ON PEMPHIGUS IN CHILDREN.

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THE name "Pemphigus" was at one time used to include most, if not all, bullous eruptions, but is now usually limited to *Pemphigus vulgaris*, *Pemphigus foliaceus* and *Pemphigus vegetans*, but as the two latter diseases do not occur in children I shall not discuss them further. *Pemphigus vulgaris* may be divided into acute and chronic. Of the acute form there is one well-defined group of cases, occurring chiefly among adults, and especially among butchers and those who have to do with hides. The disease is usually fatal. From the clear intact bullæ a diplococcus has been cultivated by Demme, by Pernet and Bulloch, and others, which, when injected into the pleural cavity of guinea-pigs, proves fatal to these animals.

The acute variety of *Pemphigus vulgaris* which is usually seen in children is of less well known, if not unknown, origin. It is characterised by the appearance of clear blebs and bullæ on a normal skin; their outbreak is rapid or sudden, and they may occur on mucous membranes as well as on the skin. The contents of the bullæ are at first clear, but may afterwards become opaque, owing to the greatly increased number of leucocytes. The base of the bulla also becomes surrounded with a narrow red areola as the inflammatory reaction increases. The onset of the disease is usually marked by fever, sickness, shivering, or even a rigor, the patient feels ill, and the lesions increase considerably in number and extent within a short space of time. The disease usually runs its course either towards recovery or death within a few weeks; in children, however, recovery often takes place, the contents of the bullæ either become absorbed or escape through rupture of the bulla, with or without the formation of a scab. A hyperæmic patch of skin is left, which may later on become pigmented.

Chronic pemphigus is rather a recurrent than a chronic disease inasmuch as the lesions appear in successive crops at intervals of a few days, each attaining a considerable size in a few hours, and here and there coalescing to form large bullæ. As in the acute form of pemphigus the mucous membranes are sometimes affected, the nose, throat and pharynx becoming covered with blebs, and even the

bronchial tubes involved. The eruption does not appear to be influenced by the general health, and although many of the patients are badly nourished and ailing there is no special kind of cachexia. Acute febrile exacerbations may supervene on the chronic disease, the temperature rises to 103° or 104° F. and a fatal result ensues.

I have recently had under my care at the North-Eastern Hospital for Children a child recovering from an acute attack of pemphigus, which may serve as an illustration.

The patient, a little girl, aged 7 years, was admitted to the North-Eastern Hospital on June 30th, having been transferred from an eye hospital, where she had been an in-patient for three or four days. When she first attended this Eye Hospital on June 9th she was ordered to have atropine ointment put into her eye previous to examination of the eye. After this had been done for a week, conjunctivitis set in with puffiness round the eye and swelling of the orbit. This increased, and she was admitted as an in-patient on the 26th. The puffiness of the face continued with some erythema and subsequent desquamation, her temperature rose to 100° to 102·5° F., and bullæ made their appearance on the chest and back and spread to the abdomen and limbs, and there was a discharge from both ears which had come on two days previously to admission. She was then transferred to the North-Eastern Hospital, and on admission she had numerous bullæ and blebs on the trunk and limbs, a temperature of 102° F. and pulse 136. I saw her on July 3rd at the request of Dr. Frederick Taylor, who kindly transferred the case to me. There were then numerous bullæ varying in size from a pea to a pigeon's egg on the chest, abdomen, limbs and back. On the back and elsewhere some had ruptured, leaving raw bleeding surfaces, which were intensely tender and caused the patient much pain when she was moved. The bullæ were irregularly distributed, and showed but imperfect symmetry, some of them being clear, some hæmorrhagic and some distinctly cloudy. Where some of the bullæ had partly ruptured and the contents to some extent escaped, they presented a depression in the centre with a similarity to the umbilication of small-pox. A few bullæ were also present on the face, but the greatest number were on the trunk. A certain number of longer standing showed an erythematous base, but in most cases they arose from what appeared to be normal skin. Some of the larger blebs had coalesced

with neighbouring smaller bullæ, and when ruptured left a raw surface of appreciable extent which cause the patient much discomfort. There were a few blebs on the mucous membrane of the mouth, but the conjunctivæ were not involved.

On July 2nd cultures were taken from two bullæ, and smears were made by Dr. Langdon, the house-physician in charge of the case, to whom I am much indebted for his able and painstaking investigation of the case. The cultures were made on sloped agar and proved to be *Staphylococcus aureus*, but a film from another recent bulla made by Dr. Langdon showed only chains of streptococci. No cultures were, at this time, made in broth or any fluid medium, and this might perhaps account for the failure of the cultures to show streptococci. On July 7th cultures were again taken from two unruptured bullæ both on blood serum and broth, and films were also made. One of the bullæ again gave cultures of *Staphylococcus aureus*, the other in broth showed a pure streptococcus culture. This was submitted to Gordon's sugar tests and showed the following results :

Positive to neutral, red, saccharose, lactose, raffinose, and milk-clot.

Negative to inulin, salicin, and mannite.

In broth the chains of cocci were short.

The organism therefore corresponds to the type of *Streptococcus salivarius*, a comparatively non-virulent type of streptococcus which is not pathogenic for the mouse.

The opsonic index to streptococci was estimated on July 7th and found to be .64. On July 7th an injection of five million (approximately) streptococci was made, and on July 14th the opsonic index was found to have risen to .88 and clinically the patient was very greatly improved. On July 14th a further injection of five million streptococci was given, and on July 21st the opsonic index had risen to 1.2, and the bullæ had all dried up and the patient was convalescent. In this connection I should like to refer to a case of chronic pemphigus in a man, published by Pernet and myself in the *British Journal of Dermatology* for November, 1906, in whom streptococci were twice obtained in pure culture in broth from the clear fluid of the bullæ. He was treated with opsonic injections of streptococci, and at times staphylococci, on account of the septic condition of his leg. He still attends University College Hospital from time to time, but when the injections are allowed to lapse he generally gets a fresh crop of bullæ.

In this case the streptococci were also of the *salivarius* type, and when a pure culture was injected intra-epidermically in the guinea-pig a circumscribed indurated nodule appeared after two days, surrounded by an erythematous ring, but no bulla or bleb resulted. The nodule became re-absorbed in a week.

The different accounts of the anatomy of pemphigus can perhaps be explained by the assumption that entirely dissimilar cases have at various times been described, and that some of the descriptions apply to cases which are not now usually looked upon as true pemphigus. But these differences are also partly explained by such observations as those of Audry, who in the same case found that the bullæ were situated in different layers of the epidermis. Kreibich, who examined a large number of pemphigus bullæ, found them to occur both internal to the rete and also between it and the horny layer, although the separation of the epidermis from the cutis occurred more frequently. That the latter occurrence is the more common is also supported by the observations of Kromayer, Luithlen, Buzzi-Joseph and Jarisch, although Jarisch has also in former observations described it as occurring between the stratum lucidum and stratum granulosum. Hebra stated that the roof of the bullæ was formed by the outer horny layer, and other observers have arrived at the same conclusion; it seems, however, established that the anatomical seat of pemphigus bullæ is inconstant.

The bullæ themselves are composed of a single chamber and contain a greater or lesser quantity of leucocytes, among which the eosinophiles predominate. The *pars papillaris corii* undergoes definite changes, more especially in the form of œdema, which shows itself partly by the formation of clefts and fissures, partly by displacement of connective and elastic fibres. Kromayer has described the changes even in the fine threads of the *cutis vasculosa*, which are unevenly displaced. The papillary vessels are but little dilated, whereas the vessels of the sub-papillary network and the upper layers of the *pars reticularis* are distended with blood. An infiltration of mononuclear leucocytes is found along the vessels. Luithlen has described a disappearance of elastic fibres in the papillary area. Weidenfeld classifies the histological changes as follows:

- (1) Marked dilatation of blood and lymphatic vessels.
- (2) More or less extensive peri-vascular infiltration.

- (3) Œdema of the papillary body and cutis.
- (4) Definite changes in the elastic fibres.
- (5) Œdema of the rete in its whole thickness or in its superficial layers.

The mechanism of the formation of bullæ is usually described as due to some acantholytic substance, whether ferment or otherwise, which can weaken the cohesion of the cells and determine the separation of the layers of the epidermis from one another. That the serum poured out has a cytolytic action seems probable, and this will account for the breaking-up of the prickle cells and the superficial connecting strands of the epidermis during the formation of a bulla. But it is a question whether this is not entirely a secondary phenomenon, the essential factors being the rapidity with which the serum is poured out and its relative quantity. The epidermis seems to be torn apart by the fluid which is poured out of the capillaries in the papillary body, assisted perhaps by contraction of the erector muscles. This fluid has a cytolytic action, and can be to some extent imitated by the intra-epidermal injection of 1 in 1000 sodium chloride solution, which causes the formation of superficial bullæ. In such an experiment it is of interest to note that at the periphery of the artificial bulla, where the fluid is tending to force its way, the vessels are constricted owing to the pressure, while at the centre, where the pressure is less, the blood-vessels are widely distended and full of blood. Were the artificial pressure high enough the destruction of tissue would, of course, be great, and all the vessels in the area of pressure constricted, but in pemphigus there is no reason to believe that such an amount of pressure does ever exist.

If the first rush of fluid is produced mechanically, it approximates to that seen in factitious urticaria where no true inflammation can be said to exist, and this is made more probable by some experiments of Weidenfeld, who finds that in pemphigus patients mechanical stimuli are capable of causing bullæ similar to those seen in *Pemphigus vulgaris*. Thus the pressure of a block of wood, edge downwards, on the skin of such patients gives rise to bullæ, whereas no such reaction occurs in healthy individuals. His experiments also show that the serum of the bullæ has a cytolytic action, and the injection of such fluid into the skin of a pemphigus patient can produce bullæ even in subjects who do not react to the pressure stimulus.

The occurrence in functional and organic disease of the central and peripheral nervous system of appearances very similar if not identical with true pemphigus, and described as *Pemphigus nervosus* and *hystericus*, led to the theory of a neuropathic origin of the disease, which has gained support through the demonstration of changes in the central and peripheral nervous systems by Eppinger and others. Eppinger reported six cases of pemphigus in which either simple degenerative changes had taken place in the peripheral nerves in the area of the bullæ and their immediate neighbourhood, or hæmorrhage into the central nervous system, or purely peri-neuritic inflammation. Sangster and Mott have described degeneration in the peripheral nerves, and Déjérine found neuritis in the area of the bullæ, which made their appearance in a case of general paralysis twelve days before death. Jamieson and Welsh in a post-mortem examination of a woman with *Pemphigus vegetans* found changes in the cells of the spinal cord consisting of vacuolation and destruction of the cells and diminution of the chromophile substance, and were of opinion that the case was one of primary toxic degeneration of the nerve-cells.

The neuropathic origin of the disease, which regards pemphigus as a primary angio- and tropho-neurosis, is supported not only by the histological demonstration of pathological changes in the peripheral nerves and central nervous system, but also by the clinical occurrence of bullous development in organic and functional nervous cases. Leloir, Mougeot and others have described cases in which the formation of bullæ followed injury to peripheral nerves, Weir-Mitchell, Morehouse, Corlett and Keen, after bullet-wounds of peripheral nerves, while Balmer, Charcot, Kopp and Leloir have recorded eruptions of bullæ in diseases of the spinal cord and brain, such as myelitis, meningitis and hemiplegia. Functional disturbances of the central nervous system have also been associated with bullous eruptions not of an artefact type, as in the cases recorded by Du Mesnil de Rochemont, by Boradet and by Neuberger. But all cases of pemphigus do not seem to fit in with a neuropathic theory, even if this is held to include an angio-neurotic element. The sudden onset of the disease in many cases, the obvious bad health of the patient, the rise of temperature accompanying the outbreak, all seem to point to something more, and emphasise the likelihood of a toxic or infective

origin. This possibility becomes more probable when we remember how closely allied pemphigus is to some drug eruptions, to toxic exanthemata, to urticaria and to Erythema multiforme. In all there is œdema of the papillary body, starting almost acutely, whereas the exudation of leucocytes is comparatively little marked. Moreover, the course of development of the bullæ is clinically similar in all these cases.

If the resemblance of these diseases to one another is clinically well marked, it is perhaps allowable to assume that there is some similarity in their ætiology and origin. In the case of drug and toxic eruptions it seems certain that some poisonous chemical or bacterial substance is the direct cause which induces them, while in urticaria and Erythema multiforme we have good reasons for assuming a like origin. Bacterial toxins and auto-intoxication undoubtedly play a considerable rôle in the causation of the diseases just indicated, and if we admit their clinical resemblance to pemphigus, it seems reasonable to presume similar ætiological factors as playing a part in the evolution of the latter. The exact nature of the toxin concerned it is difficult to guess. Whatever it is, there is a possibility that it is manufactured in excess in the alimentary canal, or insufficiently destroyed by the liver, or imperfectly excreted by the kidneys and skin. That a specific poison may act on a certain definite group of capillary vessels is shown by the action of snake poison, where the exudate from the vessels may begin locally in a few minutes, and within a few hours involve the whole body. If we assume that pemphigus, both acute and chronic, is in the first place due to the metabolic products of bacteria, we can combine with this the neuropathic theory by supposing that these products induce a functional or organic change in the peripheral or central nervous systems, which again react on the skin by disturbed innervation of the area on which the bullæ arise. This theory has been supported by Eppinger, Tommasoli and Sormani, who all consider that auto-intoxication plays a primary part in the causation of the disease, and the varying forms of the disease can then be explained by admitting that the toxic body is not the same in every case. The demonstration and isolation of this toxin is without doubt a very difficult matter, and the finding of bacteria, whether streptococci, diplococci or diphtheria bacilli in the lesions, or even in the blood of the patient, cannot be said to prove the theory at all conclusively. Up to the present it has not been possible by injection of any

micro-organisms isolated from cases of pemphigus to induce true pemphigus in a healthy animal, and from it again isolate pure cultures of the same organism. But the theory has much in its favour, and is preferable to some others, such as that of Leredde, who, indeed, presumes an auto-intoxication, but holds that the first action is on the blood-forming organs, such as the spleen and marrow, and that anomalous blood changes so induced, like eosinophilia, react upon the skin in such a way as to produce the lesions of pemphigus.

Mention has already been made of a possible analogy between pemphigus and factitious urticaria, and in this connection it is interesting to refer to the very ingenious work of Gilchrist on factitious urticaria. He induced a wheal in urticaria patients, excised portions of it at various intervals afterwards without any local or other anæsthetic, and examined the tissue histologically by the celloidin method. In even the short space of three minutes after induction of the wheal his sections showed plainly a great exudation of leucocytes, especially polymorphonuclears, and marked fragmentation of the nuclei. These results he ascribes to the action of a toxin, although as yet he has not been able to isolate the toxin. Whether this conclusion is justified or not, the sequence of events is undoubtedly very rapid and of great interest as giving a possible clue to the causation of other diseases, such as pemphigus.

Whether true pemphigus is primarily a microbic disease or not, micro-organisms have been found in the bullæ by different observers. Demme's diplococcus has already been mentioned, staphylococci have been found in many cases, and streptococci have been found by Babes, myself and others. In my case recorded above streptococci were found in film preparations and pure culture, and the patient recovered rapidly with treatment by a streptococcic vaccine prepared from cultures of the bullæ. A case of Pemphigus vegetans is reported by MacCormac in the September number of this journal from which a pure culture of a streptococcus was obtained, and I have under my care at the present moment a boy, aged 6 years, who has had recurrent crops of typical pemphigus bullæ since last Christmas, the bullæ on one occasion also yielding a pure streptococcal growth. But pemphigus bullæ are sometimes sterile, and further observations and inoculation experiments are necessary in order to establish conclusively a bacterial origin of the disease.