UK Research and Innovation
Polaris House
North Star Avenue
Swindon SN2 1FL

www.ukri.org

26th July 2019

[redacted]

[redacted]

Freedom of Information request: 2019/0160

Thank you for your Freedom of Information (FOIA) request received on 30 June 2019 in which you requested the following information relating to Medical Research Council records:

Your Request:

Under FOI I am requesting a copy of the following file which you hold:

Acquired Immune Deficiency Syndrome: Working Party Report S819/516/04/1984

Our response:

I can confirm that UK Research and Innovation does hold the information you have requested.

An electronic copy of the Medical Research Council file you requested is provided with this response as *FOI 2019-0160_S819-5 MRC Working Party on AIDS Report.*

A small amount of information has been redacted from this file under Section 40(2) of the FOIA, the exemption relating to personal information, explained further under the heading of "In summary".

We are not obliged, under section 40(2) of the FOIA, to provide information that is the personal data of another person if releasing would contravene any of the provisions of the General Data Protection Regulation and the Data Protection Act 2018. In this instance we believe that the release of information would contravene the first data protection principle and therefore section 40(2) has been applied.

Section 40(2) is an absolute exemption and therefore a public interest test is not required.

In summary:

- the names of some MRC staff, please note the names of MRC staff in senior management position and the names of members of the MRC Working Party on AIDS have been released;
- the name of one individual proposed as a member of the Working Party but who did not go on to become a member; and
- the names of researchers referred to in discussions but who were not formally involved in Working Party activities or where we have been unable to establish that they were in receipt of MRC funding for research in the area.

If you have any queries about this response please contact me, or if you are unhappy with the service you have received in relation to your request and wish to request a review of our decision, please write to:

Complaints Officer
UK Research and Innovation
Polaris House
North Star Avenue
Swindon
SN2 1FL
Email: foi@ukri.org

Please quote the reference number above in any future communications.

If you are still not content with the outcome of the review, you may apply to refer the matter to the Information Commissioner for a decision. Generally, the ICO cannot make a decision unless you have exhausted the review procedure provided by UKRI. The Information Commissioner can be contacted at:

Information Commissioner
Wycliffe House,
Water Lane
Wilmslow
Cheshire
SK9 5AF

Enquiry/Information Line: Between 9am and 5pm Monday to Friday 0303 123 1113 or 01625 545745
Further information about the Office of the Information Commissioner can be found at
http://www.ico.gov.uk/

Yours sincerely,

[redacted]
UK Research and Innovation, Information Governance Team
Email: foi@ukri.org

File No: S 819/5

MEDICAL RESEARCH COUNCIL
HEADQUARTERS FILE

File No: S 819/5.

SERIES SUBJECT

Acquired Immune Deficiency Syndrome.

FILE TITLE

A Report from The MRC Working Party On Aids

RELATED TO: 9701 ~~1708~~

REFER TO	Initials	REFER TO	Initials	REFER TO	Initials
[redacted]	✓				
Registry	✓				
[redacted]	✓				
DMS					
		PLEASE ENSURE THAT THIS FILE HAS BEEN ENTERED ON YOUR TRANSIT SHEET			
				DISPOSAL INSTRUCTIONS	Signature / Date

5819/5

[redacted]

I have drafted an alternative conclusion to the report, on the lines suggested by [redacted], as well as a short summary. Please see also draft letter to Dr Tyrrell which I would also send to both Pinching and Taylor-Robinson. I will complete the 3rd para when I have your comments on the minutes.
Do you wish to amend the drafts?

[redacted] Thank you — may we discuss?

[redacted] 26.1

[redacted]

I have had the document retyped as we discussed
I have made some minor alterations to the main body of the report in the interests of clarity and style, while resisting the temptation to rewrite completely!
I think the conclusion is still too woolly, and have suggested an alternative (not typed I'm afraid to save time).

I think this is now more or less in a form which can be sent to the trio of authors and subsequently the other members of the Working Party. Bearing in mind that time is short, we could perhaps continue with office refinements simultaneously?

[redacted] 30/1/84

[redacted]

I think the alterations make it stronger.
Please proceed.

[redacted] 31.1

[redacted]

Do you have any comments please on the draft Board paper opposite or the most recent form of the report ~~[illegible]~~ It has been approved by Tyrrell, Taylor-Robinson & Pinching, and sent to the other members for comments.

[redacted]

Please see also draft letter to Dr Tyrrell which I would also send to both Pinching and Taylor-Robinson. I will complete the 3rd para when I have your comments on the minutes.
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Do you have any comments please on the draft Board paper opposite or the most recent form of the report ~~before it~~ ~~is approved by~~ It has been approved by Tyrrell, Taylor-Robinson & Pinching, and sent to the other members for comments.

[redacted]

please send copies of the letter (attached in draft form), draft report and minutes of the last meeting to all members of the W.P. and Dr Palmer. Copies of the minutes and draft report should also go to Dr Godfrey, [redacted] and

[redacted] with an explanatory note

[redacted]

[redacted] passed this file onto me in your absence (3.2.84). I have carried out the work requested; however, I have not provided you with the papers (mentioned in the b.m. to me) as they are on file. If you do wish to have a set please let me know.

[redacted] 7.2.84

[redacted]

Do please let me have a set.

[redacted]

Draft office note is OK but a bit spare. The Board might find it helpful to have a para on which reports of the reviews have been covered by the grants awarded, or those to be considered, and which are in train (eg the CDSC review) and which if any nothing is planned on. (It might be wise to check such a para with Tyrrell as it would have some weight.)

[redacted] 8.2.84

[redacted]

Board paper for approval.
I have expanded the office note as you suggested and it has Dr Tyrrell's approval.
Minor amendments have been made to the report as a result of comments from the WP members. These have been checked with Dr Taylor-Robinson in Dr Tyrrell's absence.
Professor Lambert is the obvious D.B.M. If it were thought desirable to have an additional one who is not directly involved with the Working Party, I would suggest [redacted] as a participant.

[redacted] 17/2/84

[redacted] 22/2/84

The AIDS report has been carefully considered by WP members and it seems a clear and useful document. Would you please consider the paper for the April Board.
I think it would be of value to have [redacted] as DBM in addition to Lambert — an 'outside' view.

[redacted] 20.2

[redacted]

[redacted] 7.2.84

Please let me have a set.

[redacted]

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I think it would be of value to have [redacted] as DBM in addition to Lambert — an 'outside' view.

[redacted] 20.2

[redacted] A.

Paper approved — Lambert only I think. [redacted] 22/2/84
[redacted] Please see above & pass on.

[redacted] 22.2

[redacted] - for attention please [redacted] 27/2/84

[redacted]

Draft Board paper opposite for processing please.

[redacted] 5-3-84.

[redacted]

Would you please arrange for the Board minute recording from the paper opposite to be copied onto this file. I would also be grateful for a copy for file E819/11 on which I am preparing the WP's second report for the Board.

[redacted] 21/11/84

Circulation
Participants

MRC WORKING PARTY ON AIDS

Minutes of the meeting held at 20 Park Crescent, London W1N 4AL on Tuesday, 17 April 1984

Present:

Members:	Dr D A J Tyrrell (Chairman) Dr A J Pinching (Secretary) Professor M W Adler Professor A L Bloom Dr N S Galbraith Dr J G P Sissons Dr D Taylor-Robinson Dr R S Tedder Dr A D B Webster
Departmental Observers:	Dr R G Covell (SHHD) Dr Alison Smithies (DHSS)
MRC Office Staff:	[redacted]
Apologies for absence:	Dr J R W Harris Professor P J Lachmann Professor H P Lambert Professor K Murray Dr W M Prentice (replaced by Dr Covell) Dr R Weiss

1. Chairman's Introduction

The Chairman welcomed Dr Galbraith, who was taking up his place on the Working Party, and took the opportunity to express appreciation of Dr Palmer's work on the Working Party in Dr Galbraith's absence. He noted that Dr Tedder had become a full member of the Working Party, and expressed regret about Professor Lambert's recent illness.

2. Minutes of the meeting held on 20 December 1984

These were agreed to be an accurate record.

3. Matters arising from the Minutes

(i) Minute 3

Following the discussion at the last meeting, it had been agreed that individual Working Party members would act as referees for specific applications, rather than the Working Party trying to express a corporate view. Applications were still being circulated to members for information and any informal comment they wished to make. As members still felt uneasy about receiving copies of applications in this way, it was suggested that the Chairman and/or Deputy Chairman only should see the full papers in order to judge whether the proposed studies were within the area of work which the Working Party wished to foster. Members would receive only the abstract and "purpose of investigation", in unattributed form, and would also be informed as to the outcome of such applications.

(ii) Minute 6

The Chairman reported that the Advisory Committee on Dangerous Pathogens had had further discussions on the safety requirements for AIDS work and had referred the tentative guidelines to a smaller Working Group. He thought that new guidelines would not now be available until late summer at the earliest.

4. Report of the Working Party

The report had been noted by the Systems Board, and comments would be relayed in due course. It was noted that there would be some need to keep recommendations up to date, probably on an annual basis. This would be considered further in the Autumn of 1984.

5. EEC Meetings on AIDS

The Chairman and Deputy Chairman reported on three meetings held under the auspices of the EEC to examine possibilities for research in Europe. These had been prompted by the European Parliament, and proposals would be considered by the European Research Committee (CRM). A number of possible collaborative research ventures were discussed, and two potential areas for

action were focussed upon. One would involve collaborative ventures between different countries, and would include studies dependent upon arranging to test materials derived from many countries, perhaps by exchanging staff, reagents or test samples - for example, studies on primates. In the second case, direct funding would be needed for certain defined projects such as perhaps, clinical trials. The CRM accepted the broad suggestions, but found the proposed package too expensive. At the final meeting it was agreed that funding for basic research at the national level would not be carried out under EEC auspices: EEC funds were not to be used simply for 'topping up' of national funding. It was thought more appropriate to encourage coordinated action, to enable the exchange of material and research workers between laboratories in the community. It was felt that the EEC should not attempt to compete with the United States research effort but should engage in studies related to the particular features of AIDS in Europe, for example studies on patients with African connections. It was agreed that the MRC office staff would determine how funds might be obtained from the CRM for collaborative work of the type envisaged by the EEC.

There was also discussion of the planned central clearing house for epidemiological and possibly other information, that had been proposed by the WHO and EEC. It was hoped that further information would be available once the initial organisation had been established.

6. WHO and IUIS AIDS Working Group Meeting.

Dr Pinching reported the successful drafting by this group of a position paper, which was shortly to be published in an international medical journal. Of particular interest to the Working Party was a rather wider definition of AIDS based on immunological features and pathogenic mechanisms.

Dr Pinching also referred to two other pieces of information which had come to light during the course of his visit. Studies on primates which had been conducted at the Centres for Disease Control had been rather limited, contrary to information available earlier. It was agreed that Dr Taylor-Robinson would check what experiments had been conducted by CDC, NIH and other groups in order to focus further primate work more effectively.

The other item concerned the data from Dr Montagnier of the Pasteur Institute which was presented at a meeting in March. Evidence, on the basis of virus isolation and serological tests, that a lymphotropic retrovirus played a causative role in AIDS was outlined. A number of implications of this work were considered, including the need for caution in immunostimulation during early stages of AIDS, such as persistent lymphadenopathy, which could potentially enchance the expression of the virus and hence of immunodeficiency resulting from it. On the other hand it was recognised that alpha interferon or other antiviral agents applied early might be helpful. It was agreed that there was a need to establish the sero-epidemiology and natural history of infection with this agent, and to confirm the work.

7. AIDS Information Group discussion on contact tracing

Dr Pinching reported on a meeting to consider the scientific and ethical aspects of contact tracing that was held by the AIDS Information Group. He summarised the conclusions of the meeting that the scientific benefits of such general contact tracing would be limited. The ethical and moral problems arising from informing people that they had possibly been infected by an agent for which there were neither test nor treatment were considered to outweigh possible benefits. It was appreciated that the situation could change as tests improved and understanding increased. The particular issue of contact tracing of blood donations from AIDS patients was also discussed.

8. MRC Press Briefing on AIDS

The objectives of the MRC press briefing on AIDS which was to follow the meeting in the afternoon were outlined and specific questions were allocated to certain speakers.

9. Applications for project grant support

General comments were made on the circulated applications for project grant support. Neuropsychological function in AIDS (Green and Pinching) was considered appropriate to the MRC Working Party's broad recommendations for research. The second application on attitudes in men at risk of AIDS (Green and Pinching) was thought perhaps more appropriate for DHSS support.

It was noted that there would be some overlap between the two studies. Because both of these applications had been submitted simultaneously to the DHSS it was asked how the assessment by the Neurosciences Board would affect the DHSS decisions on these applications. [redacted] indicated that MRC liaise with DHSS over any applications of interest to both, to decide which body should assess them. Projects which were declined by the MRC on scientific grounds would not then be taken up by DHSS. The third study on AIDS and lymphadenopathy (Zuckerman, Murray-Lyon and Gazzard) was briefly considered. The overlap with other studies, the relevance of the preliminary electron microscopic findings and the ethics and the need for controls in the therapeutic sections were discussed.

10. Minutes of the CBLA Working Group

These were noted. The point was raised that the CBLA itself had no funds, but needed to seek scientific solutions to rather pragmatic questions, such as those of surrogate tests. The Working Party considered how such projects should be handled, and it was thought quite appropriate that applications should be submitted in the normal way to the MRC and/or DHSS.

11. Any other business

Two further applications had been received from Galbraith and McEvoy (CDSC) and Polakoff (Epidemiological Research Laboratory PHLS, Colindale) and were tabled. It was agreed that members had not had time to consider them in detail, but that they should send any comments on these projects as soon as possible to the MRC office.

12. Date of next meeting

It was agreed that the Working Party should meet again in the Autumn; dates would be circulated in due course.

From: Dr D A J Tyrrell

Director

MRC

Medical Research Council

World Health Organization
Collaborating Centre for
Virus Reference and Research

MRC Common Cold Unit
Harvard Hospital,
Coombe Road,
Salisbury, Wilts,
SP2 8BW

telegrams Harvard, Salisbury
telephone Salisbury 22485

reference

[redacted]

Medical Research Council
20 Park Crescent
London W1N 4AL

15 FEB 1984

13 February 1984

Dear [redacted]

Thank you for your letter of 8 February enclosing your letter to Robin Weiss. This all seems to me to be a satisfactory way of dealing with the problem; I hope that all that will now be necessary from my end is to just note this at the next meeting of the Committee.

Yours sincerely

David Tyrrell

8th February 1984

Dear Dr. Tyrrell,

I enclose a copy of a letter I have written to Dr. Weiss, to reassure him that we have taken to heart the comments he made at the last meeting of the AIDs Working Party. The refereeing of AIDS applications was discussed by Dr. Godfrey, [redacted] and [redacted] after the last meeting - unfortunately at a time when I was out of the office. They agreed that the Working Party's role as a "panel of referees" had not been a great success and that an extract from minutes of a meeting does not have the same force as conventional referee's report. In future, we plan to ask individual members of the Working Party to act as referees for AIDS applications. We will continue to send you copies of any AIDS applications we receive, and those which you regard as being of interest to the Working Party will be included in papers for meetings.

I am not sure whether [redacted] or Dr. Godfrey has spoken to you about this proposed change. We in the office believe that the modified system will run more smoothly. Do please let me know if you have any reservations about it. In general, of course the terms of reference and modus operandi of a Working Party are not open to debate among the membership. However such things are not sacronsanct and on this occasion we feel that some alteration is appropriate.

I have spoken to Tony Pinching - he will send me a list of possible dates in April for another Working Party meeting.

Yours sincerely,

[redacted].

D.A.J. Tyrrell, Esq., CBE MD DSc FRCP FRCPath FRS,
MRC Common Cold Unit,
Harvard Hospital,
Coombe Road,
Salisbury,
Wiltshire,
SP2 8BW.

7th February 1984

Dear Dr. Weiss,

I had hoped to speak to you on the telephone, but I understand from your secretary that you will not be in your office until next week. I wanted to reassure you that although the formal minutes of the last meeting of the AIDS Working Party does not dwell on the points that you raised under "matters arising", the office has in fact taken some action. We have agreed that the Working Party's role as a panel of referees has not been very effective, and in future we will instead ask individual members to give their opinion on scientific merit, in the usual way. The Working Party as a group will continue to see AIDS applications for information and informal comment.

I hope you will regard this as a more satisfactory arrangement, but do please get in touch with me if you would like to discuss the matter further on an informal basis.

Yours sincerely,

[redacted].

R.A. Weiss, Esq., PhD,
Institute of Cancer Research,
Chester Beatty Laboratories,
Fulham Road,
London,
SW3 6JB.

Extract from the Minutes of the Systems Board Meeting held on Tuesday 10th April, 1984.

172. MRC Working Party on AIDS report: The possibilities for research in Acquired Immune Deficiency Syndrome in the UK
(84/S0008: File S819/5)

The Board recalled that following an informal meeting in July 1983, the MRC Working Party on AIDS had been set up with the following terms of reference:-

(i) To review scientific knowledge and research on AIDS in the UK and abroad.

(ii) To encourage contact and cooperation between research workers in this field.

(iii) 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 had produced its first report now before the Board.

Members welcomed the report and noted that it outlined the Working Party's general view of the ways in which useful research could be done in the UK. In particular they endorsed the recommendations for epidemiological studies: the opportunities for carrying these out well were excellent. AIDS also provided an opportunity to examine the immune system: the Board considered that further weight might be given to this in the future. The Working Party's recommendations for therapeutic and prophylactic studies and virus detection were noted.

Some anxiety was expressed about the adequacy and clarity of the present guidance on the handling of AIDS samples and the performance of post-mortems: it was suggested that the Working Party should press the Advisory Committee on Dangerous Pathogens to produce their guidelines without delay.

Decision

The Board noted with interest the first report of the MRC Working Party on AIDS.

MEDICAL RESEARCH COUNCIL

MRC: IN CONFIDENCE

84/S008
Systems: April 1984

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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DBM: Professor H P Lambert

03/07

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.

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4. Action required

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

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.

Annex 2

MRC WORKING PARTY ON AIDS

Membership

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Dr D Taylor-Robinson MD FRCPath, Division of Sexually Transmitted Diseases, Clinical Research Centre (Deputy Chairman)

Dr A J Pinching DPhil BM MRCP, Department of Immunology, St Mary's Hospital Medical School (Secretary)

Professor M W Adler MD MRCP MFCM, Department of Genito-Urinary Medicine, Middlesex Hospital Medical School.

Professor A L Bloom MD FRCPath MRCP, Department of Haematology, Welsh National School of Medicine

Dr N S Galbraith MB FRCP FFCM DPH, Communicable Disease Surveillance Centre

Dr J R W Harris MB MRCP DTM&H, The Praed Street Clinic, St Mary's Hospital

Professor P J Lachmann ScD FRS, Director, MRC Unit on Mechanisms in Tumour Immunity (Systems Board member)

Professor H P Lambert MD FRCP, Communicable Diseases Unit, St George's Hospital (Systems Board member)

Professor K Murray PhD FRS, Department of Molecular Biology, University of Edinburgh

Dr J G P Sissons MD MRCP, Department of Medicine, Royal Postgraduate Medical School

Dr R S Tedder MRCP MRCPath, Department of Virology, Middlesex Hospital Medical School

Dr A D B Webster MB FRCP, Division of Immunological Medicine, Clinical Research Centre

Dr R A Weiss PhD, Institute of Cancer Research

Health Department Observers

Dr W M Prentice MB FFCM MFOM DPH DIH, Scottish Home and Health Department

Dr Alison Smithies, Department of Health and Social Security

Invited Participant

Dr S R Palmer MA MB MFCM, Public Health Laboratory Cardiff and Communicable Disease Surveillance Centre

MEDICAL RESEARCH COUNCIL

MRC: IN CONFIDENCE

84/S008
Systems: April 1984

MRC WORKING PARTY ON AIDS

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

---

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

---

DBM: Professor H P Lambert

03/07

S819/5

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.

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4. Action required

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

MRC 80/480

ADDITIONAL INFORMATION SHEET

COUNCIL / BOARD . Systems . . . MONTH . April . . . . YEAR . 1984.

TITLE OF PAPER . MRC . Working . Party . on . AIDS . - . Report : . The Possibilities for . Research . on . Acquired . Immune Deficiency Syndrome in The UK.

1. DESIGNATED BOARD MEMBERS . . . . . Professor . H . P . Lambert . . . . . .

2. REFEREES NAMES (if to be excluded from paper)*

* In cases where the paper is of direct interest to one or more members of the Council/Board

3. VISITORS ATTENDING FOR ITEM . . . . . .

They have already been approached informally: Yes ☐ No ☐

4. TIMING CONSTRAINTS . . . If . Dr . Tyrrell . comes . to . introduce . there . may . be . constraints . on . start

5. RESTRICTION ON CIRCULATION . . . . . .

6. ANY OTHER SPECIAL INSTRUCTIONS . . . . . .

SIGNED BY HEAD [redacted]

File No.

Further copies of these forms are available from Secretariat

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, high-risk groups and possible modes of spread identified. This will allow an assessment of the risks to special ~~nearest~~ 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 CDSC has insufficient staff but otherwise has all the resources and skill to do the work to a high standard;~~ 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, ~~along~~ 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 γ 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 α 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).

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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.

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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.

Annex 2

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Membership

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Dr D Taylor-Robinson MD FRCPath, Division of Sexually Transmitted Diseases, Clinical Research Centre (Deputy Chairman)

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Professor M W Adler MD MRCP MFCM, Department of Genito-Urinary Medicine, Middlesex Hospital Medical School.

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Dr J R W Harris MB MRCP DTM&H, The Praed Street Clinic, St Mary's Hospital

Professor P J Lachmann ScD FRS, Director, MRC Unit on Mechanisms in Tumour Immunity (Systems Board member)

Professor H P Lambert MD FRCP, Communicable Diseases Unit, St George's Hospital (Systems Board member)

Professor K Murray PhD FRS, Department of Molecular Biology, University of Edinburgh

Dr J G P Sissons MD MRCP, Department of Medicine, Royal Postgraduate Medical School

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Dr A D B Webster MB FRCP, Division of Immunological Medicine, Clinical Research Centre

Dr R A Weiss PhD, Institute of Cancer Research

Health Department Observers

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Dr Alison Smithies, Department of Health and Social Security

Invited Participant

Dr S R Palmer MA MB MFCM, Public Health Laboratory Cardiff and Communicable Disease Surveillance Centre

File No.

note for file 27/2/83

Comment from Dr Godfrey via [redacted]

it is not really appropriate for the MRC to comment on the staff and resources of CDSC.

I have ∴ deleted the phrase on this which comes towards the end of the first page of the report in its final form.

[redacted]

Public Health Laboratory Service

PHLS Communicable Disease Surveillance Centre
61 Colindale Avenue
London NW9 5EQ
Telex 8953942 (DEFEND G)
Telephone 01-200 6868

Our ref NSG/MHC

Your ref 17th February 1984

[redacted]
Medical Research Council
20 Park Crescent
London W1N 4AL

21 FEB 1984

Dear [redacted]

MRC Working Party on AIDS

Thank you for your letter asking for comments on the working party report.

As you will gather, I agree with the comments that Stephen Palmer has made and would like to add just three small points on page 2:-

1. Would it be possible to give in a little more detail the study currently being carried out by Haemophilia Centre Directors.

This has been amended - it is not yet underway

2. In para. 3, although 200 patients is a large number to follow-up, as it implies it may well not be enough to detect AIDS with an incidence of only 1 to 10 per cent in this group. Perhaps there would be a possibility of including more than two centres in the study.

3. As you may know the European group are planning to look at African cases of AIDS, particularly in France and Belgium.

Yours sincerely,

N.S. Galbraith

N.S. Galbraith
Director

File No.

[redacted]

21/2/84

Dr Prentice's secretary rang to say that she had inadvertantly destroyed his copy of the report of The AIDS WP, and would we please send another. Please send a copy of the draft in the same form as that originally circulated.

[redacted]

File No.

note. 17/2/84

I rang Dr Taylor-Robinson to check minor amendments suggested by Palmer, Bloom, Adler with him in Dr Tyrrell's absence. He said they were OK.

Prifysgol Cymru
University of Wales

Ysgol Feddygol Cymru
Welsh National School of Medicine

Department of Haematology
University Hospital of Wales
Heath Park, Cardiff CF4 4XN
Tel. Cardiff 755944
Ext. 2155

Professor A. L. Bloom

Ms. [redacted],
Medical Research Council,
20 Park Crescent,
London WIN 4AL

14th February, 1984

17 FEB 1984

Dear [redacted]

Thank you for letting me see the draft report from the MRC Working Party on AIDS. I only have one particular comment and this refers to paragraph 2 on page 2. The planned study to which this paragraph refers will be undertaken by Dr. John Craske of the Public Health Laboratory at Manchester with the co-operation of the Haemophilia Centre Directors. However the study is not yet under way because Dr. Craske has had difficulties with funding He hopes to submit a formal grant application to the MRC shortly and it would be nice if the report could include a statement that it is important that these epidemiological studies on U.K. patients treated with factor VIII concentrates should be supported. If I remember correctly the Working Party accorded a high degree or priority to these sort of studies.

Yours sincerely,

A. L. Bloom

UNIVERSITY of LONDON

Royal Postgraduate Medical School

Hammersmith Hospital, Ducane Road, London W12 0HS

Tel: 01-743 2030 Ext

[redacted]
Medical Research Council,
20 Park Crescent,
London WIN 4 AL.

I6th February, I984

Dear [redacted]

Thank you for the draft report of the MRC Working Party on AIDS.

With reference to the section on p 3 (Study of cases). I understand that C.D.S.C. will be concerned principally with epidemiology and the A.C.D.P. with guidelines on safety aspects. It may well be that those groups seeing most AIDS cases have already agreed on the following point, but I am not personally clear who, if anyone, will issue a specific protocol for the collection and preservation of patient samples, and whether a central repository of these will be maintained. I mention this because it seems desirable to have such protocols available for anyone seeing a case as soon as possible.

I have no queries about other sections of the report.

Yours sincerely,

J.G. P. Sissons,
Wellcome Senior Lecturer in
Medicine and Virology

File No.

note 20/2/14

Dr Shiohies rang with comments from DHSS. She apologized for being late as she is only able to devote 50% of her time to her new duties at present. One comment she had had from her colleagues was that perhaps too much time is spent talking about what to do, rather than getting on with doing it! I said that we rely on people to come in with applications rather than actively promote research in any particular area and she understood this.

She wondered whether any studies in Africa were really practicable and whether it might be better to leave them

to the American who are pouring in a lot of money.

She said DHSS were particularly keen to see the LOSC work funded + I said that if + when we received a formal application, we would liaise with her on funding.

File No.

16/2/84

Dr Prentice rang – no comments.

Prof Lambert – thinks the report is OK – is concerned about the reporting lines and dissemination of information as a general point. I suggested he raise this at the next WP meeting or indeed at the Board. I told him that Lachmann would not be present. He said he would be happy to speak to the paper.

From: Dr D A J Tyrrell

MRC

Medical Research Council

World Health Organisation
Collaborating Centre for
Virus Reference and Research

Director

MRC Common Cold Unit
Harvard Hospital
Coombe Road
Salisbury, Wilts
SP2 8BW

telegrams Harvard, Salisbury
telephone Salisbury (0722) 22485

Your reference

Our reference

[redacted]
Medical Research Council
20 Park Crescent
London W1N 4AL

15 FEB ...

13 February 1984

Dear [redacted]

Thank you for your letter of 9 February about the letters you have written to Dr Palmer and Dr Young. These seem to me to be clear and helpful and I am sure they will find Professor Bloom's letter is of assistance too.

I am also happy with the background notes.

I have not spoken further to [redacted] about his proposals but I mentioned informally to Michael Whitehead the embarrassment I felt at the Committee meeting when two apparently overlapping proposals came out of Colindale from people who had apparently not discussed them with each other. He indicated that they were going to put this right, but exactly how he didn't say. My personal view is that if we can get a good project from CDSC spelt out, funded and started, then the other studies could - if they actually materialize - be added on later. In other words I should not hold up dealing with Dr Palmer's document on the hypothesis that something may come later from Dr Glynn.

Yours sincerely

Public Health Laboratory Service

Public Health Laboratory
University Hospital of Wales
Heath Park
Cardiff CF4 4XW
Telephone Cardiff (0222) 755944

[redacted]
Medical Research Council
20 Park Crescent
London W1N 4AL

Our ref

Your ref

13th February 1984

Dear [redacted]

14 FEB 1984

MRC Working Party on AIDS.

Thank you for the opportunity to comment upon the draft report. In my opinion the report accurately summarizes the conclusions of the working party.

I have a few comments on the "Epidemiology" section. I would like to suggest that the objectives of surveillance should be spelled out more clearly. For instance the first paragraph might include something like "The occurrence of AIDS should be documented so that trends can be monitored, 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."

In the second paragraph I feel that the reference to expanding the present voluntary system of reporting is not clear. I suggest something like "It is important to extend the present national surveillance system which is based mainly upon voluntary reporting of cases". In addition, the reference to needle-stick injuries could be clarified as follows, " A record of needle-stick injuries in personnel attending AIDS cases and laboratory staff handling AIDS specimens should be kept so that individuals can be followed up and the risk of infection documented".

The use of the term "epidemic" to describe AIDS in Britain is perhaps too emotive and "incidence" could be substituted without altering the sense in para 1.

These are a few minor suggestions which you might wish to consider.

Yours sincerely,

Stephen Palmer

Dr S R Palmer.

Copy to Dr N S Galbraith.

File No.

note 15/2/84

I rang Prof Adler for comments:
he thought that on the whole the report was OK. He made the following minor points:

1) p2 para 3 – he wanted it made more explicit that the WP support the M'sex application.

2) p4 end of 2nd para – he felt that if Mary's are mentioned, Wess should also be.

3) p5 end of 1st para – it should be made clear that this depends on M'sex findings.

[redacted]

I have made alterations on the first two — the second is, I think, unnecessary.

[redacted]

MRC: IN CONFIDENCE

84/S008
Systems: April 1984

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

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

To encourage contract 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."

~~It is~~ In fulfilment of the third of these terms of reference, ~~that~~ the Working Party has produced its report.

3. MRC support for AIDS Research
~~Special Project Grants awarded for AIDS research~~

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03/07

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.

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4. Action required

(i) To note the report of the MRC Working Party on AIDS.

(ii) Decision whether to commend the report to Council.

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 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.

9 February 1984

Dear Dr Tyrrell,

I am writing to ask if you would be kind enough to comment briefly on two matters relating to AIDS before you go on leave.

You will remember that Dr Palmer presented some draft proposals to the AIDS Working Party at the last meeting, and invited comments from the members and the MRC office. I understand that many of the members have commented informally to Dr Palmer; the only letter I have received is the one from Professor Bloom, a copy of which is enclosed. I also enclose a draft letter to Dr Palmer which raises a few things from the office point of view. I wonder whether you would wish to change or add anything to the letter, and whether you would be agreeable to my writing to Dr Palmer and [redacted] in these terms.

Secondly, I would like to check with you the way in which we propose to present the AIDS report to the Systems Board. I am sure you are aware that all Board papers carry some background notes to place the issue being considered in some kind of context. I enclose a copy of the background notes which I have drafted. The aim is firstly to show that the Working Party has already achieved some success in promoting AIDS research, and secondly to focus on the gaps which still need to be filled. This latter would set the scene for applications to be considered subsequently - such as Professor Adler's at the same Board meeting, and the CDSC one at a later stage. I would be grateful for any comments you may have on the draft.

I wonder whether you have heard any further from [redacted] about the possible PHLS initiative?

Please do not hesitate to contact me by telephone if that is most convenient.

Yours sincerely,

[redacted]

D A J Tyrrell CBE MD DSc FRCP FRCPath FRS
MRC Common Cold Unit
Harvard Hospital
Coombe Road
Salisbury
WILTSHIRE SP2 8BW

File No.

9/2/84

Peter Lachmann phoned – he thinks the AIDS report is awful! It contains too many waffly generalised statements. It really needs to be rewritten in a much crisper form. He has agreed to write to me with suggestions for improvement, but he still thinks the Board will find it laughable.

He will be on leave in April and unable to attend the Board meeting (Just as well perhaps).

[redacted]

File No.

S819/5

8/2/84

Dr Webster's secretary rang to say that he is on holiday until 20/2 and will not be able to comment.

7 February 1984

Dear Dr Palmer

You will remember that at the meeting of the MRC Working Party on AIDS, on 20 December 1983, it was agreed that the Chairman, Deputy Chairman and the Secretary would produce a document summarising the Working Party's views on the possibilities for research on AIDS in the UK. This is in fulfillment of the third of the Working Party's terms of reference: "to advise the Council on the current state of knowledge in the field and on topics for research".

I now enclose a copy of the draft report and would be grateful to receive any comments you may have on it or any amendments you would like to see incorporated, subject to the approval of the Chairman of the Working Party. In order that we can prepare the report for submission to the Systems Board in April, it would be helpful if I could receive your reply, by telephone if that is most conveneient, by 17 February 1984 at the latest. If I have not heard from you by that date, I shall assume tht you have no comments..

I also enclose a copy of the minutes of the last meeting.

Yours sincerely,

[redacted].

Enc.

S R Palmer Esq MA MB MFCM
Public Health Laboratory
University Hospital of Wales
North Park
Cardiff
CF4 4XW

20/75

7 February 1984

Dear Dr Weiss

You will remember that at the meeting of the MRC Working Party on AIDS, on 20 December 1983, it was agreed that the Chairman, Deputy Chairman and the Secretary would produce a document summarising the Working Party's views on the possibilities for research on AIDS in the UK. This is in fulfillment of the third of the Working Party's terms of reference: "to advise the Council on the current state of knowledge in the field and on topics for research".

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I also enclose a copy of the minutes of the last meeting.

Yours sincerely,

[redacted].

Enc.

R A Weiss Esq PhD
Institute of Cancer Research
Chester Beatty Laboratories
Fulham Road
London
SW3 6JB

20/75

7 February 1984

Dear Dr Webster

You will remember that at the meeting of the MRC Working Party on AIDS, on 20 December 1983, it was agreed that the Chairman, Deputy Chairman and the Secretary would produce a document summarising the Working Party's views on the possibilities for research on AIDS in the UK. This is in fulfillment of the third of the Working Party's terms of reference: "to advise the Council on the current state of knowledge in the field and on topics for research".

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I also enclose a copy of the minutes of the last meeting.

Yours sincerely,

[redacted].

Enc.

A D B Webster Esq FRCP
Division of Immunological Medicine
Clinical Research Centre
Watford Road
Harrow
Middlesex
HA1 3UJ

20/75

7 February 1984

Dear Dr Sissons

You will remember that at the meeting of the MRC Working Party on AIDS, on 20 December 1983, it was agreed that the Chairman, Deputy Chairman and the Secretary would produce a document summarising the Working Party's views on the possibilities for research on AIDS in the UK. This is in fulfillment of the third of the Working Party's terms of reference: "to advise the Council on the current state of knowledge in the field and on topics for research".

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I also enclose a copy of the minutes of the last meeting.

Yours sincerely,

[redacted].

Enc.

J. G P Sissons Esq MD MRCP
Department of Medicine
Royal Postgraduate Medical School
Hammersmith Hospital
Ducane Road
London
W12 0HS

20/75

7 February 1984

Dear Professor Murray

You will remember that at the meeting of the MRC Working Party on AIDS, on 20 December 1983, it was agreed that the Chairman, Deputy Chairman and the Secretary would produce a document summarising the Working Party's views on the possibilities for research on AIDS in the UK. This is in fulfillment of the third of the Working Party's terms of reference: "to advise the Council on the current state of knowledge in the field and on topics for research".

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I also enclose a copy of the minutes of the last meeting.

Yours sincerely,

[redacted].

Enc.

Professor K Murray PhD FRS
Department of Molecular Biology
University of Edinburgh
Kings Buildings
Mayfield Road
Edinburgh
EH9 3JR

20/75

7 February 1984

Dear Professor Lambert

You will remember that at the meeting of the MRC Working Party on AIDS, on 20 December 1983, it was agreed that the Chairman, Deputy Chairman and the Secretary would produce a document summarising the Working Party's views on the possibilities for research on AIDS in the UK. This is in fulfillment of the third of the Working Party's terms of reference: "to advise the Council on the current state of knowledge in the field and on topics for research".

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I also enclose a copy of the minutes of the last meeting.

Yours sincerely,

[redacted].

Enc.

Professor H P Lambert MD FRCP
Communicable Diseases Unit
St George's Hospital
Blackshaw Road
London
SW17 0QT

20/75

7 February 1984

Dear Professor Lachmann

You will remember that at the meeting of the MRC Working Party on AIDS, on 20 December 1983, it was agreed that the Chairman, Deputy Chairman and the Secretary would produce a document summarising the Working Party's views on the possibilities for research on AIDS in the UK. This is in fulfillment of the third of the Working Party's terms of reference: "to advise the Council on the current state of knowledge in the field and on topics for research".

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I also enclose a copy of the minutes of the last meeting.

Yours sincerely,

[redacted].

Enc.

Professor P J Lachmann ScD FRS
MRC Unit on Mechanisms in
Tumour Immunity
MRC Centre
University Medical School
Hills Road
Cambridge
CB2 2QH

20/75

7 February 1984

Dear Dr Harris

You will remember that at the meeting of the MRC Working Party on AIDS, on 20 December 1983, it was agreed that the Chairman, Deputy Chairman and the Secretary would produce a document summarising the Working Party's views on the possibilities for research on AIDS in the UK. This is in fulfillment of the third of the Working Party's terms of reference: "to advise the Council on the current state of knowledge in the field and on topics for research".

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I also enclose a copy of the minutes of the last meeting.

Yours sincerely,

[redacted].

Enc.

J R W Harris Esq MB MRCP
Special Clinic
St Mary's Hospital
Praed Street
London
W2 1PG

20/75

7 February 1984

Dear Dr Galbraith

You will remember that at the meeting of the MRC Working Party on AIDS, on 20 December 1983, it was agreed that the Chairman, Deputy Chairman and the Secretary would produce a document summarising the Working Party's views on the possibilities for research on AIDS in the UK. This is in fulfillment of the third of the Working Party's terms of reference: "to advise the Council on the current state of knowledge in the field and on topics for research".

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I also enclose a copy of the minutes of the last meeting.

Yours sincerely,

[redacted].

Enc.

N S Galbraith Esq FRCP FSCM DPH
Communicable Disease Surveillance Centre
Public Health Laboratory
Colindale Avenue
London
NW9 5EQ

20/75

7 February 1984

Dear Professor Bloom

You will remember that at the meeting of the MRC Working Party on AIDS, on 20 December 1983, it was agreed that the Chairman, Deputy Chairman and the Secretary would produce a document summarising the Working Party's views on the possibilities for research on AIDS in the UK. This is in fulfillment of the third of the Working Party's terms of reference: "to advise the Council on the current state of knowledge in the field and on topics for research".

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I also enclose a copy of the minutes of the last meeting.

Yours sincerely,

[redacted].

Enc.

Professor A L Bloom MD FRCPath MRCP
Department of Haematology
Welsh National School of Medicine
University Hospital of Wales
Heath Park
Cardiff
CF4 4XN

20/75

7 February 1984

Dear Professor Adler

You will remember that at the meeting of the MRC Working Party on AIDS, on 20 December 1983, it was agreed that the Chairman, Deputy Chairman and the Secretary would produce a document summarising the Working Party's views on the possibilities for research on AIDS in the UK. This is in fulfillment of the third of the Working Party's terms of reference: "to advise the Council on the current state of knowledge in the field and on topics for research".

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I also enclose a copy of the minutes of the last meeting.

Yours sincerely,

[redacted].

Enc.

Professor M W Adler
Department of Genito-Urinary Medicine
Middlesex Hospital Medical School
Mortimer Street
London
W1P 7PN

20/75

File No.

Note 6/2/84

Dr Tyrrell is happy for the report to be circulated, subject to correction of the typing errors.

He is also preparing a report for the EEC, as a result of the meeting in Europe last week, which will be presented at a subsequent meeting early in March. He will liaise with Dr Godfrey over this as he (Dr G) will be present at the meeting.

[redacted]

[redacted]

File No.

Note 3/2/84

Dr Taylor-Robinson rang and pointed out some minor typing errors. Otherwise he is quite happy with the revised version.

Dr Pinching rang - no comments apart from those raised by Dr T-R.

[redacted]

[redacted]

1 February 1984

Dear Dr Tyrrell

As I mentioned in our recent telephone conversation, we intend to submit the report of the AIDS Working Party to the Systems Board on 10 April 1984. As I also mentioned, we propose some changes to the Conclusion in order that the report should have maximum impact on the Board. We have, in addition, included a summary to bring together the main recommendations of the report.

We have made some changes to the Introduction, but otherwise we have done only minor editing to the main body of the report. I enclose a copy of the amended draft along with a copy of the first draft for ease of reference.

I would particularly like to draw your attention to the proposed alteration to page 3 line 18 concerning post mortems.

The point needs to be expressed in a way which is consistent with the appropriate minute of the Working Party meeting on 20 December 1984.

As you know, we have only a limited time in which to finalise the report; the Board paper must be ready by 21 February. In order that the members of the Working Party have as long as possible to consider the document, perhaps you could let me have any comments you may have at this stage by telephone, preferably on 6 February. I am also asking Dr Pinching and Dr Taylor-Robinson for their comments. I apologise that this is somewhat rushed. I would then need detailed comments from everyone by 16 February.

I also enclose a copy of the minutes of the last meeting of the Working Party which have been put into MRC format and subjected to minor editing as I mentioned on the telephone. You agreed that I could circulate them to the members with the draft report.

I look forward to hearing from you and hope that the EEC meeting proves fruitful.

Yours sincerely

[redacted]

cc: Dr A J Pinching
Dr D Taylor-Robnson

D A J Tyrrell Esq CBE MD DSc FRCP FRCPth FRS
MRC Common Cold Unit
Harvard Hospital
Coombe Road
Salisbury
Wiltshire SP2 8BW

20/73

1 February 1984

Taylor Robinson.

Dear ~~Dr Pinching~~

I am writing to bring you up to date on the progress of the draft report of the AIDS Working Party. As you will see from the enclosed copy of my letter to Dr Tyrrell, we intend to submit the report to the next meeting of the Systems Board. As you will also see from the letter, we are suggesting some changes on which we would be grateful to have comments from Dr Tyrrell, yourself and ~~Dr Taylor-Robinson (Dr~~ Pinching) before circulating to the other members of the Working Party. I enclose copies of both the original draft and our amended version. In view of the time constraints, I wonder if you could let me know by telephone, on or before 6 February, whether you would be happy for me to circulate the document in its revised form to the members of the Working Party. I would then need to have detailed comments from everyone by 16 February.

I also enclose a final copy of the minutes of the last Working Party meeting. A few minor editorial changes have been put into MRC format. The only major change is that the account of Dr Weiss's dissatisfaction has been reduced as it does not seem appropriate for this to receive too much emphasis in the formal minute. If you are agreeable, I will circulate the minutes with the draft report on Monday.

I look forward to hearing from you and apologise for the short notice.

Yours sincerely

[redacted]

Enc

D Taylor-Robinson Esq MD FRCPath
Division of Communicable Diseases
Clinical Research Centre
Watford Road
Harrow
Middlesex HA1 3UJ

20/74

1 February 1984

Dear Dr Pinching

I am writing to bring you up to date on the progress of the draft report of the AIDS Working Party. As you will see from the enclosed copy of my letter to Dr Tyrrell, we intend to submit the report to the next meeting of the Systems Board. As you will also see from the letter, we are suggesting some changes on which we would be grateful to have comments from Dr Tyrrell, yourself and Dr Taylor-Robinson ~~(Dr Pinching)~~ before circulating to the other members of the Working Party. I enclose copies of both the original draft and our amended version. In view of the time constraints, I wonder if you could let me know by telephone, on or before 6 February, whether you would be happy for me to circulate the document in its revised form to the members of the Working Party. I would then need to have detailed comments from everyone by 16 February.

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I look forward to hearing from you and apologise for the short notice.

Yours sincerely

[redacted]

Enc.

A J Pinching Esq DPhil BM MRCP
Department of Immunology
Wright-Fleming Institute
St Mary's Hospital Medical School
Paddington
London W2 1PG

File No.

Note 30/1/84

Conversation with Dr Tyrrell.

1. He is happy for us to send him (and P + T-R) an amended version of the draft report with a view to subsequent circulation to members. We will aim to let him have this by the end of this week.

2. He is going to an EEC meeting this week – this may provide him with additional information for the report. Funds for AIDS research may be forthcoming.

3. Following the trip to Europe, he is likely to be in a position to suggest a

PTO

date of the next meeting of the W.P. - likely to be in March.

4. He will be going on leave on Feb 19th.

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 ~~epidemic~~ incidence in the UK is likely to increase ~~in size~~ but some features differ from those seen in the USA and Africa. ~~The course of the disease~~ The occurrence of AIDS should be documented ~~to provide information on how it is spreading and what containment measures might be effective to give a background to clinical and laboratory research for which well documented case material is needed.~~ so that trends can be monitored, 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 ~~expand~~ extend the present ~~voluntary system of reporting cases.~~ national surveillance system which is based mainly on voluntary reports of cases. Cases 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. In so that individuals can be followed up and the risk of infection documented.

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 CDSC has insufficient staff but otherwise has all the resources and skill to do the work to a high standard; 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, along with their family contacts. ~~The Haemophilia Centre Directors have such a study underway.~~ * 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, ~~two are~~ 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

* A study is planned at the Public Health Laboratory in Manchester, in co-operation with the Haemophilia Centre Directors.

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 too 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 now been successful but interferon γ 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 α 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 human 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 proper 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 sork 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.

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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 energence 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 epidemic in the UK is likely to increase in size but some features differ from those seen in the USA and Africa. The course of the disease should be documented to provide information on how it is spreading and what containment measures might be effective to give a background to clinical and laboratory research for which well documented case material is needed.

It is important to expand the present voluntary system of reporting cases. Cases 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. 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 CDSC has insufficient staff but otherwise has all the resources and skill to do the work to a high standard; 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, along with their family contacts. The Haemophilia Centre Directors have such a study underway. 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.

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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.

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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

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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 ~~human~~ retrovirus) and related viruses and antibodies against them.

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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 reach 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.

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Summary

We have identified specific areas in which AIDS research in the UK should be pursued. Cases of AIDS should be separated 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

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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, the results of this research programme should help us to cope with the disease by recognising it more effectively, assessing ~~how it is spreading~~ its spread, and thus projecting what is likely to happen in the future. The disease will probably be contained by preventive measures changing the behaviour of those at risk, and this must be based on well documented epidemiological findings.

The disease offers important opportunities to ~~understnd more about the~~ improve our understanding of the functioning of the immune system and the natural history and biology of an unusual infectious agent. We believe that research within the guidance that we have mentioned will certainly help progress on all these lines.

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.

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We have outlined a strategy which we believe is appropriate for the study of AIDS in the United Kingdom. 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. We feel that the circumstances of the emergence of AIDS in the UK and local expertise provide a unique opportunity to study this new disease at an early stage in the epidemic. ≠ We do not wish to imply that other approaches to the study of AIDS would be unproductive and suggest that funding bodies should be open to other ideas. We believe that AIDS research is important and that some of the work may contribute to fundamental knowledge or lead to applications in other fields.

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The treatment of the underlying immunodeficiency has so far proved unsuccessful: even treatment of sundry 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 sucessful conclusion of a trial. We think that the correct approach is to review new methods of treatment and let local groups 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 on even 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. Present drugs for pneumocystis and some other infections produce too many adverse reactions and a watch should be kept for anything new. Acyclovir is very satisfactory for herpesvirus 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 γ 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 α 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 need 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 has already supported a survey by restriction endonuclease mapping of the cytomegaloviruses isolated (St. Mary's) and a search for TLV (T-cell leukaemia virus: a human retrovirus) and related viruses and antibodies against them.

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, such as inoculating marmosets, which are easily available in the U.K., using a number of different routes and after they have been given 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 succeeded in isolating viruses from some other conditions in the past but there are few clues as to what to use and the possibilities are endless. 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 reacting a range of sera (and possibly lymph node extracts) from patients who are in the early stage of the disease, and might have viraemia, with those 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 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 occurring in the disease and T-helper depletion is still regarded as the best marker. However, there has been little attempt to look at the immunohistopathological changes. The reagents and facilities for undertaking immunohistology are excellent in the U.K. and this aspect should be pursued.

In considering the anxiety that AIDS has caused in relation to blood transfusion, it seems important to determine the best surrogate tests to be carried out on donor blood samples and work in this direction should be supported. Such surrogate tests will need evaluation in the longitudinal cohort studies of at-risk patients (see above).

Insert Summary here.

Conclusion

There has been much anxiety about this strange and frightening disease and this is not unreasonable in the light of the very high mortality. It is unlikely that any treatment for cases which will be beneficial in the long term will be found in the near future; nevertheless, the results of this research programme should help us to cope with the disease problem. They should teach us how to recognise the disease more effectively, give an accurate assessment of how it is spreading, and thus some reason to project what is likely to happen in the future. If the epidemic is to be contained it will probably be by preventive measures based on changing the behaviour of those at risk. This has been done in the past, for instance in the case of those suffering from diseases of smoking, but it is only likely to be effective if based on well documented epidemiological findings.

The disease is also a fascinating new problem in biomedical science. There are important opportunities to understand more about the functioning of the immune system and the natural history and biology of what must be a very

~~strange~~ infectious agent. We believe that research within the guidance that we have mentioned will certainly help progress on all these lines.

File No.

Discussed 29/1/84

[redacted] I think this is clear cut case we should send it to the WP for comment & S.A.P. It would go to the April Board with the revised Heller application.

[redacted] 13.1.84

[redacted] (I have kept a copy for future discussion)

12/1/83

We have received this report from the MRC WP on AIDS as promised. It has been written by Tyrrell, Taylor-Robinson and Pinching, the aim being to fulfil the 3rd of WP's terms of reference: "to advise the Council on the current state of knowledge in the field and on topics for research".

Dr Tyrrell would like us to circulate to members for comments with a view to sending the report to the April Board + then to Council. He sees the main purpose of the report as helping the Council to decide on its policy with regard to AIDS. The Board would presumably be asked to comment only the science.

PTO.

I would be grateful for your approval to proceed as Dr Tyrrell suggests. We need to move q. fast as I think the report may need quite a lot of work. I don't think there is any clear indication of how much of the suggested work is underway and where there are gaps, neither are there any specific recommendations.

[redacted]