Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Serum eosinophilotactic activity in eosinophilic fasciitis. Arthritis Rheum 1982;25:1352-6.
22. Aberer E, Neumann R, Stanek G. Is localized scleroderma a *Borrelia* infection? [letter]. Lancet 1985; 2(8449):278.
23. Asbrink E, Hovmark A, Hederstedt B. The spirochetal etiology of acrodermatitis chronica atrophicans Herxheimer. Acta Derm Venereol (Stockh) 1984;64:506-12.

Human immunodeficiency virus–associated vitiligo: Expression of autoimmunity with immunodeficiency?

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Persistent viral infections have been postulated to be trigger factors for the development of autoimmune disease. We report the development of vitiligo in four patients with human immunodeficiency virus (HIV)–related conditions and in one patient with hepatitis who later developed both psoriasis and acquired immunodeficiency syndrome (AIDS). Other common features were hepatitis and multiple other viral infections. Ribavirin was associated with repigmentation in one patient. Vitiligo may be an example of an autoimmune disease triggered by viral infection in a genetically predisposed host. (J AM ACAD DERMATOL 1987;17:656-62.)

Vitiligo is frequently found in association with autoimmune diseases and autoantibodies, including cytotoxic antibodies to melanocytes.[1-19] There is an increased incidence of HLA-DR4 and an autosomal dominant pattern of inheritance in some families, suggesting genetic factors.[2,16] Finally, abnormalities of T cell subsets, especially inverted T cell ratios, have been reported.[14]

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Cost of the photographs was defrayed in part by a grant from Ortho Pharmaceuticals.

Accepted for publication June 22, 1987.

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The human immunodeficiency virus (HIV), by infecting the helper T cell and other CD4+ cells, causes immunodysfunction and finally immunodeficiency, the most severe form of which is AIDS, the acquired immunodeficiency syndrome.[20-24] Early HIV infection is associated with immune hyperstimulation (lymphadenopathy, polyclonal B cell activation with hypergammaglobulinemia, activated T suppressor cells (T8+, Ia+), while AIDS patients have loss of T4 and Langerhans cells, diminished antigen response, interleukin 2 and gamma interferon production, and virus-specific cytotoxicity.[25-27] Viral infections, especially herpes simplex, activate HIV-infected cells.[28]

In the course of caring for the dermatologic problems of HIV+ positive patients, we were

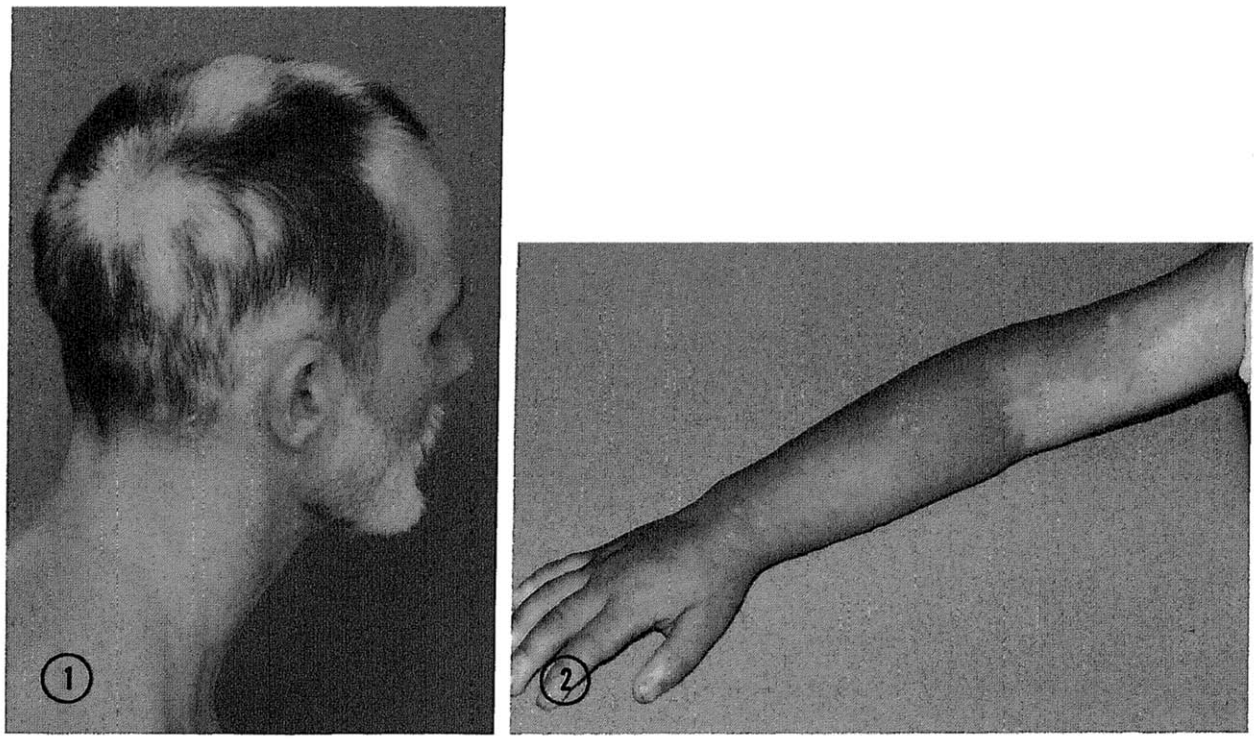

Fig. 1. Case 1. Vitiligo appearing in "areata"-like patches over the scalp in patient with AIDS-related complex.

Fig. 2. Case 2. Acral vitiligo appearing as the child developed symptoms of AIDS-related complex.

struck by the coincidence of seeing five patients over a short period of time who developed vitiligo while evolving AIDS-related complex (ARC) or AIDS. Four are reported here; the fifth was lost to follow-up. An additional AIDS patient gave a history of developing vitiligo and hepatitis concurrently, probably long before getting HIV infection. Vitiligo has not previously been reported in association with viral infections or HIV. If more than a coincidence, it suggests that viruses may indeed serve as a trigger factor for the autoimmune disease, vitiligo.

METHODS AND CASE REPORTS

Patients attended the clinical immunology and dermatology outpatient clinics at M.D. Anderson Hospital, The University of Texas System Cancer Center. We have followed over 1000 patients with ARC and AIDS, of whom about half had had symptomatic cutaneous complications during the preceding 3 years. Patients were tested for HIV by enzyme-linked immunosorbent assay (ELISA), followed by Western blot. Those receiving experimental drugs signed informed consent and the protocols were approved by the institutional review board.

CASE REPORT AND DESCRIPTIONS

Case 1

A 35-year-old male homosexual developed ARC (AIDS-related complex) in January 1983 after multiple infections, including mumps, Coxsackie virus, hepatitis, and syphilis. He received azimexon (BM 12,531) with stable symptoms until December 1985, when he developed fever, fatigue, and night sweats. At the same time he noted white patches in the scalp and beard hair and on the extensor surfaces of the arms and back (Fig. 1). His evaluation showed T4/T8 ratio of 0.29, anergy to skin tests, and markedly elevated cytomegalovirus and Epstein-Barr virus titers (Table I). Hepatitis B core antibody and HIV tests showed positive results.

Ribavirin (1-beta-ribofuranosyl-1,2,4,-riazole-3-carboxamide) was begun at 800 mg three times daily for 7 days, and then daily for 23 weeks. He developed a photosensitivity eruption after 6 weeks. At 12 weeks

Table I. Laboratory abnormalities in AIDS-associated vitiligo

Case	T4:T8 ratio or T4 count	Total protein	Platelets	WBC count	Skin tests	HIV	CMV
1	0.17	8.1	174	3,000	Anergy	+	1:512
2	380/mm^3 0.2	9.9 (IgG = 2529)	ND	12,300	Anergy	+ GP 24 GP 41	1:64
3	320/mm^3	ND	ND	7,800	Anergy	+	1:2048
4	64/mm^3	6.7	63	2,800	Anergy then moderate reaction on AZT spring 1987	+	1:128 + cultures urine, sputum
5	Decreased	ND	296	1,500	Anergy	+	1:64, sputum +

CMV: Cytomegalovirus; EBV: Epstein-Barr virus; GP: glycoprotein antigens of 24 and 41 kd; HIV: human immunodeficiency virus; LFTs: liver function tests; ND: not determined; WBC: white blood cell count.

Table II. Clinical features of AIDS-associated vitiligo

Case	Age	Sex	Risk	Existing and past infections	Onset vitiligo	Features/course	Onset HIV and course
1	35	M	HS	Mumps; 2° syphilis 1980s; hepatitis	December 1985	Patient had ARC symptoms: hair and beard turned white, and later vitiligo on forearms; ribavirin reversal	1/83, ARC
2	4	M	TR	Bilateral parotiditis 12/85	December 1985	Depigmentation acral digits and arms with onset of ARC symptoms	12/85, ARC; diarrhea, fever, weight loss
3	38	M	HS	Parotiditis 1967; mononucleosis; hepatitis 1977	December 1986	Depigmented 2 × 3-cm macules in 4/86; developed alopecia areata on ribavirin	1984, ARC symptoms; 10/85, HIV+; 1/86, AIDS
4	39	M	HS	Mumps, childhood; chickenpox, child; hepatitis 1968; chronic HSV 1977	February 1987	Guttate hypomelanotic lesions on chest suddenly appeared in patient with CMV, chronic HSV, zoster	1981, lymphadenopathy; 7/86, HIV+; 8/86, AIDS
5	42	M	HS	Hepatitis 1970; syphilis	With hepatitis 1970	Large areas of vitiligo started genitals and on thighs 4 years later; psoriasis in vitiligo appeared	6/84, ARC; 10/84, AIDS; 10/85, expired

ARC: AIDS-related complex; CMV: cytomegalovirus; HIV: human immunodeficiency virus; HS: homosexual; HSV: herpes simplex virus; MAC: *Mycobacterium avium* complex; PCP: *Pneumocystitis carinii* pneumonia; TR: transfusion.

repigmentation hair and skin lesions began; he continued to take ribavirin and showed improvement.

Case descriptions

The other cases are summarized in Table II. Patients 1 to 3 developed vitiligo within 2 years of HIV symptoms. Patient 2, a child with transfusion-induced ARC, developed acral vitiligo (Fig. 2) at the same time he developed parotiditis, fever, diarrhea, weight loss, and hypergammaglobulinemia.

Patient 3 developed 1- to 2-cm areas of vitiligo in the month following disseminated herpes zoster. These were not in previous zoster lesions, nor was inflammation noted. Three weeks after starting ribavirin he developed alopecia areata. Repigmentation did not occur in the skin.

Patient 4 had multiple persistent and chronic viral infections, including herpes simplex, for 10 years and had recent episodes of herpes zoster. In February 1987 three depigmented 1 × 2-cm macules appeared sud-

EBV	Hepatitis	Abnormal LFTs
1:2560	B+	+
ND	A+; B+	+
1:640	A+; IgG; B+; core+	+
1:160	A+; IgM−; B+;	+
1:640	core+; SAg+	
ND	A+; B+; core+; SAg+; HIV inclusions	+

HIV-associated infections/manifestations	Photograph
Seborrhea; giardiasis; staphylococcal folliculitis	Fig. 1
Facial telangiectasias; herpes stomatitis; neurologic change	Fig. 2
Generalized herpes zoster, 1/86; PCP, 5/86; dementia, 5/87	
Herpes zoster, 8/82 and 1/84; *Staphylococcus aureus*, 1983; PCP, 8/86, 11/86, 1/87; MAC, cryptosporidium, 11/86; recurrent CMV pneumonia; retinitis	Fig.3, biopsy
Psoriasis flare; Kaposi's sarcoma and PCP, 10/84; CMV retinitis and pneumonia; *Salmonella*, MAC, 10/85	

denly on the chest without prior viral vesicles or inflammation. During this time the patient had cytomegalovirus pneumonitis and retinitis, for which he received dihydroxy-2-propoxymethyl-guanine. Biopsy of a depigmented macule showed an atrophic epidermis with reduced melanin (Fig. 3). Electron microscopy revealed absent melanocytes (not shown).

Patient 5 developed genital and thigh vitiligo lesions when he contracted hepatitis. Psoriasis later developed in the vitiligo and became generalized, with ARC. Unless the incubation period of HIV exceeds 10 years, he contracted vitiligo prior to HIV, in conjunction with some form of viral hepatitis. There was evidence for previous hepatitis A and hepatitis B, as well as viral inclusions, on biopsy suggestive of non-A, non-B hepatitis. All five patients shared serologic evidence of viral hepatitis and had elevated liver enzymes in association with vitiligo.

DISCUSSION AND COMMENTS

The incidence of vitiligo in the general population has been estimated at 1% to 2%.[1] Although four vitiligo cases among several hundred HIV+ persons is not higher than expected, we rarely see new-onset vitiligo and found the coincidence of seeing four cases within months quite remarkable. Furthermore, premature graying, suggested related to vitiligo by Lerner and Nordlund,[1] is quite common as ARC patients progress to AIDS.* Thus, if HIV infection and vitiligo are related, HIV, its opportunistic viruses (especially hepatitis), or dysimmunity may trigger vitiligo in the genetically predisposed host.

Evidence for a relationship between the immune system and vitiligo exists. Immunodeficiency and vitiligo have been reported in the setting of mucocutaneous candidiasis. Indeed, patients with mucocandidiasis without vitiligo may have circulating antimelanocyte antibodies.[13] "Partial albinism" and vitiligo in association with fever, pyogenic infections, hypogammaglobulinemia, and reduced Langerhans cells were reported in two patients from the 1960s and 1970s.[29] Finally, the Vogt-Koyanagi-Harada syndrome, a viral-like illness with aseptic meningitis, hair loss, uveitis, dysacousia, and vitiligo, has a specific HLA class II antigen LDWa and antibodies cytotoxic to melanocytes.[18,19,30] Similar antibodies have also been found in vitiligo patients.[17]

The mechanism of autoimmunity (in this case vitiligo) is unknown. We suggest that the following possibilities exist and could be tested experimentally.

1. Direct viral infection of melanocytes. HIV infects central nervous system astrocytes and oligodendrocytes.[31] Melanocytes as neural crest cells might also be capable of infection. We could not find melanocytes in our biopsy to test this hypothesis.

*Duvic, M. Unpublished observation, 1986.

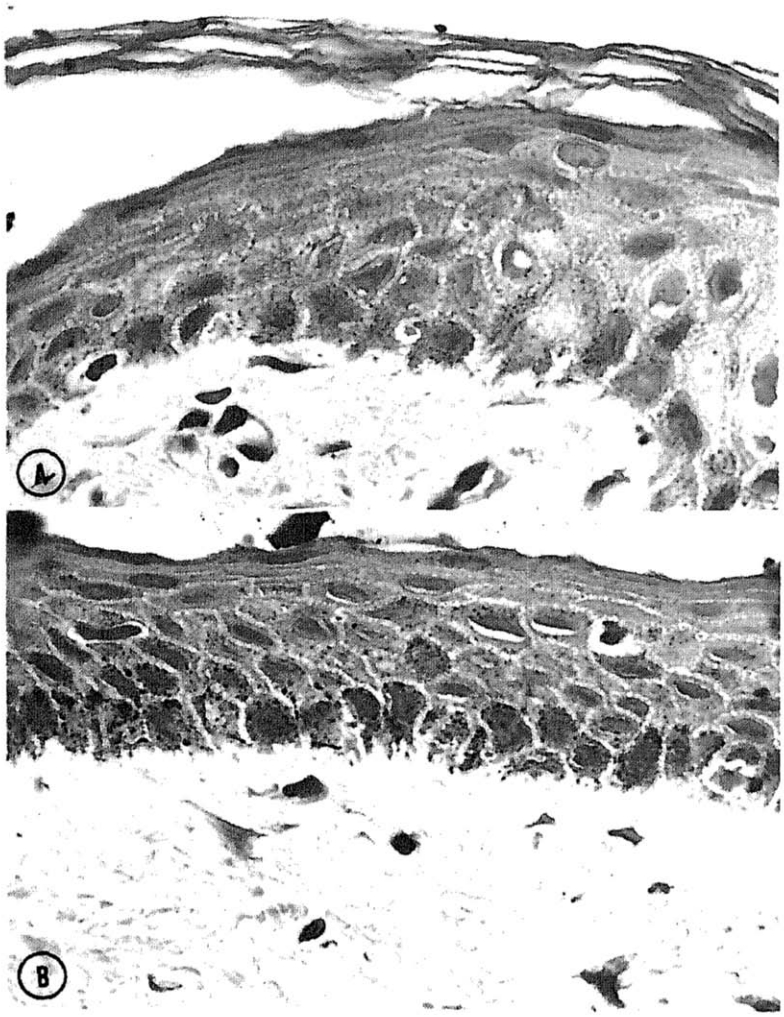

Fig. 3. Case 4. Biopsy from the hypopigmented lesion (*A*) shows reduced melanocyte granules compared with normal skin (*B*). There is mild epidermal atrophy in both. (Fontana stain; ×300.)

2. Nonspecific polyclonal B cell activation with production of autoantibodies. Human immunodeficiency virus and Epstein-Barr virus both induce this.[32,33]
3. Cellular cytotoxicity against melanocytes. This could occur through activated cells (present in ARC)[34,35] and/or through cytokine production (especially gamma interferon).[36] Gamma interferon is produced in response to viruses and induces aberrant DR expression on epidermal cells.[37-39] Aberrant DR expression on epidermal cells can induce a cellular immune reaction and could theoretically damage melanocytes.[40]
4. Changes in the balance between helper, suppressor, and cytotoxic cells due to T cell retrovirus infection.[34,35]
5. Molecular mimicry between viral antigens and HLA antigens or expression of new antigens as viruses bud from infected cells.[41]
6. Combinations of the above.

ARC-associated thrombocytopenia is a well-documented example of HIV-associated autoimmune disease. Destruction of platelets is due to an antibody that reacts with a 25,000 dalton platelet-associated protein and cross-reacts with herpes simplex–infected cells.[42] If similar antimelanocyte antibodies are being produced with antiviral cross-

reactivity, this could explain vitiligo in these reported patients.

If more than coincidental, the development of vitiligo following viral infections such as hepatitis, HIV, herpes zoster or herpes simplex, and cytomegalovirus would support the previous hypothesis that viruses trigger autoimmunity.[41,43] Vitiligo could be the second reported autoimmune disorder occurring in the setting of the human immunodeficiency virus.

REFERENCES

1. Lerner AB, Nordlund JJ. Vitiligo: what is it? Is it important? J Am Med Assoc 1978;239:1183-7.
2. Nordlund JJ. Vitiligo. In: Thiers BH, Dobson RL, eds. Pathogenesis of skin disease. New York: Churchill Livingstone, 1986:99-127.
3. Lucky PA, Nordlund JJ. The biology of the pigmentary system and its disorders. Dermatol Clinic 1985;3:197-216.
4. Dawber RPR. Clinical associations in vitiligo. Postgrad Med J 1970;46:276-7.
5. Dawber RPR, Bleehan SS, Vallance-Owen J. Vitiligo and diabetes mellitus. Br J Dermatol 1977;84:600.
6. Cunliff WJ, Hall R, Newell DJ, et al. Vitiligo, thyroid disease and autoimmunity. Br J Dermatol 1968;80: 135-9.
7. Olholm-Larsen P, Kavli G. Dermatitis herpetiformis and vitiligo. Dermatologica 1980;160:41-4.
8. Ortonne JP, Perrot H, Thivolet J. Etude clinique et statistique d'une population de 100 vitiligos. Sem hôp Paris 1976;52:679-86.
9. Brown AC, Olkowski ZL, McLaren JR, Kutner MH. Alopecia areata and vitiligo associated with Down's syndrome. Arch Dermatol 1977;113:1296.
10. Bor S, Feiwel M, Chanarin I. Autoantibodies in vitiligo. Br J Dermatol 1969;81:83-8.
11. Brostoff J, Bor S, Feiwel M. Autoantibodies in patients with vitiligo. Lancet 1969;2:177-8.
12. Betterle C, Caretto A, De Zio A, et al. Incidence and significance of organ specific autoimmune disorders (clinical, latent or only autoantibodies) in patients with vitiligo. Dermatologica 1985;171:419-23.
13. Howanitz N, Nordlund JJ, Lerner AB, Bystryn JC. Autoantibodies to melanocytes. Arch Dermatol 1981;117: 705-8.
14. Grimes PE, Halder RM, Jones C, et al. Autoantibodies and their clinical significance in a black vitiligo population. Arch Dermatol 1983;119:300-3.
15. Naughton GK, Eisinger M, Bystryn JC. Detection of antibodies to melanocytes in vitiligo by specific immunoprecipitation. J Invest Dermatol 1983;81:540-2.
16. Foley LM, Lowe NJ, Misheloff E, Tiwari JL. Association of HLA-DR4 with vitiligo. J Am Acad Dermatol 1983;8:39-40.
17. Norris DA, Bystryn JC, Kissinger R. Direct evidence for immunologic cytotoxicity as a mechanism of human vitiligo [abstract]. Clin Res 1987;35:251A.
18. Tagawa Y. Lymphocyte-mediated cytotoxicity against melanocyte antigens in Vogt-Koyanagi-Harada disease. Jpn J Ophthalmol 1978;22:36-9.
19. Nordlund JJ, Albert DM, Forget B, et al. Halo nevi and the Vogt-Koyanagi-Harada syndrome. Arch Dermatol 1980;116:690-2.
20. Gallo RC, Salahuddin SZ, Popovic M, et al. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science 1984;224:500-3.
21. Centers for Disease Control: classification system for human T-lymphotropic virus III/adenopathy associated virus infections. Ann Intern Med 1986;105:234-7.
22. Klatzman D, Champagne E, Chamaret S, et al. T lymphocyte T4 molecule behaves as the receptor for human retrovirus LAV. Nature 1984;312:767-8.
23. Dagleish AG, Beverly DC, Clapham PR, et al. The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. Nature 1984;312:763-7.
24. Gottlieb MS, Schroff R, Schanker HM, et al. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. N Engl J Med 1981; 305:1425-31.
25. Dwyer JM, McNamara JG, Sigal LH, et al. Immunological abnormalities in patients with the acquired immunodeficiency syndrome (AIDS): a review. Clin Immunol Rev 1984;3:25-129.
26. Lane HC, Depper JM, Greene WC, et al. Qualitative analysis of immune function in patients with the AIDS evidence for a selective defect in soluble antigen. N Engl J Med 1985;313:79-84.
27. Fauci AS, Macher AM, Longo DL, et al. Acquired immunodeficiency syndrome: epidemiologic, clinical, immunologic and therapeutic considerations. Ann Intern Med 1984;100:92-106.
28. Mosca JD, Bednarik DP, Raj NBK, et al. Herpes simplex type-1 can reactivate transcription of latent human immunodeficiency virus. Nature 1987;324:67-70.
29. Griscelli C, Durandy A, Guy-Grand D, et al. A syndrome associating partial albinism and immunodeficiency. Am J Med 1978;65:691-701.
30. Yakura H, Wakisaka A, Aizawa M, et al. HLA-D antigen of Japanese origin (LD-Wa) and its association with Vogt-Koyanagi-Harada syndrome. Tissue Antigens 1976;8: 35-42.
31. Koenig S, Gendelman HE, Orenstein JM, et al. Detection of AIDS virus in macrophages in brain tissue from AIDS patients with encephalopathy. Science 1986;233: 1089-93.
32. Schnittman SM, Lane HC, Higgins SE, et al. Direct polyclonal activation of human B lymphocytes by the acquired immune deficiency virus. Science 1986;233: 1084-6.
33. Kouns DM, Marty DM, Sharpe RW. Oligoclonal bands in serum protein electrophoretograms of individuals with human immunodeficiency virus antibodies. J Am Med Assoc 1986;256:2343.
34. Nicholson JKA, McDougal JS, Spira TJ. Immunoregu-

latory subsets of the T helper and T suppressor cell populations in homosexual men with chronic unexplained lymphadenopathy. J Clin Invest 1984;73:191-201.
35. Nicolson JKA, McDougal JS, Spira TJ. Alterations of functional subsets of T helper and T suppressor cell populations in acquired immunodeficiency syndrome (AIDS) and chronic unexplained lymphadenopathy. J Clin Immunol 1985;5:269-73.
36. Aubock J, Romani N, Grubauer G, Fritsch P. HLA DR expression on keratinocytes is a common feature of diseased skin. Br J Dermatol 1986;114:465-72.
37. Basham TY, Nicholoff BJ, Merigan TC, Morhenn VB. Recombinant gamma interferon induces HLA-DR expression on cultured human keratinocytes. J Invest Dermatol 1984;83:88-90.
38. Basham TY, Merigan TC. Recombinant interferon gamma increases HLA-DR synthesis and expression. J Immunol 1983;130:1492-4.
39. Suzumura A, Lavi E, Weiss R, Silberberg DH. Coronavirus infection induces H-Z antigen expression on oligodendrocytes and astrocytes. Science 1986;232:991-3.
40. Londei M, Lamb JR, Botalizzo GF, Feldman M. Epithelial cells expressing MHC II determinants can present antigen to cloned T cells. Nature 1984;312:639-41.
41. Southern P, Oldstone MBA. Medical consequences of persistent viral infection. N Engl J Med 1986;314: 359-66.
42. Stricker RB, Abrams DI, Corash L, Shuman MA. Target platelet antigen in homosexual men with immune thrombocytopenia. N Engl J Med 1985;313:1375-80.
43. McDevitt HO. The molecular basis of autoimmunity. Clin Res 1986;34:163-75.

ABSTRACTS

Comparative characteristics of sources of infection in patients with gonorrhea and syphilis

Korobeinrkova EA, Zelenina OI, Alexeeva BA, Popova SN, Novikov VM: Vestn Dermatol Venerol 1986;5:59-61 (Russian)

Data of a sociologic investigation of sources of gonorrhea and syphilis based on an analysis of a questionnaire filled in by the patients are as follows. Gonorrhea patients tended to be younger, to have started to have sexual intercourse at an earlier point in life, and were more likely to be female (67.8%). Syphilis patients tended to be single and male (55%) [Editorial note: the authors do not mention homosexuality as a factor] and were more likely to be unemployed, unskilled workers with a low educational level.

Yehudi M. Felman, M.D.

Schulman's eosinophilic fasciitis: news in diagnosis and treatment

Shaposhnikov OK, Rodionov AN, Samtsov AV: Vestn Dermatol Venerol 1986;5:4-5 (Russian)

A 48-year-old female patient with eosinophilic fasciitis of the face, cheek, neck, shoulders, and trunk responded well to treatment with D-penicillamine, 150 mg b.i.d. for 2 weeks. The authors believe, on the basis of relative and absolute increase in T lymphocytes and immune complement, that immune factors play a role in the pathogenesis of the disease. They also advocate the use of ultrasonic examination in making the diagnosis, as the thickening and induration of the fascia can show up on the scan.

Yehudi M. Felman, M.D.

Histocompatibility antigens in psoriasis

Erdes S, Yakovleva DB, Razumnik ID, Mordovstev VN: Vestn Dermatol Venerol 1986;5:8-9 (Russian)

Fifty patients with psoriasis (20 with psoriasis vulgaris and 30 with arthropathic psoriasis) were examined for A and B locuses of the human lymphocyte antigen (HLA) system. An increase in HLA-B13 and HLA-B15 antigens was observed, and the presence of HLA-B13 increasing the risk of psoriasis ninefold, compared to subjects in whom this antigen was not detected was noted.

Yehudi M. Felman, M.D.

Coadjuvant therapy with auranofin in the treatment of South American pemphigus foliaceus: a double-blind study

Auada A, Auad T, Auad A, Auad P: Anais Bras Dermatol 1986;61:131-4 (Portuguese)

Twenty-one patients with South American pemphigus foliaceus were divided into two groups. Eleven were treated only with corticosteroids, while 10 also were treated with auranofin (gold), 6 mg daily. After 1 year the gold-treated group required a medium dose of only 5.5 mg daily of corticosteroids for maintenance, whereas the non–gold-treated group required 36.5 mg. Both groups were on an average of 40 mg corticosteroid daily at the start of the study.

Yehudi M. Felman, M.D.

Chromate eczema in the food, domestic and cleaning industries

Weiler KJ, Russel HA: Derm Beruf Umwelt 1986;34:135-9 (German)

No chromium in the form of chromate was found in flour and baking powders. Contradictory reports published elsewhere have not been substantiated. The occasional incidence of chromate allergy observed in the domestic services trades, bakeries, curing houses, and bottling plants were found to be due to traces of chromate in the following substances: wood ash, 0.23 ppm, lignite ash, 0.05 to 1.7 ppm, refractory brick, 0.5 to 0.9 ppm, certain alkaline scouring agents, 0.1 to 0.2 ppm, suds produced when washing chromate-containing glasses, 0.13 to 1.61 ppm.

Yehudi M. Felman, M.D.