Drug Dosage
The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions.
This is particularly important when the recommended agent is a new and/or infrequently employed drug.
Introduction

Eva Klein

Department of Tumor Biology, Karolinska Institutet, Stockholm, Sweden

A dangerous ghost has escaped from the bottle. It appeared to us in various disguises. This volume testifies that it was soon ‘found out’. Knowing the nature and tactics of the enemy is a necessary step towards defeating it. Thanks primarily to the observant physicians, the clarification of the nature of this mysterious and frightening disease entity, manifesting in a variety of symptoms, did not take long. The state of knowledge concerning the immune system on one hand, and the characteristics of the retroviruses on the other hand, provided the background. The development in these areas, representing basic research at its best - according to some opinions of questionable practical significance - had pivotal importance. It is of interest at this time to remember that when the first transmissible virus-induced neoplasia was discovered in chicken, the finding was considered of limited value because such a mechanism was thought to be confined to birds. The mammary tumor virus of mice was first named ‘milk factor’ because research on viruses involved in cancer had little credit at that time. The boom of retrovirus research started in 1951 with the discovery of a leukemia virus in the mouse and has reached unforeseen horizons with ‘revolutionary’ discoveries. It shook the ‘central dogma’ of the molecular events governing the flow of genetic information that was assumed to be unidirectional transcription of DNA to RNA and revealed the existence of endogenous retroviruses and oncogenes. Search for retroviruses in man was intense and though such were found in primates, the human species seemed to be free from them. Then there appeared on the stage: HTLV-I and HTLV-II involved in T cell malignancies and HTLV-III/LAV, responsible for AIDS. Immunosuppression, which is
an important factor in the pathophysiology of AIDS, is not a newly discovered consequence of retrovirus infection. Previously, in the animal systems, this aspect has not received as much attention as did the oncogenic property of these viruses. A recent development in AIDS is that severe immune impairment does not necessarily accompany the diseases that follow HTLVIII/LAV infection, e.g., the brain can also be affected, and its slow progressive degeneration can occur in the absence of noticeable immune deficiency. Shortcuts in science occur seldom, if ever. The present state of knowledge was reached fast because of the well-prepared ground. At its planning stage the contents of this volume were not foreseen. The causative agent was not found yet. At that time the focus was on immunosuppression as the basic event and on the known agents that could thrive and act unhindered in the absence of host control. One infectious disease in man with a known causative agent was also selected for discussion because of the accompanying changes in the lymphocyte population in order to show that this occurs in several conditions. The parallels in the attitudes towards the afflicted individuals at an early stage of knowledge of both diseases, before the risk factors could be judged, did not influence the selection though it may have been guided by foresight. Many of the questions posed at that time got an answer and many questions that have to be posed today are already outside the realm of biomedicine. This fast development is a rewarding experience, it can evoke satisfaction and proves again that accumulated knowledge can serve in unpredictable ways and times.

The identification of HTLV-III/LAV as a cause of the disease is the most significant step in AIDS research. This was discovered simultaneously and independently by two laboratories, both outstanding in cell biology and retrovirus research. It explains the different designations of the virus which are now combined (the two papers contributed by these groups to the present volume are placed according to the alphabetic order of the first authors’ names).

The known biological characteristics of the retroviruses lead, however, to disquieting prospects. There is no effective antiviral therapy. This clever virus type outsmarts the researcher. Retroviruses have the unique property to enter into the genetic material of several cell types. The majority of retrovirus-host cell interactions are harmless, unless the virus has undergone considerable changes and exchanged genes with certain cell-derived oncogenes or when it influences a strategically important cellular genome imposing on it its hyperactive transcription signal.

Animal systems suggest that once infected, individuals will carry the
virus, and antibody response in the infected individual does not counteract

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its spread because it can be transferred with cells. Antibodies are of crucial importance, however, for detection of the carrier state. Retroviruses are protean, their genes can recombine with the host cell genomes and with other retroviruses present in the same cell. Because antigenic variants appear, vaccination is of limited value. For the HTLV-III/LAV group it is already evident that the various isolates, several hundreds tested, represent a spectrum of viruses that are related to various degrees. Conserved regions in the envelope proteins have been characterized, however, and are presently studied for their suitability to provide vaccines and to develop reagents of a wide range.

A characteristic and unique property of the HTLV-III/LAV virus is its deleterious effect on a particular lymphocyte subset, the helper T cells. They are phenotypically defined by the CD4 molecule on the surface. The function of this subset is particularly important in the development of immune responses. Transfection experiments showed that the lysis of CD4 T cells is a direct effect of the viral genome. The virus-infected T cell is destroyed just when it is needed most, when it is activated for function.

The recently discovered fact that the virus replicates in the brain has added a new dimension in the combat against it: due to the existence of the blood-brain barrier, the immunological and pharmacological intervention if made available - will be difficult.

The technology of retrovirus research has developed so well that it cannot take long until the details of the HTLV-III/LAV virus-host cell relationships are known. It is already evident that while the virus shares many features with the previously known retroviruses, it has unique properties that define a new group, including also HTLV-I, II and bovine leukemia virus. These viruses code for a ‘transactivating’ factor that promotes the expression of certain cellular genes.

Due to the dramatic clinical picture and the extraordinary rapidity at which the number of cases increased after 1981, the scientific community was alerted and requested support and manpower. This occurred at a stage when, in the developed countries, the disease was still confined to certain cities and its spread could be followed. With the help of the antibody tests, it has recently been discovered that in Central Africa almost one tenth of the population is infected. There the characteristic clinical symptoms were seen already 10 years ago. A virus closely related to HTLV-III/LAV was discovered in African green monkeys in which it does not seem to cause a disease. It is therefore likely that the virus passed from monkeys to man.
Notwithstanding the individual tragedies, the catastrophe that can follow

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the introduction of the virus into the human species may be avoided if cooperation can be achieved on many levels. We would expect that scientific awareness is sufficient to design a successful policy.
Can we force the ghost to reenter its bottle? The creativity of the scientific community has proved itself already in this field and there is reason to expect that new developments will appear at a high pace. Social and psychological factors, however, create an unprecedented problem due to the stigma this disease brands on the infected individual.

There are many examples for the dichotomy between the understanding the course of events in medicine and the possibilities to control them. The consequences of smoking are well known. A newcomer to this planet - take the proverbial visitor from Mars - would look with a questioning eye why we still live with it. However, instead of eliminating the agent, the public waits for the discovery of therapeutic measures that eliminate the consequences. What can be done presently is the sterilization of transferred blood products and screening of the organ and blood donors. The control of the latter is not absolute since antibodies appear with delay after infection and it is the antibody test that reveals the infected state.

Furthermore there are antibody-negative carriers as well. To what extent and according to what aspects do virus carrier individuals have to be placed in special categories is still debated. Theoretically, the spread of virus through sexual activities and shared injection needles could be controlled by a proper education. It is also education that can alter the attitude towards the infected individuals which is also an important factor for the feasibility of controls. The discovery of the disease in homosexuals and drug abusers contributed to the prompt public attention and shaped the attitudes. Unfortunately, this was exploited for moralistic purposes. Newspapers still report transmission of the disease by blood products or cells such as ‘victimizing innocents’. It has to be imprinted in the consciousness that AIDS can affect regardless of sex but it is a sexually transmitted, very dangerous disease, and since there is no effective therapy, the prospects for limiting it are meagre.

Therefore, only through the effort of scientists can the consequences of the epidemic be avoided before evolution establishes the balance between this deadly agent and man. Awareness has to lead to activity without the harmful effects of panic. The curiosity of the scientific mind raises the hope that this will be achieved. However, the constellation in the race between this and the amount of suffering it inflicts is unpredictable.

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