J. ROSA, Y. BEUZARD & J. HERCULES Editors

DEVELOPMENT OF THERAPEUTIC AGENTS FOR SICKLE CELL DISEASE

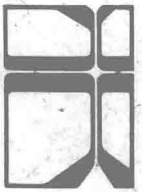
INSERM SYMPOSIUM 9

PROCEEDINGS

DEVELOPMENT OF THERAPEUTIC AGENTS FOR SICKLE CELL DISEASE

Proceedings of the International Meeting on Development of Therapeutic Agents for Sickle Cell Disease held in Paris (France), 19-21 July, 1978 .
Sponsored by the Institut National de la Santé et de la Recherche Médicale, France and the National Institute of Health, Sickle Cell Disease Branch, U.S.A.

Editors: JEAN ROSA
YVES BEUZARD
JOHN HERCULES



INSERM SYMPOSIUM No. 9

INSTITUT NATIONAL DE LA SANTÉ
ET DE LA RECHERCHE MÉDICALE

1979

NORTH-HOLLAND PUBLISHING COMPANY
AMSTERDAM · NEW YORK · OXFORD

ISBN Series: 0 7204 0653 6
ISBN Volume: 0 7204 0671 4

Publishers:
ELSEVIER/NORTH-HOLLAND BIOMEDICAL PRESS
335 JAN VAN GALENSTRAAT, P.O. BOX 211
AMSTERDAM, THE NETHERLANDS

Sole distributors for the USA and Canada:
ELSEVIER NORTH-HOLLAND INC.
52 VANDERBILT AVENUE,
NEW YORK, N.Y. 10017

PRINTED IN THE NETHERLANDS

PREFACE

This symposium was the outcome of planning that was started in 1977 by Dr. HERCULES and myself during the Fourth International Conference on Red Cell Metabolism and Function in Ann Arbor. We came to an agreement that it would be a good opportunity to organize a meeting on the antisickling drugs. Indeed for several years now, a substantial effort has been made throughout the world to develop such drugs. After the initial promise resulting from the early studies performed with urea and cyanate, it became apparent that the treatment of sickling could not be overcome without a multiple approach. Since that time, a great deal of work has been done to understand the basic phenomena underlying the polymerization of Hb S, including X-ray analysis of Hb S crystals and of Hb S fibers. The intermolecular contacts have also been studied using naturally occuring double mutants or artificial mixtures of Hbs. Several tests have been evaluated for their efficiency to analyse the action of antisickling agents. The physiology of the sickle erythrocytes has been extensively studied and compared with that of normal erythrocytes. A large number of new drugs have been studied during these last years and the extracorporeal administration of some drugs has also been assessed.

On the other hand, the prenatal diagnosis of sickle cell anemia has become operational. It appeared to us to be a very opportune moment for the first general discussion of all the results obtained on this topic. In order to allow as large a participation as possible of peoples interested in progress in the therapy of the Sickle Cell Disease, i.e. in addition to the Americans, members of the African community, it became evident to us that a very good opportunity would be to organize such a meeting as a satellite Symposium of the XVII International Congress of Hematology which will be held in Paris in July 1978.

We therefore decided to obtain support from our respective administrations. Dr. HERCULES was able to obtain the agreement of the N.I.H. Several participants from the U.S.A and from Africa could thus be supported by N.I.H. grants. On our part, we were able to interest Dr. LAUDAT, the Scientific Director of the I.N.S.E.R.M., in this project; and I.N.S.E.R.M. support was sufficiently generous to cover the conference costs as well as the travel costs of some American, African and European people. The Centre National de la Recherche Scientifique (CNRS) provided an excellent conference room in the center of Paris adjacent to the Seine and just between the Place de la Concorde and St Germain des Prés. The CNRS also provided an excellent French buffet with French wines and American bourbon ! We can claim that the Symposium was a success. Dr. Max PERUTZ opened the Meeting with a superb conference on the stereochemistry of Hb S and every one present greatly enjoyed having him again with them.

The large confrontation between all the Scientists who attended this meeting has produced results which can be very fruitful for both the scientist and physician implicated in the treatment of sickle cell anemia, particularly since one often encounters difficulties in evaluating correctly the action of the various new drugs claimed to be active as antisickling agents.

The printed papers provide the content of all the oral presentations but unfortunately, it was not possible to publish the discussions, which were very lively and sometimes very critical.

We owe to Dr. Yves BEUZARD our gratitude for the excellence of the organization of this Symposium. Our thanks should also be extended to the very efficient and courteous help of the secretaries Chantal RONCIN, Martine SEGEAR and Anne Marie DULAC.

Jean ROSA

LIST OF PARTICIPANTS

Christian ALLARD, Laboratoire d'Hématologie,
Hôpital de Bicêtre, 78, av. du Général Leclerc
94270 Le Kremlin Bicêtre, France.

Krystina ALBRECHT, Unité de Recherches sur les Anémies
INSERM U.91, Hôpital Henri Mondor, 94010 Créteil, France.

Stanley BALCERZAK, University Hospitals, Division of Hematology
& Oncology, 410 west 10th avenue, Columbus Ohio 43210, USA.

Ruth BENESCH, Department of Biochemistry, Columbia University
College of Physicians & Surgeons, 630 west 168th street,
New York, N.Y. 10032, USA.

Marcel BESSIS, Institut de Pathologie Cellulaire, INSERM U.48
Hôpital de Bicêtre, 78, av. du Général Leclerc
94270 Le Kremlin Bicêtre, France.

Yves BEUZARD, Unité de Recherches sur les Anémies
INSERM U.91, Hôpital Henri Mondor, 94010 Créteil, France.

Yves BLOUQUIT, Unité de Recherches sur les Anémies
INSERM U.91, Hôpital Henri Mondor, 94010 Créteil, France.

Brigitte BOHN, INSERM U.27, 42, rue Desbassayns de Richemont
92150 Suresnes, France.

Robert BOOKCHIN, Albert Einstein College of Medicine of
Yeshiva University, 1300 Morris park avenue, Bronx N.Y. 10461,USA.

Clotilde BOURDY, Laboratoire de Physique, Museum d'Histoire Naturelle, 43 rue Cuvier, 75005 Paris, France

James BOWMAN, University of Chicago, Department of Pathology 950 east 59th street, Chicago Illinois 60637, USA.

François BRACONNIER, Unité de Recherches sur les Anémies INSERM U.91, Hôpital Henri Mondor, 94010 Créteil, France.

George BREWER, Department of Human Genetics University of Michigan Medical School, 1137 E. Catherine street Ann Arbor, Michigan 48109, USA.

Franklin BUNN, Division of Hematology Peter Brent Brigham Hospital, 77 Huntington avenue Boston Mass. 02115, USA.

Elisabeth BURSAUX, INSERM U.27, 42, rue Desbassayns de Richemont 92150 Suresnes, France.

Anthony CERAMI,The Rockefeller University, 1230 York avenue New York, N.Y. 10021, USA.

Danny CHIU, Bruce Lyon Memorial Research Laboratories Childrens Hospital, 51 st Grove street, Oakland California 94609, USA.

Michel COHEN-SOLAL, Unité de Recherches sur les Anémies INSERM U.91, Hôpital Henri Mondor, 94010 Créteil, France.

Douglas CURRELL, Università di Roma, Istituto di Chimica Città Universitaria 00185 Roma, Italy.

Dr. DAVID, Recherche Clinique- Laboratoires Fabre 17, av. Jean Moulin 81106 Castres, France.

Dennis DIEDERICH, Department of Medicine, University of Kansas Kansas City, Kansas 66103, USA.

Bernard DREYFUS, Unité de Recherches sur les Anémies
INSERM U.91, Hôpital Henri Mondor, 94010 Créteil, France.

Anne DUBART, Unité de Recherches sur les Anémies
INSERM U.91, Hôpital Henri Mondor, 94010 Créteil, France.

William EATON, Laboratory of Molecular Biology & Chemical Physics
National Institute of Health, Bethesda Maryland 20014, USA.

Jacques ELION, Institut de Pathologie Moléculaire, INSERM U.15
24, rue du Faubourg St Jacques, 75014 Paris, France.

Folayan ESAN, Department of Haematology, University College
Hospital, Ibadan, Nigeria.

Dr. FRANKLIN, Department Clinical Haematology
University College Hospital Medical School, University Street
London WC1E 6HX, England.

Thomas GABUZDA, Department of Hematology, Lankenau Hospital
Lancaster and City line avenues,
Philadelphia, Pennsylvania 19151, USA.

Michel GARBARZ, Laboratoire d'Hématologie, Hôpital Henri Mondor
94010 Créteil, France.

Marie-Claude GAREL, Unité de Recherches sur les Anémies
INSERM U.91, Hôpital Henri Mondor, 94010 Créteil, France.

Charis GHELIS, E.P.C.M. Université Paris XI, 91405 Orsay, France.

Pierre GONNARD, Département de Biochimie, Hôpital Henri Mondor
94010 Créteil, France.

Sophie GRUSON, Service de Pédiatrie
Hôpital Intercommunal, 41, avenue de Verdun
94010 Créteil, France.

Patrick GUESNON, INSERM U.27, 42, rue Desbassayns de Richemont
92150 Suresnes, France.

Waffa HASSAN, Kars El-Einx, Center of Radiation
Oncology and Nuclear Medicine, Faculty of Medicine, Cairo, Egypt.

John HERCULES, Department of Health and Welfare
National Institutes of Health, Bldg 31, rm 4A29,
Bethesda, Maryland 20014, USA.

Joseph HOFFMAN, Department of Physiology, Yale University
School Medicine, 333 Cedar Street,
New Haven Connecticut 06510, USA.

Ernst HUEHNS, Department Clinical Haematology,
University College Hospital Medical School, University Street
London WC1E 6HX, England.

Richard JONES, Department of Biochemistry
University of Oregon Medical School
Portland, Oregon 97201, USA.

Hézékhia KAMOUZORA, INSERM U.27, 42, rue Desbassayns de Richemont
92150 Suresnes, France.

Alfred KRAUS, Department of Medicine Hematology
University of Tennessee Center for the Health Sciences
800 Madison Avenue, Memphis, Tennessee 38163, USA.

Lorraine KRAUS, Department of Medicine Hematology
University of Tennessee Center for the Health Sciences
800 Madison Avenue, Memphis, Tennessee 38163, USA.

Rajagopal KRYSHNAMOORTHY, Institut de Pathologie Moléculaire
INSERM U.15, 24, rue du Faubourg St Jacques, 75014 Paris, France.

Dominique LABIE, Institut de Pathologie Moléculaire, INSERM U.15
24, rue du Faubourg St Jacques, 75014 Paris, France.

Philippe LAUDAT, Institut Nat. Santé et Recherche Médicale
101, rue de Tolbiac, 75645 Paris Cedex 13, France.

Hermann LEHMANN, Department of Biochemistry, Tennis Court Road
Cambridge CB2 1QW, England.

Warner LOVE, Biophysics Department,Johns Hopkins University
Baltimore, Maryland 21218, USA.

Bertram LUBIN, Bruce Lyon Memorial Research Laboratory
CHildrens Hospital, 51 St Grove Street ,
Oakland, California 94609, USA.

Lucio LUZZATO, Consiglio Nazionale delle Ricerche
Istituto Internazionale di Genetica e Biofisica,
via Guglielmo Marconi 10, 80125 Napoli, Italy.

Paulo MACHADO, Departmento Clinica Medica Hematologia
Faculdade de Medicina da UNESP, Botucatu 18610, Sao Paulo, Brasil.

Béatrice MAGDOFF-FAIRCHILD, Department of Medicine
St Luke's Hospital Center, 114th Amsterdam avenue
New York, N.Y. 10025, USA.

James MANNING, Department of Biochemistry,
Rockefeller University 1230 York avenue,
New York, N.Y. 10021, USA.

Narla MOHANDAS, Institut de Pathologie Cellulaire, INSERM U.48
Hôpital de Bicêtre, 78, av. du Général Leclerc
94270 Le Kremlin Bicêtre, France.

Fabienne MOLKO, Unité de Recherches sur les Anémies
INSERM U.91, Hôpital Henri Mondor, 94010 Créteil, France.

Ronald NAGEL, Albert Einstein College of Medicine of Yeshiva Univ.
1300 Morris Park Avenue, Bronx, N.Y. 10461, USA.

Clayton NATTA, Columbia University, College of Physicians
630 west 168th Street, New York, N.Y. 10032, USA.

Marie-Louise NORTH, Centre de Transfusion Sanguine
10, rue de Spielman, 67000 Strasbourg, France.

Dr. J.I. OKOGUN, Department of Chemistry, University of Ibadan
Ibadan, Nigeria.

John PARDON, Searle Research Laboratories, Lane End Road
High Wycombe, Bucks HP12 4HL, England.

Rukmani PENNATHUR-DAS, Bruce Lyon Memorial Research Laboratories
Childrens Hospital 51 St Grove Street
Oakland California 94609, USA.

Max PERUTZ, MRC Laboratory of Molecular Biology, Hills Road
Cambridge CB2 2QH, England.

Charles PETERSON, Rockefeller University 1230 York Avenue
New York, N.Y. 10021, USA.

Darleen POWARS, Department of Pediatrics
University of Southern California, School of Medicine
Los Angeles, California, USA.

Jean-Louis PORTOS, Faculté de Médecine de Créteil
8, av. du Général Sarrail, 94010 Créteil, France.

Claude POYART, INSERM U.27, 42, rue Desbassayns de Richemont
92150 Suresnes, France.

Helen RANNEY, Department of Medicine, University Hospital
225 West Dickinson Street,
San Diego, California 92103, USA.

Simone SEYTOR, Centre Hospitalier, Service de Biologie
97110 Pointe à Pître, Guadeloupe.

Martine SINET, INSERM U.13, Hôpital Claude Bernard
10, av. de la Porte d'Aubervilliers, 75019 Paris, France.

Jeanne SMITH, 347 Webster Avenue, Englewood New Jersey 07631, USA.

Reginald STONESTREET, NIH-National Heart Lung & Blood Institute
9000 Rockville Pike, room 4A24 bldg 31,
Bethesda, Maryland 20014, USA.

Bernard TEISSEIRE, Service Explorations Fonctionnelles
Hôpital Henri Mondor, 94010 Créteil, France.

Ugo TESTA, Unité de Recherches sur les Anémies, INSERM U.91
Hôpital Henri Mondor, 94010 Créteil, France.

Joëlle THILLET, Unité de Recherches sur les Anémies, INSERM U.91
Hôpital Henri Mondor, 94010 Créteil, France.

Andréas TSAPIS, Unité de Recherches sur les Anémies, INSERM U.91
Hôpital Henri Mondor, 94010 Créteil, France.

Georges VAN ROS, Institut de Médecine Tropicale,
Nationale Straat 155, B.2000 Anvers, Belgium.

Henri WAJCMAN, Institut de Pathologie Moléculaire, CHU Cochin
24, rue du Faubourg St Jacques, 75014 Paris, France.

Marcel WAKS, E.L.M. Departement de Biochimie,
Faculté de Médecine , 45, rue des Saints Pères,
75006 Paris, France.

Dr. J.M. WHITE, Department of Haematology, King's College
Hospital Medical School, Denmark Hill, London SE5 8RX, England.

Ralph WHITE, Biophysics & Biochemistry Department,
Wellcome Research Laboratories, Beckenham, Kent, England.

Michel YOYO, Centre Hospitalier du Lamentin
97232 Lamentin, Martinique.

Isidore ZOHOUN-SOSSA, University de Cotonou,
Cotonou, République Populaire du Bénin.

INSERM Symposia

No. 1 Membrane Receptors of Lymphocytes,
edited by M. Seligmann, J.L. Preud'homme and F.M. Kourilsky, 1975.

No. 2 Immunoenzymatic Techniques,
edited by G. Feldmann, P. Druet, J. Bignon and S. Avrameas, 1976.

No. 3 Hormonal Receptors in Digestive Tract Physiology,
edited by S. Bonfils, P. Fromageot and G. Rosselin, 1977.

No. 4 Radiation-Induced Leukemogenesis and Related Viruses,
edited by J.F. Duplan, 1977.

No. 5 Solid Phase Methods in Protein Sequence Analysis,
edited by A. Previero and M.-A. Coletti-Previero, 1977.

No. 6 Cerebral Correlates of Conscious Experience,
edited by P.A. Buser and A. Rougeul-Buser, 1978.

No. 7 Cellular and Biochemical Aspects in Diabetic Retinopathy,
edited by F. Regnault and J. Duhault, 1978.

No. 8 Human Lymphocyte Differentiation: Its Application to Cancer,
edited by B. Serrou and C. Rosenfeld, 1978.

No. 9 Development of Therapeutic Agents for Sickle Cell Disease,
edited by J. Rosa, Y. Beuzard and J. Hercules, 1979.

CONTENTS

NORMAL AND SICKLE ERYTHROCYTES