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Nonhuman Primate Models of Human Hematological Malignancies

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Tremendous progress has been achieved in cancer research in the past decade. It is widely accepted that the major breakthrough is in the field of oncogenes. However, this direction of cancer research has not yet contributed significantly to an understanding of the etiology of human leukemia. On the other hand, in the past few years we have witnessed a renaissance in the field which I would call "classical virology." It began with the isolation by Gallo and coworkers [1] of the first human retrovirus, HTLV-I, implicated in the etiology of adult T-cell leukemia/lymphoma [2, 3].

Here I will describe some aspects of a nonhuman primate model of human lymphoma which we and our collaborators in many countries have been working with for almost 20 years. This model was studied within the framework of the above-mentioned classical virological approach, and we have found many interesting and unique parallels with the human system.

The story began almost 20 years ago, when, with the aim of isolating a hypothetical human leukemia virus, we inoculated some baboons of our colony with pooled fresh blood of leukemia patients. We were too optimistic and expected that in a few months we would have a human leukemia virus in our hands. But after a year the inoculated animals did not show any symptoms of leukemia. Our optimism sharply decreased, and due to some difficulties in keeping these monkeys in strict isolation we transferred them to open-air compounds where they had close contact with untreated animals.

To our surprise, approximately 2 years after the inoculation, some of the treated animals developed malignant lymphoma (Fig. 1), and, totally unexpectedly, some of their untreated neighbors developed the same disease. It should be noted that our monkey colony was established in 1927 and we now have the eleventh generation of baboons born in captivity. However, we had never seen lymphoma in this simian species before the introduction of human leukemic material.

Quite frankly, we still do not know what role this human leukemic material played in the development of malignant lymphoma in our baboons. Nevertheless, it appeared, and with these cases an outbreak of malignant lymphoma started; to date almost 270 baboons have died of this disease. The mortality of the disease fluctuates, being around 1.8%–2% per year in a susceptible age-group, which consists of animals over 3–4 years of age (see Table 1). There are now 1200 baboons in this age-group in our baboon stock, and this means that every year we register up to 20 animals as dead or killed because of malignant lymphoma [4, 5].

Our first impression was that the disease was monomorphic. But later on, after thorough morphological investigations, we came to the conclusion that there were many morphological variants of the baboon malignant lymphoma. In some cases we observed Hodgkin-type lymphomas; the rest of the cases were non-Hodgkin types including lymphoblastic, prolymphocytic, immu-

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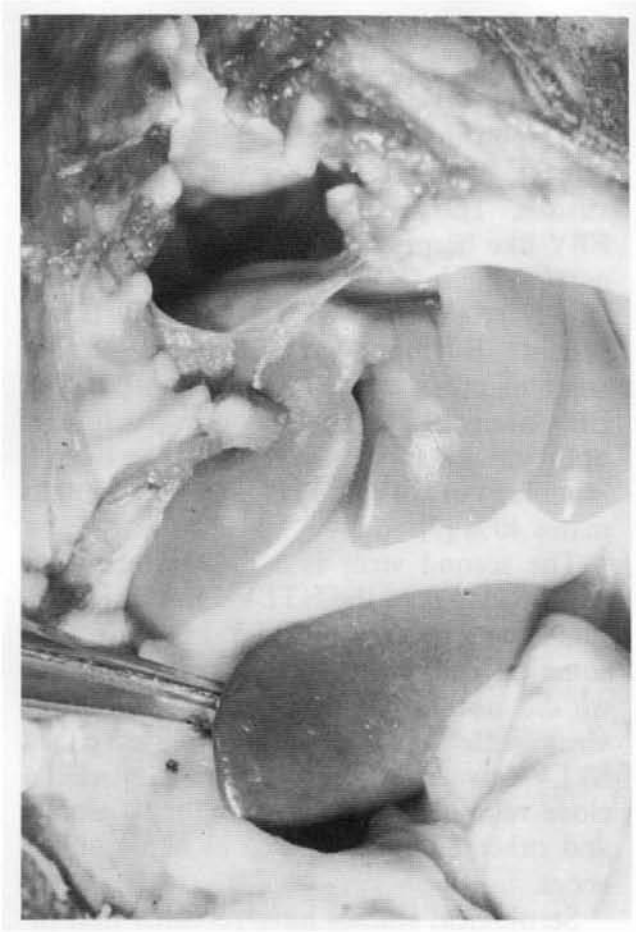
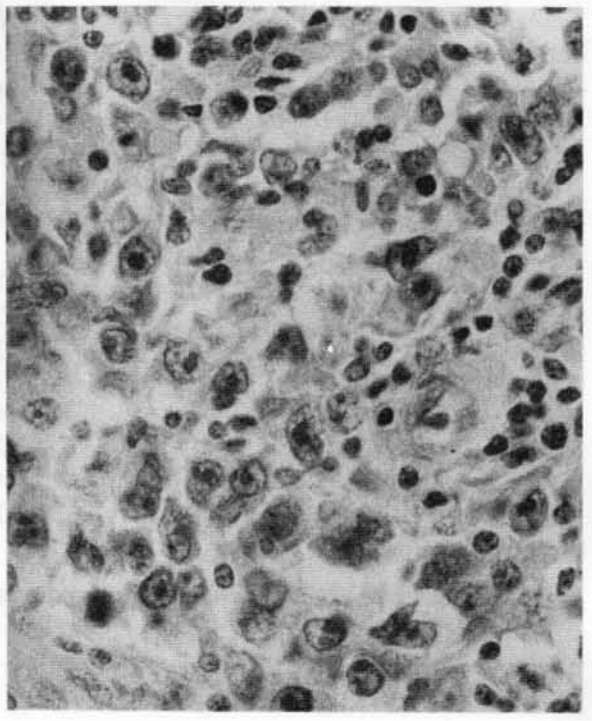
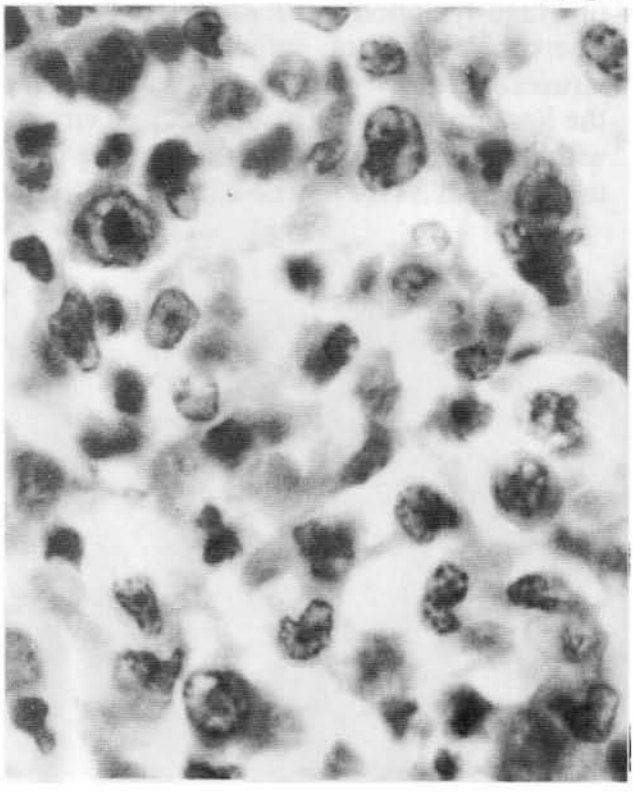


▲ Fig. 1



▲ Fig. 2

▼ Fig. 3



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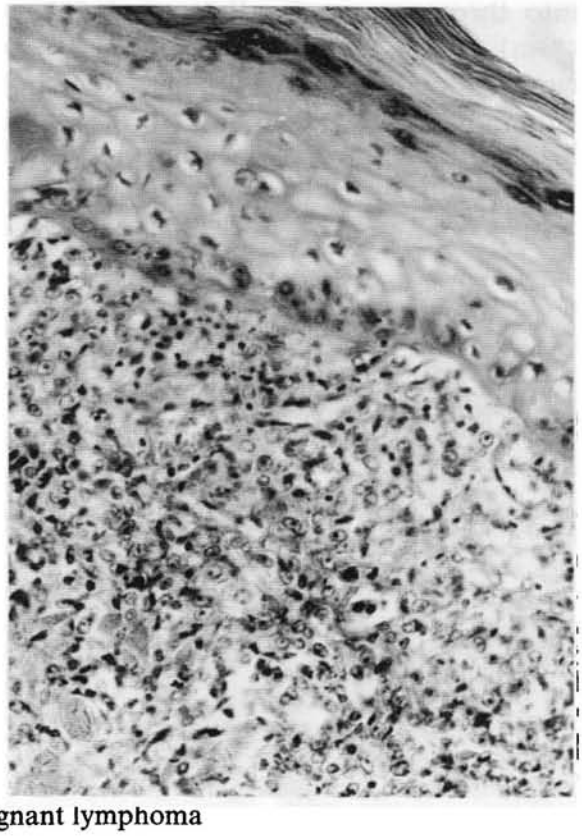

Fig. 1. Spleno- and hepatomegaly in baboon with malignant lymphoma

Fig. 2. B-cell immunoblastic non-Hodgkin's lymphoma

Fig. 3. T-cell immunoblastic non-Hodgkin's lymphoma

Fig. 4. Skin proliferation in baboon with T-cell non-Hodgkin's lymphoma

Table 1. Lymphoma mortality among the baboons of the Sukhumi monkey colony

Year	Number of adult baboons in the stock	Mortality	
		Number	%
1966	346	0	0
1967	365	1	0.27
1968–1980		179	1.85
1981	1126	16	1.42
1982	1041	18	1.73
1983	1254	13	1.04
1984	1140	14	1.22
1985	1248	18	1.44
1986 (September)	1281	17	1.33
Total number of baboons dead of hemoblastosis −276			

noblastic, and some other variants (Figs. 2–4).

Using a combination of immunological and cytochemical typing, as well as ultrastructural studies, we found that our baboon malignant lymphoma can be categorized into three groups: T-cell (around 50% of cases), B-cell lymphoma (around 40% of cases), and "null," or non-T-, non-B-cell lymphoma (around 10% of cases). Both helper and suppressor phenotypes were observed in the T-cell lymphoma group.

The disease could be transmitted with the cell-containing materials, and we started our attempts to isolate the viruses which might be responsible for the development of the disease. We isolated two types of oncogenic viruses. The first was a B-lymphotropic EBV-like herpesvirus which we called *Herpesvirus papio* (HVP) [5, 6]. This virus is very closely related to EBV [7]. It immortalizes primate B-lymphocytes in vitro and has antigens cross-reacting with corresponding EBV antigens [8]. The genome structure of both viruses is the same, and the overall homology of EBV and HVP DNAs approximates 40% [7].

The second virus is a C-type retrovirus which belongs to the HTLV-I family [9, 10]. It is closely related to HTLV-I but there are some differences [11, 12] (Fig. 5). Although we did not compare baboon HTLV-I-like virus with various simian isolates called STLV-I, we have many reasons to suspect a close relationship between baboon isolate and other STLV-I, as well as some differences.

Serological studies have revealed that infection with both viruses is quite common in our high-lymphoma-risk stock [10, 12–14]. The prevalence of infection with both viruses increases with age, which indicates the horizontal transmission of these viruses within the colony. HVP virus is more contagious than STLV-I. The data presented il-

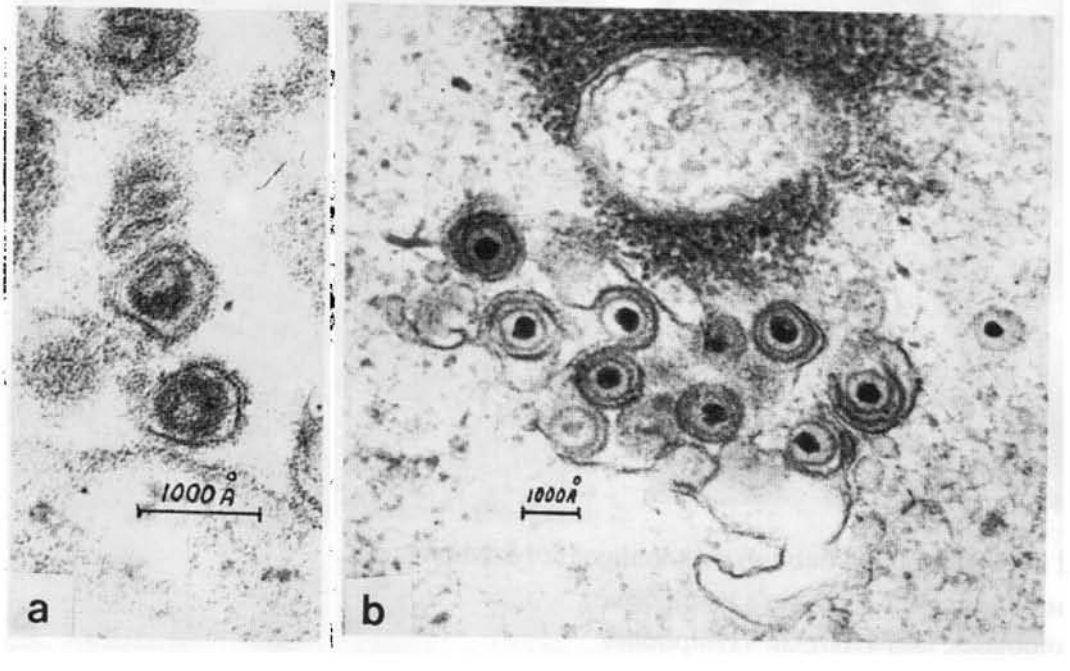

Fig. 5. a Type-C retrovirus; **b** herpesvirus

lustrate the dynamics of the infections in high-lymphoma-risk stock. It should be noted that similar studies of ours with wild animals have shown some of them also to be infected with both HVP and STLV-I. But in this case the prevalence of infection was much lower, especially in the case of STLV-I.

The level of antibodies against both viruses increases in the prelymphoma period and as a rule decreases after lymphoma development. HVP-specific DNA has been found in lymphomatous spleen tissues and some normal baboon tissues [15]. We have also demonstrated the presence of integrated STLV-I provirus in the DNA of malignant lymph nodes. The integration was monoclonal, and in some cases we found several integrated proviruses, including defective ones [12].

All these baboon lymphomas occurred in our main stock, which we called a high-lymphoma-risk stock. As controls we have another stock composed of animals imported directly from the wilderness, that have never had contact with the high-risk stock animals. This control stock numbers approximately 600 animals, a over a period of 15 years we have observed no cases of malignant lymphoma.

Thus, the material presented here shows great similarities between baboon lymphomas and those in human beings. The discovery of the two viruses HVP and STLV-I in baboon malignancy, with integration of STLV-I provirus into the DNA of lymphomatous tissue, and the characteristic dynamics of antibody titers with their elevation in the prelymphoma period make it possible to conclude that baboon malignant lymphoma is associated with DNA and RNA oncogenic viruses.

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