QUINTA CONFERENCIA DE EXAMEN DE LOS ESTADOS PARTES EN LA CONVENCIÓN SOBRE LA PROHIBICIÓN DEL DESARROLLO, LA PRODUCCIÓN Y EL ALMACENAMIENTO DE ARMAS BACTERIOLÓGICAS (BIOLÓGICAS) Y TOXÍNICAS Y SOBRE SU DESTRUCCIÓN

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DOCUMENTO INFORMATIVO SOBRE NUEVOS ADELANTOS CIENTÍFICOS Y TECNOLÓGICOS RELACIONADOS CON LA CONVENCIÓN SOBRE LA PROHIBICIÓN DEL DESARROLLO, LA PRODUCCIÓN Y EL ALMACENAMIENTO DE ARMAS BACTERIOLÓGICAS (BIOLÓGICAS) Y TOXÍNICAS Y SOBRE SU DESTRUCCIÓN

Preparado por la Secretaría

En el párrafo 22 de su informe (BWC/CONF.V/PC/1), la Comisión Preparatoria de la Quinta Conferencia de Examen de los Estados Partes en la Convención sobre la prohibición del desarrollo, la producción y el almacenamiento de armas bacteriológicas (biológicas) y toxínicas y sobre su destrucción decidió invitar a los Estados Partes que lo desearan, comprendidos los Gobiernos Depositarios, a que presentaran a la Secretaría información sobre los nuevos adelantos científicos y tecnológicos relacionados con la Convención. Esta información debía abarcar las aplicaciones dadas a esos adelantos y su pertenencia para diversos aspectos de la Convención.

El presente documento contiene la información facilitada a la Secretaría por los Estados Partes hasta el 26 de octubre de 2001 de conformidad con el párrafo 22 del informe de la Comisión Preparatoria.

Reino Unido de Gran Bretaña e Irlanda del Norte

A. Introducción

1. La Comisión Preparatoria de la Quinta Conferencia de Examen de los Estados Partes en la Convención sobre la prohibición del desarrollo, la producción y el almacenamiento de armas bacteriológicas (biológicas) y toxínicas y sobre su destrucción ha invitado a los Estados Partes a que presenten a la Secretaría información sobre los nuevos adelantos científicos y tecnológicos relacionados con la Convención. La información debe abarcar las aplicaciones dadas a esos adelantos y su pertinencia para diversos aspectos de la Convención.

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2. Invitaciones análogas fueron cursadas para anteriores Conferencias de Examen, aunque sólo se aprobaron los tres depositarios para las primeras dos. La finalidad de la invitación es facilitar información para ayudar a la Conferencia de Examen a realizar la tarea que le ha sido encomendada por el artículo XII de la Convención de:

> "*asegurarse de que se están cumpliendo los fines del preámbulo y las disposiciones de la Convención... En ese examen se tendrán en cuenta todas las nuevas realizaciones científicas y tecnológicas que tenga relación con la Convención*".

3. El Reino Unido ha presentado documentos de esa clase a todas las anteriores Conferencias de Examen. En nuestro documento presentado a la Cuarta Conferencia de Examen en 1996 se examinaban los adelantos en la esfera de la ciencia, la medicina, la agricultura y la industria que se habían producido desde la anterior Conferencia de Examen (1991). También se examinaban en él las consecuencias para el ámbito de la Convención y el equilibrio entre el posible uso indebido de la ciencia o la tecnología, por una parte, y la posibilidad de utilizarlas para fines profilácticos y de protección u otros fines pacíficos, por otra. Además, se identificaron las cuestiones que cabría abordar en el curso de la labor que viene realizando el Grupo ad hoc encargado de elaborar un instrumento jurídicamente vinculante para reforzar la Convención. Entre esas cuestiones figuraban los hechos y prácticas que podrían guardar relación con la elaboración de un régimen de declaraciones de un futuro Protocolo de la Convención.

4. En el documento del Reino Unido de 1996 se hacía observar que habían aumentado las posibilidades para la producción en gran escala de posibles agentes para armas biológicas y para la modificación genética de agentes y toxinas con miras a reforzar su utilidad en cuanto armas. Sin embargo, nada parecía indicar que un infractor capaz de fabricar armas técnicamente avanzadas optara, no obstante, por hacerlo dado el creciente riesgo de fracaso y de detección, en particular habida cuenta de un futuro Protocolo de la Convención. Era evidente que también había mejorado la posibilidad de elaborar medidas de defensa desde la anterior Conferencia de Examen.

B. Reseña de la ciencia y la tecnología

5. En el presente documento se reitera el amplio informe adoptado en el documento anterior, aunque no se intenta indicar los adelantos que podrían tener repercusiones en las medidas de fomento de la confianza o de verificación del cumplimiento que en lo sucesivo podrían proponerse para la Convención. Pocos se sentirán sorprendidos por el inmenso alcance de los adelantos en la esfera de la genética dado el nivel de sensibilización -y a veces preocupación- del público respecto de las aplicaciones relacionadas con los animales y plantas transgénicos y los productos genéticamente modificados. Nos ha parecido importante una vez más examinar los progresos en los conocimientos y aplicaciones genéticos que guardan relación con los microorganismos, toxinas y enfermedades infecciosas, que equivalen a una explosión de logros y posibilidades desde la Conferencia de Examen de 1996. No obstante, hay también otras esferas en pleno desarrollo, como la proteómica y la bioinformática, que también merecen ser mencionadas por lo que respecta a las posibilidades para bien o para mal en relación con las disposiciones de la Convención.

6. Los aspectos concretos del examen se consignan en el anexo bajo los epígrafes siguientes:

- Genómica y proteómica;
- Bioinformática;
- Proyecto del genoma humano y diversidad humana;
- Terapia genética;
- Virulencia y patogenicidad;
- Vacunas y terapias nuevas;
- Expresión de la proteína recombinante;
- Toxinas y otras moléculas bioactivas;
- Métodos de detección e identificación;
- Sintomatología de las enfermedades infecciosas humanas;
- Destrucción de la viruela;
- Resistencia a los medicamentos;
- Plagas del campo;
- Lucha contra las plagas del campo;
- Iniciativas mundiales para combatir la enfermedad;
- Aplicaciones de la biología molecular a los cultivos;
- Tendencias en los métodos de producción de proteínas;
- Cooperación internacional y bioseguridad: actividades realizadas con arreglo a la Convención sobre la Biodiversidad;
- Vectores de agentes o toxinas;
- Uso de patógenos para eliminar las hierbas malas y los cultivos "indeseables";
- Biorreparación: la destrucción del material;
- Prevención de la amenaza terrorista con armas bacteriológicas (biológicas);
- Repercusiones de la entrada en vigor de la Convención sobre las armas químicas.

C. Análisis y recomendaciones

7. El examen que se hace en el anexo de los adelantos científicos y tecnológicos que se han producido desde la Cuarta Conferencia de Examen celebrada en 1996 muestra que se ha realizado un importante avance en varias esferas que permite comprender la base genética, estructural y funcional de los microorganismos y las toxinas, así como por lo que respecta al número y la sofistificación de los métodos que permiten introducir los cambios deseados en las propiedades de los microorganismos o las toxinas. Los adelantos en genética se han descrito con frecuencia como una explosión, pero durante el período también se han observado avances importantes en otras esferas. Para algunas de ellas se han acuñado neologismos, como ocurre en el caso de la proteómica y la bioinformática. La producción de moléculas que han sido introducidas genéticamente en células microbianas o eucarióticas, o en plantas o animales "transgénicos", se ha convertido en práctica rutinaria en sectores de la biotecnología de muchos países. Se espera que esos avances se aceleren, y en la próxima etapa se tendrá una mejor comprensión de las relaciones funcionales dentro de la célula microbiana.

8. También han aumentado considerablemente desde la anterior Conferencia de Examen las posibilidades del uso indebido de toxinas y de moléculas biorreguladoras de los péptidos. Los conocimientos de que disponemos sobre la estructura y la función de las toxinas y sus subunidades, y los adelantos en la ingeniería recombinante y los sistemas de expresión, han permitido expresar varias toxinas en términos de células heterólogas hospedantes. Muchas otras toxinas podrían producirse fácilmente y en grandes cantidades por este procedimiento. Se ha informado acerca de la recuperación de péptidos de cantidades equivalentes a toneladas métricas de plantas transgénicas. Así pues, los avances en biotecnología crean la posibilidad de utilizar indebidamente los biorreguladores de péptidos tras la producción en sistemas recombinantes. Los avances en lo referente a los vectores plantean la posibilidad de utilizar vectores virales o bacterianos para introducir directamente en el objetivo la toxina o el biorregulador, sea para la transferencia genética al huésped o para la producción directa por el vector. Los avances registrados en la producción recombinante significan asimismo que ha aumentado la posibilidad de considerar a los priones como armas. El Reino Unido considera que la Conferencia de Examen debe examinar esos factores al revisar el artículo I.

9. La difusión global de los conocimientos en los campos relacionados con la microbiología, facilitada por nuevas vías de información, como el Internet, significa que es cada vez mayor el número de países cuyos científicos poseen los conocimientos y la experiencia necesarios para desarrollar armas biológicas a partir de posibles agentes y toxinas clásicos. Aún más preocupante es el hecho de que la difusión de conocimientos y aplicaciones en esferas tales como la genómica significa que una amplia gama de países podría ahora tratar de mejorar, mediante alteración genética, los agentes biológicos de guerra para reforzar propiedades tales como supervivencia, resistencia a los antibióticos y capacidad para superar determinados métodos profilácticos o de detección. Aún se conocen mal muchos aspectos relacionados con las propiedades de los microorganismos, como por ejemplo la relación existente entre sus diversas propiedades estructurales y funcionales y el carácter de sus interacciones con el huésped durante la infección. No obstante, los avances y la difusión de conocimientos ofrecen a los infractores nuevas posibilidades en lo que respecta a las armas bacteriológicas. Las posibilidades globales para los programas de armas bacteriológicas técnicamente avanzadas seguirán aumentando a medida que se desarrollan los conocimientos científicos. Los datos relativos al genoma humano

aún no permiten identificar aún las diferencias que podrían servir de base para las "armas genéticas" dirigidas contra determinados grupos étnicos.

10. Los avances en esferas relacionadas con la Convención suscitan otras dos preocupaciones. En primer lugar, la difusión global de conocimientos científicos y tecnológicos ha incrementado la posibilidad de que actores no estatales de un número cada vez mayor de países traten de producir y diseminar patógenos o toxinas en cuanto armas, aunque en la práctica el nivel de conocimientos relativamente altos que se requieren para ello puede limitar o impedir el éxito. En respuesta a esta posibilidad, varios gobiernos han comenzado a aplicar contramedidas concretas, en particular medidas de reglamentación para impedir la adquisición no autorizada de patógenos y toxinas de colecciones de cultivos legítimos, infraestructuras para hacer frente a las consecuencias del uso de armas bacteriológicas contra su población y la adquisición de vacunas y dispositivos de detección. En segundo lugar, es inevitable que aumente el riesgo de resultados imprevistos con microorganismos genéticamente modificados dado el aumento considerable del número de laboratorios en los países desarrollados y en desarrollo que aplican sistemáticamente técnicas recombinantes a los microorganismos. Un experimento publicado sobre un virus de la ectromelia que inopinadamente superó las defensas inmunológicas de los ratones huéspedes ha servido de advertencia acerca de los riesgos de las consecuencias imprevistas que podrían ser desastrosas si, por ejemplo, esos organismos escaparan del laboratorio. Ello pone de manifiesto la importancia de realizar cuidadosos análisis en cuanto al riesgo y de adoptar medidas adecuadas en lo referente al procedimiento y la contención física. La liberación al medio ambiente de un microorganismo recombinante peligroso podría suscitar preocupaciones, aunque fuesen infundadas, en relación con la Convención sobre las armas bacteriológicas y toxínicas.

11. Es probable que muchos de los vectores militares de que disponen, según se afirma, un número creciente de países, tanto desarrollados como en desarrollo, se adapten para el uso de agentes biológicos o toxinas. Cabe esperar que las mejoras en el alcance y precisión de los misiles y en el diseño de las submuniciones sigan creando mayores posibilidades para el envío de agentes biológicos de guerra a largas distancias.

12. Las posibilidades y la disponibilidad de medidas defensivas contra las armas bacteriológicas siguen mejorando en varios países, tanto por lo que respecta a los sistemas sobre el terreno para la detección e identificación de los agentes biológicos y toxinas como a las medidas profilácticas, principalmente vacunas. Cabe esperar asimismo que los programas nacionales antiterroristas a los que se asignan recursos importantes para adoptar contramedidas en materia de detección y asistencia médica contribuyan a mejorar el estado de preparación nacional contra ataques con armas bacteriológicas lanzados por otros países. Sin embargo, el largo tiempo que se requiere para el desarrollo de contramedidas prácticas tales como detectores y vacunas contrasta con la rapidez con la que las propiedades de los patógenos y toxinas pueden ser modificadas por muchos laboratorios del mundo que podrían intentar ahora tales modificaciones si emprendiesen un programa ilegal. Si bien es importante que varios países han mejorado su capacidad de defensa contra las armas bacteriológicas y se benefician de los adelantos técnicos, la creciente sofisticación técnica y los gastos concomitantes pueden hacer que sea aún más difícil para los países en desarrollo adoptar medidas de defensa efectivas.

13. La pandemia mundial del SIDA se ha agravado, y son cada vez mayores los temores de que el SIDA se propague a los países en que la tuberculosis es ya endémica. Los crecientes viajes mundiales y la intensificación del comercio mundial siguen provocando la aparición de

brotes imprevistos de enfermedades infecciosas naturales. Esas enfermedades pueden rebasar la capacidad normal de identificación y tratamiento de un país y, por lo que se refiere en particular a las enfermedades de las plantas y los animales, pueden entrañar enormes costos económicos incluso en los casos en que la morbilidad o la mortalidad no es particularmente elevada. Un ejemplo de ello son los costos directos de la epidemia de fiebre aftosa en el Reino Unido en el 2001, al paso que los costos indirectos para actividades tales como la industria del turismo del Reino Unido son incluso más elevados.

14. En lo que se refiere a los aspectos positivos, las organizaciones internacionales dedicadas a la prevención de las enfermedades en el hombre, los animales y las plantas intensifican su cooperación y alientan la coordinación de los programas nacionales y regionales. En el presente documento se dan ejemplos de las contribuciones aportadas por el Reino Unido a proyectos destinados a combatir las enfermedades en los países en desarrollo. Se ha concertado el Protocolo de Cartagena del Convenio sobre la Diversidad Biológica que permitirá adoptar medidas para reducir los riesgos a la biodiversidad que podría ocasionar el movimiento transfronterizo de organismos vivos (genéticamente) modificados. Los avances técnicos en el diagnóstico de enfermedades de las plantas y los animales, tales como el copiado genético, han permitido comprender mejor la relación que existe entre los brotes en distintos países y durante un período de tiempo. Esta nueva capacidad de diagnóstico hará que sea más fácil establecer una distinción entre las epidemias de origen natural y de origen no natural.

15. Siguen investigándose las aplicaciones pacíficas de los microorganismos utilizados para destruir los contaminantes en el medio ambiente, aunque este método ha suscitado preocupaciones en cuanto a la posibilidad de transferencias no deseadas de genes a los organismos que se dan en estado natural. Una de las aplicaciones de la biorreparación que aún sigue considerándose es la neutralización de los residuos de agentes de armas químicas en pruebas medioambientales, aunque esta técnica no ha sido adoptada por ninguno de los Estados Partes en la Convención sobre las armas químicas en relación con sus programas de destrucción en gran escala de agentes de guerra química. Es evidente que las técnicas de biorreparación cuentan con el potencial de desarrollo como medio de guerra o para fines hostiles contra el material, que como el petróleo, el caucho o el plástico, resulta indispensable para la vida civil normal o para las operaciones militares.

16. El uso de microorganismos para combatir las plagas del campo ha cobrado nuevo auge desde el examen de 1996, y se está prestando gran atención a la mejora del control de la calidad en la fabricación. Han proseguido los estudios del potencial de los patógenos microbianos para eliminar hierbas malas, aunque el número de aplicaciones comerciales sigue siendo reducido. Varios grupos han criticado los programas de las Naciones Unidas para desarrollar patógenos aptos para ser liberados como bioherbicidas específicos contra los cultivos de coca, marihuana y opio destinados a la producción de sustancias estupefacientes ilícitas. Entre las cuestiones científicas planteadas figuran las transferencias genéticas e infecciones imprevistas de plantas distintas de las especies fijadas como objetivo. También se han formulado preguntas acerca de si, dado que las localidades para los ataques contra tales cultivos se encuentran actualmente en países en que hay disturbios civiles que en ocasiones degeneran en conflictos armados, el ataque contra tales cultivos mediante el uso de agentes biológicos sería necesariamente aceptable conforme a lo dispuesto en el artículo I de la Convención sobre las armas biológicas y toxínicas. El Reino Unido considera que la Conferencia de Examen debe debatir esta cuestión para determinar si conviene aportar cualquier precisión.

17. El uso industrial de microorganismos o de las enzimas extraídas de ellos para catalizar las correspondientes etapas de los procesos de fabricación química, denominados "biotransformación", se ha diversificado considerablemente. Las instalaciones que utilizan esos procesos pueden ser identificadas merced a las declaraciones sobre el lugar de las instalaciones previstas en la Convención sobre las armas químicas. Es limitada, y es probable que siga siéndolo, la transparencia brindada por la declaración y los procedimientos de inspección sistemática de la Convención sobre las armas químicas en lo referente a la labor relacionada con la producción de toxinas y otras sustancias químicas de origen biológico. A juicio del Reino Unido, la transparencia brindada por las medidas que se adopten en relación con la Convención sobre las armas biológicas y toxínicas deberá abarcar una gama mucho más amplia de toxinas y sus análogos y subunidades.

18. Merced a los diversos estudios y consultas realizados por el Reino Unido para preparar el presente examen, se ha logrado establecer que el ritmo de cambio en la esfera de la ciencia y la tecnología que guarda relación con la Convención sobre las armas biológicas y toxínicas ha sido mucho mayor que en el quinquenio precedente, es decir, el período comprendido entre las Conferencias de Examen tercera y cuarta. Varios de los avances en los conocimientos científicos y sus aplicaciones podrían guardar relación con las disposiciones de la Convención sobre las armas bacteriológicas y toxínicas. Dado el ritmo acelerado de desarrollo científico y tecnológico, el Reino Unido se pregunta si es prudente mantener el plazo de cinco años fijado para tales evaluaciones en virtud de la Convención sobre las armas bacteriológicas y toxínicas. El Reino Unido propone que la próxima Conferencia de Examen considere la posibilidad de establecer un mecanismo para que los Estados Partes colaboren entre sí con mayor frecuencia para llevar a cabo esas evaluaciones científicas y tecnológicas y considerar las consecuencias al nivel técnico requerido.

Annex[1]

DETAILED SCIENCE AND TECHNOLOGY REVIEW

Genomics and proteomics

1. The advent of rapid methods for sequencing entire genomes has led to a massive increase in genomic data in recent years. Although sequencing technology is not a novel technique, the last five years have seen the development of faster throughput methods, and this technology is still developing rapidly. As a result, the entire genomes of many viruses and bacteria have now been sequenced. Many of these agents are pathogens and potential biological weapons (BW) agents.

2. To date, 38 bacterial genomes have been published as sequenced, assembled and annotated, and 158 are at various stages of sequencing. In 2001 the genome of *Yersinia pestis*, a potential BW agent that causes plague in humans, was sequenced in the UK. This genome provides evidence for the evolution of the current organism from an enteropathogen ancestor. Genomic information has a wide variety of applications and can underpin studies to develop improved vaccines and antibacterial strategies and to identify antigens as targets for detectors. However, information from genomics that furthers understanding of the mechanisms of microbial pathogenicity also could suggest genetic targets for modulation that could lead to micro-organisms with increased pathogenicity. Genomic information could also inform strategies to defeat vaccines or host immune defences.

3. Although genome sequence data provides information on the entire set of genes a micro-organism possesses, and genomic analysis provides information on the possible function of genes, they do not indicate which of these genes are expressed to produce proteins at any particular time in the life of the organism. Additionally, proteins expressed in organisms are typically modified, for example by phosphorylation or glycolysation, but little can be deduced about this by simply looking at an organism's genome map. Because of the functional complexities of the expression of the genetic potential of a cell, organisms may well have well over an order of magnitude more proteins than genes. The recent finding that the human genome apparently only contains 30,000 - 35,000 genes suggests that much of the complexity in humans lies in the various ways in which proteins are formed and modified.

4. A new field of studies, called proteomics, has evolved as a result of the need to address such issues. Proteomics is the study of the entire set of proteins expressed by the gene sequence of an organism. This allows the study of the total protein complement of a micro-organism, whereas traditionally individual proteins have been studied one by one. In addition, proteomics can allow the characterisation of proteins and of their level of expression under different conditions, and can help elucidate their functional roles. Recent developments have focused on speeding up the procedure of identifying proteins from two-dimensional gels through automation of instrumentation and software. Mass spectrometry has become the technique of choice to

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identify proteins, and technology developments here have led to lower limits of detection for cellular proteins and increased capabilities for protein and peptide structural studies.

5. Information from proteomic studies could, for example, not only determine which proteins are expressed during microbial infection or disease, but also how proteins interact with each other. Identifying which proteins a target protein interacts with can help in understanding its function. Proteomics can also identify protein markers of disease: this could help in the development of new methods for early diagnosis and detection of diseases such as cancer, or the development of novel therapeutics including vaccines. Possibilities for improving the stability of pathogen or proteins may be exploited in environmental release applications such as bioremediation and the use of biological insecticides and herbicides. Like genomics, such a powerful tool could also be open to misuse for non-peaceful purposes.

6. An example of a technology that is allowing a great increase in analytical capabilities is the use of nucleotide and protein microarrays. Transcriptional profiling using DNA or short oligo-nucleoteotides arrayed at very high density on chips is an enormously powerful technique which can be used to measure gene expression. These "gene chips" can show which individual genes are switched "on" or "off" under a different conditions. Using such technology the whole genome of a micro-organism can be represented on one chip. Microarrays can be used to ascertain which genes are involved in host invasion by an intracellular pathogen or which genes are expressed when bacteria encounter a host's defence systems. This technology can also provide insights into diseases such as cancer and the genetic basis of other diseases. Protein arrays are receiving widespread attention as analytical tools and can also be used to identify disease biomarkers. Protein chips can be used to study protein-protein interactions and interactions between proteins and drugs. In drug screening, protein arrays can be used to determine which compounds react with target proteins and which react with non-target proteins i.e. those which could potentially cause side effects.

Bioinformatics

7. Genome and proteome programmes generate vast amounts of information. The discipline of bioinformatics has emerged and has grown rapidly because of the need to manage this type of information explosion. Bioinformatics is the computer assisted science of processing and dissemination of biological information and involves the collection, storage, management, classification, integration and retrieval of information in accessible databases. For example, bioinformatics can search for genes of interest making it possible to sort through a genome sequence, select a gene, determine whether it has a known function by comparing it to gene databases, and predict its cellular location and molecular weight.

8. The Internet has made the data and tools for bioinformatics available widely and at low cost, and there are a number of powerful analytical programmes to allow the data for the millions of bases generated during genome sequencing to be mined relatively easily for genes of interest. Software for genome annotation, gene finding, sequence similarity searches, sequence alignments and other analytical functions is constantly being improved. Genetic and protein databases have been growing exponentially over the last few years and protein structural predictions from sequences have become increasingly possible and more accurate as more entries are posted in such databases. Bioinformatics can aid the design of novel drugs and

therapeutics, but could equally aid the design of novel toxins or improvements in pathogenicity that could be misused. In the future, bioinformatics linked with high throughput methods for proteome and genome analysis, such as microarrays, will increasingly allow the rapid targeting of biological macromolecules for any purpose, peaceful or otherwise.

Human Genome Project and Human Diversity

9. A working draft of the sequence of the human genome, providing greater than 90% coverage of the genome, was published under the Human Genome Project (HGP) in February 2001. The fact that this was achieved ahead of schedule illustrates the rate of progress in such technologies. This draft still has some short gaps and the full sequence will take a further 2-3 years to complete. So far it has been estimated that 30 000 - 35 000 human genes make up the human genome. The potential benefits of this project are enormous, providing a wealth of opportunities to improve diagnosis and understanding of disease, developing gene therapies, and rationalising drug design.

10. The human genome consists of 3 billion nucleotides of DNA of which the majority (99.9 %) is now believed to be identical between individuals. It is the remaining 0.1% which makes us individual, and much work has centred on understanding these differences and their role in disease and response to drugs. The field of pharmacogenetics has developed to study how differences in genes affect the way individuals respond to medicines. Pharmacogenetics could lead to the development of tailor-made medicines and styled therapies for the individual making safer and more effective treatments. One key to understanding this genetic variation is the phenomenon of single nucleotide polymorphism. This is the most common type of genetic variation, occurring once every 1000 base pairs. Many of these base pair changes may have no effect, while others may be involved in disease susceptibility and responses to drugs. In 1999 the Wellcome Trust Foundation set up the SNP Consortium, a $45 million initiative funded by the Wellcome Trust and 10 pharmaceutical companies as a non-profit making venture. Their aim is to make this type of information available in the public domain without intellectual property restrictions on academic or commercial researchers accessing this information.

11. The HGP has carried out studies which show that very little extra information in the areas of motif scanning, gene identification, positional cloning, single nucleotide polymorphism mapping and gene structure determination will be gained from the finished sequence as compared to the working draft. This working draft is freely available in public databases and none of the information will be patented.

12. Information from human genomic studies has increased our knowledge of receptors for natural ligands. Such information may provide information on novel receptor targets for modulation of the immune system or central nervous systems, for example. In addition, it may aid the design of molecules intended to mimic natural ligands as a means of modulating regulatory processes. The technology could however be misused to develop novel bioregulators as BW agents.

13. At the beginning of 2000, the company Celera announced their intention to sequence the genomes of 5 individuals, 3 women and 2 men. In an attempt to quantify human diversity at the genome level these individuals were chosen as representing the main ethnic groups of the human

race. Results of the analysis were published in the open literature in 2001. Notwithstanding the potential of such projects for scientific and medical benefits, a number of geneticists and medical ethics specialists have raised concerns about the potential for misuse of such information. One type of misuse could be use by a BW proliferator to design a genetic weapon able to target population specific genetic traits. The UK's paper to the 1996 Review Conference drew attention to this potential for genetic weapons, but assessed that genetic weapons could well remain a theoretical possibility. New genetic data provide no indication as yet of differences between ethnic groups that would allow targeting by weapons. Nevertheless, we consider it important that one of the Article I reaffirmations at the Fourth Review Conference stated that Article I applies, *inter alia*, to 'any applications resulting from genome studies'.

Gene therapy

14. Gene therapy, the transfer of genetic material for therapeutic purposes, is still not a widely used therapeutic technique. The major challenge associated with this technology remains the gene delivery system. However, the last five years have seen a steady increase in the number of publications about the development of replication competent viral vectors. Three virus groups are being investigated for therapeutic use: retroviruses; adenovirues; and herpes simplex virus. A more effective delivery system reduces the number of recombinant virus particles needed for effective during therapy. Such viral vectors would replicate in human cells giving improved tissue dissemination and increased expression levels of any detrimental gene carried by the virus vector.

15. Research procedures using gene therapy are being investigated in animal models to modify inappropriate immune responses associated with conditions such as irritable bowel syndrome. The expression of interleukins delivered by these virus vectors as a means to aid an immune response in cancer treatments has progressed as far as clinical trials. Adenovirus vectors have been used to deliver interleukin 4, a negative feedback chemical messenger of the host immune system.

16. Over the last five years there has been a steady maturation of related technologies such as production and purification methods for viral vectors, new non-viral delivery systems, targeted delivery of therapeutic genes, regulated expression and lung gene therapy techniques. In the long term such technologies may improve sufficiently to be used by a BW aggressor to deliver a foreign gene into human cells.

17. Among the latest technologies, antisense therapy, the use of short spans of nucleic acid to disrupt the expression of disease related gene sequences, is receiving attention as a novel therapy for diseases such as AIDS and Crohn's Disease. Normally, the code of a gene (its sense strand) is transcribed into mRNA which is then translated into a protein. This gene expression can be interrupted either at the stage of transcription or translation by the delivery of an antisense strand of nucleic acid, which by hybridising to either the DNA or mRNA would block the expression of genes and protein products, for example those involved in disease. A related area of interest which is receiving attention is the use of ribozymes as a therapy to alter gene expression. Ribozymes are RNA molecules which can cleave RNA at specific sites. By combining specific antisense targeting with enzymic cleavage of RNA by ribozymes, ribozymes could be used to

inhibit protein products associated with disease or those associated with the replication of pathogens in the host.

Virulence and pathogenicity

18. Genome sequencing of pathogens has had a significant impact on the understanding of pathogenicity. Pathogenicity islands, where clusters of virulence-associated genes are found, have been shown to be as important as plasmid acquisition in the emergence of pathogens from non-pathogenic ancestors. Many pathogenic strategies, such as Type III secretion systems, have been shown to be widespread amongst bacteria. Evidence is amassing that the virulence of many bacterial pathogens is a complex, multifactorial process requiring the co-ordinated activity of gene products. This regulation of genes is known to be crucial for the survival and virulence of pathogens *in vivo*. In recent years there have been rapid advances in experimental approaches for the study of bacterial virulence in the host which greatly simplify *in vitro* analysis. High-throughput, global approaches such as signature-tagged mutagenesis and *in vitro* expression technology have been developed. Combined with modern approaches to analysis of gene expression involving DNA micro-arrays, the effect of altered environmental conditions or a mutation on every gene in the bacterium can now be examined.

19. Many virulence studies require an *in vivo* screen in an animal model. Over the last five years there has been an ethical drive in some states to reduce experimental animal use, which has led to the development of alternative models for example using tissue culture or nematode worms. Many studies, ranging from pathogenicity studies to vaccine development will however continue to rely on small animal tests for the immediate future.

20. Advances in genomics have increased our understanding of viral pathogenicity and virus replication in the host. The function of individual genes may be assigned by the expression of individual proteins and analysis *in vitro*, production of attenuated strains, or the generation of recombinant viruses containing foreign or manipulated genes. However, because precise genetic manipulation of viruses is only possible using DNA, DNA copies of RNA viruses must be prepared before their genomes can be manipulated. This process has been aided by recent advances which have increased the fidelity of the polymerase chain reaction (PCR), and is now relatively routine for positive (sense strand) genome RNA viruses. The most significant technical advances have been in reverse genetics, the preparation of a DNA copy of a negative strand (antisense) RNA genome, particularly where the genome is segmented as in the case of influenza virus. This technology has been applied to the highly pathogenic filoviruses to study the function of the virion glycoproteins.

21. Experiments involving the production of recombinant viruses expressing foreign genes have generated unexpected and controversial results. In 2001, a research group described an unexpected lethal effect in mice following their immunisation with orthopoxvirus ectromelia (mousepox, ECTV) into which the murine interleukin-4 (IL4) gene had been inserted. The aim of the insertion was to bias the host immune response and so make the mice infertile - an attempt at contraception.

22. The implications of this mousepox data could be far reaching. ECTV is a close relative of smallpox virus and of vaccinia virus, used in the smallpox vaccine. In addition, ECTV has been adopted as a model virus for smallpox, because it causes a severe and fatal generalised disease in some strains of mice. A parallel can be drawn between some observations made with ECTV in mice and smallpox virus in humans. These results, if extrapolated, could mean that similar experiments with smallpox could result in recombinant viruses with enhanced pathogenicity in humans or the ability to overcome vaccination. Other orthopox viruses such as monkeypox could be changed in the same way. Unfortunately, such ideas could be taken up in a weapons programme. The authors considered carefully whether it was appropriate to publish the information. Ultimately, it was decided to publish so as to warn others about the potential for experiments with recombinant micro-organisms to have unforeseen results. This emphasises the importance of prior risk analysis and appropriate procedural and physical containment measures.

23. Understanding the pathogenicity of a pathogen is key to constructing an effective defence against disease. However, although an aggressor can use a pathogen without a thorough understanding of its pathogenicity, such knowledge may point to avenues which would increase an agent's effectiveness as a weapon.

Vaccines and novel therapies

24. The greatest advances in vaccine research and development have arisen from the availability of genome sequences of pathogens and high-throughput screening methods. Vaccine development requires the identification of unique structures and molecules that can be used to generate immunological protection. Using traditional screening techniques this process can be time consuming and involve the trial and error testing of vaccine candidates. Several groups around the world have now shown that it is possible to predict preferred vaccine designs from genome sequences using bioinformatics software and programs. Whole genome libraries can be screened in animal models by use of methods such as signature tagged mutagenesis. Together, these approaches mean that vaccine discovery now has the potential to proceed much faster and with a better chance of leading to acceptable vaccines.

25. Although conventional sub-unit or killed vaccines are still widely used, recombinant sub-unit vaccines are expected to gradually replace them. But for many disease targets there is a continuing debate over whether highly purified protein antigens will be more effective than a mixture of cells and/or components. Current mixtures tend to be better defined than classical mixed antigen mixtures because some of least of the components are often contributed by recombinants. Pertussis (whooping cough) is an example where a consensus strategy in favour of cellular vaccines is evolving towards a better-defined mixture. Improvements in fermentation technology allow more consistent production of classical vaccines, but on-line monitoring and feedback control of antigen expression during production is still not possible.

26. Recombinant vaccines offer advantages not only in cost of production, yield and safety of the production process but also because of the potential for reduced reactogenicity of the vaccine. Several naked DNA vaccines directed against viral or parasite pathogens including HIV and malaria are now in clinical trials. Vaccine vectors have undergone limited trials in man: for example, salmonella expressing tetanus Hc fragment has been evaluated in a phase 1

trial. However, such live vaccine vectors might equally well be misused to deliver toxins or other biologically active molecules to humans in a weapons format.

27. An area also receiving much attention is the development of more effective vaccine delivery systems. Groups in industry and academia are currently developing a range of improved vaccine adjuvants, with the objectives of enhancing the immune response and tailoring it to the type of protection required. Improvements in vaccine efficacy have been achieved by adding fragments of bacterial toxins to a vaccine. For example, the non-toxic B sub-unit of cholera toxin has proved an effective adjuvant for orally or intranasally delivered vaccines.

28. Microencapsulation technologies are also being applied to improve vaccine delivery. There is an increasing awareness of the advantages of this approach to intranasal delivery. Unfortunately, advances in the intranasal delivery of vaccines could also be misused for the design of improved systems for the airborne delivery of agents and toxins as weapons.

29. The last five years have also seen advances in the re-targeting of microbial toxins to alternative sites of action for therapeutic purposes, and this approach is being adopted in searches for novel drugs for treatment of tumours and. Production of heterologous toxins by the substitution of binding domains with those from non-related proteins has been reported. The incorporation of lectin or antibody into liposomes is being examined as method for targeted toxin delivery to specific cell types in novel therapies. The use of phage display for the production and selection of target specific antibodies for use in immunotoxins has also been widely reported.

30. There is increasing interest in the potential of transgenic plants for use in vaccine production, introducing the foreign gene by means of plant viruses. There have been reports of animal trials with plant vaccines for Hepatitis B virus, rabies virus, respiratory syncytial virus and HIV virus, and clinical trials have probably now started. Much of the work has concentrated on the use of edible plants, with two prospective benefits: that purification can then be minimised or avoided; and that the stimulation of mucosal immunity resulting from oral delivery may provide enhanced protection against infections that invade through the mucosa.

31. There have been reports of a number of national development and procurement programmes for vaccines required for 'consequence management' of biological attacks by state or terrorist actors. Announcements by the Joint Vaccine Acquisition Program (JVAP) in the US Department of Defence in 2000 indicated that it is seeking sources for several vaccines as a stockpile to protect US forces against BW. Vaccine requirements now on the JVAP list now include ricin, tularemia, smallpox, botulinum toxins (multivalent, recombinant), Venezuelan equine encephalitis, and the next generation anthrax vaccine. The new generation of smallpox vaccines use the same vaccinia strain as the old but grown in animal cell lines rather than recovered after scarification of animals. In the UK, the Ministry of Defence announced in March 2001 that it had received new supplies of anthrax vaccine, and planned to resume its programme of voluntary immunisation against anthrax for armed forces personnel deployed to the Persian Gulf. For many of the putative BW agents, the development of vaccines continues to suffer from the lack of surrogate animal markers of efficacy, and phase III clinical trials cannot be mounted because of the absence of human population groups naturally exposed to the disease.

32. There has been marked progress in the development of anti-viral drugs since the last Review Conference. Acyclovir, one of the most successful drugs against herpes viruses, has been an approved in an ester form for oral delivery. Cidofovir is currently used for the treatment of cytomegalovirus retinitis in AIDS patients. It has been shown to have activity *in vitro* against smallpox, but it has the disadvantage of high toxicity, which can lead to renal failure, and thus it is unlikely to be a realistic candidate for use in an outbreak of smallpox.

33. The targets for new candidate antiviral drugs include inhibition of a number of different functions: cell entry; viral protease; viral nucleic acid synthesis and processing; regulatory proteins; and viral release. Many of the most promising new drugs have relatively specific activity against viral agents, which generates the need for development of specific virus diagnostic tests. For antibacterial compounds, there has been continuing development of the older class of broad-spectrum antibiotics, with the objective of extending the spectrum of action and improving their efficacy against organisms resistant to the parent compound. Some new antibacterial drugs tend to have narrow spectrum activity: daptomycin, which acts by disrupting gram positive cell membranes, is an example. The first compound in the new class of oxazolidinones, linazolide, is active against gram positive bacteria and has been particularly useful in treating skin infections and pneumonias.

34. A number of other approaches to antimicrobial therapy are being explored, including immunodulators such as cytokines and non-specific immunostimulators. An example of the latter is ridostine, an RNA -salt preparation that has been reported to stimulate interferon production and to be beneficial in treating herpes virus and other urogenital infections. To date, the only drug with a proven track record is Inteferon-alpha, which is used in AIDS therapy. Other interferons are likely to find applications in the future, perhaps for use in conjunction with antibiotics in treating tuberculosis.

35. In the long term, these technical developments must increase the potential for development of improved vaccines for use to protect armed forces and civil populations against BW attack by state or sub-state actors, and for use in related consequence management.

Recombinant protein expression

36. Development of recombinant DNA techniques has facilitated the integration of “upstream” gene cloning methods with “downstream” protein purification methods. Production of recombinant proteins has developed significantly over the last five years with a vast choice of cloning and host systems now available. Hosts include bacteria, yeast, plants, filamentous fungi, and insect and mammalian cells. The new developments allow the expression of proteins with increased yield and solubility, tight transcriptional control, optimised codon usage and directed protein localisation. Developments in cloning technologies have included availability of high fidelity thermostable polymerase enzymes, pre-dispensed PCR reagents, ligase free cloning systems and cell free expression systems. Such high throughput systems significantly reduce time scales for the initial steps in protein expression and expression screening.

37. Affinity chromatography purification matrices are used for protein purification to produce high yields of specific product. The area of protein purification process development has seen major advances in instrumentation. There are now a range of platforms that can be used for

research laboratory based purification and characterisation of bio-molecules through to scale up and optimisation for industrial production. These instruments offer a high level of automation, with pre-programming that minimises run times and allows method scouting to achieve optimum conditions.

38. An example of a new technology with great potential for directed evolution is applied molecular evolution technology (DNA shuffling). DNA shuffling allows the generation of large libraries of chimeric and mutated hybrids of genes, genomes, plasmids and viruses. Target DNA is randomly fragmented and reassembled to create a large number of recombinants that can be screened for novel or desirable properties. The primary application so far has been the rapid development of proteins for a wide variety of industrial applications such as enzymes with altered substrate affinity and stability. DNA shuffling can also be used to generate novel vaccine antigens for protection against pathogens. Such a technology could be used to develop both toxins and pathogens with altered properties.

39. All these developments mean that proteins previously difficult to produce or extract on any scale can now be expressed relatively easily. With this technology it is relatively easy to produce toxins and toxin sub-units rapidly on a large scale using basic laboratory skills. Although many of these recombinant proteins may be used as vaccines and other therapeutics, there is also the potential to produce toxins and other protein agents with enhanced properties for offensive use as weapons, and on scales which are far beyond those allowed by the natural sources of the molecules.

Toxins and other bioactive molecules

40. The structure of many more toxins has now been elucidated, and the different functions of their sub-units are increasingly known. Most microbial toxins (or their sub-units) have been cloned into micro-organisms and this technology is now well established. Cloning and expression of animal toxins is as yet not as advanced, but the past five years have seen a large increase in studies where animal venoms have been expressed in *Escherichia coli*, *Pichia pastoris* or baculovirus expression systems. The range of expression vectors, host strains, purification systems and protein engineering systems available have greatly increased the potential to express toxins with enhanced toxicity.

41. Research into scorpion, snake and spider venoms is widely reported in the literature with the emphasis either on anti-venom research or use as tools for studying membrane transport systems. The potential use of the animal toxins as BW agents has previously been thought unlikely due to the difficulty of producing recombinant toxins in appreciable quantities. However, this could change as the cloning of more animal toxins continues.

42. Increasing attention is being given to developing medical applications of clostridial neurotoxins. The therapeutic use of botulinum toxin has been extended beyond its initial application in treating squint, to include a variety of neurological disorders associated with involuntary spasmodic contraction of muscles, cosmetic treatment of frowns and wrinkles, and to facilitate wound healing after surgery. Specific therapeutic uses for clostridial neurotoxins are being proposed based either on delivery and membrane binding functions of the heavy chain or on the light chain function of intracellular inhibition of neurosecretion. Botulinum neurotoxin

heavy chain offers opportunities for selective macromolecule drug delivery to the peripheral nervous system, and tetanus heavy chain to the central nervous system, which could lead to treatments for chronic pain.

43. The period has brought an enormous increase in knowledge about the structure of cellular receptors in man, animal and plants, and about the molecular basis of bioregulation, including immunomodulation. Many of the small bioactive molecules are proteins or peptides that in principle could be easily produced in recombinant micro-organisms or in transgenic animals or plants, making production on weapon scales increasingly feasible. There is also the possibility of misusing microbial vectors to deliver bioregulator genes or to cause bioregulator production directly in the warfare target.

Detection and identification technologies

44. Recent developments in molecular techniques particularly in the PCR have improved the potential for the rapid detection and identification of micro-organisms, including in the context of defence against biological attack. PCR techniques now allow highly specific and sensitive assays to be developed as a routine. With more rapid thermal cycling, PCR reaction times have been reduced from 2-3 hours to as little as 10 minutes. Although not yet available commercially, "DNA chips", microfabricated silicon PCR vessels that use the thermal properties of small volumes and silicon, have the potential to increase speeds even further. The second major improvement has been the advent of PCR instruments that combine thermal cyclers with a fluorimeter that can detect amplification by the incorporation of fluorescent components into the PCR chemistry. Taking fluorescent measurements during the amplification and thus measuring the reaction kinetics reduces analysis time and detection thresholds. These systems are now available, including versions for military and law enforcement field applications. Many of the developments improve the automation of PCR. Reagents are also now available in more convenient formats such as pre-prepared reaction cocktails and freeze dried "beads". Much of the commercial development has involved the use of robotics for laboratories needing to process large number of similar samples in parallel. These developments are not directly applicable to the biological defence objective, for which smaller numbers of samples need to be screened for a range of agents. However, some of the method improvements may be of value in a biodefence or arms control setting. For example, the closed tube assay format reduces the workload by removing many of the tedious steps, but at the same time it reduces the risks of sample contamination and thus improves the forensic utility of the technique.

45. Advances have been made in the detection and identification of closely related organisms to strain level in order to distinguish between, for example, virulent and non-virulent strains. Several gene probe methods have been reported for strain typing. Methods fall into two groups: those based on random approaches to identify differences and which require no prior knowledge of the organisms, for example random amplified polymorphic DNA and repetitive extragenic palindromic sequences analyses; and methods that target specific hypervariable regions, for example variable number tandem repeat analysis and insertion sequence analysis.

46. Detection methods are being developed which detect genetic targets indicating the presence of a natural or engineered pathogen. Genetic targets being studied include sequences related to common infection mechanisms and pathways, and sequences common to virulent

pathogens (for example pathogenicity islands, antibiotic resistance). Another type of target could be genes that confer environmental stability to organisms, such as sporulation genes, and genes for capsules and resistance to desiccation. The presence of genetically engineered organisms has also been detected by identifying sequences specific to commonly used cloning vectors.

47. Although antibody technology has progressed steadily over the preceding five years with antibody based biosensors becoming significantly smaller, such technology is still not truly man-portable. The UK national biological defence research and development programme has developed the Prototype Biological Detection System (PBDS), which utilises two antibody-based biosensors for environmental aerosol monitoring. Antibody based detection of toxins and confirmation for a panel of candidate BW agents has been successfully fielded by relatively inexperienced operators.

48. The majority of antibody based detection techniques utilise monoclonal murine immunoglobulin G (IgG) or polyclonal IgG fractions from larger animals. Advances in *in vitro* production of monoclonal murine IgG have been made over the last 5 years, partly because of increasing ethical and regulatory pressures in some countries for a ban on production in ascites tumours. Although hollow fibre technology for IgG production is not a new phenomenon, work has progressed to improve and further understand the secretion of IgG from hybridoma cell lines within these bioreactors. Bioreactors based on cell and product compartmentalisation via molecular weight cut off membranes have been developed and offered as alternatives to ascites production for the sub- 500 mg production market. These systems have reduced the cost of laboratory scale IgG production.

49. Expectations of a tightening of governmental regulations for the export of products containing bovine material have stimulated improvements in media for serum free antibody production. Many assays based on IgG previously produced by ascites may need to be re-optimised as users report a change in characteristics of IgG produced *in vitro*, and perhaps again later when there is a move to serum-free production. Attention is also being given to the use of recombinant technology to move away from production in animal cell lines, and there has been reported expression and purification of fully bioactive whole IgG in plant cells. A major step forward will be the expression of bioactive whole IgG from yeast or bacterial systems as this will make antibody production and purification cheaper, simpler and more reproducible. Single chain antibody can now easily be produced in bacteria.

50. So-called, "Dipstick" hand-held assays based on antigen-antibody specificity have become more widely available. These assays tend to be rugged, readily man-portable devices that have been used to good effect in difficult diagnostic environments. One of the most sensitive designs relies on antibodies adsorbed onto the surface of colloidal gold particles, which give a visual indication of result. These assays have been used with blood samples for the diagnosis of leprosy, bubonic and pneumonic plague, and malarial parasites. Detection of *Bacillus anthracis* bacteria in environmental samples within 15 minutes using immunogold dipsticks is now possible.

51. Considerable progress in ATP bioluminescence technology has been made over the last five years. In industrial contamination monitoring the trend has been towards simple to use and portable "one-shot" devices containing pre-packaged reagents. UK armed forces now have a generic detection capability based on this principle, providing on-line monitoring of micro-organisms recovered from aerosol particles. The key bioluminescence reagent, the luciferase enzyme, had previously been obtained only from fireflies caught in the wild, but has largely been replaced by a recombinant luciferase that is cheaper and more robust. Adenylate kinase (AK) assays are also being developed. These have allowed a hundred-fold improvement in sensitivity for generic detection, and can be designed as specific assays with limits of detection comparable to PCR. A technique using phage lysis coupled with AK has been developed to specifically detect live bacteria in samples.

52. An optical biosensor, the Resonant Mirror, has been fielded with UK forces. This allows on-line detection of aerosolised toxins. Response times of seconds are possible. A particular appeal is that the logistic burden for this system is low with a single array of detection antibodies immobilised on a sensor surface, allowing 24 hours of continuous monitoring. A matchbox sized surface plasmon resonance (SPR) biosensor is available commercially. Recent developments with a light-scattering SPR biosensor have shown the feasibility of multiplexed real-time detection of bacteria and viruses as well as toxins.

53. The last five years have thus seen the application of a wide range of principles which increase the accuracy, speed, portability and ease of use of detection techniques for field use in detecting biological attack, or for the subsequent identification of agents and toxins in environmental samples. Many of these developments also increase the potential for satisfying the high standards of forensic probity needed for any future sampling and analysis to increase transparency and even to address possible non-compliance concerns under the BTWC.

Human infectious disease patterns

54. Despite the energetic international response to the HIV/AIDS pandemic, HIV continues to spread. According to the WHO, AIDS is now the leading cause of death in Africa, and the fourth worldwide. Increasing incidence of AIDS in developing countries where tuberculosis (TB) is epidemic is expected to lead to significant new public health burdens.

55. There continue to be spasmodic outbreaks of emerging and re-emerging infectious diseases with a high morbidity and/or mortality. There have been outbreaks of Ebola in Uganda and neighbouring countries, and cases of Hantavirus in the Balkans. A new viral disease affecting horses, but communicable to man, was described in Australia and named Hendra. There have been very few human cases to date. Another emerging virus, named Nipah virus after the town in which it was first identified, killed over 100 people in outbreaks affecting pig farmers in Malaysia in 1999. The human cases were initially diagnosed as suffering from Japanese encephalitis, which causes similar haemorrhagic effects. The virus is thought to jump from pigs to humans, and hundreds of thousands of pigs were slaughtered to halt the spread of the virus. There was no evidence of human-to-human transmission, but the US Centers for Disease Control and Prevention classified the virus as a P4-pathogen.

56. There have been some significant outbreaks in developed countries. In New York there was an outbreak of disease caused by West Nile virus, apparently imported in an exotic bird. A rise in the incidence of tularemia in the Balkans has been put down to changes in the population of small mammals that act as the reservoir. Verocytotoxin producing *Escherichia coli* - the toxin is similar to shigatoxin - has a growing prevalence in animals and the environment, a development of concern given the selective impact of this pathogen on children and the old. The virulent *E. coli* strain 0157:H7 has been implicated in a number of outbreaks associated with a high mortality in humans. In spite of a number of surveys, it is still not clear how widespread it is in the environment. Sensitive tests that detect the E. coli in cattle have led to calls for more stringent cleansing methods for carcasses in abattoirs. Another food poisoning bacterium that continues to be difficult to control is *Campylobacter*, and in the UK it is now the single biggest identified cause of foodborne illness. Changes in the social structure in some countries, with the majority of armed forces now coming from urban areas, may result in populations with less natural immunity to diseases such as Q fever and psittacosis.

57. It is thus apparent that, even with well-developed public health regimes that can act quickly to detect and control outbreaks, human populations remain susceptible to natural disease outbreaks from a range of diseases. It follows that the chances of human populations being seriously affected by attack with a number of candidate BW agents remain high.

58. There have now been over 100 cases of variant Creutzfeldt-Jacob Disease (CJD) in the UK, and thus it has not (yet) reached the epidemic proportions that some scientists had feared. Increased knowledge about the natural production of prions, and the new molecular biology techniques for modification and enhanced production of proteins, have undoubtedly increased its potential for consideration as a warfare agent. The UK considers it important to recognise that the misuse of prions would contravene Article I of the Convention.

Smallpox destruction

59. Following the successful completion of the WHO's global project for the eradication of smallpox in 1980, debate continued about the need to maintain stocks of smallpox even if in a limited number of maximum containment (P-4) laboratories. Such stocks were argued to pose a potential attraction for a terrorist group, who might wish to use the virus against unprotected populations. By 1994, the WHO Ad Hoc Committee on Orthopoxviruses had reached consensus that the remaining stocks of virus, at the Centers for Disease Control and Prevention laboratories in Atlanta and the Russian State Research Centre of Virology and Biotechnology (VECTOR) in Koltsovo, should be destroyed. Concerns were however subsequently raised *inter alia* about the lack of an anti-viral agent for use in the event of a smallpox outbreak involving illegal stocks or overlooked natural sources, and that the current smallpox vaccine may not be safe for immunodeficient individuals. The 1999 World Health Assembly reaffirmed the decision to destroy the remaining stocks of virus, but authorised retention until 2002. It was also agreed that a further research priority programme be drawn up and carried out under the strict control of the WHO, and this research is now underway. Some observers have expressed concerns that smallpox cultures may be held outside the two designated laboratories.

Drug resistance.

60. Methicillin resistant *Staphylococcus aureus* (MRSA) has become a bacterium of great clinical significance in the US, Europe, and Japan, causing infections through open wounds that do not readily respond to antibiotic based treatment. The key genetic component of the resistance is not native to this bacterium, but the heterologous source of the resistance gene is not known. Studies of the genetic profiles and serotypes of strains recovered from outbreaks in several countries strongly suggest that the lineage extends back to the MRSA strains first reported in the early 1960s. MRSA is known to be a great problem in hospitals, but little is know about the incidence of antibiotic resistant bacteria in the normal population. Fears are now spreading that some new-born babies may have suffered from toxic shock syndrome caused by the bacteria's toxin. Recent UK studies reported multi-drug resistant bacteria in apparently healthy children and also that there was no reduction in levels of resistance to sulphonamide antibiotics despite a 45 fold reduction in the use of these antibiotics between 1991 and 1999.

61. Tuberculosis is a disease where multiple drug resistance is a recognised problem. The effects of the combination of AIDS and TB in some population groups is expected to be exacerbated by the multi-drug resistant TB strains which are evolving in prisons and poor communities when antibiotic regimes to treat standard TB cannot be carried through for the several months necessary. (There are several projects to develop a vaccine more effective than the 80 year old BCG vaccine - which often leaves more than 20% of a population unprotected). Drug resistance and the increasing world incidence of infectious diseases such as AIDS, malaria and TB has been cited to argue that tackling infectious disease should remain a priority and that funding should not be diverted to other pressing health needs, for example to address the rising incidence of chronic non-communicable disease in urban areas.

62. A technique that became outdated once antibiotics were developed but which may receive renewed attention in the future as a means to deal with antibiotic resistant bacteria is the use of bacteriophage (virus that infects a bacterium). One current disadvantage of known bacteriophages is that their use would depend on prior diagnosis of the bacterial strain.

63. The existence of so many naturally multiple drug resistant strains could greatly complicate the therapy of secondary (natural) infections in BW casualties.

Disease in agriculture

64. The globalisation of trade has brought with it a growing sensitivity of importers and consumers to the risks of animal and food borne diseases. The huge trade impact of outbreaks of disease in agricultural animals, with foot and mouth disease (FMD) of cattle as the foremost example, is clear to all. One major problem is the export of meat and other agricultural products for personal consumption or local sale, not declared to the authorities of the importing country. Such products can carry exotic human, animal or plant disease that can have a devastating effect. Though the cause of the 2001 outbreak of FMD in the UK may be difficult to establish with certainty, it is likely that the virus came into the UK through illegal importation of meat. The increased movement of people and agricultural products has also exacerbated the spread of economically damaging plant disease. Increased exportation of exotic plants, often not declared, has considerably complicated the job of plant regulatory authorities. In both animal and plant

disease, measures which prohibit trade with countries when a particular disease is reported leads to the concept of pest free areas, which demands survey work which can only be performed if there are internationally standardised analysis techniques used in accredited laboratories.

65. According to OIE statistics, 66 countries have reported infectious disease outbreaks due to emerging animal diseases during the last five years. Increasing attention is being given to mitigating the adverse effects of emerging animal diseases on livestock production, trade and public health. OIE initiatives include additional reference laboratories, revised international health codes (these are the standard texts used to promote the harmonisation of regulations for trade in animals and animal products), and co-ordinated international training programmes for managers of veterinary services.

66. Difficult weather conditions and persistent civil strife have caused exceptional food shortages in sub-Saharan Africa. On top of this, there is a growing realisation that many plant pests, which cause problems for trade within tropical or sub-tropical zones also, can threaten European countries through trade (and tourism) links. In the reverse direction, for countries that have diversified by fruit, vegetables and ornamentals production under the cooler conditions at high altitudes, there is a growing risk of damage from pests introduced from temperate regions.

67. The economic impact of Newcastle Disease and its effect on trade in commercial poultry in developed countries is well known, but experts also recognise the problem of the endemic presence of the disease in developing countries and the effect on village chicken production. Efforts have been made to introduce vaccination programmes in the form of heat resistant live vaccines, but experts advise that vaccination cannot resolve the problem unless matched by education programmes into disease spread and poultry husbandry.

68. Airborne spread is not generally regarded as being implicated in outbreaks of Newcastle Disease reported in recent years, and there has nearly always been a alternative, more likely, cause, particularly the movement of poultry and humans. For instance, in 1997 there were 38 outbreaks confirmed in poultry in the UK between January and April. Nucleotide sequencing and phylogenetic analysis showed close similarity between the UK isolates and virus responsible for outbreaks in Scandinavian countries the previous year, including a isolate from a feral goosander. Unusual patterns of movement of migratory birds at the end of 1996 and beginning of 1997 suggest that this may have been the vehicle for introduction of the virus into Britain. New knowledge of the molecular basis of pathogenicity of NDV have led to an OIE definition which differentiates virulent from avirulent virus on the basis of differences in a region of the F (fusion) protein of the virus. PCR tests based on this genetic difference however still need improvement.

69. Major outbreaks of avian flu in poultry with spread to numerous sites and huge economic losses continue to be reported, and occurred in Hong Kong in 1997 and Italy in 1999/2000. The high cost of vaccination, since only inactivated vaccines are available, means there is economic pressure to stop vaccination once the immediate threat is thought to have passed. Of the 18 outbreaks of Highly Pathogenic Avian Influenza between 1959-2000, in only two was vaccination used, and then in combination with increased biosecurity measures. The other 14 outbreaks were controlled by a rigorous slaughter and biosecurity regime. Although biosecurity measures in poultry farming are often regarded as costly and laborious by those involved, experts

recommend that they are an essential investment as a means to prevent the risk of introduction of avian flu and ND, as well as other endemic viruses that may affect the birds and reduce their yield.

70. An outbreak of *Thrips palmi* at a commercial site in the UK has been investigated, and an eradication programme completed.

71. In spite of some improvements in trade regulations for animal and plant products, and in diagnostic capabilities, the magnitude of the effects of natural disease outbreaks especially for animal diseases and the public awareness of this may well have increased the attractiveness of anti-animal and anti-crop BW to potential proliferators.

Pest control in agriculture

72. The peaceful use of micro-organisms as agricultural pesticides has expanded in developing countries since the last Review Conference, and the use of transgenic plants that have increased pest resistance is likely to be the most important innovation since the appearance of chemical pesticides in the 1940s. The genetic modification approach is seen by many as the best method for delivering the benefits of new crop technologies to farmers especially those in developing countries, where agricultural supplier and advice networks are often inadequate to channel new information, chemicals or equipment.

73. Genetically modified crops are being grown on a large scale in commercial agriculture in several countries, notably the United States, China, Canada and Argentina. In one type of modification, genes for an insecticide toxin of *Bacillus thuringiensis* (Bt) are inserted into crops. This modification allows the plant to produce the toxin and thus kill insects that feed on it. Data for 2000 indicates that, of the 29 million hectares of genetically modified crops grown in the USA, Argentina and Canada, 24% was transgenic maize (corn) or cotton hybrids containing *cry* genes derived from Bt. China, Mexico and Australia are also major growers of these Bt crops, and commercial production in India is planned. In many cases Bt crops allow use of chemical pesticide to be reduced, and there have been reports of significant increases in yields and profits. The chemical pesticides are still needed to control populations of secondary pests, such as aphids, plant bugs and thrips.

74. Direct application of Bt formulations as an insecticide has continued, but its share of the world pesticide market has been stable at around 1-2% in the last decade. Bt is a naturally occurring soil bacterium, and although not regarded as a human pathogen there is a report of the isolation of the bacterium, though not a serotype used in agriculture, from the wound of a severely injured soldier. Potential concerns about the risks to human health arising from the conventional spraying of Bt formulations, a technique in use as long as 40 years ago, have stimulated a very large number of laboratory and epidemiological studies, and more recently such studies have addressed the possibility of allergic responses to Bt transgenic plants. Increases in human antibody levels following exposure to Bt products have been reported, but there was no increased incidence in asthma or other illnesses, and many experts conclude that there is no reason to doubt the safety of Bt insecticides.

75. There has been increasing attention to the development of other pesticides produced using fermentation techniques, though no new products are yet in routine use. The potential for use of fungi in the field as opposed to glasshouse situations has increased as a result of improved formulation technology. The constraint of high humidity has been overcome in some cases, facilitating the use of fungi as insecticides in dry climates such as deserts, for example for locust control. An advance with major significance for crop protection is the demonstration of the use of fungi to produce the spinosyn group of insecticides. These molecules have high activity against pests that are resistant to conventional chemical insecticides, but appear to be very safe for man. The avermectin insecticides that are produced by *Streptomyces* have been used for some time but appear to have more limited potential.

76. A continuing problem that is deemed to erode confidence in microbial based control agents is the variation in performance in the field caused by variable quality of the formulations used. The lack of quality control in manufacture, even when low technology methods are used, damages the reputation of the technology and also may pose health risks to workers in production plants or to people exposed in the field. Experts in developed countries are contributing to initiatives to improve manufacturing quality control worldwide.

77. In the past five years there has been progress in developing commercial bioinsecticides in the US, EU, India and South Asia which make use of insect viruses primarily of the nucleopolyhedrosis viruses (NPV). Overseas aid from the UK has funded projects to develop an NPV industry in India, and viral pesticides to control army worm and diamond back moth in parts of Africa. Currently, NPV is produced commercially *in vivo* in several countries worldwide, and the future will see *in vitro* production in fermenters of up to 20,000 litres.

78. Some of the above technologies, including microbial manufacturing plants and field delivery systems, could be misused in illicit BW programmes.

Global initiatives to tackle disease.

79. The threat caused by the increasing globalisation of disease has been recognised by the key international bodies concerned with addressing human, animal and plant disease. By the turn of the millennium, a number of important global initiatives and partnerships in disease prevention and control had been created. These are relevant to Article X of the Convention.

80. The 1995 World Health Assembly decided to revise and update the WHO International Health Regulations, the legal framework for WHO's alert and response activities. As the first step in the revision process, the idea to replace disease-specific reporting with a system of syndromic reporting was field tested. The scheme was not taken forward because of difficulties in reporting syndromes in the field, and because syndromes could not be linked to preset rules for control of spread. There are still only three diseases for which reporting is mandatory to the WHO, cholera, plague and yellow fever.

81. WHO figures indicate that HIV has now infected 58 million men, women and children, with 22 million deaths. It is recognised that a safe, effective vaccine suitable for use especially in developing countries is badly needed to complement existing prevention strategies. WHO and the UN Programme on HIV/AIDS (UNAIDS) have joined forces to establish a new HIV Vaccine Initiative.

82. The WHO Vaccine Preventable Diseases Monitoring System collects, compiles and disseminates data officially reported by WHO member states, on the incidence of vaccine preventable diseases and on immunisation coverage. There are a number of significant international initiatives to accelerate the introduction of new and under-used vaccines, aiming to address the practical difficulties of strategy development, logistics, funding, supply and quality control. The UN has set up a Global Health Fund to tackle HIV, malaria and TB, and the manufacturers of the expensive TB drugs have agreed with the WHO to supply at cost price to poorer countries. The Global Alliance for Vaccines and Immunisation is an alliance which includes governments**,** intergovernmental bodies such as UNICEF, WHO and the World Bank, philanthropic institutions, and trade associations. With resources for 2001 -2005 in excess of US $ 1 billion, the Fund will help to provide new and under used vaccines and the means for delivery in the field, as well as funding to help governments strengthen their basic immunisation services. Under utilised vaccines include those for rubella and yellow fever, and the new vaccines being considered include hepatitis B, *Haemophilus influenzae* type b (Hib), and the pneumococcal conjugate vaccines.

83. After the successful eradication of smallpox, efforts continue to eradicate polio by 2005, concentrating on the 20 or so countries where it still occurs. Objectives include obtaining sufficient finance and political support, and particularly to secure access to immunise all children including those in areas affected by conflict.

84. The WHO has recognised that trade is often adversely affected when certain public health risks occur, and has set up links with the WTO Committee on Sanitary and Phytosanitary Measures. Other new joint initiatives have included WHO, FAO and OIE consultations on BSE (bovine spongiform encephalopathy), that considered issues of public health, animal health and trade. The BSE talks recommended that BSE and the human disease variant CJD should be considered as an international issue because potentially infected BSE materials have been distributed throughout the world through trade of live cattle, cattle products and by-products. Countries should take care not to be complacent about their risk from BSE. The meeting stated that the extremely low initial incidence and limited clustering of BSE cases, protracted latency and non-specific nature of the early clinical signs of BSE tend to mask the severity of the problem.

85. An OIE/FAO joint conference in April 2001 on FMD passed resolutions which *inter alia* recognised that strengthening of veterinary services and the creation of international control and eradication programmes for epizootic (animal) diseases was not only in the interests of developing countries but also would reduce the risk of spread of such diseases worldwide.

86. The Global Rinderpest Eradication Programme has a target to eradicate rinderpest worldwide by the year 2010. Only three small reservoirs of rinderpest remain, in Asia and Africa, but FAO experts are concerned that there is now a high vulnerability to epidemic resurgence, which demands renewed attention to elimination of the last reservoirs of disease and management of the cessation of vaccination.

87. Since the 1995 Agreement on the Application of Sanitary and Phytosanitary Measures of the WTO came into effect, many southern countries have found difficulties in meeting the extra burden and resource implication for their phytosanitary services. The 1997 revision of the International Plant Protection Convention (IPPC) emphasises the International Standards for Phytosanitary Measures and the procedures of Pest Risk Analysis (PRA), which allow import decisions to be based on scientific evidence. However, the revised IPPC has not yet received sufficient signatures to come into effect, and the lack of meaningful international guidelines for PRA five years on is causing concern. Regional Plant Protection Organisations have however been set up as co-ordinating bodies in the various geographic regions, and to gather and disseminate information and promote standards.

Molecular biology applications and crops.

88. New arthropod targeted transgenic crops and trees are being developed: this includes a transition from single to multiple Bt toxin genes, and use of entomopathogens such as bacterial *Xenorhabdus* species and the *Heliothis* stunt virus. Bt toxin expression can be increase markedly by engineering the toxin genes into the chloroplast, where toxin yields can amount to up to 50% of the chloroplast proteins. Despite the enthusiastic uptake of such technology, there are concerns regarding the potential adverse effects to human health and to the environment, and its application in some countries has been subject to government scrutiny and regulation.

89. There have been a number of projects to increase the efficacy of viruses as insecticides by incorporating genes for toxins, diuretic hormones or other genes that enhance the virus killing power. The engineering of scorpion toxin into baculoviruses is well known approach, and other polypeptides are also being considered - for example, peptides from the venom of the parasitic wasp *Bracon hebetor*. Recently, genetic modification has been used to increase the pathogenicity of baculovirus.

90. Genetic modification technologies are likely to become the primary route to producing new varieties of plants with resistance to diseases. An increasing number of projects involve incorporation of viral genes, using the promoter sequences of the virus in conjunction with the coat or movement proteins genes to build in virus resistance. Environmental impact needs careful consideration because such genetic engineering results in incorporation of viral genomes throughout the tissues of the plant, which could create opportunities for recombination with wild viruses leading to unwanted changes in their pathogenicity,
host range etc.

91. Genetically modified potatoes with resistance to potato virus Y and potato leaf roll virus have been developed, but are currently not believed to have significant commercial appeal because of public reticence about engineered foods. The UK government and other international donors are funding the development of rice with resistance to yellow mottle virus by incorporating RNA polymerase genes into the rice.

92. Gene silencing is a technique that makes use of the plant's natural anti-viral defence system. A systemic signal molecule is produced in the plant, along with short RNA molecules that are homologous to the target in the host DNA. This methodology has been developed at the Sainsbury Laboratory in the UK and is marketed. Plant virus vectors are used; they carry fragments of host plant DNA throughout the plant as they replicate, and the gene in question is silenced.

93. There have been great improvements in antibody based diagnostic tests for plant viruses, and dipstick tests developed in the UK for a number of viruses are now used in the field by plant health inspectors. Antibody tests are also used to monitor Bt toxin expression in genetically modified crops.

94. Genetic typing has also improved the direction of classical techniques for breeding disease resistant crops. An example is a attempts to reduce the impact of more virulent strains of the potato fungus *Phytophthora infestans* which have reduced yields world-wide in recent years. New varieties of potatoes have been bred by crossing with Peruvian wild type potato subspecies *Solanum tuberosum andigena* to make use of its resistance genes.

95. Genetic typing (genetic fingerprinting) carried out in investigations of animal and plant disease outbreaks provided new insights into the relationships between outbreaks in different countries and over a period of time. An example for the typing of Newcastle Disease in birds has been given above. An example for plant disease comes from the recent published finding that the strain of the fungus *Phytophthora infestans* which caused the Irish potato famine in the 19th century lacks a gene sequence found in the modern strain 1b, and this overturns the classical theory that 1b is directly descended from the Irish strain.

96. New insights into the interactions between micro-organisms and plants unfortunately will also increase the potential for design of anti-crop agents with improved properties such as a broader infection window in the life cycle of the plant. On the other hand, advances in diagnostic capabilities should make it easier to distinguish natural and unnatural outbreaks of infectious disease.

Trends in protein production technologies

97. The huge increase in the number of biotechnology ideas in the research stage has not been matched by an increase in the manufacturing capacity for the ultimate products, and in developed countries this has led to significant queuing times for the limited contract manufacturing slots. Very few new products are made by extraction from natural sources. A factor contributing to this bottleneck is the change in type of protein product in development, to antibodies - made by growing tissue culture cell lines, often in fermenter vessels. In the 1980s many drugs based on monoclonal antibodies failed to reach their potential because their repeated use led to immune

reactions to the foreign protein. A number of antibody based drugs recently launched may have largely circumvented this problem by using humanised antibody from genetically transformed cell lines or murine/human monoclonal chimeric antibody. A current estimate is that there are more than 70 monoclonal antibodies in various stages of clinical development, amounting to about 20% of all biotech drugs in development. These large and complex proteins are often poorly expressed, difficult to recover and purify, and the typical dose is up to a hundred-fold more than for a hormone or enzyme. Their production demands large fermentation and downstream processing systems. Of the licensed biological products that are produced in cells, about half come from micro-organisms and half are made in cell lines of human or animal origin.

98. The increased experience in production of antibodies suitable for human administration has increased the potential for manufacture of therapeutic antisera in dealing with significant outbreaks of bacterial disease for example after a BW attack.

99. Early ideas for pharmaceutical production in transgenic animals or plants have been slow to come to fruition. Transgenic animals may yet have considerable potential for production of high volume products, for example in cows' milk. Disadvantages are long development times, and difficulty in ensuring and demonstrating the absence of risk from transmissible spongiform encephalopathies caused by prions. Transgenic plants could also provide large quantities of material, but aberrant glycosylation could complicate the development of some products. Tobacco mosaic virus is often used as a virus vector: it spreads rapidly and systemically in the plant to give high yields of protein, and the fact that it is not seed or pollen transmitted and not vectored by insects gives a low risk of unwanted spread from the host crop. Using this technique, companies in the US claim to have produced experimental batches of hundreds of different proteins from ton quantities of infected crops, and there are reports of plans to scale up to thousands of acres. Avian transgenics may also be promising as a production vehicle: the production of eggs on a large scale is already well organised world-wide in vaccine industries; sterile separation methods are well developed; and glycosylation is unlikely to be a problem. Any of these new production routes could however, also be misused to produce significant quantities of proteins or peptides for use in BW.

International co-operation and biosafety: activities under the Biodiversity Convention

100. The Convention on Biological Diversity, one of the main outcomes of the 1992 Rio Earth Summit, is now well established and increasing its impact. The UK is the fifth largest donor to the Global Environmental Facility, a financial mechanism set up under the Convention to provide resources and expertise for projects which assist developing countries in biodiversity conservation and sustainable use. The UK also supports such work bilaterally and through the UK's Darwin Initiative. An example of a microbiological project recently completed under the latter is the three year Darwin Project on Caribbean Fungi. This was intended to raise the profile of fungi in the Caribbean, by using Cuban expertise and developing Trinidad and Tobago expertise. Scientists from the UK's International Mycological Institute delivered equipment, conducted field work, and trained staff in Cuba and Trinidad. National strategies were developed, a guide to the identification of microfungi on sugar cane was produced, more than 9 data bases developed, and hundreds of culture collections were enhanced. The infrastructure for a regional identification service is now in place.

101. The Cartagena Protocol on Biosafety to the Convention was agreed in January 2000. It aims to guard against risks to biodiversity arising from transboundary movement of living modified organisms (essentially, genetically modified organisms). Provisions under the Protocol introduce requirements prior to export of "living modified organisms" (LMOs) including commodities for food, feed and processing. An intergovernmental committee is currently developing arrangements for implementation. Key aspects of the Protocol are public access to science and information and public participation in debate on biosafety issues. A publicly accessible, Internet-based "Biosafety Clearing-House" will enable the exchange of scientific and other information about traded LMOs, while a "roster of experts" will give Parties access to scientific expertise to make informed decisions on the import of LMOs. The Protocol also requires Parties to consider, in consultation with other relevant international bodies, the potential elaboration of standards on the identification, handling, packaging and transport of LMOs. Parties are also due to consider the possible need for rules and procedures on liability and redress for damage resulting from transboundary movements of LMOs. Finally, the Protocol places an emphasis on "capacity building", whereby developing countries are assisted in developing the necessary legal, institutional and technical frameworks for effective implementation of the Protocol.

Means of delivery of agents or toxins

102. While there has been work on developing new application techniques for microbial pesticides including electrostatic sprayers, their uptake has been very limited. Most application of microbial pesticides is still through traditional hydraulic or spinning disc systems. However, the potential for effective delivery of biological agents or toxins as weapons has undoubtedly increased because of the increasingly widespread availability of long range missiles, sub-munitions and high specification multi-barrel rocket launchers which could be modified to deliver biological weapons.

Use of pathogens to control weeds and 'criminal' crops

103. Over 100 microbial pathogens of plants have been identified as potential biocontrol agents for weeds, but only a handful have entered commercial use and then only on a limited scale. Examples are the biocontrol of tough grasses, and a fungus that prevents weed growth from tree stumps. Practical difficulties typically include slow speed of action and poor selectivity for host.

104. A number of countries are involved in supporting the UN Drug Control Programme in projects to develop pathogens for release as a specific bioherbicide against 'criminal' drug crops such as coca, opium and marijuana. The fungus *Fusarium* is being considered for use against coca plants from which cocaine is manufactured, and another fungus, *Pleospora papaveracae*, is being considered to attack opium poppies. NGOs have raised concerns about whether the possible effects of persistence in the environment including unforeseen genetic transfers or infections of other plants are being thoroughly addressed. The UK believes that the use of biological agents or toxins for control of criminal crops should be discussed at the forthcoming Review Conference.

Bioremediation: the destruction of materiel

105. Studies of the potential for the release of specific micro-organisms into the environment to destroy pollutants continue. An example is the destruction of residues of ethylene diglycol (antifreeze) after its use on airport runways and aircraft. Critics of this approach have been concerned about the potential for gene transfer to the gene pool of natural organisms. Field trials attempting to address such concerns have included the release of bacteria into which had been engineered the marine bacteria bioluminescence *lux* gene, allowing the spread of the trial bacteria to be monitored with a hand held light detector. While no microbial bioremediation methods have been adopted for the large scale destruction of chemical agent in national munition destruction programmes related to the provisions of CWC, interest has continued in the potential of micro-organisms for neutralising residues of CW agents in environmental samples. For example, micro-organisms capable of utilising thiodiglycol (a breakdown product of mustard) have been isolated.

106. Bioremediation technologies clearly have the potential for development as a means of warfare or for hostile use against materiel crucial for normal civilian life or military operations, such as oils, rubbers and plastics.

Countering the threat of BW terrorism

107. In the wake of the Aum Shinrikyo's attempts at bioterrorism in 1995, several countries have taken significant measures to increase their ability to counter the use of biological agents by terrorists. Measures include increased funding to study diseases affecting human or animals and to develop pathogen and toxin detection devices; planning for procurement and stockpiling of vaccines to protect armed forces and civil populations; and regional and natural contingency planning and training which co-ordinates the activities of civil emergency and police services, health authorities and specialist scientist advisers. In the United States, the objective of preventing unauthorised attempts to obtain pathogens and toxins from legitimate laboratories was one of the rationales for a new national system to register laboratories and licence the acquisition and transfer of 'select agents' on a list, with appropriate research and clinical exemptions. Also in the US, the Advisory Committee on Immunisation Practices in February 2001 produced new draft guidelines on the use of smallpox vaccine in the event of an outbreak of smallpox, in the context of bioterrorist use of the agent. Government studies to assess the threat of bioterrorist attacks have included a Canadian study of the threat of use of FMD virus, and a Japanese study which listed 20 bacterial and virus species, including smallpox.

108. National anti-terrorist programmes where significant funding is being applied to the procurement of detection and medical countermeasures may also be expected to improve national preparedness against BW attacks by other states.

Impact of the entry into force of the CWC

109. There has been a major increase in industrial uses of micro-organisms or their extracted enzymes to catalyse single steps in chemical manufacturing processes otherwise based on conventional chemistry. These applications, known as 'biotransformations', mostly focus on production of intermediates where a directed chirality is required. This reflects a large increase

in the number of small molecule drugs where chirality is realised to be important for the therapeutic effect. When whole micro-organisms are used they are often produced on the chemical production site, but isolated enzymes are often bought in from specialist manufacturers. Facilities using biotransformation are likely to be encountered in future plant site declarations under the Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction (CWC).

110. The CWC, which entered into force on 29 April 1997, in effect precludes the development, production or use of chemicals as weapons against man or animals. The so-called general purpose criterion of the CWC covers any toxic chemical or its precursor, regardless of its origin or method of production, and so there is considerable overlap with the BTWC. Two toxins, ricin and saxitoxin, are included in the Schedules of chemicals, and as they are in Schedule 1 of the Verification Annex they are subject to licensing and declaration provisions, and limitations on transfers, which are permitted only between States Parties. The Schedule 1 entries for these two toxins are limited by CAS (Chemical Abstracts Service) numbers, which for saxitoxin does not cover a number of forms of the toxin that could be of concern. To the UK's knowledge, no uncertainties have been identified about either of these toxins during inspections of Schedule I facilities by officials of the Technical Secretariat of the Organisation for the Prohibition of Chemical Weapons. The CWC also provides for declaration and inspection of certain chemical production facilities not producing Scheduled chemicals, under the category of Other Chemical Production Facilities (DOC facilities). The UK is not aware that any facilities producing chemicals by use of fermentation technology, whether toxins or any other molecules, have been declared as DOC facilities, nor does this seem likely at present given the DOC declaration threshold of 200 tonnes (30 tonnes where the chemical contains the elements phosphorus, sulphur or fluorine). In our view, any measures, which may evolve under future agreements to strengthen the BTWC, and which are designed to provide transparency for national activities, should involve many more toxins than the two covered by the Verification Annex of the CWC.
