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Lymphadenopathy in drug addicts

A study of the distribution of T lymphocyte subsets in the lymph nodes

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Summary. Lymph node biopsies from 24 male heroin addicts and 9 control patients were studied using immunohistochemical, and in $\frac{1}{3}$ of cases, quantitative methods. 5 out of these 24 patients were also homosexual. All presented diffuse lymphadenopathy but none had any signs or symptoms of opportunistic infections nor Kaposi's sarcoma. Histologically the lymph nodes showed a very peculiar follicular hyperplasia with atrophy of the paracortex. The germinal centers appeared irregular, ill defined and contained clusters of small lymphocytes. The mantle zone was atrophic. Immunolabelling of T lymphocytes by monoclonal antibodies showed that germinal centers were invaded by small nests of Leu 2a (and OKT8) positive lymphocytes, i.e. chiefly cytotoxic-suppressor phenotype; the number of these cells increased by about 100 times in the follicles. OKT4 (and Leu 3a) positive cells, i.e. chiefly helper-inducer phenotype, appeared to decrease. These histological and immunohistochemical changes are considered to be suggestive of drug addicts' lymphadenopathy, and also possibly of other conditions increasing the risk of AIDS.

Key words: Acquired immunodeficiency – Heroin addicts – Follicular hyperplasia – T cell subsets – Immunohistochemistry

Clinical and immunological features of the acquired immune deficiency syndrome (AIDS) have been defined at UCLA conferences (Gottlieb et al. 1983). Further studies (Miller et al. 1984) have shown that in many cases lymph nodes enlargement in homosexual men preceeds the onset of the typical syndrome. Histologically these enlarged nodes present a peculiar follicular hyperplasia (Ioachim et al. 1983, Marche et al. 1984, Modlin et al. 1983) associated with atrophy of the mantle zone (Modlin et al. 1983). The same histological changes occur in the lymph nodes of subjects at risk for AIDS, that is to say, those who at the moment of investigations show no signs of opportunistic infection or Kaposi's sarcoma (Domingo and

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Chin 1983, Guarda et al. 1983, Marche et al. 1984); however these subjects usually present an inversion of circulating T lymphocytes helper/suppressor ratio (Butkus Small et al. 1983, Gottlieb et al. 1983, Kornfeld et al. 1982). Such a state is generally referred to as "pre-AIDS", the most typical example of which is diffuse lymphadenopathy in homosexual men (Chan et al. 1984, Guarda et al. 1983, Miller et al. 1984) and probably also lymphadenopathy in drug addicts (Domingo and Chin 1983, Geller ans Stimmel 1973, Guarda et al. 1983).

According to recent investigations lymph nodes from homosexual patients presenting AIDS, with Kaposi's sarcoma, show a decrease in the number of helper T cells in the paracortical areas, with an apparent increase of suppressor T lymphocytes (Modlin et al. 1983). Similar changes occur in the lymph nodes of homosexual men whether they present opportunistic infection or not (Chan et al. 1984).

The following study was done to investigate the histological changes and particularly the distribution of T cell subsets in drug addicts' lymphadenopathy.

Material and methods

Lymph node biopsies from 24 drug addict male patients were examined. Among them 19 denied any homosexual practice; 5 patients admitted occasional homosexual experiences. The age of the patients ranged between 19 and 56 years. All confessed to have abused heroin for at least one month generally associated with marijuana or similar drugs. The longest period of heavy drug abuse was 10 years. All patients had lymphadenopathy at least in two areas, in addition to the inguinal region. None was haemophilic nor did any belong to an ethnic group predisposed to AIDS. In all cases clinical charts were reviewed. In 17 cases some serological and/or immunological data were available (Table 1). Determination of T lymphocyte subsets in the blood was performed in 9 cases[1].

Lymph node biopsies from 9 patients presenting conditions unrelated to AIDS were used as controls. These 9 cases included one viral lymphadenopathy, one case of rheumatoid arthritis, one case consistent with toxoplasmosis, one case of Crohn's disease, one case consistent with cat scratch disease and 4 cases of follicular lymphoid hyperplasia of undetermined origin. 7 patients were women, 2 men. Their age ranged between 12 and 58 years (Table 2).

In all drug addict patients and in the control group, the lymph node biopsy specimen, obtained not more than 15 min after it was excised, was divided into 3 parts: one piece of tissue was immediately fixed in formaldehyde-mercuric chloride solution; another piece in formaldehyde and/or Bouin's solution; and a third piece was immediately frozen in liquid nitrogen and kept at $-70°$ C for immunohistochemical investigations. Technically sufficient frozen material was available in 21 out of 24 drug addict cases and in all 9 control cases. In 6 patients multiple lymph node biopsies were obtained (in 4 of them 2 successive biopsies, and in 2, 3 successive biopsies).

For routine histology fixed specimens were embedded in paraffin; the sections were stained with haematoxylin-eosin (H.E.), Giemsa, Gomori and Periodic Acid Schiff (PAS) stains. For immunohistochemical investigations 4 to 5 μ thick cryostat cut fresh sections were used. T lymphocytes were revealed by Leu 1, Leu 2a, Leu 3a (Becton Dickinson laboratory systems), as well as OKT3, OKT4 and OKT8 (Ortho diagnostic systems) monoclonal antibodies. B lymphocytes were stained using monoclonal pan B antibody (Dakopatts Corp.) and also commercial monoclonal (IgA, IgD, IgM, kappa, lambda) or polyclonal (IgG) light and heavy chain antibodies. The immunohistochemical stainings were done by peroxidase labelling using Avidin

1 Performed in the Division of Immunology and Allergology of Geneva Cantonal Hospital, Head: Prof. A. Cruchaud, whom we thank for this information.

Table 1. Clinical and biological findings in 24 drug addict patients

Case No.	Age	Clinical findings	Biological findings
1	27	DL for 12 months, history of viral hepatitis A and B, anemia	HBsS Ab (+), HBss Ag (−), HBcC Ab (+), Chlamydia (−), syphilis (+), CMV (−), toxoplasmosis (−), rubeola (−), EBV (−)
2	26	DL	
3	25	DL for 30 months	toxoplasmosis (−), brucella (−), syphilis (−)
4	19	bilateral axillary lymph nodes for 3 weeks	
5	25	DL for 8 months, fever, enlarged liver and spleen, lymphopenia (7%)	syphilis (−), HBsS Ag (−), HBsS Ab (+), HBcC Ab (+), mycoplasma (−), ADV (−), Q fever (−), ornithosis (−), influenza A + B (−), CMV (−), alveolar echinococcus (−), toxoplasmosis (−)
6	20	DL for 5 years	
7	24	DL for 10 months, bilateral conjonctivitis	HBsS Ag (−), HBsS Ab (−), HBcC Ab (+), CMV (−), toxoplasmosis (−), EBV (−), infectious mononucleosis (−)
8	31	DL for 5 months, enlarged liver, weight loss	toxoplasmosis (−), syphilis (−), infectious mononucleosis (−)
9	21	DL for 3 months	
10	24	DL for 5 months, lymphocytosis (55%)	syphilis (−), toxoplasmosis (−), infectious mononucleosis (−), CMV (−), viral hepatitis (−)
11	22	DL for 2 years	
12	22	DL for 6 months, history of viral hepatitis	HBsS Ag (−), HBsS Ab (+), HBcC Ag (−), HBcC Ab (+), toxoplasmosis (−), CMV (−), infectious mononucleosis (−)
13	28	DL, viral hepatitis	
14	20	DL for 3 months, fever, viral hepatitis 1 year before	HBsS Ag (−)
15	22	DL for several weeks	
16	25	DL, nasal herpes	toxoplasmosis (+)
17	22	DL for 6 months, enlarged liver and spleen, viral hepatitis, syphilis	HBsS Ag (+), HBcC Ab (+), HBeE Ab (+), syphilis (+), infectious mononucleosis (−), syncitial virus (−), ADV (−), mumps (−), toxoplasmosis (−)
18	23	DL	toxoplasmosis (+), CMV (old infection?) infectious mononucleosis (−), syphilis (−)
19	26	DL, toxoplasmosis 1 year before, history of viral hepatitis, fever, asthenia, weight loss, lymphocytosis	HBsS Ag (−), HBsS Ab (−)
20*	21	DL for 1 year, weight loss, lymphocytosis (69%), anemia	CMV (−), toxoplasmosis (−), syphilis (−), infectious mononucleosis (−)
21*	33	DL for 3 months	EBV (−), CMV (−), HBsS Ab (+)

Table 1 (continued)

Case No.	Age	Clinical findings	Biological findings
22*	23	DL for several months, lymphocytosis (42.5%)	HBsS Ag (+), infectious mononucleosis (−), CMV (−), syphilis (±), toxoplasmosis (−)
23*	56	DL for 18 months, enlarged spleen and liver, weight loss, headache, IgG increased	CMV (+), toxoplasmosis (−), herpes (−), varicella (−), measles (−), syphilis (−), mycoplasma pneumoniae (+)
24*	31	DL, weight loss, IgG increased	HBcC Ab (+), HBsS Ab (+), HBcC Ag (−), HBsS Ag (−), toxoplasmosis (−), CMV (−), syphilis (−), Brucella (−), herpes (−), Pasteurella (−)

DL = diffuse lymphadenopathy, * = admitted homosexuality

Table 2. Clinical and biological findings in 9 control cases (no drug abuse, no homosexuality)

Case No.	Sex	Age	Clinical findings	Biological findings
1	F	13	enlarged cervical lymph node for 5 months	varicella (−), toxoplasmosis (−), infectious mononucleosis (−), mycoplasma pneum. (−), mumps (−), Q fever (−), serology consistent with a recent herpes virus infection
2	F	50	DL for 3 months, rheumatoid polyarthritis	
3	F	17	cervical lymph nodes for 3 months, VS accelerated	toxoplasmosis (−), syphilis (−)
4	M	58	cervical lymph node for 2 months, VS accelerated, asthenia, weight loss	toxoplasmosis (−), infec. mononucleosis (−), listeria (−)
5	F	25	retroauricular lymph node for sev. months	
6	M	42	axillary lymph nodes consistent with cat scratch disease	viral hepatitis (−), syphilis (−), toxoplasmosis (−), infectious mononucleosis (−), CMV (−), herpes (−)
7	F	43	mesenteric lymph node, Crohn's disease	
8	F	12	bilateral cervical lymph nodes for sev. weeks, chemosis, palpebral edema, serious rhinitis, clin. diagn. = chlamydia	CMV (−), toxoplasmosis (−), infectious mononucleosis (−)
9	F	42	cervical and axillary lymph nodes, consistent with toxoplasmosis, lymphocytosis (46%)	viral hepatitis (−), syphilis (−), infectious mononucleosis (−), herpes (−), CMV (−)

Biotin peroxidase complex (ABC) (Hsu et al. 1983). Peroxidase was revealed by aminoethylcarbazol (AEC) or diaminobenzidin (DAB). The nuclei were stained by haematoxylin; in some cases no counterstaining was done.

8 lymph nodes from drug addicts and 4 from control cases were selected for quantitative analysis (Weibel and Elias 1967, Elias et al. 1981). The requirement for this choice was the availibility of large enough cryostat cut sections to observe at least 6 distinct germinal centers in the preparation. These preparations were then projected on a screen provided with a multipurpose morphometric grid and examined with an automatic Wild M20 stage microscope (Freerer and Weibel 1966). Using a low magnification (64×) the sections were placed in such a way that one edge of the germinal center would touch the upper edge of the grid (thus the observer could not select the "best" field). Under this low magnification an estimation of the number of Leu 1 (or OKT3), Leu 2a (or OKT8) and Leu 3a (or OKT4) positive cells was made. Then without moving the section, the magnification was brought up to 400× in order better to distinguish the individual cells. The number of labelled lymphocytes was counted in 7 different fields (one or 2 fields per germinal center) in each drug addict and control case. The proportion of Leu 2a (or OKT8) positive cells as well as those of Leu 3a positive cells to Leu 1 (or OKT3) positive cells was calculated.

Results

Clinical findings[2]*:* Clinical and biological data obtained in drug addicts and in control group are summarized in Tables 1 and 2 respectively. All drug addict patients presented diffuse lymphadenopathy observed by a physician for 3 weeks to 5 years duration. Their major complaints were fatigue, weight loss, abdominal pain and occasionally headache. Hepatomegaly and/or splenomegaly were very seldomly observed and when present, were considered to be slight or moderate. There were no signs or symptoms of an opportunistic infection nor of Kaposi's sarcoma.

Routine blood analysis revealed an accelerated sedimentation rate; anemia was noted in 2 patients, lymphopenia in one patient and lymphocytosis in 4 patients. In 2 cases immunoelectrophoresis showed an increased IgG. Among 11 subjects investigated for hepatitis B, 2 were HBsS-Ag positive, 5 had anti-HBsS antibodies and 6 anti-HBcC antibodies. Toxoplasmosis serology was performed in 14 cases; it was negative in 12 and positive in 2. Serology for syphilis investigated in 11 patients, was negative in 8, positive in 2 and doubtful in one. The Paul-Bunnell reaction for infectious mononucleosis was negative in 8 patients; serology for cytomegalovirus was negative in 9 patients, positive in one and consistent with an old infection in another one. Other viral serologies such as Epstein-Barr, mumps, rubeola were all negative (Table 1). A study of the peripheral T cell subsets was performed in 9 cases: helper/suppressor ratio was normal in 2 and inverted in 7 patients. Detailed clinical and hematological findings in these patients will be reported elsewhere.

Histological findings. The comparison of histological findings in drug addict patients and in the control group is summarized in Table 3. The changes in homo- and heterosexual heroin abusers were the same. A constant finding

2 We thank Prof. J. Fabre, Head of Medical Policlinics, and Dr. E. Conne, for clinical information of cases 1, 16, 17, 19, and Dr. J.F. Balavoine for that of cases 2, 21, 22, 23.

Table 3. Histological and immunohistochemical findings

	Drug addicts ($N=24$)	Controls ($N=9$)
Histology		
General appearance	architecture preserved	architecture preserved
Follicles	irregular, very large with idented ill defined countours; presence of nests of small lymphocytes	irregular, large with rounded and sharp countours; constituted essentially of transformed cells
Mantle zone	thin, mottled, in places absent	well defined, generally thick
Paracortex (T-zone)	low cellularity, very narrow between large follicles	variable
Epithelioid granulomas and/or sinus histiocytosis	occasionally present	present only in toxoplasmosis
Immunohistology		
Follicles	invaded by OKT8 (Leu 2a) labelled T lymphocytes (chiefly cytotoxic/suppressor phenotype); practically no OKT4 (Leu 3a) labelled cells	practically no OKT8 (Leu 2a) labelled cells; a few OKT4 (Leu 3a) labelled T lymphocytes (chiefly helper/inducer phenotype)
Mantle zone	interrupted rim of IgD and IgM positive B lymphocytes; reduction of their number	sharp and regular rim of IgD and IgM positive B lymphocytes
Paracortex (T-zone)	OKT8 (Leu 2a) positive cells more abundant than OKT4 (Leu 3a) positive lymphocytes	OKT4 (Leu 3a) positive cells more abundant than OKT8 (Leu 2a) positive lymphocytes

in the lymph nodes of drug addicts was the presence of an extraordinary follicular hyperplasia (Figs. 1–4). The follicles were very large, irregular in shape with idented and ill defined countours (Fig. 3). The mantle zone composed of a crown of small lymphocytes appeared very thin and mottled; in many areas this mantle zone was lacking (Figs. 2, 3). In these hyperplastic follicles, frequently showing a "starry sky" appearance, transformed lymphoid cells with mitotic figures were abundant. There were a few clusters of small lymphocytes dispersed between these large transformed lymphoid cells (Fig. 4).

The hyperplastic follicles occupied a very large portion of the cut surface of the lymph nodes. Between these follicles the paracortex appeared atrophic with decreased cellular density (Fig. 3). Occasionally there were some large basophilic cells identified as immunoblasts. In 2 cases epithelioid cell granulomas, and in 3 cases a moderate sinus histiocytosis were seen. In the medullary cords the plasma cells were abundant.

Immunohistochemical findings. Table 3 summarizes the comparative immunohistochemical data from drug addicts' lymphadenopathy and control

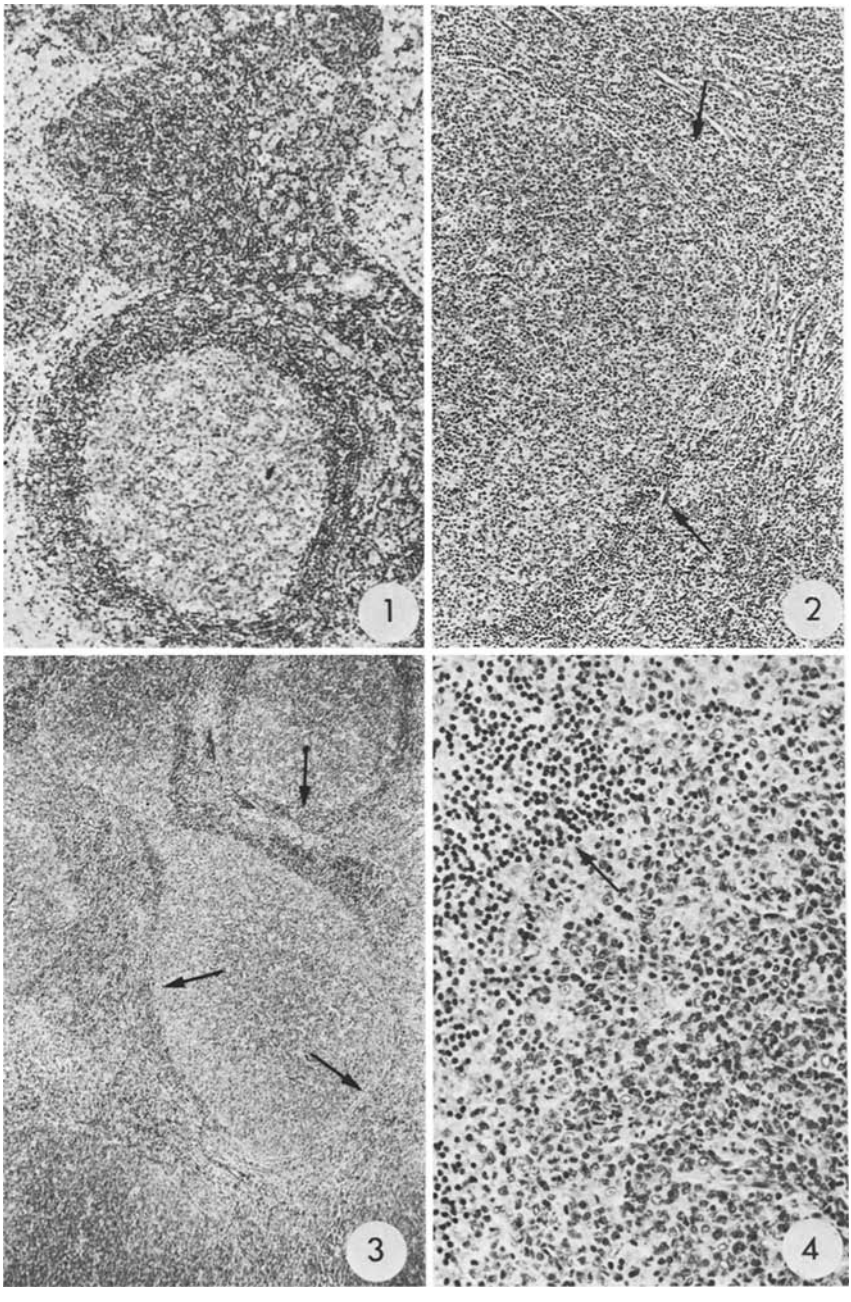

Fig. 1. Control case. Note the regular and sharply defined contours of the follicle and its mantle zone. (H.E., × 75)

Fig. 2. Drug addict (case No. 2). Same magnification as in Fig. 1. The germinal center is very large and ill defined. The mantle zone (*arrows*) is thin and absent in some areas. (H.E., × 75)

Fig. 3. During addict (case No. 2). Numerous irregular and hyperplastic follicles disrupt the normal cortical architecture. Some of them appear to be confluent. Note the atrophy of the mantle zone (*arrows*) and that of the paracortex. (H.E., × 30)

Fig. 4. Drug addict (case No. 2). Note the presence, in the germinal center, of small lymphocytes (*arrow*) occasionally clustered together and intermingled with large lymphoid cells. (H.E., × 190)

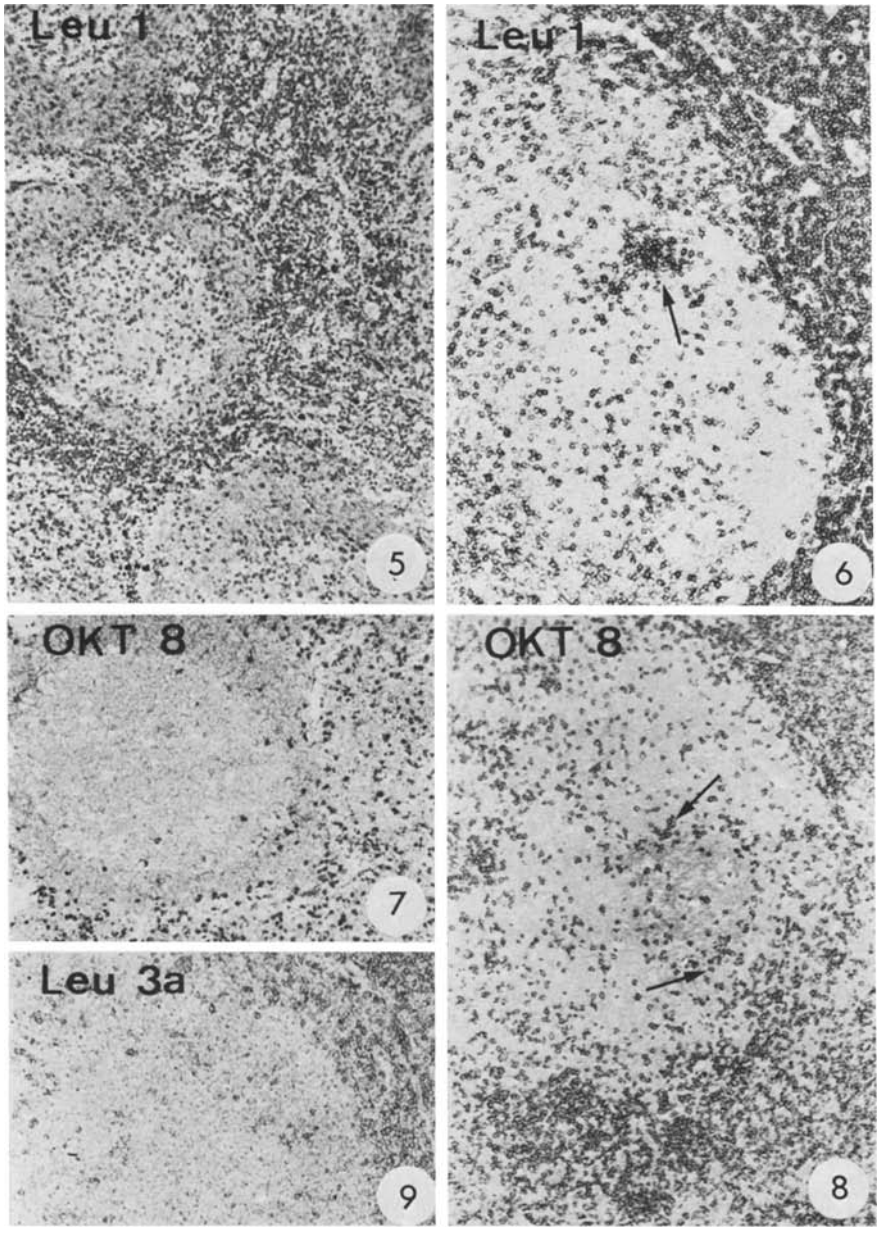

Fig. 5. Control case. Immunohistochemical labelling of T lymphocytes by monoclonal antibodies shows the presence, also in germinal centers, of some stained cells (which, when stained with OKT4 or Leu 3a, correspond mostly to "helper" phenotype). (*Leu 1*. DAB. Haematoxylin, ×75)

Fig. 6. Drug addict (case No. 17). Same labelling and magnification as in Fig. 5. T-lymphocytes sometimes clustered together (*arrow*) are more abundant in germinal center than in the control case. (*Leu 1*. AEC. No counterstain, ×75)

Fig. 7. Control case. "Suppressor" T cells are seen in the paracortex but they are practically absent in germinal centers (*OKT8*. DAB. Haematoxylin, ×75)

Fig. 8. Drug addict (case No. 16). Same labelling and magnification as in Fig. 7. Numerous "suppressor" T cells are present in the germinal center; some of them are clustered together (*arrows*). (OKT8. AEC. No counterstain, ×75)

Fig. 9. Drug addict (case No. 17). "Helper" T cells can be seen in the paracortex whereas they are very scarce in germinal centers. (*Leu 3a*. DAB. Haematoxylin, ×75)

Table 4. Number and ratio of lymphocytes labelled with Leu 1, Leu 2a (or OKT8) and Leu 3a in the follicles of drug addicts' lymphadenopathy and in controls

Case No.*	Drug addicts								
	Leu 1			Leu 2a (OKT8)			Leu 3a		
	Total No. counted	Mean (±SD) ($N=7$)	%	Total No. counted	Mean (±SD) ($N=7$)	%	Total No. counted	Mean (±SD) ($N=7$)	%
2	535	76.40(16.31)	100	484	69.57(17.80)	91.0	13	1.85(0.08)	2.4
6	463	66.14(7.06)	100	463	66.14(12.10)	100	–	–	–
9	581	83.00(13.10)	100	534	76.28(17.60)	92.0	14	2.00(0.08)	2.4
14	466	66.57(15.03)	100	421	60.10(22.60)	90.3	12	1.71(0.09)	2.6
16	408	58.28(8.97)	100	392	56.00(8.66)	96.0	5	0.71(0.06)	1.2
18	487	69.57(20.87)	100	478	68.28(17.86)	98.2	15	2.14(0.12)	3.0
20	507	72.43(14.30)	100	475	67.85(14.12)	93.7	3	0.42(0.01)	0.6
24	497	71.00(22.30)	100	495	70.71(24.10)	99.6	–	–	–
Mean (8 cases)	493	70.41(7.37)			66.89(6.30)	94.95		1.10(0.09)	1.57
Controls:									
1	203	29.00(6.75)	100	4	0.57(0.08)	1.9	194	27.70(7.41)	95.6
6	238	34.00(8.26)	100	9	1.29(0.11)	3.8	236	33.70(6.60)	99.1
8	155	22.14(7.80)	100	4	0.58(0.07)	2.6	144	20.57(9.20)	92.9
9	210	30.00(11.60)	100	2	0.28(0.05)	0.9	197	28.14(9.90)	93.8
Mean (4 cases)	201	28.78(4.92)			0.68(0.04)	2.35		27.53(5.38)	95.54

* See numerotation of cases on Table 1

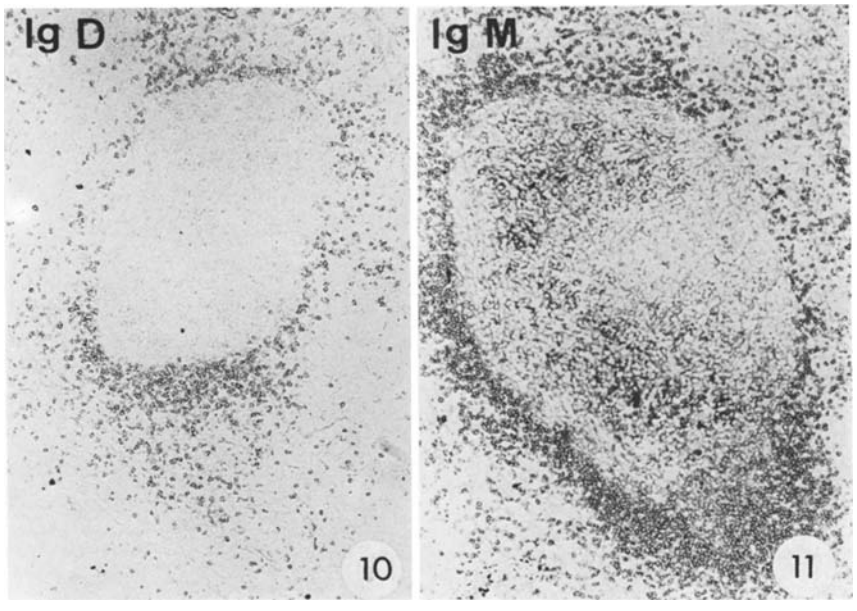

Fig. 10. Drug addict and homosexual (case No. 21). IgD labelled cells making up the mantle zone are decreased. The rim which they form around the germinal center is thin and molted. (*IgD*. DAB. No counterstain, × 75)

Fig. 11. Drug addict and homosexual (case No. 21). Staining with monoclonal IgM antibody shows a similar change of the mantle zone as with IgD staining (see Fig. 10). Note also the labelling of some cells in the germinal center. (*IgM*. DAB. No counterstain, × 75)

lymph nodes. The modifications in homo- and heterosexual heroin abusers were similar. Furthermore there was no apparent difference between nodes of subjects with or without inversion of blood T lymphocyte subsets ratio. A constant finding in drug addicts' lymphadenopathy was the presence of numerous Leu 1 and OKT3 positive T cells within the germinal centers (Figs. 5, 6). These cells were labelled with monoclonal antibodies Leu 2a and OKT8. Such cells were often clustered together (Figs. 6, 8). Only occasional T lymphocytes in these follicles stained with Leu 3a and OKT4 monoclonal antibodies (Fig. 9).

Quantitative investigations of T cells done in 8 cases of drug addicts and 4 controls are summarized in Table 4. These countings revealed that, with regard to controls, the total number of T cells in germinal centers was increased by 60% in drug addicts' lymphadenopathy. This increase concerned Leu 2a (or OKT8) positive cells which amounted for 95% of identified T lymphocytes. In those cases where no quantitative estimations were available, the general pattern of lymph node changes observed after immunolabelling of T cells was similar: in germinal centers there was a drastic increase of Leu 2a (or OKT8) positive cells, a decrease or even disappearance of Leu 3a (or OKT4) lymphocytes.

Labelling of B cells by monoclonal antibodies demonstrated that around many follicles there was a marked decrease of IgD positive cells which normally constitute the mantle zone (Fig. 10). Furthermore in these areas an apparent decrease in the number of IgM positive B lymphocytes was observed (Fig. 11).

Discussion

Our results show that in the lymph nodes of heroin addicts there is a marked follicular hyperplasia associated with atrophy of the "T zone", i.e. the paracortex. A most remarkable finding is the shading off, and in places complete disappearance, of the follicular mantle zone. The germinal centers of these lymph nodes are invaded by T lymphocytes labelled with monoclonal antibodies Leu 2a and OKT8. (This phenotype is mainly expressed by T cells of cytotoxic-suppressor variety. Such Leu 2a and OKT8 positive cells constitute the clusters of small lymphocytes observed in germinal centers. They represent 95% of T cells contained in follicles; their absolute number increases nearly 100 times. Conversely in germinal centers of drug addicts lymphadenopathy, the number of Leu 3a and OKT4 positive lymphocytes decreases. For reasons of simplicity, we shall refer to Leu 2a and OKT8 positive cells as "suppressor" and to Leu 3a and OKT4 positive cells which include mainly helper-inducer variety as "helper".

A marked follicular hyperplasia similar to that described above has been reported previously in the lymph nodes of heroin abusers (Geller and Stimmel 1973) as well as occasionally in some cases of iatrogenic lymphadenopathies (Leder and Lennert 1972). However, as would be expected, in this early work no immunohistochemical investigations have been performed. More recently Domingo and Chin (1983) and Guarda et al. (1983) reviewed the histological features of drug addicts lymphadenopathy and emphasized on peculiarities of the follicular hyperplasia. They did not study the distribution of T-cells and their subsets. Such immunohistochemical studies have been done in the lymph nodes of homosexual men presenting with lymphadenopathy, whether or not this is associated with opportunistic infections and/or Kaposi's sarcoma (Chan et al. 1984; Modlin et al. 1983). The distribution pattern of T-cells appeared similar to what we observed in drug addicts.

In normal lymph nodes and in usual follicular hyperplasias, the germinal centers are mainly composed of B cells but may include a few T cells; these are mostly of "helper" phenotype (Hsu et al. 1983; Poppema et al. 1981). According to our relatively limited control material (the restricted amount of control cases is due to the difficulty to obtain unfixed tissue in situations such as infectious mononucleosis, and other viral diseases; the inconvenience resulting from this is however compensated by the similarity of the data obtained from the literature), and other studies (Hsu et al. 1983; Poppema et al. 1981), normal and/or hyperplastic follicles contain very few and randomly distributed T lymphocytes of "suppressor" phenotype. In some acute viral lymphadenitides, such as infectious mononucleosis and cytomegalovir-

us mononucleosis (CMV), inversion of the ratio of blood T lymphocyte subsets may occur (Carney et al. 1981; Reinherz et al. 1980; Rinaldo et al. 1983). However in these cases the lymph nodes do not show changes similar to what is reported here. Hence it appears that on histological grounds, follicular hyperplasia with atrophy of the mantle zone and particularly invasion of germinal centers by "suppressor" T cells are highly suggestive of drug addicts' lymphadenopathy.

The major expression of the impairement of cellular immunity in AIDS is lymphopenia which results from decreased "helper" population. This decrease associated with a less prominent increase in "suppressor" cell number brings about the characteristic inversion of helper/suppressor ration in blood lymphocytes (Gottlieb et al. 1983; Wormser et al. 1983). A similar inversion of helper/suppressor ratio may occur in subjects at risk for AIDS. These are homosexual men presenting diffuse lymphadenopathy but no opportunistic infections and/or Kaposi's sarcoma (Kornfeld et al. 1982; Nicholson et al. 1984), female partners of homosexual men (Harris et al. 1983), haemophiliacs (Luban et al. 1983); Haitians (Malebranche et al. 1983; Vieira et al. 1983) and their children (Scott et al. 1984), Zairians (Clumeck et al. 1984) and also admittedly hard drug addicts. Indeed such an inversion of circulating T helper/suppressor cell ratio has been reported in subjects who abuse heroin (Butkus Small et al. 1983; Gottlieb et al. 1983; Wormser et al. 1983), and also in newborn children of such mothers (Rubinstein et al. 1983).

Up until recently the cause of the inversion in T lymphocyte subsets ratio was not well understood; it has been shown however that this inversion was due principally to the drop in helper phenotype number (Gottlieb et al. 1983). A series of studies (Barre-Sinoussi et al. 1983) including those of Gallo and his coworkers (Gallo et al. 1983; Gallo et al. 1984, Popovic et al. 1984, Schüpbach et al. 1984) have given a new insight into the modifications of T lymphocyte subsets in this immunological disorder. Indeed in a very high percentage of cases a retrovirus – HTLV III – seems to be the cause of the of the disease (Gallo et al. 1984; Sarngadharen et al. 1984). This virus is cytopathic replicating in "helper' T-cells and destroying them (Gallo et al. 1984).

At this point a few pecularities concerning drug addicts lymphadenopathy have to be emphasized. Firstly, in heroin abusers, lymph node enlargement with follicular hyperplasia was observed (Geller and Stimmel 1973) about 8 years before the outbreak of AIDS in USA. In these early cases, it was shown that the lymphadenopathy (Geller and Stimmel 1973) and immunological defects (Brown et al. 1974) regress in some patients if drug abuse is stopped. Secondly, lymphopenia, which is a prominent feature of AIDS or pre-AIDS, does not occur in drug addicts as frequently as in homosexual patients. In fact, in 4 out of 24 subjects that we studied, there was even a lymphocytosis, and in 7 other patients lymphocyte count was normal. Thirdly, although opportunistic infections, and hence typical AIDS, are reported in drug addicts in USA (Butkus Small et al. 1983), this occurs only occasionally in Europe. Furthermore Kaposi's sarcoma, a characteristic

lesion of AIDS in homosexual men (Gottlieb et al. 1983), is not observed in drug addicts.

At present the exact mechanism of heroin abuse in the pathogenesis of a lymphoid tissue alteration and related immunological defects is not fully understood. It is nevertheless legitimate to raise the question whether in AIDS, drugs do not play a role independently, or prior to the infection with HTLV-III. In this respect it is important to recall that lymphocytes of drug addicts possess opiate receptors (McDonough et al. 1980).

In conclusion, according to our findings, histological and particularly immunohistochemical features of lymph node changes are characteristic enough to suggest the diagnosis of pre-AIDS lymphadenopathy on a biopsy specimen.

These modifications are similar in drug addicts and homosexual men. However to be sure of the relationship of these lesions to AIDS and related conditions, more immunohistochemical lymph node studies should be performed in other conditions particularly in viral infections. In drug addicts' lymphadenopathy, some minor findings seem to indicate that the immunological defect is perhaps prepared (or potentiated) by some other mechanisms.

To understand the biological background of this condition better, a systematic search for HTLV-III and antibodies against this virus in heterosexual heroin abusers is necessary. We are at present performing such investigations.

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