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PUSTULAR PSORIASIS ELICITED BY STREPTOCOCCAL ANTIGEN AND LOCALIZED TO THE SWEAT PORE

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A woman, aged 39 years, presented with a localized, painful, pustular eruption of the neck, scalp, and finger of five years' duration. A diagnosis of pustular psoriasis was made clinically and histologically.

It was possible to reproduce the disease by the intradermal injection of killed Group A streptococcal organisms. The induced pustules, as well as those appearing clinically, were intraepidermal and indistinguishable from the Kogoj spongiform abscess, and on serial sectioning showed a distinctive localization to the acryosyringium. Immunosuppressant as well as antistreptoccocal therapy in the form of cyclophosphamide and clindamycin was of help.

The process is classified as a nonvasculitic pustular bacterid, and as a prototype for antigen localization of lesions to the occluded epidermal sweat duct unit.

Pustular psoriasis is emerging as a reaction pattern in which diverse agents may initiate or elicit acute attacks. Thus, salicylates, progesterone, iodides [1,2], coal tar [3], and most recently phenylbutazone* have each proved by oral challenge or patch testing to be responsible for specific attacks. Less convincingly, upper respiratory tract infections and the hormonal changes of pregnancy also have been incriminated as causing pustular psoriasis [4]. Nonetheless, there is usually no discernible cause for pustular psoriasis, be it generalized or localized.

The present report discloses yet another causal factor for pustular psoriasis—hypersensitivity to streptococcal antigen. Furthermore, it details the remarkable histologic localization of the pustules to the intraepidermal terminal sweat duct in both the clinical and experimental expression of the disease.

CASE REPORT

For the past five years this 39-year old woman has had an exquisitely painful pustular and inflammatory eruption of the terminal phalanx of the right fifth finger (Fig. 1). Diagnosed as acrodermatitis continua of Hallopeau, the disease proved recalcitrant to care. Topical therapy included agents varying from antiinfectives to high potency steroids. She had also been given steroids, gamma globulin, and vitamins A and E systemically, as well as irradiation locally. Avulsion of the nail was likewise without effect. For three years a similar pustular eruption had been present in sharply circumscribed erythematous plaques on both sides of the base of the neck (Fig. 2) as well as on the entire right side of the scalp, including the helix of the ear. The pustules were generally small, closely set, studding the affected area, but lakes of pus could also be seen at sites of coalescence. In the scalp the pustular element, although clearly evident, was less prominent than crusting, flaky scaling, and erythema. No interference with hair growth has been noted. The process gradually extended to cover a broad band (Fig. 3). A subjacent lymph node could be palpated on the right side. At no time has there been spontaneous involution. Flares seemed to be associated with delays in the onset of the menses. Infrequently there was gluteal cleft inflammatory change and a few pustules noted in the perianal area. Patterned erythematous changes were also noted occasionally on the tongue in association with febrile episodes.

The patient described having had an inflammatory process of the umbilicus secondary to a draining cyst nine years previously. This was cured by total excision of the umbilicus. Additional history of possible relevance included penicillin hypersensitivity and a uterine suspension (18 years previous), normal lymph node biopsy (12 years previous), operative repair of a herniated disc (5 years previous), and surgical removal of renal calculus (1 year previous). Her relevant family history was limited to the fact that her father had had an unidentified eruption of the groin at one time.

The observations which follow are a summary of the hospital studies and a year of office care. Despite the occasional isolation of *Staphylococcus epidermidis*, the pustules were repeatedly found to be sterile, on aerobic and anaerobic cultures. Likewise, KOH examination revealed no hyphae or spores, and fungal cultures showed no growth of pathogens. Gram and also Giemsa stains of pus smears showed numerous polymorphonuclear leukocytes and debris. Phase microscopy of the diluted pus revealed many polymorphonuclear cells, but only a sparse number of free-floating bacteria-like bodies. Leukocyte clot imprints of circulating blood [5] showed no bacteria within the polymorphonuclear cells, but an

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*One of us (WBS) has observed a psoriatic patient who experienced three distinct severe attacks of generalized pustular psoriasis, each appearing shortly after the administration of phenylbutazone.

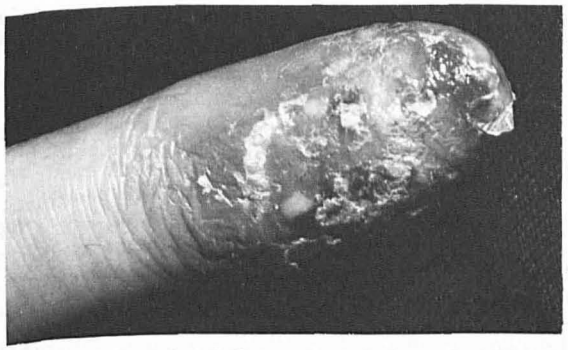

FIG. 1. Pustular inflammatory lesion of right fifth finger of 5 years' duration.

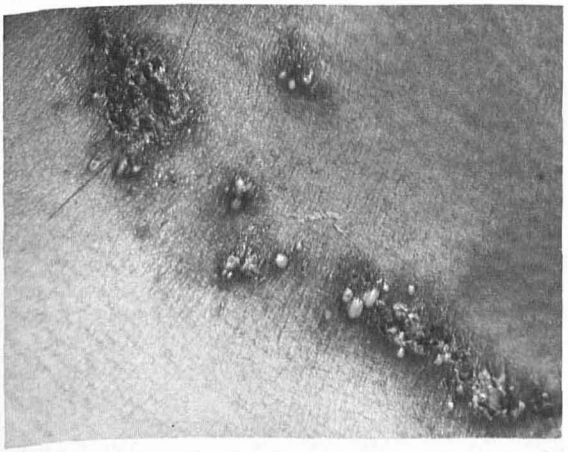

FIG. 2. Right side of neck, early lesion. Note sharply circumscribed erythematous plaque studded with closely set pustules.

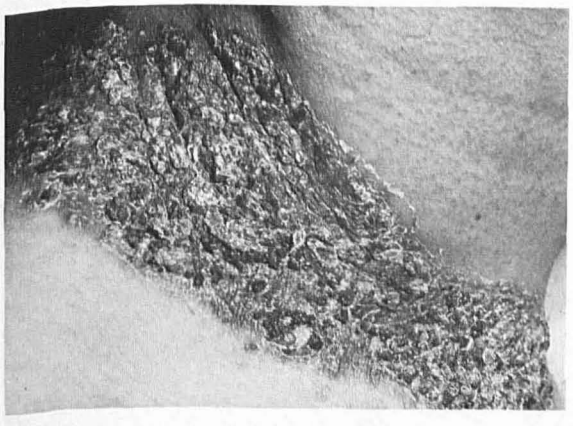

FIG. 3. Right side of neck six months later. Note scaly, crusted, deeply infiltrative lesion after pustule debridement. A few pustules can be seen at periphery of lesion.

NBT test [6] showed 35% of the leukocytes with formazan granules (normal 1–10%). Following 3 weeks of clindamycin therapy the NBT test value dropped to 20%.

Microscopic examination of skin from the scalp, finger, and neck lesions showed an edematous thickened epidermis with typical spongiform pustules of Kogoj and a dense infiltrate composed almost entirely of polymorphonuclear leukocytes involving the papillary dermis (Fig. 4). In the specimen from the neck, the infiltrate extended deeply to involve the upper third of the dermis and a few leukocytes were seen extending along the sweat ducts and scattered in the sweat gland areas. On serial sections, the pustules were found to localize in the epidermis surrounding the terminal portion of the sweat duct, producing a funnel shape with the distal widest portion in the subcorneal area and the stem formed by the dermal sweat duct (Fig. 5). Edema and widely dilated vessels were prominent in the papillary and subepidermal areas. There was no evidence of vasculitis.

Psoriasiform features were prominent in the specimen from the scalp (Fig. 6). In addition to Kogoj pustules, the scale was densely parakeratotic, the rete ridges were elongated and there was thinning of some of the suprapapillary epidermis. The papillary vessels were dilated and numerous polymorphonuclear leukocytes were present in the papillary process. Lymphocytes and a few plasma cells were also identified.

Normal or negative results: physical examination, x-rays of finger and chest, EKG, CBC, basophil count, urinalysis, STS, SMA-12, serum protein electrophoresis, antistreptolysin titer, LE test, cholecystogram, IVP, liver biopsy.

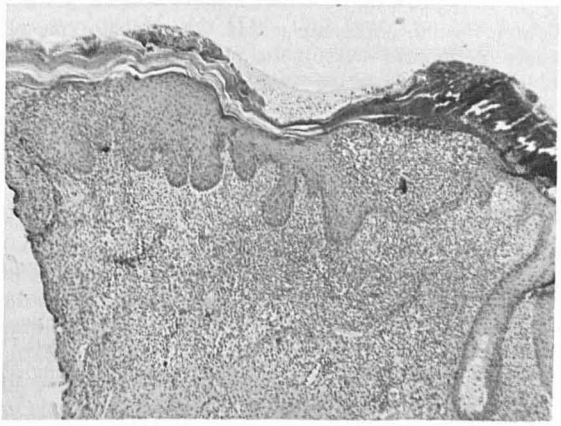

FIG. 4. Neck lesion. Note large intraepidermal spongiform pustules and dense, deeply extending infiltrate of polymorphonuclear leukocytes (H & E, × 30).

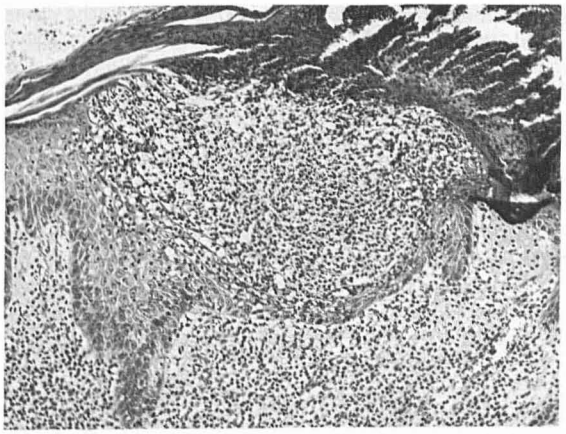

FIG. 5. Detail of spongiform pustule (Kogoj) in lesion from neck. Note probable sweat duct entering base of pustule (H & E, × 70).

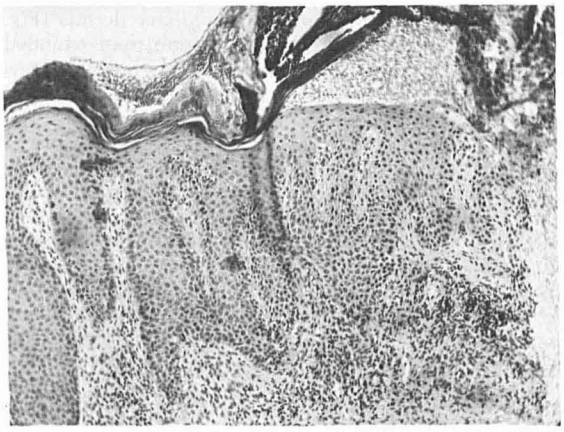

FIG. 6. Scalp lesion. Note psoriasiform epidermal contour, parakeratosis, spongiform pustule and polymorphonuclear leukocytes in the papillary dermis (H & E, × 46).

An x-ray of the lower spine showed a few drops of Pantopaque (iophendylate) remaining in the spinal canal from a prior myelogram. About 20 opaque surgical clips were seen anterior to the body of L 5 and the upper portion of the sacrum.

Patch tests to potassium iodide, iophendylate, nickel sulfate, potassium dichromate, and silver nitrate were negative. Gynecologic examination disclosed the presence of vaginal candidiasis.

Intradermal skin testing produced a local pustular and painful inflammatory reaction only at the site of injection of 0.02 ml. of streptococcal pyogenes antigen (2,000 million organisms/ml, Thimerosal-killed, Hollister Stier, Yeadon, Pennsylvania). This was associated with a fever of 101.0°, malaise, arthralgia of the knees and toes, as well as pharyngeal pain and dysphagia. Cultures of the throat at that time showed a normal flora of Neisseria and alpha Streptococci. By the following day her temperature had returned to normal and the symptoms abated. Subsequent repeated injections showed no lessening of the local reaction.

A biopsy of a streptococcal skin test pustule taken at 48 hr showed severe subepidermal edema with bulla formation (Fig. 7), overlying a massive dermal infiltrate of polymorphonuclear leukocytes. Most remarkable was the dense infiltrate of polymorphonuclear leukocytes ensheathing the sweat ducts and extending into the sweat gland acini (Fig. 8). In the epidermis, multiple small pustules were found which histologically duplicated the Kogoj pustules in the patient's neck and scalp lesions. On serial section spongiform pustules could be spatially related to the terminal intraepidermal sweat duct unit.

A grossly inflammatory but nonpustular reaction developed at the site of the *Streptococcus viridans* antigen injection. None of 9 other commercially prepared bacterial antigens (1,000 million organisms/cc, Thimerosal-killed, Hollister Stier, Yeadon, Pennsylvania) produced an unusual local inflammatory response: *Streptococcus fecalis*, *Staph. aureus*, *Staph. albus*, *Neisseria catarrhalis*, Pneumococcus, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Escherichia coli*, Klebsiella. The patient did not react to the commercial antigens, Epidermophyton, Trichophyton, and *Monilia albicans*.

From the standpoint of topical therapy, creams (chloramphenicol, iodochlorhydroxyquin, nystatin, neomycin, corticosteroid) were poorly tolerated and the lesions were invariably made worse by any type of compress (Burow's, permanganate, silver nitrate, urea). Applications of ammoniated mercury, ichthammol in zinc oxide paste, Castellani paint, as well as nitrogen mustard (10 mg/40 ml) were without effect. Steroids in petrolatum base proved soothing at least. The patient regularly drained and debrided the superficial pustules to get relief from the pain.

Orally, diphenhydramine, cyproheptadine HCl, acetylsalicylic acid, indomethacin, and hydroxyzine HCl were without effect and demerol was required at times for the control of pain. Therapy of the vaginal candidiasis with oral nystatin and candicidin intravaginally was without effect on the course of the skin lesions. Tetracycline, minocycline and avlosulfone had no discernible effect. Nor did oral prednisone or an injection of triamcinolone acetonide (40 mg intramuscularly) greatly influence the process.

Hydroxyurea in a dosage of 1.5 gm a day was of limited benefit in suppressing new lesions, but after weeks of therapy its effectiveness was lost. More dramatically, cyclophosphamide (50 mg/day orally) produced 99% clearing of the pustular element within a week. However,

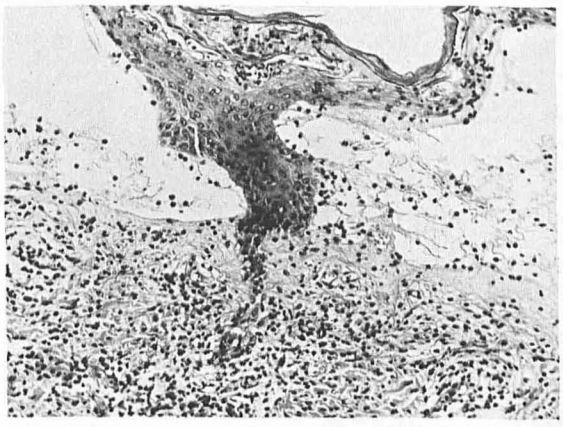

FIG. 7. Streptococcal skin test site. Note subepidermal edema, and early bulla formation. The sweat ostium, acrosyringium and portions of dermal sweat duct with lumen can be distinguished. Aggregations of polymorphonuclear leukocytes are seen in the sweat ostium (H & E, × 92).

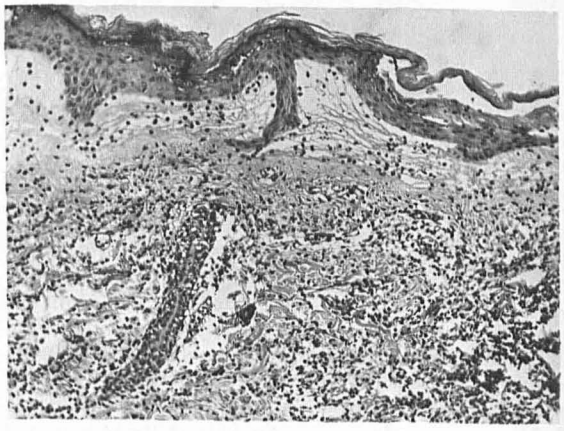

FIG. 8. Streptococcal skin test site. Note the polymorphonuclear leukocytes surrounding and infiltrating the sweat duct (H & E, × 70).

after a month of therapy the painful pustules reappeared. The lesions have been well controlled by oral clindamycin (150 mg q.i.d.).

DISCUSSION

This patient's problem, rare as it is, admits an unusual degree of diagnostic synonymy. Thus, the diagnosis may reflect the style of the times. Today, it is fashionable to view all sterile pustular eruptions as manifestations of psoriasis [7], hence our title of *pustular psoriasis*. Anyone of French provenance might be more comfortable with the label of *acrodermatitis continua of Hallopeau*, so especially appropriate for describing the initial lesion on the fingertip (Fig. 1). Acrodermatitis is a condition not limited to the fingers and toes, having been recorded elsewhere, and in particular on the scalp [8]. Those who would interpret our observation that skin testing with streptococcal antigen reproduces the disease, would surely favor a diagnosis of *pustular bacterid*. Yet this is to be distinguished from the acute generalized pustular bacterid recently described by Tan [7]. Our patient has a chronic localized pustular bacterid and does not show the leukocytoclastic vasculitis found in Tan's patient. Nor does our patient present the patterning of Andrew's pustular bacterid classically limited to the palms and soles [9]. Finally the more circumspect and reserved the diagnostician, the more likely he would give our patient a nonentangling diagnosis of chronic pustular plaques of the finger, neck, and scalp.

In contrast to the story of synonymy, our clinical, histologic, and laboratory studies as well as skin tests and therapeutic trials ruled out a wide variety of diagnoses [10], including, local bacterial, fungal, or yeast infection; subcorneal pustular dermatosis; primary irritancy or factitial reactions such as from pyogallic acid or ammonium fluoride; pellagra (necklace of Casal); pustular mycosis fungoides; familial benign chronic pemphigus; Sweet's neutrophilic dermatosis; pustular erythema multiforme; pustular drug rash; pustular necrotizing angiitis; pustular monilid or tuberculid; pyodermite vegetans; pemphigus vegetans; dermatitis herpetiformis; dermatitis repens; and, as mentioned before, vasculitic pustular bacterid.

Perhaps the most interesting findings in this patient's problem related to the polymorphonuclear leukocyte. Here was the cell responsible for the clinical lesion itself. What drew it to the upper epidermis where it produced the sterile spongiform pustules of Kogoj? Were we but dealing with a magnified example of the factor in ordinary psoriasis that attracts the leukocyte to the upper epidermis where it produces the microabscess of Munro?

Histologically, it was possible by serially sectioning to find that the focal point for early pustule formation was indeed the epidermal sweat duct unit. The primary lesion of generalized pustular psoriasis has previously been shown to be similar to pustular miliaria [11], but the precise localization has just been discerned and recorded by Neumann and Hard [12]. In both pustular and regular psoriasis they found that the primary lesion arises at the acrosyringium. We can confirm that the leukocytes swarm to the terminal sweat duct. Although the sweat unit as a site of attraction for the leukocyte could be thus recognized in our patient, the attractive force itself remained obscure. We postulated that an unidentified invisible antigen was secreted by the sweat gland, and that this in turn escaped into the periductal epidermis as a result of sweat retention, sequential to the poral occlusion anhidrosis so typically seen in the psoriatic plaque [13].

Extensive exploration of bacterial antigens as the possible attractant for the leukocyte revealed that indeed this patient did have an unusual exquisite sensitivity to killed streptococci. It was far more than the banal tuberculin type delayed response recorded by Andrews and Machacek [9] in studying their patients with pustular eruptions of the palms and soles. It was a sensitivity limited to streptococci and one which manifested itself as a persistent pustule with an intradermal challenge of as little as 0.02 ml and resembled that described by Landry and Muller [14]. This is in contrast to the gross nonspecific pustular reactions which have been described following multiple bacterial antigen skin testing of patients with generalized pustular psoriasis [15].

Ten normal control patients showed no reaction or a local erythema and edema to the same skin test. Significantly, in 2 of 10 patients with psoriasis vulgaris this antigen (*Streptococcus pyogenes*, 2000 million organisms/ml) in a dose of 0.02 ml. produced typical local scaling and a psoriatic papule approximately 10 days after intradermal injection. The other 8 patients showed no reaction or the same inflammatory response as seen in normal controls. Thus, the streptococcal antigen, and only this antigen, specifically reproduced the lesion seen clinically not only in our patient but in 2 of 10 patients with psoriasis vulgaris.

Most remarkable was the fact that serial histologic study of one of the lesions induced in our patient by skin testing with *Streptococcus pyogenes* revealed the selective localization of the leukocytes, not only along the sweat duct in the dermis, but also in an abscess localized to the epidermal sweat duct unit area (Fig. 9), possibly flowing along lines of microdissection. Thus the antigen test appeared to completely duplicate the clinical event even to the severe pain which must reflect the destructive effect of the polymorphonuclear leukocytes on the larger cutaneous sensory nerves in the dermis. Our patient appears to present a new example of the poststreptococcal diseases, so well delineated by others [16].

Possible sources for a beta hemolytic streptococci antigen in our patient include the skin, the nasopharynx, or even the abdomen where occult infection may have developed about the retained

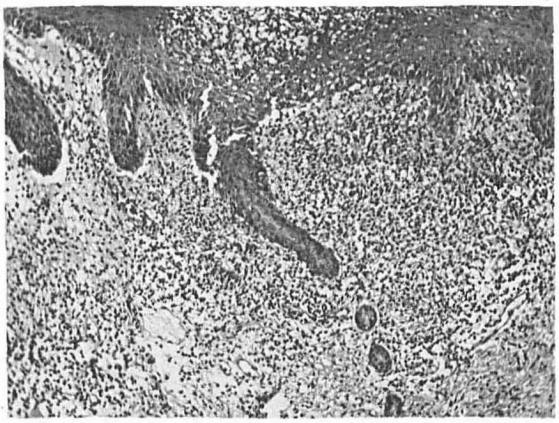

FIG. 9. Streptococcal skin test site at periphery of bulla. Note spongiform pustule replicating those of patient's spontaneous clinical lesions (see Fig. 5). Sweat duct is entering the base of the funnel-shaped lesion. Note aggregations of polymorphonuclear leukocytes about the duct as it passes into the epidermis (H & E, × 75).

silver clips. The skin as well as the nasopharynx may harbor transient A streptococci. Certainly the throat can be incriminated as a source of antigen in patients developing generalized guttate psoriasis 10 to 14 days after severe streptococcal pharyngitis [17]. Furthermore, the gastrointestinal tract needs closer surveillance as an absorptive source of bacterial antigens, inasmuch as the liver shows "pustules" in generalized pustular psoriasis [1]. Furthermore, 3 patients with sterile pustular eruptions of the palms and soles showed permanent clearing after jejuno-ileostomy for obesity [18]. The kidney, a known site of calculus formation in this patient, is an additional suspect. The subject of antigen source is indeed rendered even more complex by the fact that the glycoproteins of skin cross-react with streptococcus A polysaccharide antigens [19]. Possibly the continuing source of antigen could be the very mucopolysaccharide secreted by the sweat gland itself, which escapes abnormally into the upper epidermis when free poral egress is denied. However, the elevated NBT test value and the clinical as well as the NBT response to streptococcal antibiotic therapy favor the presence of a circulating bacterial antigen as being responsible in this patient.

The gross localization of the lesions is as deserving of comment as was the microlocalization. The process was not widespread but rather remained restricted to areas of common injury, such as we see on the neck in pellagra (necklace of Casal), or in Hailey–Hailey disease. The presence of pustular psoriasis on the scalp is unusual but has been reported previously [20]. Interestingly, the lesions themselves seemed to serve as a self-perpetuating force, possibly acting as a "sink" for the clearance of circulating antigens which might otherwise reach a critical level and initiate a new lesion at another injury site.

The role of the retained Pantopaque (iophendylate) in the spinal canal remains unclear. Truly the Pantopaque was a continuous source of trace amounts of iodine to this patient since serial x-rays demonstrated its gradual disappearance. Nonetheless, patch tests to iodides were negative, and dapsone therapy of proven value in some instances of pustular psoriasis [21] was without effect in our patient. Yet, in light of the proven adverse effect of iodides on pustular psoriasis, and the intolerance of the iodochlorhydroxyquin cream, this internal source of iodides must be viewed as a possibly significant factor.

On the basis of a recommendation by Dr. J. A. Philpott, Jr. we have found indomethacin (25 mg t.i.d.) remarkably effective in suppressing the inflammatory element of generalized pustular psoriasis of van Zumbusch in 2 patients. Yet in this patient as well as another with pustular psoriasis of the palms and soles, it, as well as hydroxyurea (0.5 gm t.i.d.), was without much effect [22,23]. In contrast, cyclophosphamide (50 mg/day) temporarily suppressed the swarming of leukocytes into the epidermis, leading to complete involution of lesions, much as observed with nitrogen mustard inhibition of the pustular reaction to tick bites in dogs [24]. Presumably, methotrexate would have been equally valuable. The most consistent therapeutic results have come from intensive attack on the presumed antigen, i.e., antistreptococcal therapy with clindamycin. Interestingly, one might surmise that the antibiotic reduced circulating bacterial antigens since the NBT test value dropped from 35% to 20% during 3 weeks of such therapy. Possibly, however, resistant strains will emerge and, in time, clinical relapse will occur as the antigen level increases.

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