NCI-AIDS Advisory Group **27**

July 18, 1983

The first full meeting of the NCI AIDS Task Force Advisory Group covered reviews and discussions across broad areas of research on the AIDS problem.

CDC:

Dr. Jim Curran summarized the CDC data and provided relevant information on individual cases of concern. Pneumocystis carinii pneumonia is the most predictive indicator for AIDS that they currently have. It was very rare prior to 1979, with only one case reported which was not associated with an underlying immune-suppression or cancer. Cases without known risk factors were detailed. Most can now be assigned to some risk group if followup is possible. Only about 1% of cases are still in doubt. The recent case of a Baltimore health worker was discussed. The case was not reported to CDC until after the man had died; the patient denied having any associated risk factors, but detailed investigation raised additional concerns. Exposure to blood was documented as part of his duties in the emergency room. The man also received pooled gamma-globulin after a needle-stick accident in 1982. This case appears to be the closest in that a health care worker developed AIDS without obvious risk factors. Although AIDS patients were treated during that time, one of the patients subsequently developed LAS. Of the opportunistic infections, Mycobacterium avium i. was most difficult to treat. Viral infections were treated with cycolvir which could, in some cases, make the symptoms worse. Although the HLA DR5 was prominent in both classical and epidemic KS, a second HLA DR2 involvement was seen in about 60% of AIDS patients whose ethnic origins were from northern Europe. Dr. Curran concluded with a plea to avoid competition for patients and resources among all the participating researchers.

Clinical:

Drs. Safai and Gold summarized their observations on patients at the Memorial Sloan-Kettering Institute. Dr. Safai outlined their observations on patients who presented with Kaposi's sarcoma and gave a breakdown on the progression that they observed in terms of immune parameters and expected outcome. A 40% response rate (20% PR) was achievable with treatment which used recombinant DNA derived alpha interferon. Dr. Gold outlined their observations on patients who presented with lymphadenopathy and also discussed a group on prospective study in Ithaca, New York, where there are currently no AIDS cases reported. About 10% of their LAS cases came down with AIDS up to this time, out of about 120 patients studied. Dr. Broder from the NCI described the basis for patients being brought to the NCI Clinical Center, outlined studies with 50 patients, and briefly described protocols based on interferon treatment, electron beam therapy, and chemotherapy. He made an urgent request from the clinical point of view to develop a reliable screening assay which would determine patients at risk for AIDS and/or be definitive for the AIDS disease. The question of whether NCI could coordinate the collection and distribution of sera in the manner of the previous resources program was discussed. It was felt that this could only be done under conditions which would minimize competition between the CDC, NCI, and NIAID. Dr. Dietrich outlined his experiences with recent outbreaks of AIDS in Hamburg, Germany, and described his studies on African KS patients and the immunological picture which they present. He considered it curious that although all were positive for E. histolytica, no invasive amoebiasi was seen.

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Past practices of importing or exporting blood between countries was questioned, particularly in reference to Haiti and Japan. Possible consequences of this practice were considered important enough for follow-up investigation.

Testing:

Dr. Goldstein described an RIA assay for thymosyn α-1 and thymosyn α-1/α-2 ratios. The data presented indicated that elevated levels of thymosyn α-1 were very predictive for the AIDS syndrome. A wide variety of other syndromes and illnesses did not show the elevated thymosyn α-1 as high as the levels detected in AIDS patients. Various problems with this assay were discussed, including possible cross-reactivity with HTLV p19 or other α1-like peptides. Comparison of the exact amino acid sequence of these peptides was deemed to be of prime importance and the availability of these sequences was pointed out. Dr. Bolognesi outlined a hypothesis of the group from Duke University based upon the possibility of cross-reactivity of the HTLV p19 with thymic peptides. The model would presuppose that infection by HTLV could induce anti-p19 antibodies which could immunologically compromise the thymus. High levels of thysomin α-1 were detected in a case of adult T-cell lymphoma.

Animal Models:

Dr. Essex presented an overview of feline leukemia virus (FeLV) in terms of causing lymphoproliferation and immunological suppression. Both of these are observed in nature. He emphasized that the immunological suppression that is observed with FeLV is not a blanket suppression but rather, certain specific agents are highly lethal to the infected cats. It was also pointed out that after FeLV has caused a primary infection, the virus can only be isolated from bone marrow in apparently virus-negative leukemic cats. Bovine leukemia was discussed briefly as a possible animal model. Its usefulness was felt to be lacking due to the absence of good epidemiological data which is a problem resulting from the herd-wide infection by this agent. The status of AIDS-like disease in primates was discussed by various representatives covering the rhesus colony in Davis, California, a New England colony, and other individual cases. After much discussion, it was agreed that the primate cases do not yet provide a good animal model for the human disease due to various parameters which do not match the AIDS syndrome.

Virology:

Evaluation was made of various viruses as candidates for a causative agent of the AIDS disease. Adenovirus-35 has been isolated from numerous urine samples at Sloan-Kettering. It was not felt to be a good candidate because of the fact that it is quite common to isolate adenovirus from urine and different types were found from different geographical areas, thus precluding any single adenovirus as the causative agent. CMV was discussed as a candidate but there was general agreement that it was not the most likely ideological agent. A similar view was held for hepatitis B.

The question of retrovirus involvement was discussed with relationship to HTLV type 1. Dr. Gallo urged caution in coming to the conclusion that HTLV was the certain causative agent but pointed out the following features which make it very attractive as a candidate:

- it is T-cell tropic;
- the p19 has homology to thymic peptides;
- env-genes of HTLV show some homology to HLA class 1 genes;
- the virus can immortalize a wide variety of T cells;

- it can cross species lines in its ability to infect a wide variety of primate cells. This is is unique in the retrovirus field and leads to possibilities for the epidemiologic development of this virus as an etiological agent.

- close contact is needed for infection of cells, consistent with the observation that extremely close contact is required for transmission of the AIDS etiological agent.

Some discussion of problems with HTLV as the etiological agent included the apparent lack of immune suppression in Japanese and the lack of any development of AIDS so far in Japan. The designation of the current HTLV typing was reviewed.

- HTLV type 1 is the predominant virus class currently isolated.

- HTLV type 2 - there is one example only, isolated from a hairy cell leukemia - it shows only weak cross-reactivity with HTLV type 1.

- HTLV type 3 is a single isolate by the French group from an AIDS patient.

The likelihood that further subclassification of the virus would be needed was pointed out; it was felt likely that subclasses of HTLV type 1 could explain the development of various disease states.

Major new findings connecting HTLV with AIDS came from studies of Dr. W. Parks in Florida. Although preliminary and confidential, 30% of Haitians tested in the Miami area are HTLV-positive. Many children with an AIDS-like syndrome were examined relative to their mothers. It is noteworthy that 95% of the mothers with such children were positive for HTLV.

The basis for various tests for HTLV were discussed, including ELISA tests with disrupted HTLV or with purified proteins. Isolation of virus from blood cell samples was offered as an equally reliable test. It was emphasized by Dr. Popovic and Dr. Guroff that in some cases one test will prove negative while the other proves positive, even on the same sample. The perfect test for the presence or previous exposure to HTLV has not yet been developed. The lack of sufficient samples to study either the immunological development or the presence of viremic during the progression of the disease has not yet been able to be done. A prospective study for this purpose was felt to be of high priority.

Needs and Recommendations:

- A panel of sera to establish a reference bank which could be utilized by a number of laboratories to establish common parameters.

- The establishment of standardized protocols so that ELISA tests or virus isolation tests could be performed in an identical manner in different laboratories.

- Either CDC or the NCI should establish a repository for these sera

- And for tissue specimens, providing access to a half dozen key laboratories so various tests could be performed on identical samples.

The samples which were felt to be of prime importance were lymph nodes, bone marrow, and whole blood. It was felt that approximately 100 patient samples should be aimed for with the ability to follow these in a perspective manner.

The availability of the Frederick Cancer Research Facility for the growth and production of some of these reagents was noted. The importance of getting information to clinicians that antibody or the virus may come and go in terms of its ability to be assayed for or isolated emphasizes the prime importance for getting multiple samples.

The question of whether the disease could be explained by an antigen overload theory was discussed. It was concluded that this is not an adequate model or explanation of the disease because of the clustering, the geographical localization, the newness of the disease, and the pattern of spread, all of which cannot be explained by mere antigen overload.

Further meetings of various members of the Advisory Group will be scheduled to discuss issues raised in more detail.