MONKEY BUSINESS AT PITSUNDA

East and West met at the Georgian resort of Pitsunda — near the Sukhumi baboon colony — to discuss the relationship between animal cancer viruses and human cancer

By JEAN McCANN

Nine hundred baboons living in cages on the slopes of the Caucausus mountains in the town of Sukhumi in the U.S.S.R. are being carefully studied by both U.S. and Soviet scientists to find out why they have a 12 percent incidence of spontaneous lymphomas ... and the possible relevance this may have in terms of human disease.

Boris Lapin, director of this, the world's largest baboon colony, goes so far as to speak of the spread of the lymphomas among his animals as being "contagious." And he calls his colony "an excellent model in primates of human disease."

So far, the finger of suspicion in the spreading lymphomas points to a baboon herpes virus that is a relative of the Epstein-Barr virus (EBV) seen in humans. "The *herpesvirus papio* [HVP] spreads horizontally, and so I can say the lymphoma disease is of viral origin," Lapin told SCIENCE NEWS. "If you cage sick and well animals together, within two years, 12 percent of the healthy animals will come down with the disease. This means that it looks like a contagious disease."

Photos: J. McCann

Baboon at Sukhumi: Why so much cancer?

But U.S. researcher Russell Neubauer of the Frederick Cancer Center, who has worked at Sukhumi, is more cautious. Herpesviruses usually spread horizontally, he says. But the fact that antibodies to HVP in this colony are elevated may mean that one component of the virus is responsible for the development of the disease, he explains. But that does not prove that the disease is infectious.

Still, both Soviets and Americans agree that whatever is causing the spread of lymphomas among the 900 caged baboons is well worth studying, since 600 baboons living in a nearby forest have not come down with the disease.

Harvey Rabin, also of the Frederick Cancer Center, calls the baboon colony "a very exciting system where there is apparently a spontaneously spreading B cell lymphoma in a defined area under conditions which make it feasible to do very carefully controlled experimental work. We are looking forward to many years of happy cooperation."

Lapin, Neubauer and Rabin were among 300 scientists, about equally divided among Western countries and Eastern bloc nations, who gathered in the pine-studded Black Sea resort of Pitsunda, in the Soviet Republic of Georgia, for the recent International Symposium on Comparative Research in Leukemia and Related Diseases. Pitsunda is about 75 km from the Sukhumi baboon colony, and regular afternoon pilgrimages were made to the site by groups of scientists attending the meeting.

There has long been a curiosity about Sukhumi among virologists, immunologists and others because several years ago 12 baboons were infused with human leukemic material. These animals later developed lymphomas, but so did animals who were not so treated, so considerable doubt remains as to what effect these infusions had, if any, on the later development of disease.

During the symposium itself, several new findings from the baboon colony were reported, among a greater number dealing with well-known virally induced cancers in lower animals, such as Marek's Disease in chickens. But the bottom line in discussions of all this comparative animal research is still this: How does animal cancer virus research relate to humans? Do viruses — exogenous, endogenous or both — cause cancer in humans?

To answer such questions, work in primates is considered especially relevant. For instance, Rabin notes that the viral genome of the HVP has now been seen in substantial numbers in some tumor tissues but not in normal tissues taken from healthy animals. "This is the classical pattern with almost all the lymphotropic herpesviruses," he adds, "in that the tumors they induce are positive for the viral genome."

John Moloney of the National Cancer Institute, who did some of the earlier studies at Sukhumi, questioned whether the horizontal (that is, infectious) transmission in the baboons was really by natural means, or whether it could be by caretakers who handle both sick and well animals. "Horizontal transmission is hard to prove unless you have controlled containment facilities." But he says he doesn't argue that the lymphomas were indeed spreading horizontally, "and I would also suggest vertically [genetically] as well, except that this is not expressed until later in life."

"It is my opinion, and has been my opinion for a number of years, and that of many viral oncologists," Moloney adds, "that

Jean McCann is a medical writer based in Cleveland Heights, Ohio.

The NCI's John Moloney (left), an early researcher at the Institute of Experimental Pathology in Sukhumi, with director Boris Lapin.

viruses play a role in the etiology of human cancer. Whether this is a single role, or a role which can be activated by a second experience such as a chemical, we think it is a necessary part of the cancer causation process. I don't mean a whole virus; I mean viral genome, which is integrated into the normal host cell genome.

"It's something that's innate to it; you inherit it, and this information can be activated or caused to be expressed by something, such as another viral infection, or unusual exposure to a chemical. We know in our experimental animal systems that every time you induce a tumor with a chemical or radiation, you have the increased expression of viral genes in that tumor."

As far as human cancer is concerned, there is general agreement among virologists now that the EBV is a co-factor in Burkitt's lymphoma, and most likely in nasopharyngeal carcinoma as well (SN: 9/9/78, p. 180). The virus is also a suspected cause of lymphomas occurring in some immunodeficiency states. For instance, Jean Joncas of the University of Montreal has found that patients with an inherited immune deficiency disease called ataxia telangiectasia have a high incidence of early antigen antibodies to EBV when compared with healthy persons. The high prevalence of antibodies and their persistence in patients with ataxia telangiectasia is interesting, Joncas says, because this phenomenon is seen in patients with EBV-associated tumors, such as Burkitt's lymphomas and nasopharyngeal carcinoma, and because there is a high incidence of lymphomas in patients with ataxia telangiectasia.

Joncas also notes that antibodies have been found to fall off when patients with Burkitt's lymphoma are treated, but to rise again with recurrence of disease.

In another study reported on at the Pitsunda research symposium, Mayo Clinic microbiologist Gary Pearson said it is now possible to tell which patients with Burkitt's lymphoma or nasopharyngeal carcinoma will do well and which will do poorly, based on a new assay. Called an antibody-dependent cytotoxicity assay, it involves an interaction between a specific antibody directed against a viral cellular membrane antigen and lymphoid cells in the circulation.

"When a patient comes in with high levels of antibody against the EBV-induced membrane antigen," he says, "these patients seem to respond well to therapy, and their survival time seems to be greatly extended. But when individuals come in with the same stage of disease, and when the antibody for some reason is very low, these patients do not do well. So the antibody is probably functioning in resisting or controlling the growth of tumor cells." As a result of these findings there is now talk of using serum with a high antibody level in therapy.

As part of their general research, Pearson and immunochemist Louis Qualtiere are also trying to develop an EBV vaccine. Qualtiere has already succeeded in identifying two major antigens that the EBV-infected host responds to. The idea now is to purify these antigens, and produce them in large enough quantities that they can be tested first in animals and then in humans.

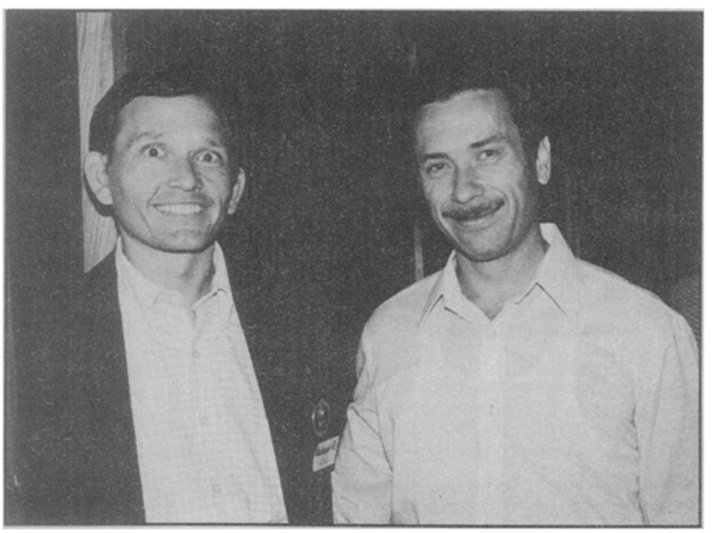
Eventually, such a vaccine could be used in young teenagers with no antibodies to EBV. This should prevent them from getting infectious mononucleosis, Qualtiere says, since mono only occurs in persons with no prior EBV antibodies. And the vaccine might also help prevent EBV-associated cancers.

While the talk at this meeting related largely to EBV in terms of human malignancies, there was at least fleeting acknowledgement of attempts to relate herpesvirus II and cervical cancer. According to M. Epstein of the University of Bristol, England, however, the evidence looks less and less convincing. He told SCIENCE NEWS that many of the reported studies were measuring antibodies to herpesvirus type I, not II, because of the cross-reactivity of the two. "In addition to this," he says, "there is no correlation with radiologic findings, so that the findings themselves are actually open to question."

Besides, he says, reports claiming detection of antigens allegedly coded for by the virus in cells of the tumor are suspect because the antigens have never been defined.

Nor has a single report of herpesvirus II DNA in a tumor been confirmed by other workers, he explains. And "more recently, work by much more refined and sensitive probes looking for messenger RNA, coded for by the viral genome, has failed to find it within the malignant tumor cells, so I think there's a very good question mark about this."

In general, Epstein says he believes that "a small minority of human tumors will be found to be induced by viruses, just as they are in animals. There will also be a considerable number related to environmental factors. The rest we will not find the explanation for until we find out exactly what the cause of malignant change is."



Russell Neubauer of the Frederick Cancer Center (left), a skeptic of Lapin's theory that lymphoma is infectious, with Sukhumi's A. G. Dyachenko.

Also reported at Pitsunda

A colony of mice being raised by Marvin Rich, scientific director of the Michigan Cancer Foundation in Detroit, is providing some hints as to why some cancers spontaneously regress ... and why they may start to grow again. Immune cells called macrophages are critical, he finds. "For remission to occur, which is analogous to remission in patients, you have to have macrophages which have not been infected by the virus. We are now able to take healthy macrophages from one mouse, put them into a mouse with conventional virus, and see the tumor in that animal regress."

Rich has also found that antibodies that develop against the leukemia cells don't really matter in terms of remission, but that antibodies against leukemia virus do. If there are antibodies against the virus, the animals will stay in remission. If there are none, or if the antibodies are weak, the animals will go into remission, then relapse. Rich says the problem is that the virus changes antigenically, so previous viral antibodies are no longer adequate to keep the disease in check.

Instead of searching for cancer markers in the blood, which most researchers are doing, Ernest Borek of the AMC Cancer Research Center and Hospital in Lakewood, Colo. has been looking at the urine of cancer patients to see what's different about it. And he says he has some good leads.

He has found that a high level of certain modified nucleosides are excreted by cancer patients. In ten patients with advanced colon cancer, for instance, he found up to a ten-fold increase in the daily

excretion of N^2N^2-dimethylguanosine. This, he says, "can result only from a very high level of tRNA turnover. There is a very high turnover of tRNA in the tumor tissue of an animal model."

Also, in a study he did with John Speer of Penrose Hospital in Colorado Springs, he found that 26 of 26 patients with cancers of different organ sites had levels two standard deviations above normal of one or more of the following: pseudouridine, B-aminoisobutyric acid, 1-methyladenosine, 1-methylinosine, N^2-methylguanosine, N^2N^2-dimethylguanosine and 2-pyridone-5-carboxamide-N'-ribofuranoside. The levels of elevation, he adds, "correlate approximately with the stage of the cancer, but the relative levels of the individual nucleosides appear to be an attribute of the tissue site of the tumor."

Also encouraging to him is that levels of nucleoside excretion reverted to normal within five days of commencement of chemotherapy in six patients with Burkitt's lymphoma and within 10 days of therapy for three children with T-cell acute lymphocytic leukemia.

* * * *

Graft-versus-host disease is a major complication of bone marrow transplants, even from closely matched donors. But now a group of German researchers has prevented its occurrence in seven out of seven patients by infusing the donor marrow with anti-T lymphocyte serum before its infusion into patients, according to Hans Rodt of the Institute for Hematology in Munich.

Rodt says that while the numbers are small, he is encouraged because ordinarily half of all transplant patients suffer the serious and often fatal problem of graft-versus-host disease. He and other researchers also described preliminary studies using similar techniques in the case of autologous bone marrow transplants.

In this instance, the patient's own marrow is removed during a period of remission of the disease, frozen for storage in liquid nitrogen, and then reinfused at a time when the patient goes into relapse. "The danger here is that you will transfuse back some of the leukemic cells," Rodt says. "However, we attempt to prevent this by incubating the marrow with anti-T cell or anti-cALL serum, to prevent the reinfusion of leukemic cells possibly present during remission."

The anti-T serum would be used in the case of T cell leukemia, and the anti-cALL in case of the common type of acute lymphocytic leukemia.

* * * *

Adult leukemia patients at M.D. Anderson Hospital in Houston, Tex., are getting individualized treatment based on their chances of doing well or poorly. Emil J. Freireich, head of the department of experimental therapeutics, feeds up to 60 pieces of information about the patient into a computer. Using a computerized regression model, he then comes up with the four or five most important factors relating to prognosis. "We are now able in this way to come up with summary statements for individuals, using multifactorial statistics, to show whether the patient has a high or low probability of early relapse," Freireich says. "If the patient has a 60 percent or better chance of doing well in the first year, we'll give him or her conventional maintenance therapy, because contained in that group are the patients who should end up with a long disease-free survivorship."

If the patient has more than a 60 percent chance of relapsing in the first year, however, then that patient will be given drugs that have been found to be effective in advanced disease.

Freireich says some of the predictors of early relapse include extensive disease prior to treatment as measured by lactic dehydrogenase levels, blasts in the blood and the amount of infiltrate in the marrow. The speed with which leukemic cells die, and the number of treatment courses required to get a patient into complete remission are also important prognostic factors, he said. (While attending the Pitsunda meeting Freireich received the deVilliers Award from the Leukemia Society for his contributions to clinical research.) □