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REPORT OF THE FOURTH MEETING OF THE COMMITTEE ON ORTHOPOXVIRUS INFECTIONS, GENEVA, 24-26 MARCH 1986

The meeting was opened by Dr F. Assaad, on behalf of the Director-General. Dr F. Fenner was elected Chairman, Dr S.S. Marennikova Vice-Chairman and Dr K. Dumbell Rapporteur. The list of participants, agenda and working papers are attached as Annexes 1, 2 and 3.

In his opening statement Dr Assaad stressed that this was a particularly important meeting. After the eradication of smallpox had been ratified by the World Health Assembly in 1980, the World Health Organization commenced a five-year programme to implement the post-eradication policies adopted by the World Health Assembly in resolution WHA33.4. This programme had been recommended by the Global Commission for Certification of Smallpox Eradication and was designed both to allay any fears that smallpox might recur and to provide for full documentation of the effort. The progress of the post-eradication programme had been reviewed year by year. In 1981 there was a Meeting on the Implementation of Post-smallpox Eradication Policy which was followed by three meetings of the Committee on Orthopoxvirus Infections: 3-5 March 1982, 15-17 March 1983 and 28-30 March 1984. This, the 4th meeting of the Committee on Orthopoxvirus Infections, was charged to review the implementation of the 19 recommendations on post-eradication policy made to the World Health Assembly by the Global Commission and to recommend to the Director-General what policies should be followed by the World Health Organization from 1986 onwards.

The meeting reviewed the implementation of the post-eradication policy, paying particular attention to the status and future of variola virus stocks, the WHO emergency reserve of smallpox vaccine, the surveillance of human monkeypox and progress in documentation of the programme. The report of the meeting is organized into eight topics:

1. Smallpox vaccination policy (G.C. 1, 2)
2. Reserve stocks of smallpox vaccine (G.C. 3, 4, 5, 6)
3. Investigation of suspect cases (G.C. 7, 8)
4. Retention of variola virus stocks (G.C. 9, 10)
5. Monkeypox surveillance and research (G.C. 11)
6. Laboratory investigations (G.C. 12, 13, 14, 15)
7. Documentation of the Smallpox Eradication Programme (G.C. 16, 17)
8. Central coordination at WHO/HQ (G.C. 18, 19)

Note: G.C. = Global Commission Recommendation number

1. Vaccination Policy

G.C. 1 Smallpox vaccination should be discontinued in every country except for investigators at special risk.

G.C. 2 International Certificates of vaccination against smallpox should no longer be required of any travellers.

WHO has been informed that all of its Member States have now discontinued routine vaccination.

No country in the world now requires a certificate of smallpox vaccination from international travellers.

The latest reports received by WHO of the number of doses of vaccine produced and distributed by vaccine production laboratories show that in 1984, seven countries produced batches of smallpox vaccine totalling 3.8 million doses. Some of this production was for vaccination of military personnel. Ten countries, however, have already informed WHO that they no longer vaccinate their military personnel against smallpox.

Substantial progress has been made in the development of recombinant strains of vaccinia, capable of inducing immunity to several infectious pathogens. The Committee expects that human trials with such vaccines may soon be instituted and that various strains of recombinant vaccinia virus may in future be produced and used in immunization programmes. A clear distinction has to be made between routine smallpox vaccination which is now universely discontinued and the use of modified strains of vaccinia virus as vectors for use in immunization programmes against other diseases. Such a new use for vaccinia virus had not been foreseen at the time the Global Commission formulated their recommendations to the WHO. The Committee was informed that a committee to coordinate the development of recombinant vaccinia antigens has been set up by WHO under the auspices of Microbiology and Immunology Support Services.

The Committee considered that the recommendations G.C. 1 and 2 had been fully implemented and commended WHO for its role in this achievement.

2. Reserve Stocks of Vaccine

G.C. 3 Sufficient freeze-dried smallpox vaccine to vaccinate 200 million people should be maintained by WHO in refrigerated depots in two countries, together with stocks of bifurcated needles.

G.C. 4 The stored vaccine should be periodically tested for potency.

G.C. 5 Seed lots of vaccinia virus suitable for the preparation of smallpox vaccine should be maintained in designated WHO collaborating centres.

G.C. 6 National Health Authorities that have vaccine stocks should be asked to inform WHO of the amount of vaccine maintained.

WHO maintains reserve stocks of smallpox vaccine sufficient to protect 200 million people, using the bifurcated needle. The 7.4 million doses packaged for use with jet injectors have been destroyed, as recommended at the third meeting of this Committee in 1984, and after consultation with the countries which had donated this vaccine. The remaining stocks are stored in two locations, one in Geneva and one in Lausanne, and periodic testing of samples for potency has assured the continuing good quality of this vaccine.

The Committee was informed that more than 102 million doses of smallpox vaccine are held in twenty-two countries and that the storage conditions for at least 80% of these stocks are satisfactory. Taking into consideration the facts that nearly ten years had elapsed since the last case of endemic smallpox and that human monkeypox had not proved to be a significant human disease problem (see section 5), the Committee felt that an unforeseen emergency was now so unlikely that it was no longer necessary for WHO to maintain a global vaccine reserve.

The Committee was informed that seed lots of smallpox vaccine virus continue to be held in four WHO collaborating centres.

3. Investigation of Suspect Cases

G.C. 7 In order to maintain public confidence in the fact of global eradication, it is important that rumours of suspected smallpox, which can be expected to occur in many countries, should be thoroughly investigated. Information should be provided to WHO, if requested, so that it can be made available to the world community.

G.C. 8 WHO should maintain an effective system to coordinate and participate in the investigation of suspected smallpox cases throughout the world. The international smallpox rumour register should be maintained.

The Committee was informed that the number of rumours of suspect cases reported to WHO had gradually declined from 31 in 1980 to 10 in 1985. Suspect cases had been adequately investigated by the relevant national authority with assistance from WHO collaborating centres and WHO epidemiologists. None had proved to be smallpox. The Committee believed that there will continue to be rumours and although investigation of most can safely be left to the medical authorities of the Member States, WHO participation and expertise may be needed in some instances to maintain confidence in the fact of eradication.

4. Retention of Variola Virus Stocks

G.C. 9 No more than four WHO collaborating centres should be approved as suitable to hold and handle stocks of variola virus. A collaborating centre would be approved only if it had adequate containment facilities. Each such centre should report relevant information on its safety measures annually to WHO and be inspected periodically by WHO.

G.C. 10 Other laboratories should be asked to destroy any stocks of variola virus that they hold or transfer them to an approved WHO collaborating centre.

The two laboratories which continue to hold stocks of variola virus, namely the Centers for Disease Control, Atlanta, USA (CDC) and the Research Institute for Viral Preparations, Moscow, USSR (RIVP) were visited most recently by WHO inspection teams in November, 1985 (CDC) and January, 1986 (RIVP). The inspection reports were satisfactory for both laboratories. Culture of variola virus had ceased at CDC and at RIVP. Neither laboratory now plans to resume experiments involving culture of variola virus.

The Committee reviewed the need for retaining the remaining stocks of variola virus. It was noted that the variola gene pool could be cloned into non-expressing sites in bacterial plasmids, for future studies of variola virus. Archival records of variola virus would be satisfied by such cloned DNA. The Committee was informed that plasmids encoding variola DNA had been prepared at the PHLS Centre for Applied Microbiology and Research, Porton Down, Salisbury, UK and at the Centers for Disease Control, Atlanta, USA. The plasmids are classed at Biosafety level 1. DNA had been cloned from two strains of variola major (Harvey and Bangladesh), two strains of alastrim (Garcia and Butler) and one strain of African variola minor (Somalia), but in no case had the cross-linked terminal fragments been cloned and the full series of internal fragments from Butler was still in course of construction. The Committee considered that it was not essential to clone the cross-linked terminal fragments, but that it would be desirable that material from a West African variola strain should be added to the collection. The plasmids containing fragments of variola DNA are available for investigators wishing to make use of them. Requests should be sent to WHO, 1211 Geneva, 27 Switzerland. WHO will then forward them to the Director of the laboratory maintaining the stocks.

Because implementation of a decision to destroy all variola virus stocks could be irrevocable, a member of the Committee had, before the meeting, consulted some 60 virologists working in 21 countries. Only 5 thought that variola virus should be maintained indefinitely. The detailed arguments and an analysis of the virologists' opinions are attached as Annex 4.

Taking these facts into consideration, the Committee concluded that the cloned DNA provided sufficient reference material to resolve any future diagnostic problem involving suspect smallpox and that research studies of variola requiring culture of the virus were no longer justified. Thus, in the Committee's opinion, there was no need to retain stocks of viable variola virus any longer.

The Committee warmly commended WHO for the implementation of G.C. 9 to an extent even further than had been recommended and for the full implementation of G.C. 10.

5. Monkeypox Surveillance and Research

G.C. 11 In collaboration with country health services WHO should organize and assist a special surveillance programme on human monkeypox, its epidemiology and its ecology in areas where it is known to have occurred. The programme should continue until 1985, when a further assessment of the situation should be made.

The number of human monkeypox cases detected each year since 1980 was reported as: 1981, 8; 1982, 39; 1983, 84; 1984, 89; 1985, 55 (provisional figure). Six of the cases detected in 1984 occurred in the Central African Republic, but the rest occurred in Zaire. Thus studies of the epidemiology and ecology of monkeypox virus have concentrated on five areas in Zaire where cases had been detected in previous years.

Routine smallpox vaccination was effectively discontinued in Zaire in 1980, so that a susceptible cohort of children now aged 0-5 years is present throughout these areas.

The number of cases detected in 1983 and 1984 was higher than in previous years but this is believed to be due to improved surveillance. In 1985 the number of cases declined despite an increasing number of susceptible children; the age distribution of cases did not change and secondary attack rates diminished.

A stochastic model had been developed based on the records of secondary cases occurring in contacts who were or were not vaccinated and who did or did not live in the same household as the index case. The model was validated by th closeness of its predictions to the observed numbers. It was used to extrapolate the probability of continuing spread of monkeypox virus as vaccination immunity declined to 50% and to 0%. Even in the absence of vaccination the model predicted that outbreaks would be self-limiting and not significantly larger than those recently experienced.

Ecological studies of the reservoir of monkeypox virus have advanced rapidly in the last two years and include the first isolation of this virus from an animal caught in the wild. The animal concerned was a small squirrel (Funisciurus anerythrus), a species which is abundant among the oil palms found in agricultural land separating villages from the primary forest.

Epidemiological investigations suggest that many human monkeypox infections were acquired in this environment and the existence of transmission of the virus among the squirrels has been confirmed by the demonstration that between 14% and 20% of over 300 squirrels captured in this area had monkeypox-specific antibody.

Intensive surveillance activities have covered a population of about 5 million people. With the very low incidence rate of human monkeypox, and growing confidence that this virus cannot sustain itself by human-to-human spread, the Committee believes that it does not pose a significant health problem. This view is strengthened by the recognition that sporadic cases of human monkeypox must have occurred over a long period without a variant arising which was capable of sustained transmission in humans.

The Committee congratulated the authors of the various reports on the monkeypox situation. The Committee recognized that human monkeypox and its ecology pose many interesting and unanswered questions which it hopes may continue to be addressed by the investigators, but believes that, after 1986, the priorities of this effort should be considered in a broader context of research priorities in West and Central Africa.

6. Laboratory Investigations

G.C. 12 WHO should continue to encourage and coordinate research on orthopoxviruses.

G.C. 13 WHO should maintain the system of collaborating centres for carrying out diagnostic work and research on orthopoxviruses.

G.C. 14 Research workers who do not work in a WHO collaborating centre and who wish to carry out experiments with variola or whitepox viruses that are approved by the appropriate WHO committee should be offered the use of the special facilities in a WHO collaborating centre.

G.C. 15 Research on poxviruses other than variola or whitepox viruses should not be performed under circumstances where there is any possibility of cross-contamination with these two agents.

Research involving the cultivation of variola virus is no longer in progress at either of the WHO two collaborating centres which maintain variola virus nor does either centre contemplate any such experiments.

Although more laboratories are active now in poxvirus research than in 1980, there is still an important role for the WHO collaborating centres in Atlanta, Moscow and Tokyo maintaining the expertise to assist with the diagnosis of suspect cases and supporting studies on the ecology of monkeypox virus. The Committee foresaw that cooperation would develop between the WHO collaborating centres and other laboratories which were interested in monkeypox or in developing new techniques which were applicable to serological diagnosis or in other ways. The Committee noted that a Japanese team had recently visited Zaire and entered into an agreement to support surveillance activities on a bilaterial basis.

The Committee commended WHO for its coordination of laboratory diagnosis and research on orthopoxviruses in the years since smallpox eradication was declared. This has permitted the accumulation of valuable information and contributed to the present assurance that smallpox eradication is complete.

7. Documentation of the Smallpox Eradication Programme

G.C. 16 WHO should ensure that appropriate publications are produced describing smallpox and its eradication and the principles and methods that are applicable in other programmes.

G.C. 17 All relevant scientific, operational and administrative data should be catalogued and retained for archival purposes in WHO headquarters and perhaps also in several centres interested in the history of medicine.

The Committee was informed about the progress made towards publication of the book "Smallpox and its Eradication" which it was hoped would be in print in time for the tenth anniversary of the last endemic case of smallpox, in October 1987.

Most of the files relating to smallpox had been catalogued by a professional archivist, but the Committee noted that more archival work would be necessary when preparation of the book "Smallpox and its Eradication" was completed.

8. Central coordination at WHO/HQ

G.C. 18 An interregional team consisting of not less than two epidemiologists with past experience in the smallpox eradication campaign, plus supporting staff, should be maintained at WHO headquarters until at least the end of 1985. At least one additional field officer should be assigned to cover areas where human monkeypox is under investigation.

G.C. 19 WHO should set up a Committee on Orthopoxvirus Infections.

The Committee was told that a Smallpox Eradication Unit had been maintained at WHO Headquarters with staff approximating that outlined. WHO planned to discontinue this Unit at the end of 1987.

As noted earlier, a Committee on Orthopoxvirus Infection had been established in 1981 and had met in 1982, 1983, 1984 and 1986. Members of this Committee considered that there was no further need for such a committee, but that WHO might need to set up ad hoc committees at various times to consider specific problems that might arise.

CONCLUSIONS AND RECOMMENDATIONS

The Committee, having considered in detail the implementation of the 19 recommendations of the Global Commission, concluded that the success of smallpox eradication was assured and that the actions recommended by the Global Commission were almost completed.

In October 1987, 10 years will have elapsed since the occurrence of the last case of endemic smallpox - a more than adequate period of time to provide full assurance that naturally occurring smallpox will not recur. Between April 1986 and October 1987 several actions are foreseen: (1) the book "Smallpox and its Eradication should be published; (2) DNA fragments of further selected strains of variola virus should be cloned; (3) WHO-supported field studies of the ecology of monkeypox virus should continue to the end of 1986, with full expectation that responsibilities for field studies would then be assumed by others; and (4) necessary arrangements should be made to place the records of the programme in a permanent archive.

Recommendation 1

The Committee recommends that an ad hoc committee be convened in October 1987 to satisfy the Organization and itself that the actions noted in the previous paragraph have been taken, and to approve the following recommendations:

1. That a reserve of smallpox vaccine is no longer required and the maintenance of the global reserve by WHO is no longer indicated. Vaccine held by WHO should be returned to those donors requesting it.

2. That seed virus stocks for preparation of the vaccine should be retained by WHO Collaborating Laboratories.

3. That remaining stocks of viable variola virus be destroyed.

4. That smallpox vaccination to protect military personnel against the disease be terminated.

5. That expertise be retained at WHO headquarters to assist in the investigation of rumours of suspected cases and to provide coordination and support to WHO collaborating laboratories able to verify diagnoses, so as to maintain the confidence of Member States in the fact of eradication.

6. That continuing investigations of monkeypox and related diseases, outside of the Organization, be encouraged.

Recommendation 2

In order to ensure that necessary tasks are completed on time, the Committee strongly recommends that sufficient WHO staff, consultants and resources be available from now until the end of October 1987. Specifically, such staff and resources are required:

1. To ensure publication of the book "Smallpox and its Eradication" before the 10th anniversary of the last case of endemic smallpox in the world - 26 October 1987.

2. To supervise preparation of cloned variola virus DNA.

3. To supervise the completion of WHO-supported field studies of monkeypox in Zaire during 1986.

4. To ensure that suitable arrangements are made to place the valuable records of the smallpox eradication programme that have been gathered since 1981 in a permanent archive.

Recommendation 3

The Committee recommends that WHO inform all Member States at an early date of the recommendations proposed for approval in October 1987 so that all may have full opportunity to consider and respond to them.

Fourth Meeting of the Committee on
Orthopoxvirus Infections
Geneva, 24-26 March 1986

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Fourth Meeting of the Committee on
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Geneva, 24-26 March 1986

PROVISIONAL AGENDA

Time	Item No	Subject
Monday 24 March 1986		
09.00	1	Opening
	2	Selection of Chairman and Rapporteur
	3	Adoption of agenda
	4	Introduction
09.30	5	Vaccination policy (G.C. 1,2)
	6	Reserve stock of vaccine (G.C. 3,4,5,6)
	7	Investigation of suspected smallpox cases (G.C. 7,8)
	8	Laboratories retaining variola virus stock (G.C. 9,10)
10.30		Coffee/tea break
11.00	9	Retention of variola virus stock
12.30-14.00		Lunch break
14.00		Miscellaneous Discussion on future policy - items 5, 6, 7, 8 & 9
15.30		Coffee/tea break
16.00	10	Human monkeypox surveillance (G.C. 11)
17.00		End of session
Tuesday 25 March 1986		
08.30	10	Monkeypox Research (continuation on G.C.11)
	11	Laboratory investigation (G.C. 12,13,14,15) Status of current research
10.30		Coffee/tea break
11.00	12	Discussion on future of investigations - items 10 & 11
	13	Documentation of Smallpox Eradication Programme (G.C. 16,17)
	14	Central coordination at WHO/HQ
12.30-14.00		Lunch break
14.00	15	Miscellaneous Discussion on items 13, 14 & 15
15.30		Coffee/tea break
15.45	16	Discussion and drafting of Meeting Report
17.00		End of session

Wednesday 26 March 1986

09.00	17	Finalization of Meeting Report
10.30		Coffee/tea break
11.30	18	Closure of Meeting
12.00		End of session
13.30-16.00		Meeting of the Editorial Board for WHO monograph "Smallpox and its Eradication"
14.00-17.00		Meeting of heads of the WHO Collaborating Centres and Zaire representatives

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WORKING PAPERS

Working Paper Serial Number		Prepared/Presented
WP 1	Status Report on Recommendations of the GCCSE Nos. 1-8 (Vaccination policy, Reserve stock of vaccine, investigation of suspected smallpox Cases)	Dr L. Khodakevich Mr J. Wickett
WP 2	Report on Visit to WHO CC - Atlanta	Dr Z. Jezek Mr V. Oviatt
WP 3	Report on Visit to WHO CC - Moscow	Mr V. Oviatt Dr Z. Jezek
WP 4	Retention of Variola Virus Stock: Yes or No	Dr K. Dumbell
WP 5	Status Report on Current Research	Dr S. Marennikova
WP 6	Status Report on Current Research	Dr K. Dumbell
WP 7	Status Report on Current Research	Dr J. Nakano
WP 8	Status Report on Current Research	Dr T. Kitamura
WP 9	Immunological Diagnosis of Monkeypox Virus Infection by Competitive Antigen Binding Inhibition Assay with Monoclonal Antibodies	Dr Y. Ichihashi Dr M. Oie
WP 10	Progress in Comparative Molecular Biology of Variola and Monkeypox	Dr K. Dumbell Dr P.J. Greenaway
WP 11	Present Orthopoxvirus Problems in India	Dr R.N. Basu
WP 12	Status Report on Monkeypox Surveillance in Zaïre	Dr Mambu-ma-Disu Mr M. Szczeniowski
WP 13	Status Report on Human Monkeypox	Dr Z. Jezek Dr B. Grab
WP 14	Results of monkeypox virus ecology surveys	Dr L. Khodakevich Mr M. Szczeniowski
WP 15	Plans for Ecological Research on Monkeypox virus	Dr L. Khodakevich Mr M. Szczeniowski

WP 16	Status Report on Japanese Bilateral Assistance to Monkeypox and VHF Surveillance in Zaïre	Dr T. Kitamura
WP 17	Stochastic Model of the Interhuman Spread of Monkeypox	Dr B. Grab Dr Z. Jezek Dr H. Dixon
WP 18	Fact sheets on WHO Monograph "Smallpox and its Eradication"	SME
WP 19	Status Report: Smallpox Eradication Surveillance, 1984-1985	SME

BACKGROUND DOCUMENTS

BD 1	Reports of the Meetings of the Committee on Orthopoxvirus Infections
BD 2	Instructions on Management of Suspected Cases of Smallpox and Reserve Stock of Vaccine in Post-smallpox Eradication Era
BD 3	WHO Collaborating Centres for Diagnosis and Research on Orthopoxviruses Laboratories Retaining Variola virus and Inspection Visits
BD 4	Articles, Reports and Papers on Monkeypox 1984-85
BD 5	Inventory List, March 1986

THE FUTURE OF VARIOLA VIRUS STOCKS

K. R. Dumbell

1. SHOULD VARIOLA VIRUS BE MAINTAINED INDEFINITELY?

1.1 Background and present position

After natural transmission of smallpox had been interrupted in 1977, much consideration was given to potential sources from which the disease might return. Prominent among these were the many laboratories which had stocks of variola virus. Intensive efforts by the World Health Organization identified those laboratories and invited them to destroy their variola stocks or to transfer them to a maximum containment laboratory at one of the WHO collaborating centres. The preliminary goal that not more than four laboratories should retain variola virus was achieved in 1982 and by 1984 only two laboratories were known to retain stocks of variola virus. These are: the Research Institute of Viral Preparations, Moscow (IVP) and the Centers for Disease Control, Atlanta (CDC). The CDC maintains its own collection of variola strains and also collections transferred there by the US army, the US Type Culture Collection, Rockville, the National Health Institutes of Japan and of the Netherlands and Dr Keith Dumbell of UK.

The situation was discussed in 1982 by a WHO Committee on Orthopoxvirus Infections. At that time variola virus was still being used for important research studies and it was recommended that the future of variola virus stocks should be reconsidered at the fourth meeting of the Committee on Orthopoxvirus Infections in March, 1986.

1.2 The Political Aspect

The debate about keeping stocks of variola virus indefinitely against a possible future need for them has both political and scientific components. The political view undoubtedly favours destruction and can be summarized as follows:

1.2.1 Variola virus anywhere remains at least a potential danger for the reintroduction of endemic smallpox.

1.2.2 Following the eradication of smallpox most laboratory directors and national governments agreed to dispose of their variola stocks in order to reassure the world that there remained no threat of the return of smallpox from that source. However, it was agreed that some further research with variola virus was required to contribute to the overall picture of the eradication programme and such research should be conducted in not more than four maximum containment laboratories, regularly reporting to and being inspected by the WHO.

1.2.3 Questions have been posed regularly at the World Health Assembly about the continued retention of any collection of variola viruses by a laboratory which was not pursuing active research with them.

1.2.4 At present (1986) it is understood that no culture of variola virus is in progress, or even contemplated, at either of the two laboratories which still retain the virus.

1.2.5 Progress in Molecular Biology since 1980 enables any future studies of variola virus to be conducted on fragmented variola DNA maintained in a non-infectious form in recombinant bacterial plasmids.

1.2.6 Even the archival retention of variola virus implies: physical security, containment laboratories, inspection visits and occasional culture to maintain the viability of the stocks. Besides the argument expressed in 1.2.1, maintenance of variola under these conditions is expensive, and this expense must be justified.

1.2.7 In the unlikely event that smallpox should return, virus would be again available. If smallpox does not return, maintenance or study of viable variola virus is unwarranted.

1.3 The research potential of variola virus DNA cloned into recombinant plasmids

1.3.1 Orthopoxviruses show extensive serological cross-reactions, even in neutralization tests, and DNA analysis has become the main criterion for subdividing the genus into species. Identification of any newly-isolated orthopoxvirus would be done by comparing the structure of its DNA with that of known species. There is no future need to grow variola virus as a "control" as the necessary information is available as published maps and could be extended if required by additional characterization of cloned DNA.

1.3.2 Analysis of cloned DNA by heteroduplexing or by sequencing can identify and analyse both homologous and heterologous regions. If required, particular sequences could be recombined into expression sites in suitable vectors to obtain samples of the translation products, for example, specific antigens that might be required for serological tests. Such experiments would be assigned to a containment category higher than that required for propagation of cloned DNA in a non-expression vector.

1.3.3 Theoretically the techniques now available that have been used to insert foreign genetic material into vaccinia virus, could also be used to insert a particular sequence of variola into another poxvirus to construct a functional poxvirus expressing some, defined element of variola. This is theoretically possible but any National Control Authority for work with dangerous pathogens or recombinant DNA would strictly regulate any proposed experiment of this nature.

1.4 Limitations to studies of variola virus using cloned DNA

1.4.1 At present the terminal, cross-linked fragments of variola DNA have not been cloned, though this has been achieved with vaccinia and with cowpox and should be possible for variola.

1.4.2 DNA from four or five strains of variola has been cloned. These include both variola major and variola minor isolates, but the sample may be less than fully representative.

1.4.3 As mentioned in 1.3.2 it would be possible to obtain variola-coded protein from cloned DNA. However, at present, the only immediately available source of variola-specific antigens would be from growth of viable variola virus.

1.4.4 Certain types of experiment, for example analysis of the antigenic mosaic on the surface of the variola virion, would only be possible using intact variola virus.

1.5 Proposals

Since it appears that no strong case can be made for the continued maintenance of variola virus it is proposed:

1.5.1 that destruction of all remaining variola stocks be agreed in principle.

1.5.2 that the consent to this of all parties with proprietary interests in existing variola stocks should be sought.

1.5.3 that actual destruction be postponed for a defined period to allow:

1.5.3.1 Cloning of DNA termini of at least one strain of variola.

1.5.3.2 Cloning of DNA from any additional strains to make up an agreed representative panel.

2. BROADENING THE BASE OF OPINION

2.1 Circulation of the views expressed in section 1

The views summarized in section 1 above were sent with a covering letter to 61 persons of whom 57 are virologists and 4 have been closely involved in virological aspects of the eradication programme. Recipients were asked to tell the extent of their agreement or disagreement and to advance any additional arguments or counter arguments. Of the 61 people written to, 38 have responded. Many of them had consulted colleagues; 20 of these were named and their opinions have been included in the analysis. The distribution of recipients and responders by country is shown in Table 1.

2.2 Consensus opinion of respondents

Replies came from a diverse group of virologists covering academic and public health activities, all degrees of involvement in smallpox eradication and from many different countries. A clear consensus emerged.

2.2.1 Destruction of remaining variola stocks

Fifty eight people have given their opinions. Fifty three thought that variola virus stocks should not be retained indefinitely. Five were in favour of retaining variola virus; the reasons they gave were:

2.2.1.1 The total absence of undisclosed stocks can never be certainly assured and some "open" retention was preferable to uncertainty about destruction.

2.2.1.2 Some experiments that are theoretically possible with cloned DNA are not immediately practicable.

2.2.1.3 Maintenance of variola in a few maximum containment laboratories presents negligible hazard and negligible expense. There is therefore no reason to eliminate the species and lose all possibility of working with it if an unforeseen reason for so doing should arise in the future.

2.2.1.4 One reply maintained variola is likely still to be circulating in the field in humans and simians and that destruction was therefore unnecessary.

2.2.2 Timing of destruction

Some virologists felt that the balance of arguments narrowly favoured destruction but were reluctant to take such an irrevocable step. They wanted the destruction to be postponed until there was provision of cloned DNA from the genome of a representative selection of strains. A few went even further than this. One was adamant that the DNA termini of at least one strain should be cloned, two wanted a practical demonstration that variola-coded polypeptides could be obtained from cloned variola DNA; two wanted destruction to be postponed indefinitely and reconsidered after ten years (one reply) and after completing the molecular biology to the extent of sequencing the DNA (one reply).

2.2.3 Control of cloned DNA

Two virologists thought it was pointless to destroy the virus unless the cloned DNA was also destroyed, and another thought that no single laboratory should be allowed to have cloned DNA covering the entire variola genome. These arguments apply not to the direct risk of handling viable variola virus, which unavoidably presents some hazard, but to the abuse of material which can be handled in complete safety. To accept their validity would equally rule out nuclear energy, dangerous pesticides and many other human activities.

2.2.4 Verification of destruction

2.2.4.1 Fears were expressed in 12 replies that destruction of variola stocks at IVP and CDC might still leave in existence some vials of variola viruses which had been overlooked during the general round of destruction a few years ago. This has been highlighted by the recent discovery, in London, of six ampoules suspected to contain variola virus and dated 1952. The suggestion was made that all laboratories known to have had stocks of variola should be asked by WHO to recheck all their stored viruses and to ensure that no variola had been overlooked. Because variola virus can persist for years at sub-zero temperatures, it was further suggested by one virologist that all freezers which once contained smallpox material should be emptied and thoroughly disinfected, lest variola still remained from any previously stored vial which had broken or leaked.

2.2.4.2 Some replies included the suggestion that WHO should seek some guarantee from the governments of Member States that there were no undisclosed variola stocks within their territory, retained by military or other agencies. It is to be noted, however, that such a guarantee could prove highly embarrassing to any country in which overlooked material subsequently came to light; nor would such guarantees carry complete, worldwide conviction.

2.2.4.3 A more realistic approach might be for WHO to ascertain from each Member State:

(a) whether the armed forces of that State were still being vaccinated against smallpox

(b) whether each Member State would undertake to discontinue vaccination of armed forces from a given date provided all other Member States gave the same undertaking.

3. CONCLUSIONS

3.1 In the continuing absence of natural transmission of variola in man or animals experiments which require viable variola virus are no longer justified.

3.2 Many investigations of variola virus are possible with cloned DNA; any that are not are no longer justified.

3.3 In the unlikely event that natural transmission of clinical smallpox should again occur, the viable, causative (presumed variola) virus would again be available.

3.4 The maps of the variola genome already available, the availability of cloned variola DNA, and the increasingly detailed knowledge of the variola genome being derived from the cloned DNA together provide a reference source fully adequate as a standard of comparison for any closely related poxvirus that may be isolated in the future.

3.5 Cloned DNA from a few representative strains of variola can at any time be fully sequenced and therefore provides adequate, archival material for this species of orthopoxvirus.

3.6 The physical hazard of keeping reference stocks of variola virus in a few maximum containment laboratories is minimal, but the political drawbacks are considerable. The scientific need for variola virus has, up to now, outweighed the political argument for destruction; this no longer applies.

TABLE 1

Country	letters sent	replies received	additional (named) replies
United Kingdom	7	5	10
France	3	3	2
Federal Republic of Germany	4	2	
Sweden	3	2	
Netherlands	4	4	3
Belgium	1	1	
Poland	2		
Czechoslovakia	1		
U.S.S.R.	4	1	
Hungary	2	1	
United States of America	6	4	1
Canada	2	1	1
Brazil	1	1	1
Japan	3	2	
Hong Kong	1	1	
Thailand	1	1	1
Indonesia	1	1	
Bangladesh	1		
India	3	2	1
Australia	3	2	
New Zealand	1	1	
Israel	1	1	
Kuwait	1		
Kenya	1	1	
Nigeria	1		
Côte d'Ivoire	1		
Zaire	1		
South Africa	1	1	
TOTAL	61	38	20

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