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The Agent of Trachoma

Recent Studies on the Biology, Biochemistry
and Immunology of a Prokaryotic Obligate Parasite
of Eukaryocytes

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Editor's Preface

Although the agent of trachoma has now been generally accepted as non-viral, it was for so long considered a virus that it seems appropriate to include this review as a Monograph in Virology. Hence, this volume should be useful not only to those working directly with the trachoma agents, but also to virologists who need an overview of the developments during the last decade which have distinguished these chlamydial agents from the viruses.

JOSEPH L. MELNICK

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Although the agent of trachoma has now been generally accepted as non-viral, it was for so long considered a virus that it seems appropriate to include this review as a Monograph in Virology. Hence, this volume should be useful not only to those working directly with the trachoma agents, but also to virologists who need an overview of the developments during the last decade which have distinguished these chlamydial agents from the viruses.

JOSEPH L. MELNICK

Preface

The opportunity to write a review on the recent developments in the research on the agent of trachoma had arisen from the invitation of Professor J. L. MELNICK to revise the review written in 1962, by the late Professor HANS BERNKOPF. As a result of marked developments in research on the immunology and biochemistry of the agent, a new review which will compile the knowledge added in the last decade seemed necessary. I have, therefore, referred mainly to studies on *Chlamydia trachomatis* which were published during the last decade. The very important studies on *Chlamydia psittaci* are beyond the scope of this monograph.

I wish to thank my colleagues, Professor I. C. MICHAELSON and Dr. B. MAYTHAR from the Department of Ophthalmology, Hadassah University Hospital, Jerusalem; Drs. Z. ZAKAY-RONES, I. SAROV, from the Department of Virology, B. GUTTER, and Y. ASHER, Y. COHEN, and H. LOKER from the Laboratory for Molecular Virology, for their continuous and enthusiastic collaboration; Professor S. E. LURIA, Department of Biology, Massachusetts Institute of Technology, Cambridge, Mass., for the critical discussions on the nature of obligate parasitism of viruses and prokaryotes in eukaryotic cells; Professor E. JAWETZ, Department of Microbiology, University of California, San Francisco, Calif., for his continuous interest and support; Dr. M. L. TARIZZO, World Health Organization, Geneva, for his continuous interest and help; Professor A. L. BARRON, on sabbatical leave from the Department of Microbiology, School of Medicine, State University of Buffalo, N. Y.; Professor H. M. JENKIN, Department of Microbiology, Hormel Institute, University of Minnesota, Austin, Minn., for the critical reading of the manuscript and for their comments; Dr. Julia Hadar for proofreading the manuscript; and my wife Miriam Becker for her continuous encouragement.

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The review of the literature was completed July 1972. However, some manuscripts published during 1973, while the Monograph was prepared, are also included.

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I. Introduction

A. Historical Notes

Etiological studies on the trachoma agent date back to the observation by HALBERSTAEDTER and VON PROWAZEK [1907] who reported on the presence, in conjunctival cells, of inclusion bodies which contain elementary particles (designated 'Chlamydozoa' or mantle bodies). They believed, on the basis of resemblance in the morphology of the developmental cycle, that the particles in the inclusion bodies were the infectious agent of trachoma. The trachoma agent was grouped together with psittacosis and lymphogranuloma venereum into the psittacosis-lymphogranuloma-trachoma (PLT) group of organisms [THYGESON, 1962] now defined as members of the order Chlamydiales which includes one family Chlamydiaceae and two species *Chlamydia trachomatis* and *Chlamydia psittaci* (fig. 1) [PAGE, 1966, 1968, 1973]. However, 50 years elapsed from the discovery of the trachoma agent until the etiological agent of trachoma was isolated by T'ANG and his collaborators [T'ANG *et al.*, 1957, 1958], propagated in embryonated eggs, and studied with respect to its properties. Although it has been known since 1938 that the agent of trachoma and similar agents of the PLT group resembled bacteria in their sensitivity to sulfa drugs and antibacterial antibiotics; these agents were, for many years, considered as viruses. The consideration of the trachoma agent as a virus resulted in a remarkable delay in the development of trachoma research. Only after the agents of trachoma were cultivated *in vitro* was the prokaryotic nature of the agent elucidated. In 1962, BERNKOPF indicated in his review on trachoma that 'the more we learn of the nature of trachoma and related agents the less fitting the term "virus" becomes'. The indecisiveness in defining the PLT group is indicated in the constant changes in the name of the group of agents and its systematic position in the microbial world. In the 1962 symposium on the 'Biology of the Trachoma Agent', the PLT agents were regarded as viruses. In the 1966 conference on 'Trachoma and Allied Diseases', the agents were named Bedsonia. The name Chlamydia was used in the 1970 symposium on 'Tra-

Obligate Parasites of Eukaryotic Cells.

PLT group of agents

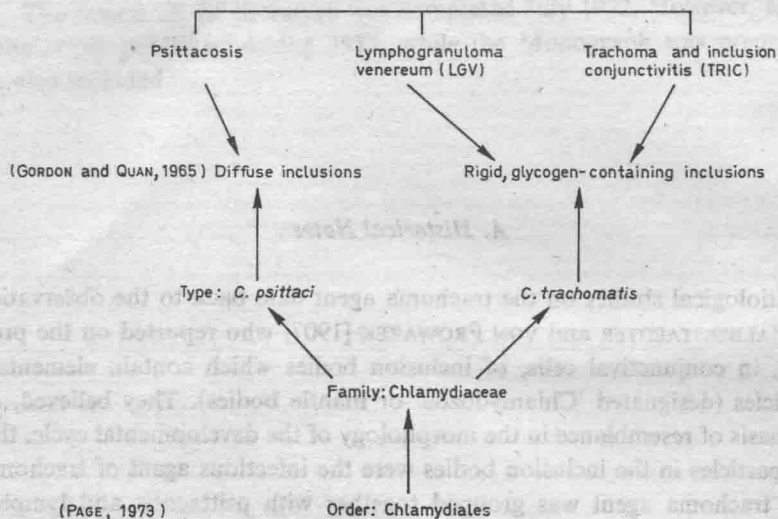


Fig. 1. The chlamydia (PLT group of agents).

choma and Related Disorders Caused by Chlamydial Agents'. However, MOULDER [1966] clearly defined the psittacosis group of agents as microorganisms which are obligate intracellular parasites of eukaryotic cells. Recent developments in the research on the molecular biology of the trachoma agent have confirmed and extended MOULDER's ideas and furthered the understanding of the chlamydial agents as prokaryotic obligate parasites. In the present review, mainly studies on *C. trachomatis* will be reviewed.

B. Recent Developments

Research on the trachoma agent has gone through several phases since the discovery by T'ANG *et al.* [1957, 1958]: the initial attempts were to isolate numerous strains of trachoma from patients in different parts of the world. This was followed by studies on the morphology and life cycle of the agent and on the effects of antibiotics on the trachoma agent. In the second phase, studies were concerned with the immunological properties of the trachoma

strains and attempts were made to develop potent antitrachoma vaccines. The developments in the research on the molecular biology of microorganisms made possible studies on the molecular processes which occur during the developmental cycle of the trachoma agent. These research activities are well reflected in the scientific reports presented in three international conferences (1962, 1966 and 1970)¹ which were devoted to studies on the trachoma agent. The developments in the understanding of the chlamydia (trachoma and psittacosis agents) were reviewed by BERNKOPF [1962a, b], BIETTI and VOZZA [1963], JAWETZ [1964] and MOULDER [1966, 1971]. These reviews contain the basic information on the medical aspects of trachoma as well as the basic concepts of the chlamydial agents. The present review will deal with some of the developments in trachoma research which took place during the last decade (1962-1972)². The aim of the present review is to present the current knowledge on the classification, molecular biology and immunological properties of *C. trachomatis*, the agents which cause trachoma, a disease of the human eye. These agents are members of a unique group of obligate microbial parasites of eukaryotic cells.

¹ a. The biology of the trachoma agent. Ann. N.Y. Acad. Sci 98 (1962). b. Conference on Trachoma and Allied Diseases. Amer. J. Ophthal. 63 (1967). c. NICHOLS R. L. (ed.): Trachoma and related disorders caused by chlamydial agents. Excerpta med. Int. Congr. Series, No. 223 (1971).

² Since the number of publications on trachoma is exceedingly high, it has become virtually impossible to quote all of them. Hence, only a relatively small number of the pertinent studies were included in the present review. A complete list of publications on trachoma is published by the Centre International de Documentation sur le Trachome, in the Revue Internationale du Trachome.

II. Definitions and Classification of the Chlamydia

A. Definitions of the Chlamydia

1. The Agents of Psittacosis,

Lymphogranuloma Venereum and Trachoma (PLT) -

Members of the Order Chlamydiales

In contrast to most bacterial and viral agents, whose distinct nature was easily recognized, the members of the PLT group of agents were constantly shifted from one class to another until they resumed a position on the border between viruses and bacteria [RAKE *et al.*, 1942; WEISS, 1955; MOULDER, 1966]. The indecisiveness regarding the nature of the agents and their relationship to other classes of biological entities was due to the absence of a clear definition of the group. The chlamydial agents were isolated in many laboratories during a period of 30 years from excretions of respiratory tracts (e.g. psittacosis [BEDSON and BLAND, 1932], ornithosis [POLLARD, 1947]); from genital tracts (e.g. lymphogranuloma venereum [FINDLAY *et al.*, 1938]); and from the eyes (e.g. trachoma [RAKE *et al.*, 1942; T'ANG *et al.*, 1957], inclusion conjunctivitis [FURNESS *et al.*, 1960b]). The agents isolated from humans and other vertebrates were maintained by serial transfers in the yolk sacs of developing chick embryos. Some of the agents were later adapted to growth in cultured cells *in vitro*. Numerous studies on the isolated chlamydial agents [summarized by MEYER, 1952; COX, 1953; THYGESON, 1953; WENNER, 1958; COLLIER, 1959a, b; LEPINE, 1960; BERNKOPF, 1962a, b; JAWETZ, 1964; MOULDER, 1966], as well as advancement in defining the class of viruses [LURIA, 1953; LWOFF, 1957; LWOFF and TOURNIER, 1966] and the recognition of the unique features of bacteria as a group [STANIER and VAN NIEL, 1962], led to the suggestion [PAGE, 1966, 1968] that the chlamydiae differ from Rickettsiae and constitute a specific order, Chlamydiales.