ADVANCES IN BIOSENSORS

Editor: ANTHONY P. F. TURNER

Supplement 1 • 1993

CHEMICAL SENSORS FOR *IN VIVO* MONITORING

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A Research Annual

MONITORING

Editor: A.P.F. TURNER
Cranfield Biotechnology Centre
Cranfield University

SUPPLEMENT 1 • 1993

JAI PRESS LTD

London, England *Greenwich, Connecticut*

JAI PRESS LTD
The Courtyard, 28 High Street
Hampton Hill, Middlesex TW12 1PD

JAI PRESS INC.
55 Old Post Road, No. 2
Greenwich, Connecticut 06836-1678

ISBN: 1-55938-630-4

Printed in the United States of America

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COMAC Biomedical Engineering
Concerted Action on Chemical Sensors for
In Vivo Monitoring

PREFACE

The series *Advances in Biosensors* presents a unique compendium of research-level publications which do not have a place in conventional journals, but have an increasingly important role to play in completing the primary research literature and offering a more incisive alternative to the exhaustive review article. This first supplementary volume is dedicated to the specific area of *in vivo* monitoring. It was written by European scientists as a result of an international collaborative programme funded by the European Community.

The European Community (EC) was founded in 1957, initially between six countries. It now has 12 Member States. In recent years, research and development have become key factors in the political and economic activity of the Member States. The Community moved towards the coordination of research with the medium-term Framework Programme (1984–87), and this was consolidated by the Second Framework Programme (1987–91). The Single European Act accorded equal status for research and technological development policy with other vital areas such as economic, social and competition policy.

Each Member State is primarily responsible for promoting and preserving the health of its citizens. However, the cost of health care is very high and is steadily increasing. Medical and public health

research aimed at improving both the quality and the economic efficiency of health care is an essential tool to contain these costs. The involvement of the EC in the field of medical and health research began in 1978 with the first Medical and Health Research Programme, which funded just three projects. It has steadily expanded to include around 170 projects by the end of the Fourth Programme, which covered the period 1987–1991. The objectives have concentrated on prevention of illness and disability, the early detection of disease, and rehabilitation. The Fourth Programme incorporated six research targets. Four were related to major health problems, that is cancer, AIDS, age-related problems, and environment and life-style related problems. The other two targets related to health resources, that is medical technology development and health services research.

The general goal of the Programme is to contribute to a better quality of life by improving health, and its distinctive feature is to strengthen European collaboration in order to achieve this goal. One of the main objectives of this collaboration is to increase the scientific efficiency of the relevant research and development efforts in the Member States by means of coordination at Community level, and also their economic efficiency through task-sharing and strengthening the joint use of health research resources. The second objective is to improve scientific and technical knowledge in the research and development areas selected for their importance to all Member States, and to promote its efficient transfer into practical applications, taking particular account of potential industrial and economic developments in the areas concerned. The final objective is to optimize the capacity and economic efficiency of health care efforts throughout the Community.

Research management in the EC is clearly an enormous task, and one approach which has been successful in fostering research collaboration is the concerted action concept. Although national expenditure for medical and public health research is high, research efforts at national level alone are limited. European coordination of these national research activities enables the individual financial resources and capabilities to be used more effectively. To this end the Community provides funds for concerted action research coordination in Member States, together with other European countries participating via the framework of European Cooperation in the field of Science and Technology (COST). The funds are not direct research

grants; the institutes concerned fund the research activities carried out within their own countries. The international coordination activities which receive Community support are: the setting up of networks of research institutes and support by means of meetings, workshops, short-term staff exchange/visits to other countries, information dissemination and so on; centralized facilities such as data banks, computing, and preparation and distribution of reference materials. Each Concerted Action is placed under the responsibility of a Project Leader chosen from among the leading scientists in the network, with the assistance of a Project Management Group representing the participating teams.

The Commission of the European Communities has set up several committees to oversee the Programme. These are a Management and Coordination Advisory Committee (CGC—Medical and Health Research), and Concerted Action Committees (COMACs) and Research Working Parties (RWP), composed of representatives and of scientific experts respectively. The committee members are designated by authorities of the Member States. The main objectives of the COMAC Biomedical Engineering (BME) are the promotion and coordination of research and development, the transfer and harmonization of medical technologies in order to improve the quality of health care and rehabilitation, and to increase the application of new technological developments in Europe.

The idea for a Concerted Action on Chemical Sensors for *In Vivo* Monitoring was formulated at an EC funded expert meeting to discuss the interface between biology and sensors, held in Milton Keynes, U.K. in March 1988. One of the main points that emerged from the meeting was that there was a very real need for microsensors in medicine to deal with both emergency situations and chronic management problems. However, it was recognized that to achieve practical sensors considerable work was necessary on biocompatibility, stabilization during use and storage, sterilization, manufacturability and safety. Research, development and application of microsensors requires a multi-disciplinary approach, and the teams need to be well integrated in order to achieve their goals. With the level of funding existing in Europe at that time, groups rarely achieved sufficient size to encompass all the necessary disciplines and facilities. Some centres had, however, achieved considerable expertise in particular areas. It was concluded that it was in the general interest to

work together in a Concerted Action. A project management team was elected by secret ballot of the 31 participants from various European countries, and this team elected Professor A.P.F. Turner of Cranfield Institute of Technology, U.K., as Project Leader. The team prepared a proposal for a Concerted Action in the field of microsensors for medical applications entitled Chemical Sensors for *In Vivo* Monitoring, which was successful in attracting funds from the COMAC-BME.

The overall aim of the Concerted Action is to promote the application of chemical sensors *in vivo*. The three general aims are to stimulate the development of advanced medical technology in order to maintain a European presence in the field, promote the development of biomedical technology which may later be commercialized by EC industries, and improve the level of medical care for the benefit of all citizens of the Community. In pursuing these aims, the Concerted Action brought together a core of 29 centres from 15 countries (see Appendix) in a coordinated programme to facilitate a major step forward in clinical monitoring.

The principal goal of the Concerted Action is to obtain reliable, continuous short-term *in vivo* monitoring of at least one analyte. This would be of immense medical value for certain categories of critically ill patients. The principal objectives are to identify clinical problems which are amenable to solution using *in vivo* sensors, to identify suitable analytes, to identify appropriate sites for continuous sensing, to establish a European network of scientists working in the field of biosensors and bioprobes, to formulate device strategies, to define the operating characteristics for each application, and to promote the design and development of new sensors for continuous clinical monitoring. The Concerted Action programme has been based on a series of workshops, which covered a progressive series of topics: Clinical aspects, Strategies, Fundamental approaches and promises of available technologies, Packaging, biocompatibility, stability, Design and development, and Advances in the use of *in vivo* sensors (Alcock, S.J. (1992) Biosensors Bioelectron., 7, 243).

This book is a product of the Concerted Action, written on behalf of the members principally by the Project Management Group. It is intended to be a critical reference which aims to present the state of the art of chemical sensors for *in vivo* monitoring. Each chapter is written by authors from two or more laboratories to provide a unique

consensus on the current position and problems facing *in vivo* sensors. The book uses the conclusions of the series of workshops as source material, and effectively it summarizes the achievements to date of the Concerted Action.

We thank the many individuals who contributed to the workshops, the workshop organizers, and especially the members of the project management group for their work in guiding the Concerted Action.

S.J. Alcock
Project Coordinator

A.P.F. Turner
Project Leader

CONTENTS

INTRODUCTION

A. P. F. Turner and P. Vadgama

The establishment of an extensive network of scientists throughout western Europe working with colleagues throughout the world is indicative of the complexity of the task facing workers wishing to develop chemical sensors for *in vivo* monitoring. No single laboratory can be completely confident of its ability to field the diverse expertise essential to solve the matrix of problems associated with such devices. This book contains a synthesis of ideas and knowledge accumulated by the Project Management Group as a result of meetings, discussions and reports produced by our colleagues in the Concerted Action over the past four years. It is intended to provide a milestone in the development of implantable chemical sensors by presenting the broad conclusions of our work to date. Each chapter is written by authors from two or more laboratories forcing a degree of consensus and forging a coherent view of the myriad of issues impinging on the area.

For the purposes of both this book and our Concerted Action, a chemical sensor is defined as a compact analytical device containing a

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ISBN: 1-55938-630-4

chemically-sensitive element either integrated with or in intimate contact with a transducer and capable of generating a continuous signal proportional to a specific chemical or group of chemicals. Molecular contact between the sensing surface and the analyte is implicit in such devices, hence generating the alternative name of molecular sensors. A biosensor is a type of chemical or molecular sensor in which the chemically sensitive element is biologically derived (e.g. enzymes, antibodies, nucleic acids). This work encompasses the use of chemical sensors as *in situ* probes to investigate, monitor and optimize the therapeutic management of disease states in humans, using in many instances animal model systems. *In vivo* sensors are those implanted within the body cavity. In recognition of the similarity of problems facing the development of *ex vivo* sensors, and the fact that in many cases they represent an early model for *in vivo* devices, *ex vivo* devices have also been considered. An *ex vivo* device is one that cannot be separated from the patient during operation and operates on a continuously, or in some cases, intermittently supplied sample which is then either returned to the patient or led to waste. The provision of such on-line information allows real-time monitoring of rapidly fluctuating chemical parameters within the body, facilitating immediate therapeutic action. This type of measurement is distinct from the use of *in vitro* sensors and diagnostics where a sample is removed from the body and presented to an unconnected device in a separate discrete step. The trend to produce decentralized instrumentation and move nearer the patient gives rise to an element of overlap between the application of simple sensors that can be used to frequently monitor the patient at the bedside and *in vivo* or *ex vivo* sensors designed to give truly continuous information.

The issue of defining precisely when *in vivo* sensors are required was our starting point and forms the subject for Chapter 1. While it is recognized that a multitude of individual research applications exist for chemical sensors, we restricted our deliberations to sensors that would be immediately clinically useful. The arguments impacting on this choice are detailed and the results of a survey of clinicians opinions are discussed. This phase of our work resulted in the adoption of clear targets for the development of *in vivo* chemical sensors. The principal goals were implantable glucose sensors for long-term monitoring in diabetes, oxygen sensors for perinatal

monitoring and critical care, and ion sensors (pH and K^+) for use during surgery and critical care.

Having established the need, we go on to discuss the technology available to meet it. Chapter 2 describes the enormous variety of combinations of molecular recognition systems and transducers, but focuses on the common features of their operating principles. By appreciating the underlying mechanisms, it is possible to evaluate the potential of various proposals and understand the basis for the common focus of several groups on closely related technical solutions. It is clear, for example, that amperometric enzyme electrodes have been pursued universally as the most viable route to achieving subcutaneous glucose monitoring.

Chapter 3 pursues the theme of how to set specifications for the devices we are developing and against what criteria their final performance should be judged. Only by adoption of common standards can we hope to compare one prototype device with another and ensure that the needs of the user are met. Technical, clinical, psychosocial, economic and quality of life factors are the basis for this evaluation.

The question of what constitutes the correct site for implantation of sensors has caused much debate (Chapter 4). The interplay between the technicians and the physicians has provided a valuable insight into the demands of patient safety, optimum sensor performance and the effects of compartmentalization within the body (Chapter 5). Solutions tend to be applications specific and must be accompanied by the appropriate sampling technique to verify sensor performance.

Recent advances in microfabrication and notable successes in mass production of biosensors prompted a thorough discussion of fabrication of sensors (Chapter 6). One of the fundamental hurdles to the widespread application of chemical sensors for *in vivo* monitoring is reticence on the part of industry to adopt this technology and launch new products. An apparently limited market, large development costs and high risk associated with such products conspire to discourage industrial take up. The demonstration of inexpensive fabrication of reproducible devices will go a long way to counter these negative influences.

The economic considerations are further expanded in the following chapter (Chapter 7) where the cost-benefit or cost-effectiveness of the proposed devices are examined. Health-care economics in a

community is concerned with how finite budgets should be spent and such analysis plays an important role in matching benefit against the cost of an illness. The authors go on to consider the ethical implications of research and application of implantable sensors.

In the penultimate chapter (Chapter 8), a summary of the technical progress of the members of the Concerted Action is presented. Detailed comparisons have been made to provide a clear picture of the state-of-the art. The data and references gathered here provide a resource to workers in the field, while also furnishing a quick reference for those who wish to update themselves on progress.

In conclusion, we discuss (in Chapter 9) future strategies to achieve both short and long-term goals in the application of chemical sensors to aid clinical practice.

Chapter 1