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AIDS 83/2

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MRC WORKING PARTY ON AIDS

Minutes of the meeting held at 20 Park Crescent, London W1N 4AL on Monday 10 October 1983

Present:

Members	Dr D A J Tyrrell (Chairman) Dr A J Pinching (Secretary) Professor M W Adler Professor A L Bloom Dr J R W Harris Professor P J Lachmann Dr D Taylor-Robinson Dr A D B Webster Dr R A Weiss
Departmental Observers:	Dr W M Prentice (SHHD) Dr Diana M Walford (DHSS)
By Invitation:	Dr S R Palmer Dr R S Tedder Dr J E M Whitehead
MRC Office Staff:	Dr M P W Godfrey Dr Katherine Levy Dr M J Fisher Dr Jane E Cope
Apologies for absence:	Dr N S Galbraith Professor H P Lambert Professor K Murray

1. Chairman's Introductions

The Chairman welcomed the members of the Working Party and introduced Dr Whitehead of the PHLS, Colindale, Dr Palmer of the PHLS, Cardiff who was standing in for Dr Galbraith and Dr Tedder of The Middlesex Hospital. He outlined the background to the setting up of the Working Party and indicated the need to ensure that the best use be made of the special combination of suitable patients for study and the clinical, immunological, virological and other expertise available in the United Kingdom. The Working Party would review the current position and seek out areas in which a UK contribution might be most effective. He invited the Working Party to make comments, both judicious and outrageous, and to generate ideas that might stimulate new research objectives. The importance of high quality work was stressed, along with the need for the Working Party to ensure that truly original scientific objectives are encouraged subject to the normal peer review mechanisms. The Working party would advise the Systems Board on the whole area of AIDS and review specific grant proposals prior to their consideration by that Board.

2. Terms of Reference of the Working Party

The Chairman reminded the members of the Working Party's remit:

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

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

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

Concern was expressed by several members that the Working Party was to act in part as a grants committee. As many of the members of the Working Party were closely involved in the projects coming before it, there was a potential problem of impartiality. It was explained that the Working Party had no delegated authority, it would act as a panel of referees and further expert opinion might also be sought. Applicants would, of course, be excluded from discussion of their own proposals. The Working Party would make recommendations to the Systems Board (which was represented on the Working Party) which would consider the applications for Special Project Grants.

3. AIDS: The current position

The Working Party reviewed the present position on AIDS, assuming that most of the major literature was known to members in advance. Members of the Working Party with particular expertise spoke on individual sections of the discussion.

(a) Clinical

It was noted that AIDS provided a good example of a problem arising in clinical medicine which was posing many new and unexpected questions of basic science. The overall clinical picture of AIDS was of a specific and severe form of immunodeficiency with a range of presenting disorders extending from Kaposi's sarcoma to multiple opportunist infections. The broad resemblance to the congenital immunodeficiency SCID was noted. The manifestations were noted to vary according to both host and environmental factors. The pattern emerging in early UK cases seemed different in some respects from the American experience, and the gastrointestinal problems were noted as a particularly important area for research. The laboratory markers for disease were well established for AIDS itself but their relevance in screening and in a possible precursor state was not established. The problems of definition and interpretation of these so called precursor syndromes were outlined by several members. The special features arising in relation to haemophilia were discussed and the possibility of identifying the role of imported Factor VIII concentrate used for UK patients was outlined. There followed discussion on the varying and considerable period of incubation (1 to 4 years) and the possible relationship between the size of inoculum of the proposed agent and the length of latency. The possibility that AIDS as currently defined was the tip of an iceberg in terms of a range of clinical or subclinical responses to infection with a putative AIDS agent was mentioned; it was recognised that the existence of milder forms would be hard to establish without a marker for such an agent.

(b) Epidemiology

The epidemiology of the disease in the United States was reviewed and also the rather limited information which had emerged from the national case control study - a study which had been widely criticised. The six months doubling time of cases appeared to be continuing and a suggestion that there was a plateau in cases had not been substantiated. There was no apparent change in the geographical or risk groupings. The UK figure of 24 cases indicated that there had been a recent increase almost conforming to a six month doubling time. Possible effects of changing behaviour/life style were indicated. It was argued that AIDS was new to the western world in 1978/9 although the disorder may have been present in Africa for much longer.

(c) Aetiology

The aetiological background to AIDS was considered with passing allusion to the antigen overload hypothesis. An increased microbiological load with multiple infections associated with active virus replication in the host was thought a possible mechanism for immunodeficiency. The more widely held view that AIDS was due to a novel "AIDS agent" was also discussed. It was noted that attempts to detect such an agent in the United States were being made in only a few centres, and it might be better to look for an agent early rather than in the later stages of severe disease. For this reason reliable identification of the early phases of disease/infection was crucial. It was possible that the agent was a zoonosis and the importance of looking to veterinary virology for models as well as for possible agents was emphasised. The analogy, in terms of transmissibility, with hepatitis B virus was noted and it was suggested that a hepatitis B mutant or an agent analogous to the delta agent should be high on the list of candidates. It was certainly possible that instead of being a totally new virus, the agent for AIDS could be a familiar one that had developed new properties.

Retroviruses were considered and it was noted that HTLV was a possible candidate on the basis of its known tropism for T helper cells. However a critical evaluation of the data led to the view that it was more probably an opportunist was unlikely to be the aetiological agent. The assumption that the agent was necessarily a virus was challenged and the need to keep an open mind on organisms such as protozoa was stressed. Systematic antimicrobial therapy might provide leads on such agents. It was noted that blood product associated cases could enable some of these alternative hypotheses to be tested.

(d) Pathogenesis

The T helper cell depletion seemed to provide the best current clue as to pathogenesis. However, polyclonal B cell activation and abnormal macrophage function had also been shown. Whether a single pathogenetic mechanism could be the cause of all these features or whether there were varying cellular responses to the same agent was not clear. The need to define mechanisms was particularly important for the logical planning of therapeutic immunoreconstitution. The limitations of studies on blood were noted and several members stressed the need to examine lymphoid tissue - the site of immune response events. It was however agreed that data available from blood studies appeared to be broadly representative of events in lymphoid tissue.

The importance of virus-like particles found on electron microscopy was considered doubtful but the need to look at such material was agreed. Rectal lymphoid tissue was thought to be a potentially important site for study in homosexuals. Release of factors into the host by organisms colonising the gut could provide an alternative pathogenetic mechanism. Another possibility, that the disease or some of its manifestations were transmitted directly by transplanting malignant or virus infected cells, was suggested on the basis of an animal model.

4. Opportunities special to the UK

The Working Party sought to identify particular opportunities for research unique or special to the United Kingdom. The fact that the epidemic was lagging some three years behind that in the USA was considered an important factor in enabling the background against which AIDS develops to be delineated. This could enhance our ability to detect the emergence of AIDS and AIDS-related conditions in high risk groups. The underlying immunological and virological status of the high risk groups before they encountered the "AIDS agent" could thus be defined.

(a) Clinical

The pattern of disease in the UK seemed somewhat different from that elsewhere and this needed careful documentation. The environmental and host factors determining the particular pattern of opportunist infections were clearly relevant to the prevention and treatment of the secondary disease. The ability to detect an increase in cases of unexplained persistent lymphadenopathy in prospective studies would be useful in establishing the background causes for this rather nonspecific syndrome before the rise in truly unexplained cases probably relevant to AIDS emerged. There were opportunities for research programmes in respiratory medicine, gastroenterology and other organ-based specialities, and for carefully monitored therapeutic trials, and such studies could readily be made in the UK. The structure of venereology in the UK allowed the highest risk group to be studied in a small number of well equipped centres with good contact in the community and experience relevant to this type of problem. Clinical immunologists in the UK had greater experience of adult immunodeficiency than their counterparts in the US, and their clinical and laboratory base was thought to be a particular advantage. Gastroenterology in the UK was thought to be in a good position to exploit the opportunities available in AIDS research. The UK system for haemophilia treatment and for blood product organisation would allow detailed study of haemophilia associated cases which has not been possible in the USA due to their system of record keeping and organisation.

(b) Epidemiology

Some of the epidemiology in the American studies was thought to be insubstantial and not of the highest quality. The erasure of patients' names from the records held at the Centres for Disease Control in Atlanta as a result of political pressure would limit the ability of CDC to conduct proper epidemiological studies. The organisation of epidemiology in the United Kingdom was well suited to studying this problem. The importance of establishing such studies early in the emergence of disease was again stressed. Further emphasis was given to the concept of identifying early phases of the disease for testing aetiological hypotheses. It was emphasised that at this stage national collaboration was possible and indeed essential on

items such as an AIDS case-control study and active surveillance. This would need to be backed up by individual centres conducting cohort studies of patients in high risk groups etc. The close liaison between clinical and laboratory medicine in the UK was again stressed as an important background for such work. Blood transfusion policy was discussed in relation to the possibility of using "clean" donor panels for blood products.

(c) Immunology

The importance of the established close links between clinical and laboratory workers in this field in the UK was again mentioned. It was noted that in addition the UK offered particular opportunities to pursue carefully controlled and monitored therapeutic trials.

(d) Virology

It was noted that there were no unique facilities in the UK but that it was important to use the available clinical material to best advantage. The importance of detailed microbiological documentation was stressed as was the need to ensure appropriate facilities for detailed virological studies in animals and in tissue culture. It was noted that, in the search for particular recherche viruses, collaborative research with units having special expertise in these areas was essential. In the course of discussion it was emphasised that research would need to be focused on particular scientific objectives rather than seeking a broad all-inclusive sweep.

(e) Genetic Engineering

A telex from Professor Murray was tabled and this made clear that there was no special expertise that was not available in other countries. Professor Murray indicated possible areas for work including the analysis of serum for AIDS-specific nucleic acids. This was thought to be rather laborious but worth exploration. Alternatively, genetic engineering could facilitate the search for proposed aetiological agents. This would involve the development of specific probes, of value in both diagnosis and possible vaccine development. The time scale for such work was thought to be relatively long. In discussion, the limitations of the first approach where it had been applied to other agents such as non-A, non-B hepatitis were mentioned. It was thought that suspect blood products could provide valuable raw materials for work of this type. Indeed, the possibility of fractionating blood from patients with "pre-AIDS" in order to concentrate the agent was a notable suggestion. Pooled material by contrast caused substantial problems as judged by previous experience in other settings. The potential difficulty of finding large numbers of different agents in such patients might pose problems of interpretation.

5. Opportunities for communication about AIDS in the UK

The clinically and epidemiologically based AIDS information group was mentioned, and it was noted that other avenues in specific areas of interest were also available.

6. NIH memorandum

The attention of the Working Party was drawn to the NIH memorandum as a useful means for rapid and confidential publication of AIDS work among active researchers. It would enable positive and negative results to be rapidly

disseminated among such teams. The memorandum system was strongly supported from its success in other settings and individuals were encouraged to contribute.

7. Role of the DHSS and relationship between MRC and DHSS activities on AIDS

The role of the DHSS in liaison with national and international groups was sketched out. The importance of cooperation between DHSS and MRC in health services research products was indicated. Avenues for communication were agreed to ensure that projects that were inappropriate for MRC funding could be taken on by the DHSS if it was considered appropriate on the advice of the Working Party. The repercussions of AIDS in respect of blood products received particular comment.

8. Safety standards in projected AIDS work

The safety aspects of AIDS work were briefly discussed in order to ensure that the Working Party was aware of the necessary standards applicable to AIDS projects coming before it. The Chairman, also chairman of the HSE Advisory Committe on Dangerous Pathogens, noted that this latter body was drawing up guidelines based on those produced by the Centres for Disease Control in response to a request from the DHSS and the HSE. It was suggested that the guidelines had to be practicable. In the meantime it was agreed that precautions similar to those used for hepatitis B should be taken.

9. Specific grant applications

Applicants were asked about aspects of their projects before being requested to leave the meeting while their applications were discussed. Further disquiet was expressed about the Working Party's ability to assess projects in this way, especially in view of the fact that a number of members not involved in any of the projects had been obliged to leave by this stage.

(a) Adler, Tedder, Crawford (Middlesex)

This large epidemiological study with extensive laboratory support was considered to be very much of the type that had been regarded as necessary by members of the Working Party earlier in the proceedings. The scope of the study and its approach seemed correct, asking good questions with an outline of high technical quality. The considerable expense of the project was noted and it was felt that while much of it could be justified there was room for judicious reductions on the laboratory side perhaps by employing Research Assistants on the 1B rather than the 1A scale and pruning out 1 MLSO. The clinical staffing was regarded as mandatory and should not be cut as this would jeopardise the whole project. Similarly the duration of the project was discussed and it was recognised that a 3-year project was essential to allow completion. The Working Party recommended that the project should be passed on to the Systems Board with approval subject to careful cost review.

(b) Jeffries and Taylor-Robinson (St Mary's)

This project was considered together with the supplementary application for technical support. The proposal represents an extension of current work on AIDS at St Mary's Hospital with a view to studying virology as well as epidemiology and immunology. The major aim is to test the hypothesis that a mutant form of cytomegalovirus (CMV) is responsible for, or contributes to, the establishment of AIDS. Although the Working Party were unsure of the

likelihood of this, it was felt that no particular viral candidate stood out and that CMV was one which should be investigated. In view of local expertise it was thought that St Mary's would be the best place for such work. The methods were thought to be appropriate although the control group of patients should perhaps be chosen differently. It was felt that it was not clear what the individual duties of the 2 proposed staff would be, and that the applicants should be asked to recast their proposal in order to incorporate the request for an MLSO in the body of the application. It was hoped that this would be possible in time for the next Systems Board meeting.

(c) Weiss (ICR)

A proposal for a single technician was submitted which would enable Dr Weiss to collaborate with several groups in research on HTLV and other retroviruses. He explained that the tentative nature of his application resulted from his existing CRC/MRC joint funding status and was reassured that there was no procedural barrier to his receiving SPG support in the present circumstances. The application was then discussed in his absence and was warmly commended in its own right as an example of specialist expertise being made available to several different collaborating groups in the best possible way. Existing work on HTLV had left a number of questions unanswered and there were methodological problems which Dr Weiss was in the best position to overcome. It was thought likely that other retroviruses would be isolated in the course of the work and that these would need to be investigated in addition to HTLV. The request was seen as very modest and it was agreed that it would give very good value for money if granted.

10. Date of the next meeting

It was agreed that this should be a half day meeting in mid December. Specific dates were to be arranged by the MRC office.

11. Any other business

There was no other business. The Chairman closed the meeting with thanks to the members and invited participants for their valuable contributions.

A J Pinching
Scientific Secretary.