present status of the systems, operational epidemiology, comparative epidemiology, positive health indicators, costs of production of biologicals, technology at different levels of care, financing of the sector, and impact of financing methods on the utilization of services.

• International agencies should lend their support and offer technical cooperation to the two systems, especially in the design of joint service programs, the formulation of research projects and their execution, and the development of methods of evaluation; and should assist in such activities as technical meetings, courses, demonstrations, publications, etc., through which national experiences could be disseminated.

At its eleventh plenary session, the PAHO Directing Council examined the Final Report of these Discussions, and adopted Resolution XXIX, in which it called upon Member Governments, in accordance with conditions in their countries, to adopt political decisions and establish mechanisms for developing institutional coordination; and urged the Governments to define and structure their national health systems with a view to applying a uniform policy of health benefits for the entire population, to foster joint institutional programming of capital investment for the health sector, and to devise solutions of a technological complexity appropriate to problems that affect all, irrespective of social insurance coverage. PAHO in turn, was requested to support related national coordination efforts and to arrange for the study and formulation of recommendations on specific aspects of the coordination and collaboration between health care institutions.

SEMINAR ON TUBERCULOSIS CHEMOTHERAPY

The III Regional Seminar on Tuberculosis, convened by the Pan American Health Organization, was held at PAHO Headquarters in Washington, D.C., 27-30 March 1979. Its objectives were to bring together the chiefs of national tuberculosis programs, professors of phthisiology and pneumonology, and scientists from the various countries of the Americas in order to review recent advances in tuberculosis chemotherapy; exchange ideas and experiences on the applicability of this new information to tuberculosis treatment, within the context of control programs; and formulate conclusions and guidelines on treatment of the disease.

The participants included clinicians and tuberculosis control specialists designated by the Governments of 21 countries of the Americas, as well as internationally recognized consultants and observers from this Hemisphere and from Europe.[3] The full text of the conclusions adopted at the meeting is as follows:[4]

Current Progress in Tuberculosis Chemotherapy

Bacteriologic Basis of Short-Course Chemotherapy

The purpose of tuberculosis chemotherapy is to sterilize lesions quickly and com-

[3] The elected officers of the Seminar were: Chairman: Prof. Helio Fraga (Brazil); Vice-Chairman: Dr. Monorajan Dan (Trinidad and Tobago); General Rapporteur: Dr. Santiago Medeiros (Bolivia); and General Secretary: Dr. Antonio Pio (PAHO/WHO).

[4] PAHO mimeographed document III-SRT/16, 30 March 1979.

pletely, and the drugs are used to avoid the failures caused by bacterial resistance and to avert relapses.

Despite the high proportion of mutants resistant to drugs among wild strains of tubercle bacilli, selection of resistant bacilli is easily avoided by appropriate combinations of active drugs, that is, drugs to which the bacilli are sensitive.

For rapid and complete sterilization, the drugs to be used must be chosen for their specific activity against various types of bacterial populations present in lesions—for example, actively multiplying bacilli, as in the walls of caverns; slowly multiplying bacilli inside macrophages; or intermittently multiplying bacilli in solid caseous lesions (called persisters).

The drug can be bactericidal or bacteriostatic, but in some conditions it can be entirely ineffective.

On the large populations of bacilli actively multiplying at neutral pH on the walls of pulmonary caverns the effect of streptomycin, isoniazid, and rifampicin is bactericidal; ethambutol and PAS are bacteriostatic; and pyrazinamide is inactive. The most active drug against the small bacterial population that multiplies slowly inside macrophages in an acid medium is pyrazinamide followed by isoniazid plus rifampicin. Streptomycin, like any other aminoglycoside antibiotic, is inactive in acid media. Only rifampicin is bactericidal for the third type of bacterial population, all other drugs being inactive.

Consequently, from the bacteriologic standpoint, the isoniazid-rifampicin combination, which is bactericidal for all these bacterial populations, constitutes the basis for short-course chemotherapy. To enhance the effectiveness of this combination and

Prof. Helio Fraga (Brazil), Chairman, addresses the III Regional Seminar on Tuberculosis in Washington, D.C. To his left is the General Rapporteur, Dr. Santiago Medeiros (Bolivia), and to his right the General Secretary, Dr. Antonio Pio (PAHO/WHO).

avert the consequences of primary and acquired resistance, it is advisable to add one or two supplementary drugs in the initial intensive phase of treatment.

Effectiveness of Short-Course Chemotherapy

From the many studies and controlled clinical trials carried out in the last 10 years in different parts of the world, a few conclusions may be drawn on which there is consensus:

- The rifampicin-isoniazid association is essential in both the initial and the continuation phase of short-course tuberculosis chemotherapy.
- Streptomycin and pyrazinamide contribute to the success of short-course chemotherapy as supplementary drugs in the initial phase, and in therapeutic regimens resorted to when rifampicin is unavailable.
- For patients with bacteriologically confirmed tuberculosis, the overall duration of the short-course regimens must be six to nine months for 100 per cent effectiveness.
- It is essential that the initial phase of the short-course chemotherapy be intensive, with the drugs administered daily.

The work done in Latin America has contributed to the scientific understanding of short-course chemotherapy and of its application in programs.

Adverse Reactions to, and Toxicity of Drugs

Though antituberculosis drugs are, on the whole, well tolerated, they can cause adverse effects. The frequency of these effects varies with the drugs and their associations, and can also vary from one country to another.

In six- to nine-month regimens, the total frequency of secondary effects varies from one country and one study to another; however, the number of cases in which treatment has to be discontinued permanently is usually lower than 3 per cent.

Effectiveness of Chemotherapy as a Means for Tuberculosis Control

The most powerful control method for reducing the problem of tuberculosis is case-finding plus chemotherapy. The two measures are inseparable: case-finding is of little use as a control measure unless followed by chemotherapy, and the latter cannot be practiced without the former.

It is difficult to gauge accurately the impact of chemotherapy, as an isolated factor, on transmission of the tuberculosis infection because this epidemiologic index measures the overall effects both of the methods applied under programs and of any improvements in general living conditions. It has been estimated, however, that case-finding and chemotherapy have accelerated the natural decline of the risk of tuberculosis infection in developed countries to an annual rate two to three times faster than prior to the discovery of the antituberculosis chemotherapeutic drugs. There are well-known examples in which the risk of infection was reduced more than 20 per cent a year, mostly as an effect of case-finding plus chemotherapy, like that recorded among Eskimos in the last 25 years.

Application of Current Knowledge of Chemotherapy to Tuberculosis Control Programs

Research has demonstrated the effectiveness of short-course regimens in the treatment of pulmonary tuberculosis. The potential advantages that have prompted consideration of its introduction in control programs are rapid bacteriologic conversion; lower failure and relapse rates; higher probability of permanent smear-negativity in defaulting patients; reduction in the frequency of emergence of drug-resistant organisms; low frequency of adverse reactions; lower demand for care from health

services; fewer defaults; and a lessening of human suffering in that the time in which individuals are considered to be ill is shortened. The principal disadvantage is the higher cost of short-course regimens compared with the standard regimens most widely used in Latin America today.

The first trials of short-course regimens under normal conditions in the health services of some Latin American countries have shown that their effectiveness does not offset administrative shortcomings, and that they do not so far appear to have much effect on overall results of the case-finding and treatment program. In consequence, it is felt that short-course regimens, if introduced, must be accompanied by continual evaluation of results and an effort to improve the organization of the treatment.

Therapeutic Regimens

Several alternative short-course regimens are available. It is up to the health authorities in the countries to select those that are best in terms of cost and availability of funds, and whose effectiveness and toxicity are acceptable to the country. The regimens must make use of bactericidal drugs and include an initial intensive phase of daily treatment with isoniazid, rifampicin, and one or two supplementary drugs. The total duration of the treatment will be between six and nine months, depending on the drugs chosen and the effectiveness desired. Six-month regimens are preferred from the operational standpoint.

Operational Aspects

The supply and distribution system must be so organized as to assure a timely and uninterrupted supply of drugs for application of the therapeutic regimens chosen. The Governments must guarantee supply of the drugs free of charge. In view of the economic advantages of centralized drug procurement, the Seminar recommends the establishment of a regional revolving fund through an international agency, to obtain antituberculosis drugs.

It is regarded as indispensable that standards and procedures be drawn up for supervision and control of short-course treatment. They must be easy to understand and apply, be suited to local conditions, and include clear instructions on diagnostic criteria, dosages, adverse reactions to the drugs, control tests, and evaluation. It is suggested that PAHO's *Manual of Standards and Procedures for Integrated Tuberculosis Control Programs in Latin America* be updated in keeping with the recommendations of this Seminar.

Doctrinal unity must be sought among the technical recommendations of the program, university instruction, and the training of auxiliary personnel. The introduction of new chemotherapeutic regimens makes it necessary to retrain the personnel, and this offers an opportunity for upgrading their qualifications. To maintain the quality and output of the program, continuous supervision is essential at both the central and regional, and the local levels. This supervision must be exercised by generalists or specialists, depending on the level of complexity.

Treatment must be fully supervised when at all possible. Its introduction in urban areas, it is felt, should present no difficulty. Action to extend primary health care must provide for implementation of the measures of the tuberculosis control programs, including supervised treatment, integrated into general health services.

The progress of patients will be monitored mainly by bacteriologic examination.

The results of treatment must be evaluated by treatment cohorts, and an analysis made of the proportion of cases diagnosed that began and completed the treatment, and positive pulmonary cases with favorable bateriologic response at the close of .the therapy and 12 months after the start of treatment.