Immunodeficiency in HIV Infection and AIDS

EC/FERS/MRC Workshop on Immunodeficiency in HIV-1 Infections, Windsor, Surrey, May 3-4, 1991

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89 figures and 34 tables, 1992

KARGER

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Library of Congress Cataloging-in-Publication Data
1. AIDS (Disease) - Pathophysiology - Congresses.
2. HIV infections - Immunological aspects - Congresses.
I. Janossy, G. II. Autran, B. (Brigitte) III. Miedema, F. (Frank)
IV. Commission of the European Communities.
V. European Federation of AIDS Research.
VI. Medical Research Council (Great Britain) VII. Title.
3. CD4-CD8 Ratio - methods - congresses. 4. HIV Infections - diagnosis - congresses.
WD 308 E171 1991]
RC607.A26E374 1991 616.97'92079-dc20
ISBN 3-8055-5547-4

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Printed in Switzerland on acid-free paper by Thür AG Offsetdruck, Pratteln
ISBN 3-8055-5547-4

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As the project leader of the Concerted Action (CA) on ‘Immunology and Immunopathology of HIV-Related Diseases’ from the Basic Science Program of the European Commission Working Party on AIDS, it is my pleasure to present the proceedings of the workshop which took place at the Anugraha Hotel, Windsor, Surrey, on May 3-4, 1991. This is one of the last European workshops that have been organized through the patronage of this CA, the aim of which has been to bring together scientists of different backgrounds working in this area - especially immunologists, pathologists and virologists - to enhance their collaboration and to allow them to place their research in a global European perspective.

The idea of the CA goes back to the fall of 1984 but, due to administrative red tape, it actually got started only in the spring of 1988. From the beginning, its objectives were: (1) to analyze the pathobiology of HIV infection at the cellular and tissular level, in its functional compared with its morphological aspects; (2) to reach a better understanding of the immunological abnormalities, and (3) to investigate the immune response of HIV-infected individuals in a pathophysiological perspective as well as in view of prognosis assessment or of vaccine development. After less than 4 years, substantial progress has been made in these areas by the groups associated with the CA: collaborations have been established, results have been obtained and shared at meetings and workshops of various formats, from special meetings of a few research groups to global workshops gathering all the participants in the CA. This has resulted in numerous publications in peer-reviewed journals, in journals’ special issues, or in books presenting the proceedings of some workshops. Such are ‘Modern Pathology of AIDS and Other Retroviral Infections’ (Racz P, Haase AT, Gluckman JC, eds), Karger, Basel 1990; ‘Accessory Cells in HIV and Other
Retroviral Infections’ (Racz P, Dijkstra CD, Gluckman JC, eds), Karger, Basel 1991; or the currently in press ‘Cytotoxic T Cells in HIV and Other Retroviral Infections’, also to be published by Karger.

Currently, productive links have been established with other CA, and a real European network has been set up, the most significant results of which will continue to come out in the following months and years. In their own words, this has been a positive experience and of considerable importance to many a scientist who has participated and to their work: it has permitted to rapidly establish collaborations, to gain access to material which is difficult to obtain by other means, and to rapidly disseminate ideas, as yet unpublished data and new techniques. The CA, which will cease by mid-1992, has thus reached its major aim, which was to permit mutual cross-fertilization of European investigators with different backgrounds and to reinforce the network of European groups dedicated to stop AIDS.

The workshop on ‘Immunodeficiency in HIV-1 Infections’, organized by George Janossy (London), Brigitte Autran (Paris) and Frank Miedema (Amsterdam) is but the living evidence of such achievements. The data discussed here stem from the latest studies, reported by molecular and cellular immunologists and virologists, on the pathophysiology of HIV infection and the pathogenesis of AIDS. They are confronted to the needs of clinical immunologists to develop new and ‘user-friendly’ immunological markers based on the insights brought by these results for monitoring the progression of HIV infection.

The fact that the workshop was also cosponsored by two national organizations, the Dutch AIDS Foundation and the Medical Research Council AIDS Directed Programme, as well as by the fledgling European Federation of AIDS Research (EFAR) bespeaks auspiciously for the future of European collaborative AIDS research. It has been argued that such large-scope CA are not useful anymore, that CA should by now address more focused research projects performed by limited numbers of cooperating laboratories. Actually, if this were so, national AIDS organizations would be sufficient and CA would no longer be required. After 3 years as the project leader of a ‘large’ CA, I remain convinced that they certainly still have to play a key role for international scientific collaboration. The group size of the CA meetings and the productivity of discussions lends a business-like atmosphere to these expert workshop. It has been truly reassuring to observe the collaborative spirit among the European participants during the successive workshops organized by the CA in Paris, Hamburg
and Pavia - and the most recent authoritative contribution by the invited American scientists at the Anugraha workshop.

Last, I am sure that the workshop’s organizers would have liked to thank me for providing support for their endeavour, but I feel certainly more compelled to thank them for the good use they made of our tax money! Thank you George, Brigitte and Frank, and thank you to all the participants and authors for the great job the reader will get now the pleasure to discover!

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Preface

The clinical application of the expanding knowledge about the immunological consequences of HIV infection is one of the most pressing tasks. Immunologists have always been eager to participate in such a challenge. In 1981 one of the first papers about the clinical description of a new syndrome, AIDS, was published [1]. In this paper Leu-3a, a CD4 monoclonal antibody, was already utilized documenting the loss of a ‘helper’ T-cell subset as a principal feature of the disease. Soon a whole range of CD4 antibodies, including those submitted to International Leukocyte Typing Workshops, was exploited to prove that the CD4 molecule itself was part of the receptor for the newly discovered LAV/HTLV-III [2, 3]. Nine years later a revised classification system for HIV infection and AIDS surveillance has been drafted by the Center of Disease Control (CDC), Atlanta, Ga., USA, in which the CDC recommends the widening of the AIDS surveillance case definition by placing all HIV-infected persons with less than 200 CD4+ lymphocytes/mm3 into the AIDS category [4] in addition to the clinical criteria established earlier [5]. The implementation of these new regulations is currently being discussed in the USA. Such a new concept would give appropriate emphasis to the laboratory findings by simplifying the classification of cases where the clinical findings are somewhat ambiguous. It could also be reconciled with the recent proposal for a WHO Staging System [6] where the ‘laboratory axis’ runs parallel with the clinical staging and both scores are recorded. Nevertheless, in Europe a stand equivalent to the CDC policy in adopting the laboratory parameter of low CD4 counts as an AIDS classifying criteria has not yet been accepted.
Similarly, the surprisingly severe immunosuppression seen in asymptomatic patients during relatively early stages of HIV-1 infection has been documented some while ago [7-9] but its significance from the point of view of patient management and preventive therapy has not yet been given appropriate emphasis. These assays have now been sufficiently simplified as whole blood methods [10], and there is consensus among the scientific community that they are suitable for routine use. AIDS is clearly a severe disease of immunoregulation which is initiated by HIV-1 infection and maintained by secondary immunopathological changes which aggravate and perhaps even determine disease development. Thus, patients need to be investigated not only by virological means but also by suitable methods which probe the relevant immune functions. The aim is therefore to measure these defects in ‘user-friendly’ tests which form an integral part of modern patient management and trial design.

At the Anugraha meeting, as part of the introduction to these issues, Dr. John Kagan of Division of AIDS, NIAID, NIH, USA, and Professor Ian Weller of Academic Department of Genito-Urinary Medicine, Middlesex Hospital, London, have discussed the concepts of the so-called ‘surrogate markers’ for AIDS development. There are two issues related to this topic. First, these so-called ‘surrogate markers’ are essential for progress in this field. HIV-1 infection, a chronic disorder, leads to established AIDS after a long period of about 6-10 years. Consequently, very long observation is needed to assess the outcome of drug trials evaluated by clinical criteria alone. This problem has paradoxically been further aggravated by the success of therapy. Prophylaxis against Pneumocystis carinii pneumonia (PCP) has been widely introduced in individuals with HIV-1 infection [11, 12]. As a result, among the reported cases of AIDS within the groups of homosexual men the proportion with PCP as AIDS defining diagnosis has decreased from 62% in 1988 to 46% in 1990 [4]. This is referred to as a ‘vanishing end-point’. Antiretroviral therapy such as AZT has also been widely initiated, further delaying the onset of illnesses that are included in the 1986 AIDS definition [5] leading to more ‘distal end-points’. Thus, the utility of the clinical AIDS definition in identifying the numbers of patients with late-stage HIV disease is likely to decrease over the next few years. This trend of ‘disappearing end-points’ inhibits efficient trial assessment at a time when a host of new drugs need to be investigated rapidly. As these drug trials would require more proximal rather than distal end-points, an early evaluation with well-chosen relevant surrogate
Table 1. Requirements for surrogate markers of AIDS progression

markers would help. This could decrease trial costs by reducing the length of trials and the sample sizes needed for obtaining significant results.

The other area where the introduction of similar concepts are warranted is resource allocation for therapy. If costs are allocated only on the basis of the number of patients with full blown clinical AIDS and the planners remain uninformed about unhospitalized patients with low CD4 counts, the cost pressures for prophylactic and antiretroviral therapy cannot be readily identified. This arrangement is relatively disadvantageous for treatment centres which practice patient monitoring and preventive medicine. Again, in such situations the acceptance of well-documented surrogate markers, such as the CD4 count, may solve problems by precisely guiding patient-oriented resource allocations.

Second, the main concepts about the optimal surrogate markers are summarized in table 1. Some of these requirements are difficult to fully satisfy in clinical practice. It is particularly hard to test the most recent candidates for progression markers on untreated patients, because antiretroviral therapy is now recommended for all HIV seropositive persons with CD4 count < 500/mm3. These issues increase the significance of analysing the various surrogate markers on established cohorts of untreated patients by utilizing stored serum and cellular samples when these are available frozen for a retrospective analysis. Probably the most important issue is that as the detailed knowledge about the pathogenesis of AIDS unfolds, these new findings provide a scientific justification for novel parameters of potential clinical importance. In addition to CD4 counts, the activation of the CD8 lymphocyte system, the poor lymphocyte performance leading to severe anergy and recently documented phenomena of cell death with apoptosis are all potentially applicable methods for disease monitoring in patients undergoing therapy.

At the workshop on the ‘Immunodeficiency in HIV-1 Infections’, held at the hotel ‘Anugraha’, Windsor, Surrey, both the practical issues of immunodiagnosis in HIV-1 infection and the recent advances in the pathogenesis of the disease have been discussed. Together with our invited American colleagues who represented leading teams in their selected areas, the participants of the workshop have followed a collaborative European
trend initiated by Herrn Kurt Körber in Hamburg by awarding the coveted ‘Green Rosette’ price to Professor L. Montagnier and his co-workers, and purported by the Concerted Action on the ‘Immunology and Immunopathology of HIV-Related Diseases’ led by Professor J.-C. Gluckman on behalf of the European Commission Working Party on AIDS. The current conference has been supported by the European Federation of AIDS Research (EFAR) as well as by the Dutch AIDS Foundation and the Medical Research Council AIDS Directed Programme of the United Kingdom. We are especially grateful to Prof. J.-C. Gluckman for helping us to organize this meeting and also to Mrs. Vanessa Lipton for efficient and cheerful administrative assistance. We are also greatly indebted to Dr. Angela Williams (Medical Research Council), Dr. Marianne von den Berg (Dutch Advisory Council on Health Research) and to Dr. Heinz Gretz (Körber Foundation) who not only supported the administrative action but also participated in person.

George Janossy

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References


7 Shearer GM, Salahuddin SZ, Markham PD, et al: Prospective study of cytotoxic T


