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SUBACUTE MALIGNANT PEMPHIGUS WITH EXTENSIVE BULLAE*

(Pemphigus Subaigu malin à Bulles Extensives, Brocq)

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INTRODUCTION

Brocq, whose studies have done much to bring comparative order out of the chaos which existed in the bullous dermatoses, has recently called attention to a group of cases of pemphigus hitherto not usually separately described.¹ He has given the name subacute malignant pemphigus with extensive bullae to the condition, which he describes as closely resembling acute febrile pemphigus, but which is differentiated from it by a characteristic clinical syndrome.

While Brocq's classification of pemphigus is the one now usually accepted, there is still enough variation in the usage of the term to warrant summarizing the conditions included under it, before describing the new syndrome, and locating it in the general scheme.

Under pemphigus Brocq includes acute febrile pemphigus (pemphigus aigu fébrile grave), pemphigus foliaceus, pemphigus vegetans and chronic pemphigus (or true pemphigus). He subdivides the last into two varieties, malignant chronic pemphigus (pemphigus chronique vrai grave), and benign chronic pemphigus (pemphigus chronique vrai bénin), thus admitting into this group the few cases of apparently true pemphigus which terminate in recovery.

We are not here concerned with pemphigus foliaceus or pemphigus vegetans.

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1. Brocq, L : Schème des éruptions bulleuses. Le pemphigus subaigu malin à bulles extensives et faits connexes, Ann. de dermat et syph. Series 5 7:449, 1918-1919. Pemphigus subaigu à bulles extensives, in Précis-Atlas de Pratique Dermatologique, Doin, Paris, 1921, P. 608. Brocq, Gougerot, Desaux et Rabreau : Pemphigus subaigu malin à bulles extensives, Bull. Soc. franç. de dermat. et syph., 1921, p. 2.

Acute febrile pemphigus is an apparently infectious disease characterized by a sudden onset and intense febrile reaction, an eruption consisting solely of serous or hemorrhagic bullae and by a fatal termination within one to three weeks, recovery being rare. It is seen almost entirely in butchers and in those who handle cadavers of animals. It is probably an acute infectious disease.

Chronic pemphigus is usually of insidious onset, is characterized by a widespread monomorphous bullous eruption which arises rapidly without evidence of inflammation of the skin, which is attended with little or no pain or pruritus, which affects the whole body and in which the bullae are reproduced in successive crops. The mucous membranes are frequently affected early in the disease. There is a fatal termination within a few months to a year, but there are frequently intermissions in the progress of the disease, with temporary improvement.

SUBACUTE MALIGNANT PEMPHIGUS

Brocq describes subacute malignant pemphigus as a syndrome presenting the general appearance of a severe infection without high temperature but with marked prostration of the patient who remains in bed without moving, immobilized by the severe pain which occurs on the surface of the excoriations whenever motion is attempted, speaking only with great difficulty on account of the lesions of the throat, of the soft palate, of all the buccal mucous membrane and that of the lips, lesions which are superficial but extremely painful.

In its evolution this syndrome is characterized by its frequent origin on the mucous membrane and in its objective appearance by the perfectly characteristic aspect of the cutaneous lesions which, on the site of the broken bullae, rapidly develop denuded, moist, sanguinolent surfaces which show no tendency to heal and which extend progressively to the edges with detachment of the horny layer of the skin.

This peripheral extension, simulating that of an extremely virulent impetigo, without tendency toward cicatrization in the center of the lesion, together with the gravity of the general condition in spite of only moderate fever and the suffering experienced by the patient, appear to him to establish a characteristic syndrome which gives this clinical picture an individual aspect, and which permits its immediate differentiation not only from dermatitis herpetiformis and dermatite polymorphe but also from all other bullous diseases. It also permits a bad prognosis. In the last twelve years Brocq has seen several such cases, six of them terminating in a relatively rapid death. There were two patients who either recovered or disappeared from observation greatly improved, but in these two cases the bleeding surfaces following the rupture of the bullae were not large, and the peripheral extension was slight.

Brocq's description of the syndrome just quoted is sufficiently detailed to obviate the necessity of summarizing the cases he reports.

We have recently had the opportunity of studying a patient who presented a typical picture of this syndrome.

History.—M. B., No. 78669, 69 years of age, was a widow born in Italy. She was admitted to the New Haven Hospital on Dec. 29, 1920, complaining of painful sores on her chest, abdomen and back. These had started six weeks



Fig. 1.—Early appearance of lesions.

before as small vesicles on her sides, back and neck, which had rapidly increased in size and number. She had had no previous illnesses of any consequence. She had had ten children, three of whom were alive and well, and seven had died between the ages of 5 months and 6 years.

Examination.—The physical examination revealed nothing of consequence except a slight soft systolic murmur at the aortic area and slightly sluggish pupils. She had no teeth. Blood examination on Dec. 30, 1920, showed hemoglobin 80 per cent, white blood corpuscles 22,600, polymorphonuclears 81 per

cent., small mononuclears 16 per cent., large mononuclears 3 per cent., eosinophils 0, basophils 0. A blood culture taken Dec. 31, 1920, showed no growth. A second culture taken Feb. 9, 1921, was also negative. Cultures from the bullae were not made because there was no possibility of obtaining uncontaminated material. The Wassermann reaction on Dec. 31, 1920, was negative with alcoholic antigen and + with cholesterinized antigen. The urine during her stay in the hospital was negative, except that an occasional specimen contained a faint trace of albumin. The temperature ranged between 98 and 102 F. and was usually about 100. Within the two weeks previous to her death it reached 103 once or twice. It was about 100 just before death.



Fig. 2.—Later appearance of lesions.

When the patient was admitted to the hospital her chest and back were covered with lesions varying in size from that of a silver dollar to that of the palm. These lesions were all covered with thick, partly dried, yellow crusts which had formed on the sites of previous bullae which had received no attention. Their appearance on the chest, where they were largest, resembled that of a severe neglected impetigo in a debilitated subject. On the back they more closely resembled the usual lesions of chronic pemphigus, as is shown in Figure 1. There were no lesions in the mouth. A few days after the crusts had been carefully removed the lesions presented smooth, red, moist denuded areas

which rapidly extended at the borders by elevation of the epidermis. There was slight inflammatory reaction at the edges. Only in a few lesions was there at any time any evidence of a tendency to heal, and the lesions increased in number and size and became confluent until nearly the whole of the chest and upper part of the back was denuded, as is shown in Figure 2. The appearance of the lesions was so like that of those in one of the cases reported by Brocq that his description may be quoted verbatim for our patient.

"There was a strikingly characteristic appearance of the bullae on the presternal region and about the middle of the back. These bullae, which had appeared several weeks before, had broken, leaving the corpus mucosum and the derma exposed as if a vesicatory had been applied, and far from showing any cicatrization, they were extending at their edges by detaching the epidermis which was raised at the periphery in large shreds. They thus formed large

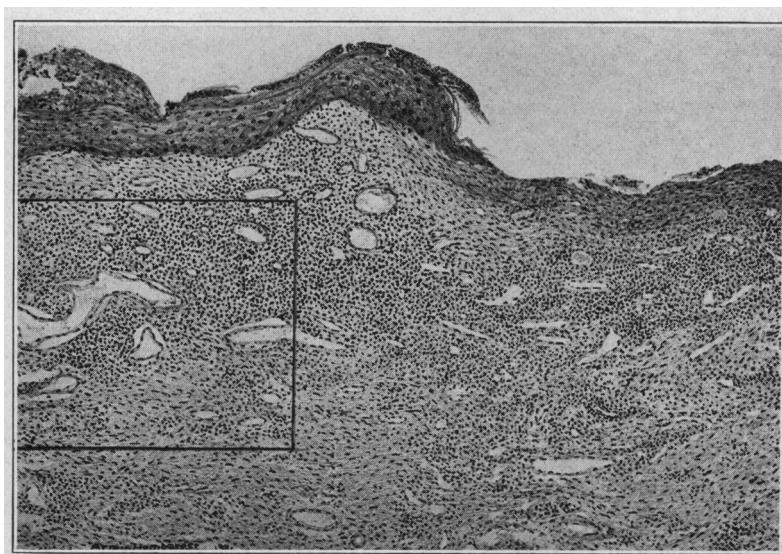


Fig. 3.—(Low power photomicrograph retouched). Margin and base of bleb, showing dilated vessels, diffuse cellular reaction and absence of regenerative activity on the part of the epidermis.

surfaces which, because of the confluence of several lesions, were irregular. The surfaces were raw, oozing, slightly hemorrhagic and very painful."

There were a few small lesions on the upper part of the arm. Except for these there were none on any part of the body except the trunk. The abdomen was not affected. A few days before death a few superficial, and not very painful lesions, appeared on the buccal mucous membrane.

Clinical Course.—During her stay in the hospital the patient continually complained of the painfulness of the lesions on the skin. She was at first not particularly prostrated. There was no marked change in her condition until three or four days before her death when the prostration became much more marked. On Feb. 24, 1921, there was a sudden profuse hemorrhage from the mouth, the source of which was never determined, and on Feb. 25, 1921, she died.

During the two months that she was under our observation various soothing applications were applied with no alleviation of the pain and with no effect on the lesions. Sodium cacodylate was given hypodermically for about two weeks with no effect.

The most striking clinical characteristics were: the extent and painfulness of the lesions, the absence of tendency toward healing, the localization on the trunk, the absence of lesions in the mouth till late in the disease, and the moderate amount of fever.

One of Brocq's patients had only a few lesions in the mouth. Perhaps the absence of teeth in our patient may have partially accounted for the lesions being so few.

No biopsy was made, but permission for a necropsy examination was obtained.

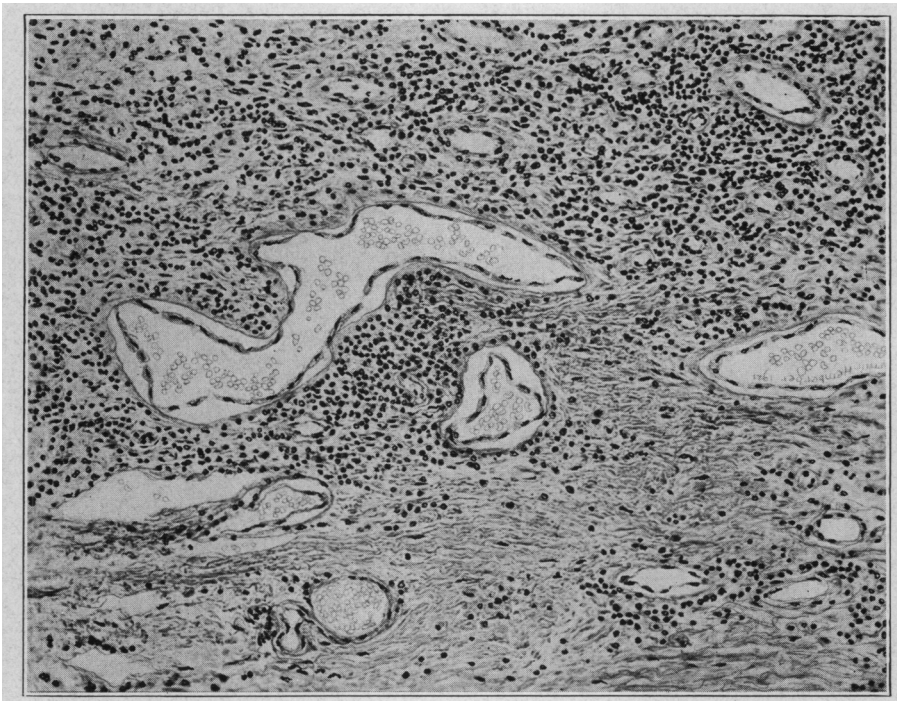


Fig. 4.—Higher magnification of an area in Figure 3. The prominent endothelial lining of the blood vessels and the mononuclear character of the infiltrating cells are well shown.

Necropsy Examination.—The skin lesions, which constituted the most striking gross feature, have already been fully described. It may be added, however, that in removing blocks of skin for histologic study, the superficial character of the lesions could be well demonstrated. The exfoliated tissue seemed to have included only the epidermis. This was clearly so in the case of the denuded patches on the anterior surfaces of the thorax and arms, on which the lesions were quite dry. The exposed derma here was bright red, but strikingly smooth and free from granulations. Over the back there was considerable seropurulent discharge from the raw surfaces and some undermining of the skin edges,

suggesting a more active secondary bacterial infection in the dependent and less protected regions.

The subcutaneous tissues and indeed the tissues in general were unusually dry, and there was little fluid in the stomach and intestines and practically no urine in the bladder (a condition referable no doubt to the painful mouth lesions and the resulting diminished fluid intake).

The gross changes in the thoracic and abdominal viscera were not striking or important, and may be briefly summarized:

There was a general atrophy of the organs of the senile type. The heart weighed only 225 gm. and its musculature was quite dark ("brown atrophy"). The liver and spleen were likewise abnormally small, the former weighing 1000, the latter 38 gm. The kidneys were slightly reduced in size and showed occasional arteriosclerotic scars and several small cysts. There was a moderate

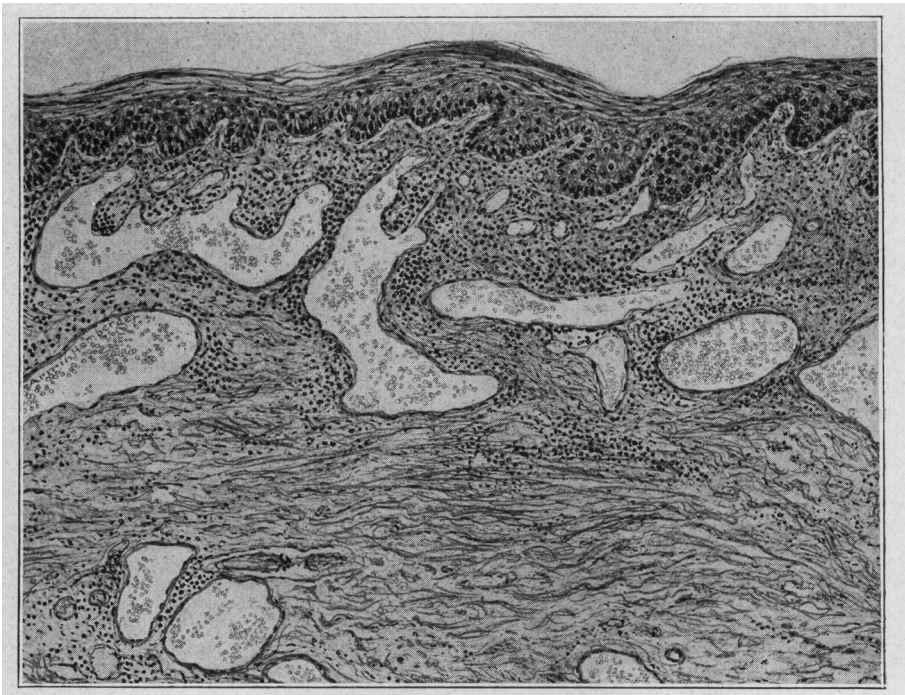


Fig. 5.—(Low power photomicrograph retouched). Intact skin in neighborhood of bleb. The vascular spaces in corium are even more prominent than in the exfoliated areas, but the cellular reaction is less marked. Note the narrow pale fatty zone just beneath the epidermis.

generalized arteriosclerosis. The most marked changes were seen in the respiratory tract. The mucosa of the larynx, trachea and bronchi was reddened and, in the trachea particularly, it had lost its normal lustrous translucency and was quite opaque. There was throughout more or less mucopurulent exudate. Scattered through the lungs were small firm, red patches, the picture of an early hemorrhagic bronchopneumonia.

Microscopically, the only noteworthy findings were in the skin and upper respiratory tract. Skin: A number of sections, including the exfoliative lesions

on the thorax, arms, thigh and adjacent normal looking skin, showed practically the same picture. The most striking feature was the presence of numerous dilated, thin walled blood vessels throughout the corium. These vascular spaces were seen not only in the areas in which the epidermis was lost, that is, the base of the blebs, but extended for considerable distances marginally beneath an intact and apparently only slightly altered epidermis. The size and frequency of these dilated vessels and their relation to the epidermis are well shown in Figures 3 and 5. In places the dilatation was even more marked than these illustrations show.

The endothelial lining of these blood spaces was quite prominent (Fig. 4), so much so that some of the smaller vessels resembled epithelial-lined ducts.



Fig. 6.—(High power drawing). Perivascular infiltration in deeper zone of corium. The cells here as elsewhere are mostly of the plasma cell type.

Fresh fluid blood filled practically all of the spaces. In a few of these just beneath the denuded surface, there was a homogeneous pink staining coagulum, but no definite thrombi were demonstrable.

The second significant feature of the cutaneous lesions was the cellular reaction. There was everywhere more or less round cell infiltration. The cells showed a tendency to a definite perivascular grouping, but in the base of the blebs they were scattered diffusely. The cells varied in type, but the dominant cell was of the plasma cell type (Fig. 6) having a fairly dense round nucleus, somewhat eccentrically placed, and a relatively large amount of deeply staining cytoplasm (hematoxylin—eosin preparation). There were a few small lymphocytes and a considerable number of the mononuclear cells of a rather

indifferent type, with vesicular nuclei and irregular pale-staining cytoplasm. No polymorphonuclear leukocytes were seen except in the detritus forming the base of the bleb, and they were scarce even here. Eosinophils, which are rather regularly present in both acute and chronic pemphigus, were rarely seen. There were indeed a few large mononuclear cells which showed a distinct acidophilic and more or less granular cytoplasm, but these were apparently large mononuclear phagocytes which had engulfed red blood cells, and not true eosinophils.

Changes in the connective tissue of the corium were not pronounced. There was relatively slight edema, no evidence of degeneration, and very little proliferative reaction. Fibroblasts were seen here and there, mostly near the denuded surface, but there was not such active proliferation as is commonly associated with ordinary bacterial or chemical injuries of the skin of similar grade, and

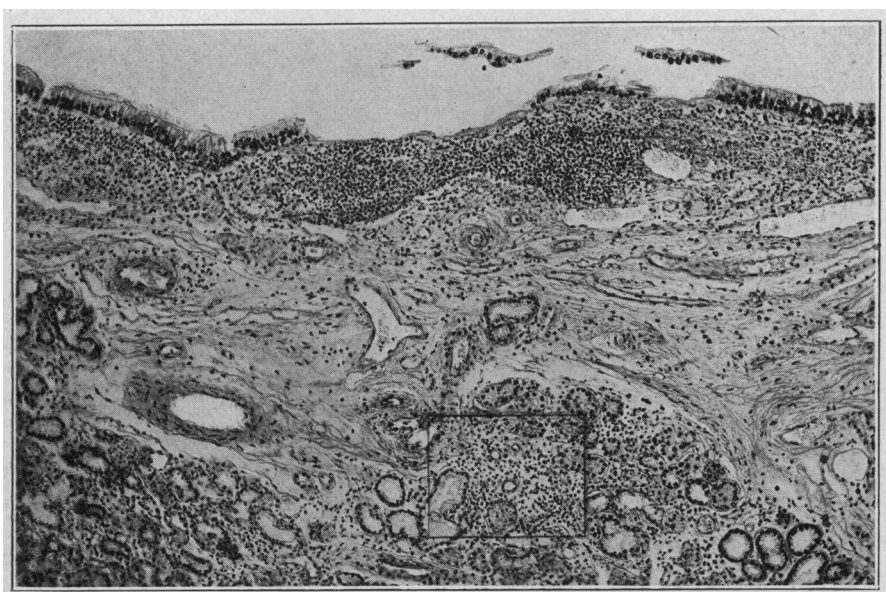


Fig. 7.—(Low power photomicrograph, retouched). Acute and subacute inflammatory reaction in trachea. Mucosa is partially exfoliated with an exudate of polymorphonuclear leukocytes, serum and red blood cells in the superficial zone. Changes in the deeper zone are shown in Figure 8.

there were no budding capillaries. In other words, a true granulation tissue was absent.

The changes in the epidermis were variable. At the margin of the bullae the epidermal layer ended rather abruptly. In some places the free edge was lifted up for a short distance by what was obviously fluid accumulation. There was little evidence of epithelial proliferation. Except near the margins of the blebs, the epithelium showed only moderate degenerative changes, swelling and vacuolization. In general, regressive changes were more marked in the lower layer of the rete mucosum. There was no vesicle formation within the epidermis itself and no cellular infiltration except at the bleb margin.

The papillae were in general flattened and just beneath the basal layer of the rete there was a narrow but well marked fatty reticular zone (Fig. 5). It

seemed possible that this change in the uppermost portion of the corium might represent the first stage of bleb formation, though this is not clear. The epidermis in general was thin, in places only four or five cells thick. This was no doubt a part of the senile atrophy of the tissues and was probably not related to the existing disease.

There was little or no reaction about the sudoriferous glands and the occasional hair follicles, and the nerve bundles were apparently everywhere uninvolved.

Respiratory Tract: Sections of the trachea and bronchi showed evidence of both an acute and a subacute or chronic inflammatory process (Fig. 7). Here and there the epithelial lining was lifted up by serum, and in places there was widespread desquamation. Bacterial stains showed numerous gram-positive

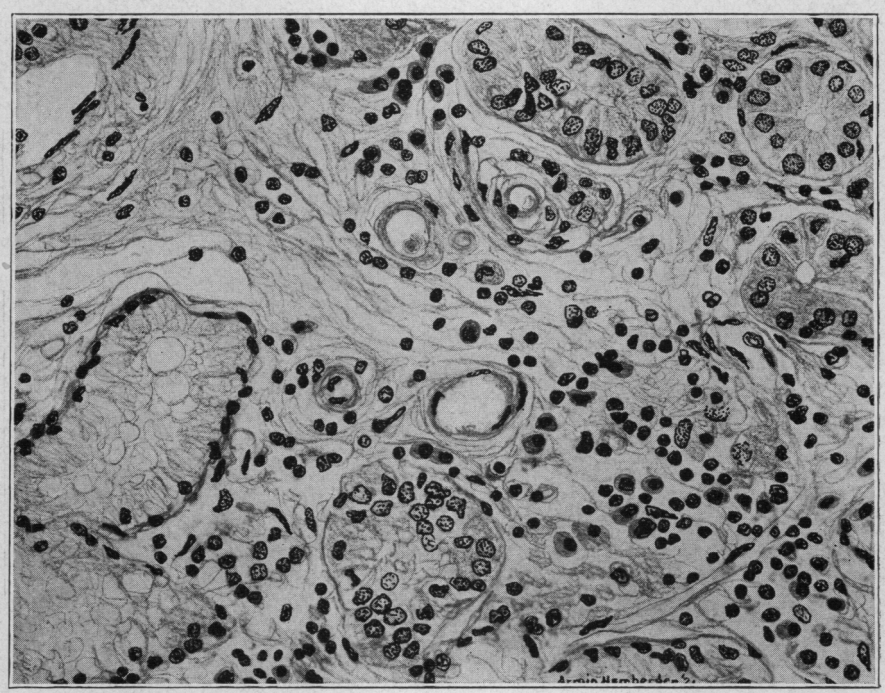


Fig. 8.—Higher magnification of an area in Figure 7 showing edema and mononuclear reaction about the mucous glands. Many of the cells are of the same type as those in the cutaneous lesions.

cocci entangled in the cilia and scattered through the submucosa. Polymorphonuclear leukocytes, fibrin and red blood cells constituted the exudate along the surface and in the superficial layer of the submucosa. In the depths of the submucosa, especially about the mucous glands, there was an infiltration by mononuclear cells, mostly of the plasma cell and lymphocyte types, and edema (Fig. 8). Connective tissue proliferation was slight. This combination of acute and subacute reaction obtained throughout the bronchial tree. In the lungs, there was about the smaller bronchi a patchy exudate into the alveoli, consisting chiefly of red blood cells and polymorphonuclear leukocytes, obviously a terminal process.

DISCUSSION

The histologic picture of the cutaneous lesions in this case correspond in general to that of chronic pemphigus as described by previous investigators.²

It is noteworthy, however, that eosinophils, the presence of which many workers have emphasized, were relatively rare in the sections from our case and that there was no increase of these cells in the blood. Plasma cells, on the contrary, constituted a prominent feature of the cellular reaction.

The widespread lesions in the respiratory tract, pharynx, larynx, trachea and bronchi, we have interpreted as a part of the pemphigus. While there is clearly present an acute bacterial infection—as evidenced by gram-positive cocci in the mucosa—and an acute inflammatory reaction, this is obviously superimposed on a subacute or chronic inflammatory process. The microscopic changes in the submucosa of the trachea and bronchi simulate closely those in the skin and leave little doubt as to their relationship. Pemphigus of the respiratory tract, generally but not always associated with cutaneous lesions, has been described by several investigators,³ but in most cases the changes have not been carefully studied histologically.

While there may have been no previous attempt to separate such cases as Brocq describes into a distinct group, it is probable that most dermatologists of large experience have encountered cases which did not conform to the usual type of chronic pemphigus and which may properly be placed in this group. In this country such cases have usually been grouped under pemphigus vulgaris (chronic or true pemphigus), and have frequently been designated as malignant.

A case of this type, which showed a slight tendency to vegetations in some of the lesions, was reported in 1905 by Ormsby and Bassoe,⁴ who also refer to similar cases. At that time the question was raised as to whether the case should be classed as pemphigus vegetans. Later, in his textbook, Ormsby placed this case under pemphigus vulgaris, remarking:

That certain examples of pemphigus belonging to this group are acute in nature seems to be a fact. A number of cases have been under observation during the past few years. One of these was reported conjointly by the author

2. Spiegler in Mracek: *Handbuch der Hautkrankheiten* 2:23, 1905. Ehrmann und Fick: *Kompendium der Speciellen Histopathologie der Haut*, Wien 1906, p. 13.

3. Trautmann: *Die Krankheiten der Mundhöhle und der oberen Luftwege bei Dermatosen*, Wiesbaden, 1911.

4. Ormsby and Bassoe: A Case of Acute Malignant Pemphigus (P. vegetans?) with Autopsy Report, *J. Cutan. Dis.* 23:294, 1905.

with Dr. Peter Bassoe. In this case the lesions originated in the mouth and the disease proved fatal in two months. Extensive cutaneous involvement occurred with the formation of bullae and severe extensive erosions of the skin. There was practically no attempt at healing in any of the denuded areas. This history could be repeated many times by patients seen during the last few years.⁵

Brocq's articles, by calling attention to this syndrome, may lead to a detailed study of a larger number of cases, which may possibly bring about a more definite conclusion in regard to these cases, though we can expect little information from the study of the histopathology and bacteriology. In one of Brocq's cases there was a growth of a mixture of staphylococci, streptococci, diplococci and bacilli, which he attributes, no doubt correctly, to a contamination from the surface of the body.

Brocq does not pretend to fix this syndrome definitely as a new clinical entity. He simply notes that the appearance and evolution of the syndrome which he sketches seems to be quite characteristic, and inquires whether this syndrome is always a primary condition or whether it may not be sometimes a syndrome which may be grafted on another bullous dermatosis, especially on a dermatitis herpetiformis, dermatite polymorphe or a chronic pemphigus. Among several cases reported, he cites one which tends to support the latter view. And in one patient, an 18 months old child, he questions whether the syndrome was not a variety of impetigo similar to pemphigus neonatorum.

Until some fruitful researches have thrown some light on the etiology and pathogenesis of pemphigus it may be idle to speculate on the place of this group of cases in the general scheme. At present, however, in their clinical characteristics they appear to us to be more closely related to chronic pemphigus and to acute febrile pemphigus.

5. Ormsby, O. S.: Diseases of the Skin, Ed. 2, 1921, p. 375.