Proceedings of the International Workshop on Interaction Between

MEDICINE AND ENGINEERING

New Horizons for Advanced Technology

The S. Neaman Institute Press

Proceedings
of
The International Workshop on
INTERACTION BETWEEN MEDICINE AND ENGINEERING: NEW HORIZONS IN TECHNOLOGY

December 8–10, 1991

Edited by

Professor Samuel Sideman
The Julius Silver Institute
Department of Biomedical Engineering
Technion–Israel Institute of Technology
Haifa 32000 Israel

THE SAMUEL NEAMAN INSTITUTE PRESS
Haifa 1992 Israel

All opinions expressed and arguments employed in this publication are the responsibility of the contributors and do not necessarily represent those of the S. Neaman Institute.

Printed in Israel by **The Neaman Institute Press**, March 1992

It is difficult to say what is impossible,
for the dream of yesterday
is the hope of today
and the reality
of tomorrow.

Robert H. Goddard

The International Workshop on Interaction Between Medicine and Engineering: New Horizons in Technology

Sponsored By

Technion–Israel Institute of Technology

The Julius Silver Institute of Biomedical Engineering
The Bruce Rappaport Faculty of Medicine
The Samuel Neaman Instutute for Advanced Studies in Science and Technology
The Technion R&D Foundation Ltd.

The Kupat Holim Health Insurance Institution

The Israel Export Institute

Advisory Committee:

Prof. M. Sela, Weizmann Institute
Mr. E. Hurvitz, President, Teva Pharmaceuticals Ltd.
Mr. N. Fassa, Director–General, Kupat Holim
Mr. S. Parag, President, Elscint Corporation
Dr. M. Mashiah, Director–General, Ministry of Health
Mr. Y. Erlich, Chief Scientist, Ministry of Industry and Commerce
Dr. M. Wiener, Chief Medical Officer, Zahal (IDF)
Prof. Y. Shapira, Tel Aviv University and Medical Director – Kupat Holim
Prof. A. Shitzer, Dean, Faculty of Mechanical Engineering, Technion–IIT

Organizing Committee:

Prof. S. Sideman, Chair, Department of Biomedical Engineering, The Julius Silver Institute (Co–Chair)
Prof. M. Silberman, Dean, Facutly of Medicine, Technion–IIT (Co–Chair)
Prof. D. Weihs, Director, S. Neaman Institute
Dr. A. Rofe, Director–General, Carmel Hospital
Prof. S. Einav, Head, Biomedical Engineering Program, Tel–Aviv University
Mr. Y. Dvir, Managing Director, Technion R&D Foundation, Ltd.
Ing. D. Kohn, Projects Coordinator, S. Neaman Institute
Dr. I. Maor, Head, R&D Liaison & Technology Transfer, Technion R&D Foundation, Ltd.

WORKSHOP CONTRIBUTORS

Dr. Rudolf Andreatta
Exploratory Research
Pharmaceuticals Division
Ciba-Geigy
Basel CH-4002
Switzerland

Professor Eliahu Antebi
Surgery
Beilinson Medical Center
Petach Tikvah

Dr. Amnon Barak
Director
Germany-Israel Foundation
Jerusalem, Israel

Dr. M. Borstein
Beilinson Medical Center
Petach Tikvah

Judge Amnon Carmi
Haifa

Mr. Yehuda Dvir
Technion R&D Foundation, Ltd.
Technion-IIT
Haifa, 32000

Professor Shmuel Einav
Head
Biomedical Engineering Program
Tel-Aviv University
Ramat Aviv, Israel

Mr. Yigal Erlich
Israel Ministry of Industry and
Commerce
Mavo Hamatmid 4
Jerusalem

Mr. Nachum Fassa
General Director
Kupat Holim Clalit
Rehov Arlozorov 101
Tel Aviv

Mr. Mark G. Frantz
President
Frantz Medical Development Ltd.
595 Madison Ave.
New York, NY 10022 USA

Professor Dov Front
Dept. of Nuclear Medicine
Rambam Hospital
Haifa

Mr. Uzia Galil
President
Elron Electrical Industries
P.O. Box 1573
Haifa, 31015

Dr. Max Herzberg
General Director
Orgenics Ltd.
New Industrial Zone
Yavne, 70650

Mr. Eli Hurvitz
President
Teva Pharmaceuticals, Ltd.
P.O. Box 3190
Petach Tikvah, 49131

Dr. Avinoam Kadouri
Dept. of Biophysics
Weizman Institute of Science
Rehovot

Dr. Yoram Karmon
President
Interpharm Laboratories
Science Based Industrial Park
Kiryat Weizmann
Ness Ziona, 76110

Mr. Peter Morgan Kash
Senior Vice President
The Castle Group Ltd.
375 Park Avenue, Suite 1501
New York, NY 10022 USA

Dr. Peter G. Katona
Vice President
Biomedical Engineering Program
The Whitaker Foundation
1133 Connecticut Ave. NW, Suite 1010
Washington, DC 20036 USA

Ing. David Kohn
Projects Coordinator
S. Neaman Institute
Technion–IIT
Haifa, Israel

Professor Noah Lotan
Department of Biomedical Engineering
Technion–IIT
Haifa, Israel

Dr. Ilana Maor
Head
R&D Liason & Technology Transfer
Technion R&D Foundation, Ltd.
Technion–IIT
Haifa, Israel

Dr. Moshe Mashiah
Director–General
Ministry of Health
Jerusalem, Israel

Professor Tom B. Miller, M.D.
Mallinckrodt Inst. of Radiology at
Washington Univ. Med. Ctr.
Nuclear Medicine
510 S. Kingshighway Blvd.
St. Louis, MO 63110–1076 USA

Mr. Robert Nicholas
McDermott, Will & Emery
1850 K St., NW
Washington, DC 20006–2296 USA

Mr. Yair Ofek
Director
Marketing Division
Israel Export Institute
Rehov Hamered 29
Tel Aviv

Professor Yoram Palti
Head
Rappaport Institute
Technion–IIT
Haifa, Israel

Mr. Shmuel Parag
President
Elscint Corporation
Science Industry Center
P.O. Box 550
Haifa, 31004

Professor Shmuel Penchas, M.D.
Haddassa Hospital
Ein Kerem, Jerusalem

Professor Michel Revel
Department of Virology
Weizman Institute of Science
Rehovot

Table of Contents

OPENING SESSION

Chairman: Professor Zehev Tadmor

Congratulations

Moshe Nissim
Deputy Prime Minister
Minister of Industry and Commerce
Government Offices
Jerusalem, Israel

Enhancing the interaction between medicine, engineering and industry will have an important humanitarian effect, and will also contribute to the development of Israeli economy.

Israel is facing a unique challenge of absorbing new immigrants and creating new employment opportunities for 500,000 people during the coming 3–4 years.

The cooperationg between the needs of medicine, engineering and industry has the potentical of creating new activities of a promising nature and to cause the establishment of sophisticated industry which the country yearns for at this time.

I wish you a fruitful workshop – and a fruitful and positive outcome – to each and every one of you and to the State of Israel.

-- * --

Professor Yuval Ne'eman
Minister of Science and Technology
Government Offices
Jerusalem, Israel

I would like to congratulate you on your initiative in organizing a workshop to enhance the interaction between medicine, engineering and industry. This is an important step, because it is important to use the vast knowledge accumulated with scientific researchers ot the benefit of mankid. The meeting is particularly important in Isarel at this time because this Workshop may be the source for entrepreneurship which will promote employment of new immigrant engineers and doctors in Israeli sophisticated industries. I would be most happy if the participants accentuate this point in thier discussions.

My congratulations to all of the participants. I wish you all fruitful and enjoyable discussions.

Ehud Ulmert
Minister of Health
State of Israel Ministry of Health
Jerusalem, Israel

My congratulations to the organizers and participants of the workshop carried out at the Technion.

Applying new advanced technologies to medicine enables us to solve difficult medical problems, helps the system, and certainly helps those who require its assistance.

At this time, when I am hard at the task of trying to find a solution to the problems ailing our medical system, I see great advantage in any activity which enables progress and multidisciplinary cooperation.

I wish you great success.

-- * --

Greetings

Zehev Tadmor, President
Technion–Israel Institute of Technology
Haifa

It is a great pleasure to open this international workshop on engineering and medicine because medicine and engineering are two great ancient professions, both dedicated to the betterment of the human condition. Medicine helps men and women cope with the well being of his body and mind, whereas engineerng helps man cope with his environment, providing for his food, shelter and his standard of living. Both are crucial in man's struggle for survival. To a large extent, these two professions have made us the only animal that does not fit into an evolutionary niche destined for it by nature, but creates out his own niche and makes its own unique physical and mental and cultural environment.

Medicine and engineering have come from *practice* and *not* from *theory*. They have both *preceded* science by hundreds of centuries but they have both been enormously enriched by the permeation of the sciences into their midst. Because, the central task of natural sciences is, as explained by Herbert Simon, to make the wonderful commonplace: to show that com–plexity correctly viewed is only a mask for simplicity. Indeed dissecting medicine and engineering by the scientific tools of analysis uncovers not only the simplicity behind the complexity, and makes them understandable to humans, but also enables the recombination, the synthesis of the components into magnificent new controllable and *understandable* complexities.

The greater the decomposition down to the cell, the molecule, the atomic levels, the greater the potential for reassembling, creating and synthesizing novel and immensely important healing solutions, properties and products.

It is science that weaves medicine and engineering together. This is why you find them both on the Technion campus.

Fusing together medicine and engineering, both permeated by the sciences, creates a synergistic amalgam of enormous potential for the betterment of the human condition, as long, of course, as an ethical plan is followed, let alone the potential it creates to enrich any economy hungry for science and technology, innovation and progress.

It is in this spirit of scientific progress that I wish you a successful deliberation.

Daniel Weihs, Director
The S. Neaman Institute
Technion–Israel Institute of Technology
Haifa

Israel is a small country, poor in natural resources. In order to compete and thrive in the global economy of the 90s and the next century, it must be an advanced, flexible, industrial power with an emphasis on high–tech, high added value exports. To develop such an industrial base, its scientific and technological infrastructure must match the best. The Samuel Neaman Institute for Advanced Studies in Science and Technology, established as a policy research center searching for solutions to national problems in science, industry, education, health and social development, has recognized the biomedical industry as one of the potential growth sectors in Israel. In view of the highly medically–oriented immigration from Eastern Europe, this area has gained immediate importance.

This Workshop has divided the subject area into three stages – the medical requirements, engineering and technological solutions, and marketing of products. Only a combination of all three can lead to the thriving export industry we all hope for.

The S. Neaman Institute is delighted to have this opportunity to collaborate with Kupat Holim, Israel's largest health insurance organization, the Israel Export Institute, and the Technion R&D Foundation in organizing this Workshop and to congratulate the men who originated the concept – Professor Sideman and Professor Silberman.

I would like to thank Kupat Holim's Bendori Center for hosting the Workshop and especially thank David Kohn, Ilana Maor, Ruth Rivkind and Lindy Papoff for all the hard work and long hours which culminated in having all of us here for what I am sure will be a great success.

Maxim Sheinfeld, Chairman
Board of Directors
Kupat Holim Clalit
Tel Aviv

On behalf of Kupat Holim and of my colleague Mr. Nahum Fassa, the Director General of Kupat Holim to say a few words of greeting to this assembly. As Israel's largest HMO, Kupat Holim has a major interest in the deliberations taking part here. My generation of physicians has seen a complete revolution of medicine during the last 25 years, where medicine is becoming less of an art, and more of a science. Unfortunately, this trend not only has benefits, but also for us, as an HMO, some disadvantages. The cost of medicine is soaring, and no insurance company or an HMO such as ours can expect to continue to insure reasonably. The benefits have been enormous from the progress done in medical engineering and biotechnology, such as: miniaturization, non-invasive examination, leading to better understanding of disease and of physiological processes. I think that time should be taken in your deliberations to consider the cost-benefit of these enormous advances, which unfortunately are benefit only to a limited part of the world, while huge parts of the Third World, and Eastern Europe are unable to benefit, not only from the advanced technologies which we take for granted, now in modern medicine but even of much more basic advances. I think that it is time for stocktaking and trying to use the knowledge and the possibilities of the science of biotechnology and medicine, to bring down the cost of medical delivery systems and medical care, and to find new ways where the existing technology will be made more readily available, cheaper, and simpler to use, where advances in Teleimaging and Satellite communications will enable better medical service by paramedics in remote areas without access to large medical establishments with which we are all familiar. I think that for all of us in medicine and engineering, the era of unlimited budgets has been ended. We no longer can rush ahead and "cost be dammed". We must make careful consideration of cost benefit. As physicians, that those decisions of setting national priorities and list of services rendered shall be made by politicians, unfortunately, it very often falls on us as physicians to make those unsavory decisions of who shall live and who shall die, because the technology is too expensive or unavailable. I think that the only hope for better and more rational use of the present state of art in Biomedical Engineering depends on groups such as yours, where you will devote your efforts to making the existing technology cheaper and more readily available, I wish you fruitful deliberations and thank you for your invitation to address the meeting.

Yair Ofek, Director
Marketing Division
Israel Export Institute
Tel Aviv

When we were first approached to be a co-sponsor of this event, we thought about it, we said yes, and we put some money into it as well. The main idea of the Export Institute to take part in this very important workshop is that we are always looking to identify and encourage the relative advantages that the Israeli industry has. We believe that the integration between engineering, skilled manpower, medical scientists and medical industry is a relative advantage that Israel has. The fact that the export of medical equipment grew from about 28 million dollars a decade ago to about more than 300 million dollars in 1991, says it all. I congratulate you on the opening of this Workshop, and wish us all productive deliberations.

Drugs and Vaccines in the Era of New Technologies

Michael Sela
Department of Chemical Immunology
Weizmann Institute of Science
Rehovot Israel

The declared purpose of this workshop is to emphasize the necessity for a fruitful interchange in cooperation between biomedical sciences, engineering and what is called "the economic and industrial ingenuity," in order to reap the fruits of progress. This involves an extremely broad range of activities, including diagnostics and therapy, as well as an immense scope of engineering developments. In this introductory lecture I shall limit myself to new approaches to drug delivery and drug discovery, and I shall give examples from our own work on synthetic approaches to vaccines and a macromolecular polymeric drug candidate against multiple sclerosis. Actually, in the great majority of cases, but not in all cases, the greatest discoveries emanate from research for its own sake, and I will give you just two examples.

Sir James Black, the Nobel laureate, was involved in pharmaceutical companies, and knowing more or less precisely what he wanted to get, worked for years and developed extremely successful drugs, both for high blood pressure and against ulcers. On the other hand, you have monoclonal antibodies. When Cesar Milstein first discovered monoclonal antibodies, he went to the Medical Research Council, suggesting that they should be patented. The answer apparently was that nobody would ever make a penny out of it. And it is only years later that monoclonal antibodies were patented – for special uses.

Concerning the whole notion of pure and applied research, I intensely dislike both expressions, because when you say pure research, you imply that the other kind is impure, and I prefer to talk about applicable research rather than applied research, because so little of what is applicable ends up being applied. I come from the Weizmann Institute where our philosophy is "research for its own sake," but whenever something comes out of this free research that might possibly be of any use, we try to follow it up energetically and to see whether we can end up by leading to a product. It is extremely important, and the example I shall give later illustrates it. Also, if we, in research in this country, reach something which might possibly be a product, we should for obvious reasons, give a great preference to have it developed by Israeli industry.

The first thing I wanted to discuss is actually an old story, the notion of the drug delivery. Approximately a quarter of a century ago, people started realizing that we keep discovering new drugs, but we administer them the way they were delivered in the Middle Ages. Instead of delivering them where we need them, or instead of having a steady level of a drug in our

bloodstream, we give pills several times a day. The levels of the drug to up and down, and they go everywhere. It if very difficult to define who was first in the efforts to develop new technologies in this area, but among the first ones was the ALZA Company. For many years this company suffered because – I think – it started too early, but they ended up in having enormous success by introducing this notion of either slow, steady delivery, or targeted delivery. In other words, you swallow something which lasts for a long time and, by the way, this is also the dream of the vaccine of the future. In the Third World, in most places, you can get up to 85% of the children for the first injection of a vaccine, but you are happy to get 20% for the third injection. This is a big challenge. I know several groups working on it but it has not been solved yet: how to have a drug that you can swallow, or something injected, of which one part would be available immediately. Only after whatever is available disappears totally, some coating starts being digested or dissolved, and several months later you get the equivalent of a second immunization and, only a year later, a third immunization. This would be the solution to vaccination. This is something not yet solved. But it is interesting, in terms of product, and here we have the intermingling of the three notions that were discussed at the beginning.

Technically, ALZA was extremely successful; they took pilocarpine needed for glaucoma and instead of putting these drops in the eye, you could put them under your eye, something which dissolves and you can apply it once every few months. It was technically very successful, but, in a marketing sense, it was a failure and they withdrew it. People still preferred to put drops in their eyes every day. Was it because of the packaging or the way in which it was sold? I do not know. But altogether, this approach today is, of course, a huge success. It is a huge industry. Somebody else came up first with the nitroglycerine patch.

I want to move to something which is rather novel: the new approaches to drug discovery. You know, to develop a drug today is extremely expensive, anywhere between one hundred and two hundred million dollars. Normally, you take whatever is available, almost at random, and you spend years checking tens of thousands of materials. Now, for the purpose of drug discovery there are several new approaches. You would like to have millions of compounds prepared extremely quickly and available to be tested. You would like to have, if not millions, at least thousands of receptors, including monoclonal antibodies. These are the substances with which you want to test whether any of these millions of compounds can react. If they can react, they might be candidates for a drug. Thirdly, you must have techniques by means of which you are capable of testing this interaction on tens or hundreds of thousands of compounds within days. There are several such approaches, and there is one company, Affymax, which I would like to mention in this connection. Their principle is to produce an enormous amount of peptides by a new technology, combining biotechnology, genetic engineering, on the one hand, and microelectronics, on the other hand. It combines techniques pioneered for the semiconductor industry, notably photolithography, miniaturization and parallel fabrication, with bioorganic chemistry to assemble peptide compounds on a silica chip. By the technique developed it is possible to prepare, on one centimeter square, 65,000 different peptides in 48 hours. In one approach, the potential drug candidate is fixed and the receptor floats. But you can also have it the other way around, with the receptors free and the peptides floating.

Now let me come to things closer to my own expertise, and I would like to distinguish between two kinds of vaccines. Generally speaking, when we talk about vaccines, we think about infectious diseases. More than 20 years ago we started thinking about how we can produce vaccines which contain only what is necessary [1]. You never want to improve on nature when nature is good. Take an example like cholera. You oblige people going to certain parts of the world to get an injection against cholera, which at best gives you three months protection for 30% of those immunized. If go there again for a second time, you should again be immunized. You would have high fever and your arm would swell, because you had in that original vaccine a lot of unnecessary junk which was very immunogenic and led to a good – but unnecessary – immune response. The notion was that you would like to "distill off" and cut out just that small chemical piece which is necessary for efficient immunization. This idea is by now both a big business and a very big research area. We first showed that it is possible to produce a totally synthetic macromolecule which produces antibodies that can neutralize a virus [2, 3]. Then, both in the case of diphtheria [4] and cholera [5,–7], we could make synthetic polypeptide antigens, leading to antibodies capable of neutralizing bacterial toxins.

The other kind of vaccine which I want to discuss here, is what I call "immunomodulatory vaccine against autoimmune diseases." Our initial experience was with a synthetic polymer of amino acids which is capable of suppressing other onset of an experimental disease in animals, allergic encephalomyelitis. We wanted this polymer to resemble to some extent a basic protein which is present in the myelin sheath of the brain. It took us some years to realize that it resembled it more than we bargained for, because actually, it cross–reacted immunologically with this basic protein. The experimental disease is caused by the myelin basic protein when injected in a mayonnaise of water and oil in which you plug in killed myobacteria, denoted complete Freund's adjuvant. We found that our synthetic polymer is never able to induce the disease but is as efficient as the original myelin basic protein in suppressing the disease when given in aqueous solution. This led to many studies, which ultimately reached the stage when we moved to humans and to multiple sclerosis.

Multiple sclerosis exists in two kinds: one in which you get an attack and you get better, called the exacerbating–remitting type of multiple sclerosis, and the other one is chronic–progressive, where you get worse and worse. I shall describe here only the double blind clinical trail which was published four years ago in the New England Journal of Medicine [8]. Only people who were rather young, 20 to 35 years of age, and who were not too sick, were accepted for the trial, but they had to have at least three documented attacks in the previous two years. The 23 patients on placebo were expected to have 69 attacks and indeed they had 64 attacks. Of the 25 that received a 20 milligram daily injection of the Cop 1, one would expect 75 attacks and they had only 16. Among those 13 less advanced in the disease, instead of 39 attacks, there were just two attacks. This was very encouraging, encouraging enough to interest the Teva company in Israel to start developing it. It is a very difficult synthesis and it actually took several years to move form our heroic efforts with one technician preparing up to 35 grams/month, to work in batches of one kilogram. At this stage, we have close to 200 people on open trial in Jerusalem. Some of them are Israelis and some of them come from different parts of the world. As of last October, eleven centers all around the United

States started on phase 3 clinical trials of 240 patients, coordinated by Dr. Ken Johnson from the University of Maryland in Baltimore.

Recent studies have shown that Cop 1 inhibits the stimulation by the myelin basic protein of T cells specific for the basic protein, both in mice and in humans [9, 10]. Thus, most probably, the effect of Cop 1 is due to its immunological relationship to the basic protein of the myelin sheath of the brain. This is the reason for my calling this polymeric drug an immunomodulatory vaccine against an autoimmune disease.

Another important technology – monoclonal antibodies which I shall not describe here in detail – will most certainly grow in its impact in the near future. I refer to monoclonal antibodies. These serve as diagnostic tools, as separation materials, as catalysts, as imagery substances, after modification with isotopes, and as chemotherapeutic agents, as such, or after derivatization with drugs or toxins. In the last case, they serve as "guided missiles" delivering the drugs or toxins to the relevant cells or tissues.

Finally, I tried in this lecture to give just a few examples of the battery of cardinally new approaches to the drugs and vaccines of the 21st century. The one thing we can be sure of is that the most important and interesting developments of the next decades are not even predictable now.

References

1. Sela M: *Bull Inst Pasteur* 72:73; 1974.
2. Langbeheim H, Arnon R, Sela M: *Proc Natl Acad Sci US* 73:4636; 1976.
3. Arnon R, Parant M, Chedid L: *Proc Natl Acad Sci US* 77:6769; 1980.
4. Audibert F, Jolivet M, Chedid L, Arnon R, Sela M: *Proc Natl Acad Sci US* 79:5042; 1982.
5. Jacob CO, Sela M, Arnon R: *Proc Natl Acad Sci US* 80:7611; 1983.
6. Jacob CO, Sela M, Arnon R: *Mol Immunol* 22:1333; 1985.
7. Jacob CO, Sela M, Arnon R: *Immunology Letters* 14:43; 1986.
8. Bornstein MB, Miller A, Slagle S, Weitzman M, Crystal H, Crexler E, Keilson M, Merriam A, Wassetheil-Smoller S, Spada V, Weiss W, Arnon R, Jacobsohn I, Teitelbaum D, Sela M: *New England J of Med* 317:408; 1987.
9. Teitelbaum D, Aharoni R, Arnon R, Sela M: *Proc Natl Acad Sci US* 85:9724; 1988.

Medicine, Technology and Karl Marx

Shmuel Penchas
Director-General
Hadassah Medical Organization
P.O. Box 12000, Jerusalem 91120

This paper presents an analysis of the problems inherent in the various health-care systems around the world. A comparison of data on health care in Israel, in which the decision to establish a National Health Law has been adopted recently, with England, where such a law has been in force since 1946, with the USA, which has no National Health Law, and with Greece will show that the health-care systems in these countries, perhaps surprisingly, produce a rather similar outcome, even though the budgets dedicated to health in each of these particular countries differ widely.

The introduction of highly sophisticated, expensive technology, computerization and ever-increasing specialization in medicine have revolutionized health care, bringing in their wake achievements which people could only have dreamt of only dozens of years ago. However, this very same technology has caused an ever-increasing expenditure on health, which few countries are able to afford. Health professionals the world over are facing painful decisions on priorities in health care, which raise the moral issue of equality, an ideal which philosophers, politicians and sociologists throughout the ages have grappled with.

Some particular aspects of dealing with issues of input/output, choices, equality and maximization of societal benefit are explored. Some conclusions on requirements for change are suggested here.

In 1865, three memorable events occurred in the life of Karl Marx. First, he completed his first draft of *Das Kapital*. Second, in poverty and misery, he borrowed 95 from his friend, Friedrich Engels, which he spent on food and on retrieving his wife's coat from the pawnbroker, so she could leave the house again. And third, while playing a parlor game with his daughters Jenny and Laura, he commented to Laura, who later noted it down: "Nothing human is alien to me." [1]

I'm not going to speak much about medicine, and very little about technology, except to say something I hadn't planned on saying. Which is: How many international conferences have you attended whose technology infrastructure failed to work? This ties up with something I'll be talking about a little later - something called Gammon's Law or the "theory of bureaucratic displacement."

I will be speaking about people – what they want, how they think about what they want, and the problems that result from this.

If we look, as human beings to whom nothing is alien, at medicine and technology during the past 50 years, four major developments strike the non–specialist. The first is medical technology itself. One of the greatest boons of modern medicine, it makes possible things we never dreamed of. At Hadassah, for example, we cut and we coagulate with light beams. We use a tiny laser beam to bore holes in the membranes of female ova, so increasing the chances of artificial insemination. Whether you look at imaging, at vaccine production, genetic engineering, molecular biology, fusing cells, the new technology has revolutionized the practice of medicine.

It has taken us to frontiers we draw back from crossing. Some of our physicians once showed me how they could create male or female infants by choice, with a predictability rate of 80%. Other have shown me how we have created genetic chimera in living beings: by transplanting single–gene bone marrow into double–gene thalassemia babies, we have given them a peripheral blood picture which shows a mixture of cells living as chimeras.

But this wondrous technology is a bane as well as a boon. One reason is its phenomenal cost, leading to built–in limitations: no barrel is without a bottom, and the deficit never disappears. Another reason is that medicine is unsure how to use its new wonder–tools. We have so much medical technology, but we have applied ourselves so little to devising the correct technology for using it. The solid work done on decision analysis – making decisions under conditions of uncertainty – has never penetrated medical practice. So the new machines are not always correctly used, which befuddles the whole issue and sends costs shooting even further upward.

The second major development in medicine in the past half–century is its ever–increasing specialization. Physicians today devote their lives to, say, antibodies or to performing one kind surgical procedure. There is an ocular surgeon in Minneapolis who does only cataract surgery. He gives his patients videos of their operation – videos that resemble performances of the Royal Ballet Company!

Specialization can be a boon. As the old joke goes, a specialist is someone who knows more and more, until he knows everything about nothing. But specialization is also a bane to medicine because it is the path to fractionalization – the shattering of the crystal into shards that cannot be pieced together again. It, too, sends costs soaring.

The third major development may sound unlikely. It is the disappearance of the doctor with his black bag from modern medicine. Today's doctors work in teams. Teams are a boon because there are things we cannot do alone. But they are a bane, too, because teams are often unsuccessful. Take, for example, a multi–trauma patient. The patient lies on the table and the trauma team works to save him. But, in truth, each member of the team is working on his own. The team concept has failed.

The last of the four developments is the socialization of medicine – in both its meanings. Let me take the less usual first: the Marxist meaning. This is the fact that people everywhere have come to regard medical care as among their basic primordial rights, together with food, clothing, shelter and security. Medicine has become part of this chain.

True, the expectations of an African in Kinshasa differ from those of an American in Philadelphia, But, whether the primary concern is clean water or AIDS vaccine, both are demanding medical care as their social right.

The more usual meaning of socialized medicine is that health care is publicly supported and financed. Both the boons and the banes of this are clear. On the plus side, life expectancy has leapt and infant mortality has plunged. On the minus, is the cost. Make no mistake. Cost colors every one of these four developments. Those of this fourth are enormous, particularly with the increased longevity which has brought average life expectancy around the world to around three quarters of a century.

To take an analogy from classical engineering with its input system, its black box which does something to the input, and its output: In today's medicine, we have new components in the black box. They are technology, specialization, teamwork and socialization. In a way, this reflects Marx's experience when he looked at inputs, black boxes and outputs in other systems. Technology is, of course, the means of production; specialization is the single worker; teams are for the workers in a social sense; and socialization is the society itself.

Having sketched the four major developments, with their boons and their banes, let's return to the idealized doctor with his black bag. In specialization, we are trying to reinvent this family doctor. In technology, we are trying to cut through the cold and the inhumane. But we should be looking further afield as well. We should be looking at what the black box does to our inputs. Crucial questions that we should be asking are: "What are we putting into the system?" and "What are we getting out of it?"

These are hard questions to answer, because we are dealing with matters that are conceptually very difficult. On the input side, the easiest item is the cost. Money can, of course, be looked at in several different ways. The classical way is to take a percentage of the GNP or similar, but this is not, in fact, very satisfactory if I want to compare Hungary with Israel, or with Greece or Turkey. Even those of us dealing with parity purchasing power get into a lot of trouble here.

The other basic input is, perhaps, simpler. It is the number of people employed in the system. But, once again, you can look at the total employed and see it as the custom of the particular country. There are certain nations were there are 27 mechanized tea–carts per physician, each tea–cart performing better than the physicians themselves. So, perhaps calculations based on numbers of employees are also unsatisfactory.

Perhaps we can take the number of physicians. But here we run into the questions of which physicians or whom do we regard as physicians. What, then, of the number of hospital beds

per capita? This, again, is misleading, as more and more medical care becomes ambulatory. Other parameters – the income of the physician, the cost per hospital bed per diem, the occupancy rate of hospital beds – are insufficient on their own. As you see, there are difficulties in calculating how much of its resources and production ability a country devotes to its health–care services.

If calculating input is difficult, output is even more so. What do you measure? Longevity is indicative, but it is influenced by many factors outside medicine – diet, housing, sewage, clothing, war, epidemics and general craziness. So longevity, which is probably the best measurement, is highly problematic. There is, of course, infant mortality, but that is distorted by all the same factors as longevity.

There are other measurements, but they are more complex still. There is, for example, not only length of life but the measure of its enjoyment by the person who lives it. There are scientific measurements for this – quality–adjusted length of life – something that I will return to shortly.

Another approach is that of Wilfredo Pareto. During a discussion based in the theories of Karl Marx, I am introducing someone whose sociological theory of elites was used – or misused – by the other end of the political spectrum. Pareto's indifference analysis underlay later measurements of a kind of social welfare function of the years of life remaining to the individual [2].

Let me explain. In essence, it's a combination of the system's efficiency with defined rights. Consumer satisfaction – not with the years of life, but with the system itself – can be brought into this calculation. This leads into Karl Marx's own area: the difference between the production of capital and its distribution, because you can be satisfied with what the system produces, but not with its distribution.

Let's look at some figures. Among the best studies of input versus output is one recently published by Milton Friedman [3], and I'm going to give you some of his figures together with a number of my own.

Milton Friedman looked at the United States over a 20–year period from the 1920s to the 1940s, and found that the proportion of the GDP spent on the health of American citizens increased by about 5% per annum. During that same period, hospital bed occupancy went up by an annual 2.5%, with the per diem cost of the patient increasing only moderately.

Compare this with the period 1946 to 1986, when inputs suddenly skyrocket. The number of people per hospital bed goes up seven times and the per diem cost of the patient increases 26 times, while the total number of beds falls by 50% and occupancy is down by 12.5%.

If we now take the year 1964 as our dividing line: the amount spent on research increased annually by 15% until 1964, with bed occupancy going down by 1%/yr and the cost of each

bed going up by 6%/yr. From 1965, research funding increased by an annual 2%, bed occupancy fell by an annual 2.5%, and the cost per bed increased by 9% each year.

In 1946, the share of hospitals in the system constituted 24% of expenses. Over 40 years later, in 1989, their share had increased to over a third – 36%.

Between 1946 and 1969, the number of health-care personnel doubled. Between 1969 and 1991, it trebled. The per diem cost per patient trebled between 1946 and 1969; between 1969 and 1991, it increased eight times.

In 1919, Americans spent about 4% of their total national income on health, and government input was only 15%. In 1946, it was up to 9%, with the government's share increasing. By 1965, the government was shouldering 25%, and 20 years later, 42%. That 42% is 6% of the USA's national income.

Private expenditure on health care remained minimal for decades. Between 1920 and 1960 it rose from 3.5 to 5%. By 1989, it was 8%.

The US is heavily endowed with physicians. In 1900, there were 150 physicians per 100,000 people. In 1987 there were 250. In 1930, American physicians were earning seven times the national mean. In 1962, their income was 12 times the national mean.

Life expectancy, however, shows some benefit from all these doctors. In 1900, white women could expect to live until they were about 50. In 1960, 75 was a realistic expectation, and by 1990 it was 80 [4, 5].

Now let's try and evaluate quality of care. The number of occupied hospital beds decreased by 1% per annum until 1965. After 1965, the decrease was an annual 2.5%, but the 6% increase in the annual cost of each bed had gone up to an annual 10% [6].

Max Gammon, the British National Health Service physician, formulated a "law" to account for this – the Law of Bureaucratic Displacement or Gammon's Law. Gammon's Law states that in large public service bureaucracies, an increase in input results in a decrease in output. Milton Friedman demonstrates this is true for the education system in the US, and I can show you it is true for Israel. Since the creation of the State in 1948, school literacy has accelerated along a downward slope.

Let's look at health-system personnel in the US, according to Gammon's Law. Between 1946 and 1969, the number of personnel doubled. In the next 20 years, it trebled. The per diem cost per patient in the earlier period trebled, and in the latter it increased eight times.

Moving on to per capita expenditure on health, and comparing that in the US, UK, Greece and Israel:[1] in round figures, the US spends $2,354 on health per person each year; in the UK the figure is $836; in Greece it is $371 [7]; and in Israel, $490 [8]. But life expectancy in each country is approximately the same. The average life expectancy figures for men and women combined are: 75 for the US, UK and Israel, and 76.2 for Greece [9, 10]. Infant mortality rates for these four countries in 1987 were 10% in the US and Israel, 9% in the UK and 12% in Greece. Gammon's Law, as you see, is in full bloom in the field of medicine.

Let's look again at the inputs, outputs and the black box. Clearly, the black box is not working well. Input and output are badly correlated and produce annoying results. Even Britain's vaunted National Health Service (NHS), increasingly a model for the US, has long waiting lists for cataract surgery. At any given moment, there are three quarters of a million Britons waiting for this simple procedure to enable them see again [11].
A prominent article in a recent *Lancet* was entitled, "Who Will Operate on the Blind in Africa?" There are three million Africans in need of cataract surgery, said the article [12]. I asked myself: "Who will operate on the blind in Britain?" Simply put, Gammon's Law.

What do we mean by a basic aim of maximizing the health of the community? We mean that we look not at individuals but at the sum of the individuals. For each person, we look at the quality-adjusted life-years (QALYs) and then total them for all the individuals in the community [13].

What we are, in fact, doing is weighing each remaining year of life by the quality of life in the year in question. This, of course, is an approach rooted in probability. It is a probability-weighted average of the quality-of-life scores associated with each of the remaining years for each person by the possible state of health of that person.

We look, for example, at someone who has suffered a myocardial infarction and make our estimate. These figures exist. The technique is practised. We look at the probability of future heart failure, repeated arrhythmias, a further myocardial infarction. We will do the double calculations with the probability, the number of years, the number of states – and get a summated function.

You may call this nonsensensical. Powerful sampling techniques exist. This calculation need not be done for every individual. And you must remember that these are invariable for individuals in the same state of health, or the whole thing becomes valueless.

It is clear that if the health of the community is to be maximized as a result of this equation, medical procedures must be ranked. Certain procedures are more positive than others. Cataract

---

[1] In Israel, per capita health expenditure is calculated as a percentage of the GNP rather than the GDP, but the actual difference is very small.

surgery and aortic valve replacement, for example, are positive in that they steer us away from blindness and coronary bypass surgery.

What becomes quickly apparent is that this equation favors the young, the employed and the "privilegentsia" among the employed. It also values output for its own sake, returning to health more quickly. What it does, in effect, is give more value to some individuals than to others [14].

How comfortable are we with that? I am comfortable with aiming to maximize society's health, but I am less comfortable with aiming for different individual care because he is older or she is different. It seems that in maximizing the health of the community, you must accept that people are not equal on an individual basis.

Maybe the aim is mistaken. Instead of maximizing the health of the society, we should perhaps aim for equal treatment for equal need [15]. Which, of course, brings us back to Karl Marx and "to each according to his need." [16] Equal needs demand equal fulfillment – something that Marx never lost sight of. And claims demand proportional satisfaction.

This ushers us into a fascinating area. To assess whether a given distribution of health care is equitable, we must define what equitable is. If the sole purpose of the health–care system is prolonging health, then our definition of equity will concern the system's output rather than its input – its distribution of health–care services.

What does Britain's NHS do about this? Lord Hailsham of St. Marylebone wrote down the facts:

"The [National Health Service] Act imposes upon the Minister of Health the duty of promoting the establishment in England and Wales of a comprehensive health service designed to secure improvement in the physical and mental health of the people, and the prevention, diagnosis and treatment of illness, and for that purpose to provide or secure the effective provision of services in accordance with the provisions of the Act. The services so provided are to be free of charge, except where the Act expressly authorizes the making of charges." [17]

The statutory duty of Britain's Health Minister in promoting a comprehensive health service is thus confined to one designed to improve the physical and mental health of the people of England and Wales. In practise, however, Britain is not restrictive and makes its health services available to aliens, as well [18]. What, then, is their aim? It is not the maximizing of the health of their society, or equal treatment for equal need. It is defined as "improvement in the physical and mental health" – something I will return to shortly, because it is a strange definition, and has peculiar results when applied.

For the moment, though, back to Marx. Karl Marx was a man who spent much of his life in destitution, but nevertheless formulated the principle of "From each according to his ability, to each according to his contribution." [19] It is a principle that seems natural to us today:

"Equal treatment for equal need." Equity requires that those in equal need of health care receive the same treatment, irrespective of personal characteristics that have no affect on "need," such as financial status [2O].

Where is justice in all this? Justice has something to do with equality and something to do with allotting appropriate weight to certain sorts of moral claim. The claim that any patient could plausibly have on the health services is a function not so much of the amount of benefit that the health services can confer, as of the person's needs in relation to the services" capacity to meet those needs effectively. Or, more succinctly: "To each according to his need. Equal claims demand equal satisfaction."

It is, however, difficult to know when someone says that "society needs" whether he means he needs it, or he believes society ought to get it, or whether a majority of the members of the society want it. Nor is it clear whether what is needed is regardless of the cost to society.

When someone is said to "need" medical treatment, we mean that treatment is required for some desired improvement in health. This is a double requirement, needing both scope for improving the persons health through treatment, as well as the extent to which the improvement in health is desired (which is a social value–judgment). This means that no one can determine how the needs of one person compare with those of any other, simply by assessing the capacity of each to benefit from treatment. First, you must determine what you want to bring the patient.

In order to establish needs, society has to decide how the health improvements of one person are to be weighed against those of every other. So, we are left with the problem not of defining equality of need, but of defining what we want to bring the individual.

The NHS in Britain, as I mentioned earlier, uses a different interpretation – one that is close to the classical Paretian indifference analysis – because they hold that any improvement in health is positive and any deviation or movement away from improvement is negative. This, however, is not as simple as it seems.

Without going up and down the Paretian curve, compare two people. One is young and mildly ill, the other old and very sick. You may find yourself giving both less weight than under a maximizing system, because you want to move along a line of 45° through the Paretian indifference curve. The ideal is to bring health from both ends to what would be the maximal possible improvement, and it is therefore easy to decide that one person will receive no treatment at all and another will be given some, because that is the maximized improvement in health [21].

This is the way that finance ministers think when they consider health services. Lord Beveredge may never have heard of Pareto, but to claim the NHS was based on an idea or definition which would minimize expenses under a scientific definition of improvement in health care is phantasmagorical. Such an approach would, in any case, be rejected today, when half your constituents receive no care at all.

The problem remains: the issue of equality of needs requiring equality of treatment. It is an immense issue, and one with which I want to conclude, because with it we enter the morass of equality. What is equality? Israel's Labor Movement claims "equality" as the hallmark of its equal health care. My belief, however, is that "equality" is an empty meaningless word. Behind it lies a principle of "rights," and I suggest that the solution to the problem lies in "rights" rather than in empty flag-words.

"Equality" is an emotive idea. It is perceived as fundamentally special, naturally wonderful. "Rights," however, are thought of as complicated, non-comparative. They are connected with deprivation – you either have something or you don't – whereas equality is only relative deprivation. Rights are there in plurality. Equality brings uniformity (think of China's Mao Tse Tung). Rights are individualistic. Equality is social.

The issue of equality versus rights goes back a long way. The US Constitution grapples with it – the Fifth Amendment guaranteeing equal rights, and the 14th (passed after the Civil War) ensuring equality. These two Amendments have engendered a longtime tug in different directions in both America's moral philosophy and in the US courts.

The idea that "people who are alike should be treated alike" and "people who are unalike should be treated unalike" [22] is no more than what Marx said in so many words. Rights are always, of course, the prerogative of the individual or group with power.

This dates back to Aristotle, who himself built on Plato. Two basic ideas are contained in the most famous of the Discourses, including that most commonly read – Plato's *Republic*. First, "equality in morals" means that "things that are alike should be treated alike, while things that are unalike should be treated unalike, in proportion to their unalikeness" [23] (a final phrase which Marx discarded).

Second, "equality and justice are synonymous. To be just is to be equal; to be unjust is to be unequal." This idea is contained both in Plato's *Republic* and in Aristotle's *Politics*. Is it, however, morally true? Is it obvious that like things should be treated alike? Why should justice be equated with equality?
This idea is mistaken, both logically and philosophically. "Is" has become "ought." "Is alike," therefore we "ought to." That is, we determine two people are alike, and then we make a moral judgment. We say: Because they are alike, we will treat them alike. If two people are alike, then we know how to treat them.

But how do we determine they are alike in the first place? Clearly, they are not precisely alike. Only abstract numbers and equilateral triangles and their ilk can be precisely alike. Nothing else in nature is absolutely alike in every respect. So, perhaps they are alike in some respects. But this, too, is nonsense because everything in nature is alike. Everyone on earth is like everyone else, in some respects.

The two possible *a priori* propositions thus make no sense. What we mean, perhaps, is two people who are morally alike in certain respects. Here we do not derive an "ought" from an

"is," but an "ought" from an "ought." We ought to be alike according to a moral law, and therefore we will now treat ourselves as alike according to that moral law [24].

We thus have a norm defined for determining equality and then for determining how to treat this equality. "People who are alike" may refer to "people who are morally alike in a certain respect." Instead of deriving an "ought" from an "is," this derives an "ought" from an "ought."

Moral alikeness is established only when people define groupings or categories. But, moving on to the treatment side, this does not work in medicine because there are no "like" treatments in nature. They can be alike only according to a moral law, otherwise you run into confused thinking, such as: "Every diabetic should be treated exactly the same as every rheumatic, because they are both people and therefore they are both alike."

So alikeness in treatment comes from a moral law based on the principle that "equals ought to be treated alike in the respects in which they are equal." They may, however, differ in that they are alike, differences which justify differences in treatment, as every doctor knows. Plato's discussion of equality in *Phaedo* illustrates the complexity [25]:

> "Did we not see equalities of material things, such as pieces of wood and stones, and gather from them the idea of an equality which is different from them? For you will acknowledge that there is a difference? Or look at the matter in another way: Do not the same pieces of wood or stones appear at one time equal, and at another time unequal?"
>
> "That is certain."
>
> "But are real equals ever equal or is the idea of equality the same as of inequality?"
>
> "Impossible, Socrates."
>
> "Then these (so-called) equals are not the same with the idea of equality?"

The connection between equality and rights is that equality is a derivative of rights. First comes the rule: We are alike because. After the rule comes equality, a logical consequence, according to one and the same rule. So what is justice? Justice is applying rules uniformly. Justice is simply the fact that we obey the rules we make for ourselves.

In our system analysis of medicine is, therefore, we have to define for ourselves the rules we want to apply. Marx recognized this defining of rules in *Das Kapital* when he wrote about capital and productive capacity [26].

> "It is, therefore, a right of inequality in its contents like every right. Right by its very nature can consist only in the application of an equal standard; but

> unequal individuals (and they would not be different individuals if they were not unequal) are measurable only by an equal standard insofar as they are brought under an equal point of view."

So, we have justice, giving every person his due. Everyone receives the treatment they deserve, according to moral rules which we have determined, and we treat by these rules. Those who are alike according to a moral rule will be treated alike by that same moral rule.

When Marx addresses the question of the Jews, he makes some comments with which I wish to end and to offer a solution [27, 28].

> "These rights are: equality, liberty, security and property.... The right of property is the right vested in every citizen to enjoy and to dispose of his goods, his revenues, the fruit of his labor and of his industry according to his will."

Man's right to private property is therefore the right to enjoy one's property and to dispose of it arbitrarily, without considering other men, independently of society. It is the right of self-interest [29].

> "Equality is nothing but the equality implicit in the liberty described above."

Equality consists of the fact that the same law applies to all. None of these so-called rights of man goes beyond the egoistic man, beyond man with his private interest and private arbitrary will. The only bond that keeps men together is natural necessity, need and private interest [3O].

We have a system in medicine and in medical technology in which in the past 5O years input and output have gone crazy, in which the emphasis on technology, specialization, team work and socialization have brought havoc and disaster, in which Gammon's Law is played out to the full. To return to sanity, we must recognize that the buzzword "equality" is bandied about too freely in medicine. There is no value to words that have no meaning.

What, in fact, do we want in medicine? We don't want equality. What we want are certain rules which we agree are moral and which we will apply. To start out with, what we want are experiments in the direction of establishing these rules, these moral choices.
Such experiments are already underway. In the US, the famous Oregon experiment is trying to formulate a societal decision on defining needs. In Israel, we are trying to establish what we call a basic basket of health care, as the sole services which health insurance is obliged to provided.

This is being done on the understanding that we can no longer operate under Gammon's Law of Bureaucratic Displacement without bringing in that most powerful of motors for human accomplishment: the equation of self-interest. Without it, the system will not work.

It is clear to those of us who are involved that this is not something that will happen tomorrow, mainly because of the large number of interested parties who are trying to manipulate the system. There are several paths to take. Marx's: "To doubt of everything." [31] Macchiavelli's maxim that any prince engaged in a revolution has few supporters at the beginning because of the large number who stand to lose.

It seems, however, that the forces in play are so powerful, so devastating in their implications, that we shall indeed see progress in the direction of moral choices defined as rules, with self-interest as the motor driving them along the correct paths.

Bibliography

1. Kamenka E (Ed): Confessions of Marx. In: *The Portable Karl Marx*, Viking Portable Library, Penguin Books, New York, 1983, p 53.
2. Wagstaff A: QALYs and the equity-efficiency trade-off. *J Health Economics* 1O(1): 1-41, 1991.
3. Friedman M: A cure for America's health-care ills. *The Wall Street J* (Europe), November 13, 1991.
4. Friedman M: A cure for America's health-care ills. *The Wall Street J* (Europe), November 13, 1991.
5. Rowland D: Data watch: Health status in east European countries. *Health Affairs* 1O(1): 2O2-215, Fall 1991.
6. Friedman M: A cure for America's health-care ills. *The Wall Street J* (Europe), November 13, 1991.
7. Schieber GJ, Poullier J-P, Greenwald LM: Health care systems in twenty-four countries. *Health Affairs* 1O(3):22-38, Fall 1991.
8. Commission of Inquiry to Examine the Operation and Efficiency of the Health-Care System in Israel: *Report*, Jerusalem, 199O, Vol. 1, p. 186 (Hebrew).
9. Rowland D: Data watch: Health status in east European countries. *Health Affairs* 1O(1): 2O2-215, Fall 1991.
10. *Statistical Abstract of Israel*, No. 4O, 1989, Table III/28.
11. Randolph B, Gibson H: Handle with care. *Time Magazine*, June 3, 1991, p 28.
12. Foster A: Who will operate on Africa's three million curably blind people? *The Lancet*, 337(8752):1267-1269, May 25, 1991.
13. Wagstaff A: QALYs and the equity-efficiency trade-off. *J Health Economics* 1O(1): 1-41, 1991.
14. Wagstaff A: QALYs and the equity-efficiency trade-off. *J Health Economics* 1O(1): 1-41, 1991.
15. O'Donnell O, Propper C: Equity and the distribution of UK national health service resources. *J of Health Economics* 1O(1):1-19, 1991.
16. Marx K: Marginal notes to the programme of the German workers' party (Critique of the Gotha Programme). In: *The Portable Karl Marx*, Kamenka E (Ed). Viking Portable Library, Penguin Books, New York, 1983, p 533-555.

17. *The National Health Service Act*, 1946, p 515, preliminary note.
18. *Halsbury's Law of England*, 4th edition, vol. 33, Lord Hailsham of St. Marylebone, ed., Butterworths, London, 1982, p 21.
19. Kamenka E (Ed): Confessions of Marx. In: *The Portable Karl Marx*, Viking Portable Library, Penguin Books, New York, 1983, p 565.
20. Marx K: Marginal notes to the programme of the German workers' party (Critique of the Gotha Programme). In: *The Portable Karl Marx*, Kamenka E (Ed). Viking Portable Library, Penguin Books, New York, 1983, p 533–555.
21. Wagstaff A: QALYs and the equity–efficiency trade–off. *J Health Economics* 10(1): 1–41, 1991.
22. Westen P: The empty idea of equality. *Harvard Law Review* 95(3):537–586, 1982.
23. Westen P: Aristotle, Ethica Nicomachea v.3.1131a–1131b (quotation). *Harvard Law Review* 95(3):537–586, 1982.
24. Westen P: The empty idea of equality. *Harvard Law Review* 95(3):537–586, 1982.
25. Westen P: Plato, Phaedo 74 (quotation). *Harvard Law Review* 95(3):537–586, 1982.
26. Marx K: Marginal notes to the programme of the German workers' party (Critique of the Gotha Programme). In: *The Portable Karl Marx*, Kamenka E (Ed). Viking Portable Library, Penguin Books, New York, 1983, p 533–555.
27. Marx K: On the Jewish question. In: *The Portable Karl Marx*, Kamenka E (Ed). Viking Portable Library, Penguin Books, New York, 1983, p 96–114.
28. Marx K: On the Jewish question. In: *The Portable Karl Marx*, Kamenka E (Ed). Viking Portable Library, Penguin Books, New York, 1983, p 96–114.
29. Marx K: On the Jewish question. In: *The Portable Karl Marx*, Kamenka E (Ed). Viking Portable Library, Penguin Books, New York, 1983, p 96–114.
30. Marx K: On the Jewish question. In: *The Portable Karl Marx*, Kamenka E (Ed). Viking Portable Library, Penguin Books, New York, 1983, p 96–114.
31. Kamenka E (Ed): Confessions of Marx. In: *The Portable Karl Marx*, Viking Portable Library, Penguin Books, New York, 1983, p 53.

SESSION I: ECONOMICS AND MEDICAL TECHNOLOGY

Chairmen: Professor Samuel Sideman and Professor Michael Silberman

Entrepreneurship, Economy and Marketing in the Field of Medicine

Eli Hurvitz
President, Teva Pharmaceuticals Ltd.
Tel Aviv, Israel

I guess that I was invited to talk about entrepreneurship, economics and medicine at the Technion, an academic institute with very practical aspects, because of the example of Teva, the company I head, in solving one particular issue that I would like to discuss today. Before starting, I would like to say a few words on the macroeconomics of Israel in the aspect I want to discuss. Israel is a country that maintains a Western standard of living. We do not have many resources and lack capital. The only solution to keep this standard of living is by having a high output per worker and high output per capita. One can achieve this goal if he invests a lot of capital resources, be it capital or human resources. Israel is quite poor in physical capital. We do not have sufficient resources and we are importing capital; therefore we will always pay more that those that are exporting capital. The only thing we have is human capital. I will discuss figures, but first I would like to state that human capital is not enough, because then you may have a very high production of paper but no production of products.

The only way, I believe, that we can solve our macroeconomic problem is by producing high tech products which are of high value. Human capital is part of the total ingredients; in order to have a high standard of living, you must have, in parallel to high human capital, quality industry large enough to work together with this human capital and produce a product. We at Teva discussed this issue for days and nights; we came to the conclusion that the only way to produce a pharmaceutical product in Israel would be by cooperating with the scientists we have here in Israel. Our objective was to bridge the gap which exists between the scientific talents in the life sciences found among Israel's various research institutes, and, the users of the products, mainly physicians, through industry. Our uniqueness, in comparison with many other companies in our field, lies in the fact that we rely mainly, and I can say only, upon Israel's academic infrastructure both for ideas for new products and the practical development of these products in the pre-clinical stages and clinical stages. This enables us to reduce our overhead expenses and thereby decrease our risk, which is very high with pharmaceutical development. With proper management, we can increase our chances of success.

We were engaged in research and development for many years, but in the days that our annual turnover was a few million dollars, a few tens of millions of dollars (and this is only less that a decade ago), we could not afford investing in R & D but only in two elements. One, adapting foreign know-how in order to produce a product here in Israel, and two,

developing a process for chemical products to be exported or to be used by us. Only recently, when our annual sales figures reached hundreds of millions of dollars, could we afford to spend money on R & D. Our expenditure on R & D has now reached some 20 million dollars/yr, spent mostly on innovative products. I would like to mention that Israel, of course, is a very minor player in innovative products, in the pharmaceutical research arena. The total global expenditure for pharmaceuticals is something like 15 billion dollars. Companies with budgets of hundreds of millions of dollars a year find themselves too small, and so merge in order to get a budget of billions of dollars. Not all smaller companies have succeeded in obtaining good results, but a few of them have indeed succeeded to come up with a product to market.

The question was how could one with a budget of ten million at that time, today with 20 million, compete with the giants. We did this in a special way and I will to describe it briefly. First of all, our strategy in the area of innovative R & D is based on two principles. The first principle is reliance upon the existing scientific infrastructure at Israel's academic institutions; the second principle is developing products in specific market niches. We define a niche as being, not the number of dollars to be sold, but the number of doctors to be addressed by our promotion, since this is our international limiting factor. If your want to get ideas, the question, of course, is how to get ideas for those projects, and how to get consultations, once you've got an idea in order to bring it up to the market while doing the research in the academic institutes. We set up a team of project scouts whose role it was to maintain contact with all relevant researchers at these institutes. There is no doubt that the R & D qualities of the Israeli academy is very high, particularly in the life sciences. If one measures it in the number of publications or the number of citations, we are number one in the world relative to our population. I assume that few of us here know that we are now not as good as we used to be a few years ago, but we are still the number one in the world. The researchers submit their ideas for research projects, the goal of which must always be the development of a medication that is new on the market. Over the last few years, we have received about 300 proposals of ideas for projects. Of these, we are currently conducting three projects and 25 feasibility studies. About 10% of the ideas that we received are at the feasibility study stage and about 10% of these, or 1 to 2% of the total ideas, enter into a full fledged research project. (Here I must say something about doctors or scientists. We had a real psychological problem. Ninety percent of the people who apply to us get a negative answer and, of course, every one of them is sure that his idea is the best in the world and we are missing his product; he may be right. But this is a real problem, a problem that disturbs us in getting ideas and maintaining a positive image in the eyes of those that are bringing us their ideas.)

The first stage in processing proposals is to refer them to four committees which are segmented according to the therapeutic areas in which we are interested – bone diseases, central nervous system disorders, skin diseases and others. Aside from our own staff who specialize in each of these fields, there is a scientific advisory board consisting of some of Israel's most prominent senior scientists in the specific fields being discussed. This scientific board includes a senior physician who understands the market and tells us the needs of the client. Throughout the entire process, this senior physician will remain as the speaker for the client. Each team also includes a scientist, usually a senior scientist who deals with the

scientific aspects of the proposal; his role is to evaluate the proposal from this aspect. Combining the marketing and the technical scientific evaluations, we are in a better position to accept or turn down a proposal.

Once we have chosen a project and support it with our budget, we must be very selective and very controlled.

A second element in our research is the professional consultation that accompanies each project throughout all stages of R & D. We use consultants from both Israel and abroad. We have some of the best people in the world in the MS field. In the field of "Bone Disease" we also have one of the best known nephrologists in Israel and abroad. Most of the laboratory, development and clinical work is done in Israel.

The first product that I would like to discuss is Osteo-D, a drug for treating a bone renal failure, which is an attractive niche for us. There are about 1,500 dialysis centers in the United States, a population of doctors whom we know how to reach. On this project, we teamed up with the Weizman Institute. The first idea came from Professor Shmuel Edelstein of the Weizman Institute. From the outset, we worked together and reached the marketplace within a reasonable amount of time, and, at a reasonable cost. I do not know what is reasonable anymore. People are talking about hundreds of millions of dollars, up to 300 million dollars to develop a product; it costs us approximately 5% of that, which is also a lot of money.

The second project is COP-1, a drug for treating multiple sclerosis, invented by Professor Michael Sela. We entered into the research process relatively late. If we had entered at the right time, we would now have a product on the market. At that time, we were too small. When Prof. Sela came to us in 1986, we wanted to become a 100 million dollar company in sales. Today, our sales are over 320 million dollars. We are currently in the second Phase III clinical trial in the United States, the last clinical hurdle before the drug is registered. The same is true about Osteo-D, for which we have final data for 80% of the patients.

TVP-101 is the third example I would like to mention. It is a product for treating Parkinsons Disease, developed from an idea proposed by Professor Mussa Yudim of the Technion. Here we entered the picture from the very first idea. We set up a small laboratory at the Technion. Our own staff is working in our laboratories on the chemistry, the pharmaceutical aspects, etc. Our aim is a commercial product. Our phase I studies were performed in France. The phase II studies will be done here in Israel and Phase III clinical studies will be performed according to the registration; part in Israel and part of it abroad.

A second guideline in determining our R & D strategy is to focus on niche products. We must market our products. In order to do so, in 1985, we entered the American market through purchase of a generic company which lost 22 million dollars with about the same annual turnover. In that year, our pharmaceutical turnover abroad was six – eight million dollars. We turned the losses of that small company around and last year our sales approached 100 million dollars in the US. In fact, the company made money from the first year while

investing in R & D, and we are now number seven in the US in generics. I believe that in two years, we will become number five or maybe four in the US. This US company which we purchased will, in two years, be bigger than our Israeli company, and all that was achieved because we believed that once we wanted to market our innovative products in the United States, we would have a network. It is very simple for somebody who is always in the US, but for us to be in the United States market means that you have to have communications and connections to a list of doctors. You have to be connected on line with 35,000 pharmacists; in Israel we have 400. You have to be connected on-line with wholesalers. You have to know the way of doing business in the United States. It takes years and we decided to enter the market through our generic business, which was very new to us, and to build up a network in the US that would take our products into the market.

We have always encouraged senior members of the academic community to spend part of their sabbatical with our company. We profit two ways. First, by way of their considerable contribution to Teva's scientific know-how over the course of an entire year or more, and second, by training a worthy ambassador of good will for Teva within the academic community. Thanks to one professor, we have a vaccine plant in Jerusalem. Thanks to another professor, our Osteo-D is registered. I must admit that the first time Prof. Shmuel Edelstein came to Teva, I was afraid. I asked myself: "What will this big important professor from the Weizman Institute do in Teva." After a few months or half a year, he came to me and said: "Eli, you'll never understand how satisfying it is to prepare a registration file for a product that I've invented." He spent two years of his sabbatical with us. Now we have another professor from Tel Aviv University, and we are now waiting for another one from the Technion to come.

I would like to mention two things that are important. I have mentioned before that the physician in the team is the one that tells us what the needs of the market are. This is very important because one can invent a product that nobody needs. It has happened, believe me, more than once. In the course of time we are getting more and more physicians throughout the world to assist us in the concept of building a marketing strategy for the product. If we have one product and it is registered in Israel, the sales in Israel will never cover the investment. But what they do is define a marketing strategy so that once we go to the international market, we know the product that we are going with; we know what the doctor's reaction is; we know the patient's reaction, etc., etc. In this respect we are using the academic environment to assist us in our marketing plans. There is a very interesting project of Wharton University and Tel Aviv University, to elaborate a business plan for an Israel product that is going to be marketed in the United States. This will be done by the teams of professors and students in both countries. The program has recently been widened to include Europe, adding INSEAD into this network. We got very interesting results and are now going to use it more. All in all, we are trying to improve our skills in developing innovative products. In popular terms: we move every year from one class to the other in gammer school. The entry from gammer school to university will be with our first innovative product on the market. The change is not by adding, but by multiplying and multiplying many times. And we are very near to it because, as I have said, we now have two products in phase III in the United States.

The process I was trying to describe to you is a process of cooperation between industry and academy. It is based on a strategy that we call in Teva – "the strategy of what we've got." Don't invest in what you don't have. Don't invent another wheel. Try to use whatever you've got. In order to develop the ideas that were developed or are being developed in academic institutions, we would have to have thousands of research people. We have only 130. In Israel, the only treasure is human capital and I want to mention one figure out of many. We have about 8% college or university graduates, similar to most of the advanced countries in the world. We are going to double it. If you assume that we are going to add 25% to our population within a few years and if you take into account that out of the 360,000 newcomers that came in the last year, 41% were academicians, you get a multiplication of our academic force. We'll have more positions and engineers per square inch than anybody in the world. The best way to use them, with the small industry that we've got, is through R & D or innovation. In our business, our real competitors, here and elsewhere, are the big boys in the pharmaceutical world, companies with sales of billions of dollars. With our strategy, we can compete and be friendly at the same time because they need us and we never get in a head to head collision. The only way to do it successfully is for us to cooperate with the academic institutions; all of our innovative products that are in the pipeline or are registered already are a fruit of cooperation between local academy and local industry.

Legal and Economic Aspects of Medical Technology

Robert Nicholas
McDermott, Will & Emery
Washington D.C., USA

I am a lawyer, in private legal practice at a large law firm – McDermott, Will and Emery. It is about the 15th largest law firm in the United States. We have a very large health care practice. We probably represent more doctors, hospitals, health care providers than any other law firm in the country, across a broad spectrum of products, including commercial arrangements, regulatory matters, reimbursement matters and that is part of what I propose to talk about today.

I worked for the U.S. Congress, on the House Science and Technology Committee for several years and also was at the President's Council on Environmental Quality. During that time, I spent time looking at questions of technology transfer between universities and industry, between industries and industry and the role of the government. I spent time looking at industrial policy and the stimulation of innovation and spent a great deal of time, looking at the development of the biotechnology industry. I now work with biotechnology companies on developing new products to bring to the market, the pharmaceutical, agricultural and industrial area. What I would like to talk about today is basically the U.S. market place and some of the factors that effect entrance into the U.S. market, at the beginning of the process of identifying successful or potentially successful or promising research ideas through the commercialization. I am certainly glad, given our previous speaker, that I do not talk about the development of beginning companies and how you develop commercial relationships with industry, with academics, setting up advisory boards, how you negotiate licenses, how you obtain funding from the government and of course, how you protect intellectual property. I realized that if I started on all those things, I would probably be here the rest of my life. So what I chose to focus on is a few areas.

First I would like to present a short overview of the politics of the health care industry in the United States. I have tried to be selective and present by example. So I am going to talk about some of the political factors that are driving decisions about health technology in the United States. Secondly, I am going to talk about regulation of the products of the interface between medicine and engineering. I am going to talk about medical devices, recognizing that drugs have a similar regulatory pathway; indeed, the regulatory pathway for drugs is substantially more onerous than it is for most medical devices. The figures that the pharmaceutical manufacturers' association gives out in terms of a ten year development phase are 250 million dollar cost to the development of a new therapeutic entity in the United States. I am going to talk about the regulation of medical devices. The third thing I am going to talk about is

the coverage and reimbursement for new technologies. More and more providers and developers of health care technologies are finding out that it is not enough just to get your product approved by the Food and Drug Administration; you also need to figure out who is going to cover that under some insurance scheme and what kind of reimbursement rates are going to be available. If you are not able to get coverage for your technology then you are not likely to find the market and to have it utilized. So with this background, let me start.

The Political Context for Developers of New Technology

An understanding of the climate in which the health care industry operates can be as critical in strategic decisions as the areas companies chose to focus on. I have chosen for the political context to talk about two issues. One is health care cost containment and two is the Food and Drug Administration's priorities. It sounds almost silly to say that for some years now the U.S. government has been greatly concerned about the skyrocketing cost of health care in the United States. Principally, the government has focused its efforts on limiting rates of reimbursement for medical services and procedures, providing incentives for cost containment, reducing tax breaks for medical deductions, encouraging competition between drug companies and between medical device companies, forcing down the payments made by government for drugs and conducting numerous studies. While no solution is yet in sight, the government will clearly continue in its efforts in this direction and one of the principal targets will be drugs, devices and other companies developing new products. By the mid 1980s, health policy experts realized that price controls addressed only part of the problem and that the cost of new technology was skyrocketing and had a dramatic increase on the cost of medical services. That is when they started to focus on outcomes research as one tool to try and bring down the cost of health care. Essentially, outcomes research looks at health care treatments from the perspective of the patient. Patients want to know: will the treatments make me feel better or will it otherwise improve my health. Outcomes research asks three questions. 1. Does the treatment and technology extend the patient's life. That is the survival question. 2. Does it reduce complications for disease. That is the morbidity question. 3. Does it improve the patient's functioning or quality of life. Outcomes research looks at the endpoints of death, illness and functioning, whereas traditional clinical studies look at intermediate clinical outcomes, usually clinical markers. For example, coronary angioplasty studies look at reopening of arteries, whereas outcomes research looks at survival. Does such a procedure increase survivability and a quality of life? Similar comparisons can be made for other technologies. Outcomes research, as I said, will become more and more prevalent and used as a decisional tool not only with regard to reimbursement of technologies but also with regard to whether the FDA will improve new technologies in the future.

There are several areas where the health care finance administration, HICFA, which operates the federal medicare program, is currently conducting research in other areas where other groups are targeting as well. The agency for health care policy and research in particular is sponsoring outcomes research on the conditions and procedures listed as follows: cataracts, acute myocardial infarction, disorders of the prostate, lower back pain, total knee replacements, gaul bladder disease. In addition, they are sponsoring planning studies in these

areas: stroke, peripheral vascular disease, hip replacements. The Institute of Medicine has studies going in the following areas: cataract removal and lens insertion, chronic obstructive pulmonary disease, coronary artery disease, gastric intestinal bleeding, gaul bladder disease, lower back pain, hip replacements and the list goes on. Companies that are looking in this field to develop new products, therefore, can expect to have to meet new stringent requirements in the future.

The second political area is the FDA, the primary regulatory agency with authority over medical devices and drugs. During the past five or more years, the FDA has experienced a sharp decline in prestige and credibility and a sharp decline in personnel with a greatly increased work load. For example, FDA had 1,000 fewer employees in 1989 than it did in 1980 while Congress passed several new laws enhancing the responsibilities of the agency. The generic drug scandal where several FDA employees were convicted of accepting illegal gratuities, of favor drug approval applications of one sponsor over another, has left the agency severely demoralized. The pace of regulatory approvals has suffered. The FDA has new leadership now. Commissioner Kessler has set a bold agenda and it looks likely that Congress will provide him with a lot of latitude as he seeks to rebuild the Agency. Already the budget of the Agency has shown some increase and the Commissioner has vigorously asserted the Agency's prerogative in several areas. So far the Agency has been very aggressive on the enforcement front challenging the advertising claims of the food industry broadly and the drug communities advertising to doctors and others in the medical community. The FDA has recently received authority to hire criminal investigators and the Commissioner has made it clear that regulatory letters, Agency warning letters about violations of the Act, are to be taken seriously. A new FDA enforcement bill is working its way through the Congress now. The bill would provide additional authorities to the Food and Drug Administration. Last year Congress passed amendments to the Vice Section of the Food and Drug and Cosmetic Act. The Medical Device Act of 1990 provides new enforcement authorities to the FDA, as well. The FDA has yet to demonstrate, however, that its new vigor extends to the pace for approval of new products. Of course, this will take more time and is a much more serious question in some ways. Studies are underway to streamline the FDA approval process and many are hopeful that Dr. Kessler will have a significant impact in the future. Proposals have either recently been circulated, or in fact some of them put in place, to provide fast tracking for important new therapeutics, early availability of certain promising new drugs and user fees which may pay for the processing of applications. Of course, user fees will cost the industry money and that is where much of the negotiation is taking place. Looking at those two examples, and in summary, you find that the field of medical engineering is closely regulated and will be subject to increasing pressure to keep the costs down in the future.

Regulation of Medical Devices

I now want to turn to government regulation as a barrier, or as a benefit, to entry into the market. It works both ways. In some cases, you need go through a process that is fairly protracted. But in many of those cases, it guarantees that your competitors who if they have a later start in the market will have to do the same thing and therefore you will have some

lead in the marketplace. Additionally, the Often Drug Act and the Patent Term Restoration Act and other provisions and the various statutes grant other kinds of monopolies and those who are skilled at developing new drugs can look at some of these statutes as ways of preserving market exclusivity even in the absence of patent protection.

Medical devices have been regulated by FDA since 1938. The primary purpose of regulating the medical devices at that point was to avoid quackery and fraud and it did not focus on safety questions. Since 1938, both the kinds of medical devices and the intensity of the regulation by FDA has changed dramatically. In 1938, there were over 400 manufacturers of surgical, medical and dental instruments and suppliers who were shipping more than one million dollars worth of devices annually. When these suppliers were brought under the FDA's jurisdiction, they were treated just like drugs. There was no premarket approval process. And drugs and medical devices were both treated by FDA based solely on the provisions and the statute that prohibit adulteration and misbranding of products. In 1962, the Act was amended and at that point drugs were subject to a premarket approval process but medical devices were not. It was not until 1976, the Medical Device Amendment that medical devices became subject to a premarket approval clearance. The reason 1976 is an important time frame is that the statute establishment a three tiered system of regulation of medical devices and essentially grandfathered in pre-existing medical devices as in the date of enactment of the statute. In 1990, the Act was again amended, the Food, Drug and Cosmetic Act to strengthen FDA's enforcement authorities with respect to medical devices, to make down classification of certain devices easier and it codified many of the things that the Agency had been doing between the 1976 amendments and the future. I want to go through this.

A medical device is defined as an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or other similar or related article, including any component part thereof which is recognized in the official national formulary intended for use in diagnosis the disease or in the cure, mitigation, treatment or prevention of disease in man or other animals, or intended to effect the structure or any function of the body of man or any animals. A device does not achieve any of its principal intended purposes through chemical reaction within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes. Thus, generally speaking, a device is an article used for medical treatment and diagnosis that is neither metabolized nor acts chemically within or on the body. That is the primary distinction between drugs and medical devices, and how something is classified, whether as a drug or a medical device has very significant ramifications both with respect to which group within FDA reviews the actual applications and secondly, with respect to the ease with which one can get on the market. Basically for all but few medical devices, the route to market entry is much easier for medical devices than it is for drugs.

Generally, when you do your strategic planning looking at therapeutic entities or new inventions, you ought to be looking not just at the economic consequences but you ought to be thinking about how you get through the regulatory process. The better examples are the two early biotechnology companies that chose to focus on the monochronal antibody diagnostic market, Center Core and Hypertec, both of which became very substantial

companies fairly quickly, in large measure because the route they chose had no, or very little, FDA regulatory consequences.

Let me talk briefly about the scheme under the Food, Drug and Cosmetic Act. All devices that were in commerce in the United States, on the market in the United States as of May 1976 were automatically classified as Class One. That was the lowest risk class. All devices that came on the market subsequent to that date were classified as Class Three, which is the highest risk category. FDA then set up panels to review the various devices and to reclassify them based essentially upon a level of risk. Devices that came on the market since 1976 are able to come through the regulatory process more smoothly than one would expect based upon FDA's allowance of devices to be categorized depending upon their substantial equivalence to pre-'76 devices. Let me explain the consequence of that. Class One and Class Two medical devices come to the market generally through a regulatory filing called the 5-10K which is the statutory section that one follows. A 5-10K requires the Agency to respond within 90 days and the requirement is to demonstrate safety to the Agency. Frequently that means substantial equivalence. Some 5-10Ks are filed solely with one or two pieces of paper, whereas more extensive requirement can mean that there will be clinical data and substantial documentation. But even so, that 5-10K route is easier and much quicker than the alternative route which is to file a premarket application, a PMA. A PMA approval process is very similar to a new drug application. It requires significant data and is really reserved for devices that are used in life sustaining or life supporting situations. Since I am covering a lot, all of this is general and it is clearly not intended as legal advice. It is intended to give you some overview of how the statute operates and how you might use it to your advantage.

As I said, substantial equivalence was a key here. A device is deemed to be substantially equivalent to a predicate device if it has the same intended use as the predicate device and the same technological characteristics or if it has different technological characteristics, and the submission contains information including clinical data, if deemed necessary by FDA, demonstrating that the device is safe and effective as the legally marketed device and it does not raise questions of safety and efficacy different from those of the predicate device. What that means is that if your device gives the same outcome as a predicate device, even where the technology is different, the FDA can consider it equivalent and indeed FDA has been very lenient in finding equivalency. On the other hand, if your device results in a similar outcome but is much more sensitive, and your new test has a much higher sensitivity than the existing test, the FDA may well find that is not substantially equivalent. The FDA has published guidance documents for substantial equivalence and clearly that is one of the first inquiries you undertake when you are looking to register a medical device.

There are rights to keep data confidential. On the other hand, with respect to the 1990 amendments, the FDA now has the power to change some of that. So if you are substantially interested in marketing a medical device in the United States, you have to pay close attention to this statute.

I want to talk briefly about another statute which is the Clinical Laboratory Improvement Act of 1988. In 1988, Congress passed a new law, CLEAR as it is known, which expanded

supervision and regulation over clinical laboratories performing diagnostic tests. Implementation of the law was supposed to be done in January, 1991, but there has not been finalization of several of the key regulations. So actual implementation has not been done. What CLEAR did was expand Federal supervision over laboratories that do clinical testing *in vitro* tests, testing on human samples for detection of disease. What CLEAR also did was expand the Federal supervision of those laboratories to include doctors' laboratories which had not previously been covered. The effect of this is, or may be, that if doctors cannot get wavers based upon the regulations; they will have to meet new standards with respect to personnel they employ, supervision of the personnel, record keeping, quality assurance programs and so forth. The likely end result will be that some physicians will no longer do these tests in their office and this market will therefore be closed to those who are looking for physicians as their marketing avenue for these products. The way the statute and the regulations are set up, it created three levels, depending upon the complexity of the test and the degree of human intervention. If a test is idiot proof, it will be subject to a waver. If a test requires substantial work on the part of a skilled technician, it will be put in Category One, triggering certain requirements on the part of the laboratory. If it requires a higher degree of sophistication and it involves more risk associated with misdiagnosis, it will trigger some few higher requirements. At the current time, the drafts of the regulations put 28 tests in the waver category. So if a doctor performs one of these 28 tests in his laboratory, he can get a waver certificate and is not required to meet these new requirements.

Coverage and Reimbursement

At the outset, there are two generalizations that I want to put forward. The first is that the U.S. does not have a comprehensive system of coverage for health care. In other words, there is no national universal health insurance. Rather what we have is a Federal insurance system called Medicare which makes payments for covered individuals for certain services. Then we have Medicaid, a federally sponsored but State run, need based, system. And we have a network of private insurance options. Each are widely free to make their own determinations as to what is covered and what is not covered and what the reimbursement rates will be for covered services.

The second general point I want to make is that questions of coverage and reimbursement and therefore the incentives to use new technologies vary based on the type of service being required, being used, where that service or product is being used and the basis of the reimbursement. The rules and the systems for determination of coverage are complex and not always consistent and frequently unclear, but what is clear is that they are going to be applied even more in the future. As a generalization, if you have a diagnostic test, or a new piece of equipment that is used in a hospital, certain insureds will be able to be covered under that and there will be a reimbursement rate established for that technology in that setting, which might be very different if that same procedure, technique or service or product was used in an ambulatory surgical center or used on an outpatient basis in a hospital or used as an over the counter. So where and how is a big difference.

The question of reimbursement is divided into two issues – coverage policy and reimbursement policy. The former addresses the question of whether the service is eligible for payment under any circumstances, while the second answers the question of, if it is eligible, how much is paid. Coverage under the Medicare program is as follows. In 1965, Congress established a Medicare program as a health insurance to provide coverage for mostly acute care for the aged, disabled and those with end stage renal disease. In 1989, Medicare expenditures were approximately 100 billion dollars of about which 54% were for inpatient hospital care, 8% for outpatient hospital care, 31% for part fee services such as physicians, suppliers and laboratory services, and 7% for other services. That was 100 billion dollars.

Medicare is in fact two programs – Part A and Part B, each with its own eligibility reimbursement coverage and financing rules. Part A is hospital insurance benefits for the aged and disabled. It is an entitlement program. Those who pay into the system through an employment tax are entitled to the benefits under the program when they reach age 65, they are covered under disability. Part A coverage of the Medicare program covers principally hospital inpatient and home health care services, skilled nursing homes and hospice care. Many devices, diagnostic products, drugs used for inpatient care of a Medicare beneficiary are covered under this broad category of inpatient hospital services, provided the technologies meet the criteria. Medicare Part B, supplemental medical insurance for the aged and disabled, is a voluntary program and requires the payment of a monthly premium to be covered. Part B is open to those covered by Part A and certain other eligibles over 65 who are residents in the United States. Part B coverage is quite extensive and it covers the following kinds of products that have some relevance to the purpose of the meeting: Physician services rendered directly to the patient including diagnosis therapy, surgery and consultation. That is covered under Part B. Services and supplies must be furnished as an integral part of the physician services in the course of diagnosis, treatment or injury. So that drugs and medical devices used by a physician during the course of treatment are covered whereas self–administered drugs are not covered. Certain services and supplies are excluded in ambulatory surgical services, including surgical procedures performed on an outpatient basis in an ambulatory center or a hospital outpatient department or a physician's office. Here there is part coverage and part no coverage. Outpatient hospital services. Physical services. Comprehensive outpatient rehabilitation facilities services. Diagnostic tests. X–rays, radium and radioisotope therapy. Surgical dressings and devices for reduction of fractures. Durable medical equipment. Prosthetic devices, braces, trusses and artificial limbs and eyes. Categories of excluded services include personal comfort items, routine physical check up, eye glasses, hearing aids, orthopedic shoes, custodial care, cosmetic surgery, dental services, and treatment for flat foot and routine foot care. Several other categories have been specifically added by legislation and this is sometimes a route for those who have new technologies that are not covered: go to the Congress and seek to get new areas covered. Mammography screening was added in 1991. Pap screening was also added. And there are several others that have been added by Federal legislation. Once we know generally what is covered then the question is how an individual coverage decision is made with respect to technologies that fit into that category.

There are four standards for the coverage determination and let me just list them. The first one is safety and efficacy. Is the treatment safe and efficacious. Secondly, is it not

experimental or investigational. Third, is it appropriate. And fourth, is it cost effective. These are the criteria used to determine whether any particular technology or service is covered under the program. Procedures for making these coverage determinations are frequently made by those carriers and providers who operate the Medicare program. So you have inconsistent local decisions. IKFA has the ability and does under certain circumstances make national coverage determinations which then become binding on local providers. This is a very involved process and involves several of the different bureaus within IKFA.

Having reached the question of having your technology covered, the question then becomes at what rate is your technology reimbursed, and this becomes even more complicated because the center for the location of the treatment will determine the reimbursement rate. It is possible to have reimbursement on a retrospective cost basis looking at the cost and reimbursing for full cost. It is also possible to do it on a prospective basis giving you essentially an averaged out fee for each category or service; it is also possible to do it on a scheduled basis or on a blended fee basis. Each of the Federal programs has different requirements. Historically, reimbursement for hospitals was on a reasonable cost basis. That meant that IKFA looked at what the cost of delivering that actual service to the patient was and reimbursed either the actual cost or a reasonable cost. This provided no incentives to contain cost but, in fact, was a boom to the development of new technology because new technologies that were used then became adoptable and payable by the government if they fit within a coverage category.

In 1983, Congress adopted a prospective payment system which totally restructured the financial incentives for hospitals. Under this system, a patient classification system was established through diagnostic related groups (DRG). Upon discharge, patients were assigned to a DRG which is composed of cases that are clinically coherent and require the same resources. The payment provided for the patient is intended to cover the necessary cost of the average patient in the DRG and not the actual cost. About 500 DRGs exist. Unlike cost based reimbursement, perspective payment rates are set in advance. Under the perspective payment system, the hospital keeps the difference between the actual cost for the patient and the DRG rate. Similarly, the hospital absorbs any loss. DRG rates are readjusted and adjustments can be made for outlines. The impact of the system has been immense. Medicare is by far the largest single payer of hospital services. Hospitals are quickly motivated to operate in ways to maximize IKFA reimbursement. In fact the perspective payment system has led to a dramatic rise in outpatient services and a decrease in the length of stay in hospital. This is just one of the reimbursement mechanisms used by the government. To go through the actual system would take quite some time but with respect to each provider of new technology, you need to look at the kinds of issues your technology raises and whether, in fact, it raises reimbursement questions. For many technologies and products that do not really represent either major new markets or very expensive new technologies or those with unproven track records, the question of reimbursement and coverage can be relatively routine. But for major new products, the question of reimbursement and coverage becomes as important as the FDA approval process.

Technology and Engineering for the Benefit of Medicine

Peter G. Katona
Vice President, Biomedical Engineering Programs
The Whitaker Foundation

Introduction

Technology in medicine has been developing primarily along two lines (Fig. 1). The first utilizes the physical sciences to develop devices and systems for use in medicine; this endeavor is often called "biomedical engineering". The other uses biological organisms to create new medical products, primarily drugs. This second path is often referred to as "biotechnology". Considerable and increasing interaction exists between the two approaches. One is "bioprocess engineering" that uses engineering techniques to ensure the economical large scale manufacturing of biotechnology products; the other is the intentional artificial mimicking of materials and processes found in biological systems; such mimicry is becoming increasingly sought when developing new devices and systems for medical use. My presentation concentrates on the development of devices and systems.

Many of the new medical devices and systems fall in a category that I'll call "Informational Systems" (Fig. 2). In these, sensors may transduce physiological variables into measurable signals that provide knowledge about the physiological or biological process. Computers may then take the recorded signals, and after suitable processing, transform the signals into useful information about the patient. This information then can be used to guide therapy, most often provided by nurses or physicians, but occasionally by automatically controlling an actuator such as an electrical stimulator or drug delivery device. Examples of such informational systems include patient monitoring, automated drug infusion, functional electrical stimulation, or imaging.

Probably all of us at this conference believe that the medical use of technology is beneficial to society: it helps to improve the health of patients. The theme of my paper is that there are also important problems: these include the need to match technology to real medical needs, and ensuring that the cost of technology is justified. Technology should be a tool for cost reduction, rather than a scapegoat, used by some, for the sharply increasing health care costs. I'll illustrate both promises and problems through several examples.

Sensors

My first example is the use of miniature sensors for biological investigations and for patient monitoring. Accurate and unobtrusive sensors is a prerequisite for all informational systems, and advances in microelectronics has greatly facilitated the development of such sensors.

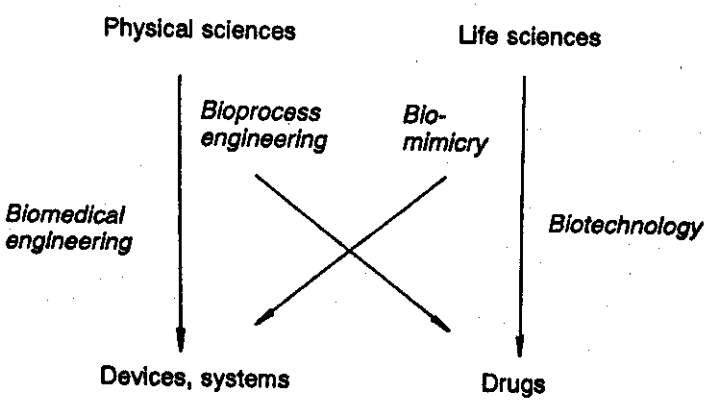
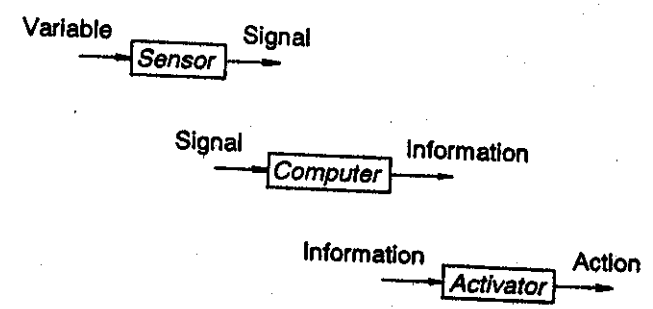


Figure 1: Technology in Medicine



Examples:

Patient monitoring, automated drug infusion

Functional electrical simulation

Imaging

Figure 2: Informational Systems

Dr. Otto Prohaska of Ottosensors, Inc. has developed a line of electrodes to record extracellular electrical potentials from nerves and muscles. On a scale of millimeters the array of electrodes appears similar to many other multiple contact miniature dagger–type electrodes used in neurophysiological studies, but at a larger magnification the electrodes appear as hollow rectangular chambers with a circular hole that connects the chamber to the outside. The chambers are made by fabricating a Si_3N_4 insulating layer over the silicon substrate; the electrode itself is Ag/AgCl. The chamber is filled with an electrolyte solution; contact through the outside world is through the circular hole. The advantages of such chamber electrodes are said to include a small electrode to electrolyte impedance due to the large surface area of the electrode itself, the presence of the electrolyte buffer making the electrodes insensitive to chloride ion concentrations at frequencies above 1 Hz, and the elimination of potentially toxic direct contact between the metal electrode and the tissue.

Similar technology can be used to make chemical measurements as well. An amperometric oxygen sensor consists of a gold working electrode and two Ag/AgCl reference electrodes. Electrolyte solution is now introduced through two circular holes. Advantages of this construction is a high signal–to–noise ratio, and the consumption of only 1/10th of the amount of oxygen compared to conventional systems. Oxygen sensors can be combined with temperature and electrical potential sensors on the same dagger for recording these variables at multiple locations simultaneously.

Multiple miniature sensors hold great promise for making vital measurements both for basic research and clinical applications. Achieving long term stability and biocompatibility are the major remaining technological problems.

Actuators

Electrode arrays can be also conceived as activators rather than sensors. As an example, consider the electrode array designed by Dr. Richard Normann at the University of Utah. The array, consisting a total of 100 electrodes, is intended as an investigational tool to stimulate the visual cortex of blind individuals. The concept, first explored briefly by Brindley some two decades ago, is that some visual sensation in the blind might be restored by appropriate electrical stimulation of the visual cortex. As a great oversimplification, one might assume that a pattern of phosphenes, light flashes elicited by electrical impulses, can be generated that bears some resemblance to an actual visual image. While there are those who doubt that this is feasible, Dr. Normann is developing the techniques that might indicate whether such a restoration of some measure of visual perception is possible. Using silicon technology, he can now successfully manufacture the 100–electrode array on a square with a linear dimension of 4.2 mm. The shape of the needles can be controlled to close tolerances.

When trying to introduce the electrode array into the cortex, one encounters difficulty because the electrode array has a tendency to depress rather than penetrate the cortical surface. A special tool needed to be developed that uses hydraulically generated impact to implant the

electrode into the brain. Establishing biocompatibility of the electrodes is the first step in assessing the feasibility of the overall approach.

Functional Electrical Stimulation

Sensors and activators are effectively combined in systems that provide functional electrical stimulation to paralyzed patients. For example, many patients with spinal cord injury between segments C5 and C6 retain their capability to move their shoulders, but they loose their ability to move their hands. Electrical activation can be used to stimulate muscles that control the hand; such stimulation replaces the natural neural activation of muscle that is lost due to the spinal cord injury. The electrical stimulation may be controlled, for example, by the movement of the shoulder. For the system to work, one needs a transducer to measure shoulder position, a set of electrodes to stimulate the hand muscles, and an electronic system to determine the appropriate stimulation parameters derived from the shoulder measurements.

Dr. P. Hunter Peckham's group at Case Western Reserve University developed the first system some 5 years ago where the stimulating electrodes are totally implantable, obviating the need to provide failure-prone transcutaneous connectors. The system provides individual stimulation to arm and hand muscles through eight individual electrodes. In the current system the shoulder transducer is on the surface of the skin, but in the future the sensors may be also implantable.

The recipient of the first system has been using it for over 5 years; he is now performing manual tasks that he could not have even attempted prior to receiving the implant. Dr. Peckham emphasizes that the success of such a system does not only depend on the technology, which is now quite standard, but on the meticulous attention devoted to the detailed needs of the individual patient, and on very time consuming and extensive training of the user.

Other Technological Aids to Individuals with Disability

Similar views were expressed by Dr. Larry Scadden, director of the rehabilitation engineering center of the Electronics Industries Foundation. It is striking that over the past few decades numerous technologies have been explored through probably hundreds of projects to develop obstacle detection aids to the blind. Such systems have employed ultrasound, coherent and incoherent light beams, and miniature radar to warn the blind of obstacles in his path. Yet, in spite of all these efforts, only approximately 25 blind people in the US use these high-tech devices regularly; most of these people were blinded in battle and received extensive training in the use of rehabilitative devices. Some 150 people use high-tech aids occasionally, while the rest overwhelmingly prefer the low-tech approach: the long cane. The reason why high technology has not yet been accepted as an aid to the blind is that existing systems are judged to be a nuisance to use, they require too much training, and they are too costly.

My last illustration of matching needs and being conscious of costs is a program that was initiated at the Biomedical Engineering and Aiding the Disabled Program of the National Science Foundation by Dr. A. Zelman some 4 years ago. Under this program, NSF funds are made available for undergraduate design projects that provide aids to specific disabled individuals. The agency grants $500/project, some travel expenses, and summer undergraduate help. The total cost is very small since the maximum grant is $15,000 to any one institution. It is stipulated that the devices must be given to the individuals for whom they were designed, and yearly progress reports must be provided.

This program has proved to be a great success. Some of the projects are sophisticated technologically, others use an apparently low-tech approach but in an innovative and unusually humane way (Table I). A videotape provided by Dr. Joseph Mollendorf at the University of Buffalo shows dramatically how engineering students can bring joy to children with spina bifida by constructing individually tailored mobility aids.

Table 1: Undergraduate Design Projects
Examples

- Ice crampon crutch attachment for above knee amputee
- Computer interaction through voice recognition
- Adapting toys for disabled tots
- Exerciser for a person with multiple sclerosis
- Intelligent wheel chair controller

Conclusions

I described briefly some promising technologies for use in medicine, but I emphasized that one must be careful to ensure that the technology utilized matches the clinical need. The cost must be reasonable and justified, something that academically oriented biomedical engineers sometimes forget. Individualized attention and training must supplement any technology used in rehabilitation medicine.

Acknowledgment

Thanks are due to Drs. Normann, Peckham and Prohaska for providing the pictorial slides of their work.

Economic Aspects of Biotechnology

Peter M. Kash
The Castle Group Ltd.
375 Park Avenue
New York, NY 10152, USA

Today we heard a lot about science; now I am going to talk about how to finance this science. More specifically explain the different routes and alternatives one can take in order to get the maximum exposure on a global basis, and to detail why biotechnology is so interesting today.

There are several alternatives by which to market your product. You have the public market and the private market. Companies such as Interpharm, Elscint and Biotech General have demonstrated how Israeli companies can perform in the public market. Let's take a quick example. If you look at all the industrial sectors in public venture capital and venture capital at large, biotechnology has been the number one performing sector during the last three years. If you look at the S&P 500, in 1988–89, it was up 27%. Biotech was up 77%. In 89–90, when there was an overall market decrease of 7%, there was a 42% increase in biotechnology. In 1991, the S&P was up 27%, and Biotechnology was up in excess of 75%.

Fidelity Select Biotechnology Fund is number one of the top equity funds in the world today. Everybody has heard of that one. Actually, seven of the top ten best performing funds are in biotechnology. Three of these are Fidelity, Financial Strategies and Vanguard. All of these funds can currently invest in Israeli companies, they all have both private and public capital, not in the thousands, or hundreds of thousands, but in the billions. Biotech mutual funds have grown significantly. For example, five years ago, John Kaweske the manager of Financial Strategic Health Care in Colorado, was managing five million dollars; today he is managing $1.2 billion dollars.

I have spoken to people during the conference breaks and the popular question is, what will happen if the stock market goes down and you can't find public venture capital. My own personal belief is that interest rates in the United States, are going to stay relatively low. What are large investors going to do? They will seek investment alternatives other than money markets.

They are not going to invest in art because the Japanese have inflated that market. Emerging growth stocks have a 28.8% return...but the volatility is relatively high, 14.1%. Venture capital has an 18% rate of return versus a 7.5% rate of return for real estate, and an 11.6%

return for the S&P 500. A conservative and secure investment, U.S. Government bonds, and U.S. Treasury returns only 4.5%. Thus leaving Venture Capital as a viable alternative.

Today venture capital is not as risky as it once was. Why? Venture capital is much more sophisticated. For example, in The Castle Group we have 10 medical doctors on staff not as advisors, but full time. They have left medicine and work full time evaluating technology. It's interesting to note that Japanese companies, who are probably known to be the most diligent researchers, in regard to venture capital, have a minimum of 11.4 billion dollars available for investment in venture capital today. If you look at most company financing, 59% is private, 19.5% public. Within the next year and half, public financing will probably increase to 25%. Why is that? Because Americans, Japanese and European O.T.C., (over the counter), markets are expanding with increased activity and interest on the NASDAQ and JASDAQ. The JASDAQ was just started last month; it is the equivalent of the NASDAQ for Japan. Last month, Japan started legislation stating that they would fund 1,000 new companies, over the next eight years (1,000 new underwritings.) The majority of these companies will specialize in biotech and health care and will need joint venture partners. Because of political and sociological reasons, these partners will be difficult to find in the States. Therefore, Japan will be interested in developing new sources here in Israel. This week I came to Israel with a Korean contingency looking to invest money here. Next month, I am returning with a contingency of Japanese companies to promote their interest in investing in Israel. These joint ventures offer exciting possibilities for the Israeli market.

If you look at American joint ventures, 62% of American joint ventures happen between indigenous American companies while about 11.2% of the biotech companies are doing strategic alliances in Japan. However, in Japan, 82% of strategic partnerships are with non-indigenous Japanese companies. They are willing to deal with companies abroad. I would hope to see Israeli companies get involved.

Therapeutics is a high growth area which is going to increase tremendously. Another dynamic area, coming out of Southeast Asia, is agro-biotech. Possibly agro-biotech will be a profitable niche for Israel. I don't know if the Technion is involved in medical waste management, a very hot area in the United States. If Israel can combine engineering and medicine, to solve this problem, medical waste management will be a lucrative venture when dealing with Japan, the States and probably Southeast Asia.

In Bangkok they predict that by the end of this decade, there will be 2 million cases of AIDS in Bangkok alone. It is absolutely devastating. We need to find both diagnostic and therapeutic treatments for this disease.

There are about 800 biotech companies in the United States. 15,000 academic institutions and 80 biotech centers. I'd like to see Israel do more joint ventures with the United States which is why I'm here. The sub-specialties that interest me are Antisense and the Immune response science. Another hot area in the Unites States, Japan and Sweden is oligosaccride synthesis.

An important aspect of creating new businesses in Israel is raising funds. However, a strong basis for receiving Japanese and American funding, is by developing a precise business plan detailing the amount of money you will need, over what time period and how you expect to achieve your goals. I work with about 25 fund managers around the world. These fund managers do not ask me about Israeli technology, instead they ask me about Israeli companies. Several years ago, the consensus was that Israel had only good technology. Today, people are also respecting Israeli management, production, marketing, operations and quality control. There are tremendous opportunities available to you. Working with Japanese companies can be the catalyst.

Several people mentioned that there are three major markets – the U.S., the European and the Japanese. I think there is an even larger market, Southeast Asian, which is basically untapped. Over the last four years, in excess of 5 billion dollars has been channeled into developing biotech in Taiwan, Hong Kong and Singapore. Taiwan alone is spending 300 billion dollars to develop their own biotech infrastructure over the next few years. There is no reason why Israeli companies cannot bypass Japanese companies and tap into Southeast Asia directly. What are the benefits to everyone here? You develop a fourth market which creates new licensing agreements thereby generating up front fees and royalties.

The Japanese value a solid relationship prior to conducting business. The Japanese have told me that they like Israeli technology; however, they dislike their aggressiveness when demonstrating their technology, instead of developing a long–term relationship. This applies specifically to Japan, Southeast Asia is a little different. From my own experience, I must stress the need to learn about the Japanese culture before attempting to work with them. Before taking them up to the Technion, take them out for a falafel. Take them for a tour around Israel. Before doing any business with the Korean gentleman, we took him to the Kotel, Yad Vashem, Masada and Bethlehem. We didn't talk business; just introduced him to the people and the culture. Next time he visits Israel, he'll talk business. People say, we don't have enough time for that. But by developing a solid relationship slowly, you'll be able to advance much quicker later on.

When trying to develop a specific science you have two choices. First, instead of trying to start many different companies within your specific university or universities, you can develop one company and add related technologies that will increase the companies value, especially with publicly traded companies. Public announcements of new technologies, even if they're unrelated,but of scientific value, generate interest amongst fund managers. The anticipation of future revenues and future profits increases the value of the stock which decreases the cost of capital.

Second, in addition to trying to develop your own companies, license out technology and form joint ventures. By the year 2,000, the biotech industry will be doing a minimum of 55 billion dollars in revenues; 22 billion dollars attributable to the United States alone. The actual prediction is 74 billion, I'm being a little bit conservative with 55 billion. There is no reason why Israel cannot have seven to ten percent of this market. There is no reason whatsoever.

When speaking to Israeli scientists and to Israeli small growth companies, I have been told that they expect to be acquired one day. However, you won't be seeing a lot of acquisitions. Biotech companies will eventually have evaluations higher than pharmaceutical companies. Everybody knows what the NIH is: "Not Invented Here". If they didn't invent it, they don't want to speak to you. But this attitude is changing today. The beauty about working with companies in the United States, is that last year the NIH gave approximately 8 billion dollars in grants. If you associate yourself with a company, make sure that the company has an affiliation with a university which insures access to a lab.

People tell me that Japan will ultimately be the primary biotech market. After meeting with people from MITI and from the Kroshaysho in Japan, I strongly believe that Japan will not come close to the United States within the next 15 years. People say I'm crazy but here are two reasons why I believe I am right. Firstly, Japan is extremely homogeneous. Of the Ph.D.'s in the United States today, at least 35% are non-indigenous Americans. Unfortunately, many of them are Israeli, but also Japanese, Korean, Chinese, Swiss and Italian. They are not here on a one year fellowship. They come to the U.S. to live in Westchester, Long Island, etc. They buy a nice house, and they stay. So, the American Ph.D. pool is very diversified. Secondly, America has an advantage in that we can make decisions within a matter of days or minutes. I have seen my company hand over checks to scientists for ten, fifteen, or twenty five thousand dollars before they leave our office. We sign them up before they go across the street to show it to Alex Brown, H & Q, Montgomery Securities or the Rockerfeller Institute. We have a much quicker decision making process than Japan which puts us at an advantage. I believe that the years ahead will be exciting for the biotechnology industry in the United States.

SESSION II: DEVELOPING MEDICAL TECHNOLOGY

Chairman: Professor Daniel Weihs

Development of Medical Technology The Support of Research & Development

John Watson

Director
Devices & Technology Branch
NHLBI – National Institutes of Health
Bethesda, MD, USA

First, I would like to congratulate the effort that is being developed in Israel in terms of cooperation between medicine and engineering. I hope one day we can emulate it in the United States. Professor Sela emphasized the importance of invention and discovery and the excitement that it brings, but also the long road to actual application. I share that enthusiasm and I will talk to you today about some of the long roads to actual application. Professor Penchas discussed at considerable length concerns about cost, quality adjusted life as a result of new technologies, and the importance of trying to evaluate progress in a technology as it goes along. I agree with both of those points of view, except that the creative skills of our colleagues around the world will always surprise us in what they are able to accomplish if given the opportunity.

I head up the artificial heart program in the United States. If we were to evaluate its cost effectiveness today, if we were to start that program, there is no way that the program would have ever been started. We started in the Kennedy era when the United States planned to go to the moon, to build an artificial kidney and to build an artificial heart. They thought that no technological development was beyond the imagination of our scientists and technologists. Well what has the artificial heart done? We have been working on it since 1966. Why is it not yet a reality? What has happened as a result of the artificial heart program? Well, a lot has happened. Anyone who went to the last American Heart Association meetings in Anaheim and saw all the exhibits there, saw that almost all of those exhibits were a result of the artificial heart program. Some examples are: the interocular lenses that are used for surgical repair after cataract removal; low temperature pyrolitic carbons that are used for eliminating clotting on most of the artificial heart valves; and mechanical artificial heart valves that are used around the world came from the artificial heart program. The myocardial infarction research units that were developed in the United States came from the artificial heart program. The specialized centers of research in ischemic heart disease, which many credit with developing the worldwide trend in the reduction of myocardial infarction rates, came from the artificial heart program. The point I would like to make here is that the technological goals in a directed program are important, and may be technically feasible, but one cannot predict where the spinoff will come from, and what benefits may accrue. When I came to

NIH, the pacemaker was considered to be the least cost effective medical technology in the United States. Recently, in a conference I attended on atherosclerosis, it was pointed to as the most effective medical technology in the United States. It is incumbent upon us to be responsive and to help inform our colleagues on the value of technology. People tend not to understand technology; they tend to fear that it is somehow out of control and leads to high costs. But it leads to many other things that we do not expect and technology provides men and women with more control of their surroundings. The second thing is that the natural progression of technology is to reduce costs. For example, the electric lights in this room. When Edison first made an electric light, probably only a few rich people around the world would have electric lights if the bureaucrats had been around, but allowing technology to flourish and to follow its normal course, it is now available to everyone. So even though we do not understand electricity, we can make use of it. I would like to present another technology and show an example that shows where this technology is used. If the non-scientific experts had had their way, this technology would not exist today, but you will see the benefits of it.

I was asked to talk about the support of research and development. I think we tend to forget that there is not just basic and applied research, but that there is a process between each of these areas. For example, on the total artificial heart, we just can't put components together and build an artificial heart. We have been working since 1966 to develop the scientific basis for this technology. Applied research and development does not always follow basic research but sometimes proceeds it.

Where does the line begin and end for Federal and private support? My feeling is that it is after the introduction of a new technology and demonstrating its safety and effectiveness, the actual clinical use should be taken over by the private sector. There are others that feel that it should stop after applied R & D is accomplished. I believe this is too early and that the different areas of the innovation may require a basic or applied component. We need to do basic research on the liability. We need to do basic research on process control to provide quality so that the concept, and I will introduce a new paradigm at the end of my talk, is that the step by step progression to actually marketing a new medical technology is no longer appropriate and we have to think of this in different terms.

The US Institute of Medicine was formed under the charter for the National Academy of Science, to which our Congress, in 1963, gave the responsibility of evaluating policy matters related to public health. The Institute of Medicine was chartered in 1970. Building of an implantable artificial heart began in 1966. Every two years since 1966, there has been a major review of the artificial heart in the United States. People outside of technology were trying to evaluate the technology for which there was no data. The requirement of the Institute of Medicine is that anyone that does the review cannot be an expert in the field. So this panel of very intelligent experienced people outside of the artificial heart area reviewed this technology for two years. It cost $650,000 to do this study. They concluded that we should continue research on the artificial heart and that, in the United States, there should be at least 10,000 to 20,000 people with heart failure that could benefit from this technology and 25,000 to 60,000 people who could benefit from a left ventricular assist system, that is a system that

you could put in place and leave the heart intact, that would assist the heart without removing the heart. They concluded that it was technically feasible, even though there was no expert on the panel. That it was marginally cost effective. Again, there was no data but they were able to make that conclusion.

What is the funding pattern within the United States? Prior to the Second World War almost all funding for medical research came from private industry. After the war, all of it came from the government. Support from NIH has gone up and down but the trend is clearly that a greater proportion is coming from private industry than from the public sector. We expect that trend to continue. Now what is the need for such a complex technology as the artificial heart? Death from cardiovascular disease in total is declining, but with an aging population, death from heart failure is increasing for both men and women. The only current medical treatment for heart failure is heart transplantation. Last year, we did 2,071 heart transplants. We have more candidates on any one day than we can transplant in a single year. So the need for some other treatment for these patients is increasing. In South Africa they showed that not only could you do orthotopic transplant, where you removed the patient's heart and supplied the donor heart but you could also do heterotopic transplant where the donor heart was placed in the right chest and the recipient's heart remained in the left chest. These patients had two blood pressures, two EKG signals and in one reported case after two years, they were able to remove the donor heart and the recipient heart, the natural heart was able to take over function and the patient lived for several years with their own heart. Now we take that same heart that was in the right chest and make a mechanical analog that is put in the abdomen where blood is taken from the left ventricle enters the pumping device and then is returned to the aorta. This is a mechanical analog of the Barnard experience. The mechanical heart can be powered by a pneumatic tube from the outside to the inside and we now have a patient that is powered by electric batteries and the engine and control mechanism for the internal pumping system are inside the patient.

Why don't we have an artificial heart? Let me go through some of the psychological and biological problems to build an implantable technology. We have got to power the motor and we have to have a control system for that. We also have to manage a volume pressure relationship because all systems which are used currently clinically are vented to the atmosphere. So they are not a closed loop, but to make an implantable system that is really going to benefit patients, we have to eventually close off this vent. Meanwhile we work with an open vent. 90% of our scientists thought that the surfaces inside an artificial heart should be completely smooth, that there should be no flaws in the surface larger than a platelet, so that you could minimize thrombosis and potential embolic problems and also minimize bacterial colonization. On the other hand, there were people who thought if you made a textured surface, you would produce a blood clot on that surface and the surface would then change and become biocompatible. So on the flexing diaphragm there is a textured surface on the flexing part and titanium mircospheres on the stationary part. The polyurothane diaphragm has to be blood compatible. It has to be reliable for at least ten years. That is 500 million pumping cycles. It has to be impermeable to water so that water is not transferred into the engine portion and it has to be permeable to gases so that changes in barometric pressure can be accommodated. So what happened when these were implanted in patients? The

polyurathane surface begins to take on a cellular form that no one quite understands. We have seen some surfaces that have actually developed endothelial cells and others that have developed collagen cells. But in any case, these surfaces have been remarkably biocompatible. Now that by itself is not the solution to the blood material interface but it opens up a whole avenue of how these polyurathane textured surfaces can act as a receptor sight for cells to be attached and then to differentiate in the biocompatible surface.

I would like to finish with the need for a new paradigm for innovation. I am not exactly sure how to accomplish it yet but we have to think in these terms. In terms of circulatory support for the patient, I do not know whether we have to have a pulsatile system but we may be able to develop a system that operates at two or three times the normal heart rate or even a continuous flow. Both of these concepts seem to have feasibility and in the next generation of circulatory support systems they could be made much smaller, much more reliable, and much less costly. I think the innovation paradigm should have three phases, all of them involving basic research and applied research: the conception phase, the realization phase, that is the reliable phase, and then the transition into the private sector. We need to develop innovation cycles of less than ten years. It will take somewhere on the order of 40 years to develop the first artificial heart.

The conception phase is basically focuses on the quality of life. That is the clinical need, the performance. Usually we know performance pretty well and we have to develop levels of reliability to go far beyond what we have done in the past and this requires considerable fundamental research. In the realization phase we have to show that it is reliable in some formal testing way. We have to carefully, clinically evaluate it and demonstrate conclusively its safety. And then as we go through the transition phase into the private sector, that we have to develop the process optimization so that we continue to receive a quality product for the next hundred years and that we develop a data base that shows where we are going with this technology. As a consequence of this, I can assure you, we will have cost reduction.

Let me close by congratulating the concept and Israel of the close interaction between medicine and engineering. I think it is the wave of the future and I think you are further out on the wave than most of us.

Creating a Biotechnology Community

Elaine Richman
Director, BIO SCI INFO
P.O. Box 65271
Baltimore, MD 21209 U.S.A.

1. INTRODUCTION

I am going to be describing how one U.S. city – Baltimore, Maryland – is working to transform itself from an industrial center into a home for the life sciences.

Baltimore is a coastal city of approximately ¾ of a million people. For most of the 20th century, tens of thousands of Baltimoreans have made their living in the city's giant steel mills and in the shipping industry.

Until about 20 years ago, Baltimore was a sleepy town. Most of the nation regarded it as a place to pass enroute from Philadelphia to Washington, D.C. In the early 1970s, a new mayor named William Donald Schaeffer introduced a campaign to upgrade Baltimore and to make it an exciting metropolis. Baltimore has developed and grown. I would like to use what happened in the restaurant industry as a metaphor for what is occurring in biotechnology in the city.

Today, one can know all the biotechnology centers, businesses, and players in Baltimore, just as we knew all the restaurants 20 years ago. However, a very strong sense is in the air that the intimacy of this nascent industry is giving way to a burgeoning new way of life and that within the next few years biotechnology will be so big that it will form the basis of Baltimore's economy. Like the restaurants, soon there will be no more knowing every joint in town. And this is just in time because steel manufacturing and shipping businesses are on the decline.

The leaders of the city support this growth. The have a "vision to create a new economic machine by building Baltimore into a leading center for research, development, manufacturing, and support of the life sciences. Just as Boston, and the Silicon Valley have become synonymous with the computer and electronics industries, they believe that Baltimore can play a leading role as a center for biotechnology and related frontiers in the life sciences." A slogan has even been coined by the city leaders: *Baltimore – Where Science Comes to Life*

This is a realistic goal. Baltimore has a strong business, academic, and science community. Table 1 shows Baltimore's biotechnology–related institutions, beginning with its universities.

Table 1: Baltimore's Biotechnology-Related Institutions

The Johns Hopkins University
- Undergraduate school
- Graduate school
- Engineering school
- Hospital and School of Medicine
- Welch Medical Library Genome Database (receiving $16 million toward building a computerized database)
- School of Hygiene and Public Health
- Bayview Research Campus

University of Maryland
- Hospital and School of Medicine
- School of Nursing
- School of Dentistry
- School of Pharmacy
- UMBC undergraduate school
- UMBC graduate school
- Medical Biotechnology Center

Maryland Science Center
The National Aquarium
Christopher Columbus Center for Marine Biotechnology*
Maryland Bioprocessing Center*

*Planned

There are the three campuses of the Johns Hopkins University in Baltimore ... one with the undergraduate, graduate, and engineering schools. Another with the medical school, Welsh Medical School Library (with its new genome database), and the School of Hygiene and Public Health. The third is the relatively new Bayview Research Campus.

The University of Maryland in Baltimore and the neighboring county is home to a hospital and school of medicine.

Baltimore is located only 50 miles up the road form Washington, D.C. What makes that important is the many research and support agencies in the D.C. area. Some major neighboring biotechnology-related institutions are listed in Table 2.

A successful industry that is based on biotechnology requires more than the output of a couple of universities and proximity to national agencies and the airport. The infrastructure that is coming together to create the biotechnology community in Baltimore is identified by 10 arenas for biotechnology-related activities in Baltimore and the surrounding area.

Table 2: Neighboring Research and Support Facilities

- **The National Institutes of Health (NIH)**, based in Bethesda is actually composed of 13 research institutes. Collectively they house more than 5,000 researchers and a support staff of 16,000
- **National Science Foundation (NSF)**
- **U.S. Food and Drug Administration (FDA)**
- **U.S. Department of agriculture**
- **National Institute of Standards and Technology**
- **U.S. Patent Office**
- **B-W International Airport**
- **Foreign embassies**

Table 3: Arenas of Biotechnology

1. **Universities.** Basic research still tends to be their primary focus. However, each now has its own *Office of Technology Transfer* to help move discoveries from the laboratory into the marketplace.

2. **Biotech Institutes.**
   - The Medical Biotechnology Center of the University of Maryland
   - The JHU Bayview Research Campus
   - The Christopher Columbus Center for Marine Biotechnology

3. **Private and state-run organizations** have gotten into the act by providing advice and by sponsoring meetings and workshops on biotechnology (more details will be given later).

4. **Private biotechnology companies.**
   - NOVA Pharmaceutical Corporation (an R&D firm emphasizing treatment of symptoms of the common cold, pain, central nervous system disorders, and carcinomas).
   - Becton Dickinson Co. (a developer and manufacturer of diagnostic kits).
   - Chesapeake Biological Laboratories (an R&D and manufacturing firm specializing in antimicrobial products).

5. Interaction with **international** biotechnology community, through the:
   - Maryland International Division of DEED (Department of Employment and Economic Development).
   - JHU/Weissman Institute
   - Medical Biotechnology Center / Tel Aviv University
   - Marine Biotechnology Institute / Ben Cavari (Haifa) / Oceanographic Institute (Eilat)

Table 3: (continued)

6. **Venture capital firms, brokerage houses**, and **banks**

7. **Accounting, insurance** and **law firms.**

8. **Educational** programs are underway or under development to **educate** a work-force to meet present and future needs of biotechnology centers and biotechnology companies in Baltimore (more details later).

9. **Incubators**, where new biotech (or high tech) companies rent inexpensive laboratory space to develop their products. Three incubators exist in Baltimore - one at University of Maryland, one at the Johns Hopkins University, and one run by the State of Maryland. None are more than a couple of years old and the State-sponsored incubator was only opened in October of 1991.

10. A **bioprocessing facility** (called the Maryland Bioprocessing Center), a planned $15 million center that will help biotechnology firms prepare their products for the market. This is actually a "scale-up" facility where scientists/entrepreneurs will be able to produce large enough quantities of their compounds for clinical tests and reviews by the FDA.

That is a lot of activity for a town which only began to think entrepreneurially about the life sciences less than five years ago.

For the remainder of my talk I will describe (i) what the private and public organizations are doing to keep the scientific an business communities excited and up date about biotechnology and (ii) the educational efforts that are underway to create a well-trained work-force.

II. NETWORKING

There are several private and public organizations in the Baltimore area that are particularly active in biotechnology. They keep the scientific and business communities tuned in by holding biotechnology-related workshops and seminars. In other words, they sponsor *networking* sessions. The agencies or types of organizations in the Baltimore-Washington area who presently sponsor workshops and seminars are named in Table 4.

Most of the networking opportunities sponsored by these groups have been developed only in the last couple of years. I present this list, not because the names have significance for most people outside of Baltimore, but to illustrate the amount of involvement that has occurred in such a short time.

Table 4: Agencies Sponsoring Workshops and Seminars

Greater Baltimore Committee (GBC)
University of Maryland Office of Continuing Education
University of Maryland School of Law
University of Maryland College of Business and Management
University of Maryland Engineering Research Center
University of Maryland Technology Advancement Program
Maryland Biotechnology Institute
Center for Advanced Research in Biotechnology
The Johns Hopkins University School of Medicine
World Trade Center Institute
Montgomery County High Technology Council
Suburban Maryland High Technology Council
Maryland International Division
Maryland Office of Technology Development
U.S. Department of Commerce
Law Firms, accounting firms, insurance firms

The topic of biotechnology networking is particulary intriguing. In the U.S., women and minorities are traditionally outsiders to networking opportunities. This was confirmed by a recent report from the U.S. Department of Labor stating that women and minorities get excluded from corporate pipelines. These pipelines are conduits to top managerial and executive jobs. The Department of Labor study used the term "glass ceiling" to describe this thing that prevents upward mobility. The upward mobility is thwarted because women and other minorities typically have not had access to opportunities to informally hobnob with people in powerful, decision-making positions. In other words, they have not been invited to network.

What I see in biotechnology networking in the Baltimore-Washington area is that no potential players are being excluded. **Everyone** is invited to network, have breakfast, lunch or dinner with the State Secretary for Economic and Employment Development, with elected officials, financiers, or the CEO or a large biotechnology operation.

It is likely that opportunities to network are relatively unlimited at this juncture because the numbers of people involved in biotechnology are still small. It is rather like a pick-up game of basketball. Anyone who comes along can play in order to get enough people on the court. Once there are enough players, not everyone who comes along is welcome.

The point is that there is now a window of opportunity for women and minorities to make professional gains. (Networking is probably old hat to people who have had to depend on it for survival. But, for the majority of Americans, it is uncharted territory. In today's slow economy, millions of U.S. workers are having to learn fast how to network in order to find jobs.)

Leaving this social commentary, we now return to networking in biotechnology in Baltimore. There are several widely-advertised networking opportunities each month. I have received notices of more than 45 seminars scheduled between September 1991 and April 1992.

Table 5: Biotechnology Seminar Topics

- Financial issues (raising money)
- Marketing and distribution strategies (bringing products to market)
- Quality assurance (keeping the product good without affecting income)
- Patenting and licensing
- FDA regulations
- Liability insurance (protecting the company against unexpected dangers from their product)
- Current trends in treatment and diagnosis (e.g. dental decay and genetic engineering; prognosis of human cancer -- new methodologies)
- Case presentations (product and strategies are critiqued in front of an audience by a panel of experts).

Those seminars having to do only with financing, for the months of September and October, are given in Table 6.

Table 6: Financial Seminars for Biotechnology Entrepreneurs
(September - October 1991)

- The Venture Capitalist and the Investment Banker - How to Win Their Hearts
- National and International Trends in Compensation Packages for Biotechnology Firm
- Finance for the Non-Financial Entrepreneur
- Early Stage Investing in Maryland
- Mid-Atlantic Venture Fair
- LBO, IPO, and 2001
- International Financing, Marketing and Distributing in the Biotechnology Industry
- Baltimore-Washington Venture Capital Luncheon
- Letters of Credit and Export Financing

The meetings may have as few as 20 people and as many as several hundred. Some are didactic, like the seminar sponsored by JHU on Genes, Drugs, and Devices, where Dr. Bert Vogelstein talked about the molecular genetics of colon cancer and Dr. Peter Pearson described the Human Genome Project and Database. Other seminars, like *Meet the Researchers*, sponsored by the University of Maryland, are more social. Some meetings are

free. Others last for days and cost hundreds of dollars. For example, a meeting in January of 1992 called BioEast '92 is 5 days long and costs between $400 and $600.

You might think of this Baltimore network that has grown around biotechnology to be a kind of *educational program*. It developed out of necessity because so few scientists and engineers are familiar with business, financing, international trade, patents, etc. and so few business people are familiar with science and engineering. I do not think it would be in correct to say that one could spend three months in the Baltimore–Washington area and leave well–versed in everything from biotechnology techniques to ways of keeping customers happy.

I want to close this section on networking by mentioning Soviet emigres in the U.S. and a special program in Baltimore called EURUS, Inc. EURUS, Inc. has created a network to reach newly arrived Soviet scientists and engineers to help them market their inventions.

There are a fair number of engineers, physicians, scientists, and technicians in the group – – perhaps as many as 40–50% of the total. EURUS contacts these people through informal, word of mouth channels and with newspaper advertisements in a Russian language newspaper. As of mid–November, over 90 people had called. EURUS' objective is to determine the commercial potential of their inventions. If ideas have merit, EURUS, Inc. will help the inventor license the product or help the inventor take the product to the marketplace. I might add that the director of the program, Eva Burdman, arrived in Baltimore this summer and holds degrees from the Soviet Union in semiconductor microelectronics and patent law.

III. PREPARING A WORK–FORCE

I would like to look now at a few programs for training a work–force in skills that biotechnology companies need in Baltimore. Everyone agrees that as biotechnology grows in Baltimore and the surrounding area, the demands for a well–trained work–force will increase.

First of all, who are the people to train to work in biotechnology (and hi–tech, too), today and in the future? They are graduate students, undergraduate students, community college students, high school students, middle school students, elementary school students, teachers, workers from other fields (retraining). About a dozen academic programs in math, science, and engineering have been developed for these groups. Most of the programs are new. And some are only in the proposal stage.

I would like to describe three of the programs, beginning with one that has been in existence longer than any of the others. It is a JHU program for young math stars. It is called the City Talented Youth Program (CTY). The youngest children are about 7 years old and the oldest are 16. CTY has several components including the Young Students Commuter Program and the Young Students Talent Search. The Young Students Commuter Program began in 1985. About 100 students/yr enroll in its advanced math classes. Classes of about eight students meet once a week form October through April. CTY offers fewer than a handful of courses for this age group. The courses are: Individually–Paced Mathematics, Scientific and Logical

Thinking, and Basic Experimental Design and Analysis. The children who attend are very normal, every day kids who find learning fun. One of the greatest advantages of the program is the self-confidence it gives the children.

Naturally, the hope of the people who design the CTY program is that the children will pursue careers in science and mathematics, and hopefully at JHU.

The CTY Young Students Talent Search is a much larger program than the Young Students Commuter Program. It is for mathematically-talented junior high and high school students from around the world. The children are identified through testing. Successful applicants are eligible for summer math, computer, or science courses at residential or commuter sites throughout the U.S. and Europe. Last summer, over 3000 students from 39 countries participated in the Young Students Talent Search.

The courses that JHU offers in math, computer and science to these children are: precalculus mathematics, linear algebra, introduction to advanced mathematics, history of number theory, introduction to mathematical logic and reasoning, calculus, computer science 1, data systems and algorithms, digital logic, introduction to laboratory sciences, fast-paced high school biology, genetics, fast-paced high school chemistry, selected topics in advanced chemistry, fast-paced physics with calculus, fast-paced physics without calculus, archeology, astronomy, ecology, geology, and paleobiology.

You might ask, "What does this have to do with training a Baltimore biotechnology work-force?" A great deal, in fact. If you were to come to Johns Hopkins, you would see what looks like a mini-United Nations. Scientists, physicians, and intellectuals from all over the world come to spend time there, some for a few weeks and some for many years. The academic programs for children is one of the ways JHU *networks* to bring some of the best scientific talent in the world into its family... and into Baltimore.

Shifting gears, we now look at a program for middle school and high school science teachers that places them in laboratories of research scientists. The program is called Science Teacher Enhancement Program (STEP). It is a seven week summer fellowship program, funded by the National Science Foundation and sponsored by the University of Maryland School of Medicine in Baltimore. The program is designed to give classroom teachers a taste of frontline scientific research.

Most middle school and high school science teachers have never worked as scientists. So, they are not able to convey to their students what work as a laboratory researcher is really like. Until they entered STEP, they had no experience with the preparation, frustration, excitement, and set-backs that are an intrinsic part of bench research. As a STEP Fellow, each teacher spends three summers in the laboratory of a mento-scientist, usually in biochemistry, genetics, molecular biology, pharmacology, or physiology. They work with laboratory animals and sophisticated concepts and equipment. The teachers also attend workshops, lectures, classes, journal clubs and seminars. Their summer work contrasts sharply with the middle school and high school experience where laboratory experiments are

free. Others last for days and cost hundreds of dollars. For example, a meeting in January of 1992 called BioEast '92 is 5 days long and costs between $400 and $600.

You might think of this Baltimore network that has grown around biotechnology to be a kind of *educational program*. It developed out of necessity because so few scientists and engineers are familiar with business, financing, international trade, patents, etc. and so few business people are familiar with science and engineering. I do not think it would be in correct to say that one could spend three months in the Baltimore–Washington area and leave well–versed in everything from biotechnology techniques to ways of keeping customers happy.

I want to close this section on networking by mentioning Soviet emigres in the U.S. and a special program in Baltimore called EURUS, Inc. EURUS, Inc. has created a network to reach newly arrived Soviet scientists and engineers to help them market their inventions.

There are a fair number of engineers, physicians, scientists, and technicians in the group – – perhaps as many as 40–50% of the total. EURUS contacts these people through informal, word of mouth channels and with newspaper advertisements in a Russian language newspaper. As of mid–November, over 90 people had called. EURUS' objective is to determine the commercial potential of their inventions. If ideas have merit, EURUS, Inc. will help the inventor license the product or help the inventor take the product to the marketplace. I might add that the director of the program, Eva Burdman, arrived in Baltimore this summer and holds degrees from the Soviet Union in semiconductor microelectronics and patent law.

III. PREPARING A WORK–FORCE

I would like to look now at a few programs for training a work–force in skills that biotechnology companies need in Baltimore. Everyone agrees that as biotechnology grows in Baltimore and the surrounding area, the demands for a well–trained work–force will increase.

First of all, who are the people to train to work in biotechnology (and hi–tech, too), today and in the future? They are graduate students, undergraduate students, community college students, high school students, middle school students, elementary school students, teachers, workers from other fields (retraining). About a dozen academic programs in math, science, and engineering have been developed for these groups. Most of the programs are new. And some are only in the proposal stage.

I would like to describe three of the programs, beginning with one that has been in existence longer than any of the others. It is a JHU program for young math stars. It is called the City Talented Youth Program (CTY). The youngest children are about 7 years old and the oldest are 16. CTY has several components including the Young Students Commuter Program and the Young Students Talent Search. The Young Students Commuter Program began in 1985. About 100 students/yr enroll in its advanced math classes. Classes of about eight students meet once a week form October through April. CTY offers fewer than a handful of courses for this age group. The courses are: Individually–Paced Mathematics, Scientific and Logical

Thinking, and Basic Experimental Design and Analysis. The children who attend are very normal, every day kids who find learning fun. One of the greatest advantages of the program is the self-confidence it gives the children.

Naturally, the hope of the people who design the CTY program is that the children will pursue careers in science and mathematics, and hopefully at JHU.

The CTY Young Students Talent Search is a much larger program than the Young Students Commuter Program. It is for mathematically-talented junior high and high school students from around the world. The children are identified through testing. Successful applicants are eligible for summer math, computer, or science courses at residential or commuter sites throughout the U.S. and Europe. Last summer, over 3000 students from 39 countries participated in the Young Students Talent Search.

The courses that JHU offers in math, computer and science to these children are: precalculus mathematics, linear algebra, introduction to advanced mathematics, history of number theory, introduction to mathematical logic and reasoning, calculus, computer science 1, data systems and algorithms, digital logic, introduction to laboratory sciences, fast-paced high school biology, genetics, fast-paced high school chemistry, selected topics in advanced chemistry, fast-paced physics with calculus, fast-paced physics without calculus, archeology, astronomy, ecology, geology, and paleobiology.

You might ask, "What does this have to do with training a Baltimore biotechnology work-force?" A great deal, in fact. If you were to come to Johns Hopkins, you would see what looks like a mini-United Nations. Scientists, physicians, and intellectuals from all over the world come to spend time there, some for a few weeks and some for many years. The academic programs for children is one of the ways JHU *networks* to bring some of the best scientific talent in the world into its family... and into Baltimore.

Shifting gears, we now look at a program for middle school and high school science teachers that places them in laboratories of research scientists. The program is called Science Teacher Enhancement Program (STEP). It is a seven week summer fellowship program, funded by the National Science Foundation and sponsored by the University of Maryland School of Medicine in Baltimore. The program is designed to give classroom teachers a taste of frontline scientific research.

Most middle school and high school science teachers have never worked as scientists. So, they are not able to convey to their students what work as a laboratory researcher is really like. Until they entered STEP, they had no experience with the preparation, frustration, excitement, and set-backs that are an intrinsic part of bench research. As a STEP Fellow, each teacher spends three summers in the laboratory of a mento-scientist, usually in biochemistry, genetics, molecular biology, pharmacology, or physiology. They work with laboratory animals and sophisticated concepts and equipment. The teachers also attend workshops, lectures, classes, journal clubs and seminars. Their summer work contrasts sharply with the middle school and high school experience where laboratory experiments are

predictable. High school biology, chemistry or physics laboratories are rarely places where children get turned on to science. One of the goals of STEP is to excite the teachers so that they will generate enthusiasm in their students.

This approach is working. The teachers report that after STEP they have been able to inspire their student because of their own excitement about research. One middle school teacher reports,

> "I am now able to comfortably discuss with my students the role of the research scientist in our universities and industries. The laboratory technology, which was foreign to me a short time ago, is now becoming second nature."

STEP's ultimate goal, of course, is to bring Baltimore's students, well-prepared, into the work-force in science and math related fields.

I might add here that science and math education in the U.S. is just beginning to receive attention. The educational focus of the past decade was reading. The new focus reflects the concern that American students are falling behind students of other nations in math and science and that action has got to be taken for the U.S. to remain a leader in science and engineering.

Finally, I want to mention an educational program of a different nature. If you ask workers who are already in the biotech laboratories, what they want in order to do a better job, they often say they want *managerial training* rather than the chance to learn new laboratory skills. They are looking for advancement to the front office. They do not have to look far. The University of Maryland, in the Graduate School of Management and Technology, offers an M.Sc. degree in Biotechnology Management. The course description at the University of Maryland reads:

> "The Biotechnology Management Track is designed for scientists and engineers in the emerging biotechnology fields to teach them skills in management and marketing that complement their technical skills and increase their likelihood of success in ventures in biotechnology. The courses expose students to sociatal issues in biotechnology, as well as presenting commercialization approaches and methodologies for evaluating, selecting and managing projects in biotechnology."

Courses available for the management track student are: Societal Issues in Biotechnology, Commercializing Biotechnology in Early-Stage Ventures, Selection and Evaluation of Biotechnology Projects, Issues in Automation and Productivity, Project Management, and Managing Technology Innovation and Creativity.

I would be remiss if I did not also mention that there are two biotechnology programs in Baltimore that are currently graduating students. One is a two year, post high school "Tech Prep" program at the Baltimore Community College and the other is a master's level program,

the Applied Molecular Biology Program, at the University of Maryland. The "Tech Prep" program essentially trains laboratory assistants while the Applied Molecular Biology Program trains laboratory scientists.

I would like to close this section about preparing a work-force for biotech and hi-tech industries by saying that many programs have been proposed. The governor of Maryland, the mayor of Baltimore, University chancellors, private and public organizations, are all looking for ways to (i) identify talented and interested people, primarily from *middle schools and high schools*, and (ii) to encourage them to enter science and math training programs. In the planning stages are: outreach programs for students and teachers, special high schools for math and science, mentorships with university faculty, parternerships with industry, apprenticeships with industry, community college programs (A.A.) in biotechnology and B.Sc. programs in biotechnology.

Maryland's Secretary of Economic and Employment Development has recently declared that the state's new focus for economic growth was to be driven by the *Life Sciences*. His office acknowledges that *education* of a work-force must be a major thrust. That is the kind of news the schools and biotechnology industry want to hear.

IV. CONCLUSION

I hope I have given you a taste of the way Baltimore and its surrounding area is working to become a biotechnology mecca. It requires the cooperation of the scientific, financial, and educational communities.

I see the growth of biotechnology in Baltimore through the eyes of the anatomist that I am. Biotechnology is like a small child that has all the physical parts needed in order to grow-up big and strong. With good health, stamina, and thoughtful guidance, Biotechnology can become a productive member of the community.

Economics & Marketing – Entrepreneurship at the Technion: The Frantztech Experience

Mark G. Frantz
President
Frantz Medicals, Ltd.

The subject is entrepreneurship at the Technion. Our company formed a joint venture at the Technion four years ago. First, I am going to tell you how this American company, which actually started in France, came to form a joint venture with the Technion. Then I am going to tell you why we are supporting an entrepreneurial joint venture at the Technion and why we think it is a good idea. Lastly, sort of a side issue, I will discuss whether or not to invest in new technology.

Before I start describing our relationship with the Technion and how it evolved, I will tell you a few things about Frantz Medical Group. The group is formed of five companies, one of which is Frantztech which is the subject of today's discussion. We have about 350 employees now, and we have joint venture equity relations with a number of companies. The last one, the IBM relationship, was a result of our Frantz Tech operation. Our main building is in Cleveland, Ohio where we have research and manufacturing. We have an imaging company in California; we have a turn key operation so we can take a product or a concept all the way through clinical studies, prototyping, engineering, plastic injection molding, molding, production, and also we prepare marketing strategies before we go to potential distributors.

Frantztech is a joint venture company which is 20% owned by the Technion through its Divotech subsidiary and 80% owned by the U.S. corporation. Our facility is on the Technion campus. We like being here and we are not going to move. The reason that I thought this was a good opportunity for Frantz Medical was because I felt that the Technion would be a good entrepreneurial partner. I felt that you have technology here. If anyone has any doubts about the technology in Israel, they honestly do not know what is happening over here. I think it is very important for Israel is to get that word out. There is a lot of technology in Israel in general, and in the Technion there is a tremendous amount – the type of technology that relates to our company. We are in the imaging field, in diagnostics. We are in parenteral feeding, and we have had the good fortune to be involved in laparoscopic procedures for many years through our French subsidiary in the endoscopy field. This meshes very nicely with what's happening at the Technion. We saw here some new state of the art advanced work. Professor Sideman showed some imaging things which are extremely exciting. This is clearly the future of imaging. We've figured every possible way to dissect the body, cut it, angle it, flip it, pull information out of it. What we need to do now is to extract that information and analyze it. The computer has offered us tremendous capability to do that.

Clearly that's an area that you are working in and the Technion in Israel obviously has tremendous computer capability, both software and hardware. So you've got the technology. That was obviously critical for making the decision to come here and form the joint venture.

The second element that was very important is that the Technion is a good environment for an entrepreneurial operation. When I say it to audiences in the United States, they find it to be a little bit strange, I'd like to tell you why the Technion fits that profile. I've heard every definition of an entrepreneurship and entrepreneurial environment. Every article that I've read over the last 20 years has a different definition. Mine, very simply, is that it is a new approach or a unique approach to beginning or fostering a new activity. It is very broad. But it contains several elements that are common to most classic entrepreneurial organizations and I'm not talking about a new subsidiary. I'm talking about true entrepreneurial, classical entrepreneurial operations, where you are trying to do something, not just making a minor state of the art improvement over something that already exists. Along with that element of newness comes a high risk element in it. A new company at the Technion, Eyesight, is a very good example: They try to do something in the state of art, looking at optics from a totally different point of view. It can be very exciting. Very high potential return, but it is high risk. Another element is that there is less structure in the organization. You do not 20 levels of management.

The third element is that you have limited resources, so you've got to spread those resources very carefully. You can't have all the people that you want to have, and you are just going to have to do some things from the seat of the pants and hopefully you'll make more right guesses than wrong guesses because you are not going to be able to analyze every last element of your company or development process. And that also increases the risk.

There are a number of entrepreneurial activities that have taken place through and around universities. The classic model, again using Eyesight as an example, where you have a technology within the university. The university may provide some sort of incubator or maybe some sort of joint venture with a venture capital group, and then eventually, whether the process is incubated inside the university or not, it is moved outside the university. Our model is substantially different. We are within the universities. We feel very much within the environs of the campus and that's where we are going to stay. We want to provide an outlet and a development capability for many products to be developed, not ones that just meet a certain profile and that is similar to our type of company that we are. So we plan on staying here at the Technion and hopefully being a good partner in a number of different fields.

Staying within the university is an important element. I believe that the Technion is the natural partner for us. Again, because you've got the technology. More important in some respects, is that you have got the right type of environment. The possibility of having this kind of relationship starts at the top, with the senior administration of the Technion. At the time, Dr. Rice was calling the shots; he had some industrial background and gave us his blessings. Then we had people at the Foundation like Yehuda Dvir, the managing director, and operating managers behind this concept. And then, very important, we have got a group of professors within the various departments – physics first, now chemistry and some of the

other departments – who are very much in tune with the commercial realities of the world, taking technology that otherwise would be a nice scientific paper in some congress, and trying to commercialize these. We are very proud joint venture partner with the Chemistry Department through Professor Michael Case – the first products will be shipped next week, and Professor Zeevi, in Eyesight and Professor Palti who we are also working with. This is amazing. Within most universities in the States, with the exception of a few of the DNA biotech type groups, you can not point to this sort of diversity across many disciplines within a university. The one thing that seems obvious to me is that you want to have the inventor continue to be the champion of the product with the technology, at least until it hits the marketplace, and in some cases even beyond that. What you get is you have the best person in the whole world helping to further develop that product and they know more about their product than anybody else.

The last important element, which has been a bit of a surprise, is that the Technion has provided us with a fabulous networking possibility within Israel and, to some extent, within the United States. The Technion provided our little company with opportunities that I could not even imagine. The fact that we have a joint venture with IBM is something that would not be possible in the United States. The people that I have had occasion to meet in the United States even through the auspices of our work in Israel is pretty incredible. This has been something that I did not anticipate when we made the decision to come here. But it has been fabulous and its been the work in many cases of the R&D Foundation. We have received BIRD foundation support which has been very helpful, and countless contacts and suggestions. I would say that the Technion has provided us with a tremendous opportunity and we are extremely happy.

What have we accomplished in the last four years? We have built the team, and developed the facilities. We have gotten the equipment and we now have a list of what I consider to be reasonably developed or adolescent products that have come through this system. The first one was the Naga, an indirect calorimeter, and then the Q-scan, which is an ultrasound attenuation device. That also was in clinical trials in the United States last summer. We have got to do more work on it. The clinical trials were successful to the extent that we learned what we did not have and what issues we had to deal with and we are now working on those now. We have been working for over a year with Professor Palti on a respirator. We have gone through the prototypes and hopefully we will soon start clinicals. There is a fetal heart monitor, developed at the Rothschild Hospital, reconfigured and made into a product. It was used in animal studies for the past year in Toronto; we have the first products of the diagnostics filtering system built by Professor Case and his associates, which is now in production. A large British company is going to distribute the product worldwide and we hope to have a family product built around that technology, from the chemistry department. That is what we have and I think we are doing pretty well.

I want to close with a comment. You can find in Israel, not only established technology but also scientists, engineers, practical people, and now new Soviet scientists. This is something you are not going to find anywhere else in the world, and that is why we are here.

SESSION III: IMAGING

Chairman: Mr. Uzia Galil

Imaging: A Diagnostic Tool

Tom R. Miller
The Edward Mallinckrodt Institute of Radiology
Washington University School of Medicine
St. Louis, MO, USA

I will try to cover what I view to be essentially the entire field of medical imaging, emphasizing recent clinical applications of medical imaging and showing how they relate very strongly to science and engineering. Then, I will briefly mention a few future developments that I see occurring in medical imaging.

Medical Imaging Modalities

There are various medical imaging modalities which use many different kinds of radiation. What I will call conventional radiology uses X-rays; that is the traditional kind of radiology. Then, we have computed tomography (CT), again using X-rays but now adding the power of the computer. Nuclear medicine uses radionuclides which emit gamma-rays and X-rays. Ultrasound does not use this kind of radiation; it uses sound waves. The newest area, magnetic resonance imaging, applies electromagnetic fields to make images. I will briefly discuss each of these areas.

Conventional Radiology

Conrad Roentgen discovered the X-ray in 1895. Conventional X-ray radiology is still by far the mainstay of medical imaging. Probably most of you have had chest X-rays. Many of us have had X-rays of bones, kidneys and other parts of the body. X-rays are used to image virtually all organs and parts of the body. So even today, with these many more modern and technological imaging modalities, the largest number of radiologic examinations are still conventional X-rays.

Computed Tomography

In 1979, Hounsfield and Cormack received the Nobel Prize for the development of computed tomography which came into clinical application earlier in the 1970s. Hounsfield is an engineer who at that time was with the EMI company in Great Britain. He did the

engineering development of the CT scanner. Cormack is a physicist in Australia who developed the mathematics of the reconstruction algorithm. CT represents the union of conventional radiology with mathematics and computers. Up to this time in the early 70s, radiology had been developing only slowly. There was progress in angiography, the use of contrast materials to study blood vessels and other organs. So there had been what seems now to be slow, steady progress in radiology from 1895 to the early 1970s. After development of the CT scanner, there has been explosive change in the field of radiology with remarkable, fundamentally new imaging modalities being developed every few years and put into clinical practice amazingly rapidly.

In a typical CT scanner, the patient lies on a cot which can be moved into the scanner to image any part of the body. There is a fairly conventional X-ray tube which emits an X-ray beam in a fan shape, passing through the patient's body and then into a detector on the opposite side. This apparatus with tube and detector will rotate, sometimes as frequently as once every one to two seconds. It is quite an engineering development to spin accurately such a heavy devise. By taking radiographic images at all positions around the patient's body, Cormack's reconstruction algorithm produces cross-sectional slices as if the patient were a loaf of bread, and we sliced him up. The images are truly remarkable.

The impact of computed tomography was rapid and has been very profound. Principally, CT leads to more accurate diagnoses in many conditions than were previously possible. In addition, dangerous or painful invasive studies have in many cases been eliminated. The CT scanner is quite expensive, costing around half a million dollars. Because of the price, when CT was introduced there was great concern about the cost of the examinations and whether a society would be able to support such expensive imaging technology. Actually, it has turned out that the CT scanner reduces medical costs. There are two reasons. One is that other tests are eliminated. Frequently a patient would have five or ten different tests, some of which were expensive invasive procedures which are no longer necessary. Secondly, the diagnosis can frequently be arrived at more quickly than before the advent of CT. Therapy can be instituted and the patient can be discharged from the hospital sooner, so patients will incur lower hospital charged. Overall, these very expensive machines have reduced medical costs.

Nuclear Medicine

Let me go now to nuclear medicine, the field of my specialization. In the 1940s, The use of Iodine-131 began with the diagnosis and treatment of thyroid diseases. In the 1960s, modern imaging devices were developed to present two-dimensional images from nuclear medicine. Early in the 1970s computers were introduced. Nuclear medicine continues to be an area of pioneering uses of computers within medical imaging. Also, the development of radiopharmaceuticals was occurring all through this period, accelerating in the seventies and continuing today. In the 1980s positron-emission-tomography or PET has come into its own. Other tomographic devices not employing positrons are also now widely used in clinical practice.

The principal idea underlying nuclear medicine is somewhat different from that of conventional radiology or CT where the images are produced by measurement of the attenuation of X-rays passing through the patient's body. In nuclear medicine, the physicians and scientists develop an understanding of the biochemistry and physiology of organ systems and then decide what biological molecules will exhibit altered behavior in various disease processes. Then, radioactive tags will be attached to those molecules whose properties will already have been studied by non-radioactive means. The radio-labelled molecule, called a radiopharmaceutical, is injected, usually intravenously, into the patient. The distribution of the molecule in the organ of interest will be evaluated by looking at the gamma-rays or X-rays emitted by the radioactive label from that molecule. Thus, in nuclear medicine images are formed of the biochemistry and physiology going on within the body.

For example, in a bone scan a phosphate compound is injected intravenously which goes to the bones. The radioactivity coming from the patient's bones is a reflection of the distribution and metabolism of that phosphate compound. Nuclear medicine is not dangerous because only minute quantities of radiation are injected because of the very sensitive detectors that are employed.

Single-photon emission computed-tomography is a more recent development, principally in the 1980s. The imaging device looks much like a CT scanner. Again, there is a cot where the patient will lie that can be moved in and out of the scanner. The nuclear medicine detector will rotate through 360 degrees around the patient. The geometry is exactly the same as the CT scanner. By collecting gamma-rays emitted in a 360 degree arc around the patient, it is possible, using the same tomographic algorithm that Cormack invented for CT, to get cross-sectional images from nuclear medicine.

In the United States, heart disease is the leading cause of death, largely through coronary artery disease. In that disease there is a blockage of blood flow to the heart muscle which is accentuated by exercise. A nuclear medicine study of blood flow is becoming one of the most widely used tests of the heart in the United States for evaluation of people with chest pain. It is used to determine if the pain is due to coronary artery disease or to determine if coronary bypass surgery is needed. This study emphasizes not the anatomy but the physiology, the blood flow, to the myocardium.

Ultrasound

Although ultrasound was developed quite a long time ago, in the 1970s there was important progress in development first of one-dimensional and then two-dimensional cross-sectional displays. Ultrasound does not use ionizing radiation, unlike the other imaging modalities discussed before. Ultrasound is like a sonar in a submarine. Sound waves are emitted that bounce off of structures inside the patient and come back to the detector and be measured. Just as with sonar, it is possible to perform an image of the body by the reflection of the sound waves. Because ionizing radiation is not employed, ultrasound is considered quite safe,

permitting fetal imaging in the uterus before a baby is born. Because there is no ionizing radiation, ultrasound is often the favored imaging modality in children.

There is a new development in ultrasound called color-flow doppler. As you know from the doppler effect, the sound waves, when directed at blood vessels, will be reflected by the moving blood cells. If the blood is moving towards the transducer when the reflected signal comes back to the transducer, it will have been shifted to a higher frequency by the doppler effect. If the blood is moving away from the transducer when the reflection occurs, the doppler phenomenon will cause the sound to be shifted to a lower frequency. Thus, by looking for frequency changes, it is possible to tell whether the blood is moving towards or away from the detector.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is the newest of the major revolutions that have occurred in medical imaging during the last 20 years. In 1952, the Nobel Prize was awarded to Bloch and Purcell for their independent discoveries late in the 1940s of the phenomenon of nuclear magnetic resonance (NMR). There was some talk during the 1970s about using this NMR principle to create images, but clinical scanners first came into use in the early 1980s and now are quite widespread throughout the world. The NMR imaging device looks very much like the CT scanner and the nuclear medicine scanner. In the MRI principle, magnetic fields are used to cause precession of the magnetic moments of protons, just as with a spinning top set loose on the table. The magnetic moments of protons in the nuclei can be thought of like spinning tops, and they will precess in the presence of a magnetic field. If appropriate magnetic fields of the correct frequency of the precession are applied, the magnetic moments flip directions, and that change can be recorded. Thus, these MRI machines employ this very interesting physics, and they are remarkable pieces of hardware. I find it amazing that devices like this can exist in ordinary hospitals all over the world, apart from physics departments. The MRI scanners frequently employ superconducting magnets to give extremely large magnetic fields, leading to the requirement for liquid helium to maintain the magnets at a few degrees Kelvin. Much technical apparatus is required to maintain liquid helium at superconducting temperatures. There is a considerable expertise required in radiofrequency concepts and in detection of the signals and in the mathematics of the reconstruction algorithms. These devices cost several million dollars but, because of their utility, they have proliferated quite widely around the world and represent easily the most technologically advanced pieces of equipment in medicine today. For overall medical complexity, I think the MRI scanner is a remarkable thing to be in routine clinical use.

Again, as with ultrasound, an advantage of magnetic resonance imaging is that ionizing radiation is not used. MRI is useful primarily in the central nervous system. More recently there has been work in bone and heart. When MRI was first developed, there was some question that, because of the wonderful images, it might supplant CT. That has turned out definitely not to be the case. Part of the reason is that the MRI machines are still much more expensive than CTs, thus leading to much higher patient charges. Additionally, CT is at least

as good or better in giving diagnostic information in several situations. It is now clear that MRI will have an important but limited role and will not cover everything in medical imaging.

Characteristics of Medical Imaging

Medical imaging plays a very central role in medicine because of its powerful diagnostic capabilities. As you have already seen, there is a very strong reliance on science and technology, probably more so than in any other field of medicine. Medical imaging is multi-disciplinary, involving important interaction with many kinds of scientists, engineers, mathematicians, biologists and physicians. There has been an explosion in medical imaging since Hounsfield and Cormack, but there are still innovations occurring constantly.

Future Developments

I will discuss just a few things in the future, but not very far in the future, partly because my crystal ball isn't any better than anybody else's and partly because I want to tie the discussion to things that will soon be clinically used. In conventional radiology, X-rays are now being digitized with high accuracy. Modern computer capabilities now permit storage of X-rays of any part of the body, CT scans, and all the other imaging modalities. Increasingly these images are being stored on optical discs and moved around the hospital through very high-speed image networks and displayed with large and flexible computer workstations. Many computer science concepts are being pioneered in radiology. CT is quite a mature field now, so basically people know how to use it, and the equipment is quite mature. One development is in three-dimensional display used in planning for surgery, and in radiation therapy to help decide positioning of a beam to match the tumor. Using a fairly sophisticated computer algorithm, two separate sets of tomographic data from different imaging modalities, such as MRI and PET, can be registered to overlap.

In nuclear medicine, tomographic three-dimensional displays are available and are beginning to be used clinically. A major area of research in nuclear medicine is development of new radiopharmaceuticals, biological molecules that are of interest in which radio-chemists can attach labels to them. Examples of that development are monoclonal antibodies, neuroreceptors, and other kinds of receptors. Positron-emission tomography (PET) was developed by Dr. Michel Ter-Pogossian at Washington University in the 1970s. Again, the geometry of a PET scanner is the same as for all of the other tomographic devices. In PET, radiation is detected that occurs when positrons annihilate with electrons. An example is a study in which a positron tracer is attached to a molecule that is taken up by dopamine receptors in the brain. The concentration of dopamine receptors is believed to be important in schizophrenia; this illustrates a possible use in the future of nuclear medicine in diagnosis of schizophrenia by quantitatively measuring the number of dopamine receptors in vivo in the human brain in a completely noninvasive way. There is also work going on with many

other neuroreceptors. Research is underway employing flow measurements in patients with Alzheimer's disease. There is also work in AIDS patients with dementia.

In magnetic resonance imaging there are new contrast materials in which paramagnetic substances such as gadolinium are used.

Summary

The remarkable revolutions in Medical Imaging occurred in the 1970s and 80s with the development of many new imaging modalities; I do not see another such revolution occurring. There will not be the explosive progress that occurred during that era, but medical imaging is still advancing very rapidly, and there is room for many new, innovative ideas.

A few comments of interest: It may be somewhat difficult to start a new company in the medical imaging field. Possibly in ultrasound, in the development of radiopharmaceuticals and nuclear medicine or with the gadolinium paramagnetic pharmaceuticals. There are great opportunities for people skilled in pharmaceutical chemistry. Companies that you might have in Israel may be involved in that, or they could be. You already have the Elscint company in Haifa, a major manufacturer of medical imaging equipment, and you have pharmaceutical companies.

I would like to close by making a plea to all scientists and engineers to work more closely with physicians. I have had training in both areas, so I think I understand somewhat how both feel and think about each other and how they both work. Frequently, the physicians are intimidated by the knowledge of the scientists and engineers, and they are afraid that they will not be able to understand what the scientist or engineer is talking about. The scientists and engineers, on the other hand, may be intimidated by lack of medical knowledge and, sometimes, they will have the perception that physicians do not understand research. Thus, physicians' research is impeded because they don't have the help of the engineers and scientists, while the engineers and scientists, who are equally intelligent and hard working, may do fine work which may turn out in the end not to be in quite the right direction because they have not had input from the clinicians who deal every day with the clinical issues. So, please, try to establish close collaborations!

Imaging as a Diagnostic Tool in Heart Research

Samuel Sideman
R.J. Matas Professor of Biomedical Engineering
The Julius Silver Institute
Technion–Israel Institute of Technology
Haifa 32000 Israel

I would like, in this brief presentation, to relate to two aspects of imaging which come out of our imaging work with the heart at the Technion. Since the heart is constantly in motion, (contracting, relaxing and twisting), you have some unique problems which have to be looked at, and special tools must be designed to do so. The aspects that we look at are the quantitative analysis of muscle function and the quantitative determination of cardiac dynamics.

Three–Dimensional (3D) Reconstruction of the Heart

To reconstruct the heart in three dimensions (3D) we use two–dimensional (2D) slices from Cine–CT or MRI (Fig. 1). The Cine–CT is not a regular computerized tomography (CT) scanner. The Cine–CT scanner was developed originally in the Mayo Clinic and is now produced commercially by the Imatron Corp. in San Francisco. Essentially, this is a technique in which you take pictures very quickly, something like 18 pictures per heartbeat. The physician receives these 2D scans, taken at different cross–sections during the heart beat, on one sheet of film, and he has to make some mental reconstruction to determine the state of the heart. What we attempt to do is to make this construction automatically on the computer, rather than just in the mind of the physician. Thus, we first have to teach the computer how to identify the boarders of the heart. The very difficult part is to correctly identify the myocardial boundaries in cases where you do not clearly see where the edges melt into the surrounding. Once we have these edges determined on the slices, we can construct the heart in 3D and get some quantitative description of the heart so that we can relate to it analytically and quantitatively.

The important step that we have made at the Technion is that we have learned to reconstruct the heart very quickly, and to quantify it's shape. This is achieved by placing the slices inside an arbitrary cylinder and measuring the distance from the cylinder to the heart. We thus obtain a one dimensional equation which we can approximate by a simple mathematical expression, the Fourier Series. We now have a unique quantitative description for the 3D shape of the heart. If this concept is correct, then we should find that all normal hearts haveapproximately, or on average, the same equation; indeed, this is the case. Moreover, any deviation identifies a certain pathology. So, just by defining the 3D shape of the heart, we

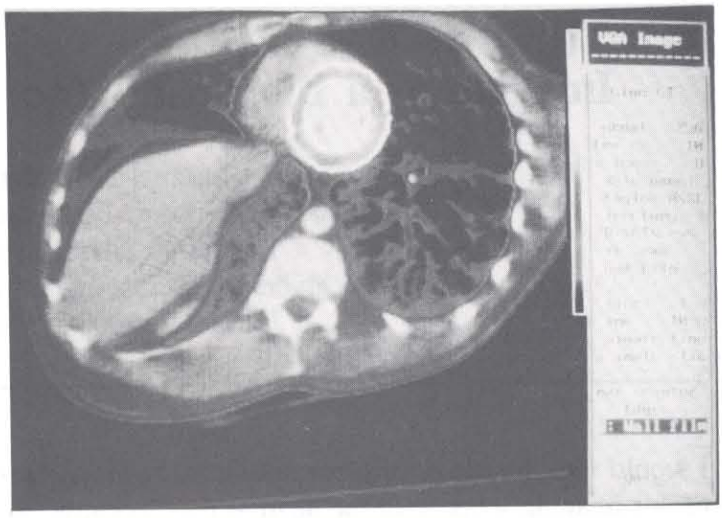


Figure 1: *2D scan of the torso showing the cross-section of the heart (color).*

have a quantitative tool to define a pathology. At first we get a wire mesh grid, and we measure the distances between the arbitrary cylinder surrounding the heart at finite points along the helix which is winding the cylinder. Most important, we can quantify it! The line and the grids in Fig. 1 convey exactly the same information but in a different mode. If we now color code the local difference between the normal and the abnormal shape, say the local deformation, then we get a color picture which conveys both shape and function. Figure 2, an image of a normal heart, is the first picture we ever got and one can see that the surface, shading is still a little coarse; it was very exciting to get it.

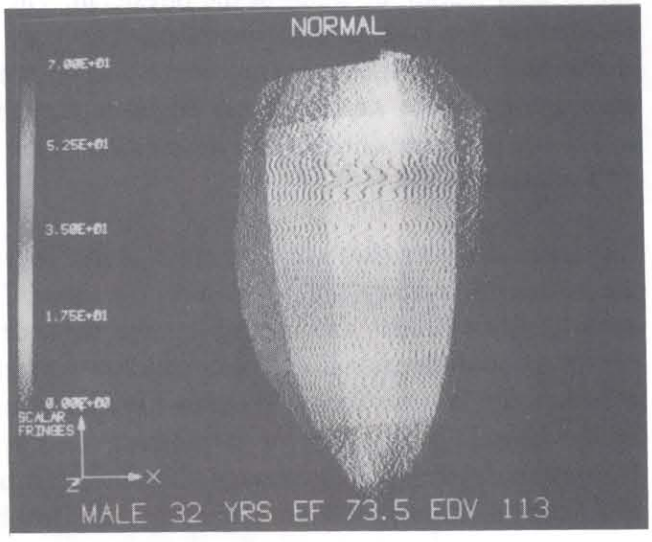


Figure 2: *3D reconstruction of the normal heart; color coded to show normal local function in light blue.*

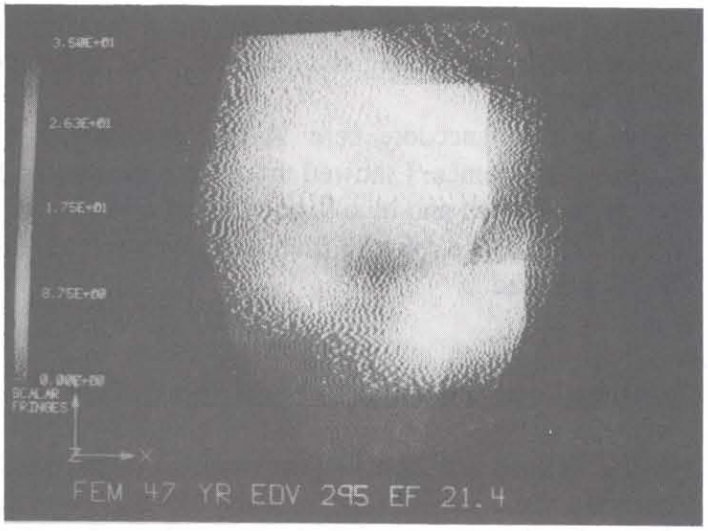


***Figure 3:** 3D reconstruction of a pathological heart; color coded with dark (red) color indication of local dysfuction.*

The pictures shown here are images of real hearts of real patients and the pathological heart in Fig. 3, is obviously different from the normal heart. The advantage of the information which these pictures give is that the doctor does not have to imagine what he sees; rather, he can see in one glimpse what is the state of the heart and, he can turn it around and view it from any angle in space on the computer.

To make sure that what we see is indeed correct, we have had to do experiments with healthy animals, infarcted animals, and then study the pathology of these the hearts. We then compared the pathology to the picture of the infarcted heart, which we obtained non-invasively. Good agreement of some 82 to 85% of confidence was obtained, thus confirming the quantification of the shape and the classification of the different pathologies. So far, we have quantitatively distinguished four classes of pathologies and each has common, specific geometric characteristics.

Regional Function in the Heart Muscle

The next step was to define local function and to analyze the effect of local disfunction on the global heart function. Here we studied 9 patients with myocardial aneurysms and quantified local thickness and wall motion (thickening) and the effect of this aneurysm on the muscle surrounding the aneurysmal area. The aneurysmic thickness is in the order of one to two millimeters; the thickness grows as you move away from the aneurysmic region to the normal region. However, if you measure the function of this heart, you find something different. You find that there is a large region which looks pretty good, as far as the wall thickness goes, but its function is poor, only moderately returning to normal. The influence of the aneurysm is visually evident by proper color indexing. We color code these local phenomena and show the thickness and the function; you can see that thickening is quite

different from thickness, which means that the dysfunction region is much larger than what we see just by inspecting the original scans and seeing the anatomic region.

I have a little anecdote here. A few months ago we had some visitors from the Soviet Academy of Science. I showed them these pictures on the computer, and said that in our color coding "red is bad and blue is good." One of them gently suggested that these days red is not so bad.... So, in the spirit of friendship, we reversed the colors, and from now on, red is good and blue is bad...

Relating Local Function to Local Blood Flow

Having defined the function, we want to relate the local function to the local blood flow. There are many ways to measure the blood flow in the laboratory, but none are very useful when related to human patients in real life. However, we can get useful information from some basic calculations. The first step is to superimpose the angiogram picture of the coronaries on the heart; the second step is to calculate, for this particular heart under study and the particular stenosis, the regional blood flow and the relation between the estimated regional flow and regional function (Fig. 4). Thus we have the calculated area of risk due to the stenosis and we can compare it to the area of abnormal thickness and the regional function as determined by thickening.

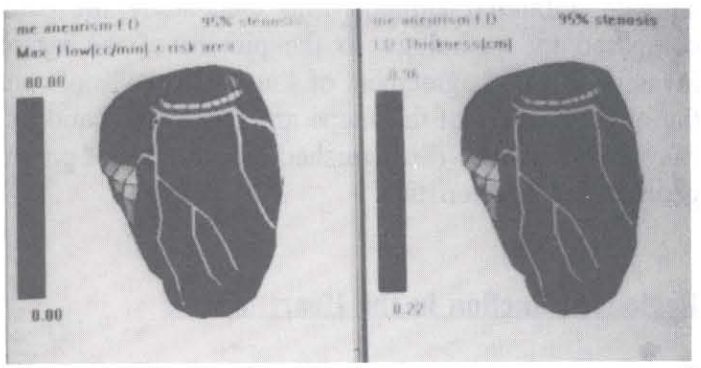


Figure 4: 3D reconsruction of an aneurysmal heart, color coded for comparison of local wall thickness and local perfusion.

3D Vessel Stenosis

Last, we can present a 3D view of the stenosis. Since we work with computers, we can reconstruct, with a little imagination and some good computer science, the stenosis in 3D and view it from any angle. You can see inside it, but usually, you will want it enclosed. In Fig. 5 we demonstrate the effect of the balloon in angioplasty of the artery, showing the artery before and after the ballooning. The effect of this therapeutic procedure is obviously quite dramatic.

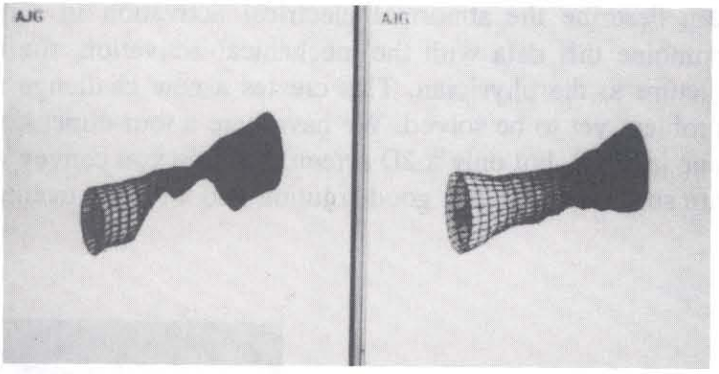


Figure 5: 3D reconstruction of a stenosed artery before (left) and after (right) balloon angioplasty.

Cardiac Dynamics

We are now working on developing tools for the analysis of cardiac dynamics. In other words, while the above presentation was related to two end situations in the cyclic scale, before and after the contraction, we want to learn if there is any additional information between these end–points. We do not know yet if this information will be very useful, partially useful or useless, but nevertheless, we would like to study what happens during the entire cardiac cycle, and hopefully gain some additional information which is useful to the cardiologist. Preliminary studies on normal heart dynamics has shown that whereas the two end points were normal, the intermediate states may not always be normal: we studied healthy students and found one who had started to develop a myocardiopathy which was not evident from the two end states. Thus, part of the motivation for continuing this study is that we do know that something undesirable may happen in between the end states of the cardiac cycle. The question is: how to manipulate the data to get quick information? We have done some initial work on that and we are, at this stage, completing this phase of the study.

Another study that is closely related concerns the temporal, dynamic, nature of the blood flow in the coronary arteries. In other words, the blood flow is phasic; due to the contraction, the blood in the coronaries and in the vascular bed moves in a certain temporal pattern. We want to know whether deviations from the normal phasic flow can add information useful to the diagnosis and analysis of pathological states.

Some Related Studies

In collaboration with Ichilov Hospital, we study 3D ultrasound visualizations of the arteries from inside. By reconstructing the arteries from inside, we can visualize the stenosis (Fig. 6). Another study is the simulation of the electrical activation of the 3D heart. The heart can not beat without the electrical impulse which initiates the myocardial contraction. Can we relate the electrical activation sequence to the mechanical activity of the heart? We are trying to simulate the activation of the heart under pathological conditions. This is a very difficult task

since the electrical system becomes quite unstable. Still, we are trying to follow it so that we can describe the abnormal electrical activation in a quantitative manner and, hopefully, combine this data with the mechanical activation, the blood flow, etc., to give a coherent picture to the physician. This creates a new challenge for those who play with imaging, a problem yet to be solved. We have here a four dimensional (4D) situation (3D in space and one in time), but only a 2D screen. How do you convey 4D information on a 2D screen? We are sure that there is a good solution and we hope eventually to find the technology to do it.

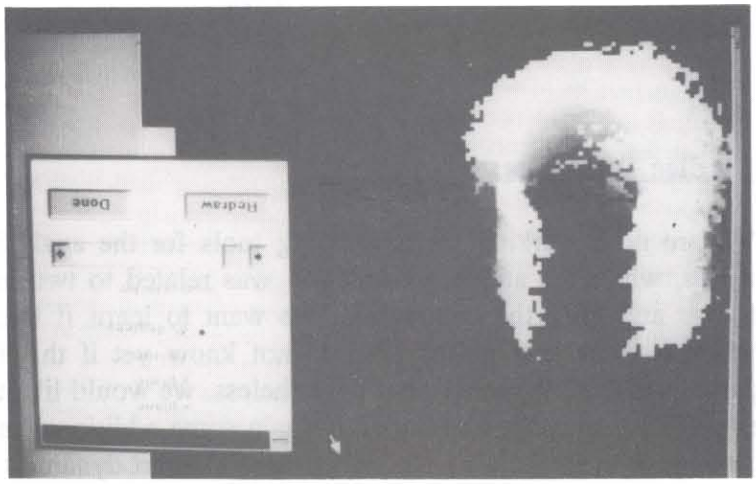


Figure 6: 3D reconstruction of a stenosed artery as seen by an ultrasound probe inside the vessel.

Conclusion

Imaging of the heart is an important tool for enhancing diagnostics and allowing better design of therapeutic modalities. The presentation concentrated on a few important aspects of cardiac imaging and quantification of cardiac phenomena. Once developed, these tools will help the physician in the diagnosis and provide and objective tool to determine global and local function.

Acknowledgements

The work reported here represents many years of work performed by a number of people. Top and foremost, I would like to acknowledge the contribution of my colleague and collaborator, Assoc. Prof. Rafael Beyar, M.D., D.Sc. Others include Dr. Haim Azhari, Dr. Jonathan Lessick, Dr. Alexander Taratorin, Doctoral Student Menachem Halmann, and a few others.

The study was sponsored in part by the Israel Ministry of Commerce and Industry, the Ministry of Science and the Ministry of Absorption, and by financial grants from the American Society for Technion, Technion–2000 Club, Los Angeles, CA, the Joseph Jackier Fund, MI, and Mr. Yochai Schneider, NV, USA.

Imaging: From Theory to Application

Yehoshua Zeevi
Technion–Israel Institute of Technology
Haifa 32000 Israel

In the fascinating overview of imaging in medicine, one important aspect that is missing is imaging with the visible range of electromagnetic energy. Perhaps it is missing because we do not have as yet too much high tech of imaging with visible light, for the following two reasons. One reason is that photons are scattered by tissue and, therefore, most of the tissue, with the exception of the cornea, is opaque to light and you cannot really see through. There are some new results in imaging with visible light that may be of interest to some of you. There is a new emerging technique based on a new, very promising approach of working with ballistic photons. Photons that penetrate through the tissue without being scattered. The percentage of such photons is very small; perhaps one out of ten million photons, six can penetrate through the tissue without being scattered. If you open a very short window and collect only those photons, you get direct imaging with light. As a matter of fact, several innovative companies in the United States and in Japan are already working on the development of such imaging systems, in particular as a diagnostic tool for breast cancer. Light, after all, at the right wavelength, offers resolution which is good enough to see very small tumors and therefore, it is a very nice approach. More interesting, and it would fit very nicely with the title of my lecture on theory, is to collect the photons that are scattered and to solve the inverse problem for those scattered photons. There is one company that was started by Professor Jay Singer of U.C. Berkeley, which solved the inverse problem of the photons that are scattered. When you look at the direct image, it does not appear as anything, but if you solve the inverse problem, then you obtain a spatially coherent image.

I want to bring up some progress with imaging that makes it possible to change various aspects of medicine. We are now talking about the new revolution in surgery in which "butchery" is not permitted anymore. In order to extract the gall bladder, for example, it is not necessary to cut muscles or bones. The surgeon penetrates the body with two small probes. One is the microrobotics which permits micro–surgery in a remote control mode of operation, and technology has advanced far ahead of what surgery really needs for that. The other probe is the "eye" which penetrates the body in order to image internal organs or tissue with visible light. There is no problem anymore with tissue that is opaque, because you bring the electronic eye into the right spot where you want to see. In such a way you can, by re–mote control, penetrate the body and, for example, extract the gall bladder. The patient can, in this case, return home after two hours of ambulatory service, instead of one or two weeks of recovery from the surgery. The New York Times claims that such a procedure cuts the operation price to at least half the price, including the hospitalization. With some advance–

ment in the tools of microsurgery, one may even bring down the price to 25%. However, the surgeons are not very happy with the electronic eye because it is not at good as our eye.

The challenge appeared to be interesting and important but formidable. When we undertook to extend the dynamic range of the camera, we were convinced that we had the theoretical solution and that it is "do-able." But, to convince others we needed a prototype rather than a schema and equations. So we decided to implement mechanisms based on our understanding of the biological retina and come up with a retina that can make the surgeon happy.

Since the basic theory and its technological implementation are based on models of biological vision, I wish to take a minute and offer some comments about models. I was very influenced by Mark Kac, who used to be a regular visitor at Harvard in the Division of Applied Sciences where I spent many years. Kac drew an analogy between models in science and natural selection in biology:

> The main role of models is not so much to explain and to predict, though these are the main function of science, as to polarize thinking and pose sharp questions. Above all, they are fun to invent and to play with, and have a peculiar life of their own. The "survival of the fittest" applies to the models even more than to living creatures, they should not, however, be allowed to multiply indiscriminately without real necessity or purpose.[1]

It is very instructive because quite often we expect the model to explain what the phenomenon is, but it is more important to use the model in order to stimulate our ideas. I take it one step further and suggest that even if the model is wrong, and as engineers we come up with a solution to a problem which is stimulated by the model, the latter is important because it has facilitated the impact of basic scientific investigation on advancement in medical (and other) technology.

Now, in the spirit of what has just been discussed, what are we after? Quite often one draws analogy between the camera and the eye, but, as those who are experienced with endoscopy observe, and all of us who have experience with any kind of electronic camera know, it is not as good as the eye. In what respect? In particular with regard to the dynamic range and sensitivity. You probably experienced some problems in photography when you face the light source, e.g. when you face the sun. You want to take the photograph of someone who is standing in front of you but your camera faces the sun, or whatever the light source is, and the camera is blinded. The same problem is experienced by the surgeon who penetrates the body with the endoscope in laparoscopic surgery. The camera is blinded because of specular reflections from the tissue. In fact, it often happens at the critical time when the surgeon has to decide whether or not to cut. The physics of the solid state imaging device, i.e. the CCD, permits only a limited number of levels of intensity difference that can be communicated by the camera. Because of signal-to-noise ratio it is only of the order of 100 at room

---

[1]M. Kac: Some mathematical models in science, *Science*, 1969.

temperature, and with the best and most expensive and cumbersome camera, it can reach 1000, but those cameras cannot be as small as two by three millimeters, to penetrate the body. Our eye, on the other hand, operates over an extremely wide dynamic range spanning about ten log units of intensity, and it adjusts its operating point and sensitivity to where the information is. The question is: why can't we build something that will be as good as the eye? The reason is that engineers, and in particular electrical engineers are spoiled because we have created linear theory and electronic tinker toys (i.e. devices) with which we can go a very long way in implementation of sophisticated technology. Natural systems, and in particular biological systems, are highly nonlinear. So we have to understand some of the nonuniform and highly–nonlinear mechanisms which are characteristic of the retina, and to learn to implement them in electronic imaging.

I brought with me a relatively simple (in terms of its dimensionality) toy to give you an idea about what kind of complex behavior a simple nonlinear system can generate. I have here a magnetic pendulum constrained by a field made up of four magnets. This is meant to show you what the simplest nonlinear oscillator can do in terms of the complexity that it generates. A similar (in terms of its complexity) nonlinear oscillator is sometimes used as a model for the activity of a neuron. Of course, it is over simplistic for representing the activity of a neuron, but nevertheless it is instructive for understanding the richness of nonlinear mechanisms. Now, the field is made of four poles, and I have the nominar (or non–linear) oscillator and the pendulum is a nominar oscillator once you have the amplitudes. I now bring the pendulum to some unstable initial condition and let it oscillate. You look at the projected trajectory of the pendulum and wonder what is so special about it. This is what you are used to from a pendulum, or so it seems at first. But, keep watching it and it constantly changes its mode of oscillation in a way that one cannot predict and cannot solve, even with the most powerful computers that we have, we cannot completely solve this problem. If we record it, it would generate a chaotic trajectory that is generated by the simplest nonlinear system that one can come about. Now imagine taking a retina where we have millions of cells that are nonlinearly interacting. What is interesting is that it does not really matter what kind of nonlinearity you assign to each of the components, but you have to let them interact with each other. From the theoretical point of view, this is a most complex problem that we really know. In terms of the universe, it is similar to the many body problem that you have in a galaxy, where the interaction is between stars. Some of the leaders in computational astronomy are using, most of the time, some of the most powerful computers available in order to solve many such body problems. There they are trying to solve the interaction of a relatively small number of stars. Here we are talking about a retina which, in its simplest form, has millions of cells. Here you have a model and this is taken from a recent Scientific American article of Carver Mead where, he, like us, or perhaps I should say that we, like him, are trying to model the retina in silicone. In other words, to build a silicone retina that will do what the biological retina does. Now imagine taking all of these nonlinear components, coupling them and trying to solve what the system does in terms of its function. Obviously, if we could not solve it, I would not be talking about it. The reason that we can solve it is that the retina is highly structured with repeated circuitry of connections and the interactions are confined to small neighborhoods.

Is there a concept of neighborhood which is related to the structure of natural images? If you take a natural image and you analyze it, you find that there is a finite and quite small correlation distance. This implies that if indeed the retina had evolved to optimally process natural images, direct interaction between receptors and neurons in the retina would not have to extend across the entire population, and could decay as a function of the distance. This is one observation that helps.

Secondly, when you analyze the type of interactions that occur there, and I am not going to burden you with equations, you find that the type of interaction that you have can be simply described by equations that are reminiscent of those that describe our electronic tinker toy components of linear systems. Instead of the convolution, it is an integral equation in which instead of the simple component that subtracts the effects of a neighbor on the receptor that responds, will have some kind of nonlinear interaction. It does not really matter what type of nonlinear "synaptic" interaction you have. Only time will tell if indeed we fully understand the retina, and I believe that in our lifetime we will understand this piece of the brain. Once we have this model which reproduces the important characteristics of the retina, we can move on and try to build up some kind of a device that will mimic what the eye does in terms of its adaptive sensitivity over a wide dynamic range. I have one example that is taken from a brochure of "iSight." Here we are trying to record the filament of the light bulb and at the same time to see the background. So it is even a more severe situation than what you face in trying to record an image of tissue with the endoscope. Here you have a dynamic range of more than 100,000! As I mentioned, most imaging devices (i.e. electronic cameras), have a dynamic range of 100 to at the most 1,000, are very large and extremely expensive. Here we are trying to do it with a very small camera that eventually will penetrate the body, say a two by three millimeter camera. Now if you want to see the filament with a conventional camera, and some cameras do it automatically, you reduce the sensitivity and you still do not see the filament itself. By comparison, with our dynamic range camera, spanning a dynamic range of more than 100,000, you see all the detail, all the boundaries, everything that is written in the background and the filament of the light bulb. In fact, it is even not possible to see it with the naked eye! (I do not suggest that you try to do it because you can burn your retina.)

Then there is the example of how images look with adaptive sensitivity. Again, this is a scenario generated in the lab using a very bright light source. We want to see the front of that shadowed area and at the same time penetrate the shadow. In order to penetrate the shadow, one has to increase the sensitivity but then the camera is blinded over most of the area. This is what happens with tissue when you have the specular reflections. What we want is to adjust the camera pixel–wise, so that each receptor or each pixel in the electronic camera will adjust itself according to the information distributed in its neighborhood. That is what this camera does, making it an example of what technology can bring into medicine when you test it in the context of laparoscopy. Since laparoscopy is becoming a standard technique, I think that pretty soon we will find that one will do more and more with imaging in the visible light range. Relating it to other areas mentioned by Michael Sela, you would like to apply drugs locally by probe activities, biochemical local activities; with the endoscope and another probe, it is becoming possible. For example, you can attach certain antibodies to the tip of an optical

probe and monitor the reaction locally at the particular sight of the tissue, instead of what is done nowadays by flooding the system with the drugs and observing from the outside by the reaction which encompasses on the way many other parts of the body. This example, I believe, gives you some idea of what application of basic understanding of a biological concept to technology can contribute to medicine.

IMAGING: INDUSTRIAL AND ECONOMIC ASPECTS

Shmuel Parag
Elscint Ltd.
Advanced Technology Center
P.O. Box 550, Haifa, 31004, Israel

Introduction

I will talk on a selected group of socio-economic aspects which have strong influence on the medical imaging industry. I will first review the escalating cost of healthcare, then turn to the state of the imaging market and finally to the economic forces that shape the course the market is likely to follow.

The Spiraling Cost of Healthcare

Healthcare expenditures have been rising at a rate that is causing nightmares to legislature and citizens alike. A typical example: the health expenditure in the US has risen from 5.9% of the United States gross national product (GNP) in 1965 to 12% in 1990 (Fig. 1). At the current rate that number may reach 15% by the end of this decade. Year after year costs rise two to three times faster than the rate of the inflation. An average family of three who is used to spend $ 800 per month in 1990, may be required to triple this amount to $ 2,500 per month by the year 2000. Scientific achievements, advancements in technology and the advent of miracle drugs are the major contributors to this steady growth pattern.

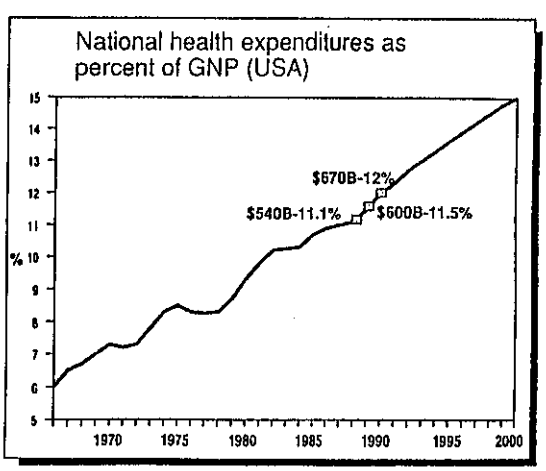


Figure 1: Ever-Increasing Medical Expenses (Source: Health Care Financing Administration Forecast.

The medical imaging industry which comprises only a small segment of the healthcare industry, has also enjoyed an explosive growth in the last 20 years. Spectacular advances in imaging equipment technology, are largely responsible for the tremendous versatility of medical imaging today. In particular the application of computer technology to imaging has made possible a vast range of new applications. As a result, the worldwide high-tech imaging market has grown rapidly, from around $ 1.6 billion in 1980 to around $ 5.8 billion in 1990 (Fig. 2). The largest segment of the high-tech medical imaging equipment market is Ultrasound with $ 1.9 billion, CT is second at $ 1.6 billion, MRI $ 1.5 billion and Nuclear Medicine last at $ .6 billion. The geographical distribution is as seen in Fig. 3. The U.S. is the world leader using approximately half of the world consumption. Japan is a close second in total consumption and a world leader in the use per capita. Europe, surprisingly, is a distant third among the highly industrialized regions. The rest of the world, comprising 7/8 of the world's population consumes only 1/8 of the world medical imaging production.

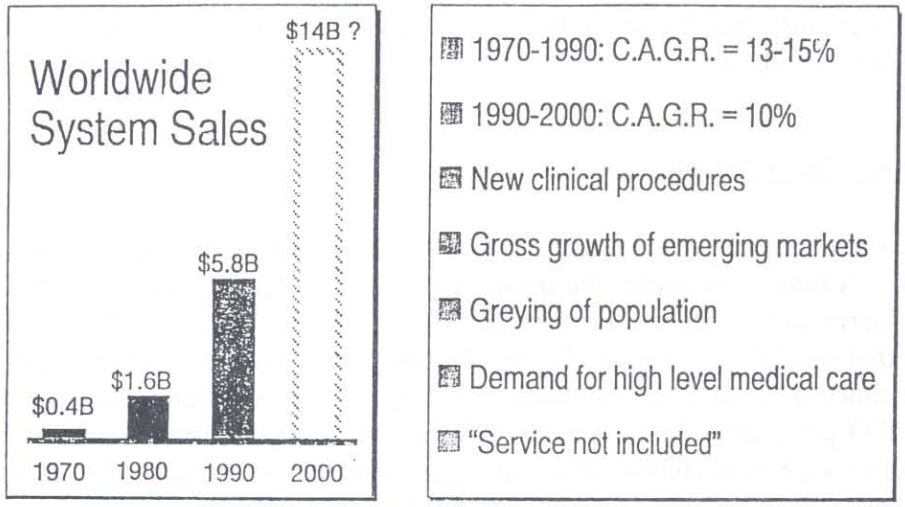


Figure 2: Worldwide Medical Imaging: The Next Decade

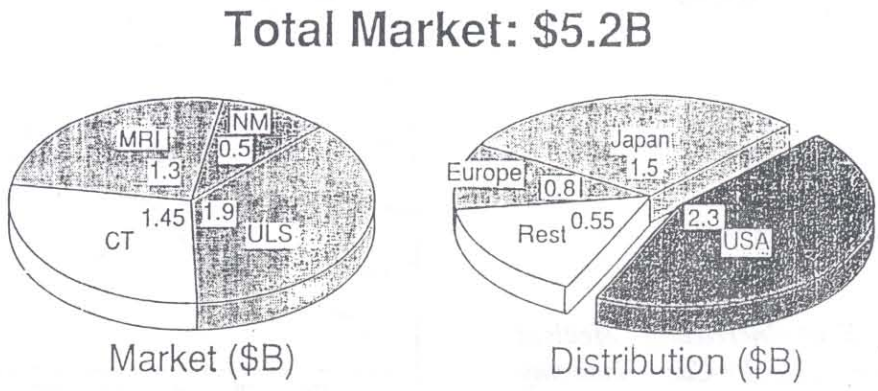


Figure 3: 1990 ULS, NM, MRI, CT Equipment.

Technology, aging of the population and the rise in the standard of living are the three engines that have propelled this explosive growth and they will continue to shape our behavior toward healthcare. In an effort to curb the spiraling cost, the legislature has enacted measures including tougher approval requirements of new medical devices, more stringent monitoring of medical effectiveness and cost containment measures aimed at reducing the doctor's payments. These and other steps have already taken their toll by slowing down innovations and by softening the demand for expensive technology. However we believe that in the long run these measures will have only a subtle effect on the industry specifically since it has been demonstrated that the use of the new technologies actually save money by reducing the use of less effective procedures and by reducing hospital stay.

While the highly industrialized countries are struggling to cap the growth in spending, by reducing the use of expensive procedures, the developing countries in the pacific rim and the former eastern block countries are heading in the opposite direction and are actually increasing their demand for modern medical imaging services. This trend will narrow the existing large gap in the provision of medical services between highly developed and less developed countries, propelling the growth in these markets.

The Characteristics of the Imaging Business

The imaging equipment business is subject to the difficult economics of all electronic equipment businesses. In particular, the imaging business suffers from the following negative characteristics:

- Manufacturers sell their equipment at very high prices when they can offer differentiated technology. However, when they offer "Me too" technology prices tend to drop significantly. Cost however remains the same.

- Companies sell few systems at relatively high prices. Therefore the loss of a few orders or delay in delivering of few systems can lead to large fluctuations in revenues and profits.

- In the absence of major technology breakthroughs the market for imaging equipment is subject to saturation. After a period of overall market growth, sales depend on replacements and market share "grabbing", as the industry players chase larger pieces of relatively smaller pie.

- The customers for imaging equipment are hospitals and radiologists. Both tend to be much more concerned about the cost of new devices than their physicians' counterparts (who are the customers of drugs and interventional devices companies).

These difficult economics are becoming still more difficult as the effects of the high cost of healthcare on the economy attracts the attention of the legislatures and third party payers. The high cost of imaging devices is and will continue to be a convenient target.

Marketing Strategy

In this uncertain environment, manufacturers must decide where to focus R&D programs in the 1990's. Even more important they must decide how much to invest and whether to hedge their bets.

Cost effectiveness, and equipment price are becoming key factors in the purchasing decisions. Hospitals are changing their traditional technology oriented attitude and are becoming more price conscious. The industry will have to accommodate these needs by extending the life cycle of current equipment through an extensive upgrade strategy and by reducing the total cost of ownership. The reduced pay to radiologists will encourage technology developer to make procedure oriented technologies that take the doctors less time, thus, offsetting the reduced pay per procedure by increasing the number of procedures they can perform per day. We may also see a change, down the road, in terms of physician product mix and practice pattern. For certain products it could be more sales, for others it could be less.

However, for the longer term companies must consider reinvesting in new technologies. Efforts to ignore new technologies are as effective and no less harmful than the efforts to ignore progress. The main challenge for the healthcare industry in the 1990's is to reestablish public confidence in the value of the overall expenditures and overall patterns in healthcare. Figure 4 outlines few of the new promising technologies.

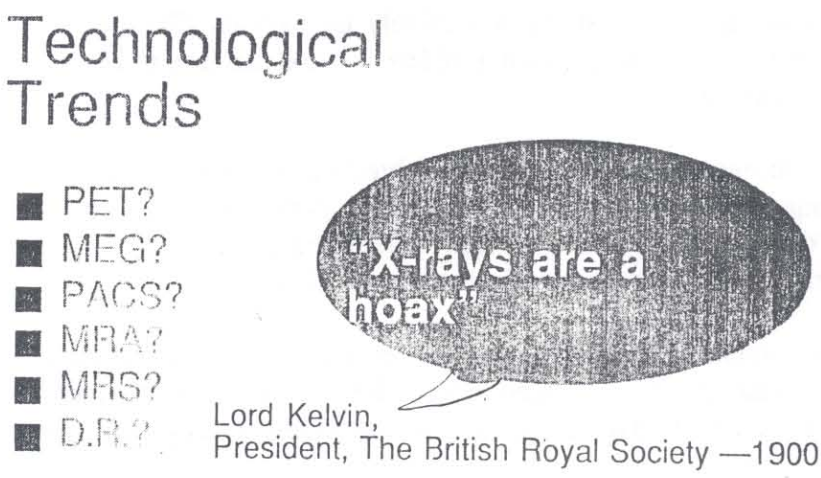


***Figure 4:** Strategy for the 1990s*

SESSION IV: BIOMATERIALS

Chairmen: Dr. Amnon Barak and Professor Avraham Shitzer

Medicinal Chemistry: Future Training Needs

Rudolf Andreatta
Research Laboratories, Pharmaceuticals Division CIBA-GEIGY Ltd.
CH-4002, Basel, Switzerland

During the last few years spectacular progress has taken place in the area of biological sciences. Not only a major advancement in methodology and technology, but a true revolution of thinking and philosophy of research, have overwhelmed the individual as well as the whole scientific community. Medicinal chemistry, the central discipline and driving force in drug discovery, also participated in this process although in a less vigorous manner. The dramatic development in this specific field is reflected in the changing requirements for an aspiring medicinal chemist.

Table 1: Classical Prerequisites for a Medicinal Chemist

Good practical and theoretical knowledge in **Synthetic Organic Chemistry**
Experience in the area of **Natural Products and Heterocyclic Chemistry**
Understanding of **Stereochemistry**
General comprehension of **Pharmacology and Biochemistry**

Not more than 20 years ago a chemist working in pharmaceutical research was considered adequately trained, once he or she had good practical and theoretical knowledge in synthetic organic chemistry, experience in the area of natural products as well as heterocyclic chemistry, an understanding of stereochemistry and had acquired a general comprehension of pharmacology and biochemistry.

Knowledge of molecular structure was important in relation to the compounds to be designed and synthesized but much less so in relation to targets at which the compounds were aimed. A typical medicinal chemist's approach to "rational drug design" in those days can be exemplified by the development of Volatren®, one of the most potent and successful NSAID's.

In the late sixties Geigy scientists decided to start a project aimed at a new non-steroidal anti-inflammatory drug, which would be superior both in activity and tolerability compared to the existing drugs of this type. The first entrance into this area was made by our company some 20 years before by developing and introducing to the market phenylbutazone, the first highly active anti-inflammatory compound after aspirin. Thus, there were available the essential expertise in the area as well as the necessary biological tests.

Table 2 describes the situation in this segment of the market in the early sixties:

Table 2: Non-Steroid Anti-Inflammatory Drugs

Active Principle	Most Important Representative	Discovered by
Salicylic acid	Acetylsalicylic acid	Hofmann, 1898
Pyrazole	Phenylbutazone	Stenzl, 1946
Fenamic acid	Mefenamic acid	Scherrer, 1960
Indolylacetic acid	Indomethacin	Shen, 1960

There was no information available about the molecular structure of the target with which the new drugs were to interact. Its identification had to await the discovery of Vane and coworkers in 1971 of cyclooxygenase, an enzyme acting in the first step of prostaglandin biosynthesis from arachidonic acid. But one could at least consider the structural requirements and physico-chemical properties appearing to be essential for the desired biological action, by analyzing the typical characteristics of the already known therapeutically active drugs.

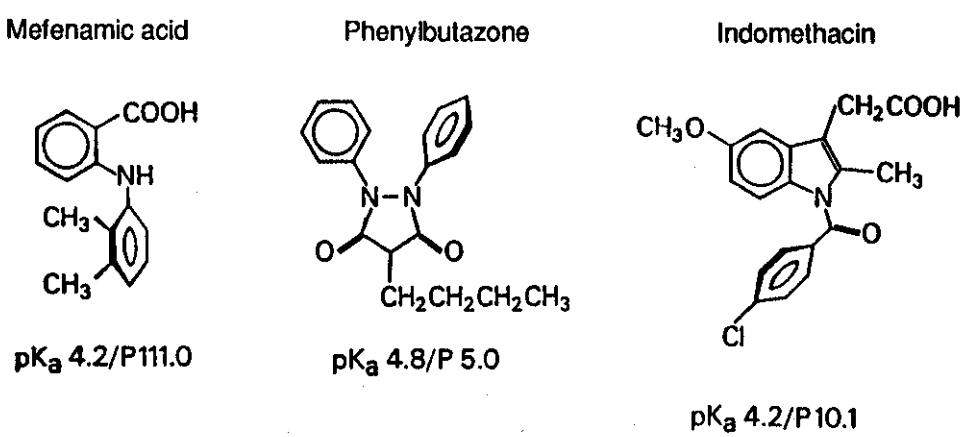


Figure 1: Structure of three anti-inflammatory substances.

Various models have been proposed for the putative receptor having a common binding site for arachidonic acid and the NSAID's, derived by complementary cavity mapping. In 1965 Shen proposed an anti-inflammatory receptor site for indomethacin, a feature of which was the presence of a cavity to accommodate the p-chlorobenzoyl substituent, which has been shown to be twisted out of plane and out of conjugation with the indole nucleus. Consequently, our new structure would have to be as well accommodated into this 3D-receptor model.

A closer inspection of the formulae of mefenamic acid, phenylbutazone and indomethacin, along with certain of their physicochemical properties reveals the following common features (Table 3):

Table 3: Physico-Chemical and Steric Properties of Three Anti-Inflammatory Agents.

	Acidity Constant (pK_a)	Partition Coefficient[1] (P)	Twisted Aromatic Rings
Phenylbutazone	4.8	5.02	+
Mefenamic acid	4.2	111.0	+
Indomethacin	4.2	10.1	+

- all compounds are weak acids with pK_a-values between 4 and 5
- all three contain a twisted aromatic ring; and finally
- the lipophilic character of the three compounds is similar.

As a consequence, three fairly simple and straightforward criteria were postulated as prerequisites for a new anti-inflammatory agent:

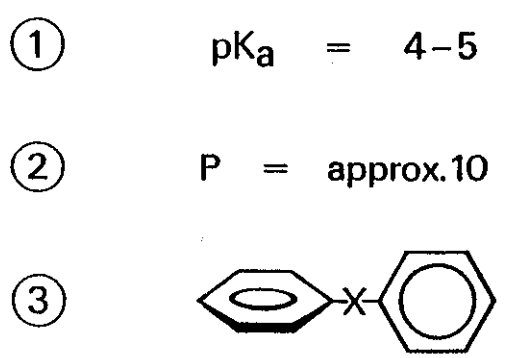


Figure 2: Criteria which an effective antirheumatic agent should fulfil.

Out of a large series of new phenylacetic acid derivatives fulfilling the above criteria, diclofenac was considered to be the best choice for clinical testing. Its structural elements are given in Fig. 3. They comprise a phenylacetic acid moiety, a secondary amino group and a phenyl ring substituted by two chlorine atoms. These two substituents cause a strong twisting of the phenyl ring, as revealed by x-ray analysis.

A crucial aspect of the topography of diclofenac is thus the torsion angle between the two aromatic rings. Also of importance is the hydrogen bond between the carboxyl oxygen and the hydrogen of the amino group. A more authentic picture of the molecule is given in Fig. 5, using space filling models. In addition Fig. 5 shows how the molecule can be accommodated into the hypothetical "receptor cavity."

Figure 6 shows how the physico-chemical properties of diclofenac fit with our additional criteria.

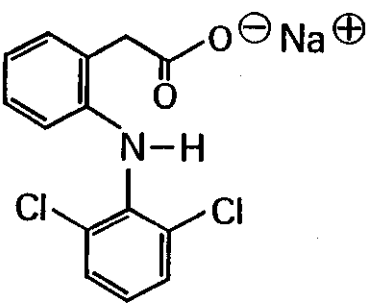


Figure 3: The structural elements of Diclofenac
1 phenylacetic acid; 1 secondary amino group; 1 phenyl ring; 2 chlorine atoms

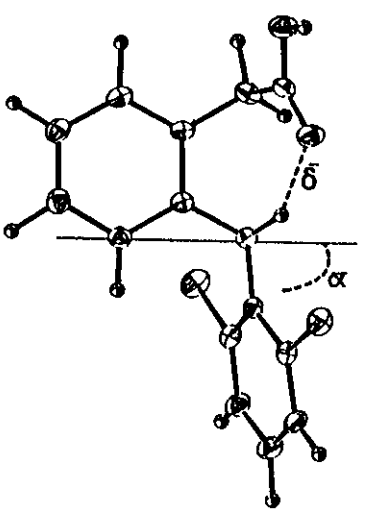


Figure 4: X-ray analysis of Diclofenac
The phenyl rings are twisted angle of torsion α=69°; hydrogen bond δ = 2,000Å

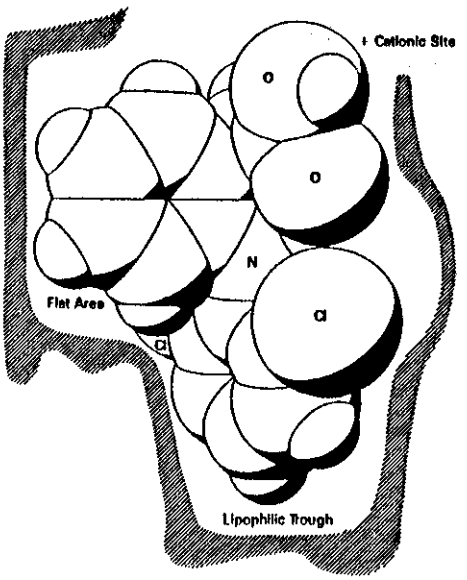


Figure 5: Binding of Diclofenac into the hypothetical receptor cavity (Scherrer et al. 1964).

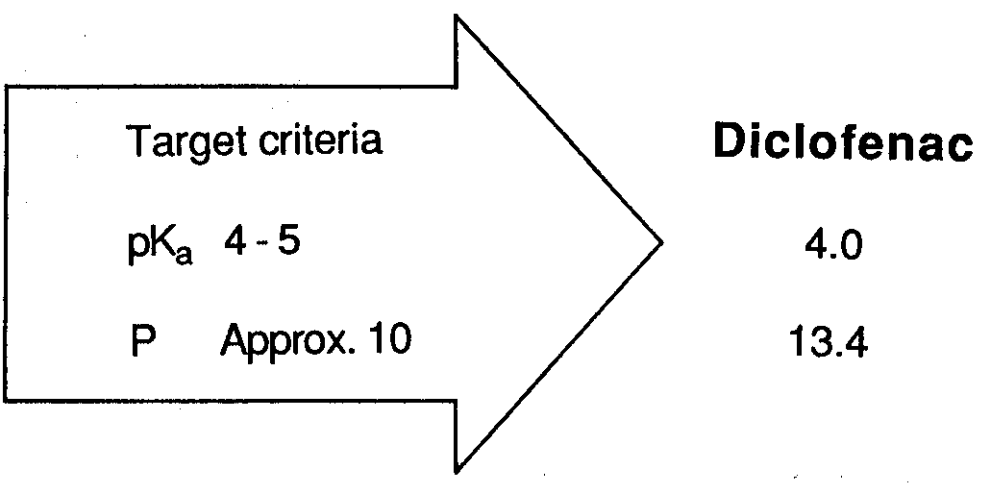
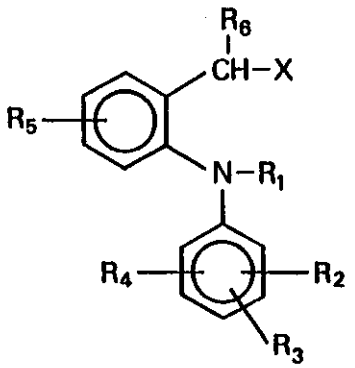


Figure 6: Physico-chemical target criteria.

In addition, some modifications of the diclofenac structure, typical for the classical medicinal chemistry approach, are indicated in Fig. 7.

Finally, in Fig. 8, we see the influence of the variation of the substitution pattern of the N-phenyl ring on its twisting, on the partition coefficient and on the most important parameter – the biological activity – given as the ED_{50} value in the kaolin-edema test.

Figure 7: Some possible structural modifications of the diclofenac parent molecule.



	Torsion	Partition coefficient	Biological activity ED_{50}
1.	●	●	●
2.	●	●	●
3.	◪	●	◪
4.	◪	●	◪
5.	●	◪	◪
6.	●	○	◪
7.	○	◪	◪
8.	○	○	○
strong:	●	~ 10 ●	● 1–10
medium:	◪	6–8 ◪ 17–19	◪ 11–50
weak:	○	5 ≤ ○ ≥ 20	○ > 50

Figure 8: Modifications at the N–Phenylring.

More than 200 analogues have been synthesized and subjected to biological testing, but none of them exhibited properties as attractive as those of diclofenac, which represents today, under the name of Volatren® a major contribution to therapeutic progress in the area of rheumatoid diseases.

The described classical approach has of course its great merits. It is sometimes still considered to be the method of choice in different areas of pharmaceutical research. On the other hand, today's search for selectively acting drugs is for the most part based on the so called concept–based research. Starting points and targets of most of the modern

pharmaceutical and agrochemical projects are macromolecules like receptors, enzymes and hormones or more generally, compounds structurally based on proteins, nucleic acids, lipids and saccharides. One characteristic approach to the solution of this type of objective, where a protein/protein interaction is involved, will be exemplified by the IL–1 project which was started in our research department some 4 years ago.

Interleukins belong to the family of cellular mediators known as cytokines. They produce a variety of biological and physiological responses (Fig. 9). IL–1 is a member of the above group of cytokines appearing in two distinct forms, α and β, which possess a broad spectrum of biological properties, e.g. inflammatory, metabolic, physiologic and immunologic activity. IL–1 has an effect on various types of cells and organs, including proliferation of lymphocytes, epithelial cells, synovial cells, etc. It induces the expression of a variety of genes and the synthesis of several proteins, which in turn induce acute and chronic inflammatory changes (Table 4).

The biological properties of IL–1 and its pathophysiological significance suggest that an antagonist of IL–1 could be of considerable pharmacological interest. A natural protein showing a 20% homology in respect to both IL–1α and β is being currently tested in clinics and preliminary results seem to confirm this assumption.

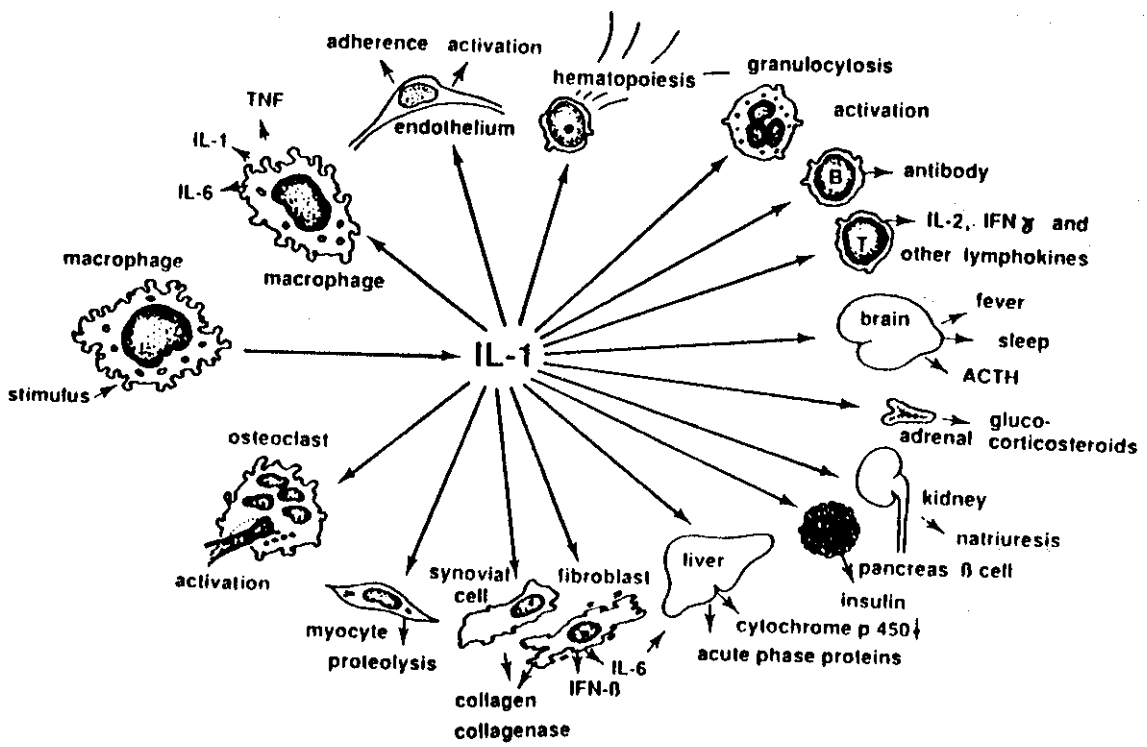


Figure 9: *The multiple biologic activities of IL–1. IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; ACTH, adrenocorticotropic hormone (taken from W.E. Fibbe et al., Blut [1989] 59: 147).*

Table 4: Evidence for an important role of IL-1 in inflammation.

Experimental effects of IL-1 explain cardinal symptoms of inflammation.

Increased levels of IL-1 in patients with inflammatory conditions.

IL-1 induces inflammation in animal models.

-> Antagonists of IL-1 should prevent inflammation.

Development of a lower molecular weight antagonist with potential anti-inflammatory activity, which thus could be used as an effective drug in various types of rheumatoid diseases, is, as we shall see, a typical interdisciplinary project. It can be formally divided into 7 distinct steps (Tables 5 and 6).

Table 5: Clinical Significance of the Effects of IL-1

Clinical Symptom	*in vivo*	*in vitro*
Immune response	Immune response Lymphocyte proliferation Lymph follicles	T-cell proliferation
Inflammatory exudate	Cell infiltration	Endothelial adhesiveness
Pain	Increased prostaglandins	Induction of inflammatory mediators:
Fever	Fever	- Prostaglandins
Cartilage and joint destruction	Cartilage proteoglycan loss	- Proteases
Increased CRP and ESR	Induction of acute phase proteins	Induction of acute phase proteins

Table 6: IL-1β Project

Expression of IL-1 in an appropriate cell-line, its isolation and purification

Use of the primary sequence for preliminary chemical work

Crystallization of IL-1β and determination of its x-ray structure

CAMM-analysis of the IL-1β structure

Chemical mapping of the IL-1β structure

Search for the binding sites of IL-1β by point mutations

Exploitation of the results of point mutations for the design of potential antagonists

Table 7: Properties of Interleukin-1

Produced by macrophages and many other cells types
Two molecular forms, IL-1α and IL-1β - 30% sequence homology - functionally indistinguishable
Synthesis as MW 31 000 precursor
No signal peptide recognizable
Proteolytic processing to mature IL-1α and IL-1β (159 and 153 amino acids; MW 17500)
Secretion
Binding to specific receptors on target cells

IL-1β and IL-1α-DNAs were cloned from human blood monocytes and from a mouse macrophage line respectively. The two types of IL-1 were initially expressed as pro-forms, i.e. as large precursors (31 Kd) consisting of 269 or 271 AAs which were easily cleaved by proteases, to generate the corresponding carboxy terminal (17 Kd) "mature" peptides.

The 153 residues containing IL-1β and the 159 AAs comprising IL-1α, in spite of less than 30% of AA sequence homology, possess a close similarity of their tertiary structures, equal biological function and they bind to the same receptor.

In the frame of our project we have focused on the study of human IL-1β which was expressed in Escherichia coli.

The primary sequence from the cDNA is given in Fig. 10.

Analyzing the primary sequence of IL-1β and taking into consideration the results of published hydrodynamic studies (Wingfiled et al., 1986), which showed the protein to have a nearly spherical shape, one could make an "educated guess" and place the hydrophobic residues preferentially to the central core, and the more hydrophilic ones on the surface of the macromolecule. From CD-measurements it was deduced that no helix-type secondary structures were present.

According to Dinarello, a partial asymmetric cleavage of IL-1β generates biologically active fragments. To test this assumption, some 25 peptides were synthesized, consisting of 8 to 42 AAs corresponding to various sequences of IL-1β, which incorporated e.g. a larger part of the N-terminal region of the molecule. In spite of a very low binding affinity of all of these sequences in our standard receptor assay, additional cleavage ex-periments with different proteases were performed to obtain some new types of fragments.

Ala 117	Pro	Val	Arg 120	Ser	Leu	Asn	Cys	Thr	Leu 126
Arg 127	Asp	Ser	Gln 130	Gln	Lys	Ser	Leu	Val	Met 136
Ser 137	Gly	Pro	Tyr 140	Glu	Leu	Lys	Ala	Leu	His 146
Leu 147	Gln	Gly	Gln 150	Asp	Met	Glu	Gln	Gln	Val 156
Val 157	Phe	Ser	Met 160	Ser	Phe	Val	Gln	Gly	Glu 166
Glu 167	Ser	Asn	Asp 170	Lys	Ile	Pro	Val	Ala	Leu 176
Gly 177	Leu	Lys	Glu 180	Lys	Asn	Leu	Tyr	Leu	Ser 186
Cys 187	Val	Leu	Lys 190	Asp	Asp	Lys	Pro	Thr	Leu 196
Gln 197	Leu	Glu	Ser 200	Val	Asp	Pro	Lys	Asn	Tyr 206
Pro 207	Lys	Lys	Lys 210	Met	Glu	Lys	Arg	Phe	Val 216
Phe 217	Asn	Lys	Ile 220	Glu	Ile	Asn	Asn	Lys	Leu 226
Glu 227	Phe	Glu	Ser 230	Ala	Gln	Phe	Pro	Asn	Trp 236
Tyr 237	Ile	Ser	Thr 240	Ser	Gln	Ala	Glu	Asn	Met 246
Pro 247	Val	Phe	Leu 250	Gly	Gly	Thr	Lys	Gly	Gly 256
Gln 257	Asp	Ile	Thr 260	Asp	Phe	Thr	Met	Gln	Phe 266
Val 267	Ser	Ser 269							

Figure 10: *Interleukin 1β (h. IL-1β).*

Another systematic apprach consisted of the synthesis and testing of a series of 90 overlapping hexapeptide sequences corresponding to the assumed surface-forming peptidic structures. Unfortunately, no significant binding was observed.

A great step forward in our study was achieved by the crystallization of the recombinant human IL-1β by Schär and his colleagues in our company.

It consists of 12 β-strands connected by a complex net of hydrogen bonds, forming a tetrahedron-like structure with a β-barrel core.

These strands are attached to each other by 11 (A-K) unstructured loops of varying length mainly of polar AAs.

Using a special program, the "most accessible surface," i.e. the most exposed side-chains of the AAs forming the surface of IL-1β were calculated and expressed in square Å (see Tables 8A and 8B).

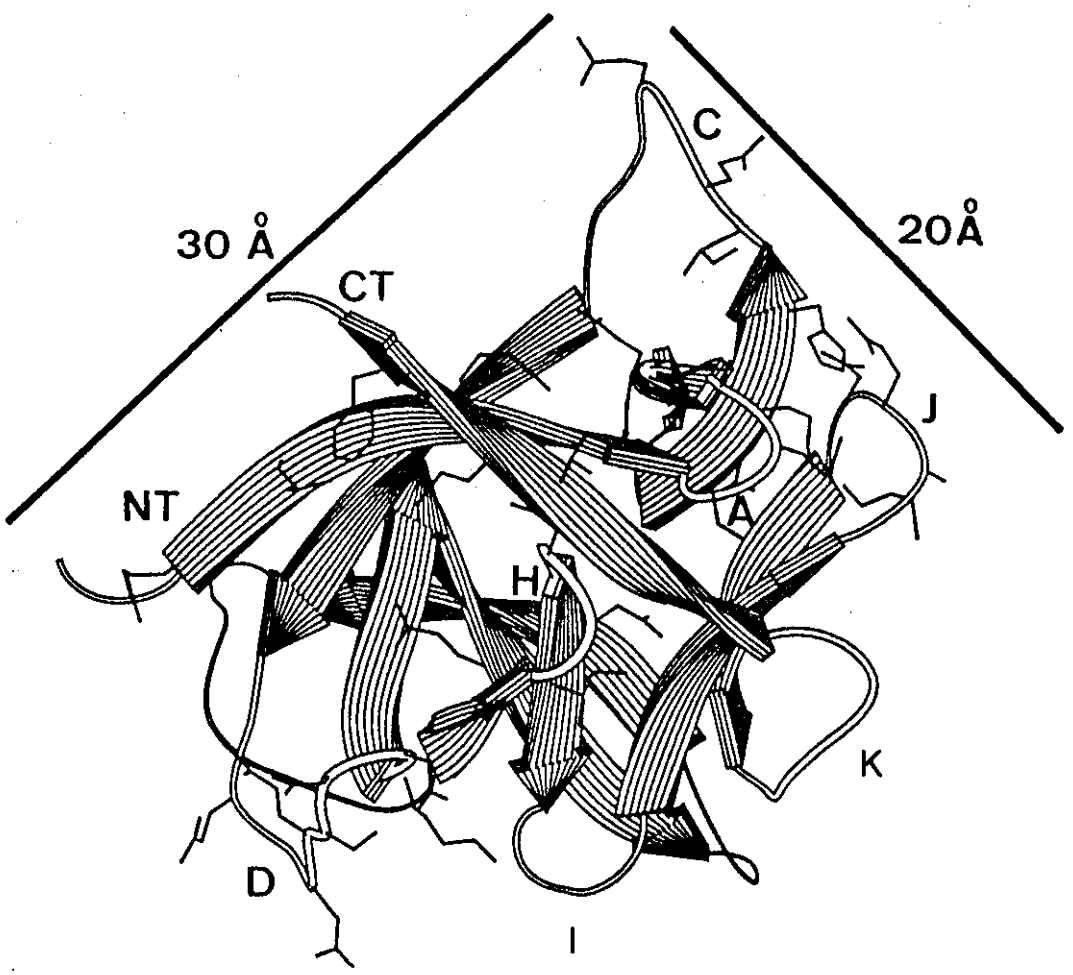


Figure 11: Interleukin-1β

Table 8A: Surface analysis of Interleukin-1β based on a refined crystallographic structure (2.4 Å resolution).

	Residue			S(Å²)
1.	A	117	Ala	97.3
2.	P	118	Pro	116.9
3.	V	119	Val	15.3
4.	R	120	Arg	118.5
5.	S	121	Ser	63.7
6.	L	122	Leu	38.6
7.	N	123	Asn	16.1
8.	C	124	Cys	0.0
9.	T	125	Thr	6.4
10.	L	126	Leu	6.0
11.	R	127	Arg	52.7
12.	D	128	Asp	0.9
13.	S	129	Ser	41.4
14.	G	130	Gln	91.6
15.	G	131	Gln	107.1
16.	K	132	Lys	0.2
17.	S	133	Ser	0.2
18.	L	134	Leu	
19.	V	135	Val	
20.	M	136	Met	
21.	S	137	Ser	
22.	G	138	Gly	
23.	P	139	Pro	
24.	Y	140	Tyr	
25.	E	141	Glu	
26.	L	142	Leu	
27.	K	143	Lys	
28.	A	144	Ala	
29.	L	145	Leu	
30.	H	146	His	
31.	L	147	Leu	
32.	G	148	Gln	
33.	G	149	Gly	
34.	G	150	Gln	
35.	D	151	Asp	
36.	M	152	Met	
37.	E	153	Glu	
38.	G	154	Gln	
39.	G	155	Gln	
40.	V	156	Val	
41.	V	157	Val	38.3
42.	F	158	Phe	0.8
43.	S	159	Ser	27.1
44.	M	160	Met	0.4
45.	S	161	Ser	1.3
46.	F	162	Phe	51.6
47.	V	163	Val	8.7
48.	G	164	Gln	107.5
49.	G	165	Gly	34.7
50.	E	166	Glu	130.4
51.	E	167	Glu	129.7

	Residue			S(Å²)
52.	S	168	Ser	51.2
53.	N	169	Asn	161.4
54.	D	170	Asp	82.8
55.	K	171	Lys	64.7
56.	I	172	Ile	39.2
57.	P	173	Pro	1.0
58.	V	174	Val	0.0
59.	A	175	Ala	0.0
60.	L	176	Leu	0.4
61.	G	177	Gly	0.4
62.	L	178	Leu	5.3
63.	K	179	Lys	74.0
64.	E	180	Glu	167.7
65.	K	181	Lys	104.6
66.	N	182	Asn	63.2
67.	L	183	Leu	17.9
68.	Y	184	Tyr	14.9
69.	L	185	Leu	3.6
70.	S	186	Ser	0.0
71.	C	187	Cys	0.8
72.	V	188	Val	23.8
73.	L	189	Leu	107.4
74.	K	190	Lys	104.7
75.	D	191	Asp	132.0
76.	D	192	Asp	138.7
77.	K	193	Lys	115.4
78.	P	194	Pro	15.9
79.	T	195	Thr	35.0
80.	L	196	Leu	29.3
81.	Q	197	Gln	51.4
82.	L	198	Leu	12.5
[illegible]			Pro	
92.	K	208	Lys	61.9
93.	K	209	Lys	72.9
94.	K	210	Lys	98.7
95.	M	211	Met	12.2
96.	E	212	Glu	58.8
97.	K	213	Lys	91.0
98.	R	214	Arg	73.4
99.	F	215	Phe	0.0
100.	V	216	Val	4.6
101.	F	217	Phe	0.0
102.	N	218	Asn	19.9

	Residue			S(Å²)
103.	K	219	Lys	15.7
104.	I	220	Ile	24.5
105.	E	221	Glu	108.3
106.	I	222	Ile	89.6
107.	N	223	Asn	111.0
108.	N	224	Asn	131.4
109.	K	225	Lys	53.1
110.	L	226	Leu	3.8
111.	E	227	Glu	8.7
112.	F	228	Phe	0.4
113.	E	229	Glu	20.8
114.	S	230	Ser	0.6
115.	A	231	Ala	20.1
116.	Q	232	Gln	82.8
117.	F	233	Phe	30.0
118.	P	234	Pro	83.4
119.	N	235	Asn	90.8
	W	236	Trp	72.1
	Y	237	Tyr	13.2
	I	238	Ile	7.2
	S	239	Ser	0.6
	T	240	Thr	0.0
	S	241	Ser	23.2
	Q	242	Gln	102.1
	A	243	Ala	57.6
	E	244	Glu	85.4
	N	245	Asn	75.9
	M	246	Met	84.8
	P	247	Pro	43.9
	V	248	Val	13.5
	F	249	Phe	58.2
	L	250	Leu	13.7
	G	251	Gly	9.1
	G	252	Gly	33.1
	T	253	Thr	81.5
	K	254	Lys	107.8
	G	255	Gly	52.1
	G	256	Gly	73.9
	G	257	Gln	127.3
142.	D	258	Asp	46.7
143.	I	259	Ile	11.2
144.	T	260	Thr	8.1
145.	D	261	Asp	40.0
146.	F	262	Phe	1.1
147.	T	263	Thr	35.9
148.	M	264	Met	40.8
149.	G	265	Gln	36.9
150.	F	266	Phe	142.7
151.	V	267	Val	55.2
152.	S	268	Ser	111.3
153.	S	269	Ser	137.5

Average radius of the solvent..... 1.500 Angstroems

SURFACE = 8147.57 A**2

VOLUME = 30556.30 A**3

Table 8B: Surface analysis of sequence 185 – 198 of IL–1β showing stretches of low medium and high exposure (excerpt from Table 8A).

Residue		Surface $(\mathring{A})^2$	
185	Leu	3.6	area of low exposure (sequence almost totally buried)
186	Ser	0.0	
187	Cys	0.8	
188	Val	23.8	
189	Leu	107.4	area of high exposure
190	Lys	104.7	
191	Asp	132.0	
192	Asp	138.7	
193	Lys	115.4	
194	Pro	15.9	area of medium exposure
195	Thyr	35.0	
196	Leu	29.3	
197	Gln	51.4	
198	Leu	12.5	

A CAMM analysis and the assumption that the AAs of the hydrophobic inner core are serving only for the stabilization of the tertiary structure allowed a systematic mapping of the IL–1β molecule. The analysis showed the problem to consist of 12β–strands of low accessibility and 11 loops (A–K) of high accessibility, the latter ones being the potential binding sites of the protein.

In this context numerous peptides were synthesized containing rigidized parts of the exposed structural elements, i.e. of the potential binding sites of selected surface regions. They were designed to mimic as closely as possible the spatial arrangement of the involved residues in the native protein (Fig. 12).

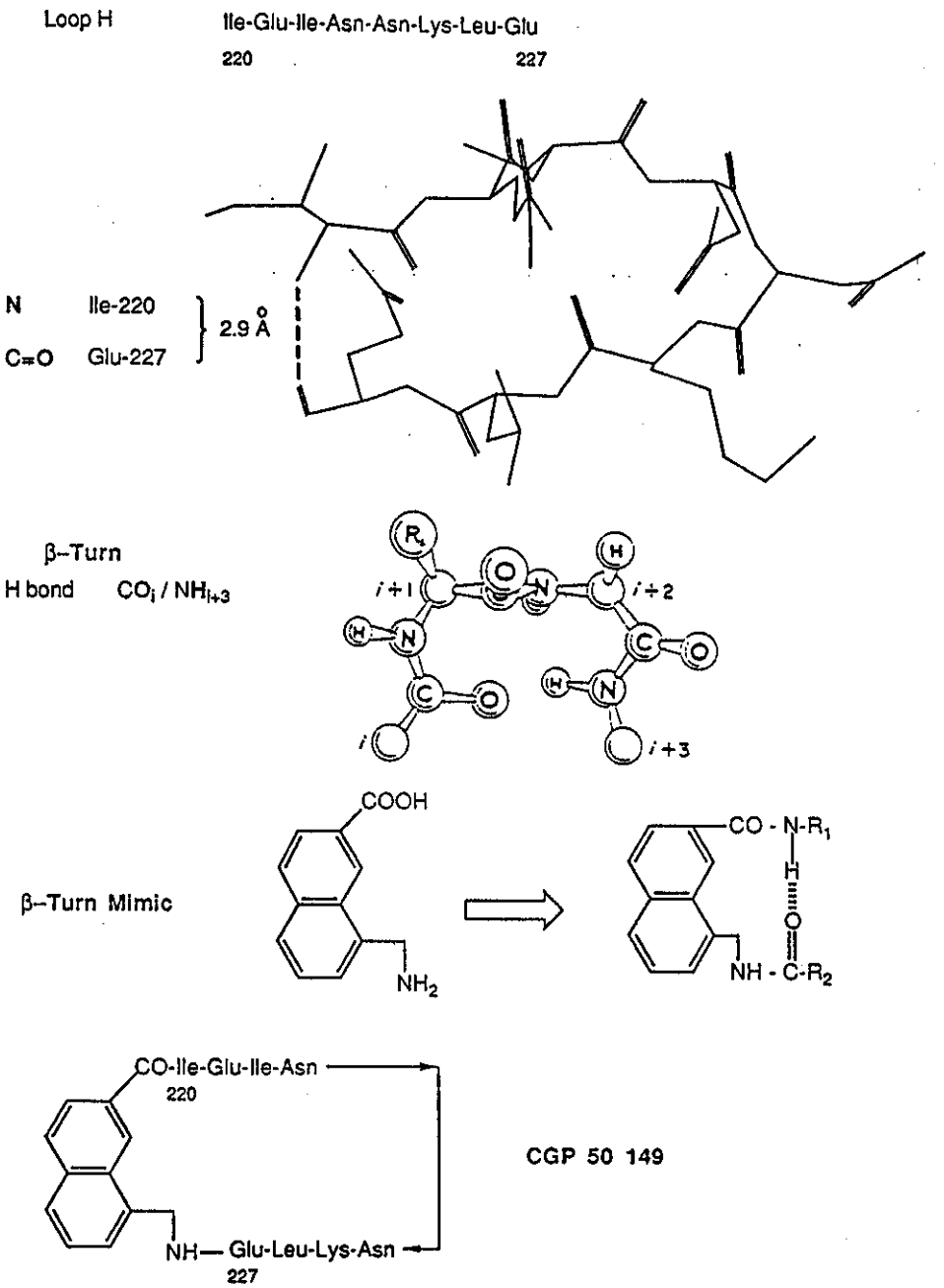


Figure 12: *(from top to bottem): Linear sequences and spatial arrangement of Loop H; spatial requirements of β–turn; a naphthalin derived β–turn mimic and its use in the build–up of a Loop H mimic.*

As it is known that in protein/protein complexes the points of interaction, i.e. the binding sites, can be dispersed over a large area, such a surface region can be formed of residues which are fairly distant in respect to their position in the primary backbone sequence. To combine the individual components, special linkers (spacers as well as new types of turn-mimics) had to be incorporated into the planned molecules. To generate the desired "IL-1β-mimics" which would bind to the IL-1β receptor, it was proposed to cut out and rigidize one or more neighboring loops (Fig. 13).

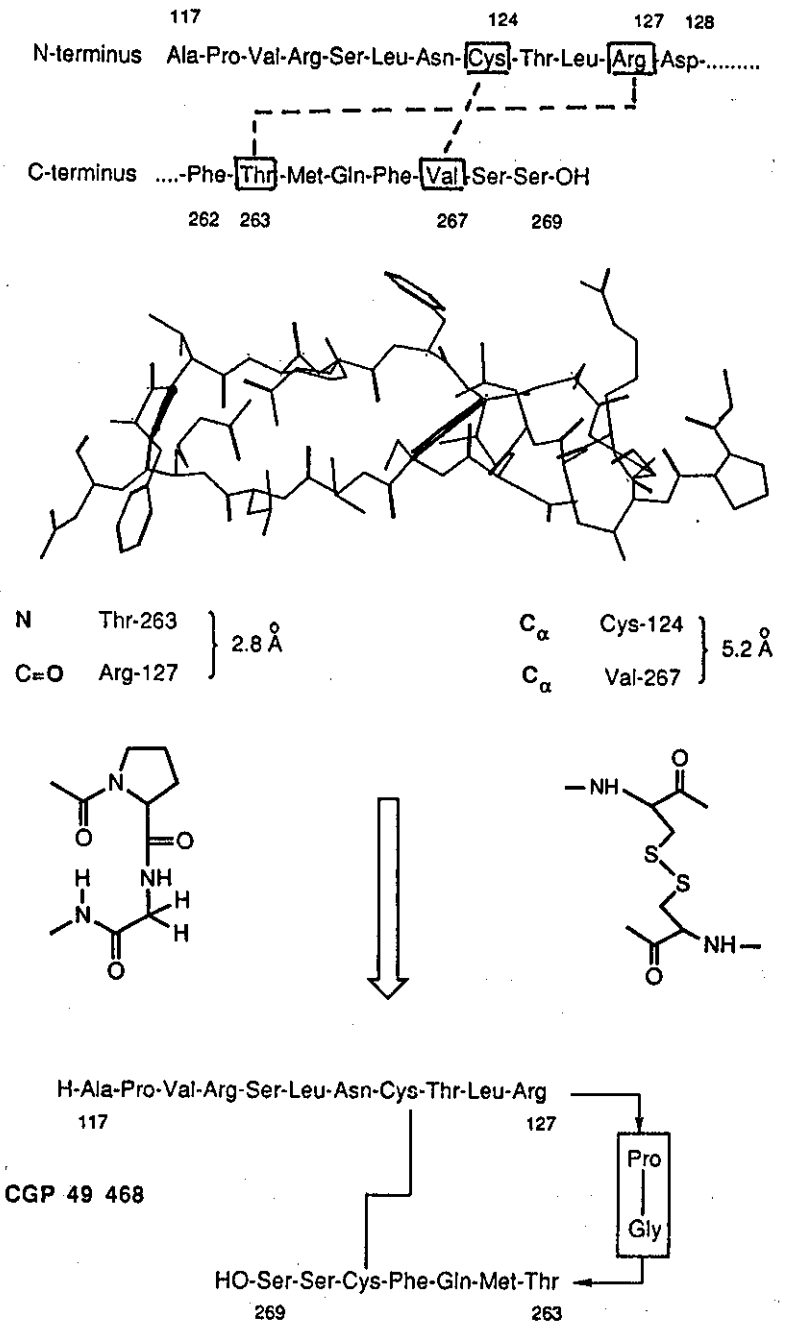


***Figure 13:** (from top to bottem): primary sequences of N- and C-termini of IL-1β; their respective arrangement and proximity in space; their interconnection using special chemical linkers, a Pro-Gly-β-turn to connect Arg 127 and Thr 263, a Cys-Cys-disulfide spacer fixing amino acids 124 and 267.*

The design of rigid building blocks which would fix 3 or 4 AA side chains in a defined topographical situation (in a distance of about 10–15 Å) is a rather ambitious goal. One does not have to adhere too strictly to the derived model and should not try to synthesize a "tailor-made" compound, since it could be assumed that the natural flexibility will in any case help to correct the in-built inconsistencies.

Substantial help to our synthetic attempts was provided by the next step accomplished in the Biotechnology Department.

Some 20 residues preferentially situated in the various loops as well as the N- and C-termini of the protein were substituted by different types of AAs, using the standard point mutation technique. It was thereby assumed that the exchange of an AA which is essential for the interaction of our protein with its receptor would lead to a drop in binding affinity (Fig. 14).

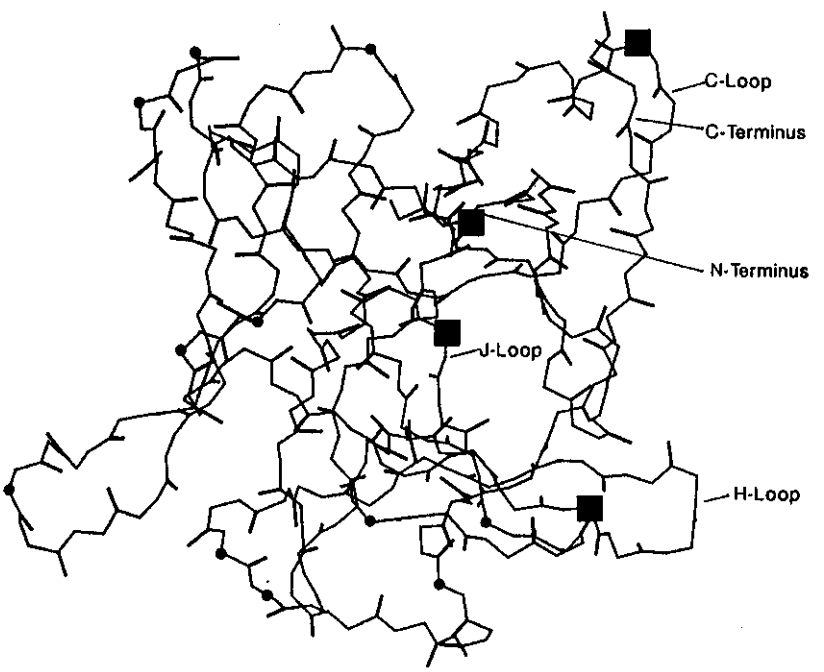


Figure 14: *Spatial structure of IL-1β. ● indicate point mutations leading to no drop in binding affinity; ■ indicate point mutations leading to drop in binding affinity; these amino acids are assumed to be essential for interaction of protein with receptor.*

As can be deduced from the presented results of point mutations, the few identified "essential" residues are spread over a very large area of the surface, making the design of a potential antagonist even more difficult. In a few cases the mutated interleukins were crystallized. No significant change in their overall structure was observed, when compared to the wild-type molecule.

One attractive possibility consisted in defining a formal square built out of known or specifically designed β–turn mimics and 2 to 4 of the exposed "essential" AAs (Fig. 15).

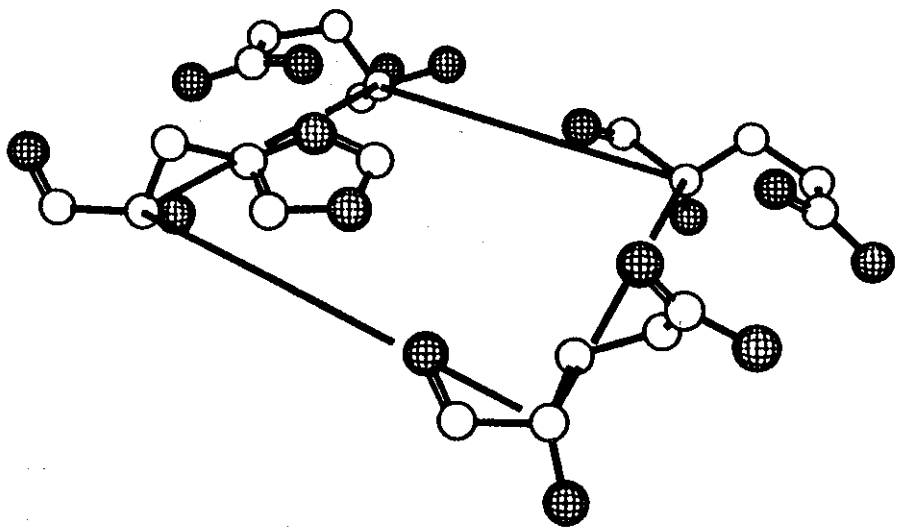


Figure 15: Four "essential" residues of IL–1β placed in the corners of a formal square; the shape of the square is determined by crystal analysis of IL–1β.

A next higher level of sophistication corresponds to a concept wherein two relevant partially rigidized cyclic areas would be joined by linkers as expressed in Fig. 16.

Finally, lets turn our attention to a completely different approach, using a new version of the so–called TASP (Template–Assembled–Synthetic–Proteins) concept of Mutter, which we call TASM (Template–Assembled–Surface–Mimics) (Fig. 17).

Atop the four lysine ω–amino groups of a semi–rigid gramicidin S–type cyclic template with two in–built synthetic β–turn mimics the side–chains of four of the "essential" AAs were fixed by acylation. The spatial arrangement of these residues important for the binding should spontaneously be corrected and adapted during their interaction with the receptor. The first results obtained using this approach in another area confirmed our expectations (Fig. 18A,B).

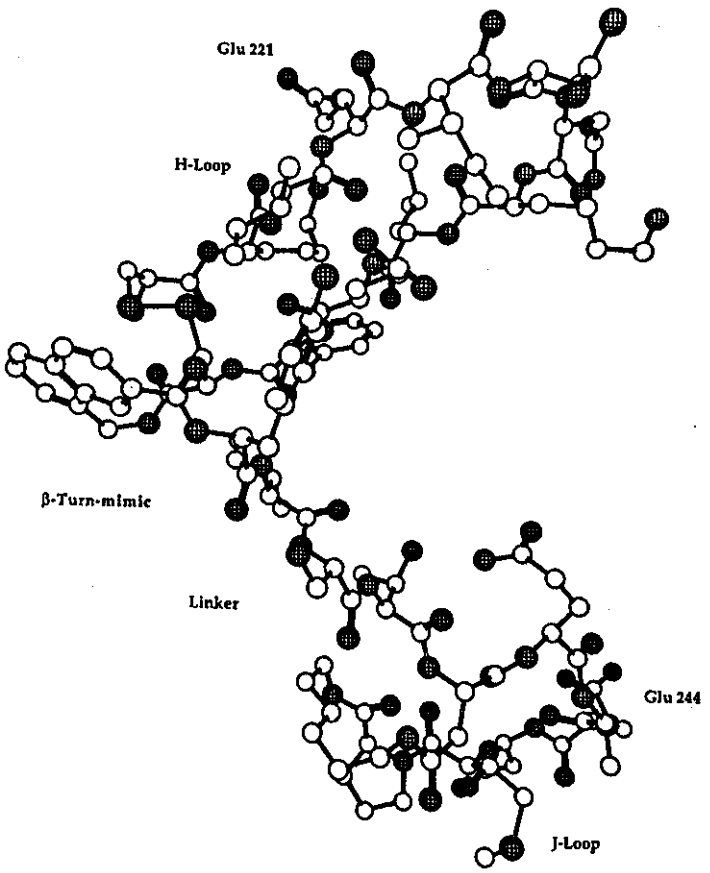


Figure 16: *Loops H and J of IL-1β, each rigidised by cyclisation; the two loops are interconnected by a linker allowing them to take up the desired respective positions in space.*

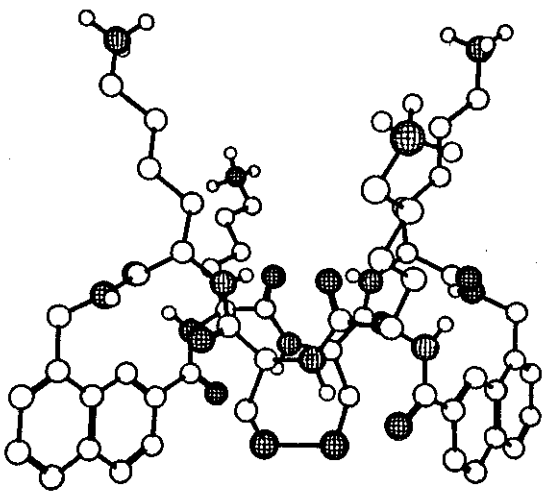
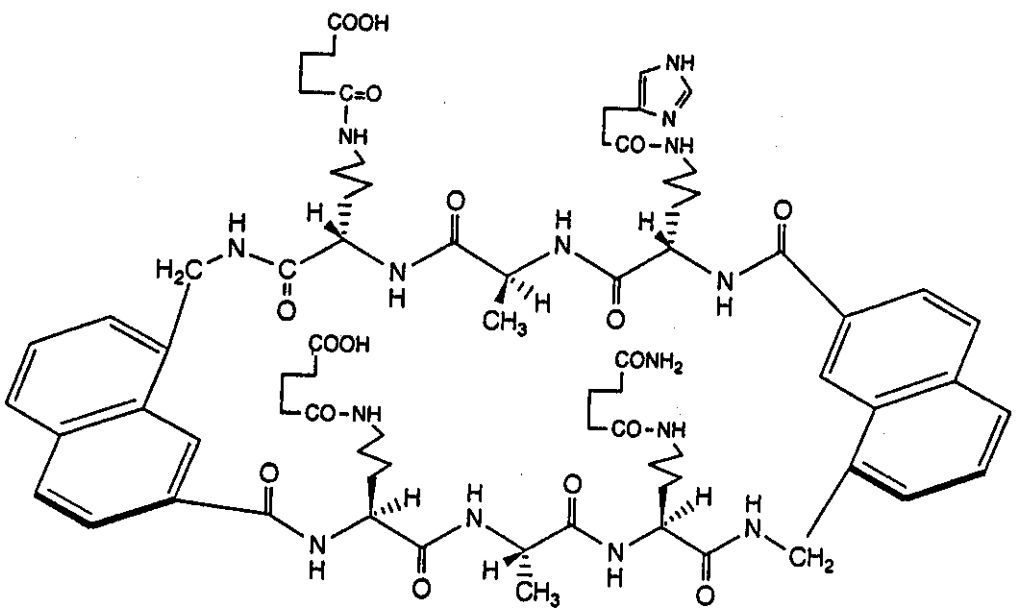
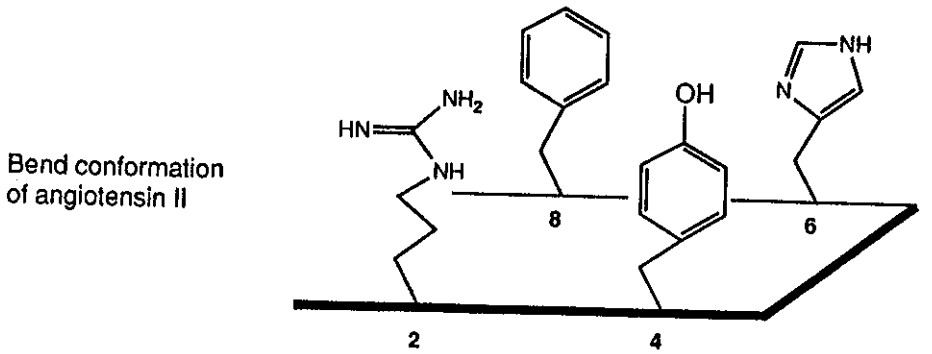


Figure 17: *Tetrafunctional cyclic template containing 4 lysine residues. The 4 ∈-amino functions serve as attachment points for the build-up of constructs mimicking the topological features of proteins and peptides.*

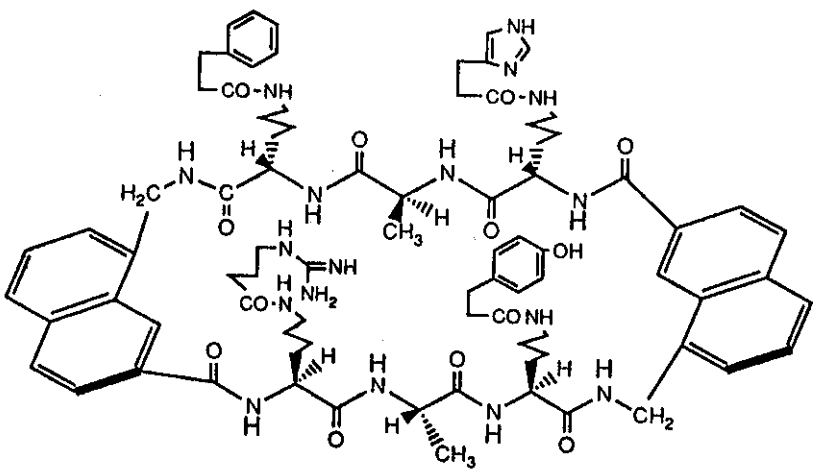


CGP 53533 A

Figure 18A: *Gramicidin S-type cyclic template containing the side chains of four AAs of IL-1β essential for biological activity.*

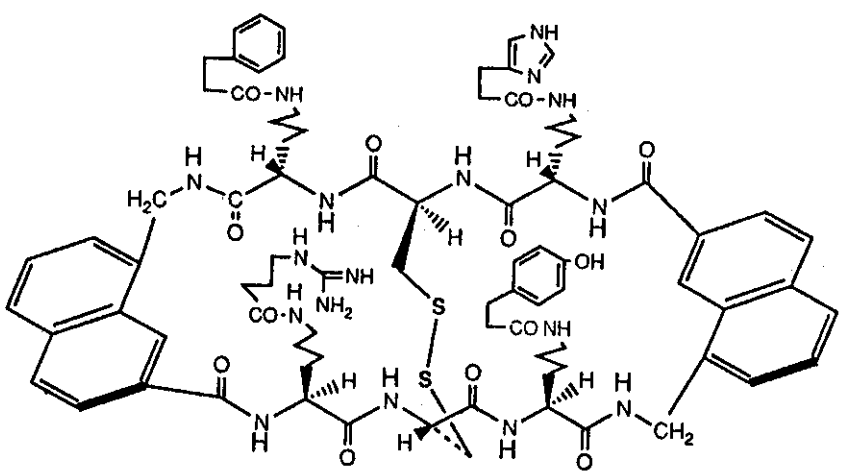


A II-Receptor
Binding (hU)
IC_{50}(M)



$4 .10^{-6}$

CGP 49 538A



$3 .10^{-6}$

CGP 49 539A

Figure 18B: *Schematic presentation of Angiotensin II (bent conformation) and two examples of template assembled mimics containing the side chains of the four essential AAs Arg, Tyr His and Phe of A II. In CGP 49 539 A the cyclic template has been further rigidised by an S–S–bridge.*

The rational approach to the search of a receptor antagonist can thus be summarized as follows:

Table 9: Rational search for receptor antagonists.

Deduction of the primary sequence
Cloning of the gene and preparation of the recombinant material
Determination of the structure – Crystallization and x-ray analysis – NMR
Identification of the binding sites and of other important structural elements by: – Point mutations – Synthesis of partial sequences – Synthesis of partial structures and mimics – Physico-chemical methods
CAMM (Computer assisted molecular modeling)

The second example discussed has given you an illustration of today's approach to a new type of research project in the pharmaceutical industry. Our original question concerning the prerequisites for a young chemist who will tomorrow enter the area of medicinal chemistry can now be easily deduced (Table 10). Thus, in addition to classical knowledge and experience in synthesis, a more profound understanding of the following disciplines is required.

Table 10: Future prerequisites for a medicinal chemist.

– Chemistry and biochemistry of biomacromolecules
– General molecular biology
– Protein structure analysis
– Production of proteins and protein mutants by recombinant DNA technology
– Molecular modeling and computational chemistry

Besides the classical knowledge and experience needed for the preparation of new compounds which have grown in quality and quantity especially in the area of enantio-selective synthesis and metallo-organic chemistry, he or she must be prepared to participate actively in areas closely related to molecular architecture and to the molecular basis of biological functions.

In this sense a more profound understanding of all the disciplines shown in Table 10 will be essential for the medicinal chemist, who will have to become a critical partner of his or her colleagues forming the interdisciplinary team of the future.

Medicinal chemists are still the "stars" of drug development, but today, in contrast to yesterday, they are helped by numerous specialists, as becomes apparent from the following acknowledgment (Table 11):

Table 11: Acknowledgement

VOLTAREN	
Alfred Sallman	Medicinal Chemistry
4 colleagues	Biology
THE INTERDISCIPLINARY IL-1-TEAM	
Albert Schmitz Jan van Ostrum Klaus D. Vosbeck Urs Joss	Protein expression Point mutations Biological evaluation
Markus Grütter John P. Priestle Hans-Peter Schär	Crystallization and X-ray crystallography
N. Claude Cohen Marina Tintelnot	CAMM
Andreas Flörsheimer Albert Hartmann Jaroslav Kalvoda Bruno Damber Bernhard Riniker	Chemistry, synthesis of peptides and protein mimics

Biomaterials Science: New Needs and New Products

Noah Lotan
Department of Biomedical Engineering
The Leonard and Diane Sherman Biomaterials Research Center
Technion–Israel Institute of Technology
Haifa 32000 · Israel

I certainly appreciate the opportunity to address this distinguished audience as part of our meeting on Medicine and Engineering. In so doing, I would like to recall that exactly 100 years ago, Lord Kelvin, one of our mentors instructed us that "When you can measure what you are speaking about, and express it in numbers, you know something about it." Today, 1991, we continue along the same line.

In this presentation we would like to consider future needs in the field of biomaterials. It is certainly not easy to be a prophet, and particularly not in your own town, but I will, nevertheless, try. To this aim, let us first consider how various industries have developed during the last fifteen to twenty years (Table 1). The top ten industries are shown on the left while the last ten are on the right. We can see that four out of the top ten industries are related to the medical field. Thus, quite a lot of progress involves medicine, one way or another.

Table 1: Growth of Various Industries: 1988 shipments, relative to 1972 shipments (1982 $). [From "Emerging Technologies – A Survey of Technical & Economic Opportunities," U.S. Dept. of Commerce, 1990.]

TOP 10	RATE %	LAST 10	RATE %
Computing Equipment*	8823	Turbine Generator Sets	17
Semiconductor Devices*	6072	Photoengraving	23
Optical Devices/Lenses	940	Cigars	35
X-ray Apparatus	537	Leather/lined Clothing	38
Lithographic Services	394	Railroad Equipment	42
Biological Products	**387**	Bldg. Paper/Board Mills	42
Electronic Connectors	356	Primary Zinc	44
Medicinals & Botanicals	**347**	Textile Machinery	48
Surgical Appliances	**337**	Rubber/Plastic Footwear	50
Surgical & Medical Inst.	**327**	Wood TV, Radio Cabinets	50

*The growth rates of these two technologies have been adjusted for technical changes as well as price change. Source: Dept. of Commerce, U.S. Industrial Outlook, 1998.

Related information is collected in Table 2, in which two groups of technologies are presented: One lists the emerging technologies, as viewed by the US Department of Commerce. The second one is a list of critical technologies, as viewed by the US Department of Defense. We can see that medicine–related areas are on both lists: in the first, under the general heading of Biotechnology and on the second one as Medical Devices and Diagnostics. Different names, but the same topics.

Table 2: Comparison of the Emerging Technologies (DOC) with the Critical Technologies (DOD) ("The Dept. of Defense Critical Technologies Plan," Dept. of Defense (DOD), Washington, DC, May 1989. The numbers in the figure refer to the mumbers used in the DOD document). [From "Emerging Technologies – A Survey of Technical & Economic Opportunities," U.S. Dept. of Commerce, 1990.]

Emerging Technologies (DOC)	Critical Technologies (DOD)
Advanced Materials	(20) High performance composite materials
Advanced Semiconductor Devices	(1) Microelectronic circuits (2) GaAs & other compound semiconductors
Artificial Intelligence	(5) Machine intelligence/Robotics (9) Sensitive radars (11) Automatic target recognition (13) Data fusion
Biotechnology	**(22) Biotechnology materials & processing**
Digital Imaging Technology	(9) Sensitive radars (11) Automatic target recognition
Flexible Computer-Integrated Manufacturing	(5) Machine intelligence/robotics
High-Density Data Storage	(7) Integrated optics
High-Performance Computing	(3) Software producibility (4) Parallel computer architectures (6) Simulation and modeling (13) Data fusion (15) Computational fluid dynamics
Medical Devices & Diagnostics	**(22) Biotechnology materials & processing**
Optoelectronics	(7) Integrated optics (8) Fiber optics
Sensor Technology	(5) Machine intelligence/robotics (10) Passive sensors
Superconductors	(21) Superconductivity
	Also Listed: (12) Phased arrays (14) Signature control (16) Air breathing propulsion (17) High power microwaves (18) Pulsed power (19) Hypervelocity projectiles

Table 3: Example of Products Made by Biotechnological Methods. [From "Sultzer Technical Review," 3:29, 1990].

Product	Application
Growth Hormones	Promote growth
Insulin	Diabetes
Calcitonin	Bone diseases
Chorion-Gonadotropin	Pregnancy test, female sterility
Enkaphaline	Pain killer
Interleukine	Immunotherapy, tumor therapy
Interferone	Immunotherapy, tumor therapy
Tumor-necrose-factor	Tumor therapy
α-1-Anti-trypsin	Lung emphysema
Human serum albumin	Blood plasma production
Factor VIII	Blood coagulation, haemophilia
Urokinase	Dissolution of blood clots
t-Plasminogen activator	Dissolution of blood clots
Antibodies	Cancer diagnosis and therapy

A more detailed picture of the relationship between biotechnology and medicine is shown in Table 3. Here is a list of biomaterials drugs which are supplied by biotechnology, and have already reached the market. Not only one or two, but quite a long list of efficient and highly valuable therapeutic biomaterials. What is the market value of these compounds? The data are shown in Table 4. The cardiovascular drugs are on top of the list with about US$600 million, while the total value of these biotechnological products passes the billion dollar mark. And, if we consider the expectations for the near future, we see that there is one drug, Erythropoietin, which will pass the billion dollar mark in a few years. It is thus only too obvious that we are speaking here about a heavy industry, heavy not in the amount of products, but as to the market value.

Considering again the market value of therapeutic biotechnological materials, we must ask ourselves – how does this market compare to other markets? Are we dealing with something which is worth investing time and effort, or are we considering a little corner where we just play and enjoy? To answer this question let us come back to the list of emerging technologies, recently set by the US Department of Commerce (Fig. 1). We see here that emerging life sciences applications, namely biotechnology products and medical devices, are expected to reach about US$20 billion by the year 2,000. This size market compares rather favorably with emerging manufacturing systems and the numbers are indeed very high. We therefore consider here a technology which is characterized by products sold in small quantities but at extremely high value. We are speaking here not only of the high moral value attached to medical care, but from a strictly economical point of view.

Table 4: Erythropoietin Leads U.S. Biotech Drug Market. [From A.M. Thayer, Chem. Eng. News, p. 27, Feb. 25, 1991].

$ Millions	1991	1996	2001
Cardiovascular	**$ 600**	**$1145**	**$2250**
Erythropoietin	350[a]	800	1300
Tissue plasminogen activator	225[a]	225	450
Blood factors	25[a,b]	50	100
Superoxide dimutase	0	20	100
Others	0	50	300
Cancer	**145**	**685**	**1850**
Colony-stimulating factors	20[a,b]	250	650
Interferons	125[a]	200	350
Interleukins	0	210	550
Others	0	25	300
Hormones/growth factors	**420**	**890**	**1605**
Epidermal growth factor	0	65	230
Human growth hormone	250[a]	470	650
Human insulin	170[a]	250	325
Others	0	105	400
Vaccines	**15**	**170**	**825**
AIDS	0	50	300
Herpes	0	15	150
Hepatitis B, others	15[a]	105	375
Monoclonal antibodies			
Therapeutics	**20**	**200**	**490**
Others	**0**	**210**	**680**
TOTAL	**$1200**	**$3300**	**$7700**

a C&EN estimates based on analyst reports and company projections. b Not yet approved but may reach market in 1991. Source: Consulting Resources Corp. and C&EN estimates

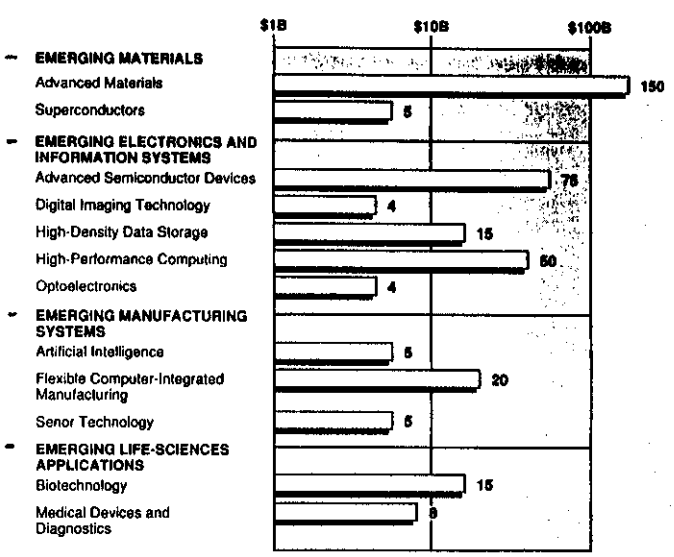


Figure 1: Emerging Technologies and Markets: Annual sales of $356 billion in the U.S. by the year 2000 [From "Emerging Technologies – A Survey of Technical and Economic Opportunities," U.S. Dept. of Commerce, 1990].

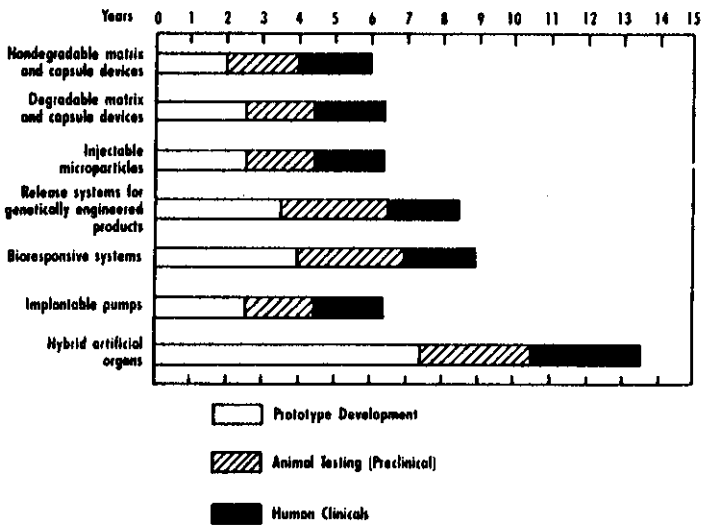


Figure 2: Time Line for New Controlled-Release Devices. [From S.A. Barenberg, Medical Devices & Diagnostic Industry, March 1990.]

What kind of materials then can we envisage will go into this market? A large part is expected to originate in products and services which we already have today. We speak here about implants, drugs and devices, and these will be further developed, modified and improved. In particular, implanted materials which are not to be metabolized will continue to account for a significant part of our activities in the coming years. Certainly, not all of the properties of currently available implanted materials are exactly what we like. It is therefore our feeling that the future materials which will go into this particular niche will be composite materials, polymer-type and ceramic-type, and these will be "coated" in order to make them biocompatible. The tools for so doing are to be found in chemistry.

Now let us consider a second topic, namely drug delivery systems. Until now we have mentioned drugs, but drugs are to be dispensed. Accordingly, drug delivery systems are expected to take a large share of the world market: some US$2 billion by the year 2000. These devices come in response to the need that drugs will not be given once every few hours or few days, but drugs will be provided at a constant rate or, even better, drugs will be provided as required. What we have in mind here are drug delivery systems which will be responsive to the physiological demands, that is to the status of the physiological system. Some of the options considered are shown in Fig. 2. I would like to point the attention to two classes: the bioresponsive systems and the hybrid artificial organs. We note that the time required for developing them will be rather long, but it seems that these are indeed the kind of devices which we are looking after.

Other biomaterials which we would like to consider today are the metabolic artificial organs. When the metabolism does not function well, there is a need to intervene. One approach is to have an artificial organ connected to the patient; this artificial organ will supplement the activity of the non-functioning or malfunctioning system of the patient. Figure 3 shows the results of some of our work in this field, and, particularly, the engineering aspects involved.

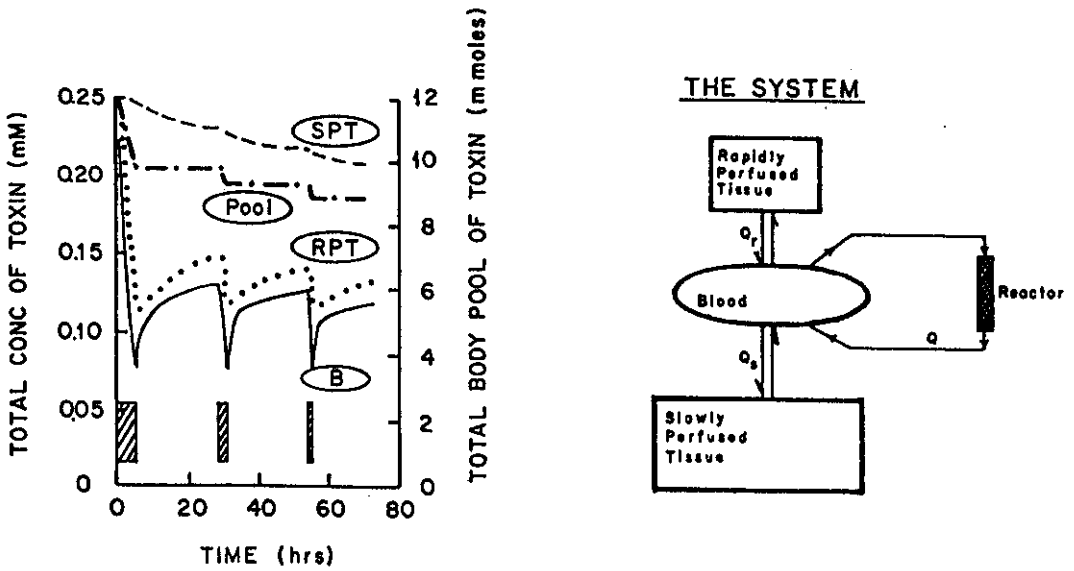


***Figure 3:** Multi-Session Treatment (Rest time: 24 hrs)*
(K = 0, K_p = 0)

The artificial organ considered is an enzymic reactor for blood detoxification, and the patient is treated as a set of three compartments: rapidly perfused tissues (RPT), blood (B) and slowly perfused tissues (SPT). In order to describe the performance of the entire system, patient and enzymic reactor, we follow the concentration of the toxic materials in the various compartments, and do so as treatment is performed. We can see that while the reactor is operating (time periods marked ▦), the concentration of toxin in blood and in the RPT are reduced significantly and, accordingly, the total amount of toxin in the system is reduced as well. When we stop the treatment, toxin from the SPT returns to the blood and RPT compartments, while obviously, the total amount of toxin in the system remains constant. A second period of treatment again causes the lowering of toxin concentration in the blood and in the RPT, and so on. This is a good example of how a medical problem is handled by an attending physician which takes advantage of the chemistry and engineering skills of the biomedical engineer.

To here we have mentioned implants, drug delivery systems and metabolic artificial organs. As a matter of fact, this was to take what we know today and to extrapolate it into the near future.

The next topic which I would like to address is Molecular Bioelectronics Biomaterials. It is the field of activity in which attempts are made to further miniaturized information processing elements and reduce them from today's micron size down to molecular dimensions. The reasons for so doing are the physical limitations of current microelectronics technology, as well as the desire for understanding logic related molecular phenomena in physiological systems. It is expected that achievements in one of these areas will allow for progress to be

made in the other one. Is this a realistic view? The comparative analysis of Drexler (Table 5) provides part of the answer, and it is a positive one.

Table 5: Relations between Engineering Systems and Molecular Devices [Modified from: K.E. Drexler, PNAS, 78:5275, 1981.]

Engineering	Function	Analogous device at the Molecular Level
Pillars, framework	Support	Microtubules, cellulose
Cables	Maintaining tension	Collagen
Fasteners, glues	Binding of objects	Intermolecular forces
Solenoid	Movement of objects	Conformational changes in protein molecules
Motor	Transmission of torque	Flagella
Bearings	Support for rotating objects	σ bonds
Containers	Containment of liquids	Vacuoles
Pipes	Transport of liquids	Tubular structures
Pumps	Movement of liquids	Flagella, membrane proteins
Conveyor belt	Movement of objects	Movement of RNA in ribosomes
Clamps	Immobilization of objects	Binding site of enzymes
Tools	Various functions	Functional groups
Production line	Construction of complex objects	Enzyme systems, ribosomes
Numerical control system	Storage & reading of information	Genetic system
Fuel, electricity	Source of energy	ATP

What have we done in this field at the Technion? Our activities are concentrated on two main topics. In the first we consider logic elements which rely on enzyme–promoted biochemical processes. Depending on the operating enzyme system chosen and on the logic rules employed, these elements are brought to perform various logic functions, such as OR, AND, NOT or others. The second topic considers biomolecular switches. These are molecular devices operating in the yes–no mode, and represent basic elements for more complex systems. As a representative example we have designed such a device using the enzyme lysozyme as the active biochemical species. Into it, a molecular barrier was built at the entrance of the active site, and it allows or prevents the access of substrate to this site. The device is presented in Fig. 4, where the "open" and "closed" ("YES" and "NO") states are shown.

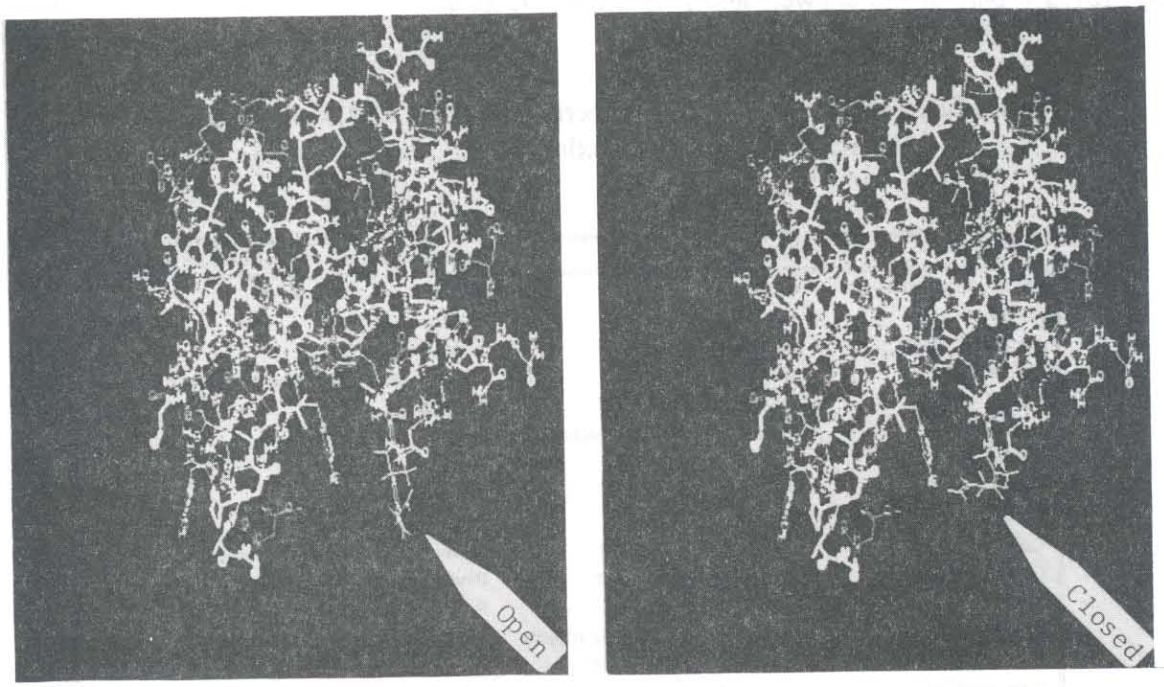


Figure 4: A Molecular Switch on the Enzyme Lysozyme.
[From: G. Ashkenazi, S. Sideman and N. Lotan, in press.]

In summary: We have mentioned the extension of current activities, namely implants, drug delivery systems and artificial organs for metabolic support; and we have pointed out at the birth of molecular bioelectronics, a new and multidisciplinary field of activity in which biomaterials are expected to play a key role.

Scaling-up of Cell Culture System

Avinoam Kadouri
Department of Membrane Research & Biophysics
The Weizmann Institute of Science
Rehovot 76100 Israel

For a decade now, researchers have been re-examining the use of eukaryotic cell cultures for the industrial production of biologically active materials. The products involved, including monoclonal antibodies, polypeptide growth factors, and viral insecticides, among many others, are produced by various cell systems, including normal, transformed and genetically engineered varieties.

When genetic engineering was in its infancy, it was believed that proteins with biological activity could be engineered and manufactured in bacteria only. But it soon became clear that this is not so. Many proteins of interest require post-translational modifications, such as glycosylation, which are not carried out by bacteria. Eukaryotic systems were then sought as the preferred source for genetically engineered proteins that exhibit the molecular properties of the native product. This new notion brought cell culture, which was dormant for many years, back to the forefront of biotechnological interest.

At this point, biotechnology experts began to realize that large scale cell culture was an extremely primitive and underdeveloped field and would not be able to fulfil the burgeoning needs of the industry. The major problem that had to be dealt with was the anchorage dependence of most cell systems of biotechnological interest. Such cells must be attached to a solid surface in order for efficient metabolism and cell proliferation to take place. For this reason, cell-culture processes were developed initially in Petri dishes or flasks, and scaling up for industrial requirements is not trivial.

In general, scaling-up is carried out along two major paths: a) linear scaling-up - expansion and multiplication of the laboratory unit without changing the basic configuration of the system, and b) process development. With regard to cell culture, the linear approach would involve moving from laboratory-sized Petri dishes to large industrial Petri dishes to multiple dishes, such as the multi-tray system ("Nunc cell factory"). If the basic working system is a flask, scaling up would involve progress to multi-roller bottles. However, all of these systems have a basic limitation - small surface to volume ratios typified by low cell density in a large volume and they are uncontrolled.

At first, biotechnology enterprises committed themselves to the linear scaling-up track. This resulted from a) a lack of alternative technology, b) lack of knowledge to develop such

alternatives, and c) the appeal of the linear scaling–up, which, at first glance, seems quick and easy. However, it soon became apparent that massive cell culturing in dishes or flasks, no matter how sophisticated, is operationally difficult, labor consuming, and expensive. Moreover, linear scaling–up was sometimes chosen on the basis of commercial considerations. The development of a new drug from the laboratory to the pharmacist's shelves, requires some ten years and an investment of 100 million to 300 million dollars. The first stage in the development process is very competitive and critical for business success. Linear scaling–up is a fast way to obtain enough material for clinical trials and beat out the competition. In this case, management will choose this clearly–more–expensive route in order to get a jump on the market.

It is now realized that scaling–up via process development is usually the preferable choice. This path could lead to a controlled, optimized, highly–efficient process that is convenient to run and involves minimal operational costs. The production system of choice should be characterized by a large surface area for cell growth within a very small volume, that is, an extremely high density of cells.

Scientists all over the globe are working diligently to develop cell culture systems with large surface–to–volume ratios. Out of many systems developed, the most promising is the microcarrier system, designed originally by Van Wezel. Microcarriers are small spheres with diameters of 50 to 300 m made of various materials, including sepharose, collagen, gelatin, glass, and plastics. Cells fixed with the carrier are attached to the microcarriers and suspended in the culture medium. From the cells' point of view, they are attached to a solid surface; but as far as the operator is concerned, he has a stirred suspension system which resembles bacterial fermentation units. Because bacterial fermentation is well known, and has been steadily improved over decades, microcarrier systems became very common and popular. For many years, it was believed that this was the ultimate answer to industrial cell–culture technology. But it was eventually realized that this system too has inherent and operational problems, which will prevent it from fulfilling its initial promise as the optimal biotechnological large–scale cell culture process.

In the technology of choice, cells are seeded and grow to a large mass. Then these cells are used for production of a given product in a batch or continuous mode over a prolonged period of time preferably using serum–free medium.

At present there are wide varieties of cell culture systems to choose from Each system has its own advantageous and disadvantageous. A good process development should adapt the cell culture system to the biological process, to give an optimize process with high product yield convenient to operate with minimal cost. The process development of the production of tissue plasminogen activator from normal human fibroblasts will be served as an example to demonstrate a Scheme of process development of a biotechnological system.

Plasminogen activator is a serine protease that acts with high specificity on plasminogen to convert it to plasmin, The plasmin is a powerful fibrinolytic agent which degrades insoluble fibrin mash into a soluble fragment. This simple scheme is the basis for the therapeutical use

of tissue plasminogen activator as a fibrinolytic drug for the treatment of cardiovascular disorders such as heart attacks, pulmonary embolism and deep vein thrombosis. Treatment with tissue plasminogen activator immediately after the appearance of the thrombosis and before irreversible changes occurs, could prevent the necroses and death of the tissue and minimize the damage of the attack.

The first step in this research was to locate and identify the plasminogen activator producing cells. It was found that certain strains of normal human diploid fibroblasts can be adapted (1) to produce and secrete large quantities of tissue plasminogen activator. The adaptation is done by cultivating the cells in a medium supplemented with serum other than fetal calf serum, on a substrate precoated with poly-D-lysin. Once the cells were adapted, they continue to produce enzyme for prolonged period of time only in a medium devoid of serum and proteins. In which cell division is minimal - practically close to zero.

Study of the time course of tissue plasminogen activator production revealed, that its formation is controlled by a negative feed back inhibition. The production and the secretion of the enzyme stops when its concentration in the medium reached a critical value. However, removal of the enzyme by continuously replacing the medium results in continuous production and secretion of the enzyme by the cells at a constant rate for several weeks.

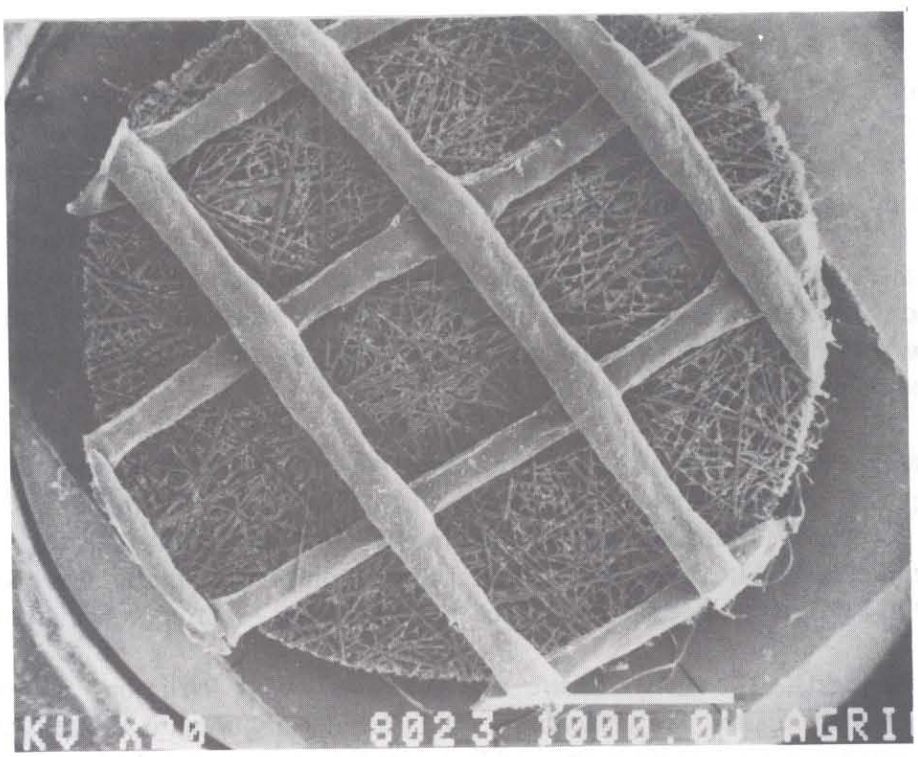


Figure 1: Non-woven fibric carrier (Fibra-Cel).

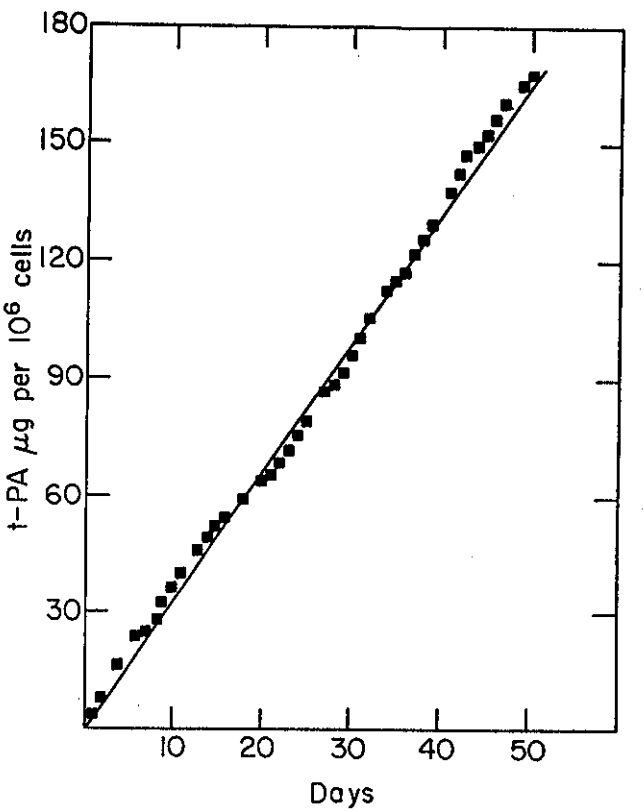


Figure 2: Tissue plasminogen activator production in stationary bed reactor packed with non-woven fabric carrier (Fibra-Cel). Note the constant rate maintained for more than 50 continuous days.

The second step in this research was to find the best biotechnological configuration for this process. Three factors affect the production process and were dictated the biotechnological design of this system; a) the cell adaptation, b) the feedback inhibition of enzyme formation and c) production must be maintained in serum free medium.

The best theoretical configuration for such a process should be a stationary bed reactor with a continuous feed and harvest system. The reactor should be packed with a cell carrier that will allow very high cell density and that the cell will stay on the carrier upon changing to serum free medium during production.

Unfortunately, at the time of this study, there was no cell culture and no large scale technology that could be suitable for such a process. Therefore a new and special technology had to be developed to fulfil the above requirements. The basis of this technology is a unique cell culture carrier (Fig. 1) which is built from a non-woven fabric made of polyester laminated to a polypropylene screen and cut into small discs – 6 mm in diameter (Fibra-Cel,

Sterilin, England). The cells adhere to and grow very well on and within this three-dimensional matrix. They reach a very high cell density of up to 10^8 cells/ml. Yet they are well protected against shear forces and therefore they remain attached to the carrier even when the medium is changed to serum free. This carrier was then packed in a stationary bed reactor and used successfully for the production of tissue plasminogen activator in a

perfusion's mode for a duration of 30–60 days in a medium completely devoid of proteins (Fig. 2). During the production phase the cells do not divide. This system practically mimic the situation in the eukaryotic body where cells do not divide but continue to produce a product for prolonged period of time.

We believe that this system is a break though in cell culture technology. So far this system has been used in various processes: tissue plasminogen activator from normal human fibroblasts, antileukemic factor from stroma cells isolated from mouse bone marrow (2) for production of various recombinant.

References

1. Kadouri, A. and Bohak, Z., 1983. Production of plasminogen activator in cultures of normal human fibroblasts. Biotechnology 1: 354–358.
2. Kadouri, A. and Zippori, D. 1988. Production of Anti-leukemic factor from stroma cells in a stationary bed reactor on new cell support. Advances in cell Biology and technology for Bioprocesses, R.E. Spier et al (eds.) In: Butterworths & Co. Ltd. 327–332.
3. Kompier, R., Kisler, N., Segal, I. and Kadouri, A. 1991. The use of stationary bed reactor and serum free medium for the production of recombinent proteins in insect cells. Enz & Microbial. Tech. vol. 13: 822–827.
4. Wang, G., Zhang, W., Freedman, D., Eppstein, L. and Kadouri, A. 1992. Modified cell: Gen–packed bed bioreactors for hybridoma cell cultures. Cytotechnology (In press).

SESSION V: DIAGNOSTICS

Chairmen: Mr. Yehuda Dvir and Professor Yoram Palti

Future Demands in Medical Diagnostics

Max Herzberg
President, Orgenics, Ltd.
Israel

Rather than speak about the future demands of the diagnostics, which we do not really know, I would like to discuss the future trends, or the present trends and the future products which are beginning to appear in the market. First we have to understand that in the last few years there is polarization of the diagnostic world. There is a polarization between high volume, highly automated systems, which are supposed to answer to the problematics of big health centers, big hospitals and on the other hand, the bedside and the home testing which is becoming popular. The second polarization is what I would call the wet diagnostic world and the dry diagnostic world. The wet diagnostic world is the "old" immunology, the "old" biochemistry, and the "old" bacteriology. The dry side of it is the new techniques which are the DNA probing and "one step assays" and the biosensors. Future products, which were described by Prof. Sela, include peptides grown on microchips, and may give rise to a completely new way of doing diagnostics.

A new situation has developed in the last few years. The new situation is that we are a health conscious population and the consequence of that is that we want some bedside results. Also, we have cost conscious health authorities. This is very important and becoming more and more important. It means that there are two things which are going to happen. One of them is that we are going toward preventive medicine more than curative medicine. Preventive medicine costs less than curative. That means more and more diagnostics, more and more sophisticated. And then we have a very highly competitive industry. But the diseases are the same for everybody. The edge which is necessary for this industry is very often the technological edge which various companies are looking for. This general situation gives rise to a matrix between the two polarizations. The new trends in diagnostics are dry chemistry: the noninvasive biosensor. By noninvasive biosensor, I mean a biosensor which enables one to measure glucose by putting a finger in a cavity where, by infrared measurement, the concentration of glucose is measured. We are going to see a very high volume automatic systems for wet chemistry, immunology and bacteriology. But we are also going to see, or want to see, high volume automatic systems using dry chemistry.

When we speak about industry, we have to consider markets. If we look into the market research studies in the 80s, we find, for instance, for DNA probing a prediction of one billion dollar by 1990. Today the market is around one hundred million dollars, or one tenth of it. And the reason for the big error of the market studies is that they saw the polarization but they didn't see the matrix effect and the consequences of this matrix.

Very recently there was a big show of diagnostics in Dusseldorf. Of the systems which were there, the Behring system, allows for a very small number of tests, up to 64 tests. So there is quite a big flexibility. It will allow to look for testing where there is one patient or more and the very important fact here is that this is a walkaway system. Walkaway systems are the new trend in diagnostics where you push one button, or two, maximum. The Serono group presented from very small machines to big systems, and again, there was this concept of walkaway and of touch button and minimum use of personnel and of particularly trained personnel which is expensive. Another example is from Vitech. This is an example of "old" bacteriology made on a regular Agar media with various nutrients and put in a walkaway system. This system has no DNA probes or any technological advances, but it is automatic.

Then we have the biosensors. The first industrial looking product, I believe, was presented in Italy by a small Italian company some weeks ago and this is called Immunosense. It has a cone shape and the cone is an electrode, an analyzer plate is to measure the enzyme immunoassay. It measures not by color but by current. If there is strong response, the current is higher. It measures a potential, in place of measuring a color. This is very interesting as this is the first time that we have something which looks like a product. It is not specific for any disease or for any examination. It is a general concept. I do not think it is much better than colorimetry, but we have here the first biosensor appearing in the market. So this is the direction of the biosensors.

The other direction is the bedside testing, the one step testing systems. For instance, an Italian product is for research of the Chlamydia, a sexually transmitted disease. The sample is introduced and the result appears in a window. There is nothing else to do. In reality, when we look into the instructions for use, there are few more steps but not many. It also exists for the most popular one step testing which is pregnancy. Another example is a card: on the card you introduce a drop of urine and then you will see in a window whether the response is negative or positive. Again, there is no other operation to do. These are the three kinds of diagnostic devices which are now being developed: The walkaway system for high volume, biosensors and one step units.

What is the ultimate goal, when we want to get into this new world of diagnostics? Well, it should be a project with the following qualifications: It should have 100% precision. No production costs. Zero time. It should give an immediate answer. One step. Total flexibility. Unlimited shelf life. And High-Tech. High-Tech, because this is what you will sell. This is a kind of difficult goal to achieve. However, one can try to get as close as possible. The 100% precision is almost there. The no production cost, I don't know how to do it. No time does not exist, but you can already go to the minute time. One step – is on the way and we will see it in a moment. Total flexibility – we saw already some systems and some more are coming. Unlimited shelf life – indeed, for all practical purposes, all dry systems have an unlimited shelf life and it is unlimited for all practical purposes, which means one to two years. Hight tech – is a precondition any way. If it is not, you will call it high tech anyway.

I would like to address what we are doing now at Orgenics Ltd. This is a small entity in Yavne which is trying to cope with this changing world in diagnostics and these new

tendencies. I would like to present some of the products that we are putting together. One is the Immunocomb family, which is a very simple way of rapid testing; it has high accuracy because it uses the principle of ELISA. What is the Immunocomb? The Immunocomb is a closed system in which there is a small comb of plastic on which we print antigens to recognize antibodies or antibodies capable of recognizing antigens and then there is a box and in this box, which is covered by aluminum foil, we have all the solutions which are necessary for the development of an enzyme animo assay already dispensed and prediluted. The sample is put in these compartments and then the comb is introduced inside these compartments and then it goes into a wash system, a second antibody system, two wash and then again a substrate and then it gives rise to a color. The system is very flexible because you can cut the comb at any place and use any of the compartments which are there. So today, the Immunocomb exists for most of the infectious diseases. In virobiology we have an HIV AIDS test for antibodies, CHV, rubella and hepatitis B. We are using a surface and not a volume, as in a regular enzyme immunoassay, where one is using a volume. Here we are using a surface and because we are using a surface, we can put two spots one on top of the other and we recognize by the spot which is reacting what is the disease and here, for instance, we are able to recognize the HIV1 and the HIV2 and differentiate between the HIV1 and the HIV2, a very important feature for African countries. Indeed we just got news that this system is now the system that the WHO is going to use.

In bacteriology we have chlamydia, which I already mentioned. Chlamydia is also transmitted by birds and we can recognize the nature of the chlamydia just by the situation of the spot; this is one family of products. The second family of products is the DNA probing family. The DNA probing family is constructed around a system of non-radioactivity labeling of DNA which is called the chemiprobe and which allows to label DNA, even dirty DNA, and this is very important because if you have to separate the cells, clean DNA completely and then do a DNA probing, you are in a bad situation for the clinical lab which in general will not have the capacity to do all this. The DNA chemiprobe system is a very simple system. The butterfly is a monoclonal antibody. This monoclonal antibody is going to recognize a chemical modification of cytosine on the DNA. The way this is done is that you take the DNA and put it in contact with sodium sulphate and then you get a sulfone which is attached on the cytidine; this monclonal antibody will recognize only those sulphonated cytidines which are inside of the DNA, and will recognize only those. Thus, even if you have proteins around or any other things around, this is not very important. Also, this labeling system is totally nonenzymatic. It is a chemical modification. It is just a contact between two solutions for half an hour to one hour and there is no need for any action.

The DNA probes and the Immunocomb family gave us the possibility of putting together two of the elements of the diagnostic which are generally put apart completely. One is the immunoassay, and the other is DNA probing. What we did was to put these two things together in one single object which we call the Hybricomb. The hybricomb is again a plastic comb on which we are going to imprint not antigen to see antibodies or antibodies to see antigens but DNA to see DNA. The hybridization is going to be conducted on exactly the same substance or same surface as the immunoassay. Here we are taking advantage of something that is called reverse hybridization. What is reverse hybridization? On the teeth

of the hybricomb we are going to put a short probe which is unlabeled and what we are going to label is not the probe but the sample. So the sample of DNA is generally much bigger than the actual part of the DNA which can hyridize with the probe. If we have a small probe for a virus, the sample DNA is 50 to 100 fold bigger than the place, than the sequence for the probe. Here we are going to have a hybridization between part of the DNA and the probe but the labeling is going to be on a much bigger amount of DNA and we are going to get an amplification which is not an amplification by PCR or one of these enzymatic amplification technique but physical amplification due to the size of the DNA. We have now two products on this hybricomb system. One of them is for the testing of a very important virus in the pathology of the cancer of the cervix which is the human papilloma virus. Here there are two main risk groups, a "high risk" group and a "low risk" group, and we are able to differentiate between them with the same technique. We have a second product which is very useful for people using cell culture of which we spoke quite a bit today and which demonstrates the presence of mycoplasma in cell culture. This is very important because when cells are infected with mycoplasma then there are troubles.

I will now present a new dry chemistry product, shown here for the first time. There is no such a thing as "dry chemistry." They are always wet. Dry chemistry comes by the fact that the blood is going to bring a liquid which is necessary to the chemical reaction and we succeed in putting together an object which contains a membrane with all the enzymatic apparatus, all the enzymatic reagents so that the drop of blood is going to go in the desired direction and the red blood cells are going to stay on top. Then the serum passes through to a second membrane and a reaction is developing, a color reaction is developing and can be measured by reflectometer. We put this up for cholesterol and for glucose.

But again, we have the three classical elements of the diagnostic world and we have to go one step further. This one step further is to have one step assay and these "one step assays" should have certain characteristics. The specimen could be anything: blood, serum, urine, whatever you want to test. Here we are using the technology that we developed for the cholesterol and glucose testing. The specimen is applied to a pretreatment part of the dry chemistry and then we have some latex beads which contains some antibodies to the element we want to measure. These coated beads have receptors. The receptors are for the same element which is going to be recognized by these antibodies and if this contains the element, let's say HCG, the hormone which we measure for pregnancy, then HCG is going to be trapped. The HCG which is bound is going to attach to immobilized monoclonal antibody, and you are going to have a signal. So this is in the immunoassay. The new elements are that we have a pretreatment, or a group of pretreatment, which allows to look for one step assay not only at very aqueous media like urine or saliva but also in blood.

Because we want to put together the world of immunology and the world of DNA probing, I want to show you another concept which is the DNA probing concept made on the same way. Here we are putting a sample and this sample uses a PCR reaction, i.e. a polymer chain reaction. A PCR reaction occurs when you have two primers, two original oligonucleotides which are flanking the two sides of a gene that you are looking for. If this gene is present in the DNA of your sample, the hole between these two primers will be filled and by a chain

reaction you are going to get a very big number of copies of this field between the two primers. This means that we can get an amplification of 100,000 times, one million times, a very big amplification in a very short time. What if in an amplification reaction, the first primer would contain the sulphone group like we have for the chemoprobe and the second primer will contain another marker like byotine. What we will have at the end of the reaction, provided the gene was present in the DNA, is indeed a complex containing in one side suphone and on the other side biotin, but it will be together. If we use the same device discussed above, then we are going to capture the sulphone because we are going to have a monoclonal antibody which is going to capture all of the sulphone member of this complex. If you have a signal, it means you have biotin. If you have biotin, it means that this reaction was complete and was done by the sulphone. Or, if the gene was not present, the biotin member and the sulphone member are detached; the catcher of the sulphone takes place but the biotin is just passing through, so you will not get a signal.

These were a few words on the "state of the nation" as far as diagnostics or immuno–diagnostics are concerned and, to summarize, I want to come back to the ultimate goals and see how far we are. "One hundred percent precision"? With the DNA probing we are quite close with usual actual peptides from immunoassay. The HIV testing systems in general are around 99.9 percent specificity and 100% sensitivity. "No production cost." We came a long way because the systems are lighter systems as compared with the bacteriological systems which were used a few years ago, and if you use this dry chemistry or this DNA probing system, the cost of production is much lower. "No time." Here we have a lot to do. Because for DNA probing, we are still on an hour scale. For immunoassay, many assays are on the five minute to half an hour range which is more than enough for bedside. "One step." Here we have come a long way. More and more one step assays are being developed using all the fluids. "Total flexibility." Again, even automatic systems are now using a number of samples which are flexible from one through a few tens. "Unlimited shelf life." This is true for the dry system. This is not true for the liquid systems and it is something which we have to continue.

The Medical Element, Genetic Engineering

Marcel Revel
The Weizmann Institute
Rehovot, Israel

It is a hard act to follow Max Herzberg who gave such a broad and futuristic view of the field of diagnostics. I hope that between my talk and Dr. Yoram Karmon, the director general of Interpharm, you will hear some of the science and some of the future. I will dwell mainly on the more down to earth science and medical testing that we have done in a field of biotechnology which uses genetic engineering, in particular for the purpose of producing a substance called cytokines. Cytokines are mediators of inflammation.

Consider the host defenses that we have, for example against virus infection. If you have a cell that is infected by a certain virus, the cell will react by producing a group of proteins, one of them is interferon beta. There are other types of interferons and this interferon will defuse in the tissue to other organs to alert cells which have not yet been infected that a viral infection is going around. By interacting with receptors in the cell surface, the cell is able to produce biochemical and genetic change in the cell which result in protection against virus infections; the replication of the virus that will try to infect this cell will be prohibited.

We also have other ways of defending ourselves from viruses. We all know that microphages are able to pick up viruses, and present them to the immune system, in particular to the lymphocyte which eventually lead the lymphocyte to produce antibodies. In addition we have what is called a complement system which, together with certain toxic lymphocytes attacks the infected cell and destroys it. That's very important because when we have a virus infection, it is not enough to inhibit the virus but it is important also to destroy the virus infected cell. When you cannot do so, you get chronic disease like hepatitis A. So we have been interested for many years in chemicals like interferons that mediate the activation of some of these processes and, in the Weizmann Institute, we have cloned a number of them. I will talk today mainly about interferon beta, which is part of the interferon family, and acts mainly by viral and cell growth. Note that interferon not only attacks virus growth but also the growth of tumor cells. Other compounds which are in their development include an antagonist and a monitoring system for the 2'5' acetate, one of the enzymes induced by interferon itself, and protects the cells against the viruses. To those who are far from the cloning – a word on what cloning actually means. If you have a human cell with a human gene that you can identify one way or another, and a bacterial cell with its DNA, you can introduce the piece of the human gene into the bacterial DNA. This recombined DNA is now introduced into the bacteria and the bacteria is able to produce a molecule which this gene was normally producing when the interferon was introduced and you can develop a system

to produce large amount of the desired protein. This biotechnological approach, which dates from about 15 years has brought many products to the market. Companies like Genotec and others have developed many products using the bacterial collection systems. Like interferons, TPA, insulin, etc.

The bacteria produced proteins which are used in humans make problems. Bacteria do not glycosylate protein while many of the proteins in a human body are glycosylated. Non-glycosylated proteins are active, they actually produce antibodies or produce other problems. And there is a recent interesting turn of event: a few hundred patients who have been treated by bacterial insulin have now sued the company, especially Lilly, because they developed antibodies. They did not have antibodies when they were using natural insulin. Therefore, we thought that it would be very important to produce the human proteins in a way which would be very similar to their natural state. This was done by using mammalian cells, in particular the Chinese hamster ovary cell, to produce these proteins.

Many years of work characterize a product, including toxicity testing and activity tests in animal systems. Only then can you hope to bring the product to the market. This is the technology which is presently being used and developed at Interpharm for many its products.

Let me now describe briefly where we are with human fiberblast interferon and where the world is with interferon in general. As you know, interferon was the first biotechnology product and it really helped the whole biotechnology industry to prove that it was viable. Interferon is being applied essentially in two types of therapy: virology and oncology. So first look at some of the virology applications. There are some typical applications of interferon which we find interesting. We have especially studied its use in herpes simplex. It affects a significant reduction in the rate of recurrence of the disease and this is the most important point because there is no other topical treatment of herpes that can give a reduction in the recurrence of the disease. Recently, we saw a decrease from 10.3 to 3.5 recurrence per year while the placebo group showed a slight but insignificant change.

Some eye infections and genoviruses can also be treated, but this is not a very major application. In combination with antiviral diagram, interferon helps to treat herpes which is a major eye infection. Systemic use of interferon is the most important one. This has found a field of application in a specific virus infection which can be associated with the development of cervical cancer, so it is important to treat lesions and not to leave them alone. Another type of lesion caused by popula myovirs is associated with a very painful infection of the vagina. So this group of diseases are now treated by interferon with a rather high percentage of response in the patients; about 60% of the patients eliminate their popula virus after interferon treatment.

Another area where interferon is being used more and more is chronic hepatitis, mostly of the B type and C type. Hepatitis C very often causes chronic hepatitis and it is very satisfactory that interferon can reduce the liver damage by this chronic hepatitis. Promising results can be obtained in asymptomatic HIV infection. These are AIDs patients that have not yet

developed symptoms of the disease and the virus can be decreased or even eliminated. This opens up many hopes to bring positive patients back to a negative state.

Now, on the effect of interferon in cancer: There are five ways by which interferon is thought to act on cancer cells. One is by blocking the proliferation of cells. This is actually the cell cycle and interferon is able to slow down the cell cycle, the growth of the cell. Second, it blocks the expression of oncogen. As you know genes are mutated in our geno and are following cancer cell. Sometime the gene is over-expressed and interferon can inhibit its expression. A third way by which it can work is by causing the cancer cells to return to their normal behavior and this has caused differentiation. And a last way is by activating lymphocytes to kill the tumor cell. So there are different ways by which interferon can affect tumors. Does interferon have any effect on human cancer? Hairy cell leukemia was the first human disease in which more than 90% of the patients were shown to respond to interferon by having complete elimination of the leukemic cell from their blood and none was complete in the bone marrow. Today there are better treatments for leukemia. It is an anecdotal disease for interferon but it is still the first time that it was shown to be really active in human disease. A major disease that is treated by interferon today is chronic leukemia which is one of the major forms of leukemia. These responses are not always 100% and if interferon helps in this cancer, it is not the universal panacea. I believe there is no panacea for any disease and eventually we'll have to have combinations of interferon with other drugs. The point is that interferon is used today for a number of human tumors.

Let me now shift to a new cytokine which we are studying, Interleuken-6, a product which is under development at Interpharm. It is a major negator in the response to infections and inflammation. And being a major mediator of inflammation, it activates many of the physiological response. For example, every time we have a viral infection or a bacterial infection, any shock or accident, our liver stops to make albumin and starts to make mini-proteins which are needed for the physiology of the body to recover. This is one of the functions of Interleuken-6 which is produced when there is an aggression. It goes to the liver and activates the liver cells. It activates the immune system to produce antibodies. It activates lymphocytes to kill cells and actually it does a host of activities, the important one being to change the phenotype of malignant cells to a more normal phenotype which we call differentiation. We have tried it in acute milo leukemia because it can cause differentiation of the leukemic cell and in a study with Professor Slaven in Jerusalem, it was shown that if you needed transplantation of the acute milo leukemic cells in mice, you can inhibit the progression of the disease. With Professor Nechama Geller at the Weizmann Institute, we were able to show that it blocks the natural leukemia which is endured by radiation. The type you got after Hiroshima. But this is in mice again: You can block the formation of this leukemia. And we are very optimistic for this one application.

Some experiments indicate that Interleuken-6 may have a potential in preventing metastasis which is the main cause of death from cancer and the primary cancer is less danger than the metastasis developed later. Interluken-6 shows a complete decrease in the metastases of melanoma in mice. The control mice had a high number of metastases at three months while the Interleuken-6 treated animals showed a complete inhibition. There is another Interleuken,

Interleuken–2. It is not active in this model but it is active in other models. Interluken–2 is nearly toxic but fortunately Interleuken–6 does not seem to be toxic. With the melanoma, 60% of the mice survived for a long period of time whereas the control died. With carcinoma, where there are many metastases, we saw an increased survival as compared to the control. But still this was not good enough for what we wanted to do.

We are now developing, with Professor Feldman, what is called a tumor auto–immunization. We have found that we can take cancers in the mice which are resistant to Interleuken–6 and we can make them react if we give Interleuken–6 together with a tumor cell. One of the reasons that cancer can grow is because it escapes the normal detection by the immune system. Take, for example, a biopsy of a tumor and mix it with Interleuken–6, or use a gene therapy type of experiment in which you transform the cell by producing a gene, and then take this cell, irradiate it to kill the cancer cell and use it as a vaccination for the animal in which the tumor is growing. You will observe that even with a resistent tumor, there is no metastasis. If you follow the current trends in cancer research, this is one of the most modern approachs which use the immune system to boost it by the tumor cell, not by the lymphocyte or other cells which have been used in the past, using the tumor cells themselves as a vaccine seems to be the best approach, at least at the present time.

Interleuken–6 also has a strong effect on thrombocytosis. It increases the platetlets and it can be shown that in animals which are normal, but with a decreased activity of the bone marrow following chemotherapy, after radiation, Interleuken–6 can be used to increase the platelets. This is a major problem in chemotherapy today. Interleuken–6 seems to be acting for the platelets.

What do we want to achieve? Classically, in cancer, the approaches are: surgery, radiation, chemotherapy. Chemotherapy is effective, but it gives many side effects. The new approaches which we are trying to develop are to use of self–regulatory cytokines like interferon and Interleuken–6 and others which are also called, sometimes, biological modifiers and which together with immune approaches like monoclonal antibodies to the tumor, will be able to activate the natural immune defense system. I believe that what we are seeing is a futurist trend. Moving from the classical chemical industry, chemical based drugs, to drugs based on agents which are normally found in our body but which are, maybe, lacking in quantity and which we can affect thanks to the biotechnology processes related to.

State of the Art, Research & Development and Marketing: From Concepts to Products

Yoram Karmon
President
Interpharm, Inc.

Biotechnology seems to be growing very fast: it is now somewhere in the range of two billion dollars in business, and rising (Fig. 1). It is indeed a combination of many factors, but it does show a trend. If such is the potential, where is the problem? Generally, the problem is that it takes a lot of time and money to develop a drug. The characteristics of the Biotechnical Industry are summarized in Table 1. Take ourselves as an example. We started with Michelle Revel in the Weizmann Institute. This was referred to here earlier as a concept. It was a lot more than a concept. It was an invention. It went on to a patent. It was a kind of core technology. But still in front of us was a 12 year project with an investment in the range of 200 million dollars. Nor was this all of the problem. I would also say that special expertise was required in order to go through this Via Delarosa and reach the market.

What, then, is the answer? The answer seems to be a different one in each case. In our case, here in Israel, we found a strategic answer, Fig. 2. This answer consists of three different forces that we have combined in the hope for success. First was the infrastructure in Israel, the academic world, the Weizmann Institute, more specifically, Michelle Revel's lab and Professor Revel himself. This is where it all started. Then there is the innovation and the capability of InterPharm to take the core invention and turn it into a developed product which can be presented to someone outside of Israel, someone with enough force to go through the regulatory barrier, to register the drug all over the world, and, in due time, to market it. To give you the picture, let us start from the end. Let us start from our marketer. Our marketer is ARES-SERONO, a worldwide marketer with operations headquarters in Geneva and Boston, and the executive headquarters in Geneva. It is in part a publicly traded company. Serono is not a big pharmaceutical company. As a matter of fact, it is a small pharmaceutical company, ranked somewhere around the 40th in the world, with a turnover of 650 million dollars last year, and a nice profit of 64 million dollars (Fig. 3). The difficulties arise from the fact that it is a very fast growing company. Serono originally started with fertility hormones and is still very much an OB-GYN related company. You can see here a change in the international company effected by the developments in Michelle's lab and by our own activity. We influenced the large company and changed its attitude towards our own product and towards the immunology products in general, which are increasing in the Serono basket (Fig. 4).

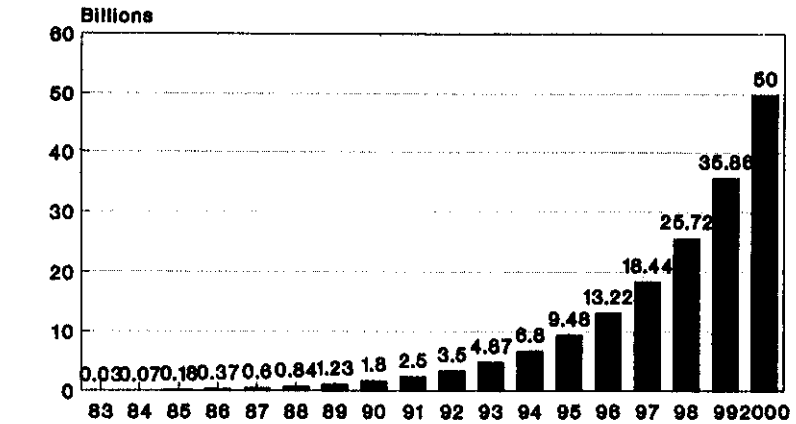


Figure 1: U.S. Sales of Biotechnology, 1983 - 2000.

Table 1: The Characteristics of BioTech Industry

- A large number of reserach organizations that lack financial and marketing resources
- The long period of time (10–12) years and resources ($200 M) required to bring a product from the lab. to market.
- The importance of securing patents in large and profitable secured markets.

RESULT IN

- Marketing alliances between small BioTech firms and large multinational business organizations.

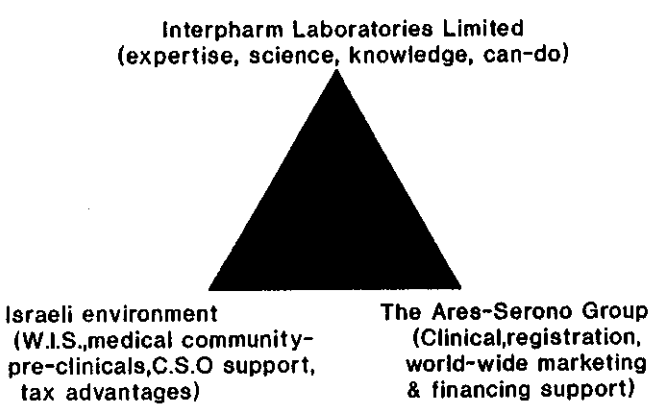
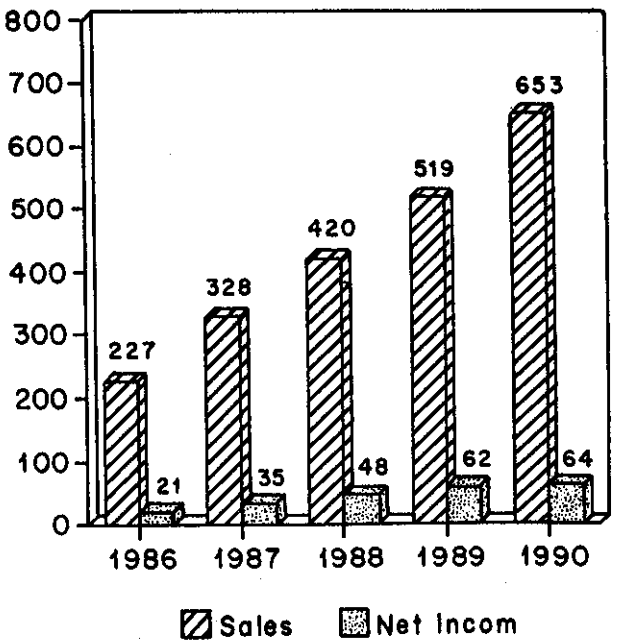


Figure 2: InterPharm's Strategic Advantages

Figure 3: Ares Serono sales and net income for 1986–1990.



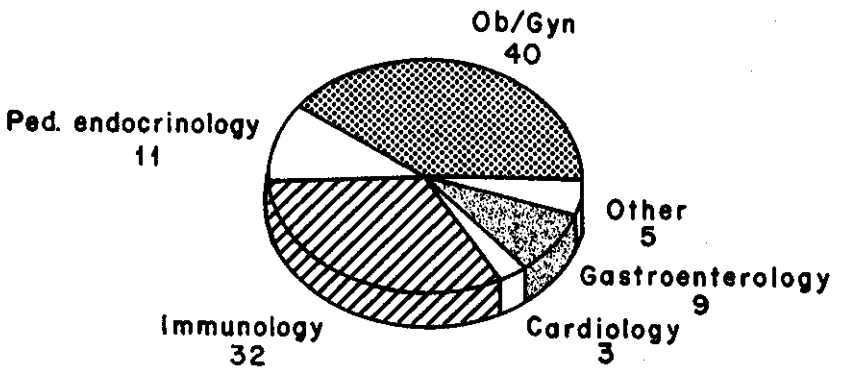
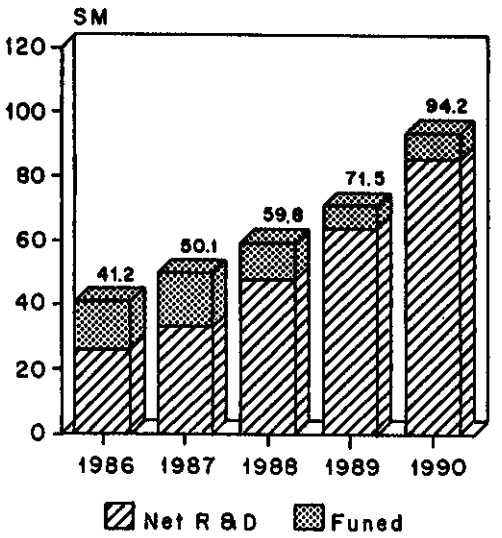


Figure 4: Pharmaceutical sales by therapeutic field (%).

Serono is mainly a European Based Company, as most of the sales are in Europe, but it has an international attitude, a 100 million dollar company in the United States and a rapidly growing venture in Japan. The success of a drug is measured by indication and geography. Geographically, a multi–national endeavor should be effective in three locations – Japan, the United States and Europe – where people, or governments, still pay for drugs. The impressive part of Serono's activity is its high investment in R&D (Fig. 5). The amount funded by the different governments, is becoming smaller and smaller with time, because the bulk investment is in the clinical trials where the company has to finance most of the development. InterPharm is a Science–Based Company, big enough to be called a leader in biotechnology in Israel. At the moment, we are already selling one product in the market, mostly in Italy, but entering markets in other European countries as well. This product is Native Beta–

Figure 5: The Ares Serono Group, Research and Development.



Interferon, a drug used for viral diseases and different cancers as Michelle Revel has just described to you. It sold for around 90 million dollars in the market this year. InterPharm is also a publicly traded company in NASDAQ with a turnover of 25 million dollars last year. In the first three quarters of this year, we have already reached the same level. The Company is profitable, a surprising fact for a biotech company, but true. Behind its success stand in part, luck, and, in part, the proper development of the drug.

Our R&D expenses are quite high in proportion to the size of the company. Again, the amount funded by the government of Israel is becoming smaller and smaller all the time. It was 35% last year. At the same time, the company invests more and again, for the same reason: the more you go into development, the less the government will finance you.

What do we have in the market and in the pipeline? We have Native Interferon or, what we call human fiberblast interferon. We have to walk almost all the way to the market, from discovery, through isolation and analytical methods, which should be applied in order to reach a level where you can describe and identify and characterize the drug for the physicians. We had to work on process development. Dr. Avinoam Kadouri can tell you a lot about process development in InterPharm. We had to go through the process validation to make sure the process development is properly done. Then we worked on the construction of the plant in order to reach the right scale for the market. Then comes registration and marketing. You can see a pipeline here. However, this drug is limited because of the human cells used to produce it, and the difficult control mechanisms. Those are very spoiled cells, very difficult to handle, and very difficult to control scientifically, managerially or administratively. For these reasons, we developed a Recombinant Beta–Interferon, with which we have made a lot of progress. We are now in the stage of clinical trials all over the world and we are constructing a large production plant in Israel for the drug to be supplied to the rest of the world. We are past discovery, isolation, bioactivity bioassay and process development. Hopefully, very soon, you will be able to see this drug registered all over the world. It is considered to be a blockbuster. A recent financial analysis shows a potential of a few billion dollars per year. In the pipeline,

we also have TBP, the TNF binding protein, a potential drug that can be used for septic shock indications and again, with a huge potential.

Let us examine how money was spent with time with regards to projects. Looking at the years 1988 to 1991. In 1990, no R&D money was spent on Native Interferon. On the other hand, the Recombinant Beta–Interferon took a lot of money but reached a peak somewhere in 1990, decreasing already in 1991. At the same time, Interleuken–6 is becoming the leading R&D project. Later will be growing R&D expenses on TBP. The number of other drugs is decreasing as well, since with the maturity of the company, we are more selective in choosing drugs to invest in, so that we have less drugs, but hopefully successful ones.

The success of InterPharm can be attributed to the people who work with the company. Manpower is growing, but very selectively. We are at the moment in the range of 230, growing to 280 by the beginning of next year. The growth is mainly in Operations and Quality Assurance where we believe the most important effort should lie. We try to keep administration as low as possible, so as not to load the company and not to spoil it.

The investment pattern (Fig. 6) is perhaps the most interesting part of our activity. You can see a huge jump in 1991. This is not spending. This is money invested in transferring an R&D company into a commercial company, which has to face audits from FDA in the near future. There is no other way but to invest a lot of money in order to reach the level of international standards and face the globalization and stratification all over the world. I believe this process is going to be crucial to the survival of our company. Our proportional investment is well justified, based on the high criteria required in order to reach the international level.

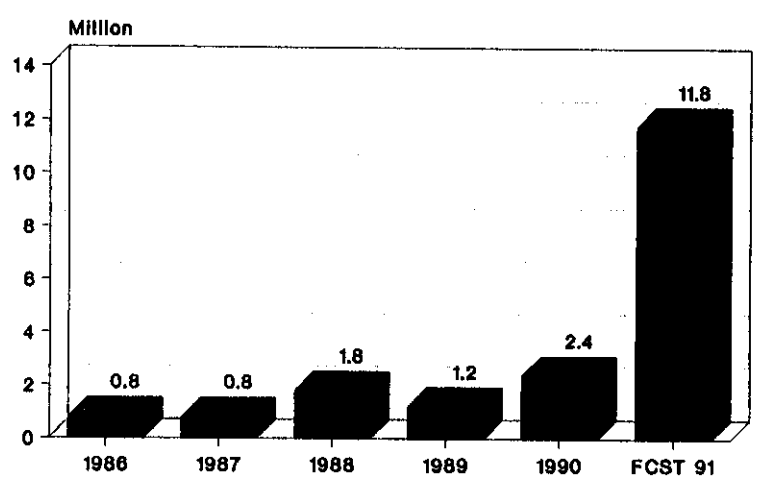


Figure 6: Capital Investment from 1986 to 1991.

If you ask what is the combination, what are the ingredients needed for an achievement like ours – it is again the triangle of the Swiss company, the Weizmann Institute and an Israeli typical company. It took a lot of patience, a lot of understanding, communication, some global culture, a lot of, group culture, a realistic sense of proportion, and a good sense of humor.

Open Forum

Chairmen: Professor Michael Silberman and Professor Samuel Sideman

Computerized Storage of X-Ray Pictures

Eliahu Antebi
Department of Surgery
Beilinson Medical Center
Petak Tikveh, Israel

I am going to speak about storing X-rays, the pictures and not the data. The idea of electronic storage of X-ray images was first introduced with computerized axial tomography, CAT scanning, in the 1970s. The pictures are stored as digital information on disk or diskette. In newer modalities of digital subtraction angiography and nuclear resonance imaging, the DSA and MRI increasingly spread this technology into our routine medical world. However, the images are still usually converted into hard copy on X-ray film for storage and retrieval.

Research today is directed to changing from the old familiar X-ray machines and archives to computerized systems. Storage of pictures will be in the digital form and images will be displayed on television screen at a touch of a button, rather than on celluloid on X-ray screen. These systems are known as PACS: Pictures Archiving and Communication Systems. For most of us, however, these sophisticated computerized system are some way into the future. In the meantime, we are left with the familiar problems of conventional X-rays, their storage and their availability.

We at the Ichilov Hospital have embarked on a project aimed at the storage of existing X-ray celluloid film pictures on a simple personal computer. We were fortunate to have the cooperation of an engineer with the knowledge of the method of storage and improvement of pictures taken from unmanned, small aircraft or drones which are used for military reconnaissance purposes. The pictures are viewed on TV screen and sophisticated software is used to enlarge and enhance the quality of the picture to the greatest possible degree. On the basis of this experience, we have developed a system in which an ordinary X-ray picture on conventional film is photographed by TV camera or scanner. The image is stored in digital form on an optic disk and can be retrieved and processed using a personal computer and a television screen. The actual image on the monitor is black and white. Using our system, it takes less than 30 seconds to store an individual X-ray picture on the computer. Retrieval and display of the image also takes 30 seconds. We can now process the image of the arteriogram by selecting the appropriate modality. The image processing menu has wide options – window definition, contrast enhancement and so on. The window can moved around on the screen by using the computer mouse attachment, and its size altered. The zoom modality enlarges the pictures two and a half times and using the mouse we can turn to the area of special interest to us. We find the added definition of enhancement especially useful when looking at the carotid bifurcation.

The computer program allows rotation of the image in one plane and a mirror image as well. A further option is a split screen which shows four pictures side by side allowing easy comparison. The system can be applied to all kinds of X-rays. The television camera can take an enlarged picture of an original small X-ray such as a CT scan. The camera can also record any text and the system application could be widened to include, for example, electrocardiograms. A further option available on the image processing menu is the artificial color modality in which the gradation of grey are assigned different colors by the computer program. Pseudocolor helps to enhance graphic information.

In conclusion, we now have the ability to archive an X-ray and to retrieve them within seconds as and when we need them. Each optic disk can store up to 1400 pictures. If more expensive hardware were to be used the storage can easily be enlarged. Our system is based on an inexpensive IBM PC XT compatible computer. We hope that the system will be widely used in the future replacing prolonged searches through dusty film stores for pictures which can never be found when needed.

Development of a New Biodegradable Vascular Graft

Gideon Uretzky
Hadassah University Hospital, Jerusalem
and
Lady Davis Carmel Hospital, Haifa
Israel

Cardiac surgery is coupled intensively with technology and engineering. Only 30 years ago, the medical field of cardiac surgery did not exist at all. In 30 years, due to the development of heart–lung machine, artificial valves, assist devices, etc., the field developed to such an extent that coronary bypass is nowadays the most frequent major operation performed in surgery. I would like to demonstrate here one development which is clinically oriented and how it stemmed from a clinical problem.

Arteriosclerotic heart disease is now the number one killer of the western world and this is due to the process of arteriosclerosis in blood vessels, mainly in the heart and brain, necessitating the development of artificial blood vessels. I would like to focus on one aspect in the field of congenital heart disease. There are few anomalies that need repair. There is one kind of repair which is intracardiac and another one that cannot be corrected intracardially and therefore should be repaired by an extracardiac conduit. For example, in pulmonary atresia there is no outlet for the right ventricle. In order to solve this problem, one has to connect the right ventricle to the pulmonary artery by a conduit which conventionally is made of Dacron. In another anomaly, called truncus arteriosus, where only one vessel stems from the heart instead of two vessels, the repair is performed by the use of extracardiac conduit. In tricuspid atresia, where there is no tricuspid valve, one should connect the right atrium into the pulmonary artery and by that maintain the continuity of the circulation.

What is the fate of these grafts? During the seventies, conduit operations were very frequent but after a few years most of the children came back with obstruction of these conduits, necessitating repeated operation. The Dacron which we use in heart surgery is very tightly woven Dacron, impermeable to blood, because during the operation heparin is used for anticoagulation. With time, a thick peel is formed; this peel is dissected from the conduit because of lack of incorporation and slowly it obstructs the lumen of the graft. So, all these children, after, four or five years, have to be taken back to surgery and another conduit had to be introduced. The question is how to solve this problem. When we X–ray this conduit, we see calcification in the area of the valve. This is an obstructed part of the conduit. Looking at histology, we can see a thrombus formation dissecting the peel from the conduit. So, clearly, the prosthesis is not incorporated well in the body and one has to find a solution.

The question is how to develop a conduit which will be impervious to blood in implantation but will be porous at a later stage so that tissue can ingrow into this conduit and incorporate the graft. So our concept is to find a way to have a minimal intraoperative loss with high healing property. The idea is to take a porous graft, such as knitted Dacron or other such graft, and to coat it with a material which will impregnate the graft but will be biodegradable with time. With time, the material is dissolved by the body and tissue can grow and incorporate into it. What do we require from such a material? It should be biocompatible. It should be compliant. It should have by itself appropriate mechanical properties. The timing of degradation is very important; if the time of degradation is too long, tissue will not grow into the graft and we will have the same phenomenon of dissection and obstruction. Also, the products of the degradation should be non-toxic.

One such type of material which we have developed, PELA, is an alternative to polymer. The compliance of the material is much closer to the natural vessel than the conventional Dacron. We implanted the coated PELA graft in animals as a right ventricular to pulmonary artery conduit. We kept the dogs for one year. In one group, the tightly woven Dacron was implanted and in the other group we implanted the coated PELA graft. Inspection of the results show that the graft is impervious to blood in implantation. The field is dry. After one year there were three thrombosed grafts out of seven in the woven graft. There were peel detachments in five out of seven. In the coated graft group, there was no thrombus and there was no peel detachment at all. There was full incorporation. The pseudo-intima is thin, glistening, without any thrombus formation. The ECM study of the woven Dacron graft shows no incorporation whatsoever. The pseudo-intima is completely detached from the woven Dacron and between them one can find thrombus formation. On the surface, one can see fenestration, and through this fenestration there is dissection of the pseudo-intima obstructing the graft. When we look at the coated graft, we see full incorporation and hardly distinguish the graft itself. Tissue grows between the individual fibers which we didn't see in the woven graft. We have checked the force which is required to separate the pseudo-intima from the graft. In the coated graft, we could not separate it by any force.

The more critical performance of the vascular graft is expressed by the patency of the small diameter graft, less than five milimeters. In those grafts, we cannot use the conventional method. The small diameter grafts tend to thrombos and obstruct very early.
One possibility to overcome these obstacles is to develope a graft by different methods from those we are used to, not by knitting and not by weaving, but by the use of composite materials, using the process known as filament winding. In this filament winding technique, we use fibers from degradable and nondegradable materials composed together, and this is the only way that one can produce a graft with the same mechanical properties as a natural vessel. By changing several parameters, the angle, and the quantity of different materials, we can get a graft with good elasticity, compared with conventional grafts used today for small diameter.

The conventional graft was implanted in the carotid arteries and compared to the gortex graft that is the most widely used graft today for small vessels. You can see that there is thrombus formation on the surface of the gortex graft. The intima is quite thick. In the filament graft

one can see that the intima is transparent. You can see the structure of the native graft through this intima. This filament graft that we made is incorporated in the body. Again, the gortex graft shows separation of the intima. Here you can see the filament wound graft with the penetration of tissue into the graft. This filament winding technique is one direction for the future, to manufacture a graft which is made in different ways by a composite material technique. The future lies in the development of hybrid prostheses.

The best result that one can achieve is with a live graft: you can take a small diameter graft and coat it with live endothelial cells that can excrete prostocycline, and a thrombosis will probably be prevented. We have developed a process to coat regular grafts with extracellular matrix. We put implant corneal cells on gortex. This is done by tissue culture technique. After two weeks, one can scrape all the corneal cells and get a graft which is completely covered with extracellular matrix. The extracellular matrix attracts endothelial cells. And when we just put it in an endothelial cell environment, in tissue culture, one can see that all this graft was covered with endothelial cells. I believe that a combination of good mechanical prosthesis as a hybrid coated with extracellular matrix with endothelial cells could be the answer for the future of small diameter grafts.

Concluding Remarks

Concluding Remarks

Uzia Galil
President, Elron Electrical Industries
P.O. Box 1573
Haifa 31015 Israel

We have gotten a glimpse of the limiting factors, in addition to the scientific ones, regarding the challenges to improve our standard of living. The biggest task is to combine this major scientific development, the technological challenges with the capability to reduce cost. Give the best for the least in cost and this is, I think, what Elscint has done.

Imaging in medicine is only one area of imaging. We should all be aware that in this country not only imaging for medicine is a highly developed discipline. Imaging in general, starting from basic design or basic components to applications in industrial, military and many other areas, is highly developed. One of the major strengths of the society, from science to industry is in the field of imaging.

This country and this society's survival depends very much on its capability to be creative, to be innovative, and to be up to the challenges of the world. What we have seen in Japan and in the Western world, shows us that if we do our job right, we can be one of the focal points that will combine science, technology and industry in an effective way.

International Workshop on Interaction Between Medicine and Engineering

Prof. D. Weihs, Mr. Y. Ofek, Prof. Z. Tadmor, Prof. M. Sheinfeld

Mr. E. Hurvitz, Prof. S. Sideman and Prof. M. Silberman

TECHNION — ISRAEL INSTITUTE OF TECHNOLOGY

THE S. NEAMAN INSTITUTE

FOR ADVANCED STUDIES IN SCIENCE & TECHNOLOGY

TECHNION CITY, HAIFA 32000, ISRAEL . TEL. 237145 / 292329 . FAX 231889