III-3498 der Beilagen zu den Stenographischen Protokollen
des Nationalrates XVII. Gesetzgebungsperiode

BUNDESMINISTERIUM FÜR
WISSENSCHAFT UND FORSCHUNG

GZ 10.001/2-Parl/88 Wien, 4. März 1988

Parlamentsdirektion

Parlament
1017 Wien

1459/AB
1988 -03- 15
zu 1501/J

Die schriftliche parlamentarische Anfrage Nr. 1501/J-NR/88, betreffend neue Wege in der AIDS-Bekämpfung, die die Abg. Haupt und Genossen am 22. Jänner 1988 an mich richteten, beehre ich mich wie folgt zu beantworten:

ad 1)
Die Auswertung der bisherigen medizinischen Forschungsergebnisse in der Bekämpfung von AIDS fällt nicht in die Zuständigkeit des Bundesminsteriums für Wissenschaft und Forschung, sondern in die des Bundeskanzleramtes (Sektion VI - Volksgesundheit).

Das Bundesministerium für Wissenschaft und Forschung fördert die medizinische Forschung in diesem Bereich durch laufende Dotationen an einschlägig tätige universitäre Einrichtungen (Institute und Kliniken), an außeruniversitäre Forschungsinstitutionen (die Ludwig Boltzmann Gesellschaft errichtete 1986 an der Universität Innsbruck das Institut für AIDS-Forschung) sowie über direkte Finanzierung von Forschungsprojekten (Auftragsforschung; Fonds zur Förderung der wissenschaftlichen Forschung). Siehe Beilage 1

ad 2)

Dr. Braathen's Aussage, daß der genaue Infektionsweg des HIV-1 innerhalb des menschlichen Körpers nicht feststeht, ist richtig.

War man ursprünglich der Ansicht, daß dieses Virus lediglich CD-4-positive T-Helfer-Zellen befällt, weiß man nun, daß HIV-1 auch andere CD-tragende Zellen (Monozyten/Makrophagen, Nibta Langerhanszellen der Haut, Zellen des Zentralnervensystems) befällt.

Da z.B. Langerhanszellen in der normalen Immunantwort den T-Zellen vorgeschaltet sind, ist es denkbar, daß diese oder ähnliche Zellen zuerst befallen werden. Solche HIV-tragende Langerhanszellen könnten dann von sich aus T-Lymphozyten infizieren.

Der Befall der Langerhanszellen der Haut durch HIV wurde übrigens erstmalig von einer aus österreichischen (Angehörige der I.Univ.-Hautklinik Wien: Prof. Wolff, Prof. Stingl, Doz. Konrad, Dr. Tschachler, Dr.Groh) und US-Wissenschaftern (Mitarbeiter der Institute der NIH, vor allem Dr. Popovic vom National Cancer Institute) bestehenden Arbeitsgruppe beschrieben (s. beil. Sonderdruck 2).

Wenn auch der genaue Infektionsweg von HIV-1 im menschlichen Körper mangels geeigneter experimenteller Modelle (Tiermodelle) noch nicht genau bekannt ist, ändert dies nicht an der Tatsache, daß HIV-1 der Erreger von AIDS ist.

Wenn Dr. Duesberg nicht durch stichfeste epidemiologische, serologische und virologische Daten überzeugt werden kann, so vielleicht doch durch jene Personen, die nach entsprechender Virusexposition an AIDS erkrankt sind.
Die Tatsache, daß das Azidothymidin, ein gegen die Vermehrung von HIV-1 wirksames Medikament, das Fortschreiten der Erkrankung verlangsamt, darf wohl als ein weiterer Hinweis auf die ursächliche Rolle von HIV-1 am Zustandekommen von AIDS gewertet werden.

Es wäre daher zu hoffen, daß Dr. Duesberg von einer Selbstinfektion mit HIV-1 Abstand nehmen wird.

ad 3)
Dr. Gallo ist seit 1982 und nicht schon seit 1979 in der AIDS-Forschung tätig. Nach der Entdeckung des AIDS-Virus durch L. Montagnier gelang Gallo die in vitro Züchtung des Virus.

Es ist richtig, daß Dr. Gallo's Labor in Kooperation mit universitären und industriellen Forschungsinstituten an der Entwicklung eines Impfstoffes gegen AIDS tätig ist. Die Behauptung, das Team von Dr. Gallo hätte die Antikörperforschung aufgegeben, dürfte doch nicht ganz stimmen. Die Erläuterung der der "Antikörperforschung" zugrundeliegenden Überlegungen erfordert Vorkenntnisse des Informationsempfängers (vor allem auf dem Gebiet der Immunologie und der Virologie). (Prof. Stingl von der I. Univ.-Hautklinik Wien wäre allenfalls bereit, den Fragestellern im Rahmen eines Gesprächs die erforderlichen Basisinformationen zu vermitteln.)

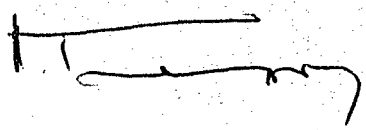
ad 4)
Das HIV ist nach HTLV-1 das zweite bekannte Retrovirus beim Menschen.

Das Studium des HIV-Virus kann zu grundlegenden Erkenntnissen über diese Gruppen führen; es ist zu erwarten, daß die genaue Kenntnis der Retroviren den Weg zur Entdeckung von Erregern bisher nicht erklärbarer Krankheiten und in Folge auch zu deren Heilung bereiten wird.

Aufgrund der eigenen Forschungsleistungen konnten österreichische Wissenschafter Kontakte mit international führenden Forscherteams in Europa (Institut Pasteur) und Übersee (National Institutes of Health, USA) anknüpfen und sie zur dauerhaften Zusammenarbeit ausweiten. Darüberhinaus gibt es zahlreiche bilaterale Kooperationsprojekte und regen Informationsaustausch mit ausländischen Experten.

Da die Zusammenarbeit mit den renommierten Arbeitsgruppen eine effiziente Einsetzung der in Österreich vorhandenen Forschungskapazitäten und - nicht zuletzt - auch der finanziellen Ressourcen ermöglicht, wird das Bundesministerium für Wissenschaft und Forschung auch in Hinkunft der internationalen Forschungskooperation auf dem Gebiet der AIDS-Grundlagenforschung höchste Priorität einräumen.

Der Bundesminister:



Beilagen

1

AIDS

Auftragsforschung BMWF

Radioimmunologische Untersuchungen zur Korrelation von Interferon gamma und Neopterin in vivo und zum Biosyntheseweg des Neopterin mit besonderer Berücksichtigung der GTP-abhängigen Cyclohydrolase
(Korrelation von Interferon gamma und Neopterin in vivo)

Institut für Med. Chemie u. Biochemie der Univ. Ibk.

1986 - 1988 (31.1.) S 495.631,--

Zielsetzungen: in vivo Beweis einer Korrelation zwischen der endogenen Interferon-gamma-Produktion und der Höhe der Neopterinspiegel in Harn und Blut von Patienten mit Erkrankungen, bei welchen der zellvermittelte Immunsystem involviert ist.

Installation einer Radioimmunoassay-Methode zur Messung der GTP-abhängigen Cyclohydrolase-Aktivität in Gewebshomogenaten

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AIDS - Analyse einer gesellschaftlichen Herausforderung

L.Boltzmann Institut für Medizinsoziologie

1986 -1988 (1.3.) S 841.760,--

Zwischenbericht liegt vor.

Zielsetzungen: Aufarbeitung der Komplexität des Phänomens als Grundlage für politisches Handeln; Rekostruktion und Analyse der verschiedenen Diskurse (Vergleich mit ausländischen); Beschreibung und Evaluation des Analysatorcharakters von AIDS hinsichtlich allg. Probleme und Veränderungen der Gesellschaft (insbesondere der Medizin); Herausarbeiten der auch in Österreich zu erwartenden Problemlagen anhand internationaler Trends.

Inhalt: Gesellschaftliche Bedeutung von AIDS - daher nicht nur die medizinische Bewältigungder tödlichen Krankheit, deren gesundheitspolitisches Ausmaß und der gesellschaftliche Umgang mit den Betroffenen sondern allgemein: sämtliche durch AIDS-motivierten gesellschaftlichen Aktivitäten - mit der Gesamtresonanz von AIDS in der Gesellschaft.

Zur Sozialpsychologie der Immunschwäche AIDS

Inst.f. Allgemeine Soziologie und Wirtschaftssoziologie der WU Wien
(Prof. SCHÜLEIN, ad personam)

1987 -1988 S 482.295,--

Zielsetzung: Untersuchung der sozialpsychologischen Hintergründe und psychodynamischen Aspelte der Reaktionsweisen auf die Immunschwäche AIDS auf individueller und gesellschaftlicher Ebene

Zielgruppe: Sozialberufe

Thesen: AIDS als reale Gefahr, welche besondere Vorkehrungen und Schutzmaßnahmen erfordert

AIDS spricht alle wichtigen Tabuthemen an, löst irrationale Angst und untergründige Faszination

AIDS als Abwehr für andere Ängste (Verschiebungsersatz und Projektionsfläche)

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in Genehmigung:

"Expression von Genabschnitten des HIV-1 und HIV-2 in bakteriellen Expressionsvektoren"

Institut für Hygiene der Univ. Innsbruck; Projektleiter: Univ.Prof.Dr. M. DIERICH

S 650.000,--

Kooperation mit Prof.L. MONTAGNIER, Institut Pasteur
Prof. FLECKENSTEIN, Univ. Erlangen

AIDS

Fonds zur Förderung der wissenschaftlichen Forschung

laufendes Projekt

Die Bedeutung des Neopterins bei AIDS - AIDS-related complex and AIDS-Risikogruppen

Prof. WACHTER, Inst. f. Med. Chemie und Biochemie, Univ. Ibk.
1986 -1988 S 1,085.500,--

2 Neuanträge

AIDS - die individuelle, subkulturelle und gesellschaftliche Dimension einer komplexen Stigmakategorie (DDr. KOHLBACHER, 2 Jahre, Antrag S 597.757,--)

AIDS - Chemotherapie
(Prof. GRIENGL, TU Graz, Inst.f. Org. Chemie u. org.-chem. Technologie,
1 Jahr, Antrag S 570.126,--)

AIDS

Technologieförderung

Entwicklung und Herstellung spezifischer Diagnosesysteme (Immunofluoreszenz) zur sicheren Diagnostizierung von Viruserkrankungen (AIDS, FSME) resp. Prognostizierung der Verlaufsentwicklung)
1986/87
Gesamtkosten 11,6 Mio. S; Technologieförderung: S 5,05 Mio.

RAPID COMMUNICATION

Epidermal Langerhans Cells—A Target for HTLV-III/LAV Infection*

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Langerhans cells (LC) are bone marrow-derived, Ia$^+$, CD1$^+$, CD4$^+$, ATPase$^+$ dendritic antigen-presenting cells within the human epidermis. Since the CD4 molecule has been implicated as a receptor structure for HTLV-III/LAV (human T-cell leukemia virus/lymphadenopathy-associated virus), we asked whether LC from HTLV-III/LAV-seropositive individuals display signs of HTLV-III/LAV infection. In skin biopsies from 7/40 HTLV-III/LAV-infected persons (1 asymptomatic carrier, 2 patients with acquired immunodeficiency syndrome (AIDS)-related complex and 4 patients with AIDS), LC were the only epidermal cells to react with a monoclonal antibody specific for the HTLV-III core protein p17. A varying percentage of p17$^+$ LC were morphologically altered with blunt dendrites and poorly demarcated cellular contours. In one of these biopsies, the presence of LC-associated viral particles characteristic of HTLV-III/LAV as well as cytopathic changes in approximately one-third of the LC population were demonstrated by electron microscopy. These results strongly suggest that LC may harbor HTLV-III/LAV. The infection of LC with this retrovirus may have deleterious consequences for the immunologic functions of this cell system and may thus contribute to both the acquisition of immunodeficiency and the infectious and neoplastic complications of AIDS. *J Invest Dermatol 88:233–237, 1987*

It is generally believed that the immunodeficiency in ARC/AIDS (AIDS-related complex/acquired immunodeficiency syndrome) patients is a direct consequence of a pronounced affinity of HTLV-III/LAV (human T-cell leukemia virus/lymphadenopathy-associated virus) for CD4 (T4)$^+$ helper/inducer T lymphocytes, which results in lethal damage of this critical immunocompetent cellular subset [1]. Indeed, it is well established that HTLV-III/LAV can frequently be detected in and isolated from culture fluids of lectin/lymphokine-driven peripheral blood mononuclear cells from ARC/AIDS patients [2,3]. Furthermore, when peripheral mononuclear cells from healthy individuals are inoculated with HTLV-III/LAV, virus replication reportedly occurs predominantly in CD4$^+$ lymphocytes [4]. This tropism is currently explained by the capacity of certain domains of the CD4 molecule to serve as specific binding/receptor structures for the retrovirus [5–8]. There now exists evidence that HTLV-III/LAV can be encountered in follicular dendritic cells [9] and certain mononuclear phagocytes [10,11] which also bear CD4 antigens [12,13].

Langerhans cells (LC) are bone marrow-derived dendritic cells which preferentially populate stratified squamous epithelia. Within normal human epidermis they are the only cells to exhibit ATPase activity, class II alloantigens, Fc-IgG and C3 receptor sites, CD1 (T6) and, to a lesser extent, CD4 antigens [13–15]. In 1984, Belsito et al reported that ARC/AIDS patients have decreased numbers of Ia$^+$/ATPase$^+$/CD1$^+$ epidermal LC [16,17]. Such quantitative phenotypic alterations within the LC population of ARC/AIDS patients may either occur as a direct consequence of HTLV-III/LAV infection of LC or their precursors or, alternatively, represent a secondary phenomenon superimposed on an already existing state of HTLV-III/LAV-induced immunodysregulation. In this study, we used immunofluorescence techniques employing monoclonal antibodies specific for HTLV-III core proteins as well as electron microscopic techniques to determine whether LC from HTLV-III/LAV-seropositive individuals display alterations indicative of HTLV-III/LAV infection.

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Abbreviations:
AIDS: acquired immunodeficiency syndrome
anti-p17: monoclonal antibody against HTLV-III core protein p17
anti-p24: monoclonal antibody against HTLV-III core protein p24
APC: antigen-presenting cell(s)
ARC: AIDS-related complex
FITC: fluorescein isothiocyanate
HTLV-III: human T-cell leukemia virus
KS: Kaposi's sarcoma
LAV: lymphadenopathy-associated virus
LC: Langerhans cell(s)
moAB: monoclonal antibody(-ies)
PBS: phosphate-buffered saline
PE: phycoerythrin

0022-202X/87/$03.50

PATIENTS AND METHODS

Patients Our study population consisted of a total of 40 HTLV-III/LAV-seropositive (Abbott Elisa and/or specific bands by Western blot analysis) individuals suffering from either AIDS, ARC, or the asymptomatic state of HTLV-III/LAV infection (Table I). Controls included HTLV-III/LAV-seronegative healthy volunteers as well as HTLV-III/LAV-seronegative patients suffering from a variety of inflammatory and neoplastic skin disorders, including, in particular, classical Kaposi's sarcoma (KS) and cutaneous T-cell lymphoma (Table I).

Tissue Sampling and Processing Incisional or 4-mm punch biopsy specimens were obtained from skin overlaying KS lesions in patients suffering from either AIDS-associated or classical KS and from lesional skin of control individuals with various pathologic skin conditions. In all other subjects, biopsy specimens of normal skin were taken from randomly chosen body regions. Fresh biopsy specimens were snap-frozen in liquid nitrogen and stored at −70°C until use. Four-micron cryostat sections were mounted on glass slides, air-dried, acetone-fixed, and subjected to immunohistologic processing. In some patients, epidermal sheets were prepared from fresh biopsy specimens applying an ammonium-thiocyanate separation technique [18], fixed, and subjected to immunohistologic processing in the same manner as were cryostat sections. A biopsy specimen from one individual with anti-p17/anti-p24 (HTLV-III core proteins)-reactive LC was processed for conventional electron microscopic analysis.

Monoclonal Antibodies The following monoclonal antibodies (moAb) were used. (1) Anti-HTLV-III core protein p17 [19]:IgG_1. (2) Anti-HTLV-III core protein p24 [20]:IgG_1. The optimal working dilutions for anti-p17 (5 μg/ml) and anti-p24 (2 μg/ml) were determined on lymph node cryostat sections from an ARC patient. In accordance with earlier reports [21] we found that anti-p17 and anti-p24 reactivity was essentially confined to germinal centers and associated with dendritic cells. (3) Fluorescein isothiocyanate (FITC)-OKT6 (Ortho Inc., Raritan, New Jersey):IgG_1; working dilution = 1:50. (4) Phycoerythrin (PE)-anti-Leu-4 (Becton Dickinson, Sunnyvale, California):IgG_1; working dilution = 1:20.

Immunohistologic Studies Fixed cryostat sections (fixed epidermal sheet preparations) were incubated for 30 min at room temperature (16 h at 4°C) with the appropriately diluted first-step monoclonal reagent. To detect reactive cells, FITC-labeled goat antimouse IgG $F(ab')_2$ (Tago, Inc., Burlingham, California) or Texas Red AP rat antimouse IgG, F'2 (Jackson Immunoresearch Laboratories, Inc., Avondale, Pennsylvania) were used. For double labeling purposes, the incubation chain was prolonged by first a 30-min incubation with phosphate-buffered saline (PBS)/5% normal mouse serum followed by exposure of cryostat sections (epidermal sheets) to FITC- or PE-labeled moAb. Sections (epidermal sheets) were mounted with PBS/glycerine and examined under a Leitz-Ortholux II fluorescence microscope with an appropriate FITC and PE filter setting.

Table I. Anti-p17 Reactivity of Epidermal Langerhans Cells in HTLV-III/LAV-Infected and Noninfected Individuals

	No. of Persons with $p17^+$ LC / No. of Persons Tested
HTLV-III/LAV-seropositive persons	
Asymptomatic	1/7
ARC	2/11
AIDS	
KS	4*/16
OI	0/6
Total	7/40
HTLV-III/LAV-seronegative persons	
Healthy volunteers	0/24
Inflammatory skin disease	0/40
Neoplastic skin disease other than KS	0/14
Classical KS	1/6
Total	1/84

Abbreviations: AIDS, acquired immunodeficiency syndrome; ARC, AIDS-related complex; KS, Kaposi's sarcoma; OI, opportunistic infection(s).

*In one of these patients, anti-p17 reactivity of LC was accompanied by anti-p24 immunolabeling of these cells. In this specimen, the presence of LC-associated viral particles characteristic of HTLV-III/LAV as well as cytopathic changes in approximately one-third of the LC population were demonstrated by electron microscopy.

RESULTS

We have identified anti-p17-reactive epidermal cells in skin biopsies from 7/40 HTLV-III/LAV-infected individuals, only one of which additionally showed the presence of $p24^+$ epidermal cells (Table I). These cells were dendritic in shape, uniformly expressed CD1 antigens, lacked CD3 (T3) antigens and, thus, represented LC (Fig 1). In certain sections, $p17^+/CD1^+$ LC appeared to be severely damaged with blunt dendrites and a loss of morphologic integrity. Serial sectioning revealed that the percentage of anti-p17-reactive LC in a given biopsy specimen was quite variable and ranged between 0–90%. The reason for this large variability may be due to the rather irregular and occasionally patchy distribution pattern of anti-p17-reactive LC as evidenced on epidermal sheet preparations.

Replacement of anti-p17/anti-p24 by either isotype-matched mouse moAb or normal mouse serum consistently yielded negative results, as did the use of FITC-labeled antisera against human Ig. This latter finding essentially excludes the possibility that anti-p17/anti-p24 staining has occurred as a consequence of p17/anti-p17 (p24/anti-p24) immune complex binding to LC Fc-IgG receptors. To determine whether reactivity of LC with moAb against HTLV-III/LAV core proteins is indicative of the presence of LC-associated HTLV-III/LAV, we examined by electron microscopy the epidermis of the biopsy specimen containing both $p17^+$ and $p24^+$ LC for the presence of virus particles. With the exception of slightly widened intercellular spaces the overall structure and organization of the epidermis was well preserved. Inflammatory cells were consistently absent. Whereas keratinocytes as well as melanocytes appeared entirely unaltered, we found that approximately 30% of all LC—as identified by their characteristic Birbeck granules [14]—displayed signs of moderate to severe damage, as evidenced by condensation of both cytoplasm and nuclear chromatin, swelling of cytoplasmic organelles, vacuole formation, and, occasionally, frank cytolysis (Fig 2). Since even the most severely injured cells regularly contained Birbeck granules, we conclude from these observations that ultrastructurally visible epidermal cell injury in this given biopsy specimen is confined to the LC population. While intracytoplasmic viral particles were not detected, mature viral particles were seen in intercellular spaces between normal-appearing LC and neighboring keratinocytes (Fig 2). While signs of early viral budding could not be unequivocally demonstrated, intact LC occasionally exhibited surface protrusions indicative of late viral buds. Intercellular spaces between keratinocytes were devoid of these particles as were the surfaces of and intercellular spaces surrounding damaged LC. Viral particles were 90–110 nm in diameter with a dense round-cylindrical central core and a peripheral unit membrane. Thus, both the morphology and size of these viral particles were consistent with that of HTLV-III/LAV. Although we cannot definitively prove that the cytopathic changes seen in a subpopulation of LC are due to injurious effects of these viral particles, we know of no other skin condition where, in the absence of any inflammatory cells, moderate to severe structural changes are entirely confined to the LC population.

Immunohistologic examination of skin biopsy specimens from both healthy volunteers (n = 24) and patients with a variety of either inflammatory (n = 40) or neoplastic (n = 20) skin diseases

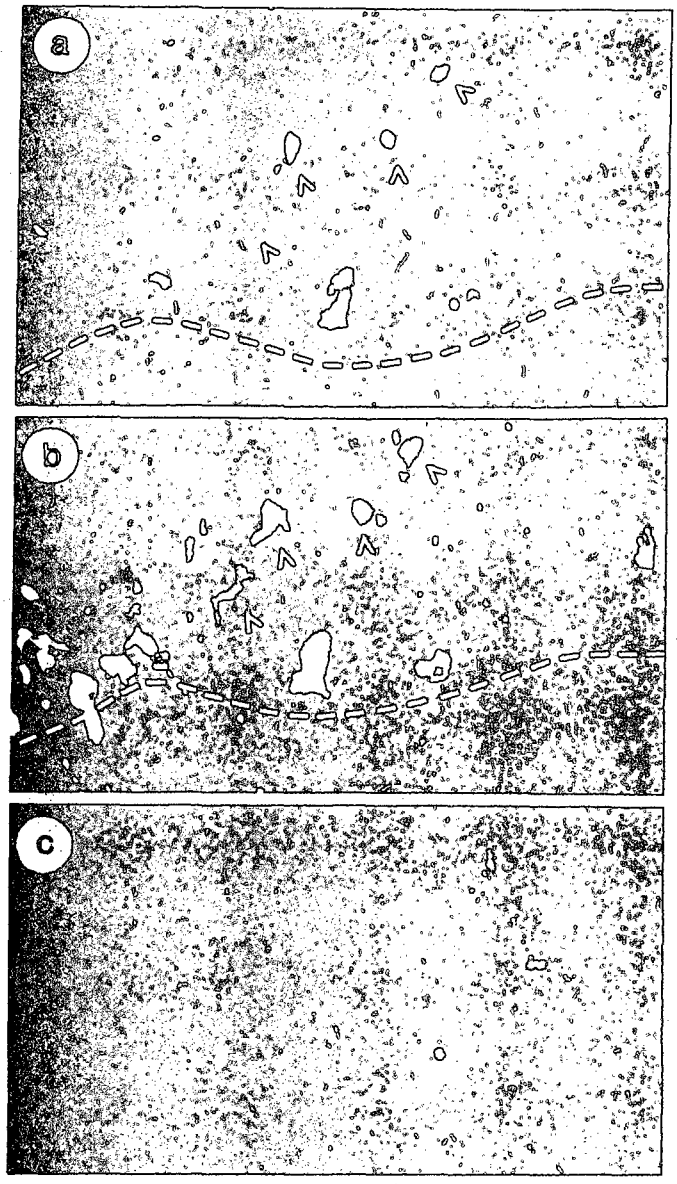

Figure 1. Immunohistologic micrographs of cryostat sections (*a,b*) and an epidermal sheet preparation (*c*) of clinically normal skin from a 31-year-old ARC patient; using indirect immunofluorescence, anti-HTLV-III core protein p17 moAb selectively reacts with dendritic epidermal cells (*a, arrowheads; c*); these cells uniformly express CD1 antigens as visualized by FITC-OKT6 double-labeling (*b, arrowheads*). The *dotted lines* mark the dermal-epidermal junction (*a,b*). × 250.

for the presence of anti-p17/anti-p24 immunolabeling consistently yielded negative results with one notable exception: a 40-year-old male patient with KS of 7 years' duration (Table I). A biopsy specimen of lesional skin revealed the presence of anti-p17-reactive, $CD1^+$ dendritic epidermal cells. Since repeated attempts to detect circulating HTLV-III/LAV-specific antibodies were negative and since this patient neither belongs to an ARC/AIDS high-risk group nor displays signs of immunodeficiency, a diagnosis of classical KS rather than AIDS-associated KS is warranted. Attempts to rescue the virus from skin biopsies and peripheral blood mononuclear cells from this patient by coculture with HTLV-III/LAV-permissive cell lines are planned. It should be noted, however, that the presence of serum antibodies to HTLV-III is not an absolute determining factor in identifying virus-infected individuals since, in infrequent instances, virus has been isolated from clinically normal, seronegative donors [22].

DISCUSSION

In view of recent studies showing that the CD4 antigen—which serves as a critical binding/receptor structure for HTLV-III/LAV—is present on epidermal LC [13–15], we asked whether this cell system could be a site of HTLV-III/LAV infection. The results presented here strongly support this contention. We showed that in 7 of 40 HTLV-III/LAV-seropositive individuals reactivity of LC with HTLV-III-specific antibody occurred, and when one of these positive biopsy specimens was examined electron microscopically we detected LC-associated viral particles whose size and morphology were consistent with that of HTLV-III/LAV. Additionally, this biopsy specimen clearly showed that while other epidermal cells were spared, approximately 30% of LC displayed signs of moderate to severe damage.

While in this particular patient, epidermal LC reacted with both anti-p17 and anti-p24 moAb, anti-p17 reactivity of LC in 6 additional biopsy specimens from HTLV-III/LAV-seropositive individuals was not accompanied by anti-p24 staining. The reason(s) for this discrepancy is (are) presently unknown, and only limited experience exists regarding the application of moAb against HTLV-III/LAV for immunohistologic purposes. It may simply be a quantitative phenomenon, i.e., antibody-reactive epitopes of p17 antigens may be more abundant and more accessible than antibody-reactive moieties of p24 antigens.

The possibility that anti-p17 reactivity of LC is due to cross-reactivity of anti-p17 with non-HTLV-III-encoded proteins—similar to the regularly observed cross-reactivity of anti-HTLV-I p19 with certain epithelia [23]—cannot be definitively excluded. Since, however, 83 skin biopsy specimens from both healthy donors and from patients with a wide variety of skin diseases were not reactive with anti-p17, a cross-reactivity of this antibody with non-virus-encoded moieties appears extremely unlikely. While anti-p17 has been shown to be non-cross-reactive with HTLV-I and HTLV-II antigens (F. diMarzo Veronese, unpublished results), the theoretical possibility remains that anti-p17 cross-reacts with an as yet unknown human (retro) virus capable of inducing the morphologic alterations we observed in positively stained LC. Whether such a putative virus may even be linked to the occurrence of KS in the only anti-p17-reactive HTLV-III/LAV-seronegative individual is highly speculative and remains to be determined in further studies.

In spite of these caveats, we feel that, collectively, our results (antibody reactivity, presence of retroviral particles, damage of LC) favor the concept that LC can be infected and, subsequently, injured by HTLV-III/LAV. There are numerous possible sites at which such an infection may occur, since LC originate from bone marrow precursors [24] and travel along an as yet unknown migration pathway to their epidermal residence.

The elucidation of the mode and site of infection may help to account for the variability in the number of antibody-reactive cells seen in different sections of the same biopsy. Since LC turnover in normal epidermis is a slow phenomenon, only an HTLV-III/LAV infection of long duration could lead to a high proportion of antigen-positive cells at this site, should the precursors be the initial target. If an infection of resident LC occurs, a phenomenon similar to that seen with T lymphocytes may be operative: a possible "activation" or alteration of these cells may promote their susceptibility to invasion by the virus. Since numerous factors may influence the turnover rate and the phenotype of these cells (e.g., physicochemical agents, drugs, soluble mediators), multiple biopsy specimens from various sites taken at different times throughout the infectious process are needed to determine the actual frequency of LC involvement in the course of HTLV-III/LAV infection.

In general, detection of HTLV-III/LAV in lymphoid cells from infected individuals is a rare event [25]. Virus detection in non-T cells (mononuclear phagocytes, follicular dendritic cells) is at least comparable in frequency to that encountered in T cells [21]. It may well be that T cells are more prone to HTLV-III/LAV-

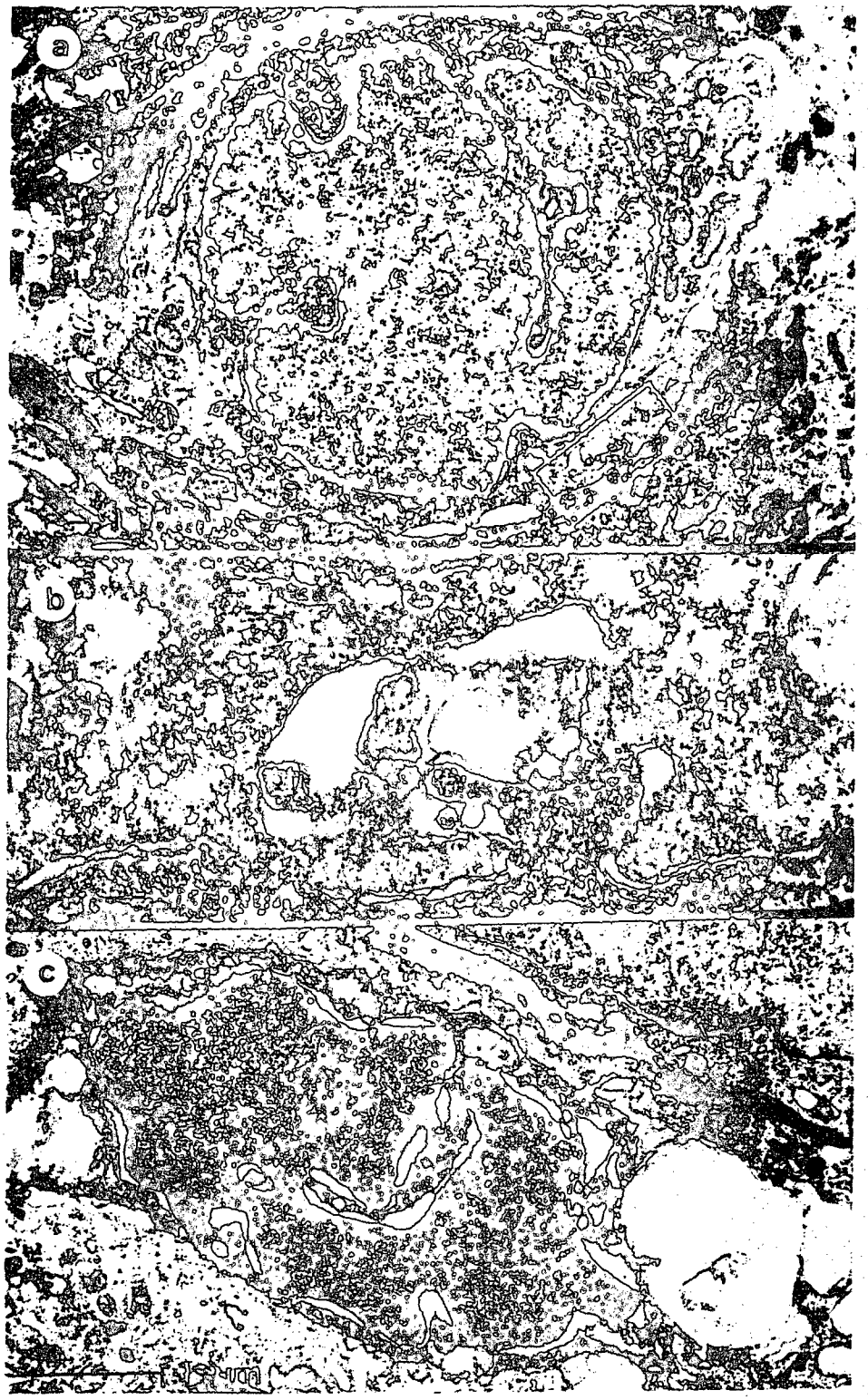

Figure 2. Electron micrographs of clinically normal epidermis overlaying a KS lesion of a 56-year-old AIDS patient. Whereas the majority of LC, as identified by the presence of Birbeck granules (*arrows*), appear morphologically intact (*a*), approximately 30% show severe cytoplasmic degeneration and cytolysis (*c*). Typical 90–110 nm retrovirus-like particles with a dense core were found in about 5% of the ultrathin sections examined and were confined to the intercellular space between normal-appearing LC and adjacent keratinocytes [*rectangulated area* in (*a*)]. Figure *b* shows a higher magnification of this area revealing viral particles between small villous processes of a LC (top) and a keratinocyte (bottom). One of these villous processes shows surface protrusions indicative of a late viral bud (*arrowhead*).

induced cytopathy than $CD4^+$ non-T cells [26]. Should this be true, cells of the mononuclear phagocyte system as well as LC might serve as a reservoir for this retrovirus and thus critically influence the course of the disease.

Further implications of our results can be deduced from what is known about the biologic functions of epidermal LC. It is firmly established that, similar to monocyte/macrophages, these cells are antigen-presenting cells (APC) and are responsible for elicitation of T-cell responses toward antigens introduced via the skin or, perhaps, even neoantigens originating in the skin [14]. The consequences of HTLV-III/LAV infection of APC may be twofold. On the one hand, it may impair the capacity of these cells to present antigen to T cells in an immunologically relevant fashion. Should, on the other hand, HTLV-III/LAV-infected APC maintain their capacity to interact with lymphocytes, a transmission of this retrovirus into the T-cell compartment might

occur. Either event or both events would result in a state of immunodeficiency contributing to the infectious and neoplastic complications of AIDS.

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Note added in proof: Following submission of this manuscript, ultrastructural examination of an additional biopsy specimen from the patient with p17$^+$/p24$^+$ LC now revealed unequivocal signs of HTLV-III/LAV-like virus budding from LC. (P. Schenk et al, manuscript in preparation).

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