British Journal of Dermatology (1987) **116,** 131–138.

Molluscum contagiosum and the acquired immunodeficiency syndrome: clinical and immunological details of two cases

M.KATZMAN, J.T.CAREY, C.A.ELMETS, GRETTA H.JACOBS AND M.M.LEDERMAN

Departments of Medicine, Dermatology and Pathology, Case Western Reserve University School of Medicine and University Hospitals of Cleveland, Cleveland, Ohio, U.S.A.

Accepted for publication 14 July 1986

SUMMARY

We report here the clinical and immunological findings in two patients with molluscum contagiosum poxvirus infection and the acquired immunodeficiency syndrome (AIDS). These cases support earlier evidence that the molluscum contagiosum virus may act as an opportunistic pathogen. There is now evidence that members of all five families of double stranded DNA-containing human viruses have been associated with unusual clinical manifestations in AIDS patients, and the significance of DNA virus infections in patients with AIDS is discussed.

We have reported previously a case of severe molluscum contagiosum in a patient with the acquired immunodeficiency syndrome (AIDS).[1] We report here the clinical and immunological details of this and another case.

CASE REPORTS

Case 1

This 24-year-old black homosexual male presented in June 1984 with oral thrush and cryptococcal fungemia and meningitis. He responded clinically to intravenous amphotericin B and oral flucytosine, although blindness developed. Because visible yeast and high titres of antigen (1 : 128) persisted in the cerebrospinal fluid after administration of 2·5 g amphotericin B, weekly infusions of 60 mg were continued on an outpatient basis. Evaluation of diarrhoea in July 1984 revealed histological changes consistent with cytomegalovirus (CMV) on rectal biopsy; this virus was also cultured from the patient's urine in August 1984.

Correspondence: Michael M.Lederman, M.D., Division of Infectious Diseases, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, Ohio 44106, U.S.A.

Two weeks after initial presentation, several single and grouped papules appeared on the patient's forehead and nose. These lesions were 1 to 6 mm diameter, firm, non-tender, dome-shaped papules which appeared waxy and white but were occasionally erythematous; some were umbilicated (Fig. 1). A biopsy of one lesion on the temple showed the characteristic histological features of molluscum contagiosum (Fig. 2), which was confirmed by detection of poxviruses on electron microscopy (Fig. 3). Attempts at control with tretinoin cream (Retin A®, Ortho Pharmaceutical, 0·1% and 0·05%) twice resulted in unacceptable local irritation. Despite repeated cryotherapy with liquid nitrogen, the lesions continued to increase in number and size over his scalp, forehead and nose (Fig. 4), causing much distress and frustration to the patient. The source of this poxvirus infection was not identified; the patient denied sexual contact for the previous 2 years.

In February 1985, a chest X-ray revealed extensive infiltrates; *Pneumocystis carinii* and CMV were found on bronchoscopy. The patient died of respiratory failure some days later. Permission for an autopsy was not granted.

Case 2

A 23-year-old black homosexual male presented with a 6-month history of fatigue, anorexia, weight loss and diarrhoea. A lymph node biopsy showed sinus histiocytosis and non-caseating granulomata. When seen 3 months later, he had oral candidiasis, extensive perianal herpes

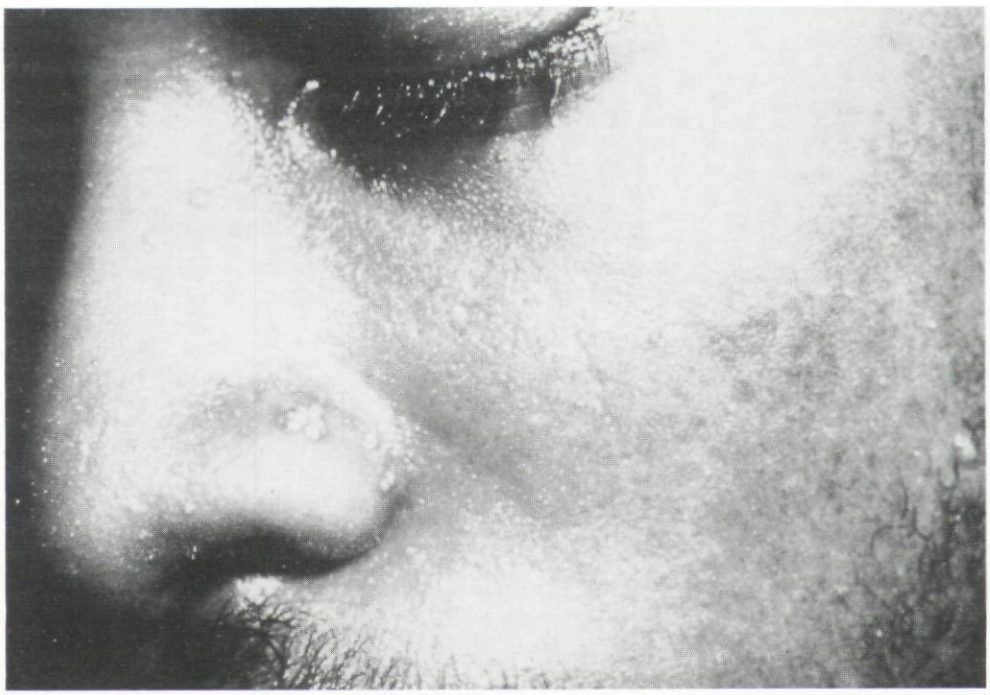

FIGURE 1. Case 1. Facial lesions (July 1984), showing waxy papules occurring singly and in clusters on the nose.

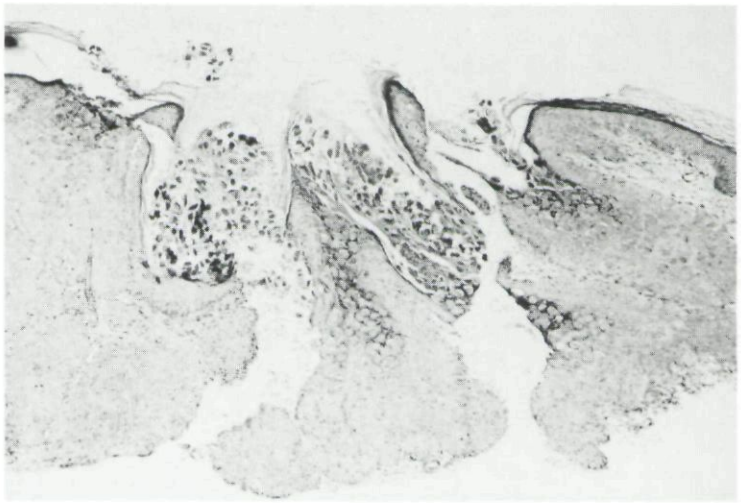

FIGURE 2. Case 1. Biopsy of an umbilicated papule from the temple. Note the large number of intracytoplasmic inclusions, known as molluscum bodies, in the epidermal cells. (Haematoxylin and eosin; original × 90).

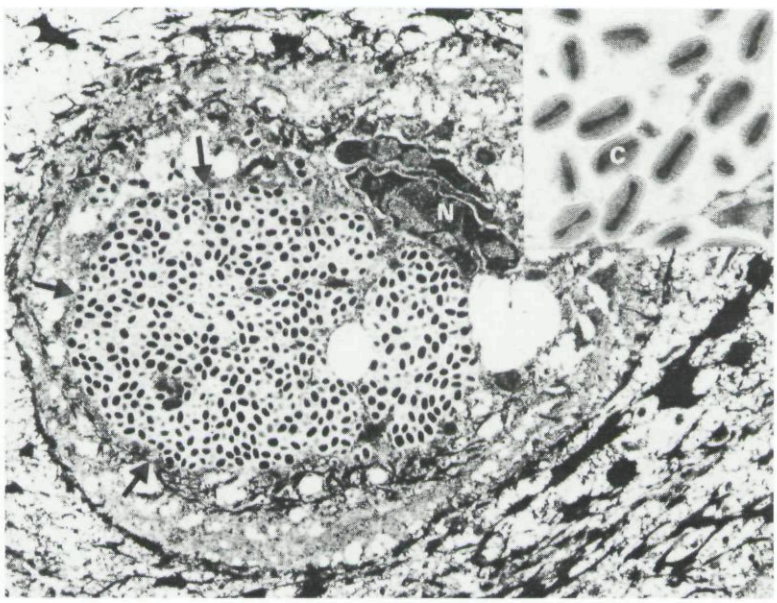

FIGURE 3. Electron micrograph showing numerous intracytoplasmic virions (arrows) displacing the epidermal cell nucleus (N). (Uranyl acetate and lead citrate original × 9000). Inset: higher magnification shows the typical appearance of the oblong, enveloped molluscum contagiosum poxvirus with a dumbell-shaped central core (C). (Original × 50 000).

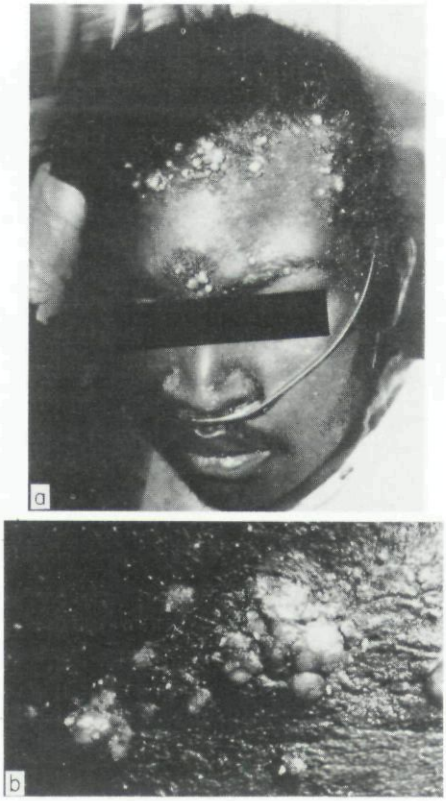

FIGURE 4. Case 1 (February 1985). (a) The lesions have increased in number, size and distribution and are associated with surrounding lichenification and hyperpigmentation. (b) Individual lesions can still be identified as molluscum contagiosum.

(culture positive for herpes simplex), and thoracic lesions suggestive of resolving herpes zoster. Multiple papules were also present on his neck. Biopsy of one of these papules was consistent with molluscum contagiosum. The herpes infections resolved clinically after treatment with intravenous acyclovir, and the patient was begun on protocol therapy with transfer factor.[2] The molluscum contagiosum lesions received no specific therapy and remained stable, but the patient subsequently died with central nervous system toxoplasmosis and disseminated *Mycobacterium avium-intracellulare* infection.

METHODS

Blood was drawn into heparinized tubes. Peripheral blood mononuclear cells were then separated by Ficoll-Hypaque density gradient sedimentation of whole blood. B lymphocytes were identified by binding of fluorescein-conjugated polyvalent mouse anti-human immunoglobulin (Kallestad Laboratories, Chaska, MN, U.S.A.). Other lymphocyte phenotypes were identified with murine monoclonal antibodies (Ortho Diagnostics, Raritan, NJ, U.S.A.) and fluorescein-conjugated goat anti-mouse immunoglobulin (Cooper Biomedical, Malvern, PA, U.S.A.). OKIa1 recognizes the human DR antigen complex expressed on B cells and activated T cells, OKT3 is a pan-T cell marker, OKT4 recognizes the helper/inducer subset and OKT8

recognizes the suppressor/cytotoxic subset. Cell populations were enumerated using an EPICS V flow cytometer (Coulter Electronics, Hialeah, FL, U.S.A.). Lymphocyte blastogenic responses to the mitogen phytohaemagglutinin (0·5 μg/ml) (Burroughs Wellcome, Research Triangle, NC, U.S.A.), and to the antigens *Mycobacterium tuberculosis* purified protein derivative (PPD) (100 μg/ml) (Burroughs Wellcome), tetanus toxoid (1:1000 dilution) (Lederle, Pearl River, NY, U.S.A.), and streptolysin (1:200 dilution) (Fisher Diagnostics, Orangeburg, NY, U.S.A.) were assessed by measurement of ^{3}H-thymidine incorporation. Natural killer cell activity was assayed by measuring release of ^{51}Cr from labelled K562 tumour targets at a 30:1 mononuclear cell to tumour cell ratio. These methods have been described in detail previously.[3] Control values were normal laboratory ranges (mean ± 2 standard deviations, or in the case of blastogenic responses, lowest to highest values) obtained from healthy individuals. Delayed type hypersensitivity was assessed 48 h after the intradermal injection of 0·1 ml of the following recall antigens: mumps skin test antigen (Eli Lilly & Co., Indianapolis, IN, U.S.A.), candida and trichophyton (Iatric Corp., Tempe, AZ, U.S.A.), and *Mycobacterium tuberculosis* PPD (5 TU) (Connaught Laboratories, Willowdale, Ontario, Canada).

RESULTS

Results of immunological testing are listed in Table 1.

TABLE 1. Lymphocyte phenotypes and function, and skin test results in two patients with molluscum contagiosum

	Case 1	Case 2	Healthy controls
Total lymphocytes/μl	880	44	806–2446
B lymphocytes/μl	161	14	48–734
OKIa1 + cells/μl	172	15	48–734
OKT3 + cells/μl	707	25	576–3802
OKT4 + cells/μl	216	12	374–2938
OKT8 + cells/μl	478	14	115–1469
OKT4/OKT8 ratio	0·45	0·86	1·3–4·6
Lymphocyte blastogenic responses (cpm)			
Phytohaemagglutinin	13 232	10 282	31 241–107 882
Mycobacterium tuberculosis PPD	1097	576	5689–59 981
Tetanus toxoid	2208	632	1109–39 725
Streptolysin	1118	1307	20 301–74 544
Natural killer activity, % lysis	9·1	3·1	22–66
Skin test reactivity			
Mumps	Not done	Negative	
Candida	Not done	Negative	
Trichophyton	Not done	Negative	
Mycobacterium tuberculosis PPD	Not done	Negative	

DISCUSSION

Protozoa, fungi, bacteria and viruses have all been reported to cause opportunistic disease in patients with AIDS.[4] In particular, there have been many descriptions of infection or

colonization by double stranded DNA-containing viruses in patients with AIDS or belonging to groups at risk for AIDS. All four members of the family herpetoviridae have been associated with clinical illness in AIDS: herpes simplex virus has produced severe mucosal and perimucosal infections in patients with AIDS,[5,6] varicella zoster virus has reactivated or disseminated in AIDS patients or as a prodrome to AIDS,[6,7] Epstein-Barr virus DNA has been found in lymphoma cells from AIDS patients,[8,9] and disseminated infection with CMV is a common complication of AIDS.[6,10] Adenovirus, of the family adenoviridae, has been isolated from the lungs, urine and cerebrospinal fluid of patients with AIDS.[10–12] In addition, infection by viruses of both genera within the family papovaviridae have been reported in AIDS patients: papillomavirus associated with condylomata acuminata[13] and oral leukoplakia,[14] and polyomaviruses of the JC-BK group associated with progressive multifocal leukoencephalopathy.[15,16] Recently, hepatitis B virus, a member of the family hepadnaviridae,[17] has been reported to undergo spontaneous clearance and reactivation in homosexual men who were chronic hepatitis B virus carriers,[18] although in a more recent report only one of three such patients was seropositive for antibody to the human T-lymphotropic AIDS virus, HTLV-III.[19] Members of each of the above viral families contain predominantly double-stranded DNA; all have also been associated with latent or chronic infections.

The fifth family of double-stranded DNA-containing viruses is the poxviridae, large, complex enveloped viruses which include smallpox (variola), vaccinia and the virus causing molluscum contagiosum. This report describes two cases of molluscum contagiosum in patients with AIDS. Although virological methods are not available to identify this virus, the clinical appearance, histological changes and electron microscopic findings (in Case 1) were characteristic of molluscum contagiosum.[20] Recently, a case of disseminated vaccinia in a patient who subsequently developed AIDS has been reported.[21] Thus, the entire spectrum of human double-stranded DNA viruses has been described in this population of patients.

It is not yet clear why RNA viruses have not been identified similarly as opportunistic pathogens in this syndrome, although there is one report of coronavirus-like particles in the stools (and one serum sample) of homosexual AIDS patients, unrelated to enteric symptoms.[22] Presumably, those aspects of cell-mediated immunity which are perturbed in AIDS are more important for control of DNA virus infections, which often persist in a latent phase. It is also conceivable that infection with the HTLV-III retrovirus confers an advantage to transcription of viral DNA, thereby favouring both retroviral RNA replication and reactivation of DNA viruses.

The underlying susceptibility to opportunistic infections in AIDS appears to stem from an absolute depletion of T-helper lymphocytes, the same cells that are selectively infected by HTLV-III.[23] In addition, natural killer cell function is consistently impaired in these patients, as are blastogenic responses to mitogens and antigens. Deficient numbers of HLA-DR positive epidermal Langerhans cells have also been described in AIDS.[24] Our two patients had lymphopenia, decreased T-helper cells, inverted ratios of T-helper to T-suppressor cells, depressed natural killer activity, diminished proliferative responses to mitogens and antigens, and in the one patient tested, cutaneous anergy. It seems reasonable to assume that the severe poxvirus infections in our two patients were somehow related to their immune deficiency. Although healthy individuals, particularly sexually active homosexual men, may develop molluscum contagiosum, the striking progression of lesions in Case 1 has not been observed in healthy adults. In addition, the distribution of lesions in these cases was reminiscent of childhood molluscum contagiosum, in contrast to the usual anogenital distribution of lesions in adult cases related to sexual transmission.[20,25]

Previous reports have described severe molluscum contagiosum in patients receiving chemotherapy[26] or corticosteroids,[26,27] and in patients with sarcoidosis,[28] or with eczema.[27,29–31] Authors of these reports have suggested that immune defects were involved, [26,28,30,31] but the methods used for quantifying immune function were not extensive.

The incidence of molluscum contagiosum in AIDS is not known, but since the appearance of our brief report describing the first patient,[1] we have become aware of other cases.[32–36] This virus thus joins the list of opportunistic DNA viruses that may cause significant morbidity in patients with AIDS. Whether the apparent predilection of AIDS patients to illness from double-stranded DNA-containing viruses is due to the tendency of these organisms to persist in a latent phase, to a specific impairment of cellular immunity to these agents, or to a selective advantage in intracellular replication by these viruses requires further study. Physicians should consider the possibility of an underlying immunodeficiency in patients presenting with severe molluscum contagiosum.

ACKNOWLEDGMENTS

We wish to thank Drs Susan Edelstein and J.Walton Tomford for referring Case 2, and Drs Max R.Proffitt and Jerrold J.Ellner for review of the manuscript.

REFERENCES

1. KATZMAN, M., ELMETS, C.A. & LEDERMAN, M.M. (1985) Molluscum contagiosum and the acquired immunodeficiency syndrome. *Annals of Internal Medicine*, **102,** 413.
2. CAREY, J.T., LEDERMAN, M.M., HODDER, S. *et al.* (1985) Augmentation of skin test reactivity and blastogenic responses in patients with acquired immunodeficiency syndrome (AIDS) treated with transfer factor. *Clinical Research*, **33,** 562A (abstract).
3. LEDERMAN, M.M., RATNOFF, O.D., SCILLIAN, J.J., JONES, P.K. & SCHACTER, B. (1983) Impaired cell-mediated immunity in patients with classic hemophilia. *New England Journal of Medicine*, **308,** 79.
4. MACHER, A.M. (1984) Infections in the acquired immunodeficiency syndrome, pp 94–96. In Fauci, A.S., moderator: Acquired immunodeficiency syndrome: epidemiologic, clinical, immunologic, and therapeutic considerations. *Annals of Internal Medicine*, **100,** 92.
5. SIEGAL, F.P., LOPEZ, C., HAMMER, G.S. *et al.* (1981) Severe acquired immunodeficiency in male homosexuals, manifested by chronic perianal ulcerative Herpes simplex lesions. *New England Journal of Medicine*, **305,** 1439.
6. QUINNAN, G.V., MASUR, H., ROOK, A.H. *et al.* (1984) Herpesvirus infections in the acquired immune deficiency syndrome. *Journal of the American Medical Association*, **252,** 72.
7. COLE, E.L., MEISLER, D.M., CALABRESE, L.H., HOLLAND, G.N., MONDINO, B.J. & CONANT, M.A. (1984) Herpes zoster ophthalmicus and acquired immune deficiency sydrome. *Archives of Ophthalmology*, **102,** 1027.
8. PETERSEN, J.M., TUBBS, R.R., SAVAGE, R.A. *et al.* (1985) Small noncleaved B cell Burkitt-like lymphoma with chromosome t(8;14) translocation and Epstein-Barr virus nuclear-associated antigen in a homosexual man with acquired immune deficiency syndrome. *American Journal of Medicine*, **78,** 141.
9. LIND, S.E., GROSS, P.L., ANDIMAN, W.A., STONE, G.C., SCHOOLEY, R.T. & HARRIS, N.L. (1985) Malignant lymphoma presenting as Kaposi's sarcoma in a homosexual man with the acquired immunodeficiency syndrome. *Annals of Internal Medicine*, **102,** 338.
10. GOTTLIEB, M.S., SCHROFF, R., SCHANKER, H.M. *et al.* (1981) Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. *New England Journal of Medicine*, **305,** 1425.
11. DE JONG, P.J., VALDERRAMA, G., SPIGLAND, I. & HORWITZ, M.S. (1983) Adenovirus isolates from urine of patients with acquired immunodeficiency syndrome. *Lancet*, **i,** 1293.
12. Horoupian, D.S., Pick, P., Spigland, I. *et al.* (1984) Acquired immune deficiency syndrome and multiple tract degeneration in a homosexual man. *Annals of Neurology*, **15,** 502.
13. CROXSON, T., CHABON, A.B., RORAT, E. & BARASH, I.M. (1984) Intraepithelial carcinoma of the anus in homosexual men. *Diseases of the Colon and Rectum*, **27,** 325.

14. GREENSPAN, D., GREENSPAN, J.S., CONANT, M., PETERSEN, V., SILVERMAN, S. & DE SOUZA, Y. (1984) Oral 'hairy' leucoplakia in male homosexuals: evidence of association with both papillomavirus and a herpes-group virus. *Lancet*, **ii**, 831.
15. MILLER, J.R., BARRETT, R.E., BRITTON, C.B. *et al.* (1982) Progressive multifocal leukoencephalopathy in a male homosexual with T-cell immune deficiency. *New England Journal of Medicine*, **307**, 1436.
16. HO, J.L., POLDRE, P.A., MCENIRY, D. *et al.* (1984) Acquired immunodeficiency syndrome with progressive multifocal leukoencephalopathy and monoclonal B-cell proliferation. *Annals of Internal Medicine*, **100**, 693.
17. ROBINSON, W.S. (1985) Hepatitis B virus and the Delta Agent. In: *Principles and Practice of Infectious Diseases* (Ed. by G.L. Mandell, R.G. Douglas, Jr. and J.E. Bennett), 2nd edn, p. 1002. John Wiley and Sons, Inc., New York.
18. PERRILLO, R.P., CAMPBELL, C.R., SANDERS, G.E., REGENSTEIN, F.G. & BODICKY, C.J. (1984) Spontaneous clearance and reactivation of hepatitis B virus infection among male homosexuals with chronic type B hepatitis. *Annals of Internal Medicine*, **100**, 43.
19. DAVIS, G.L. & HOOFNAGLE, J.H. (1985) Reactivation of chronic type B hepatitis presenting as acute viral hepatitis. *Annals of Internal Medicine*, **102**, 762.
20. BROWN, S.T., NALLEY, J.F. & KRAUS, S.J. (1981) Molluscum contagiosum. *Sexually Transmitted Diseases*, **8**, 227.
21. KOVACS, J.A., KOVACS, A.A., POLIS, M. *et al.* (1985) Cryptococcosis in the acquired immunodeficiency syndrome. *Annals of Internal Medicine*, **103**, 533.
22. KERN, P., MULLER, G., SCHMITZ, H. *et al.* (1985) Detection of coronavirus-like particles in homosexual men with acquired immunodeficiency and related lymphadenopathy syndrome. *Klinische Wochenschrift*, **63**, 68.
23. LANE, H.C. & FAUCI, A.S. (1985) Immunologic abnormalities in the acquired immunodeficiency sydrome. *Annual Review of Immunology*, **3**, 477.
24. BELSITO, D.V., SANCHEZ, M.R., BAER, R.L., VALENTINE, F. & THORBECKE, G.J. (1984) Reduced Langerhans' cell Ia antigen and ATPase activity in patients with the acquired immunodeficiency syndrome. *New England Journal of Medicine*, **310**, 1279.
25. FELMAN, Y.M. & NIKITAS, J.A. (1983) Sexually transmitted molluscum contagiosum. *Dermatology Clinics*, **1**, 103.
26. ROSENBERG, E.W. & YUSK, J.W. (1970) Molluscum contagiosum: eruption following treatment with prednisone and methotrexate. *Archives of Dermatology*, **101**, 439.
27. HELIER, F.F. (1971) Profuse mollusca contagiosa of the face induced by corticosteroids. *British Journal of Dermatology*, **85**, 398.
28. GANPULE, M. & GARRETTS, M. (1971) Molluscum contagiosum and sarcoidosis: report of a case. *British Journal of Dermatology*, **85**, 587.
29. SOLOMON, L.M. & TELNER, P. (1966) Eruptive molluscum contagiosum in atopic dermatitis. *Canadian Medical Association Journal*, **95**, 978.
30. PEACHEY, R.D.G. (1977) Severe molluscum contagiosum infection with T cell deficiency. *British Journal of Dermatology*, **97** (Suppl. 15), 49.
31. PAULY, C.R., ARTIS, W.M. & JONES, H.E. (1978) Atopic dermatitis, impaired cellular immunity, and molluscum contagiosum. *Archives of Dermatology*, **114**, 391.
32. REICHERT, C.M., O'LEARY, T.J., LEVENS, D.L., SIMRELL, C.R. & MACHER, A.M. (1983) Autopsy pathology in the acquired immune deficiency syndrome. *American Journal of Pathology*, **112**, 357.
33. LOMBARDO, P.C. (1985) Molluscum contagiosum and the acquired immunodeficiency syndrome. *Archives of Dermatology*, **121**, 834.
34. REDFIELD, R.R., JAMES, W.D., WRIGHT, D.C. *et al.* (1985) Severe molluscum contagiosum infection in a patient with human T cell lymphotrophic (HTLV-III) disease. *Journal of the American Academy of Dermatology*, **13**, 821.
35. SARMA, D.P. & WEILBAECHER, T.G. (1985) Molluscum contagiosum in the acquired immunodeficiency syndrome. *Journal of the American Academy of Dermatology*, **13**, 682.
36. PENNEYS, N.S. & HICKS, B. (1985) Unusual cutaneous lesions associated with acquired immunodeficiency syndrome. *Journal of the American Academy of Dermatology*, **13**, 845.