VIRAL DISEASES OF THE FETUS AND NEWBORN

By
Hanshaw
and
Dudgeon

Volume XVII in the Series
MAJOR PROBLEMS IN CLINICAL PEDIATRICS

VIRAL DISEASES OF THE FETUS AND NEWBORN

By

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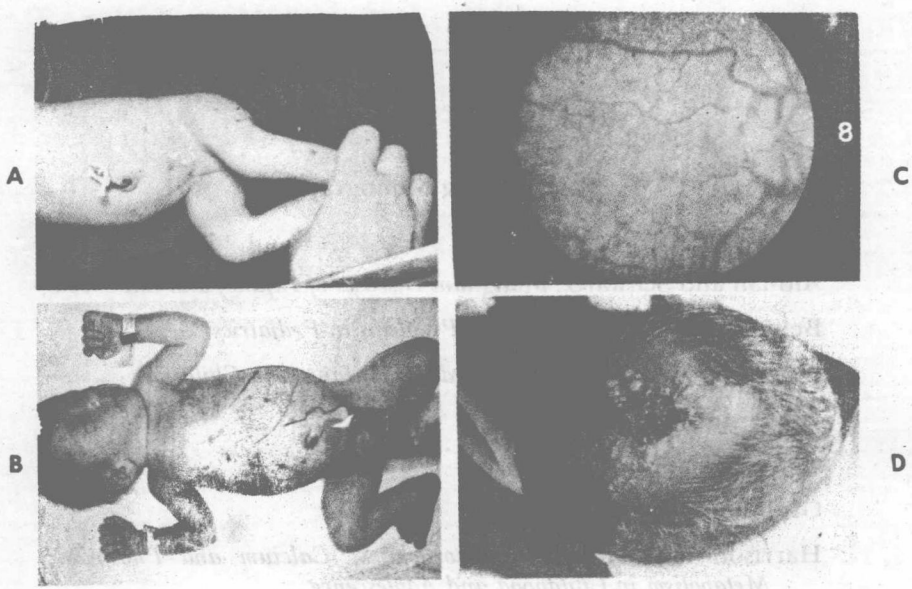

Figure A Two day old infant with severe neonatal purpura, enlarged anterior fontanelle, bilateral corneal edema with increased ocular tension, osteopathy, and persistent ductus arteriosus. Platelets fell to 17,000/cu mm. She weighed 3 lb at birth. There was a history of maternal rubella at eight weeks' gestation. The infant died at six weeks of age from heart failure and severe hepatic involvement due to hepatitis. The infant's case was diagnosed by virus isolation and persistence of rubella antibody. (By permission of the Board of Governors, The Hospital for Sick Children, Great Ormond Street, London.)

Figure B Generalized purpura and hepatosplenomegaly in a newborn infant with cytomegalic inclusion disease. (Courtesy of Dr. Joseph L. Butterfield, Denver, Colorado.)

Figure C Pigmentary retinopathy. (By permission of the Board of Governors, The Hospital for Sick Children, Great Ormond Street, London.)

Figure D Herpes simplex vesicles of the scalp of the newborn infant.

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Foreword

We have been awaiting with keen anticipation the completion of this volume. So much new knowledge has been added in the past decade to this major segment of perinatology that we pediatric generalists have found it difficult to remain *au courant*. This book should solve our problem.

To those who have kept abreast of the pediatric literature the names of the authors will be quite familiar, since they have both contributed heavily to advances in the field. The name Hanshaw may be more closely associated in your minds with cytomegalic infection and that of Dudgeon more closely with fetal rubella than with the other viral infections, but neither has by any means limited his research and writing to one topic.

James Barry Hanshaw, M.D., earned his A.B. degrees at Syracuse University, and after an internship and a stint in the army in Japan he moved over to Rochester for his residency training in Pediatrics. Then, after two years at Harvard in the Department of Public Health he returned to Rochester, where he remained many years, rising from the rank of Instructor to that of Professor of Pediatrics and Microbiology. In 1975 he was asked to establish and head the pediatric department of the newly created University of Massachusetts Medical School at Worcester.

His publications number about 50 to date, the majority being on cytomegalovirus infection but a significant minority concentrating on rubella, rubeola, herpes simplex, infectious lymphocytosis, and other viral diseases. Although his fame rests upon his laboratory work primarily, his profound interest in the clinical aspects of child health and disease becomes obvious to anyone who sees him in action or reads his contributions.

Professor John Alistair Dudgeon, C.B.E., M.A., M.D. (Cantab.), M.R.C.S., L.R.C.P. (London), F.R.C.P., F.R.C.Path., received his early training at Trinity College, Cambridge, and St. Thomas' Hospital, London. After completing his residency years as House Physi-

cian at St. Thomas' his further training, teaching, and research in pediatrics, pathology, and virology were carried out at the National Institute of Medical Research, St. George's Hospital Medical School, and the Hospital for Sick Children, Great Ormond Street. In 1960 he was appointed Consultant Microbiologist to the Great Ormond Street Hospital, and from 1962 until the present he has been a member of the Board of Governors of this renowned children's hospital.

Professor Dudgeon's publications number about 60, plus chapters in six books. Honors bestowed upon him include the Military Cross and Bar, the Territorial Decoration (three clasps), and Officer of the Order of St. John of Jerusalem.

Reading the manuscript of this book has been a rewarding experience for me not only because of the wealth of information it contains but also by virtue of the sheer excellence of its writing. I have no doubt that you will be equally impressed.

ALEXANDER J. SCHAFFER

Preface

This book is about the effects of viruses on the fetus and the newborn. It is concerned with the short-term as well as the long-term effects of viral infections upon normal fetal development and upon the child after birth. It is concerned with identifying the causes of these infections and with methods of diagnosis without which little progress can be made toward the final and most important aspect of the subject—that of management, treatment, and prevention.

Textbooks of pediatrics published prior to the Second World War contained virtually no reference to intrauterine infections, with the exception of congenital syphilis. The reasons for this are self-evident. At the time, pediatricians and family doctors were concerned with treating the severe communicable diseases—whooping cough, diphtheria, tuberculosis, measles, poliomyelitis, and gastroenteritis. As a result of improved health care and specific measures directed toward treatment and prevention in many countries, these previously serious problems have markedly declined in importance. The effect of these measures is reflected not only in a progressive fall in the childhood mortality rates but also in the order of disease conditions of children requiring admission to hospital. Whereas in the 1930's the communicable diseases were the predominant causes of death and ill health, their place has now been taken by neoplasms, congenital malformations, and accidents of all types. For example, a comparison of the causes of death among children at The Hospital for Sick Children, Great Ormond Street, London, during the period from 1914 to 1954 showed a fall of 52 per cent in deaths from environmental causes and an increase in deaths from congenital malformations and neoplasms, or from conditions that were due wholly or in part to genetic causes (Carter, 1956).

The discovery in 1941 that such a mild disease as rubella contracted in pregnancy could lead to severe congenital defects in the offspring led inevitably to the expectation that many other viruses would have the same effect. This has not proved to be the case, and

although comparatively few viruses appear to play a significant part as a cause of congenital defects in terms of actual numbers of children involved, they are important in other respects. The damage they cause is extremely variable; it may be severe, even fatal; the fetus may be infected without obvious sign of damage or may escape infection altogether. The outcome is unpredictable, but the investigations that have led to the identification of these viruses have also led to a better understanding of the mechanisms responsible for the damage they cause. And so in the ensuing chapters of this monograph we shall seek to bring together for the clinician and pediatrician the information they must have in order to diagnose and manage the case and to advise the families of patients exposed to infections from conception throughout pregnancy into the first few weeks of life.

The study of intrauterine infections is yet another example of the way in which modern pediatrics has had to adapt to the changing pattern of medicine and an example of the need for those who practice to think in terms of events that occur before birth and that may be harmful to subsequent development.

Carter, C. O.: Changing patterns in the causes of death at The Hospital for Sick Children. Great Ormond Street Journal *11*:65–68, 1956.

J. B. Hanshaw
J. A. Dudgeon

Acknowledgments

I am grateful to Dr. T. H. Weller of Harvard University, who introduced me to virology during an exciting age of discovery. He is unquestionably one of the great clinical scientists of modern medicine. Dr. W. L. Bradford of the University of Rochester taught me pediatrics and a type of interaction with patients and parents that has not been surpassed in my experience. There have been many other people who took time along the way to teach by their example, especially Drs. G. B. Forbes and G. Miller. To many co-workers, Drs. A. P. Schetner, R. F. Betts, G. Simon, M. M. Melish, L. A. Glasgow, H. Steinfeld, and V. Abel, I am especially grateful. The National Institutes of Health provided generous support through Career Research Development Awards (1962 to 1972) as well as through project grants (NICH & HD, NIAID) from 1960 to 1975. My debt to the National Foundation began in 1958 with a postdoctoral fellowship to the Harvard University School of Public Health. In addition, I am grateful to the Board of Governors of the Hospital for Sick Children, Great Ormond Street, and the Institute of Child Health in London, for providing me the opportunity to serve as a Visiting Professor in Professor J. A. Dudgeon's Department of Microbiology during the 1972–73 academic year. It is this opportunity that made the present monograph possible. Last, I wish to thank Mrs. K. Stowe and Mrs. S. Rochette for their excellent assistance in the preparation of the manuscript and Ms. K. Pitcoff, Associate Medical Editor of W. B. Saunders Company, for bringing extraordinary competence and efficiency to the completion of this effort.

J.B.H.

Acknowledgments

I wish to acknowledge with gratitude the help and encouragement I have received from so many people throughout my medical career. My interest in virus and rickettsial diseases was first aroused in 1944 when I joined the Scrub Typhus team under the late Dr. Marius van den Ende. As World War II drew to a close, it was feared that there might be another influenza pandemic similar to that which followed the First World War, and I was posted by the War Office to the National Institute of Medical Research at Hampstead to learn the intricacies of growing influenza viruses under the expert guidance of Dr. Christopher Andrewes, F.R.S. (now Sir Christopher Andrewes). A few years later, soon after I joined the staff of The Hospital for Sick Children, Great Ormond Street, fortune again came my way as the Board of Governors of The Hospital for Sick Children and the Nuffield Foundation arranged for me to work as a Research Fellow under Dr. Macfarlane Burnet (now Sir Macfarlane Burnet, O.M., F.R.S.) at the Walter and Eliza Hall Institute, the Royal Melbourne Hospital, Victoria. I owe much to these three great scientists as it was largely due to their stimulating teaching and training that I acquired an interest in virology that has continued throughout the ensuing thirty-odd years, the greater part of which has been spent at The Hospital for Sick Children. It is, therefore, a great pleasure to acknowledge my indebtedness to so many colleagues at the Hospital throughout this time and to record what a great experience it has been to work in such close association with so many great pediatricians. I should like to mention one by name, the late Sir Alan Aird Moncrieff, Nuffield Professor of Child Health at the Institute and Consultant Paediatrician to the Hospital. It was Alan Moncrieff who, in his quiet persuasive way, directed my attention at an early stage from the purely laboratory aspects of virology to the wider and more practical problems of preventive medicine. He was a great physician and a great teacher and, like so many others, I owe him a great deal.

I also want to express my thanks to the nursing staff of the Hos-

pital, who, despite many demands on their time, have never failed in their help and have always risen to the occasion when special investigations were underway. Throughout my time at the Hospital, I have received constant help from the Board of Governors, both collectively and from individual members. To them I am grateful for their permission to include details of the case material from patients at the Hospital in this monograph. In expressing my thanks to my colleagues at the Hospital, I wish to make special reference to Drs. William C. Marshall and Catherine S. Peckham for their constant help and advice in our joint research efforts and for their helpful advice in the preparation of the manuscript for the book.

Much of the research into congenital defects has been supported by research grants from the Medical Research Council in London, Action Research for the Crippled Child, the Wellcome Trust, and the Board of Governors; to all of these bodies I am much indebted. I also want to add a note of appreciation to the members of the Department of Medical Illustration for the preparation of the figures, tables, and clinical photographs, to the library staff of the Hospital and to my research secretaries, Mrs. Elizabeth Ryan and Mrs. Mary Whelan, who took so much trouble in preparing the details of the National Congenital Rubella Surveillance Programme. Finally, I would like to express my thanks to my personal secretary, Mrs. Sandra Hyder, who has given most valuable assistance in the preparation of the manuscript, proofreading, and checking of the bibliography.

Writing a monograph with a co-author on the other side of the Atlantic is no easy task. This could never have been accomplished without the forebearance and constant advice of Dr. Barry Hanshaw.

J. A. D.

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Chapter One

INTRODUCTION

One of the major unsolved problems in medicine today involves the great number of children born each year with congenital malformations. The problem is a serious one because many of these malformations affect those organs of the body, such as the central nervous and cardiovascular systems, which are vital to normal function. They frequently occur in combination and thus lead to severe dysfunction and to permanent handicap for those who survive. The most important factor, however, is that so little is known about their causation despite the remarkable advances in medical science in the past three decades. The causes of congenital malformations can be classified under three main headings: (1) purely environmental, in which the cause can be directly attributed to an infection, a drug, or ionizing radiation; (2) purely genetic, due to chromosomal anomalies and mutant gene defects; and (3) mixed genetic and environmental, which may account for the majority of congenital malformations. It seems probable that the genetic predisposition in this large group of cases is polygenic (Carter, 1968).

This classification is convenient for a general approach to the study of congenital malformations, but it would be a mistake to regard the grouping in too rigid a fashion. There is some evidence from the work of Menser, Forrest, Honeyman, and Burgess (1974) that there may be a genetic susceptibility to rubella infection, and although there is as yet no proof that the cause of the more common malformations can be explained on the basis of an interaction between genetic factors and infectious agents such as viruses, the possibility should be borne in mind, particularly as so many viral infections occur in an asymptomatic form.

The incidence of the more common malformations is shown in Table 1–1, with an overall incidence of between 20 and 30 per 1000 depending on the definition (Carter, 1968). These disorders are all major malformations that, by virtue of the organs involved, should be recognizable at or soon after birth. They are also, in the strict sense of the term, "malformations"; that is to say, they are structural abnormalities and do not include defects due to destruction of anatomically normal organs, which is a recognized feature of some intrauterine viral infections. Other important defects such as mental retardation and congenital deafness are also not included, mainly because they can be difficult to diagnose in the early months of life.

The question of definition or terminology is of some relevance to the subject of this book. The subject of terminology was discussed at the First International Conference on Congenital Malformations held in 1960 in London. Speaking at that conference on the role of environmental teratogenic factors, Dr. Joseph Warkany said, "A remark about terminology may be in order here. It has been suggested that the anomalies produced by prenatal rubella are not congenital malformations but embryopathies. Similarly, some have recommended that the defects produced by toxoplasmosis should not be considered as congenital malformations because they are due to secondary destruction of originally normal organs. There is little justification for such hair- or term-splitting. The term congenital malformations should be applied to gross, structural anomalies *present at*

Table 1–1 Incidence of Malformations (Per 1000 Total Births): Estimates Based on Observations Beyond the Neonatal Period*

	BIRMINGHAM (UK)	NEW YORK (US)	JAPAN
Period of observation	(to 5 years)	(to 1 year)	(to 9 months)
Total births	56760	5749	16144
Anencephalus	2.0	1.6	0.6
Spina bifida	3.0	1.6	0.3
Hydrocephalus	2.6	0.9	0.5
Cardiac malformation	4.2	8.5	7.0
Cleft lip and palate	1.9	1.6	3.0
Dislocation of the hip	0.7	1.2	7.1
Talipes equinovarus	4.4	5.2	1.4
Mongolism (Down's syndrome)	1.7	1.9	0.9
All individuals with major malformations	23.1	(not given) total malformed 75.3	24.5

*From McKeown, T., and Record, R. G.: Malformations in a population observed for five years after birth. Ciba Foundation Symposium on Congenital Malformations. London, J. and A. Churchill, 1960.