

**World Health Organization**  
**Technical Report Series**  
**No. 26**

**EXPERT COMMITTEE ON**  
**ANTIBIOTICS**

**Report on the First Session**

*Geneva, 11–15 April 1950*

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WORLD HEALTH ORGANIZATION  
PALAIS DES NATIONS  
GENEVA  
OCTOBER 1950

## EXPERT COMMITTEE ON ANTIBIOTICS

### First Session

#### *Members :*

Professor E. B. Chain, F.R.S., Professor of Biochemistry, Istituto Superiore di Sanità, Rome, Italy (*Chairman*)

Professor R. V. Christie, Professor of Medicine, University of London; St. Bartholomew's Hospital, London, United Kingdom (*Rapporteur*)

Professeur M.-M. Janot, Professeur à la Faculté de Pharmacie de l'Université de Paris, France (*Vice-Chairman*)

Professor H. Theorell, Professor of Biochemistry; Director, Section of Biochemistry, Nobel Institute of Medicine, Stockholm, Sweden

Professor S. A. Waksman, Chairman, Department of Microbiology, Rutgers University, New Brunswick, N.J., USA

#### *Secretary :*

Dr Mélanie Craipeau, Co-ordination of Research Section, WHO

The report on the first session of this committee was originally issued in mimeographed form as document WHO/Antib/8, 19 April 1950.

## EXPERT COMMITTEE ON ANTIBIOTICS

### Report on the First Session<sup>1</sup>

The Expert Committee on Antibiotics held its first session in Geneva from 11 to 15 April 1950.

The session was opened by Dr Brock Chisholm, Director-General of WHO.

At its first meeting, the committee unanimously elected Professor E. B. Chain as Chairman, Professeur M.-M. Janot as Vice-Chairman, and Professor R. V. Christie as Rapporteur.

The agenda submitted by the Director-General was adopted.

The committee had been established, in accordance with the decision of the Executive Board at its third session, "to deal with research in this subject [antibiotics] and in technological problems in general".<sup>2</sup>

The First Health Assembly provided that:

"the immediate object of WHO in this field should be to make technical knowledge on penicillin production available to countries contemplating

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<sup>1</sup> Acting on behalf of the Executive Board, the ad hoc committee of the Board adopted the following resolution:

The ad hoc committee of the Executive Board

1. NOTES the report of the Expert Committee on Antibiotics on its first session;
2. AUTHORIZES its publication;
3. APPROVES the recommendations given under Section 1, Difficulties in Production of Antibiotics; Section 2, Facilities for Training and Research; Section 4, Abstracting Service on Antibiotics; and Section 5, Type Culture Collections;
4. EMPHASIZES
  - (1) the views expressed by the committee concerning the use of Podbielniak extractors (section 1.2), and
  - (2) the importance of providing training facilities for scientists and technologists (section 9);
5. REQUESTS the Director-General to take the necessary steps to implement the recommendations set out in the sections mentioned above;
6. TRANSMITS the report to the Third World Health Assembly, and
7. POINTS OUT that recommendations of expert committees which concern WHO policy and operations remain recommendations unless and until they are implemented by the Executive Board or the World Health Assembly in adopting and putting into action the annual programme of WHO.

<sup>2</sup> *Off. Rec. World Hlth Org.* 17, 13

the erection of plants ; to facilitate procurement of penicillin for countries unable to obtain this and similar drugs.”<sup>3</sup>

The committee understood that its first task was to advise on how technical information for the design, installation, and initial operation of plants, and how continued training and research in the production of penicillin and other antibiotics could best be given to countries in need of this type of assistance.

### 1. Difficulties in Production of Antibiotics

The committee carefully considered the difficulties which prevented certain countries, particularly those of Eastern and Central Europe, and some underdeveloped areas, from undertaking the production of antibiotics, particularly of penicillin. Three principal factors appear to be involved :

#### 1.1 *Design of antibiotic plants*

As regards the design of plants, the committee was of the opinion that the Member States concerned could approach private firms. A number of private firms, both in Europe and the USA, are in a position to provide this assistance on commercial terms.

If for any reason this avenue were not open to a Member State, an alternative would be to utilize the training facilities referred to in section 2.<sup>4</sup> As the methods of penicillin manufacture are now so standardized, a team of competent scientists and technologists trained in microbiology, microbiological engineering, etc., at the suggested national centres would be able to design its own plant.

#### 1.2 *Procurement of equipment*

The difficulty of procuring essential equipment, such as the Podbielniak extractors for penicillin production and certain types of stainless-steel equipment for streptomycin production, was a serious obstacle in various countries to the construction of efficient antibiotic plants. The committee considered other possible uses of the Podbielniak extractors, e.g., for the concentration of toxins for bacteriological warfare, and was of the unanimous opinion that at the present state of knowledge the extractors could not be used for such purposes. The committee considered that serious

<sup>3</sup> *Off. Rec. World Hlth Org.* **18**, 164

<sup>4</sup> See page 6.

harm had already been done to the prestige of WHO through its inability to help various governments to obtain this essential equipment.

### 1.3 *Personnel*

The difficulty of obtaining highly trained personnel capable of designing and running penicillin and other antibiotic plants is, in the opinion of the committee, the most serious obstacle to any increase in the production of antibiotics in different countries. The committee considered that the greatest contribution WHO could make towards the solution of this problem would be to implement the recommendations of the committee regarding training referred to in section 2.

Possibilities should be created for Member States to make full use of the training facilities available and to study ways and means of extending such facilities. The committee was of the opinion that the best way of increasing the production of antibiotics would be by stimulation of basic research in this field. Although financial charges would obviously be involved, the committee considered that they would be relatively small and fully justified by the results.

The committee adopted the following resolutions :

#### I. The Expert Committee on Antibiotics,

Considering that, in the view of the committee, Podbielniak extractors are absolutely essential for the economic production of penicillin, and that certain types of stainless-steel equipment are necessary for the production of streptomycin,

##### RECOMMENDS

1. that the World Health Organization should do everything possible to assist Member States to procure these essential items of equipment ; and
2. that, in particular, where inability to obtain the necessary currencies is an obstacle, WHO should provide assistance in collaboration with the economic organs of the United Nations.

#### II. The Expert Committee on Antibiotics,

Considering that the best way to increase world production of antibiotics is to extend training facilities,

RECOMMENDS that the World Health Organization assist Member States to use to the full the training facilities recommended in section 2 of this report for creating teams of highly trained scientific and microbiological engineers.

## 2. Facilities for Training and Research

The production of antibiotics involves methods of microbiology, chemistry, microbiological engineering, and pharmacology, a combination which requires training and research facilities far beyond those offered by most universities.

The committee, therefore, adopted the following resolution :

The Expert Committee on Antibiotics

### RECOMMENDS

1. that the World Health Organization grant fellowships to persons with a sound knowledge of chemistry, engineering, or microbiology, for periods of one year with the possibility of extension for another year or more, to enable such persons to take part in research work in antibiotics ; and

2. that WHO should approach institutes where adequate research facilities in the above subjects are available, requesting them to accept WHO Fellows for participation in their research programmes.

The committee was of the unanimous opinion that full assistance to Member States in the production of antibiotics could be achieved only if such postgraduate training were given in an atmosphere permeated by research.

The committee recommended that the following institutes should be approached :

*Istituto Superiore di Sanità, Rome, Italy*

Facilities are available for training in microbiological engineering, pharmacology, biochemistry, and microbiology. Pilot-plant equipment with fermenters from 50 to 18,000 litres as well as semi-scale and full-scale processing equipment are available.

The Institute could take up to 14 students a year (seven in microbiology, and seven in microbiological engineering and biochemistry), beginning with three students on 1 May 1950, the remainder in September 1950.

*Department of Microbiology, Rutgers University, New Brunswick, N.J., USA*

Facilities are available for training in microbiology.

The Department is prepared to accept up to six students in microbiology, as follows : two in September 1950, four on 1 January 1951.

The new Institute of Microbiology, in process of construction, will be ready within two years. It will have excellent facilities for research in microbiology, biochemistry, and microbiological engineering. When completed, consideration could be given to as many as 15, possibly more, Fellows.

*Department of Biochemistry, University of Madison, Wis., USA*

Facilities are available for training in microbiological engineering, biochemistry, and microbiology.

*Nobel Institute of Medicine, Stockholm, Sweden*

Facilities are available for biochemical training with biochemical semi-scale equipment.

*Sir William Dunn School of Pathology, University of Oxford, England*

Facilities are available for microbiological and biochemical training.

The committee noted that the Istituto Superiore di Sanità had already been approached by WHO.

The committee adopted the following resolution :

The Expert Committee on Antibiotics

RECOMMENDS

1. that the World Health Organization make full and immediate use of the facilities for postgraduate training provided by the Istituto Superiore di Sanità, Rome, and that the other institutes referred to in this report be approached without delay ;
2. that, on agreement being reached, WHO recognize these institutes as national centres providing international research and training facilities in antibiotics ;
3. that WHO assist these institutes in securing necessary supplies and chemicals, by means of its supply and procurement mechanism and by attempting to obtain relaxation of import licences, customs duties, and other barriers to the free flow of material, particularly equipment and chemicals ; and
4. that WHO encourage the closest collaboration between these centres.

### 3. Feasibility of International Conferences on Antibiotics

The committee considered whether the time was opportune for the holding of an international congress, as a contribution towards the spread of scientific and technical knowledge on antibiotics. The Chairman conveyed a suggestion from the Director of the Istituto Superiore di Sanità that such a congress could be held in Rome in 1952 under the auspices of WHO and the Italian Government.

The committee, in agreement with the Expert Committees on Tuberculosis and on Venereal Infections, recommended that the Council for the Co-ordination of International Congresses of Medical Sciences be asked to consider the advisability of organizing a symposium on one or more aspects of antibiotics in 1951, at some convenient date and place. It further recommended that consideration be given to the possibility of convening a larger congress in 1952.

The committee proposed that the following subjects be given primary consideration for discussion at such a symposium :

- (1) the newer antibiotics now finding application in chemotherapy ;
- (2) antibiotics in relation to tuberculosis ;
- (3) antibiotics in relation to venereal disease.

### 4. Abstracting Service on Antibiotics

The rapid increase in the scientific literature on antibiotics and its wide distribution throughout the various branches of science makes a survey of this subject a formidable, if not impossible, task for the research worker. This is particularly true of countries where library facilities are inadequate. There is, therefore, an urgent need for an abstracting service covering antibiotics and related subjects.

A suggestion that a journal on antibiotics should be sponsored by WHO was discussed, but it was agreed that no recommendation should be made to this effect.

The committee adopted the following resolution :

The Expert Committee on Antibiotics

RECOMMENDS that the Director-General of the World Health Organization ask the Co-ordinating Committee on Abstracting and Indexing in the Medical and Biological Sciences to consider what steps might best be taken to develop a rapid and comprehensive abstracting service on antibiotics, covering microbiology, chemistry, biochemistry, microbiological engineering and the relevant patent literature, pharmacology, and clinical applications, such abstracts being published as an independent section.

### 5. Type Culture Collections

The urgent need for improving existing type culture collections of strains capable of producing and testing antibiotics was stressed, and, after full discussion, the committee adopted the following resolution :

The Expert Committee on Antibiotics

RECOMMENDS that the World Health Organization ask certain institutions responsible for type culture collections in different countries whether they would be willing to serve as depositories of official cultures for the production and testing of antibiotics, with the obligation of keeping these cultures in a satisfactory state (i.e., with regard to their antibiotic-producing capacity and specific antibiotic-sensitivity respectively) and of making them generally available at the request of WHO ; such institutions should be asked in addition (a) which type cultures of antibiotic-producing organisms are in their collections ; and (b) what specialized collections of antibiotic-producing organisms and of test organisms they would like to keep.

### 6. Survey of Penicillin Requirements

The committee noted a report on penicillin requirements and production.<sup>5</sup> It was agreed that too much reliance should not be placed on the figures of estimated requirements, particularly if these estimates are used to assess the need for further production of penicillin in certain areas.

### 7. Modernization of UNRRA Penicillin Plants

The committee was in agreement with the opinions expressed in the joint report of the Secretariats of WHO and the Economic Commission for Europe on efforts to increase penicillin production.<sup>6</sup>

Three of the penicillin plants supplied by the United Nations Relief and Rehabilitation Administration (UNRRA) are now reported to be in production, though on an uneconomic basis owing to the lack of Podbielniak extractors. The committee considered that the best way of increasing the output of these plants would be to obtain this equipment for the countries concerned. The few usable parts of a fourth plant, in Italy, have been incorporated into a pilot plant for research purposes.

No recent information was available on the state of the UNRRA plants in the Byelorussian SSR, China, and the Ukrainian SSR. If WHO were

<sup>5</sup> Unpublished working document WHO/VD/41

<sup>6</sup> Unpublished working document EB3/20 Add. 1 ; see also *Off. Rec. World Hlth Org.* 17, 36.

to be approached by the governments of the countries concerned, the committee would gladly consider any problems that may have arisen.

### **8. Availability and Stimulation of Production of Streptomycin**

The committee noted the production figures for streptomycin in different parts of the world furnished by its members. It appeared from this survey that the quantities now available were sufficient to meet normal requirements in producing countries. Nevertheless, it is true that for economic reasons streptomycin is not universally available, and the possibility of establishing new plants capable of meeting national requirements was discussed.

As the committee had already pointed out, the provision of equipment is not in itself a solution to the problem, for it is necessary to supply also the trained personnel which is not at present available in many countries.

The possibility of establishing a modern plant in Europe supported by WHO was dismissed because of the economic difficulties involved and the conflicts with private interests that might arise.

The committee again recommended that attention be paid primarily to the training of qualified personnel and to the provision of research laboratories and pilot plants in the countries to which the trained personnel will return, so that the latter may continue their research, keeping in touch with new developments in the field of antibiotics and, if necessary, assisting their countries to proceed with domestic production.

The committee was informed that advice had been sought on the financial risks involved in setting up plants for the production of antibiotics which might soon become obsolete. It was the view of the committee that, irrespective of the capital expenditure involved in setting up an antibiotics manufacturing plant, such work should be started at once and help should be given to as many countries as possible. The committee was of the opinion that no significant risks would be involved, since the large-scale use of antibiotics is not likely to be a passing phase in therapeutics. If one antibiotic became obsolete, the same equipment, with some modification, could be used for the manufacture of others.

### **9. Present Position of Antibiotics**

The committee agreed that much of what had been recommended regarding penicillin and streptomycin was already applicable to aureomycin and chloromycetin and that it was clear that other antibiotics would have soon to be considered. The rapid changes in this branch of therapeutics

add weight to the suggestion made earlier in this report that every effort should be made to train scientists and technologists who are capable of keeping abreast with new developments.

The committee emphasized that WHO should encourage Member States to keep abreast of developments both as regards laboratory facilities and the training of specialists in research, so that they could take advantage of any opportunity to produce a new antibiotic as the necessity arises.

### 10. Development of Research in Therapeutics

There can be no doubt that in therapeutic research scarcity of the drug which is being investigated may be an asset, for the following three reasons :

(1) If the drug is not generally available, its use can be restricted to centres chosen because they are capable of carrying out a controlled investigation.

(2) If treatment is restricted to a few centres, adequate numbers of patients suffering from the condition to be investigated can be collected.

(3) If the amount of drug available is not sufficient to treat all available patients, it may be possible to select at random a control series of either untreated patients or of patients treated without antibiotics.

It was suggested that organized investigations of this type should be sponsored by WHO in areas where antibiotics of proved therapeutic value are in short supply. Such a project would enable new contributions to knowledge to be made which would not be possible in places where the drug was plentiful, and would stimulate backward areas to take part in research in the use and production of antibiotics.

The suggested method of approach was as follows :

(a) A list of centres with adequate laboratory control should be drawn up, and, if necessary, steps should be taken in the form of fellowships, etc., to ensure that the personnel in these centres be properly trained, particularly from the point of view of laboratory control.

(b) Such investigations should, when possible, provide adequate numbers of patients to be statistically significant, adequate control groups, a rigid system of treatment, and a uniform method of recording.

The discipline and co-operation required to satisfy these criteria is unlikely to be possible except in areas where the drug to be tested is of known value and yet in short supply.

(c) Institutions such as medical research councils in various countries should be informed of the existence of these centres and of their purpose, and should be asked to pass this information to their relevant committees with the request that WHO be informed of their suggestions which, if possible, should be supported by a detailed account of how the problem should be tackled. Other WHO expert committees, such as those on tuberculosis, venereal infections, and health statistics, should be similarly informed.

In making these suggestions, the committee appreciated and endorsed work of a similar nature which is being conducted under the auspices of other WHO committees.

### 11. Relations with Other Expert Committees

The possibility of designating special institutes to serve as depositories for standard preparations of antibiotics was discussed. It was pointed out that the existing mechanism of the National Institute for Medical Research, London, for the distribution of WHO international standards established by the WHO Expert Committee on Biological Standardization, already served this purpose. The Expert Committee on Biological Standardization was, however, anxious to establish as soon as possible international reference preparations of new antibiotics to enable comparisons of potency between different research workers or different commercial houses, with a view to the eventual adoption of international standards when the stability and purity of such preparations was sufficient to warrant it.

The committee recommended that the Expert Committee on Biological Standardization be given full support in obtaining international standards and reference preparations of antibiotics which, although still in the experimental stage, would appear to be of importance. It was also suggested that the attention of the Expert Committee on Biological Standardization be drawn to the unsatisfactory terminology sometimes used in the assay of new antibiotics; the attention of authors and editors of scientific journals might be drawn to the preference for the use of the term "provisional unit" instead of "unit".

The committee, in response to a request from the Expert Committee on the Unification of Pharmacopoeias, agreed to collaborate in the preparation of monographs and appendices on penicillin and streptomycin.

The committee also agreed to collaborate with the Expert Committees on Venereal Infections, on Tuberculosis, on Health Statistics, and all the bodies which might request through WHO specific advice on problems relating to antibiotics.

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