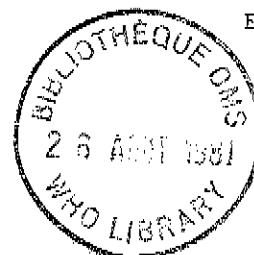




*Tub. <sup>pub.</sup> <sup>Doc.</sup> <sup>Proc.</sup>  
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IDENTIFICATION OF PROBLEMS REQUIRING FURTHER RESEARCH IF THEY ARE TO BE SOLVED

*Tub. <sup>pub.</sup> <sup>Doc.</sup>  
 Hyperbacterium Zimmuner*

by

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Comments on the report on Research in Tuberculosis by a Committee of the British Medical Research Council, 1980

In a report to the Director-General of WHO in March 1959, a highly competent scientific group on tuberculosis research, with Dr Johannes Holm as secretary, outlined fields of research of special importance (1). It is of interest to see to what extent the ideas of this group of 1959 have materialized and to know where we stand in the 1980s.

The current global WHO programme on research and services in tuberculosis has recently been summarized (2). A survey of recent European research activities in mycobacteriology gives information on the present status of this field (5). In the report of the BMRC committee, current research in all areas of tuberculosis is reviewed and future research prospects are studied (4). These background documents broadly cover the present status of research and can be used for comparison with the 1959 report.

Fundamental research

The WHO group of 1959 wanted a more precise analysis of the antigenic structures of different types of tubercle bacilli, and the isolation in a more highly purified state of antigenic fractions, as well as studies on induction of tuberculin-type allergy with bacillary components. Much work has been done since then on these subjects. We now have more purified preparations from the tubercle bacillus, as well as sensitins from other mycobacteria. They are, however, not yet specific enough to distinguish in practice between infections caused by different mycobacteria in skin-tests or in serological tests, which would be highly desirable, as infections by "atypical" mycobacteria seem to be of growing importance.

In view of the technical improvements as regards studies of the protein structure and the DNA relatedness, it does not seem improbable that such specific preparations will be within reach for immunologically based diagnostic tests distinguishing infections with different mycobacteria, nor for diagnosis of infection in inaccessible sites - as suggested by the BMRC committee and possibly for determination of activity. They should also be useful in diagnosis and evaluation of activity in non-bacillary tuberculosis, e.g. most cases of tuberculosis in children.

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Further laboratory studies on characterization of antigens from mycobacteria and field studies on this topic should therefore be strongly encouraged

The WHO group of 1959 also wanted studies on production of specific immunity with bacillary components as distinct from whole bacilli.

Little of practical importance has been achieved in this field since then. We need much more knowledge of the interplay between agent and host in mycobacterial infection before we can hope to have more effective immunizing procedure than at present. Such studies were also on the list of the 1959 group. The importance was stressed of studies on "cellular antibodies" responsible for the tuberculin type of allergy and on cellular mechanisms that are the basis of immunity. The group also wanted studies of the non-specific effects produced by anti-tuberculosis immunity, such as increased resistance to other infections and heightened capacity to develop sensitivity to other organisms.

Very active immunological research has given many clues in these areas. Studies on T-cell activated macrophages and other mechanisms of host defence have been rewarding. The BMRC committee stressed the importance of studies within different sectors of immunology, saying that although the short-term practical value of such studies might not be great, the area is one offering great intellectual opportunities.

Recent studies on different forms of cell-mediated response to mycobacteria - "necrotic" and "non-necrotic" - and their influence on the efficacy of BCG have, for example, thrown light on the relationship between allergy and immunity. It now seems probable that knowledge derived from basic immunological research might in the future be used for studies of practical importance on immunization as well as for other purposes in clinical research.

In 1959, nutritional factors and hormones and their influence on the response of the organism to tuberculous infection were mentioned as important areas of research. Very little new knowledge of practical importance has so far emerged from such studies and there is little reason to believe that increased activity in these fields in the near future will lead to results of practical value.

Since 1959, a new field of research has been opened up. Molecular biology is focusing on detailed analysis of structures within the area which lies between the small molecules of the biochemist and the visible structure of the morphologist. It has thrown light on the abstract entities and processes previously described in genetics. The microbial geneticists have made remarkable achievements in, for example, genetic recombinations. There is no reason why the mycobacteria should behave differently from other bacteria, and further research on mycobacteria with the concepts and methods of molecular biology will no doubt lead to achievements useful in clinical medicine, for chemotherapy as well as for immunization.

Closely linked with this area are studies on mycobacterial phages. As pointed out by the BMRC committee, "phage typing" should be useful both for studies on virulence and for determination of geographical origin of different strains.

Efforts by the mycobacteriologists to keep in pace with general bacterial genetics should be strongly encouraged.

In summary:

Research in mycobacteriology, immunology and related subjects form an indispensable basis for medical work in the field of tuberculosis. Such research should therefore be encouraged by all agencies concerned.

#### Clinical Research and Epidemiology

Research on BCG vaccination was given a high priority in 1959, when the expert group stated that many problems remained to be solved in this field, although BCG vaccination had long been used on a large scale.

Research on BCG remains of primary importance and has been strongly supported by WHO. Following the publication of the results of the Indian BCG trial, a Study Group was convened in June 1980 to advise on national policies. A research programme has been formulated and is recently reviewed (2). It gives priority to studies that contribute directly to elucidating the problems raised by the Indian trial.

Special attention is rightly given to conducting the essential field-studies on protection in man in a fast and economical way. Such studies are no doubt necessary, but they are difficult to organize and usually time-consuming. It is to be hoped that experimental work as outlined above will help to solve some of the problems raised.

The 1959 group stressed the urgent need for studies on the epidemiology of tuberculosis.

The last decades have brought much knowledge into this field, for instance through the work of the Tuberculosis Surveillance Research Unit (TSRU): the natural history of tuberculosis in the community is now well understood (5). It is at present more a question of applying this knowledge on epidemiology and surveillance in different areas of the world and of using it for decision-making in practice rather than for inventing new approaches.

Highly important areas of research are case-finding and diagnosis of tuberculosis. It is now clear that active as well as passive case-finding of pulmonary tuberculosis through bacteriological investigations alone have many limitations in practice. Operational studies on methods of diagnosis of tuberculosis in countries at different stages of development should be encouraged. Also of considerable interest is diagnosis of non-pulmonary tuberculosis - where most cases of tuberculosis in children belong - and of non-pulmonary tuberculosis.

Skin-tests or other immunological tests based on highly specific antigens and differing in practice between, for instance, infection with virulent tubercle bacilli and other mycobacteria should not - as pointed out above - be out of reach in the future. Clinical studies on case histories, symptoms and signs should, however, be of value in the meantime. Such studies might not be very spectacular, but could possibly lead to useful practical knowledge.

Already in the 1950s, effective drug regimens existed. Since then, a wealth of knowledge has been collected on antituberculous chemotherapy. Short-course regimens have been established and side effects have been thoroughly evaluated.

The BMRC committee urgently stressed the need for new drugs for treatment of tuberculosis. It is not very likely that pharmaceutical firms or other agencies will put more effort and money into big research projects with this aim. It seems to be more realistic to hope for a reduction of prices of existing drugs.

Our present arsenal of drugs already gives us excellent possibilities of treating pulmonary tuberculosis - in theory. As pointed out by the BMRC committee, many treatment regimens under research conditions approach 100 per cent effectiveness, but it is difficult to achieve similar results under service conditions.

Studies on chemotherapy under field conditions are urgently needed and should be given a high priority, as should further studies on cost-effectiveness of different drug regimens.

Clinical studies on treatment of extrapulmonary tuberculosis should also be encouraged, as well as treatment of diseases caused by atypical mycobacteria.

In summary:

Operational studies under different field conditions on all aspects of medical care in tuberculosis - immunization, case-finding and diagnosis, treatment and surveillance - should be given a very high priority and should belong to the main concerns of WHO and IUAT.

REFERENCES

1. WORLD HEALTH ORGANIZATION: Report to the Director-General. Scientific Group on Tuberculosis Research. WHO/PA/62.59.
2. WORLD HEALTH ORGANIZATION: (1981) The Current Global WHO Programme of Research and Services in Tuberculosis. Presented by Dr A. Pio at Regional Research Study Group on Tuberculosis. WHO Regional Office for South East Asia. New Delhi.
3. GRANGE, J.M. (1981) Recent European Research Activities in Mycobacteriology, Tubercle, 61, 259.
4. RESEARCH IN TUBERCULOSIS. (1980) - A report of a committee set up by the British Medical Research Council to study future prospects. Bulletin of the International Union Against Tuberculosis, 55, 86.
5. STYBLO, K. (1980) Recent Advances in Epidemiological Research in Tuberculosis. Advances in Tuberculosis Research, 20, 1. Karger, Basel.