What's New in Clinical Research

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Therapeutic Parameters of the Goeckerman Regimen. Mark J. LeVine, M.D., and John A. Parrish, M.D. Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

Thirty patients with chronic stable plaque psoriasis vulgaris were studied to determine the relative effectiveness of the components of the Goeckerman regimen. We carefully adhered to the bilateral comparison technique. All patients were hospitalized for no longer than 4 weeks and evaluated daily regarding scale, induration and erythema. All received daily total body UVB except for 2 bilaterally paired 4 cm x 4 cm control patches. Prior to the initiation of therapy, each patient was tested on non-sun-exposed areas for an MED and many for an MPD to the substances used in their therapy. Fifteen patients were separated into 3 groups receiving the following topical medications to one entire side: (a) 5% crude coal tar (CCT) + base vs base alone, (b) base alone vs no topical therapy, (c) 5% CCT vs no topical therapy. The initial UV dose was 80% of the MED and the daily increments were 20% of the previous dose as tolerated. Another 15 patients were evaluated to determine whether the response varied with the choice of base (lubricator) or tar preparation. Our results were: (1) UVB without any topical therapy was beneficial to all but never completely cleared any patient; (2) The response to the various coal tar preparations was identical; (3) The clinical response to UVB + base was similar to UVB + base + 5% CCT, therefore, we conclude that: (1) Maximal aggressively UVB therapy in a hospitalized population will improve psoriasis, but, unless combined with 5% CCT or a lubricator, will not clear psoriasis vulgaris within 4 weeks; (2) There is no difference in clinical response between 5% CCT, 5% LCD, and Estar; (3) The 5% CCT we used offered no clear advantage or benefit over the use of UVB + base.


We have previously reported that the erythema produced by u.v.B (297 nm) and u.v.C (254 nm) irradiation of human skin is associated with increased concentrations of arachidonic acid and prostaglandins E₂ and F₂α (Black, Greaves, Hensby & Plummer, 1977; Camp, Greaves, Hensby, Plummer & Warin, 1978). Sixty sq cm of clinically normal skin of patients with psoriasis were irradiated with 3 times the minimum erythema dose of u.v.A (305 nm). 2 hr after oral 8-methoxy-psoralen administration (0.6 mg kg⁻¹ body weight), using a Philips TL 20W/09 lamp placed at a distance of 2.5 cm from the skin. Exudate was obtained from irradiated and non-irradiated skin using a suction bulae technique (Black, Greaves, Hensby & Plummer, 1976) at 24, 48 and 72 hr after irradiation. Exudate was also obtained from normal non-irradiated skin of healthy volunteers.

The exudates were examined for PGF₂ by radioimmunoassay and for arachidonic acid and PG₂E₃ by gas-liquid chromatography-mass spectrometry. The concentrations of PG₂E₃ and PGF₂α did not differ significantly in erythematous and non-irradiated skin nor in normal skin of healthy non-psoriatic volunteers. Arachidonic acid concentrations, likewise, were not significantly different in irradiated and non-irradiated skin, although they were significantly greater than in normal healthy skin.

These results suggest that, unlike u.v.B and u.v.C-induced erythema, u.v.A (combined with oral psoralsen) -induced erythema is not associated with elevated prostaglandin concentrations. Whether the elevated concentrations of arachidonic acid in unirradiated skin of patients with psoriasis is of significance in the pathogenesis of psoriasis requires further study.

Porphyria Turcica: (Hexachlorobenzene) Intoxication 20 Years After. D. J. Cripps, M.D., H. A. Peters, M.D., and A. Gocmen, M.D. The University of Wisconsin, Dept. of Medicine, Div. of Dermatology, 1300 University Avenue, Madison, Wisconsin.

Porphyria occurred in Eastern Turkey in 1856 until 1960 involving more than 4000 persons due to ingestion of hexachlorobenzene (HCB) a fungicide added to wheat seedling. Many children under 2 yr died with weakness, convulsions and toxic erythema—Pembe Yara. This study involved a site visit which included clinical examination of 32 porphyrin Turks, mean age 29.5 yr, 19F and 13M. Porphyrins were determined on urine and stool; on 29 porphyrins and controls, 10 Turks and 40 USA (Cripps, Wis Med J 73:104, 1974). HCB determinations in serum, fat, and maternal milk by hexane extraction and gas chromatography (FDA 1976).

Clinical examination of porphyrin subjects revealed hypopigmentation (53%), hirsutism (41%), scarring of hands and face (50%), pinched facies and rhytides (22%), fragile skin on hands and face (12.5%), large liver (9%), small hands, sclerodermoid thickening, shortening of distal phalax and painless arthritis (44%), enlarged thyroid (38%) in a goiter area of less than 5%; family history of Pembe Yara (12.5%). Porphyrins were still significantly elevated in 5 subjects. Stool uroporphyrin r = 12.6-189 µg/dm dry wt. Controls, Turks mean 1.8, SD 1.1; USA mean 2.8, SD 2.7. Urinary uroporphyrins in porphyrin subjects r = 50-1607 µg/L. Control Turks, mean 5.2, SD 3.7. USA mean 9.0, SD 4.0. A porphyrin's maternal milk revealed significant elevations of HCB, more than 7 ppm (none in controls), fat .21 ppm, and serum of 4/8 porphyrins (.003-0019 ppm).

Abnormal porphyrin metabolism, distinctive symptomatology and detectable HCB in tissue still persists 20 yr after HCB ingestion.

Chemotactic Proteininduced Polymorphonuclear Leukocyte Accumulation in Psoriasis. G. S. Lazarus, M.D. and C. A. Thomas, Ph.D. Department of Medicine, Division of Dermatology, Duke University Medical Center, Durham, NC.

One of the characteristic histological changes in psoriasis is the accumulation of polymorphonuclear leukocytes in the stratum corneum. Tagami and Ofuji have shown that psoriatic scale contains leukotactic substances which are products of complement activation. Several laboratories have shown that psoriatic scale contains increased amounts of proteinase. Our studies suggest that psoriatic epidermis contains increased amounts of a serine proteinase which activates complement and induces polymorph accumulation.

Biopsies of involved and uninvolved skin from patients with psoriasis, appropriate disease controls and normal patients were obtained. The epidermis was harvested from the biopsy by treatment with KBr and extracted. The epidermal extracts were adjusted for protein concentration and DNA content of the extracted epithelium. 0.5 mg aliquots of epidermal protein were injected into the peritoneal cavity of mice and polymorph accumulation was measured after 12 hr by the technique of Snyderman. Psoriatic plaque, as compared to uninvolved psoriatic tissue or extracts of pityriasis rubra pilaris tissue, contains increased amounts of factor which induces PMN accumulation (p < 0.05). Polymorph accumulation is completely inhibited by incubating the extract with the proteinase inhibitor diisopropyl fluorophosphate (p < 0.01). The chemotactic factor is only one-quarter as effective in evoking PMN accumulation in mice genetically deficient in the fifth component of complement (p < 0.05). The specific activity of lysosomal hydrolases was identical in involved and uninvolved psoriatic tissue. These data suggest that psoriatic plaque contains increased amounts of a proteinase which cleaves complement and induces PMN accumulation.

In Vitro Production of Autoantibodies in Bullous Diseases. A. R. Ahmed, Andrew Saxon, Ronald Stevens, John L. Fahey, De-
ABSTRACTS

department of Medicine, UCLA School of Medicine, Los Angeles California.

Since the availability of immunofluorescence testing, much has been learned about in vivo tissue bound antibodies and circulating antibodies in sera of patients with lupus erythematosus. Unrelated patients with pemphigoid (B.P.) and pemphigus vulgaris (P.V.). Our studies were directed towards understanding the cellular mechanisms involved. Firstly, we studied peripheral blood T cells, EA rosette-forming cells, Ig staining cells and PHA response in 13 untreated patients with pemphigus and 19 untreated patients with bullous pemphigoid. No statistical difference was found between patients and the age and sex-matched controls.

Efforts were then directed towards this in vitro production of an intercellular substance (ICS) antibody in pemphigus and basement membrane zone (BMZ) antibody in bullous pemphigoid. Peripheral blood lymphocytes from 5 untreated patients with P.V. and 3 patients with B.P. were cultured in RPMI 1640 with pokeweed mitogen. After 6 days the cultures were pulsed with media that were deficient in methionine or leucine and had been supplemented with S3 methionine or H leucine respectively and cultured for additional 18 hr. S3 cultures were assayed for total protein, cellular Ig and synthesized Ig. H leucine cultures were assayed by autoradiography using patient skin, normal skin and monkey esophagus for in vitro produced Ig that bound to ICS or BMZ.

Results showed that there was no significant difference in the total protein cellular Ig and secreted Ig produced in vitro between normals and patients with both B.P. and P.V. Using autoradiography we found that cells from patients with pemphigus produced 3x more ICS bound to the ICS of patient and normal skin and monkey esophagus. In bullous pemphigoid we could demonstrate that the Ig produced in vitro bound only to monkey esophagus and not to human skin. The activity in both groups of patients could be removed by absorption with rabbit anti-human Ig. PBL from normal controls in both experiments did not produce such antibodies. Addition of pemphigus sera markedly diminishes the capacity for patients' cells and normal controls to produce ICS bound to the ICS of patient and normal skin and monkey esophagus.

The Clinical and Immunological Features of Patients with Subacute Cutaneous Lupus Erythematosus—A Distinct Lupus Erythematosus Subset. RICHARD D. SOTHEIMER, M.D., JESSE R. THOMAS, M.D., JAMES N. GILLIAM, M.D. The University of Texas, Health Science Center At Dallas, Southwestern Medical School, Department of Internal Medicine, 5323 Harry Hines Blvd. Dallas, Texas.

We have observed a clinically distinct pattern of skin disease in 26 of 299 lupus erythematosus (LE) patients that we have studied over a 7-yr period. This previously uncharacterized type of LE skin involvement is marked by a sudden, localized, erythematous eruption occurring in a predominately reticulate pattern over the face, upper trunk, and extensor surfaces of the upper extremities that persists for weeks, or months, or years and resolves without scarring (subacute cutaneous LE). The cutaneous pathology was consistent with LE in all lesional biopsies studied. Direct immunofluorescence showed granular immunoglobulin (Ig) deposits at the dermal-epidermal junction (DEJ) of lesional biopsies in 75% of the patients studied; whereas, DEJ Ig was seen in visibly normal flexor forearm skin biopsies in only 32%. Fifty-five percent had a positive antinuclear antibody (ANA) determination; however, there was a low incidence of renal disease (12%) and central nervous system disease (15%). Subacute cutaneous LE was seen in both ANA negative patients without extracutaneous disease as well as in ANA positive patients who had 4 or more of the ANA criteria for systemic LE. The clinical pattern was present in patients with systemic LE there appeared to be a lower than expected incidence of significant renal disease. Thus, subacute cutaneous LE is a clinically distinct marker for a subset of LE patients who have a form of serological and clinical disease intermediate in severity between scarring discoid LE and systemic LE without subacute cutaneous LE.


Previous studies with photochemotherapy have suggested this to be a suitable treatment for mycosis fungoides. This study is an attempt to evaluate further the histological response and remission times with this form of treatment. Nine patients with stage 2 and 3 mycosis fungoides and 1 patient with Sézary syndrome were treated with oral methoxsalen and long wave ultraviolet light. The patients had failed or achieved only partial control with previous therapy. Skin biopsies were taken before and after clinical clearing. Satisfactory control was achieved in all but one of the patients. Histological improvement was seen in all patients but complete clearance of lymphoid infiltrate was only noted in epidermal and papillary dermal infiltrates. Lower dermal infiltrate remained largely unchanged. The Sézary patient was inadequately controlled with systemic prednisone and cyclophosphamide, addition of methoxsalen and ultraviolet light improved his symptoms. This is further evidence that photochemotherapy may have a place in early mycosis fungoides treatment both alone and perhaps in conjunction with other treatments. An early relapse was seen on stopping photochemotherapy in most of these patients with mycosis fungoides.

Treatment of Mycosis Fungoides with Topical BCNU. HERSCHEL S. ZACKHEIM, M.D., ERVIN H. EPSTEIN, JR., M.D., and DAVID A. GREKIN, M.D. University of California, School of Medicine, Department of Dermatology, San Francisco, California. 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) is widely used in the treatment of lymphomas and other malignancies. The commercial preparation BCNU-Carmustine (Bristol Lab) is easily adapted for topical use.

In the past 5 years 51 patients with mycosis fungoides were treated topically with BCNU, 39 to the total body and 12 to localized lesions. In the first 4 years total body treatment usually consisted of courses of 14-21 days at a dose level of 0.05% in 40-50 ml dilute alcohol (total 560-1260 mg). In the past year alternate day treatments applied in 2-3 weeks (total 350-600 mg) were used.

With the exception of 4 patients with the Sézary syndrome and 1 with universal poikilodermata who had not improved with topical nitrogen mustard, all patients experienced clearing of lesions with topical BCNU. Periods of complete remission following single total body courses ranged from less than 1 month (1 patient) to 1 year (2 patients) to over 12 months (2 patients). Individual plaques usually clear in 2-4 weeks after 1-2x daily applications of 0.2% BCNU in 95% ethanol (stable in refrigerator), or 0.4% BCNU in petrolatum (stable at room temperature).

Some degree of irritant dermatitis occurred in most patients but was manageable. Hypersensitivity occurred in 4. Telangectasia occurred in about half, but usually involved in only 1-2x daily applications. Moderate, reversible bone marrow depression occurred in 3. None of 22 patients who were allergic to nitrogen mustard showed evidence of cross-sensitization to BCNU. Recent favorable results with the alternate day schedule suggests that the hazards of hematopoietic depression and other complications may be minimized.

Mechanisms of Regression Induced by DNBC of Melanomas. G. F. PIEARD, M.D., A. B. ACKERMAN, M.D., C. HENRY, M.D., M. LAPIERE, M.D. From the Department of Dermatology, University of Liege, Belgium, and the Department of Pathology. New York University, New York, New York.

Surfaceal primary melanomas (SPM) commonly undergo partial spontaneous regression associated with a dense inflammatory-cell infiltrate. In contrast, deep primary melanomas (DPM) do not induce a marked inflammatory-cell response. We therefore applied dimethyldichlorobenzene (DNBC) to 40 DPM and dermal metastases (DM) in the hope of recapitulating an inflammatory host response against the neoplastic cells. By optical microscopy, we studied the sequence of events of the effects of DNBC on DPM and DM, compared them with spontaneous regression of SPM, and considered the implications of our findings for prevention of metastases.

Repeated applications of DNBC to DPM and DM prompt a dense perivascular inflammatory-cell reaction that extends to the superficial fascia. Local regression of DPM and DM ensues as a result of both direct effects of caustic necrosis and of immunological factors associated with the presence of numerous macrophages, reactive lymphocytes, and eosinophils. These inflammatory cells penetrate the DPM and DM. The cytotoxic action is specifically directed against well defined clones of neoplastic cells. Others clones are either spared by the surrounding infiltrate or specifically infiltrated by plasma cells. The superficial dermal lymphatics dilate widely, come to be filled with many mononuclear cells and contain, in some instances, micrometastases. Eventually, the inflammatory-cell infiltrate is joined by fibrin thrombi which subsequently cause fibrosis. The epidermis becomes hyperplastic and contains no more melanocytes, either normal or atypical.
DNCB causes regression of DPM and DM by inducing an inflammatory-cell infiltrate which is denser, deeper, and involves more basic mechanisms than that associated with regression of SPM. Clinopathological correlation indicates that DNCB may effect complete resolution of treated sites and prevent development of micrometastases only when each of the clones of melanoma becomes a target for a cytotoxic immune response.

**Cutaneous Allergy to Insulin: Zinc, A New Allergen. Brian V. Jegasothy, M.D. and Mark N. Feinglos, M.D. Department of Medicine, Division of Dermatology and Endocrinology, Duke University Medical Center, Durham, North Carolina.**

Delayed hypersensitivity reactions to insulin, at injection sites, are not uncommon and can be alleviated by changing to single source or mono-component insulin. These reactions are thought to be due to impurities in the insulin preparation.

In this study we report 2 patients who had typical delayed responses to insulin in the form of erythematous, pruritic nodules developing 24 to 48 hr after injection and confined to the sites of injection. Purin sources of insulin caused the same reactions. However, injections of zinc-free insulin produced no allergy.

Peripheral blood lymphocytes of these patients were induced to transform and proliferate by zinc-containing insulin and by zinc sulfate but not by zinc-free insulin. Further, these lymphocytes made a specific leukocyte inhibitory factor (LIF) in the presence of zinc.

Intradermal skin tests to zinc sulfate showed a positive delayed reaction. Histology of the skin test site showed an infiltrate of mononuclear cells around capillaries and post-capillary venules of the upper and middle dermis identical to that of the site of zinc-insulin injection. Controls in whom the studies were negative included a normal volunteer, 2 diabetics on insulin without allergy and one diabetic with insulin allergy corrected by switching to single source insulin.

We suggest that in some patients with delayed allergy to insulin the allergen is zinc rather than impurities in the insulin.


The recently described method to enumerate peripheral blood lymphocytes resistant to TG inhibition of phytohemagglutinin (PHA) stimulated tritiated thymidine (HTh'dr) incorporation in vitro was used to determine the frequency of variant lymphocyte induction in humans receiving PUVA. Seventeen psoriatic patients receiving PUVA and 16 severity matched conventionally treated psoriatic controls, 10 vitiligo patients receiving PUVA and 8 untreated vitiligo controls, and several normal non-PUVA treated subjects were studied. A cumulative normal control group of more than 70 individuals has established a reference frequency for TG resistant peripheral blood lymphocytes in healthy individuals of 1.3 x 10^-5. Normal non-PUVA treated individuals in the concurrent control and non-PUVA treated vitiligo patients were indistinguishable from the cumulative normal controls with variant frequencies ranging from 8.5 x 10^-5 to 1.6 x 10^-4. Of 17 PUVA treated psoriatics, 15 had elevated variant frequencies (range 2.4 x 10^-3 to 2.2 x 10^-3); of 10 treated vitiligo patients, 9 had elevated variant frequencies (2.2 x 10^-4 to 4.2 x 10^-3). However, as opposed to the non-PUVA treated vitiligo patients, 14 of 16 non-PUVA treated psoriatics showed elevated frequencies (range 1.6 x 10^-4 to 1 x 10^-3) at least as great as those found in PUVA treated psoriatics. If variant lymphocytes are somatic cell mutants, results with this new system are consistent with the findings of others that PUVA therapy results in cellular genetic damage. Furthermore, elevated variant frequencies in non-PUVA treated psoriatics implies either (i) that the conventional therapy of this disorder is also genetically damaging to human cells or, (ii) that the disorder itself is associated with these changes.

Decreased Cutaneous and Systemic Levels of Polyamines with Clinical Improvement in Treated Psoriasis. Michael S. Procotor, M.D., Elaine K. Orenberg, Ph.D. and Eugene M. Farrer, M.D. Department of Dermatology, Stanford Medical Center, Stanford, California.

Polyamines are thought to be involved in the control of cell proliferation. Since psoriasis is a hyperproliferative process, we suspected that aberrations in polyamine metabolism might play a role in psoriatic pathophysiology. We have previously reported increased systemic levels of the polyamines, spermidine and spermine, in the blood of psoriasis patients and this has been confirmed in the urines of these patients. The same compounds have been reported increased in psoriatic skin as well. This study was undertaken to determine whether changes in polyamine levels accompany clinical improvement in the skin following superficial therapy.

Nine hospitalized patients, treated with a Stanford modified Ingram technique utilizing anthralin, were examined at the beginning and end of their hospitalization. Samples of 24 hr urine collections were hydrolyzed and examined for polyamines (per mg creatinine) on a modified automatic amino acid analyzer. Skin biopsies were homogenized, extracted and analyzed for polyamines (per mg DNA) on the same apparatus.

With treatment, urinary levels dropped significantly (P < .05) for both spermine (decreased 35%) and spermidine (decreased 20%) while putrescine levels were not significantly affected. In the skin, treatment resulted in a highly significant (P < .01) decrease in spermine (decreased 36%), a significant (P < .05) decrease in spermidine (decreased 24%) and no significant change in putrescine. Average estimated involvement of skin surface by psoriasis decreased 37% during treatment.

It is concluded that cutaneous and systemic levels of some polyamines decline in patients who improved clinically in this study. It is suggested that polyamine inhibitors may lead to clinical improvement in psoriasis.
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