that is implicit in good medicine, and we all be the poorer if we forget that.

Outlook in Psoriasis

Psoriasis is such an extremely variable disease in its manifestations and in its effect on patients that it is unwise to generalize about the outlook. The course varies from a single attack, never to be repeated, to progressive skin and joint lesions leading to increasing invalidism or rarely death. The large majority of patients fall somewhere between these two extremes, some suffering only trivial lesions, others having sufficient eruption to embarrass them when on the beach or at the hairdresser, and some combining these features with an arthropathy of varying severity. To the embarrassment—which depends very much on the attitude of the public (often deplorable) and of their spouses (usually understanding)—is added a variable amount of itching; but that seems to depend more on the emotional state than on the extent and severity of the eruption, though the eruptive phase is intrinsically itchy.

The one aetiological factor universally agreed is heredity, but the mode of inheritance is debated. Twin studies[1] and clinical observations suggest that environmental factors are also concerned. Probably there are many latent psoriatics, and until these can be identified progress in understanding the mode of inheritance is likely to be slow. Advance is also impeded because there is no experimental model, psoriasis being confined to mankind. Most races are affected, but it is probably absent in pure South American Indians[2], while Caucasians are particularly susceptible. Was this perhaps why the ancients called psoriasis the leprosy of the Greeks? The high incidence and early onset observed among the Faroese[3] is probably due to a combination of an unfavourable climate with hereditary factors concentrated in an isolated community. Emotional stress plays an important though ill-defined part, while haemolytic streptococcal infections provoke attacks of guttate psoriasis, the one form carrying a good prognosis. Physical trauma provokes lesions during the "active" phases of the disease (the isomorphic response or Koebner phenomenon), the nearest thing there is to an experimental model.

Attempts to define the course of psoriasis have always had to contend with the great variability of the disease, making it impossible to find a really representative group of patients, for some never see a doctor. The dermatologist's view is biased towards the more severe end of the spectrum. A recent survey by Molin[4] suggested that psoriasis runs a more severe and progressive course in men than in women, but he thought himself that the method of selection might have contributed to this result. No support was found for the commonly-held belief that psoriasis protects from other diseases, and in fact the psoriatics were ill oftener than their controls.

If advances in treatment have done a little to improve the lot of the psoriatic they have also made psoriasis a more dangerous disease. Systemic or fluorinated topical steroids suppress the eruption, but initial enthusiasm has changed to caution in view of the vigorous rebound of symptoms, including the severe generalized pustular form[5], that is apt to follow their withdrawal. Not only is the dose required as a rule too high to contemplate for long-term use, but it is not unusual for the steroid requirement to increase progressively until an impasse is reached. Antimitotic agents, usually methotrexate, given systemically and intermittently are the latest method of treatment. These drugs are not suitable for those who may beget or conceive children, owing to the risk of genetic damage, and the treatment may cause cirrhosis of the liver (particularly in alcoholics), and bone-marrow depression, and may interfere with the natural defences against infections and neoplasia. Its use is therefore limited to incapacitated patients, especially those with severe arthropathy or exfoliative dermatitis, and then only under conditions that allow for careful monitoring throughout. Azathioprine[6] is perhaps safer than methotrexate but seems less effective.

The time-honoured applications of tar or dithranol and exposure to ultraviolet light remain the basis of local treatment. Topical fluorinated steroids should be used, if at all, either to get a rapid initial response or to treat difficult areas such as the palms and soles. Tar and dithranol are too messy to be popular for home use (the non-staining alternatives are less effective), and hospital outpatient clinics providing a local treatment regimen have a definite place.[7] The combination of application of 8-methoxypsoralen and exposure to "black light" (wavelength <360 nm) has recently been described as a clean method[8] for use at such a clinic. Some patients come to accept their spots philosophically and cease to treat them except with an emollient, while others never become reconciled.

If this assessment of the outlook in psoriasis appears rather depressing, the gloom is not unrelieved. Much of the large body of available information and current work on psoriasis is of academic rather than therapeutic interest at present, but the stage is being set for a synthesis of knowledge that will illuminate the scene. One spark is the discovery of a humoral anti-psoriasis factor.[9] If this substance could be isolated it might be used therapeutically.

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Fibrinolysis and Venous Thrombosis

Ever since thrombosis was first regarded as an imbalance between the coagulation and fibrinolytic mechanisms of the human body[1] drugs have been sought which will reduce the one or stimulate the other. Unfortunately our poor understanding of the mechanisms by which blood coagulation is initiated has hindered any real advance on this front, and there is no satisfactory laboratory test which will tell the clinician when a patient's blood is hypercoagulable.

Fibrinolysis, on the other hand, is almost certainly controlled in man by alterations in the circulating level of a single active compound, plasminogen activator.[2] Activator is stored in the endothelial cells lining vessel walls,[3] and there are several laboratory tests such as the euglobulin clot lysis time and the fibrin plate and fibrin slide techniques[4-6] which measure the concentration of plasminogen activator in the blood or the vessel wall. At present, however, all these tests require considerable technical skill and care in the interpretation of

individual results. Despite this the artificial stimulation of fibrinolysis is of considerable therapeutic potential.

Streptokinase was the first active compound to be developed,[7] and it was later followed by urokinase. Both these drugs activate fibrinolysis in vivo, and streptokinase has been shown to lyse completely venous thrombi in the legs[8] and emboli in the lungs,[9] with very satisfactory clinical results; but the occurrence of complications such as haemorrhage has left this treatment in the hands of a few specialized centres. Furthermore, because both streptokinase and urokinase activate fibrinolysis without altering the circulating concentration of plasminogen activator, tests to control their use are outside the scope of most routine laboratories.

There was, therefore, considerable interest at the Second International Conference on Synthetic Fibrinolytic-Thrombolytic Agents in Paris in October in the combination of the antidiabetic drug, phenformin and the oestrogen, ethyloestrenol. This combination has been shown to increase the fibrinolytic activity of the blood,[10] and these drugs can be safely given to patients for prolonged periods of time. The conference was told by I. M. Nilsson *et al.* of a clinical trial of this combination in which 60 patients suffering from recurrent idiopathic deep venous thrombosis, 10 patients with recurrent superficial thrombophlebitis, and 5 patients with retinal vein thrombosis were treated with 100 mg phenformin and 8 mg ethyloestrenol daily for periods ranging from three months to four years. Either the plasminogen activator content of the vessel walls or the fibrinolytic response to venous occlusion was initially reduced in all of the patients, and some of them had decreased values in both tests. The response to venous occlusion was restored to normal in all the patients after treatment for three months, and the plasminogen activator content of the vessel wall was normal in all except two patients after treatment for twelve months. Furthermore, the frequency of thrombotic episodes was reduced in all the patients. There were few side effects, but four patients had amenorrhoea while taking the drugs, one patient developed acne, another became obese, and one man developed severe lactic acidosis which required cessation of the treatment.

Unfortunately in two further trials the same treatment did not reduce the incidence of postoperative deep venous thrombosis.[11 12] Possibly in these studies the treatment was not given for long enough before operation, nor was there an adequate effect on the dilute-blood-clot-lysis time or the euglobulin-clot-lysis time immediately after operation. Further trials of this therapy in surgical patients are, therefore, needed.

For the future, it seems likely that newer and more effective compounds which stimulate fibrinolysis will be developed, and there may also be available simple laboratory tests which will enable the clinician to monitor the effects of treatment. Routine therapeutic activation of fibrinolysis will then become a real possibility.

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Human Tumour Xenografts

It has been known for many years that human tumours can be grown, under certain conditions, in laboratory animals as xenografts.[1-3] The tumour tissue can be introduced into an immunologically privileged site, such as the hamster cheek pouch or the anterior chamber of the eye, where it remains free from attack by the host's immunological defences. Alternatively the host can be rendered immunologically incompetent so that it is unable to reject xenografts. Mice and hamsters, for example, can be prepared by ablating the T-lymphocytes responsible for graft rejection by a combination of irradiation, thymectomy, antilymphocyte serum, and corticosteroids. In addition to these specially prepared animals, xenografts can be grown in mutant nude mice, which are genetically T-cell deficient and unable to reject foreign tumour grafts.[4]

The past two years have seen several reports of human tumours grown as xenografts.[2 5] The original morphology and differentiation of the tumours seem usually very well preserved in the grafts, and apparently may be sustained over a few transplant generations. The rate of the tumour growth in irradiated mice is similar to that observed in man, so that the inoculum of cells may take two to three months to produce a nodule a few mm in diameter,[3] but they seem to grow a little faster when the xenografts are carried by nude mice.[4] The tumours appear to lose their property of metastasizing in the system; as yet the reason for this is unknown.

Several authors have hastened to point out that the character of the original tumour, albeit growing in a foreign environment, should be a good target for experimental chemotherapy studies. Unfortunately, such optimism overlooks the fundamental rules of drug testing on transplanted tumours, which require there to be an end point, be it tumour size or survival of the host, that can be measured and is modified by standard reference drugs. The system appears still to be an object of scientific curiosity and is not being exploited seriously—for several reasons.

The preparation of immunosuppressed host animals is a demanding technique, while the nude mouse needs to bereared under special conditions. There is often considerable diversity both in the number of grafts that take and the eventual growth rate among the grafts coming from the same primary tumour and in their stromal content. The growth characteristics of the primary xenografts are such that classical methods of assessment of a drug effect are not readily applicable to this system. There are some reports of histological assessment of damage inflicted on tumour xenografts by chemotherapeutic agents, but these cannot be accepted as a reliable guide—a kill of 95% of the tumour cells looks dramatic at 24 or 48 hours but is hardly noticeable a few days later. In one series 44 tumours grown as xenografts were treated with single common chemotherapeutic agents and examined histologically 10 to 30 days later, when only three showed any significant change.[7]

The practical application of human tumour xenografts to clinical medicine has yet to be worked out. The slow growth and uncertainty of the primary tumour make the system of doubtful use as an individual screening test in tumours such as carcinoma of colon and breast; in present circumstances the clinician would have to wait several months before he had an answer. On the other hand, if lines of transplantable differentiated cancers could be established then they might be used as a laboratory system for screening new drugs. However this step can probably be made just as easily by using some of the newer transplantable differentiated cancers that have been developed