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REPORT OF THE AD HOC COMMITTEE

ON ORTHOPOXVIRUS INFECTIONS

Geneva, 11-13 December 1990

Dr G. Torrigiani, Director, WHO Division of Communicable Diseases, welcomed the participants to the meeting on behalf of the Director-General. Dr Torrigiani declared the meeting open and indicated that its major objectives were to assess progress and current activities of the post-smallpox eradication programme and, more specifically, to review the previous recommendation that all remaining stocks of live variola virus should be destroyed. Dr F. Fenner was elected Chairman and Dr P.J. Greenaway Rapporteur for the meeting. The list of participants is provided in the accompanying annex.

An overview of the post-smallpox eradication programme since its inception in 1980 was presented and the Ad Hoc Committee was reminded of the recommendations made at the conclusion of its previous meeting. The recommendations are provided below with comments as to their current status:

Recommendation 1

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

   The reserve of smallpox vaccine held by the World Health Organization has been reduced to 500,000 doses and should no longer be retained by December 1993, following the destruction of all live variola virus stocks.

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

   The World Health Organization should request that these seed stocks are maintained at the National Institute for Public Health in Bilthoven, at least until the destruction of all variola virus stocks has been confirmed.

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

   Discussions on the destruction of viable variola virus stocks were the subject of this Ad Hoc Committee meeting.

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

   Smallpox vaccination of military personnel had ceased in many countries, including the United States of America and the Union of Soviet Socialist Republics. However, this did not represent a change in USA policy as it was prompted by practical considerations relating to the non-availability of immunoglobulin. Up-to-date information on the policy of vaccinating military personnel by a number of different governments was not available. It was recommended that all countries should again be advised that there is no necessity for vaccinating military personnel against smallpox.

   Vaccination is still in use for personnel handling live or recombinant orthopoxviruses.

5. **That expertise be retained at the World Health Organization 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.**

   Expertise to support WHO Collaborating Centres for poxvirus infections is still retained at the World Health Organization.

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

   The Ad Hoc Committee endorsed the previous recommendation that continuing investigations of monkeypox and related diseases, outside of the World Health Organization should be encouraged.

Recommendation 2

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 - 26th October 1987.**

   The book entitled "Smallpox and its Eradication"[1] has been published. Members of the Ad Hoc Committee felt that the book gave a succinct and comprehensive account of the smallpox eradication programme and wished to congratulate all contributors on its quality.

2. **To supervise preparation of cloned variola virus DNA.**

   Studies on the cloning of variola virus DNA were the subject of this Ad Hoc Committee meeting.

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

   Field studies of monkeypox in Zaire supported by WHO had been completed in 1986 and the results summarized and published in a book entitled "Human Monkeypox" (Karger, 1988)[2].

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.**

   Records of the smallpox eradication programme have been archived at the World Health Organization headquarters.

Recommendation 3

The Ad Hoc Committee recommends that the World Health Organization 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.

The World Health Organization informed all Member States in 1986 of the recommendations proposed for approval in October 1987. Sixty-one favourable

responses were received. The meeting planned for October 1987 had been postponed until a propitious date.

The Ad Hoc Committee then reviewed the current inventories of virus stocks held within the designated repositories in Atlanta and Moscow. Over 100 samples are held in Moscow of which many represent primary isolates. The Centers for Disease Control (CDC) repository holds over 400 specimens of variola virus in two different locations. This repository also holds stocks of purified variola virus DNA and cultures of recombinant bacteria containing cloned sub-genomic DNA fragments. It was reported that five other laboratories also hold stocks of bacterial clones that contain recombinant plasmids with inserts of variola virus DNA.

The need to destroy all stocks of variola virus was unanimously reiterated by members of the Ad Hoc Committee and it was agreed that a deadline of 31 December 1993 should be set for the destruction.

The Ad Hoc Committee noted that it had previously concluded that cloned DNA samples of different variola strains could provide a useful archival source as well as reference material for the resolution of any future diagnostic problem involving suspected smallpox infections. However, the Ad Hoc Committee was made aware that developments in molecular techniques now made it possible to determine the nucleotide sequences of large DNA molecules. It was therefore suggested that the complete nucleotide sequence of specified variola virus genomes might represent a useful and potentially safer archival record. Two proposals, one from the Research Institute of Viral Preparations, Moscow and the other from the Centers for Disease Control, Atlanta were proposed to support this suggestion. The Ad Hoc Committee agreed that these were worthwhile and expensive programmes of work, but that every attempt should be made to obtain sufficient funds to ensure that foreign nationals could participate in the project. It was suggested that the DNA sequences generated should become part of the public domain so as to be incorporated in readily accessible DNA sequence databases. The Ad Hoc Committee endorsed the recommendation that the proposed studies should involve close cooperation and collaboration between the WHO Collaborating Centres for poxvirus infections in the USA and USSR and with other interested countries willing to commit resources to the project.

On the basis of the above proposals the Ad Hoc Committee then considered the proposal that all recombinant DNA material containing variola virus DNA sequences should be destroyed along with the virus stocks. This proposal engendered considerable debate during which arguments in favour of maintaining and those in favour of destroying cloned stocks of variola virus subgenomic DNA fragments were presented. The final consensus of opinion favoured recommending the destruction of cloned material providing that the complete nucleotide sequence of at least one variola virus strain had been determined.

The Ad Hoc Committee then considered which strains should be selected for sequence analysis. It was felt that the strains selected should be derived from smallpox cases with a well documented clinical history; that the pedigree of the isolates should be fully known; that they should not be derived from cultures potentially contaminated with vaccinia virus where recombination was possible; that they should contain both major and minor variants and that the isolates should be derived from different geographical regions of the world. On this basis it was decided that the order of priority for sequence analysis was:

1. a highly virulent Asian major strain, Bangladesh-1975; 2. a South American minor Alastrim isolate, Garcia-1966; 3. a highly virulent African major strain, Congo-1970 and 4. a low virulence African minor strain, Somalia-1977.

It was recognized that the final number of strains sequenced would ultimately depend on the project requirements and on the finances available. One complete sequence was regarded as the absolute minimum scientific requirement for the programme. Strategic requirements would indicate if additional full sequences were to be determined or if sequences from specific regions of other isolates were sufficient.

It was reported that the current available technology was capable of generating approximately 150kb of sequence information within 6-9 months and that a three year period represented a reasonable time frame for the successful completion of the proposed projects.

The establishment by the World Health Organization of an expert Technical Committee to oversee the sequencing efforts of both countries was also decided. Specific details on qualifications for Committee Members are provided in 'recommendation 5'.

The meeting terminated with a tribute, by the Chairman, to the late Dr James Nakano who had served as Chief of the Poxvirus Laboratory, at the Centers for Disease Control, Atlanta, and as a participant in the previous meetings of the Committee on Orthopoxvirus Infections.

SUMMARY OF RECOMMENDATIONS

1. All stocks of variola virus and materials containing variola virus must be destroyed by 31 December 1993.

2. All recombinant plasmids and other related materials that contain variola virus DNA sequences should be destroyed at the same time as the variola virus stocks, provided that the Technical Committee (see recommendation 5 below) is satisfied that sufficient sequence information is available, and serious scientific objections have not been raised.

3. In the interim, all recombinant plasmids that contain variola virus DNA sequences should be registered with the World Health Organization (WHO). These plasmids may only be provided to requesting scientists after informing WHO and on the strict understanding that they must not be distributed to third parties or used in laboratories handling other orthopoxviruses.

4. WHO should endorse the proposals made by representatives from the USA and USSR for determining the nucleotide sequences of the genomes of specific and representative variola viruses; the order of priority should be an Asian major strain, an American minor strain, an African major strain and an African minor strain.

5. WHO should establish an expert Technical Committee to oversee the above DNA sequencing efforts; this committee should consist of a Chairman who is an expert in poxvirology, a representative from each of the sequencing laboratories, at least two other people with experience in the sequence analysis of large DNA molecules and a member of the WHO secretariat.

6. WHO should provide the financial resources and administrative support for the Technical Committee; an officer within the WHO Division of Communicable Diseases should continue to take responsibility for concluding the post-eradication activities.

7. WHO should establish a Commission to certify the destruction of all variola virus stocks and, when appropriate, all recombinant plasmids and other materials containing variola virus DNA sequences; this Commission should prepare a final report on post-eradication activities in time for presentation to the World Health Assembly in May 1994.

8. The WHO Collaborating Centres [illegible]