innovations in biotechnology

EDITED BY

ERIC H. HOUWINK

ROBERT R. VAN DER MEER

progress in industrial microbiology

volume 20

innovations in biotechnology

EDITED BY

ERIC H. HOUWINK

Scientific Development Group, Organon International, Oss, The Netherlands

and

ROBERT R. VAN DER MEER

Central Institute for Industrial Development, The Hague, The Netherlands

progress in industrial microbiology

volume 20

ELSEVIER

Amsterdam — Oxford — New York — Tokyo

ELSEVIER SCIENCE PUBLISHERS B.V.
Molenwerf 1
P.O. Box 211, 1000 AE Amsterdam, The Netherlands

Distributors for the United States and Canada:

ELSEVIER SCIENCE PUBLISHING COMPANY INC.
52, Vanderbilt Avenue
New York, NY 10017

Library of Congress Cataloging in Publication Data
Main entry under title:

Innovations in biotechnology.

(Progress in industrial microbiology ; v. 20)
Organized by the Netherlands Biotechnological Society.
Bibliography: p.
1. Biotechnology—Congresses. I. Houwink, Eric H., 1929- . II. Meer, Robert R. van der, 1946- . III. Netherlands Biotechnological Society. IV. Series.
QR53.P7 vol. 20 660'.62 s [660'.6] 84-8185
[TP248.2]
ISBN 0-444-42275-7 (U.S.)

ISBN 0-444-42275-7 (Vol. 20)
ISBN 0-444-41666-8 (Series)

Printed in The Netherlands

FOREWORD

Biotechnology in the Netherlands has presented itself in this one-day symposium. A survey was given of the results of biotechnological research carried out at universities, institutes and industries in the Netherlands. At the same time, Dutch biotechnologists were provided with a meeting place where many aspects of their work could be thoroughly discussed. The decision to have the presentations in the form of poster sessions, covering eight areas each elucidated by a convener, allowed maximum exchange of scientific information by the attendants of this symposium.

Three categories of participants

The interests of the more than 400 participants differed according to their various backgrounds - research, industry or the civil service.

The research scientists will primarily have participated with the idea of learning more of the work carried out in fields related to their own and to establish new contacts both with colleagues in research and with industrial people. Furthermore, over 150 of the participating scientists took the opportunity to present their own work.

The industrial people will have participated because this symposium gave them a chance to get acquainted with the newest developments at universities and institutes, and also to give others some idea of the work carried out in industrial laboratories.

The third category, the civil servants, will have been primarily interested in the infrastructure of Dutch R&D in biotechnology. They are the people who have to implement government policy with respect to the Innovation-Oriented Research Programme (IOP) for biotechnology that is beginning to emerge.

The visitors from abroad, numbering over 70, were most probably taking the opportunity to obtain a birds-eye view of the Dutch biotechnology scene.

In summary, the question of *why such a symposium was needed* has certainly been answered in different ways for the three different categories of participants. But that such a survey of research work in biotechnology in this country was opportune was a matter of general consensus.

Why such a symposium in the fall of 1983?

In answering the question *"Why such a symposium now?"*, two points are of importance.

The first relates to the organizing society, the Netherlands Biotechnological Society, which celebrated its fifth anniversary on the day of the symposium. This fifth anniversary was thought to be an excellent opportunity for organizing such a multi-purpose scientific happening.

The second relates to the Innovation-Oriented Research Programme that is being established by the Netherlands Government. The preparations for this programme were started early in 1980. Two years ago the programme started unofficially, and half a year ago the green light for the programme was given by the Minister for Science and Education. It was felt that November 1983 was an appropriate moment for the presentation of the work being carried out in the scientific fields that together form the scope of this programme.

What has been presented at this Symposium?

Owing to the large number (158) of posters presented, it is not easy to convey *what has been presented at this Symposium*. We shall attempt to do so with the help of several tables.

In accordance with the main fields of the study groups of the Netherlands Biotechnological Society and the priority fields of the Innovation-Oriented Research Programme, the posters submitted were distributed over eight sections.

TABLE 1

Distribution of the posters over eight areas and indication of the multidisciplinary character of the work presented

Area	number of posters presented	number of interdisciplinary posters presented
A. Biocatalysts	25	10 (40 %)
B. Environmental Biotechnology	26	5 (20 %)
C. Plant/Animal Cell Technology	13	5 (38 %)
D. Somatic Cell Hybridization	8	1 (12 %)
E. Bioreactors	18	6 (30 %)
F. Downstream Processing	8	1 (12 %)
G. Applied Molecular Genetics	33	2 (6 %)
H. Applied Microbial Physiology	27	2 (8 %)
Total	158	32 (20 %)

In Table 1, the number of posters in each section is shown. It is clear that the section Applied Molecular Genetics accounts for the largest number of posters. This implies a relatively large research activity in this field in the Netherlands. Other actively developing fields are: Biocatalysts, Environmental Biotechnology, and Applied Molecular Physiology. The field of Bioreactors is developing somewhat more modestly. In the case of Plant and Animal Cell Technology, Somatic Cell Hybridization and Downstream Processing it might be supposed that, because of the small numbers of posters presented, these areas are still relatively undeveloped. But for somatic cell hybridization this does not agree with the actual situation. Here, the low number can be attributed to the fact that many groups active in this field do not yet bring their work in relation to biotechnology but still place it in a medical context.

For the two other fields, especially Downstream Processing, which could correctly be considered an undeveloped area, stimulation by means of the Innovation-Oriented Research Programme on Biotechnology is in progress. In Downstream Processing in particular, there is an urgent need for more process-integrated research and development work, since the economy of many biotechnological processes in the future will depend to a large extent on efficient product recovery.

The second column of Table 1 reflects the interdisciplinary or multidisciplinary nature of the work presented. This is an indicator for the involvement of two or more basic disciplines, which after all is essential for the development of biotechnological applications. Roughly 20 % of the work presented (32 posters) is of an interdisciplinary nature. The highest scores are found in Biocatalysts, Plant and Animal Cell Technology and Bioreactors. The low figures of around 7 % for Applied Microbiological Physiology and Applied Molecular Genetics imply that the term "applied" does not cover the more basic type of work in these fields.

In Table 2, the posters presented have been catalogued according to their place of origin. The fact that biotechnology is still in its early days shows clearly from the high percentage of posters that originates from universities (60 %). About 25 % of the posters were submitted by institutes of applied research, while 15 % comes from industry. Comparing this last figure with the figure of even less than 10 % for industrial work presented at the second European Congress on Biotechnology in Eastbourne (1981), it may be concluded that Dutch industry has participated actively in this poster symposium.

TABLE 2

Origin of the posters presented

Place	number of posters		percentage
Delft University of Technology	37		
Agricultural University Wageningen	24		
State University Groningen	14		
Free University Amsterdam	13		
State University of Leiden	4		
University of Amsterdam	3		
Erasmus University Rotterdam	3		
Eindhoven University of Technology	2		
State University of Utrecht	1		
TOTAL FOR UNIVERSITIES		101	60 %
Organization for Applied Research, TNO	27		
National Institute of Public Health, RIV (Bilthoven)	7		
Institute for Storage and Processing of Agricultural Products, IBVL (Wageningen)	2		
Research Institute ITAL (Wageningen)	2		
Central Veterinary Institute, CDI (Lelystad)	1		
Research Institute of Animal Production, IVO (Zeist)	1		
Netherlands Institute for Dairy Research, NIZO (Ede)	1		
Netherlands Cancer Institute, NKI (Amsterdam)	1		
Sprenger Institute (Wageningen)	1		
TOTAL FOR INSTITUTES		43	25 %
Gist Brocades (Delft)	10		
Co-operative Starch Manufacturers, AVEBE (Veendam)	3		
Central Sugar Manufacturers, CSM (Amsterdam)	3		
Organon (Oss)	3		
Unilever (Vlaardingen)	3		
Heineken (Zoeterwoude)	1		
Dutch State Mines, DSM (Geleen)	1		
TOTAL FOR INDUSTRIES		24	15 %
OVERALL TOTAL (10 collaborative posters)		168	

In Table 2, the number of contributions from each laboratory is indicated in descending order. It shows concentrations of biotechnological work at the universities of Delft, Wageningen, Groningen and Amsterdam. Of the institutes, TNO (the Organization for Applied Research) and RIV (the National Institute of Public Health) show the highest scores.

The quality of biotechnological research in the Netherlands

The question just dealt with leads to another: *"What was the quality of the work presented?"*. This question of course will not be answered in detail here since the conveners will give this point some thought in their respective introductions.

It may be stated that the overall quality of the work presented was very good. Furthermore, it is encouraging that quite a number of posters, including many of industrial origin, present new and original findings and approaches. This indicates that in several modern biotechnological fields, research in the Netherlands meets high international standards.

Another point worth mentioning is that in the "strong" fields (Biocatalysts, Environmental Biotechnology, Applied Molecular Genetics, Applied Microbial Physiology and also Bioreactors) there appears to be not much overlap between the various research groups involved. This points clearly towards complementarity among the groups, in many cases leading to symbiotic relationships through co-operative projects. In this connection, it must be stressed that biotechnology in the Netherlands has a very open character. Furthermore, it is noteworthy that international collaboration has already been established in a number of cases and will certainly be developed further.

Participants

Two groups of participants should be mentioned: those who organized the symposium and the participants among whom the authors of the posters may be considered as the most active part.

The symposium was organized by the Netherlands Biotechnological Society, but in the preparation and the actual running of the symposium the eight conveners played a crucial role. They described the main lines of development in their respective fields and focussed attention on the various poster presentations as Dutch contributions to the advancement of science. At the same time, the uninitiated in the audience were given a glance at the headlines of scientific areas related to their own disciplines, thus bridging the gaps in professional understanding between the basic sciences of biotechnology, which is the main purpose of the Biotechnological Society.

The more than 400 participants originated from:

abroad	- 15 %
universities	- 46 % (students 7 %)
research institutes	- 12 %
industry	- 24 %
civil service	- 3 %

These percentages lead to the conclusion that biotechnology in the Netherlands :

- is internationally oriented
- has a solid base in the universities
- is of active interest to institutes for applied research
- is an attractive field for industry
- is actively followed by the Dutch Government.

It is a pleasure to see many of the posters presented taken up as full papers in these proceedings. A total of 42 papers, based on one or more of the posters, has been collected in this book. As a result, the scientific work presented at the symposium will remain available for later consultation and will serve as an introduction to everyone seeking rapid orientation on biotechnology in the Netherlands. Consequently, the objectives of the symposium were not only attained on this memorable day of November 22, 1983, but will last much longer.

The editors:

Eric H. Houwink
President, Netherlands Biotechnological Society, Microbiological R&D Labs, Organon International, P.O. Box 20, 5340 BH Oss, The Netherlands.

Robert R. van der Meer
Secretary/coordinator the Netherlands Programme Committee on Biotechnology, Central Institute for Industrial Development CIVI, P.O. Box 18531, 2502 EM The Hague, The Netherlands.

ACKNOWLEDGEMENT

The organisers gratefully acknowledge financial support from:

- The Netherlands Innovation Oriented Programme on Biotechnology (IOP-b)
- The Biological Council of the Royal Netherlands Academy of Sciences (KNAW)
- The Royal Netherlands Chemical Society (KNCV)

CONTENTS

Innovations in Biotechnology, edited by E.H. Houwink and R.R. van der Meer, 1984
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

WEAK POINTS IN BIOTECHNOLOGY

N.W.F.KOSSEN
Bioengineering Group, Delft University of Technology.
Julianalaan 67, 2628 BC Delft

Biotechnology is a serious subject. It is also considered to be a promising activity. During meetings with coleagues from other diciplines, biotechnologists are often congratulated for their relatively comfortable position . Therefore, someone might ask, is "weak points in biotechnology" not a "contradiction in terms"? I don't think it is. It is about time to take a relativist's point of view concerning biotechnology and to deal with the subject less seriously than usual.
One of the reasons is that the audience of today must be satiated with biotechnology after a whole day's poster session. Another good reason is that taking one's activities too seriously is prohibitive for the development of new ideas. This however is a serious reason for not being serious, and therefore a true contradiction in terms.

Today I will use team sport as a model for biotechnology. I think this is a useful model. Teamwork is typical of biotechnology, and so is competition. For example we come together a couple of times a year for national or international tournaments. Referees carefully ensure that all participants in biotechnology stick to the rules. The analogy can be developed further.

If there are weak points in a match, there is a general tendency to blame someone or something. The players blame the playground and/or the referee. The public usually blames the players. In my opinion all those involved in the match can be blamed from time to time. If one of the three groups of participants involved (team, referees and public) doesn't live up to expectations, the result is an unattractive match. Extreme circumstances aside, the condition of the playground is usually less important than the contribution of the participants.
Because one cannot say that the playground for biotechnology is in bad shape, weak points must necessarily be the result of the behaviour of the players, the referees and the public.
Who are they?
The players are the scientists, engineers and commercial people involved in research, development, plant design, production and marketing. The referees are a mixture of scientists and authorities. They set up the rules and control them. The public is society as a wh . If they are not able to attend the match, their opinion is formed mainl / the newspapers.
Now let us see how this system behaves, starting with the "pure" sciences, and ending up with the authorities and the public.

BIOCHEMISTS:

Their contribution to biotechnology is considerable, as nobody will deny. They experiment very carefully too. However, they sometimes tend to believe that they are the only ones who really understand what is going on in biology. Furthermore they only want to work with very pure systems, generally one enzyme/one substrate systems. A biochemist who works with two substrates or enzymes simultaneously is quite someone. Insofar as he is interested in impurities, it must be a "pure" impurity: one well defined chemical substance. Consequently it is often quite difficult to translate the laboratory results to production scale, where enzymes and substrates are seldom pure.
For the development of pure sciences, well defined systems are necessary;

however "filling the gap" between the laboratory and the plant is a necessity too and cannot be left entirely in the hands of engineers.

A very strong point of biochemists is that they posses a songbook (Baum, 1982). An example of this contribution to civilized scientific life is a strophe of the song "Photosynthesis" from the book as shown below (tune: "Auld Lang Syne").

When sunlight bathes the chloroplast,
And photons are absorbed
The energy's transduced so fast
That food is quickly stored.
Photosynthetic greenery traps light
The spectrum through
Then dark pathway machinery
fixes the CO2.

Reprinted with permission from:
H. Baum, The Biochemists' Songbook
Oxford 1982, Pergamon Press

This gives them a 1-0 advantage over all other contributers to biotechnology.

MOLECULAR BIOLOGISTS:

They are the successors of the classical geneticists. Classical genetical methods are very empirical. Someone from Gist Brocades once gave a good comparison for the methods in classical genetics. Suppose he said that you are standing alone in one of the pastures around Delft, blindfold and with a shotgun in your hands. You have to pull the trigger at an arbitrary moment with the barrel in an arbitrary direction. Under these circumstances one is expecting you to shoot a parrot, a green one of course. (For those not familiar with the Dutch wild life: green parrots are rather scarce in the Netherlands). The weak points of this method are rather obvious, but it is still a very important one.

The molecular biologist is not an empirist. In fact he really works as an engineer. Genetic engineering therefore is a very good word to describe his activities. However, engineering methods are usually easy to understand even for the layman. This of course can never be the intention because it has a very negative influence on the status of his activities. Therefore he had to conceal what he is doing, to create a barrier as it were. This is where molecular biologists have been very successful indeed. It is absolutely impossible to understand their cryptography if one is not an expert in the field. Whether this is a weak point or not depends on the point of view of the observer. Personally I have some doubts.

MICROBIOLOGISTS:

One of Murphy's laws reads: "Never repeat a successful experiment". There is no need to teach this to a microbiologist because the majority of them never does, and for good reason; it is very difficult to reproduce biological experiments. Let me make clear what I mean with an example. In many microbiological publications one growth curve has been measured under one particular condition, a second growth curve under another condition and so on. Virtually never has an attempt been made to repeat the measurement of one growth curve under one particular condition. Fortunately the positions of points on a curve and of curves relative to one another already give some idea about the reproduceability of the results. Therefore the results of this weak point are neutralized to some extent. I have to admit that many other scientists (and engineers) suffer from the same shortcomings in experimental design, but it is a weak point.

Microbiologists cannot work with systems as pure as those of the biochemist.