggregation of the keratin fibrils.⁸¹ The crystalline proteins which can be obtained from the psoriatic scales⁸² is thought not to be homogeneous.⁸³ Of greater interest is the observation that the histidine-rich

*It is important to appreciate that this conclusion in no way excludes a humoral component, but it does imply that any such component will only be significant in relationship to the skin.

protein, which is associated with keratohyaline, is absent in the abnormal keratinization which occurs in psoriasis;⁸⁴ certain isoenzyme abnormalities have been attributed to faulty keratinization.⁸⁵

The many other abnormalities found in psoriasis are now thought not to be central to the problem.

There is an increase in the epidermal neural elements in the plaques⁸⁶ but this is probably a non-specific response to the increased turnover of cells. Another feature of the plaque is the dilated capillaries which rise close to the surface and which can be seen with a lens or microscope. Unfortunately these are not specific to psoriasis,⁸⁷ though really convincing studies have still to be done. Blood flow is increased in the lesions as shown by measuring the clearance of ¹³³xenon and 99m technetium in the plaques^{88 89} and plethysmography when the whole limb is affected.⁹⁰ There have been several studies on skeletal muscle in psoriasis⁹¹ but the evidence for a myopathy remains suggestive rather than definitive. On the other hand, there have been surprisingly few studies of the immunological aspects. The interesting observation that during treatment with methotrexate patients were less easily sensitized by simple chemicals such as chlorodinitrobenzene requires further study.⁹²

Looked at the other way, rabbits do not produce specific antibodies to psoriatic skin.⁹³ Psoriasis has an age-specific and sex-specific distribution and this has been interpreted as meaning a lymphocyte-borne immunological disease.⁹⁴ Unfortunately this analysis appears to apply equally well to most diseases⁹⁵ as well as to situations which are only marginally pathological, such as the age of promotion to the grade of professor (Newell, personal communication). This means, of course, that Burch has discovered too general a description. Like Aristotelian innate properties and phlogiston, Burch's theory explains too much—which is another way of saying that it explains nothing. It is, of course, easy to fit an immunological hypothesis into psoriasis, particularly one which would be applicable to the newer ideas on epidermal control mechanisms. A new look at the immunology of psoriasis would certainly be worthwhile.

Role of Diet

There is no convincing evidence that psoriasis is influenced by diet.³⁸ Dietary zinc has also attracted some attention, because of the parakeratotic rash in pigs taking a zinc-deficient diet. Plasma zinc concentrations have indeed been found to be decreased in psoriasis by some^{39 41} but not by others.⁹⁶ The administration of zinc does not improve the rash^{41 54} and it has been suggested that there is an increased loss of zinc through the skin in psoriasis and other dermatoses^{39 41} as there is with iron.¹⁴ Zinc deficiency is probably another of the many metabolic consequences of a rash. These abnormalities have been systematically investigated by S. Shuster and J. Marks:¹⁴ the changes are not specific to psoriasis, occurring equally in eczema and other dermatoses, and tend to depend on the extent of the rash. They affect the general metabolism of proteins, purines, iron, folate, and vitamin B₁₂; haemodynamic and thermoregulatory function; and endocrine and renal function. Part of the general effect of psoriasis is on the small bowel, causing dermatogenic enteropathy, a predominantly functional malabsorption. These abnormalities occasionally lead to diagnostic and therapeutic problems, but these are not central to the problem of psoriasis.

The absence of sweating in the plaques, which has been known for many years,⁹⁸ has been re-examined recently and it has been found that in addition to the blockage of the superficial ducts⁹⁹ there is also a specific defect of sweat duct function.¹⁰⁰ The increased water loss through the epidermis¹⁰¹ is presumably due to the poor waterproofing properties of the parakeratotic scale.

Genetic studies have been surprisingly few; the disease is thought to be dominant with poor penetrance or expression, those ubiquitous non-identical twin genetic knockabouts. Concordance has been shown in monozygous twins¹⁰² and, interestingly, an increase in digital whorls on almost all the fingers of patients with psoriasis.¹⁰³ Coarse chromosome

structure is probably normal in cultured fibroblasts from psoriatic patients.¹⁰⁴

Possible Mechanisms

Facts are as common as beard hairs, and by themselves are as useless. Ideas, concepts within which we design experiments, are the only routes through the undergrowth of facts. We must now look at those critical aspects of psoriasis which give us some insight into mechanisms of the disease.

The Aladdin phenomenon—the ability of psoriasis to appear, genie-like, where we rub the skin—has now been studied by several investigators and it is clear that clinically detectable lesions occur only with simultaneous epidermal and dermal injury.^{8 105 106} Nevertheless, “subclinical” psoriasis, with increased mitoses and abnormal capillary loops, will occur with simple Cellophane tape stripping⁷⁸ and superficial scratching of the skin.¹⁰⁷ The Aladdin phenomenon means, of course, that the whole skin is abnormal in psoriasis. Other evidence for an abnormality of the whole of the skin and not just the rash is the abnormal capillaries,^{108 109} and the occasional histological finding of “mini-psoriasis”. The most important evidence comes from the finding of an increased DNA synthesis in the normal looking skin of psoriatic patients^{78 110} and of a more rapid epidermal turnover of glycine and methionine.⁷⁹ Epidermal appendages may also be abnormal, and the clinically normal nails in patients with psoriasis grow faster than normal.¹¹¹ Finally metabolic evidence indicates a faster turnover of skin in patients with quite localized rashes.¹⁴ In the past our concepts of skin disease have been unduly restricted by the anatomical boundaries of the rash and it is now quite clear that in many skin diseases the whole skin is in fact abnormal.¹⁴ The spots on which we labour may in the deepest sense turn out to be the most trivial aspect of a disordered skin.

The Aladdin phenomenon and other evidence of whole skin involvement leads to the following formulation of a current and popular working hypothesis. The genetic defect of psoriasis is to be found throughout the whole skin and one property of this abnormal skin is its capacity to develop the rash of psoriasis. The definition of the responsible stimuli and the analysis of their mode of operation offer a research project with a greater likelihood of therapeutic success than any attempt at removing the buttercup from the genetic daisy chain.

CELL TURNOVER

Though we know little about the eliciting stimuli, other than in a very general sense, we have gone some way to defining the abnormal response, and all workers now agree that a major abnormality is the increased rate of epidermal cell turnover. What is not yet clear is whether this is the primary event or whether it is secondary to a defect in the dermis or to a change in the granular layer. The many studies which have been done so far have produced conflicting views about the prime event in the developing lesion.^{76 106 107 112} The difficulty with descriptive studies of sequential events is that the first change detected is much more a function of the refinement of techniques used by the investigator than of the actual sequence of events. What is required are critical experiments in which alternatives are excluded, and these remain to be done.

AUTOGRAFTS

Autograft experiments have been difficult to interpret because of the Aladdin phenomenon and because so many of the psoriatic transplants die, it is thought because of their increased rate of metabolism. But the experiments do show “donor

dominance," in that both the psoriatic lesion and normal looking skin tend to maintain their characteristics. Another approach to a definition of the defect has been to grow skin in vitro; organ cultures of psoriatic skin have shown a tendency to longer survival,^{113 114} but little else of value has come out of these studies. The dermis has an extremely important effect on epidermal differentiation, though the precise mechanism for this is unknown:¹¹⁵ this aspect of psoriasis has received little or no attention. There has been no recent support for the earlier idea of a primary defect in keratin such as that described in the early x-ray diffraction studies.⁸¹

It has been suggested that the parakeratosis is due to an inadequate lysosomal destruction of the keratinocytes in the granular layer.⁷¹ Though this interesting idea has not really gained support, is it possible that the absence of a granular layer, together with a parakeratotic keratinocyte layer, itself initiates an increased rate of epidermal cell division? Conceivably, for example, delayed maturation of keratinocytes could increase the pool of germinative cells—and hence the overall rate of turnover. The difficulty of the faulty granular layer idea is that there is no direct correlation between granular layer and cell turnover. For example, cell turnover is high in psoriasis in the absence of a granular layer, but cell turnover is also fast in certain types of ichthyosis where there is an abnormally thick granular layer. Furthermore, a high turnover and increased granular layer can be maintained by Cellophane tape stripping and by topical vitamin A.⁹¹ The various theories are well discussed by Fry.¹¹⁶

Conclusions

Though much more experiment will be required to distinguish between the various possibilities I find the evidence on the whole favours a more central role for the increased rate of epidermal cell division. On this hypothesis it is considered that the dermal changes—mostly vascular—are trophic, and the faulty keratinization are due to a too rapid passage of cells through the epidermis for full keratinization. The analogy here is the nuclear remnants in rapidly produced erythrocytes (reticulocytes). One important piece of evidence for this theory of disordered "epidermopoiesis" is that all the features of the rash—both dermal and epidermal—can be controlled by the administration of cytostatic drugs as different in their mode of action as methotrexate, cyclophosphamide, hydroxyurea, and triacetylazauridine.

One reason why the idea of psoriasis as a disorder of epidermopoiesis is particularly attractive is of course that it suggests some really delectable research. The epidermis is a self-replicating system: cells divide in the basal layers, pass up to the granular layer where death transmogrifies them into keratinocytes—the barrier between us and our environment. It is self evident that such a self-replicating system must know when to turn off, or overcrowding would be an even greater environmental problem. The need for organ growth control is obvious in many tissues, and we see this with compensatory hypotrophy of the liver and kidney. In the skin such "consumer control" implies a predominantly local mechanism: it would not do, for example, if the response to new boots was thick skin on the buttock as well as on the blister. The local response to a wound is epidermal proliferation and the idea of a local wound hormone was therefore inevitable. A stimulator control has been suggested by some¹¹⁷ and is obviously a possibility. A contrary view—and one more in keeping with the law of negative feedback (surely one of the greatest ideational consequences of technology?)—is of an inhibitory control. At present most of the little work which has been done is on the inhibitor systems—the chalones of Bullough¹¹⁸—and there is now some evidence of chalone control of the kidneys,^{119 120} lungs,¹²¹ and blood cells,^{122 123} as well as skin. While it is far too soon to be certain about the nature of epidermal chalone,¹²⁴ there is enough

evidence to suggest that it exists. The next step—for which there is now a line-up for a healthy scientific race—is establishing whether psoriasis is a chalonosis.

To sum up then, the feeling at the moment is that psoriasis is a disease of faulty epidermopoiesis possibly due to impaired autocontrol mechanisms. If it proves possible to unravel the autocontrol of epidermopoiesis in the next few years we shall then see psoriasis enter the most exciting phase of its long history.

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Therapeutic Conferences

Atrial Fibrillation—I

FROM THE DEPARTMENT OF THERAPEUTICS AND PHARMACOLOGY, ABERDEEN UNIVERSITY

British Medical Journal, 1971, 3, 239-240

PROFESSOR A. G. MACGREGOR: The treatment and prognosis of atrial fibrillation depend on its cause (see diagram overleaf). There are nine patients in our male ward who are, or have recently been, in this rhythm. We are to see four of them.

Case 1—Atrial Fibrillation: Palpitation, Angina

HOUSE PHYSICIAN: This 73-year-old man has mild chronic respiratory disease and, perhaps partly because of varicose

veins, has had ankle swelling in the last few months. Three days ago he developed palpitations, and then central chest pain, and was admitted to hospital. He was in atrial fibrillation with an apex rate of 120/min. and some pulse deficit. His blood pressure was 130/80 mm Hg and there was no evidence of valvular disease.

DR. R. A. WOOD: The chest pain, though not severe, lasted for three hours and we thought that he had probably had a myocardial infarct. However, the E.C.G. has shown no characteristic changes, and the transaminase levels, white blood cell count, and E.S.R. have not risen. I am not saying he does not have coronary artery disease; that is more or less inevitable if angina results from a modest increase in ventricular rate. But we think his fibrillation had a different cause.

Appointments of Speakers

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