MEDICAL RESEARCH COUNCIL

MRC: IN CONFIDENCE

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MRC WORKING PARTY ON AIDS

REPORT: THE POSSIBILITIES FOR RESEARCH ON ACQUIRED IMMUNE DEFICIENCY SYNDROME IN THE UK

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1. Papers

Annex 1 - report

Annex 2 - membership of the Working Party

2. Background

As a result of an informal meeting on AIDS in July 1983, chaired by Sir James Gowans, an MRC Working Party on AIDS was set up with the following terms of reference:

"To review scientific knowledge and research on AIDS in the UK and abroad.

To encourage contact and co-operation between research workers in this field.

To advise the Council on the current state of knowledge in the field and on topics for research."

In fulfilment of the third of these terms of reference, the Working Party has produced its first report.

3. MRC support for AIDS research

Three special project grants for AIDS research were awarded during 1983:

Dr D J Jeffries (Virology, St Mary's Hospital Medical School) and Dr D Taylor-Robinson (Clinical Research Centre, Division of Sexually Transmitted Diseases). Virological Investigations of Patients with the Acquired Immunodeficiency Syndrome. Total cost: £88k over three years.

Dr A J Pinching (Immunology, St Mary's Hospital Medical School). A study on the killing of intracellular pathogens by macrophages derived from homosexual males with AIDS and related disorders. Total cost: £43k over three years.

Dr R A Weiss (Institute of Cancer Research). Retroviruses associated with Acquired Immune Deficiency Syndrome. Total Cost: £48k over three years.

These studies involve investigation of the T-cell defects in AIDS (Pinching) and the possible role of cytomegalovirus (Jeffries and Taylor-Robinson) and retroviruses (Weiss) in the aetiology of AIDS. Longitudinal studies of homosexual attenders at clinics who show possible "pre-AIDS" symptoms are

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under way at St Mary's Hospital. Proposals from the Middlesex Hospital for further studies of this type (in line with the recommendations on page 2 of the Working Party report) are to be considered at this meeting. The Communicable Disease Surveillance Centre is preparing proposals for a full epidemiological study of AIDS in England and Wales. Investigation of treatment methods, the search for a surrogate test for donor blood samples and studies in animals are areas in which further initiatives are required.

4. Action required

To note the report of the MRC Working Party on AIDS.

April 1984

Annex 1

MEDICAL RESEARCH COUNCIL

MRC: IN CONFIDENCE

The Possibilities for Research on Acquired Immunodeficiency Syndrome (AIDS) in the UK

A report from the MRC Working Party on AIDS

Introduction

As a first step towards fulfilling our terms of reference, we have had discussions on the present knowledge of the condition, the possible course of events in Britain, the questions which require answers and the resources and expertise available. We have put together this document which outlines what we think are the most likely ways in which successful research could be done. We assume that readers are aware of the general state of knowledge and we have tried to avoid a general list of all the conceivable possibilities. We give instead a short and selected list of projects which we believe are practicable and would be helpful both for clinical practice in this country and for adding to overall scientific knowledge. Our aim has not been to try to match the very substantial research effort of the United States, but to identify specific areas in which a UK contribution is likely to improve our understanding of the disease. The circumstances of the emergence of AIDS in the UK and local expertise provide an opportunity to study this new disease at an early stage. We do not wish to imply that other approaches to the study of AIDS would be unproductive, and we suggest that funding bodies should be open to other ideas as well. As multidisciplinary work is essential to success in this field, it is important to ensure that a series of different studies are undertaken and that there is free cooperation and exchange of information between the different research groups.

Epidemiology

The incidence in the UK is likely to increase but some features differ from those seen in the USA and Africa. The occurrence of AIDS should be documented so that trends can be monitored, and high-risk groups and possible modes of spread identified. This will allow an assessment of the risks to special-interest groups such as homosexuals, haemophiliacs, blood transfusion patients, health care and laboratory personnel, and provide the basis for formulating advice to the medical profession and public.

It is important to extend the present national surveillance system which is based mainly on voluntary reporting of cases. Patients should be seen by an experienced epidemiologist/physician and a uniform report completed documenting any contacts with other persons and other possible risk factors. A record of needle-stick injuries should be kept so that individuals can be followed up and the risk of infection documented. In some centres, such information is being collected already and needs only to be assembled and collated. In others, visits by a centrally supported research worker will be needed. To establish the significance of these observations, subjects in comparison groups will need to be interviewed too, i.e. clinic controls or social-group controls (the gay community, for example) or both. A detailed protocol for this type of study is being prepared by the Communicable Disease Surveillance Centre (CDSC); the methods proposed are compatible with those used at the CDC, Atlanta. In our opinion, such work is urgently needed before the early stages of the epidemic are past.

In addition, although it is said that staff of clinics and laboratories are not at risk, they should be monitored for some years as the incubation period is long and some cases do not fall into the known risk categories.

Cases of AIDS have occurred already in haemophiliacs and more are likely. Because of the specially high standard of record-keeping in the UK, it is possible to trace which batches of factor VIII cryoprecipitate etc., any patient has received and also all others in the country who have received the same batches, with their family contacts. A study is planned at the Public Health Laboratory in Manchester, in co-operation with the Haemophilia Centre Directors. We support this as it offers a special opportunity to study attack rates, incubation periods and other important factors. It would seem desirable to link this study with the one proposed by the CDSC.

There is much concern about homosexual attenders at clinics who are at high risk, show T-cell abnormalities and may have lymphadenopathy, fever, etc. There is an opportunity to study groups of such cases attending the Middlesex and St Mary's Hospitals. We recommend that these studies be undertaken and continued for at least 3 years. Longitudinal studies of such cohorts will give much-needed information on the natural history of the disease and may provide ideal material from which to attempt to recover an aetiological agent. One such study is funded (at St Mary's), but in our view, a second one at the Middlesex is desirable to provide a study population of at least 200 patients at each centre since the proportion going on to develop AIDS is likely to be between 1 and 10 per cent.

Kaposi's sarcoma has been known to occur in young men in Central Africa for many years. The clinical and epidemiological features of such cases should be reviewed, with particular regard for immunodeficiency in the same or associated cases and the epidemiological features found significant in the USA and Europe. The MRC still has contacts with these parts of the world and even quite a short survey might provide valuable information.

Study of cases of AIDS

It is important that all cases are well studied clinically and documented completely - it can never be forecast when an apparently chance observation on perhaps a single patient will provide an important idea for future research. These patients require a heavy commitment but clinical resources are not likely to be swamped as yet. Some aspects of the disease are not well understood and we recommend that studies of, for instance, the pathophysiology of diarrhoea and malabsorption be encouraged. There are considerable resources in skill and experience in this field in the UK.

It is important that samples, particularly of blood and lymph node biopsies, are taken, wherever possible, from carefully studied patients, including early AIDS and 'pre-AIDS' cases, and are preserved in appropriate ways for subsequent attempts to isolate an aetiological agent. Samples from infants who develop AIDS are particularly important because they are not likely to contain extraneous agents. Post mortems should be done whenever possible for the purposes of research, so long as adequate safety precautions can be taken. The Advisory Committee on Dangerous Pathogens will shortly produce guidelines for the handling of AIDS samples and the performance of post mortems.

Therapeutic and prophylactic studies

The treatment of the underlying immunodeficiency has so far proved unsuccessful; even treatment of associated opportunistic infections is often

disappointing. It has been suggested that randomized multicentre trials are needed and indeed attempts have been made to write protocols for these. The problem is that cases are variable in their presentation and treatments are so unpromising as yet that it may be difficult to reach agreement on a suitable set of indications and indeed on the form of treatment. Furthermore, rigid adherence to a protocol may not be seen as being in the patients' interests, thus undermining the successful conclusion of a trial. We think that the correct approach is to review new methods of treatment by allowing local groups to try them on a few patients as a pilot study. Since patients often have to be retreated for the same condition, it is possible to have some sort of comparison even on a single patient. If promising results are obtained, then a trial should be set up, although it may be necessary to obtain collaboration from other European centres in order to have enough patients. Drugs presently available for treatment of pneumocystis and some other infections produce many adverse reactions and a watch should be kept for any new products. Acyclovir is very satisfactory for herpes virus infections. Ribavirin and perhaps other new antiviral drugs might be tried by inhalation for pulmonary virus infections. Bone marrow transplantation has not been successful but interferon δ and interleukin 2, just available for clinical trial, may reverse at least part of the immunological defect and should be tried. Cytotoxic drugs for the treatment of Kaposi's sarcoma may make the clinical condition worse. However, interferon δ looks promising and should be explored further.

Virus detection

It would be unwise at the moment to ignore any aetiological theory although we do not favour those involving protozoa, fungi or toxins. Virus involvement seems more promising and there are two broad hypotheses to explore. One is that a special strain or mutant of a common virus is the basic cause. Tests for such viruses require the use of very carefully selected and stored clinical specimens (see above), real experience in such work and good supplies of cultures, technical assistance, etc. It is quite impossible to do a comprehensive series of tests. In our opinion, groups of workers with enthusiasm and high skill for studying candidate viruses should be encouraged to do so. Council already supports a survey by restriction endonuclease mapping of the cytomegaloviruses isolated (St Mary's) and a search for HTLV (human T-cell leukaemia virus, a retrovirus) and related viruses and antibodies against them (Institute of Cancer Research).

The other hypothesis is that a hitherto unknown virus or virus-like agent is responsible. An essential experiment is to inoculate higher primates, for example chimpanzees, with materials from AIDS and "pre-AIDS" patients. This has been done in the USA and Holland and we could add little. However, some variations on this theme would be worth supporting, for example inoculating marmosets, which are readily available in the UK, using a number of different routes, with and without administration of immunosuppressive drugs. In preparing material for inoculation it should be remembered that a putative virus may be bound to cells (for example, leucocytes or platelets) and not necessarily be free in serum.

Cocultivation with a variety of cells over long periods of time has been successful as a means of isolating viruses associated with other conditions in the past, but there are few indications as to which cells are most appropriate and the possibilities are numerous. It might, therefore, be worth trying a strategy which does not require the organism to be grown. By analogy with work on hepatitis B virus and parvoviruses, it would be worth testing whether sera (and possibly lymph node extracts) from patients who are in the early

stage of the disease and might have viraemia, contain antigens which react with antibodies in sera from patients who have had adenopathy and may have recovered from an infection. Electron microscopy or immuno-electron microscopy might also be used. If immunoreactive material or possible virus particles were found, it would be possible to use recombinant DNA techniques to recover the viral nucleic acid, replicate it and study it. The group at the Middlesex Hospital in conjunction with Professor Murray are equipped to make such studies.

Immunology and pathogenesis

A good deal of work has been done on the immunological changes occuring in the disease, and T-helper depletion is still regarded as the best marker. However, there has been little attempt to study the immunohistopathological changes. The reagents and facilities for undertaking immunohistology in the UK are excellent, and this aspect should be pursued.

In considering the anxiety that AIDS has caused in relation to blood transfusion, it seems important to determine which are the best surrogate tests (i.e. tests for markers which are associated with AIDS) to carry out on donor blood samples, and work of this nature should be supported. Such surrogate tests should be evaluated in the longitudinal cohort studies of at-risk patients (see above).

Summary

We have identified specific areas in which AIDS research in the UK should be pursued. Cases of AIDS should be reported as fully as possible, and samples taken and stored for studies of aetiology. Longitudinal studies of patients in "high-risk" categories should be performed, and staff in contact with AIDS patients should also be monitored. Pilot studies of treatment methods, both of opportunistic infections and the immunological disorder, should be attempted, and any successes followed up with controlled trials. The search for a potential AIDS virus should continue, both through laboratory investigation of clinical specimens and inoculation of marmosets. There is a need for work on the immunohistopathological changes associated with AIDS, and surrogate tests for donor blood samples should be developed.

Conclusion

There has been much anxiety about this new disease with its high mortality. It is unlikely that any treatment for the underlying cause will be found in the near future. Nevertheless, a research programme such as that which we propose should lead to clearer diagnosis, a greater understanding of AIDS and its modes of transmission, and more confident prediction, both of individual outcomes and the course of the epidemic in this country. It is likely that containment of the disease could be achieved through changes in behaviour of those at risk, but any advice to patients must be based on well-documented epidemiological findings.

The disease offers an unusual opportunity to improve our understanding of the functioning of the immune system and to study the natural history and biology of a novel infectious agent. We believe that research along the lines we propose will lead to progress on both fronts.