Cholera and Related Diarrheas

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Cholera and
Related Diarrheas

Molecular Aspects of a Global Health Problem

Editors
Oerjan Ouchterlony and Jan Holmgren,
Gteborg

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Foreword

The present Nobel Symposium on Cholera and Related Diarrheas-Molecular Aspects of a Global Health Problem took place on August 6-11, 1978 at the Nordic Education Center (IBM) at Elfvik, Liding, in the County of Stockholm, Sweden. The opening session was held at the Wenner Gren Center in Stockholm. Dhiman Barua, John P. Craig, Jan Holmgren and rian Ouchterlony served as the organization committee for the symposium. The Nobel Foundation and its Nobel Symposium Committee
sponsored the symposium and as co-sponsor acted the World Health Organization. The symposium was financed by grants from the Nobel Foundation, by the Bank of Sweden Tercentenary Foundation, from the Swedish Medical Research Council and from the Walter, Ellen and Lennart Hesselman Foundation of Scientific Research, Stockholm. The IBM Svenska AB housed the symposium. The members of the organization committee would like to express their sincere thanks to all those who, in various ways, made this symposium possible.

rjan Ouchterlony

Opening Remarks

rjan Ouchterlony
Institute of Medical Microbiology, University of Gteborg, Gteborg

Cholera, the scourge of ancient times, is again a menace in several parts of the world. The pandemic counted as the seventh began in the early sixties and is still with us. It is true that the genius epidemicus of the classical, 19th century cholera nowadays has changed to a somewhat less threatening pattern, maybe due to a gradual takeover by the El Tor variant, but its impact on human health is still considerable particularly in some developing countries. It should also be mentioned that during the last decade it has been revealed that bacterial species other than Vibrio cholerae can cause a choleralike disease induced by their production of enterotoxins. Especially strains of the species Escherichia coli are implicated in this connection. Taking into consideration all kinds of infectious diarrheas classifiable as enterotoxic enteropathies, the burden of these diseases upon mankind all over the world is immense and developed countries are by no
means excluded from this evil. Therefore, the theme of the present Nobel symposium is most pertinent to world health and consequently WHO is co-sponsoring our meeting.

Under the auspices of the Nobel Foundation, we have been able to bring together several experts in basic and applied sciences in order to let them for a couple of days exchange and discuss their experiences from laboratory and clinical research as well as from field investigations. I am convinced that the outcome of our sessions and workshops will show that the seeds coming from this crossbreeding of ideas are going to be fertile.

However, before we attempt to elucidate the future of cholera and choleralike diseases, it might be worthwhile to look for a moment into the past. During the last centuries, numerous scientific and pseudo-scientific meetings on cholera have been held. A typical example of the latter kind of colloquia is recorded in the mocking lithograph by G. Cruickshank appearing in his Political Satires of 1832. The first truly successful scientific conference on cholera was held in Berlin in 1884 under the chairmanship of the German Nestor in pathology, Robert Virchow. At this occasion, Robert Koch reported on his findings concerning cholera in Egypt and India the previous year thereby creating a breakthrough in cholera research- Vibrio comma isolated and characterized as the etiologic agent of the disease. For the benefit of the present audience, I would like to quote Koch's opening sentence at that particular session. `Meine Herren! Wir brauchen fr sanitre Massregeln mglichst fest begrndete wissenschaftliche Unterlagen ... aber leider ist das noch nicht berall der Fall und
namentlich der Cholera gegenüber fehlt es an einer solchen festen Basis.' For several years, however, Koch's findings were seriously questioned, but it became gradually evident that he by the aforementioned report and subsequent bacteriological as well as epidemiological investigations had laved the foundation stone for the preventive work on cholera that followed.

How the cholera vibrios cause the dominating symptom of the disease, excessive diarrheas, remained for several decades an unsolved problem. It was therefore difficult to establish a rational basis for an adequate therapy. Not until some 60 years after Koch's discovery of the cholera vibrio an opening came about at the cholera epidemic in Egypt in 1947-48. There and then we find the origin to the modern trend in cholera research implying a clinically oriented combination of basic and applied sciences. Dr. Robert Phillips from the US and collaborators were working in Cairo and some fundamental studies on the fluid and electrolyte disturbances in cholera patients were undertaken. 11 years later, during an epidemic in Bangkok, Phillips et al. put on trial the fluid-electrolyte replacement therapy based on the aforementioned findings in Egypt. The new treatment was successful and made it possible to reduce the mortality of the dreaded disease to less than 1%.

The pathogenic principle or principles of the cholera vibrios remained obscure, mainly due to the lack of a good, experimental animal model. In the early fifties, the situation changed, when two groups of investigators
in India, De and Chatterjee, Dutta and Habbu, showed that the intestine of adult or infant rabbit could be employed for detection of the choleragenic action of vibrios. By the important finding some years later that the same effect could be obtained by filtrates of V. cholerae cultures the old concept by Koch was revived concerning the existence of a true, enteropathogenic exotoxin. This new knowledge induced a rapid progress of experimental cholera research. I will briefly mention some of the major achievements.

So for instance was the existence of a vascular permeability factor (PF) in culture filtrates reported and a very useful skin test was developed. The presence of heat-labile exotoxin or toxins identifiable by the action on the gut of various experimental animals was also revealed. The immunogenicity of the toxic product was demonstrated and the neutralizing action of antitoxic antibodies was applied to antigen identification and quantitation. By physiochemical separation procedures, the exotoxin named choleragen was obtained as a pure preparation. Regarding its toxicity, extensive structure-function studies on the cellular and molecular level were performed. A specific toxin-receptor substance in the surface part of target cells was identified. Studies also disclosed the existence of subunits of the toxin which are non-toxic. This finding pointed out a new approach to immunoprophylaxis against cholera.

I think that the few examples given
suffice to illustrate the impressive progress in recent cholera research. May I add that we are very fortunate to have with us at this symposium several of those investigators who have made major contributions to our present, quite extensive knowledge about the disease, its pathophysiology, therapy and prevention. Of those not being able to participate at our meeting there is one scientist, already mentioned, whom I would like to bring back in thought before coming to the end of my opening remarks. Our colleague Dr. Phillips passed away at the time of the early planning of this symposium some years ago. I think that it would be most appropriate to dedicate our symposium to the memory of Bob Phillips recalling his pioneer work on cholera.

Detail from `Cholera Consultation`. 