cluded that, in general, it has little to offer the practising clinician. It seems doubtful whether the relative inaccuracy of the methods suitable for clinical application can be held completely responsible for this state of affairs; rather should one ascribe it to the inherent variability of pregnanediol excretion both in the same and in different patients. Consideration of the factors responsible for this variability is beyond the scope of the present discussion, but it does seem permissible to observe that there are no solid grounds for believing that pregnanediol excretion reflects at all closely the progesterone levels of the blood, and undoubtedly the latter are of far the greater physiological significance. Simple direct means of assessing the blood progesterone would surely supply evidence of much more clinical value than could ever be expected from the pregnanediol excretion in the urine.

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VESICO-BULLOUS DISEASES AFFECTING THE EYE*

BY

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There are few skin diseases which may not at some time involve the eye and its appendages. It is impossible to consider all of them here, even in the most summary way. I propose instead to survey a single group—the vesico-bullous diseases of internal origin—affecting the skin and mucous membranes. Even with this restriction the survey must necessarily be a brief one.

The more one considers the vesico-bullous diseases the more one is struck not by their clinical differences but rather by their essential similarities. A common factor seems to operate in all of them, producing a particular type of cell reaction. It is this which makes a study of the group of special interest. In some diseases a virus, in others an unknown toxin, exercises a destructive action on the mucosae or on the deeper cells of the epidermis, with resultant cellular liquefaction. This seems to release a physico-chemical force, which in turn increases capillary permeability and attracts the filtrate as well as the local tissue

fluid to the injured area. In this way a vesicle is formed. When the hydrostatic pressure within the vesicle has reached a certain point the movement of the fluid is checked. Whether the vesicle breaks down to form an oozing erosion or not depends largely on the thickness of its roof. Naturally, in the conjunctivae and other mucous membranes the covering is thin and the vesicles are correspondingly transient, so that the clinical picture is a raw oozing surface, whereas the skin may still show intact vesicles. But though the distribution and clinical appearance in the different diseases of this group are varied and characteristic, histologically we can distinguish only grades of severity in an essentially similar reaction.

Percival and Hannay (1949) have published an excellent study of the pathology of bullous formation, from which the following interesting sentence is taken: "To state the problem differently, it can be asked why the exudate remains in the dermis in urticaria, becomes localized at the dermo-epidermic junction in dermatitis herpetiformis, in the rete mucosum in eczema, and under the stratum corneum in pemphigus foliaceus, when the mechanism which made the exudate available is common to all four conditions, and is in all probability initiated by a common factor."

The diseases of this group which affect the eye are: herpes simplex; herpes zoster; erythema multiforme, including the severe form known as the Stevens-Johnson syndrome; foot-and-mouth disease; Touraine's aphthosis; dermatitis herpetiformis; and pemphigus. (Conjunctival scarring is associated with other skin diseases, such as bullous eruptions following vaccination, erythroderma ichthyosiforme of Brocq in its bullous form, epidermolysis bullosa dystrophica acquisita, and congenital syphilis, but these conditions do not belong to the group under consideration.)

Herpes Simplex

This well-known disease is characterized by the often-repeated occurrence of little groups of blisters on a base of oedema and redness. Its virus origin is amply proved, and corneal inoculation of a rabbit gives positive results. In contrast with what occurs in many virus diseases the host develops no immunity. On the contrary, a local hypersensitivity often causes the same small patch to respond on each occasion. The lips and face are most frequently affected, but lids, conjunctiva, or cornea may suffer instead.

The evidence suggests that the virus is a saprophyte living in happy matrimony with the tissues until a *tertium quid* disturbs the harmony. This may be any one of a variety of agents which include cold, heat, sunlight, food, drugs, and bodily upsets. The injured cell then goes through the processes of liquefaction and vesicle formation already described. Individual eruptions heal easily and need only to be kept clean. But to prevent recurrence is a difficult matter. Irradiation of the affected area of skin with x rays may produce an alteration which increases local immunity, or repeated inoculations with smallpox vaccine may raise the general resistance, but disappointing results are common.

Herpes Zoster

This complaint is not transmissible by inoculation. But as specific antibodies have been found in the blood, and inclusion bodies have been demonstrated in the vesicles, the evidence is in favour of a virus disease. The cutaneous reaction is greater and deeper than in herpes simplex. Haemorrhagic, purulent, or necrotic vesicles may occur and leave severe scarring. Many cases have been described as

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sequelae of nerve infection or injury. So that here, again, it seems that a cell injury may open the door to a virus attack.

Herpes zoster is of special importance when it affects the eye, because of the risk of permanent injury. Becker (1948) has published a paper claiming good results in this condition by the injection of blood or serum from people who have recovered from the disease. This was for some time thought to be useless, because of statements such as that of Rivers (1939) that "convalescent blood or serum is of no value in the therapy of virus diseases, because by the time the disease is evident the organism has already penetrated the cell, a barrier which no antibody can transgress." Despite this view the method seems to give hopeful results. Becker used blood transfusions, blood plasma, and whole blood injections, with material taken from a donor any time from three weeks to two years after his having the disease.

Erythema Exudativum Multiforme

In 1866 Ferdinand Hebra described a disease affecting the face, the limbs, and sometimes the mucosae. The rash, as the name suggests, takes on many forms, such as macules, weals, bullae, or large annular or serpiginous plaques, of an angry blue-red colour. The eruption is short-lived but often recurrent. A somewhat similar rash, more rosy in colour and more varied in its distribution, can be elicited by a wide range of toxins. It is not clear whether Hebra's erythema multiforme is a specific entity or not. Ocular involvement generally takes the form of a pseudo-membranous conjunctivitis which may lead to shrinkage or uveitis. Lacrimation and photophobia are also seen, and corneal ulceration and perforation have been described. No causative agent has been found.

In 1922 Stevens and Johnson described a severe form of erythema multiforme which, in English-speaking countries, is now generally known under their name. An earlier account had, in fact, already been published by Rendu in 1916 under the name of "ectodermose érosive superficielle," and the condition is also referred to as "dermatomatitis" or "eruptive fever with ophthalmia." This begins acutely with a rash like erythema multiforme, but the general symptoms are much more severe and the patient is feverish and looks gravely ill. The eyes, mouth, and genital mucosae are so inflamed and eroded as to be extremely tender, so that micturition becomes an ordeal and feeding may have to be done through a tube. Despite this disturbing start, improvement takes place in a week or ten days, and recovery is usual in about three weeks. Unfortunately, the eyes may be irreparably damaged. The conjunctivitis may leave adhesions or scars, or the corneal damage may end in opacities or in perforation. An effort should be made to keep the lids open with tiny strips of adhesive tape, but on account of the photophobia the patient is apt to struggle against this.

Patz (1947) made a study of six cases. He tried various methods of discovering a virus by making smears from the conjunctiva and vagina, by complement-fixation tests with psittacosis antigen, by cultures in chick embryos, and by the intracerebral and intraperitoneal injection of vesicular fluid into rabbits, guinea-pigs, and mice. All results were negative.

Vincent's stomatitis has been found associated with erythema multiforme in three cases, and it was suggested that the fuso-spirochaete, by altering tissue sensitivity, might lead to the Stevens-Johnson syndrome. But proof of this is not forthcoming, and the association of the two complaints has scarcely ever been found.

Anderson and his colleagues (1949) claim to have found a virus with cytoplasmic inclusion bodies following rabbit cornea inoculation. Their study was limited to one case.

Treatment is symptomatic. Nicotinic acid is said to be of use, but as most cases clear up spontaneously it is difficult to be sure of its value.

Foot-and-Mouth Disease ("Fièvre Aphtheuse")

This may be acquired by direct contact with infected animals or, less often, by drinking their milk. The distribution is not unlike the preceding condition, but the skin around the nails is chiefly affected and the lips and mouth are dry and burning, whereas in the Stevens-Johnson syndrome lesions are more often seen on the wrists and ankles, and there is profuse salivation. Ocular involvement is not common. If there is any difficulty in diagnosis, guinea-pig inoculation in foot-and-mouth disease gives a positive result.

Touraine's Aphthosis

There is a fearsome dermatological jungle in which various diseases with resounding eponymous titles struggle for life. They are the chronic erosive conditions affecting the eyes, mouth, and genitalia. Each specialist is naturally absorbed in his own field, which for him takes precedence of all others, and so a number of syndromes have arisen, such as Sutton's (1911) "periadenitis mucosae necrotica recurrens," Loblowitz's (1910) "ulcus neuroticum oris et vulvae," Lipschütz's (1923) "acute vulval ulcer," "pustulo-ulcerous balanitis," and others. Behcet (1937, 1940), a Turkish dermatologist, described a triple symptom-complex in which all three areas—eyes, mouth, and genitalia—are affected simultaneously or in sequence. Little round or oval ulcers with yellow sloughs succeed one another in the mouth, vulva, or glans penis, associated with inflammation of the cornea, conjunctivitis, or sclera. The skin has a tendency to develop acneiform pustules or deep-seated lesions of the erythema nodosum type.

In 1941 Touraine made an extensive study of this whole group. He suggests that the various conditions belong to one single systemic disease, which he ascribes to an ultra-virus, and to which he gives the name "aphthosis." He thinks that this agent, like the virus of herpes simplex, becomes established in the body and manifests itself clinically when for divers reasons the individual becomes anergic. Touraine divides his aphthosis into three groups according to severity and extent.

1. A generalized form, affecting the skin, mucosae, and joints. This is severe and starts with fever and general systemic disturbance.
2. A milder form, involving the mouth and genitalia, with a few scattered vesico-pustules on the skin.
3. Aphthosis of the mucosae alone, in the form of small recurrent ulcers, or, less often, a single large ulcerative area, which may be mistaken for a venereal infection. There is much variety in the severity and duration of the ulcers, and also in the length of the free periods. Recurrences may be precipitated by any bodily upset, such as infectious fevers or pregnancy, or by local trauma or operative procedure.

Touraine's view is substantially in accord with Whitwell's (1934) conception of "embolic showers" causing necrotic apthae in mucosae and skin. It may be that future research will show the conception of "aphthosis" to have oversimplified the problem. But until further knowledge is obtained the harassed dermatologist can only feel relief at having so many odd sheep neatly penned into one fold.

Dermatitis Herpetiformis

It is unnecessary to dwell on the clinical appearance of this well-known disease, particularly as the eyes are rarely affected. Only a few points of special interest will be mentioned. There is a special sensitivity to iodine, and in one case involving the eyes and nasopharynx painting with iodotannic spirit produced a disastrous exacerbation. There is some evidence that hypersensitivity to a bacterial toxin may be an important aetiological factor. It is often possible to control the disease, and sometimes even to cure it, by long-continued small doses of sulphapyridine. The aim is to raise the resistance of the body rather than to eliminate the supposed toxin.

Pemphigus

The cause of pemphigus is unknown, and it follows that the validity of the different divisions or varieties is still uncertain. Dermatologists, however, clearly distinguish between four clinical types—acute pemphigus, chronic pemphigus or pemphigus vulgaris, pemphigus foliaceus, and pemphigus vegetans. Acute pemphigus is a fulminating disease generally occurring in people who handle animal carcasses. It begins on the hand and spreads over the whole body, leading rapidly to death in 80 to 90% of cases. In pemphigus vulgaris the development is more insidious, but, according to Lever and Talbott (1942), death occurs in 83% within one year of onset and in 97% within two years. It follows from these figures that treatment does no more than alleviate the symptoms. Grace and Hellman (1946), however, claim to have cured two cases of pemphigus vulgaris with blood transfusions from two patients who had recovered. One cannot generalize on the strength of two cases, but as spontaneous cure is rare this claim is of great interest.

A brief survey of the literature on ocular pemphigus reveals an almost inextricable confusion, and the term is manifestly used in the loosest way. One author talks of "ocular pemphigus" under one heading and "pemphigus vulgaris with ocular involvement" under another. A different prognosis and a different racial distribution are given, but no criteria for distinguishing one from the other. Klauder and Cowan (1942) have stated the issue clearly. They use the original term "essential shrinkage of the conjunctiva," and believe that this occurs in a number of dermatoses, of which some are very rare. The list includes: severe erythema multiforme or the Stevens-Johnson syndrome; bullous eruptions following vaccination; erythroderma ichthyosiforme of Brocq in its bullous form; dermatitis herpetiformis; epidermolysis bullosa dystrophica acquisita; and congenital syphilis.

Klauder and Cowan would confine the term "ocular pemphigus" to a benign affection of old age often associated with pemphigus of the nasopharynx and with a trivial bullous eruption of the skin, especially of the lids and face. The genitalia may also be involved. It is not found more often in Jew than in Gentile, though, as is well known, the Jewish race is particularly sensitive to pemphigus vulgaris. The question therefore remains to be answered, Is ocular pemphigus a special entity with a benign course, occurring late in life and with no particular racial distribution, or is it a mild form of pemphigus vulgaris, to which disease Jews are so sensitive that if affected at all they develop the severe form?

Discussion

A group of diseases exist which produce vesicles or bullae, breaking down into erosions of the skin or mucous membranes. Despite clinical differences the histopathology is

essentially similar throughout the group. Some are caused by viruses; in some no virus origin can be discovered. A connecting thread seems to run through the group, as shown by a symmetry of distribution and a susceptibility to precipitating factors of many different kinds which alter the reactivity of the cell and lead to its liquefaction. Somewhere in this complexity we should be able to find the master key which would fit all the doors. It may be that this will be given to us by research in pure science, and, indeed, this seems already possible. Before the war Peters (1936), considering the biochemistry of the cell and the perpetual shuttle of its metabolic life, made an incidental note of the fact that very small quantities of arsenic could, as it were, stop a cell "breathing" by interfering with one of its enzyme systems—the pyruvate oxidase system, which is instrumental in breaking down glycogen or glucose into carbon dioxide and water. At the onset of war, when scientists were directed to problems of immediate practical importance, the Department of Biochemistry at Oxford, under the charge of Professor Peters, began to consider possible antidotes to arsenical poisoning in the form of lewisite. This earlier observation provided a starting-point for research, and in a short time Thompson (quoted by Carleton *et al.*, 1946) discovered that a dithiol—dimer-captopropanol—could combine with arsenic and even remove it from the cell, to be harmlessly excreted in the urine.

Now, acute arsenical dermatitis has features not unlike the diseases we have been considering. A drop of lewisite on the skin brings out a large bulla. In the conjunctiva it produces a penetrating destruction of the eye. In arsenical poisoning, such as may arise in the treatment of syphilis, bright-red blotches appear on the limbs and spread to a generalized exfoliative dermatitis. Interference with a single enzyme system can therefore cause cellular liquefaction and breakdown. A known poison acting in an understood manner produces results which are partly reversible by an antidote of known chemical composition. In the vesico-bullous diseases, we know neither the poison nor its precise manner of acting, still less the antidote. But we have here an excellent example of the fruitfulness of correlating clinical with purely scientific research in the solution of our joint problems.

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