האקדמיה הלאומית הישראלית למדעים
ACADEMIA SCIENTIARUM ISRAELITICA

ISSUES IN SCIENCE POLICY

Proceedings

of an International Comparative Workshop:

Strategies for the National Support of Biomedical Research

Jerusalem, December 2-3, 2009
at The Israel Academy of Sciences and Humanities

Workshop Sponsored
by The Israel Academy of Sciences and Humanities
and The C.H. Revson Foundation

Issues in Science Policy

Proceedings of an International Comparative Workshop: Strategies for the National Support of Biomedical Research

Proceedings

of an International Comparative Workshop:
Strategies for the National Support
of Biomedical Research

Workshop Sponsored by
The Israel Academy of Sciences and Humanities
and The C.H. Revson Foundation

Jerusalem, December 2-3, 2009

Ruth Arnon and Alex Keynan

Co-chairpersons

Irvin Asher

Chief Editor

The Israel Academy of Sciences and Humanities

Jerusalem, October 2010

In memory of

Dr. Irvin M. Asher z"l

Science Policy Advisor and Science Editor

Devoted Zionist, Friend and Scholar,

who passed away during the preparation of this publication

ISSN 1565-9070

Preparation for Press: Dr. David Friedman, Avital Baer

Design & Production: Studio Amitai

Printed in Israel

Table of Contents

Opening Remarks and Greetings

Prof. Menahem Yaari

President, Israel Academy of Sciences and Humanities

We are delighted to open this Conference on the National Support of Biomedical Research and what can be done to reinforce it. We are particularly grateful to our distinguished guest from many countries; and we are convinced that this conference will help lead to a better approach to funding Israeli biomedical research than our present one. There is much to be done to better support biomedical research in this country.

This December also marks the beginning of the Israel Academy of Sciences and Humanities' 50th anniversary. So this important international workshop also helps mark our Jubilee.

The immediate context of this gathering is a report issued by a distinguished Academy committee, chaired by the Academy's vice-president, Prof. Ruth Arnon, about six months ago, which proposed ways to reinforce Israeli biomedical research, based on their detailed analysis of the current situation. That report also marshaled the efforts of experts from all over the world via visiting committees.

Total Israeli government-financed support for competitive basic research grants (all fields) has grown substantially in recent years, but it's still only about $65 million a year. In the United States, a country with admittedly about 50 times the population of Israel (and about 60-65 times the GDP of Israel), the total federal government support for such basic research is about (after recent special additions) on the order of $65 billion. That is, a country that is fifty or sixty times the size of Israel spends a thousand times as much on such basic research than we do. That's one indication of the relative position of basic research in the general priorities of these two countries.

The situation in biomedical research is even more bleak. The United States has a separate, well-funded National Institute of Health (NIH) specifically devoted to biomedical research, whereas, in Israel, biomedical research is just one field within the Life Sciences Division of the Israel Science Foundation (ISF), and its resources are quite limited.

A related issue, now being discussed in Israel, is the status of intellectual property derived from biomedical research in governmental hospitals. The draft legislation now before our Knesset seems seriously outdated. Currently, the State is the owner of such intellectual property, which severely hampers innovation. Perhaps this gathering can address that issue as well.

MK Meir Sheetrit

Chairperson, Science and Technology Committee, Knesset

Biomedical research in Israel has a very bright future, but a very cool present. We need, in my opinion, to invest much more in this area, especially for academic researchers. Today their main budget comes from the Israel Council for Higher Education; very little such funding exists in the Ministry of Health. This is a far from satisfactory way for Israel to realize its full potential. One of the major recommendations of the Committee headed by Prof. Ruth Arnon is to create a new, independent biomedical fund, with an annual budget of at least $100 million a year. I agree with that.

I think that is what we should do; and I don't think that we need to look for different sources of money. The money exists, it is simply being spent for different purposes by the government. In my opinion, that is not the right approach. This year the budget for the Chief Scientist of the Ministry of Industry and Trade is about $350 million. This money goes mainly to industrial R&D. I believe that the government's job is to look much further ahead. The government should not be funding industrial R&D at this level. It is more important to use $100 million of that money for more forward-looking basic biomedical research. Industrial R&D can find different money, the considerable venture capital which exists in Israel. They are actively looking for opportunities which can provide more short-term returns. The Israeli government is allocating almost the same amount – about a billion shekels a year – for applied industrial R&D. I recently read in The Marker, which belongs to the Haaretz group, research on the effects of the government funds given to different industries. It showed that the areas which got those government grants did no better than other areas which did not. That is, those government grants made

no difference. In my opinion, therefore, the government should establish the proposed biomedical research fund, because the potential for long-term gain is very, very high. Government support will matter since, as you know, biomedicine and biotechnology can take many years to pass from basic research to industrial R&D to a product that you can hold in your hand.

In my opinion, what is going on today in biomedicine approaches science fiction. It can dramatically change the lives of so many people for the better. Not only by giving us longer life expectancies, but also to giving us better lives, and curing many problems that now seem intractable. But it needs money to do it.

It is very hard when we see, as we do today, that many Israeli scientists must go abroad to do their research. The United States, as Prof. Yaari said, spends $65 billion a year on health-related research, so the area is much larger there and Israel's brightest scientists go there, while we lose their potential contributions to new Israeli technologies and projects. Basic research has long brought Israel research-based products that have created huge revenues for both Israeli industries and for the State of Israel itself. Prof. Sela and Prof. Arnon could cite Copaxone, based on their own research, as a very good example of this. So we must do something about this.

I'm going to initiate a discussion of the Arnon report in the Committee for Science and Technology in the Knesset. I'm going to do it. I think it's very important to do it. And I'll involve the relevant people, including in the Ministry of Finance, in order to effectively discuss this area. As a past Minister of Finance, I will have no hesitation in changing this allocation of existing money, even without new R&D money being added to the budget. I think this is much more important than giving all of this money to industry, which has a very strong, well-developed lobby (which makes life hell for every government

which tries to reduce this kind of money!) I don't suggest reducing the money needed to eventually best help new Israeli industries; I suggest channeling it differently to better help us all. We will find a way to support this kind of science which, in my opinion, is real science for the near future.

I read the Arnon Committee's report with great interest; and I decided, even before coming here, to initiate this discussion in my Committee. I wish you great success in these two days; and we hope to learn from you and your colleagues from abroad, because we don't have to reinvent the wheel from scratch every time. We can also learn from the experiences of others.

I'm sorry to say that today, when I leave here, I'm going to present a bill in the Knesset to give independence to the Israel Academy of Science and Humanities; and I wonder about the position of our government on that. It should be self-evident. I was just speaking with Prof. Harvey Fineberg, President of the U.S. Institute of Medicine in Washington to learn more about the corresponding position of the United States. We can learn a lot from such comparisons. The U.S. Institute of Medicine is, as a matter of fact, independent; and it can scientifically and objectively advise Congress, the government, and the national academies in areas in which, sometimes, politics cannot work. One example is advice on stem cells, a big U.S. political problem in the United States that requires considerable scientific insight and advice. The U.S. Institute of Medicine is completely free to put forward its own stance. We need something like that.

My dream is that, in Israel, we will also have an Israeli NIH that will make similar recommendations and science-based policy suggestions to the Ministry of Health, and to the government as a whole. This could be done inside the Academy, if it has the money, opportunity

and independence to do it. I want to assure you that I'll fight for this Law, and really try to pass it. If it doesn't pass now, we will submit it again and again until it passes, or until we change the government, and then we'll pass it.

Prof. Manuel Trajtenberg

Chairperson, Planning & Budgeting Committee of the
Israel Council for Higher Education

I think we should start by asking, "Why do we have to single out biomedical research for special government support?" After all, in both science and industrial R&D the Israeli government usually has an explicit policy of neutrality. We don't pick winners, we let demand and quality set the agenda. Scientists come to the Israel Science Foundation and ask for grants in all fields. Why take concerted action to support his particular one? The generic answer is that we should take such action whenever we identify a latent comparative advantage in a particular field, but there are specific obstacles that prevent that advantage from manifesting itself in practice. That is the case with biomedical research; but the case needs to be argued carefully and precisely before we can talk about strategies.

What are the indications of a latent comparative advantage? First, Israel has a very good scientific base in the life sciences. We have young and eager scientists that are intimately connected with the U.S. scientific community; they thrive in it, and many of them end up there and not here. That is something that we have to deal with. Young Israeli scientists also have an interesting quality called "chutzpah," the ability to say, "Hey, you know I'm going to do it, even if it is an incredibly difficult problem!" That is really quite an asset.

We have a good healthcare system (although we Israelis have a big problem acknowledging that anything is good here). We have several excellent hospitals and medical centers. We have a thriving high-tech sector, with spillovers to biomedical research in such areas as bioinformatics. We have a highly diverse population that

constitutes an incredibly interesting laboratory for medical research. It's very hard to find another compact country with that level of genetic diversity. Our HMO's, the Kupot Cholim, on which the healthcare system is based, have developed (over the last twenty years) computerized medical record systems. We are so used to them that we barely notice them; but in the U.S. that is just becoming a big issue (we can certainly contribute to that effort). Thus, without our paying much attention to it, we have created a highly valuable database that consists of the medical histories of seven million people over fifteen years. In my view, that can turn into a national asset for promoting medical research all over the world. There are not many countries with such a valuable data resource. We have one big pharmaceutical company, Teva. Although it's mostly generic, it has also had its successes developing ethical drugs. We have an embryonic biomedical industry. These are some of the elements of our latent comparative advantage.

However, there are also many obstacles. Funding for biomedical research has to come from many, diverse sources, with different time horizons, interests, etc.; otherwise we are not going to make this happen. Our clinical trial facilities are not good enough. There are serious deficiencies in regulating the current system, both in the introduction of new drugs and intellectual property. We have big problems moving ideas from academia into industry, including not enough incentives; and we lack the managerial talent to manage the process. Managing the translational research is extremely difficult, and it is not a skill that can be simply moved from the high-tech sector into this one. It is something that we must pay much closer attention to.

The result of having both these elements of comparative advantage and these limiting deficiencies has been much "action," with little results. In view of all this, we need to design strategies to deliberately

leverage our comparative advantage and deal with our obstacles. There is much that can be done and the Arnon Report is an important steppingstone towards designing and implementing such a national policy. I want to congratulate the Committee for its work.

Finally, I can only say that I will do my best in my current position to help this happen. As you know, I'm not (yet) in politics but in higher education, and promises count more there.

Prof. Daniel Hershkowitz

Minister of Science and Technology

When it comes to biomedical research in all its forms, as much as we spend on it, there will never be enough, because the more we study, the more we will find to study. The Ministry of Science and Technology is very aware of the importance of funding biomedical research but, unfortunately, we also have one of the very lowest budgets – and that has to be split between quite a few fields and investments. We do devote some small amounts to strategic research (research that is still rather basic, has a high chance of becoming applied, but is not ready for MIT/OCS funding). We try to identify promising targets and help researchers join together, in order to push things forward a bit; and we do devote a significant part of that to the life sciences and biomedical research. Indeed, I hope to somewhat increase their share of that rather small cake. But we can have only limited influence on the much greater national problem.

I have read the very interesting report of the Arnon Committee; and I was quite impressed by the quality of the biomedical research Israel has done with so few funds. Of course, I can't tell that to the government or they would see no reason to fund biomedical research at all, since somehow it manages to get along. However, I definitely do intend to bring the cogent conclusions of your study before our Interministerial Committee for Science and Technology. That Committee has the full authority of the government. That is, its decisions become official decisions of the government, unless someone appeals. We will request the allocation of more governmental funds for this very important discipline. Independently, we will try to devote more of our own limited resources for biomedical research; but that will be far from enough. We can all benefit from the very rich and impressive biomedical research carried out here in Israel.

MK Yaakov Litzman

Deputy Minister of Health

The Ministry of Health has a responsibility to secure the delivery of modern healthcare to all Israeli citizens. Our mission includes the supervision of all the national insurance funds, the management of all government hospitals and the overall supervision of Israel's entire hospital system. It also includes a responsibility for public health and preventive medicine, including vaccines.

The Ministry of Health has no special priority to initiate or conduct biomedical research, although we are very much aware of its importance. One hallmark of modern society is the continued increase in life expectancy. In 1900 in the United States the average life expectancy was 47 years; in 2002 it was 77 years. This achievement is due primarily to biomedical research, so we do try to encourage this.

Our ministry has a chief scientist, and a small research foundation, which I am trying to make bigger. I can only hope that the Finance Ministry will cooperate, because we hear that our budget is being cut again. However, even if there are budget cuts, there is always a way to find the money for a really serious agenda item. We will try to do it.

Prof. Ruth Arnon

Vice-President, Israel Academy of Sciences and Humanities
And Chairperson of the Committee for the
Assessment of the State of Biomedical Research in Israel

I will say just a few words about the *raison d'être* for holding this conference. One role of the Israel Academy of Sciences and Humanities is evaluating the level of research in Israel. While involved in this process, we found that there are quite a few areas in which Israel really excels. For example, using bibliometric (e.g., citation impact) and other parameters, we found that Israel is number one in the world in computer sciences. In mathematics, chemistry (particularly theoretical chemistry) and physics, Israel is also ranked exceptionally high. Israel also holds a high position in molecular biology. But Israel's position in clinical research is suboptimal, in fact, below the world average.

We believe that a high level of Israeli medical care and biomedical research raises the quality of life in our country. Hence, the finding that we lack high-quality clinical research is both important and puzzling, something we must address.

Having that in mind, the President of the Israel Academy of Sciences established our committee to investigate various aspects of medical, biomedical and clinical research in Israel, including basic, clinical and translational research. We have also considered how to best promote these areas in the future. In this workshop, we want to learn from what is being done in other developed countries, and to benefit from the advice of our distinguished guests, in order to see how we can improve the biomedical and clinical research done here in Israel.

Many thanks, in advance, for taking part in this workshop and sharing your wisdom with us.

National Policy for Support and Funding of Biomedical Research: Basic, Clinical and Translational

The View from the United States

Prof. Harvey Fineberg

President, Institute of Medicine of the U.S. National Academies

I will provide a general perspective on how biomedical research funding proceeds in the United States, adding a few reflections on some of the strengths and weaknesses of the U.S. model. My colleague, Prof. William Paul, will then discuss the U.S. National Institutes of Health (NIH), a particularly important part of this system, in more detail.

The U.S. spends over $130 billion a year on health-related R&D, divided by source as follows:

Industry	**$74.8 Billion**
Pharmaceutical	$37.7
Biotechnological	$27.5
Other	$9.6
Federal Government	**$38.6 Billion**
NIH	$29.3
Other	$9.3
Other Sources	**$17.1 Billion**
University Institutional Funds	$10.4
States, Philanthropy, Other	$6.7

These figures come from estimates of an organization called Research!America (the ! is not a typographical error), whose members represent the most important U.S. public organizations supporting more biomedical research. Such public opinion and support is very powerful in every aspect of U.S. funding decisions. In fact, the NIH became what it is today largely because of the

advocacy of determined members of the public, particularly Mary Lasker, who was influential in getting the idea established in the United States. Still, an even larger investor in U.S. health-related R&D is industry. In fact, the share of industry investment has been gradually increasing, partly because government funding has leveled off. This industrial investment is almost entirely devoted to product development, and I will come back to that later.

Breaking the categories down a bit, industrial investment is largely pharmaceutical ($37.7 billion), although biotechnology is also quite important ($27.5 billion). The largest single government component, by far, is the NIH. Our National Science Foundation (NSF), roughly analogous to your ISF, invests across the board in all sciences. Even so, its total $6 billion budget is only about 1/5 that of the NIH. About a third of the NSF budget also goes to biomedical research – on top of the NIH investment. Even our Department of Defense funnels about $2 billion a year into biomedical research (for somewhat peculiar political and historical reasons). Of the $17 billion from "other sources," a large fraction ($10.4 billion) comes from direct university investment in the infrastructure and core funding of biomedical research (institutional funds). Thus, in the U.S. model, the notion of investing in health-related research is deeply embedded in every sector: government, industry, academia, hospitals: they are all very comfortable with and committed to investing in biomedical research.

I suspect that the estimate of about $900 million from private foundations is a strong understatement. The Howard Hughes Medical Institute (HHMI) alone has about $14 billion in resources and supports more than 350 Howard Hughes senior investigators at more than 70 U.S. institutions. This represents core funding for biomedical research, in largely unrestricted ways. In 2006 the HHMI invested significantly in a new research campus (Genella Farms),

devoted specifically to neurological research, genetics and imaging science. The HHMI alone thus probably spends about $830 million per year. Next consider the Bill and Melinda Gates Foundation. Only a small fraction of its annual budget is spent on research; but it's a small fraction of a very large number. I would estimate a minimum of $100 million. Then you have other investments from "smaller" foundations, like the Keck Foundation and the Doris Duke Foundation. These private funds are particularly important, not only because of their ability to make targeted investments, but because of the flexibility and speed with which foundation money can be redeployed by their Boards.

U.S. health costs are by far the world's largest, over $2.3 trillion a year (2008). Health-related R&D, as a percentage of this total investment, has remained more or less steady at about 5.5% throughout the last decade. In fact, it is about 0.5% of the entire national GDP.

The course of the NIH budget in recent years illustrates one of the deficiencies of the U.S. model, its uneven character. For example, a decision to double the NIH budget from about 1998 to 2003, was followed by holding it flat for the next five years. However, this past year, when votes were needed to pass an economic stimulus plan, one U.S. senator insisted that his vote would be dependent on giving an additional $5 billion per year to the NIH. So the budget is going up again, but it's not part of the core budget. So what happens next is anyone's guess.

Compared to other federally funded research programs, the NIH has historically done very well indeed. Prof. Trajtenberg's "comparative advantage" reasons are quite cogent; but in the U.S. there are two other major reasons. First, people deeply value health, and they would rather invest in research to improve their health than in research for practically anything else. This is a deeply held public value, reflected

in the decisionmaking of our Congress over many, many years. Second, there is a conviction that the biomedical industry is going to be one of the winning industries of the 21st century, particularly in the U.S. As for public attitudes, about 70% of the public want more of their health dollars spent on biomedical research, than at present! (An incredible 25% would spend more than 15% of the nation's entire health budget on it.)

I will now reflect a bit on some recent trends, and then on some strengths and weaknesses of the U.S. system. The first obvious trend is globalization. U.S. industry is distributing its research investments more globally. Even the NIH, more gradually, has increased spending on projects taking place outside of the United States. Global growth also means that the U.S. share of the world's total investment in biomedical research is diminishing. That can be good in that it indicates a widening of the investment base and increased opportunities for "coopetition" – both cooperation and competition – between countries.

A second trend is a growing emphasis on interdisciplinary problem-oriented research. This can be valuable, because it points toward solutions more directly relevant to public interests and public health needs. But it also has the danger of distracting one from important core investments. Basic research does not always have an obvious problem-oriented endpoint, although it is crucial to further progress, nonetheless. This is related to a third trend, an increasing investment emphasis on targeted and "accountable" research. Just last night, for example, I saw two news stories that illustrate this point. The Gates Foundation just announced a new $30 million investment in "Point-of-Care Diagnostics for the Developing World." This is a research investment, but it is a very targeted and focused one. It seeks to develop inexpensive field-ready, non-refrigerated diagnostic tools that can be deployed without requiring reagents, water or special

equipment. Important this surely is, but very targeted. In the second item, our Secretary of Health and Human Services, looking at the problem of vaccine availability, said, "We don't do a good job of focusing our research on our top priorities, so we don't get enough discoveries that are candidates for advanced development … Even when we end up with a useful countermeasure, there might not be a big enough incentive for a company to manufacture it on a significant scale." Both reflect the same shift in interest toward research that has an immediate practical payoff.

Finally, in biology, there is the beginning of a trend that has long been prominent in other sciences, particularly physics: a shift toward "big science" as opposed to individually focused research. The Human Genome Project is a prime example.

Let me now summarize some of the strengths and weaknesses of the U.S. model for funding biomedical research. The scale of funding is impressive. It's large, and it comes from many different sources. This reflects a national ethos favoring investment in biomedical research. However, the somewhat erratic funding pattern displays a lack of consistency and commitment over a multiyear period. There is an important diversity of research settings, but the multiplicity of settings and funding sources means that there is no real national research strategy. There are corporate strategies, an NIH "roadmap," proposed NSF strategies and many university strategies; but there is no concerted effort that encompasses the totality, because there is no entity that actually controls the totality.

Public support is very strong but, at the same time, the great influence of interest groups can distort investment priorities. We also have ideological problems and restraints; stem-cell research and (in the very early days) HIV are examples. We have a problem of earmarked funds, when legislators give specific funding for particular needs of

their own district without merit review. Still, the U.S. merit review system is quite strong, which represents a great strength.

Industry, which used to invest significant amounts in basic research, has largely withdrawn from it; and while we have excellent research universities, we do not adequately support young investigators. Until very recently, the average age of a new NIH grantee getting his first RO1, was about age 40. If David Baltimore, who received his Nobel Prize at age 37 or 38, had followed today's standards, he would have been still looking for his first RO1 instead!

The U.S. tradition of strong research in medical centers, as well as at universities, is very important; and it reflects their entrepreneurial spirit. Just to take a single example, the University of Pittsburgh Medical Center, which 10-15 years ago would have been counted in the second or third-tier in its biomedical research capacity, has catapulted itself into our nation's top-tier through a very careful, systematic and successful institutional recruitment and investment strategy. This kind of opportunity still exists.

In closing, we hope that some of our strengths will be of interest, while some of our weaknesses will be avoided, as you move ahead.

Comments

Prof. Michael Sela: There may be no coordinated strategy in the U.S., but maybe that huge diversity is preferable to a unified strategy.

Prof. Harvey Fineberg: If you can put enough money on the table, then diversity is indeed an advantage. If you have limited resources, it can be a costly approach. I personally like the idea of a mixed strategy.

Prof. Olle Stendahl: You noted that U.S. industries invest about $75 billion a year in health research. Then you noted, as a weakness, that industry is moving out of the more basic aspects of such research. What is their motivation? Is it purely money (return on investments) or is their strategy now to buy small companies once technical progress is visible or pay for new drug licenses? Finally, has the U.S. pharmaceutical industry also moved out of basic research?

Prof. Harvey Fineberg: As for the general problem, the oft-cited, classical example is Bell Laboratories, the source of many Nobel Prizes in physics and chemistry. It's now literally close to nothing. As for the pharmaceutical industry, the trend has been toward the acquisition of companies that have already passed through the first stages of product development. There has been considerable consolidation in the industry, and the number of companies making substantial research investments is now quite limited. While there are still very good opportunities for individual scientists within these companies to do quite "liberated" research, it is largely regarded as an investment, which can be dramatically changed depending on the scientist's progress toward a marketable product. That's simply in the best immediate financial interest of the company and its shareholders.

Dr. Yaacov Bergman: There is sometimes a conflict between the interests of the scientific community and the public, as Sir David recently wrote: "Translation of live research is less attractive to the public science base [scientific community], and this creates a barrier to the effective translation of U.K. research into practice."

Prof. Harvey Fineberg: I agree that the scientific community itself can also be an interest group. We all have our own desires and aims, which may or may not track the larger public interest. Nonetheless, we know of no country that has succeeded in building a successful

biomedical industry, without a strong basic-research enterprise. You cannot piggyback forever on others. This is where policymakers have a special responsibility, and why our political decisionmakers should represent the public interest and not just a particular constituency. They have to judge the legitimacy of the scientists' arguments and what is truly in the public interest, and come to a conclusion. If you want to have long-term success in health, you need a comprehensive research strategy that includes basic, clinical and translational research. This was one of the things I like in the Arnon Committee's report.

Prof. Michael Sela: This reminds me of the classic expression, "There will be no applied science, if there is no science to apply." For example, Israel's Copaxone, a great financial success, started from basic research by Prof. Arnon and myself.

Prof. Harvey Fineberg: Actually, there have been many U.S. case studies that trace back the origin of major products, and they all have their foundation in basic research. None would have been possible with just development.

Prof. Christopher Kennard: You mentioned industries at several levels in your presentation. Biotech startup companies have been a strong driving force in both biomedical research and industry. On the other hand, it's a fragile system because it's affected by financial events, and it might divert some people from basic research, particularly when a crisis pushes them to do more clinically oriented research. What is your evaluation of these biotech startup companies, apart from big industry, in stimulating the American biomedical research system?

Prof. Harvey Fineberg: In the U.S., entrepreneurship and investment capital formation are the fuel that drives the biotech industry. It began in a relatively small number of major centers, such as Silicon Valley (California) and the Metropolitan Boston area. Now Research Triangle Park (North Carolina) and others are emulating them, attempting to concentrate in the same way. Concentration provides the combination of scientific expertise, discovery and venture capital that are the formula for new industry development in the U.S. – not only for computing and information technology startups, but also for the biotech industry.

The View from the U.S. National Institutes of Health

Prof. William Paul

U.S. National Institutes of Health (NIAID)

Prof. Harvey Fineberg has beautifully outlined the general U.S. strategies for supporting biomedical research. I will give a more technical presentation about the NIH experience. Despite great diversity in the U.S. system, there is, nonetheless, a "nine hundred pound gorilla" in that system, namely the U.S. National Institutes of Health (NIH). Even major private foundation budgets, the Howard Hughes Medical Institute being the largest, are only 2-3% the size of the NIH budget. Even when you add in the American Cancer Society and other such organizations, the fundamental driving force for U.S. biomedical research is the government-funded NIH.

The NIH represents a national decision to specifically fund biomedical research; this is in contrast to the current policy of Israel's ISF, which is open to all comers in all fields, something which is laudable but extremely difficult to run. I personally would find it extraordinarily hard to compare a project in particle physics to one in molecular biology. In fact, by creating twenty separate, quite specific institutes, the U.S. has provided further commentary about just what areas of biomedical research it wants to support. Of course, the names of these institutes do not fully describe the areas of science they support. For example, the National Cancer Institute also supports considerable research on fundamental biological science; but the existence of a disease-specific institute does ensure good funding for that particular area. So, the NIH is basically a community of twenty institutes, plus several centers.

There is also a great diffusion of power. Although the NIH Director is probably the single most powerful individual, he does not direct the whole process. The Director only gives "guidance" to the institutes about what kind of budgets they may request, reflecting the guidance he/she has received from the Department of Health and Human Services and the U.S. Office of Management and Budget (OMB). Then each institute develops its own budget request. The OMB reviews such budgets requests separately, and then each institute director presents their budget to the Congress (House and Senate) and testifies to defend it. In fact, the Congress appropriates the money directly to each individual institute, not to the NIH as a whole! The NIH Director has only a relatively modest capacity to move monies. For the last few years a common fund – now 1.7% of the budget, a small percentage but a substantial absolute amount – has given Directors an opportunity to focus on certain areas of their choice. But the twenty institutes make most of the critical decisions about how their resources are utilized.

Finally, the NIH supports both extramural research grants to universities, medical schools, research hospitals and medical research institutes throughout the country and intramural research. The latter is largely based in its Bethesda, MD, campus, whose 1,200 principal investigators probably constitutes the largest single biomedical research enterprise in the world. The intramural research program dates back to the late 19th century; until World War II, it was by far the largest component of the NIH budget.

Now, how is the NIH's extramural money spent? The majority supports research grants; but the NIH also issues contracts to carry out critical elements of its research. The ratio varies, but it is now a relatively healthy ratio of almost 5 or 6:1 in favor of grants. However, many different types of support mechanisms are lumped together under the rather general term "grants" Most basic scientists rely on RO1

grants; but many types of research cannot be supported adequately by such grants to individual principal investigators. The most dramatic example is clinical research, which requires research nurses, study coordinators, large statistical centers and all sorts of other facilities to work together. The NIH provides a series of large Clinical Translation-Science Awards for that purpose. There are approximately sixty of these, mainly at medical schools throughout the country. They average about $9 million each, although some are substantially greater, and they provide a place where funded scientists carry out this kind of work. To do science-driven or curiosity-driven research, rather than industry-funded drug testing, such support is essential.

There are also other kinds of large mechanisms. Comprehensive cancer centers throughout the U.S. mount a focused attack on cancer, providing large infrastructures which funded scientists can access. There are also large cooperative groups, including one doing HIV clinical research, an AIDS clinical trials group, and a very large grant to support an immune tolerance network. That grant is given to one institution which, in turn, distributes resources throughout the nation.

Even within the investigator-initiated pathway, there are multiple mechanisms. The classical pathway is the RO1 grant. Over the last ten years that has evolved somewhat; it is now a modular grant consisting of $25,000 modules capped at $250,000 in direct costs. Most applicants, of course, ask for the largest number of modules, so most grants today are of the order of $250,000. These are generally three to five-year awards; and each year's portion is supported by that year's Congressional appropriation. This leads to a complexity that I will describe later. In addition to direct costs, the NIH recognizes that the investigator's institution bears valid costs while supporting such research, and it reimburses such indirect costs up to about 70% of direct costs.

The NIH peer review process for conventional grants often places a premium on work likely to succeed, but there is a growing effort to support more "high risk" research. Of course, one person's "high risk" research may be another person's "off-the-wall" research; but, in any case, the NIH devotes a relatively small proportion of its budget to a series of large grants for very innovative work, of which the Pioneer Awards are the best known. The NIH also recognizes the special difficulties of new investigators. Although there is no special mechanism for them, the NIH's review groups (study sections) are urged to give special thought to funding new investigators; and the individual institutes also give them some preference. NIH grants can also cover the salaries of principal investigators, even if they occupy endowed chairs in universities. The operating principle is that the U.S. government should pay the full costs of the research it is supporting.

Now the complexity I mentioned. In any given year, the NIH budget has a certain amount of money already committed to prior-year awards. In 2008, that commitment base consisted of about 29,600 awards that had to be funded; thus there were only 6,900 new awards. Now consider the recent era of NIH budget doubling and "undoubling." In a generous budget year, one can make a large number of new commitments. When that is followed by a poor-budget year, the commitment base eats up most of the available budget, and the money available for new grants is greatly diminished. Various strategies are used to try to lesson this problem but, in any such system, problem years can arise.

The NIH budget over the last seventy years (1938-2008) shows slow growth, then rapid growth, then doubling (1998-2003), and then a very modest increase ("undoubling"). Of course, the ability to get a new NIH research grant over the last several years has been substantially more difficult than usual, due to the large commitment

base. This has led to a crisis in success rates (the ratio of grants-funded to grants-submitted), which fell rather dramatically from about 32% to about 21%. Although pay lines are of the order of 6-10%, they represent an artificial type of calculation. Most of us think that a success rate of about 21% is too low to provide proper encouragement to scientists.

Although there is no central policy, the NIH has a very substantial role as chief funder. Thus, the U.S. Congress, which determines the NIH budget to a large degree, controls the resources available for biomedical research. In contrast, no one controls the size of the enterprise itself. Thus, during the era of budget doubling, no one could prevent all sorts of U.S. biomedical research institutes increasing their capacity and competing. Each felt that not doing so would leave them at the starting gate, while their competitors forged ahead. The size of the U.S. biomedical research enterprise increased dramatically; but that increased enterprise needed to be fed, even once the budget became flat. The crisis was implicit from the beginning.

As for the application process, the NIH is making its applications much shorter. I think they will be limited to twelve pages. The goal is to increase the speed of turnaround. In 2009 the time from the submission of a grant to a decision was as short as three months, which is very valuable for a scientist trying to get support. The NIH is also allowing only a single resubmission. Finally, the previous onerous review process may have discouraged senior scientists from participating in the study section review process. There is now a major effort to bring them back into the system, to utilize their vast knowledge.

We are, however, facing a crisis of our own making by placing barriers in front of scientists that limit their ability to support themselves as

independent heads of laboratory. Today, on the average, MDs receive their first NIH grant at age 44! So we are discouraging our brightest people. In contrast, one can get a bachelors degree, go to law school, and three years later be out on their own, earning substantial sums of money. If you take six years to get your PhD, spend five years as a postdoctoral fellow, and several more trying to get a grant, you'll be in your mid-forties before you really get started. This crisis really needs to be dealt with.

What about Israel? First, comparing the U.S. and Israel is problematic. The U.S. is about 50-60 times larger, so we have flexibilities that a small nation cannot readily replicate. It may be more useful to examine other advanced nations in the five to ten million population range, such as Sweden among others.

Second, really innovative clinical research cannot be managed with research project grants alone. Advanced infrastructure is absolutely essential. A special problem in Israel is the inadequate time that physicians have to do research. Israeli leadership needs to face that. Even in the U.S., a single $250,000 grant is probably inadequate to run a competitive laboratory. The relatively small size of grants in Israel makes the problem even more acute. Israel may offer economies, but I doubt that they suffice to enable the recipient of a single small grant to be competitive on the world stage. Spending large amounts of time seeking small amounts of money from various sources seems a fundamentally inefficient approach.

Finally, can Israel be an international force? I would say that, among nations of its size, Israel is extremely efficient in terms of citations per GDP, where it is the leader, although it lags Switzerland and Sweden in citations per capita. However, biological science is now moving into its "big science" era. Recent technologies are quite remarkable. We are facing next-generation sequencers that cost

a half-million dollars each, advanced optical imaging systems, etc. All this has to be dealt with or one runs the risk of being marginalized. So Israel needs mechanisms to support high-end, technically advanced technologies.

Israel also needs to decide if it wants to be a consumer or a producer. The building of a strong biotech industry will depend on the existence of strong research-oriented universities. Southern California, Silicon Valley, and the greater Boston area built vibrant biotech industries because of the research universities and intellectual property that were available there. A similar approach in Israel would be incredibly valuable.

Comments

Prof. Yossi Klafter: Here physician-researchers are a vanishing species. I believe the NIH tried to establish special grants to give these special scientists protected time to conduct basic research within their clinical facilities.

Prof. William Paul: There is no doubt about the importance of this problem. Without "excused time" it's virtually impossible for clinicians to carry out sophisticated, first-level research. First, just competing for grants against a full-time, basic researcher is incredibly difficult. Mechanisms need to be found that recognize this problem, without compromising quality. Clinical research is a very special kind of enterprise, which needs special support mechanisms, and advanced infrastructure has to be created. I suspect that you know that all too well.

Prof. Rafael Mechoulam: I note that the NIH is an extremely liberal organization. I've had NIH grants for 40 years now, and they have never ever interfered with my grants, nor commented negatively on

anything that we have done. The only way they comment is by not giving you another grant!

Prof. William Paul: The NIH has two distinct funding mechanisms. In the grant mechanism, you propose a line of research; and the NIH position is that you are free to do that work or any work that grows out of it. The NIH contract mechanism is, of course, very different. Also, it has now become very difficult for non-U.S. scientists to get NIH funding. So your doing so testifies to the great quality of your research.

Prof. Reinhard Kurth: Many young domestic researchers are unable to launch research careers and disappear into industry. To what extent is that gap filled by young foreign postdocs coming with their own scholarships? Second, you showed a beautiful slide about how the NIH institutes negotiate their own budgets. But who refocuses the system? Take the Institute for Aging, for example. Demographic changes should make this more important with time, but who can decide that this is an important area that needs additional support?

Prof. William Paul: As for young scientists, although the growth of the NIH budget has been modest lately, it is still a very large budget. Young scientists are simply staying longer and longer in postdoctoral research associate positions. This is unhealthy, because their best, most creative years are being spent in subservient situations. Some institutions encourage their initiative even in such settings, so it's not such a problem there; but it's still a fundamentally bad idea. It is now very difficult to find a first-rate position in the U.S.

As for competition among institutes, the OMB and/or the Congress may deal with that; and, from time to time, they do decide that some area should receive increased funding. That was true of cancer

research for many years; and my own institute (NIAID) grew enormously, largely because of a decision to increase HIV research. A more recent beneficiary is bio-defense research. But usually the institutes maintain their current ratios within relatively narrow margins, with only modest changes.

The View from the United Kingdom

Prof. Christopher Kennard

U.K. Medical Research Council

The National Insurance Act of 1911 started the MRC by requiring every working person to give one penny a year to support sanatoria for patients with tuberculosis, a major disease at that time, and for "purposes of research." Some enlightened individual then sequestered the relatively small sum of £57,000 per annum for a National Fund for Medical Research. Then, in 1919, a Royal Charter established a national Medical Research Council (MRC), whose funding came from the Ministry of Health. The MRC retained its own executive powers and Lord Haldane further proposed that it make its scientific decisions independent of the government, a feature of all subsequent U.K. research councils. This "Haldane Principle," is something that most British scientists would go to the wall to defend.

The MRC's mission is, obviously, to encourage and support high-quality research related to improving human health, to produce skilled researchers, and to promote a dialogue with the British public about medical research. MRC-funded research ranges from molecular-level science to public health. Much is basic, discovery-oriented biological and biomedical research, because having good basic research is essential to undertaking translational medical research.

The MRC's annual budget is now (2008/09) about £704 million per year. Until World War II, most MRC-fund research was intramural. That is, the MRC established research units throughout the country in specific strategic areas, such as toxicology and virology. These units were set up, largely, in universities; but interaction between

these MRC units (today there are 29) and their host university varies significantly. Currently, about 50% of all MRC funding is extramural response-mode funding, in which program and project grants are awarded to individuals or to groups of university researchers (who can join together into centers to get core funding via five-year MRC center grants). Another key funding component involves human resource development; and just over £58 million per annum is spent on training and career development. In all, the MRC employs about 4,000 staff and supports about 3,300 research grants, 350 research fellows and 1,400 postgraduate students.

The MRC is now funded by the Department of Trade, Innovation and Skills (although its name frequently changes) rather than the Department of Health (DH). The DH has its own research funding, about £800 million per annum for research and development (R&D) in the National Health Service (NHS). Historically, the large medical schools and hospitals in London took the lion's share of this funding. The allocations were completely non-transparent; and they largely supported patient care rather than research. In a recent report, *Best Research for Best Health* (2006), the government agreed that this was inappropriate. They then set up a new National Institute for Health Research (NIHR), having lumped the MRC and NIHR budgets into a single £1.4 billion "ring-fenced" fund. This was important because, previously, whenever the NHS suddenly found itself in financial difficulty, it simply reduced its R&D budget; but this new, united fund receives its £1.4 billion directly from the Treasury.

In 2006, Sir David Cooksey, a well-known British industrialist, was asked to review the U.K.'s institutional arrangements for funding health research. His key recommendation was to establish an Office for the Strategic Coordination of Health Research (OSCHR) to consider the advice, needs and priorities set out by the NIHR, the MRC, the devolved administrations (Scottish and Welsh), and the

NHS itself. It is charged with formulating a strategically coherent approach to publicly funded health research, with an agreed set of health research priorities that target the U.K.'s most important health challenges over the next decade. It must also facilitate the more efficient translation of U.K. health research into benefits, and deliver an annual budget and research strategy to the Treasury.

OSCHR's membership encouraged a strong *de facto* partnership between the government, health industries and large charities in health-related research. The chairman, Sir John Bell, is Regius Professor of Medicine at Oxford University and President of the Academy of Medical Sciences. The Chief Executives of the MRC, NIHR, the Wellcome Trust (representing the medical charities), and GlaxoSmithKline (representing industry) are all included, so it is an exceptionally high-powered group that makes these decisions. They communicate the U.K.'s health priorities, set objectives, monitor progress and report to Parliament. They are a coordinating group, not a funding body; so they distribute their funds to the NIHR and MRC and it is up to them to spend it. Instead, OSCHR plays an overview role and ensures that strategically important areas are discussed. Although it cannot make the NIHR and MRC do what they say, obviously neither organization would wish to bite the hand that feeds it.

How do we develop priorities? First, an assessment of the burden of illness in the U.K. is commissioned by the DH. Then meetings of scientists and stakeholder groups identify a series of specific U.K. health-research opportunities. For example, using "disability-adjusted life years (DALYs)" can help distinguish the impacts (burdens) of neuropsychiatric conditions (=1970 DALYs) and cardiovascular diseases (=1310) from those of endocrine disorders (=100). Neuropsychiatric conditions present the largest burden, because they rarely kill their victims at once and they require treatment over

many years. Of course, many important research topics, especially in basic science, don't fit neatly into a specific medical diagnosis or disease. Also, some important burdens of illness are not as inherently amenable to medical or public health intervention as others. Finally, focusing on final diagnoses may ignore common causal pathways and potentially reversible risk factors.

On the basis of all this, the MRC has identified ten general areas where focusing on a strategic research approach is most likely to lead to significant advances in health outcomes:

- Stratification of phenotype
- Regeneration and replacement
- Tracking response to intervention
- Measuring, understanding and modifying environmental and inherited influences on health
- Exploiting hypothesis-generating science to deliver improved health
- Early detection for effective intervention
- Primary prevention
- Behavior modification
- Understanding the burden of illness
- Developing new interventions

As a result of this exercise, the MRC has formulated and published a new strategic plan: *Research Changes Lives: MRC Strategic Plan 2009-2014*. This will be used to convince our government that their funding is being well-spent and that there are significant opportunities for further expansion. We also need to explain why, if the government must make cuts, they should not be in biomedical research.

The plan identifies four broad strategic aims. The first comprises two priority themes: Resilience, Repair and Replacement (including natural protection, tissue degeneration, mental health, and regenerative medicine) and Living a Long and Healthy Life (including genetics and disease, imaging, biomarkers, life-course research, lifestyles, and environmental change). The second strategic aim is Translational Research (bringing the benefits of research to society). Its practitioners must also be involved in regulation, ethics, governance, working with decisionmakers, and enhancing communication. Indeed, if the general public doesn't think what we are doing is important, we will not get much support from politicians for future funding.

The third strategic aim is Progress in International Medical Research. The MRC has always been involved in research in other countries, particularly in Africa, and its chief executive wants even more global partnerships and more emphasis on global health. The fourth strategic aim, Supporting Scientists, seeks to strengthen our research capacity, to facilitate our use of population-based data, and to create a world-class research environment.

The MRC undertakes basic discovery and exploratory research leading up to experimental medicine, proof-of-concept and first trials. Then the NIHR takes matters forward, through applied research, Phase II and III trials, etc. NIHR research is still embedded in our NHS hospitals, although there are increasing links with universities. They support a group of senior clinical researchers, trainees, and paramedical associates (who are also very important to successful clinical research).

The NIHR has made several rounds of awards for these posts; and they have set up specific research projects, programs and research units at medical schools. Of course, they are also responsible for

maintaining research information systems, governance systems and ethical committees. They support infrastructure for translational medical research through two different channels. First, they have established seven NIHR Topic-Specific Clinical Research Networks – in mental health, diabetes, stroke, dementia and neurodegenerative diseases, cancer, primary care and medicines for children – set in hospitals around the country. There is also one more comprehensive network to cover all other diseases.

These networks provide infrastructure resources for undertaking exploratory clinical trials and Phase II and III clinical trials. Although the U.K. has a very strong pharmaceutical base, many drug companies were taking their clinical trials abroad, because it was too complicated and expensive to do them in the U.K. These networks could help the pharmaceutical industry undertake their large multi-center trials in the U.K.; but the financial "bottom line" suggests that it is still much less expensive for them to do high-quality clinical trials abroad. However, these networks could be valuable in promoting exploratory medicine, including first introduction in man.

Most of the MRC's £702 million budget (2007/08) is spent on underpinning research and etiological research. Funding for translational clinical research is relatively limited, in comparison. Following the Cooksey Report, the government gave the MRC an additional £250 million over three years to boost translational research. Although some in the science community worried that the MRC might cut its budget for basic science, that has not been the case.

The MRC is governed by an MRC Council, half of whom (approximately twelve) members are scientists. Its four main boards select the awards for the MRC's response-mode funding: Neuroscience and Mental Health, Molecular and Cellular Medicine, Populations and Systems Medicine, and Infections and Immunity.

Another four groups address cost-cutting topics: Training, Global Health, Translational Research and Population Health Sciences. These do not have their own funding; rather, they develop strategies in their areas and have representation on the other four boards. The chairs of these eight boards comprise the MRC Strategy Board chaired by the CEO. Recently, the Strategy Board retained about £40 million to fund areas of strategic need. This allows a rapid response to sudden problems and opportunities. It also provides a mechanism for making large commissioned awards that could prove very useful for translational medicine.

The U.K. is unique in having a private charitable foundation, the Wellcome Trust, whose £702 million per year budget (2007/08) rivals that of the MRC. They have a considerable international portfolio (which they want to increase), but historically most of their funding has gone to U.K. biomedical research. They don't have their own intramural research units, except for such major infrastructure facilitating research centers as the Sanger Center. They devote much of their money (more than the MRC) for strategic awards, which adds value to the research groups that they are already funding. They also have a response-mode program, project grants, and many other schemes, similar to those of the MRC, for funding clinical and non-clinical scientists all the way from Ph.D. studentships, to clinical training fellowships, to more senior research fellowships. In two calls over the last eight years, the Wellcome Trust has established clinical research centers in major U.K. medical centers, leveraging co-funding from the government. They also have a large program devoted to public communications, helping society better understand biomedicine.

Translational research turns discoveries into clinical benefits, a process that can take a very long time. For example, Milstein and Kohler discovered mouse antibodies in 1973. Humanized ones

followed in 1983; but it took another 30 years before they were first used to treat arthritis.

OSCHR recommended, and the government funded, a relatively rapid, recent increase in the MRC budget (an increase of £132 million over three years) for translational medicine. The MRC quickly funded targeted initiatives to set up patient research cohorts, to develop models of human disease, to validate various biomarkers and to develop stem-cells. The Developmental Pathway Funding Scheme (DPFS) and the Developmental Clinical Studies (DCS) are really the cornerstone of the MRC's whole translational strategy, with one to two-year projects of £250,000 to £750,000 each (larger projects can be considered). All these translational initiatives are more goal-oriented than hypothesis-led; and they are milestone based. Researchers must submit quarterly reports; and if they don't meet their milestones, their funding may be terminated. We are about eighteen months into this scheme, so it's too early to judge its effectiveness.

Some DPFS funding involves working directly with universities, supporting capital expenditure and strategic appointments to recruit key international players into the U.K. (including ex-patriots working abroad). These appointees receive about a £1 million each, which helps them set up their laboratories. After a year or so, they should be able to apply for program grants from the major funders, so this initial grant simply helps them get rapidly established in the U.K. The MRC also engages in proactive "pump priming," by putting Research Translators (RT) into ten U.K. universities to interact with a wide range of academics who might be interested in translational research, but who are insufficiently aware of what is available, the steps to be taken, and the hurdles to be overcome. These RTs go around the biomedical community to explain what translational research is all about, and to awaken interest and enthusiasm.

More generally, funding organizations must ensure a proper distribution of funds, equity of access, and a proper (if difficult) balance between intramural and extramural research, and between top-down and bottom-up initiatives. Although many scientists might prefer all research funding to be bottom-up, strategic investment in certain areas at certain times is also essential. We must also try to ensure more effective collaboration, evaluation and guidance on best practice.

Comments

Prof. Bracha Rager: Is there any special relationship between the MRC and the EU?

Prof. Christopher Kennard: Yes, the MRC is very actively involved in discussions with the EU, trying to see where their research areas which overlap with ours. Two years ago, for example, we had a strategic review of neurodegeneration research in the U.K., and came up with a number of specific areas that required more funding. We then issued a large call-for-proposals, jointly with the Wellcome Trust. At the same time, we held discussions with the Germans and French to see whether there were opportunities for bringing in European funding. This led to a joint programming initiative with the EU to establish a European strategy for neurodegeneration research, which will hopefully lead to more EU funding in this area.

Prof. Alex Keynan: Is there any coordination between the MRC and the Wellcome Trust, since both have large, roughly equal budgets?

Prof. Christopher Kennard: It is variable. There are regular discussions between the CEOs of both organisations. As I mentioned, after our strategic review, we were keen to set up some multidisciplinary centers in neurodegeneration research. We then

found out that the Wellcome Trust, after an internal review, had embraced the same idea; so we got together. The initiative's £30 million budget is the largest sum ever put forward for that kind of thing. More commonly, there is a lot of discussion, but the schemes are undertaken by either the Wellcome Trust or by the MRC individually.

Prof. Ruth Arnon: Israeli clinicians particularly need protected time for research. Does the NIHR budget include such protected time for clinicians?

Prof. Christopher Kennard: A few years ago U.K. clinical research was felt to be dying, due precisely to the issue you raise and the lack of training opportunities. So the NIHR established a series of "new-blood" Senior Lectureships, which were 50% research and 50% clinical work. About 150 such posts have been created over the last 3-4 years. Any university can bid for them; and I think that they are working out very well. These individuals are appraised each year; and if they are spending more time on one focus than the other, then their Head of Department will go to the NHS managers and negotiate a reduction in the clinical load. In the U.K., all hospital consultants, whether NHS or academic, have job plans that allocate their time in four-hour sessions. Thus, it is relatively easy to see if clinical work is encroaching on academic time, since everything is clearly defined.

The NIHR has also introduced Clinical Lectureships (equivalent to registrar/senior residencies), where appointees devote 50% of their time to clinical training and 50% to research. Hopefully, this program will create a cadre of future clinical scientists who will move into more senior academic positions.

The View from France

Prof. Jean-Francois Bach

Permanent Secretary, Académie des Sciences

For many years, particularly after the Second World War, the first research priority of the French research system was physics, particularly nuclear and high-energy physics, which involve considerable large and expensive equipment. This persisted for many years, with only slight inflections in the percentage allocations of the national research budget. This prevented France from investing in biomedical research at financial levels comparable to those of other major Western countries. Fortunately, this has begun to change. Indeed, when the President of France recently provided research institutions and universities with a total of €20 billion in loans, a significant percentage was earmarked for translational medical research.

The French research system is complex and somewhat unique. For example, nearly all scientists, including both basic and clinical biomedical scientists, are civil servants. They get tenure at age 35; in physics and mathematics, tenure comes even earlier (around age 25 or 26 in many cases). This model, dating from the 1980s, has certain advantages, because young French scientists don't have to compete for their salary. Theoretically this allows them more risk-taking, creativity and originality. Such a system is very good for consistently excellent scientists, but highly counter-productive for less good ones, who simply remain in the system, consuming salaries and resources, even once their productivity becomes unsatisfactory. One hopeful sign is a recent decision to competitively allocate grants (but not salaries) on the basis of projects submitted to a new Agence Nationale de la Recherche (ANR), which competitively directs project money to the best projects and scientists.

A major source of complexity in the French biomedical research system is the high number and diversity of participating institutions. This complicates research coordination and the daily life of French scientists, who must write and submit many redundant applications. The existence of national research institutes that are separate from universities is another French peculiarity many of us regret. Historically, French universities lost their research capacity after the Second World War. It seemed more efficient to start new central institutions, such as CNRS and INSERM, from scratch, than to reestablish research in individual universities, which were busy reorganizing teaching. A recent law will finally give autonomy to French universities; and that should help reorganize university research and promote better connections with the national research institutions. Still, complete "reunification," which is supported by many, will take at least a decade.

Biological research is done both at the Central National de la Recherche Scientifique (CNRS), which covers all scientific disciplines, and at the Institut National de la Sante et de la Recherche Medicale (INSERM), which is the French counterpart of the intramural program of the U.S. National Institutes of Health (NIH). However, unlike the NIH, INSERM research units are not concentrated in one campus; rather, they are scattered all over the country within hospitals. Biological research is also done in the Institut National de la Recherche Agronomique (INRA), in nuclear research institutes, and in private foundations, such as the Institute Pasteur and Institut Curie.

The task of improving the quality of university research is enormous. It includes better evaluation of individuals at the time of recruitment and promotion, remodeling and updating research laboratories, and acquiring and allocating sufficient resources. The recent government loan, mentioned above, should prove helpful; but it will not be

sufficient without a change in the attitudes of most professors. The aim of "reunification" still finds major resistance from full-time scientists in the CNRS and INSERM, who are not confident in the reform capacity of universities. However, a recent government decision allocates €800 million to five university-run centers-of-excellence in biomedical research, located within major university hospitals. These centers, with major activity in translational research, are another essential component of our new national biomedical research policy.

The autonomy of universities and the boosting of hospital research centers present new opportunities for modernizing French biomedical research, including the possibility of introducing merit-based salaries, something impossible under previous uniform administrative rules. This new framework could also allow French research to attract foreign talent, something that has proven to be quite difficult so far. Meanwhile, the separation of universities and research institutions is worsened by the further separation of the CNRS from INSERM, who both employ approximately 3,000 biologists. Until recently they could collaborate; but they operated under totally distinct statutes. Efforts are now being made to reduce this barrier.

Another important problem involves scientific strategy. Until recently, science policy was limited to supporting research groups on the basis of their quality, independent of their research topic or field. Even such recognition of excellence was not systematic, since a large fraction of grants were given to all groups independent of any evaluation. Thus, the new Agence Nationale de la Recherche (ANR) represents major change. The ANR allocates grants based on its assessments of both the scientific excellence and research-discipline of proposed projects, although the relative importance to be attached to "free research" versus thematically oriented research remains an open question. The French Academy of Sciences favors

restricting grants to specific competitive projects, rather than providing recurrent funding for all groups, and devoting 70-80% of all grants to excellent "free research," regardless of field or topic. This is important to protect creativity and originality, independent of "fashionable topics," that are often better appreciated by reviewers, particularly at the technological level. A persistent problem is the very high percentage of France's research money spent on salaries (up to 80% in research institutions and even more in universities). Thus, the creation of the ANR, whose grants do not include permanent salaries, represents major progress.

The crucial problem of evaluation has been a matter of hot debate in France over the last few years. The quality of evaluation is insufficient in universities, with insufficient consideration of research activity. Evaluation is better in such research institutions as CNRS, but the final ranking is often flawed by serious conflicts of interest. Two new national agencies have been created to evaluate research groups (the Agence d'Evaluation de la Recherche et de l'Enseignement Superieur, ARES) and projects (ANR). A National University Council still performs individual evaluations; but its functioning, while improved, remains unsatisfactory. The French Academy of Sciences has recently published a report on individual evaluation.

A recent national decision, following the NIH model, has formed a number of specialized "institutes of biology" within CNRS and INSERM to better cover part of their activities in the life sciences. However, the objectives of these institutes are still relatively vague, partly due to the lack of resources, which are essentially in the hands of ANR.

This already complex diversity is augmented by such well known private foundations as the Institute Pasteur and Institut Curie, which are funded by both private money (industrial revenues and donations)

and government allocations (about half). Whether research in these private foundations is really less constrained than in public centers remains unclear. The recently founded Fondation de Cooperation Scientifique (FCS) gives €5-15 million a year to discipline-oriented networks. Its status as a private foundation frees it from many of the strict administrative constraints typical of France's highly centralized national administration.

One should also mention the role of French charities, both the Fondation pour la Recherche Médicale (FRM), which covers all domains of biomedical research, and more disease-specific charities, such as our Cancer Association and Téléthon. France is not a leader in charity budgets (their combined budgets total €100-200 million a year); but such "soft" money can be used in a relatively free way, an important advantage. Finally, industry is only a minor contributor to French biomedical research, with a few exceptions such as cardiovascular research. This handicap is worsened by the insufficient development of the French biotech industry.

Overall, the present French funding system is satisfactory for good or excellent research teams, although too much paperwork is required due to the multiplicity of institutions and agencies. The less productive groups receive permanent salaries despite decreased project funds and productivity. This loss of resources is regrettable, particularly during a time of tight budgets; however, to do otherwise invites significant (politically unpopular) union protest. In any case, greater concentration of resources on our best research teams is necessary.

Clinical and translational research are weak points within French research. The French Ministry of Health gives some clinically-oriented grants, although the quality of their allocations is uncertain. The five new centers-of-excellence for translational research,

mentioned above, which receive €160 million each, should help change this picture. Problems in French clinical research include insufficient scientific training and insufficient dedicated research time for clinicians, which lead to uncertain motivation. The functional deterioration of French public hospitals is a significant factor, but not a fully acceptable excuse.

In conclusion, the complexity of the French biomedical research system has long prevented the emergence of high quality research centers, although it has ensured the survival of many excellent individual units, as shown by the good ranking of French research groups in the life sciences in European Research Council (ERC) grants competitions and projects. Hopefully, the major changes of the last 4-5 years will improve French research excellence, a real challenge in the context of a large cadre of civil-servant scientists who are hardly affected at the personal level by evaluations of their individual performance.

Comments

Prof. Raphael Mechoulam: There seems to be a huge difference between research financing in the U.S., for example, where money is mostly allocated for projects rather than for institutions, and in France where the opposite is the case – although that now seems to be changing. Your comments about clinical research seem particularly relevant to Israel. We have to put more money into having clinicians spend more prime time on research, rather than doing it at 12:00 o'clock at night.

Mr. Yigal Erlich: I understand that the ANR does not bring new money to the research universities who apply, which could affect their attitudes towards it. But I couldn't understand why the French Union of Scientists doesn't like it.

Prof. Jean-Francois Bach: I don't want to appear to be against unions, which are necessary for developed (and other) countries, but our unions were quite happy that their members got their salary money, with complete security, as soon as they became scientists at age 30 or 35. They don't want evaluation. So they don't like the ANR, because maybe one-third of their civil servant scientists are not good enough to ever get ANR grants. They feel that peer-reviewed competition is intrinsically unfair. Two years ago, there was a big meeting followed by a movement, created by the unions, that basically said, "We are tired of the word excellence." In science, the concept of unions is appropriate when you want to discuss salaries, but when they try to set scientific strategies, something seems basically wrong. Still, the government is afraid of the unions, because they don't want to have scientists protesting in the streets, as happened a few years ago, another peculiarity of the French system.

Prof. Christopher Kennard: In the U.K., unions are also opposed to new proposals regarding performance evaluation, particularly a recent proposal to base 25% on the impact of one's research. So unions are virtually the same all over the world. My question regards your new Agency for the Evaluation of Research (ARES). Is it under the auspices of the universities, or is it an independent entity?

Prof. Jean-Francois Bach: It is independent from both the universities, CNRS and INSERM. It's a government organization, but it is largely independent – something interesting and almost unique. When ARES came to my university, they evaluated all of our research groups; it took them almost six months. Then published explicit rankings: A+, A, B or C. Most of the new teams did very well, and so did ARES. I liked the fact that they published their results, because people could see exactly who was A+ and so on. Unfortunately, the ARES evaluation had few if any consequences. Perhaps people with B or C's were not very happy, but nothing

happened to them. That lack of change has to change, but it will take time. Nonetheless, that ARES itself worked relatively well was a nice surprise, because it's not easy to start an evaluation system in a country like ours.

The View from Germany

Prof. Reinhard Kurth

Former President, Robert Koch Institute

When the Federal Republic was founded after World War II (1949), the allies divided Germany into sixteen semi-independent federal states, such as Hamburg and Bavaria. This greatly complicates German research and education, although the federal government does have tremendous influence, largely because it has more money than the state governments. Also, as in France, we have several very strong research societies outside both the governments and universities.

Germany has about 188 universities, many small; only about fifty are full-scale universities. Then there are almost 300 colleges, where students study only for three years or so and then enter practical jobs in industry. Altogether, we have over two million tertiary education students. In 2007, 43% of all graduating high-school students entered university, a very high percentage. The universities are officially financed by the federal states, but their support is limited. So they ask the federal government for additional grants, which allows the central government in Berlin to focus the universities' major research into desired directions.

As for our well-known research organizations, most of you know the publicly funded Max Planck Society (MPS), which does not finance fields, but people. In fact, the Senate of the Max Planck Society increasingly identifies and selects individuals from abroad, who fill almost 50% of all new positions. I think this is good. Of course, they do discuss the advanced basic research fields of those people, and then they decide to either create a new MPS institute or a new

department to house them. There are now 76 such institutes all over Germany (including eastern Germany). There are 13,000 scientific and technical people on the MPS staff; but only about 1,300 have tenure. Thus, many scientists have to leave after five to ten years. About 82% of the €1.72 billion budget comes from federal or state funding (50:50).

In contrast, the Fraunhofer Society for the Promotion of Applied Research funds German applied research, two-thirds of which is contracted research for the industrial, service and governmental sectors. Thus, their research results can be translated rather easily into products. They have about 80 research facilities, about 17,000 employees, and an annual budget of €1.5 billion, of which €1.3 billion is from contracts.

The Helmholtz Association has only fifteen, quite large research centers, mostly in the natural sciences, and 26,500 employees. Only two research centers focus on biological and medical research, namely the German Cancer Research Center and the Center for Infectious Biology. These are financed mostly (90%) by the central government in Berlin, with the state governments paying only 10%. Their annual budget, for all fields, is over €2 billion. The G.W. Leibniz Association is a scientific community of relatively small research institutes. Altogether, they employ about 14,000 people. Their annual budget of about €1 billion is guaranteed by the federal states (mostly), including grants.

Germany's Federal Research Institutes operate under the auspices of federal government ministries. There are about 53 such facilities, such as the Robert Koch Institute and Paul Ehrlich Institute within the Ministry of Health. The total annual budget for all these institutes, which employ about 19,000 employees, is about €1.7 billion. Many focus on the life sciences, consumer protection, and defense. Over

half of the federal government's expenditures on science, research and development (SRD) goes to and through the Federal Ministry of Education and Research (FMER, BMBF). Only about 2% of the total SRD expenditure goes to the Federal Ministry of Health. That's not too much; but as long as it actually reaches us, it's enough. The rest supports industry, defense and other tasks.

How does Germany allocate long-term institutional funding for its scientific organizations? Ministries, departments and institutes, such as our Robert Koch Institute, all must formally submit their requirements. Then we have to negotiate, in person, with representatives of the Finance Ministry. Then we have to go to our parliament. I did that every year for the past twenty years. It was not always fun, and one usually had to compromise somewhere. Finally, the results of these negotiations are incorporated into the national budget plan. The major sponsor and recipient is FMER. Only about 3% of Germany's €300 billion federal budget for 2008 went to education and research. It is slowly increasing, but 3% is still a low level for a highly developed country, whose main resource is the creativity of its citizens. More financial support (46%) goes to labor and social affairs. *C'est la vie*.

Germany's self-governing scientific organizations may suggest several useful ideas for Israel and others. The Deutsche Forschungsgeimeinschaft (DFG), the German Research Foundation, promotes research at universities (mostly), and other major and minor institutes throughout Germany. It is an independent authority, and we are very grateful to have it. It involves about 30,000 German scientists and foreign scientists working in Germany who all can vote for members of the DFG's various organs, including its Senate, which makes all the major decisions. Its annual budget of about €1.75 billion comes from both the federal and state governments (60:40); but the government does not interfere with its decisions and

actions, which is ideal. Sometimes the government does suggest new fields, etc. in Senate meetings; but asking, "How much money can you give us for that?" usually ends the discussion.

As in the U.K. and France, the DFG increasingly funds collaborations, networks and research groups, including those with colleagues from abroad. Connecting Germany's various institutes and getting them to cooperate in networks is a high priority. The budget is increases about 3% to 5% a year, mostly from federal allocations, but also from some state government funds.

The DFG sponsors young scientists from their early Ph.D. studies all the way through their post-doc period. Many such German scientists take their scholarships and go abroad, particularly to the U.S. The DFG also helps qualified young professors, and even some mature professors, prepare for "scientific leadership roles," as long as their research work remains excellent.

About €740 million of the DFG's €1,923 million annual budget goes to the life sciences; and another €500 million or so goes to the natural sciences, although these two areas sometimes overlap. About €400 million of the life science funds goes to medicine and €300 million to biology, although again there is some overlap. Many of these grants are individual investigator grants, the most flexible funding program (equivalent to the NIH's RO1 grants), although more and more collaborative research centers are being financed. German scientists are increasingly being asked to join collaborative research centers to receive funding, which is actually helpful. The DFG provides comparatively little to clinical research groups (about €18 million out of €1,450 million in total DFG project funds). Clinical trials are usually funded by interested pharmaceutical companies.

Until about 10-15 years ago, German clinical research involved tired doctors who, at 5:00 or 6:00 p.m., went to their laboratories and tried to solve major scientific problems. That simply didn't work. Thus, our policy emphasis is now on developing clinical research groups to better finance doctors and other scientists within hospitals. We need scientists who can do research all day long, but who also have access to clinical probes and to patients, when necessary.

On the government side, FMER finances mostly short and middle-term research projects. The life sciences receive about €856 million (19.4%) per year; and the natural sciences receive another €460 million (10.4%). Taken together, those are reasonable numbers; but a far bigger chunk (€2,575 million; 58.5%) goes to the engineering sciences, which have been Germany's emphasis for the past several decades. FMER and the Ministry of Health also support several joint programs. This includes providing additional resources for dealing promptly with new situations that require improved diagnosis, therapy and prevention. Thus, when a new disease shows up, such as avian or swine flu, the Ministry of Health can immediately shift financial support into those fields to help come up with (comparatively) rapid solutions. Actually, it usually works out quite well.

Only about 400 (out of 700) German foundations promote science in one way or another; and only about 100 of those focus on the biosciences and medicine. The German Cancer Foundation collects about €90 million all over the country every year. The Volkswagen Foundation, the next biggest, funds biology, in the broadest sense, with a more modest budget of €9.5 million; and the Hertie Foundation (€5.1 million) supports the neurosciences.

As for industry, it sponsors about two-thirds of all German R&D. Most of the rest comes from the public sector (tax money), and some grants come from abroad. Most is engineering research, in the broad

sense; and it includes research by pharmaceutical companies. As in the U.S., more and more large German firms are moving out of basic research. They look around worldwide and buy small, new, research-based biotech companies, instead of spending money on their own basic research. That's rather unfortunate.

As for European Union funding, EU Framework Programme VII (2007-2013) has a €54 billion budget. This sounds quite large, but dividing it by six gives less than €10 billion a year to cover all research. Many of its programs require a minimum of three countries to be involved; and it's quite bureaucratic. (It's certainly not much fun to fill out all these forms!) The EU has to think again about how to minimize bureaucracy when they roll out Framework VIII. They also need to try harder to fund truly creative scientists, although that's always difficult to determine.

Finally, the German Council of Science and Humanities (Wissenschaftsrat) evaluates all of our research institutes (but not societies, like the Max Planck Society) – a huge piece of work – and they come up with recommendations. "Recommendations" sound nice, but you don't have to follow them. Still, their recommendations are being taken ever more seriously by leading science administrators and politicians, with one exception. Whenever they recommend actually closing an institute, then local politicians step in and say, "No way. You cannot destroy 100 jobs!" About the best you can do is change the direction of the institute and its boss and hope for improvement. The strong research organizations that dominate German research are outside Wissenschaftsrat review, although they are much more visible than most university research groups.

Briefly, that is the structure, organization and finances of German research. The budget is, of course, never enough; but it could be much worse. The bureaucracy involved in applying for grants and

money from various sources is burdensome; but one gets used to it. And, meanwhile, good research gets done.

Comments

Prof. Raphael Mechoulam: What is the real difference, if any, between university and foundation (e.g., Max Planck Society) research? Does it have to do with focus, governance, or something else?

Prof. Reinhard Kurth: It has to do with governance. Until two or three years ago, the universities were largely under the control of their local state governments. Since the state governments had little else to do in education, they decided to concentrate on universities, which was not good. The Max Planck Society and other societies are highly independent. When they have strong leadership, they can nicely but firmly tell politicians to desist, if they don't know what they are talking about. Starting in the late 80s, the societies began conducting external evaluations of their institutes and departments, and actually accepted many recommendations and tried to implement them. The universities are much bigger, but they also have a heavy teaching burden. And they are not so independent. Thus, if a country can afford to set up such research societies, they are fortunate. But it's difficult; you have to sell it to the politicians.

The View from Sweden

Prof. Olle Stendahl

Former Secretary General, Swedish Medical Research Council

First, just to help you compare Sweden to other countries, in the last (2009) Shanghai ranking of universities, the Karolinska Institute ranked third in Europe and 15 worldwide in the biomedical sciences. It ranked first in Europe in clinical medicine, and 8 worldwide (after seven U.S. universities). Clinical research has been very strong in Sweden for many years now, but we have lost some overall impact over the last 15 years. Sweden and Switzerland tie for the first worldwide in publications per million inhabitants, although Israel (fourth) also does extremely well. In impact on biomedical research, Sweden held its level of average citations per paper rather steady during 1995-2005, while Switzerland and Denmark have forged ahead and passed it. So we do worry a bit; and our government would like to push our R&D trends upward.

How much does Sweden invest in research? The total budget for Swedish R&D is about €11 billion or about 3.5% of our gross domestic product (GDP). That is pretty good. Only Israel allocates a larger percentage (although much of it is industrial R&D). Biomedical R&D accounts for about 20-25% (€2-4 billion) of the total. As in Germany, about two-thirds of that is from industry. However, the one-third from government represents a national investment in biomedical research of about €100 per person. Most of this is curiosity-driven research. Industry's money goes mostly to industrial R&D, with very little spillover to universities. Even Sweden's big biomedical and biotech companies, which do invest heavily in their own intramural research, rarely invest in university research. Sweden's politicians are proud of our overall R&D record,

but our investments in university, curiosity-driven research are what is really important.

How do we decide what to invest in? Every four years, our Ministry of Education and Research (MER) presents a research plan and bill to our legislature. The MER lays out their research priorities and strategies (all fields), and propose specific allocations of money for our universities, research institutes, government agencies, and research councils. Those institutions then distribute their money among their research projects and activities. About 90% of the funds eventually goes to research conducted in the universities (not in the institutes or agencies themselves). We also have some private foundation, charity and international money (about 10% total).

MER funds biomedical research both directly and via the large, omnibus Swedish Research Council (SRC, total budget about €460 million). The Medical Research Council (MRC), as part of the SRC, gets about €100 million of that. As elsewhere, the Ministry gives the money to the SRC, but leaves all the decisions to the SRC Board, which is dominated by researchers elected by the universities. Of course, the government and the politicians do want to influence overall strategy, etc.; but when it comes to setting scientific priorities, evaluating projects, and distributing money, the SRC (and MRC) is a rather independent entity. About 90% of our biomedical research funding (MRC) goes to our six medical schools. The Karolinska Institute is both a "one-faculty university" and a medical school.

Funding clinical research is even more complicated. The MER (direct funding of universities), MRC, charities, and international sources are still there; but Sweden's County Councils, which provide Swedish healthcare, also allocate some of their local tax money and federal funding. They are, in fact, the most important player (50% of total funding) in supporting clinical research within our six medical

schools and six university hospitals. It's a little bit like the British National Health Service supporting clinical research through their NIHR.

To summarize, in biomedical and clinical research, the universities chip in some money (25-30%), the research council also chips in some (15%), and industry chips in very little (about 10%). International sources, such as the Bill and Melinda Gates Foundation and the EU Framework Programme are becoming more important players, as are domestic foundations and charities (and the County Councils for clinical research). So the universities are losing their own funding. Since the County Councils are directly responsible for healthcare, they should be a strong driving and supporting force for clinical research.

As for the Karolinska Institute, which accounts for about 40% of all Swedish biomedical research, about 50% of their €300 million research budget comes from external funding, with the County Council and government making up the rest. As external funding becomes ever more important, the Research Council's strategy is not matched by sufficient funding.

The research process involves basic research, applied research, clinical trials, implementation and assessment. Funding, however, is not equally distributed between these steps. Everybody likes to fund basic research and exciting new clinical research. We are pretty good at identifying really good basic and clinical research and benchmarking it. But the closer you go towards implementation, the harder it becomes to get research funding and to evaluate the results and impact of that funding. Coping with that deficit is a big, politically important challenge. The politicians don't care about the number of papers you published in Science unless it leads to something useful or profitable within a reasonable time. They will

not wait twenty-five years for monoclonal antibodies to have a clinical impact. After four to six years they will shift their focus. We must improve the whole research process with respect to long-term funding and commitment.

In summary, the Swedish funding process is very bottom-up, university-driven and investigator driven. Every attempt to make top-down strategic decisions will be opposed by most researchers. So we have very few top-down initiatives. However, infrastructure and basic government support to the universities has decreased. The available support is fragmented, short-term and increasingly involves external funding and co-funding. Most EU and other programs require university co-funding, which will affect the long-term strategies of the universities. We have to think about how to cope with this. Similarly, although the SRC budget has increased by 250% over the last ten years, at the same time, clinical trials have decreased by 20%! So challenges remain, particularly in clinical research.

In the future, there will be more national and global initiatives. The research-driven bottom-up process must be linked to more proactive initiatives, or politicians will not increase Sweden's research budget. We have started, therefore, new centers of excellence, concentrating our expertise and money. Swedish research is strong, but too fragmented: a small country (9 million people) with many scientists spread between six medical schools and several colleges. Most grants are allocated for only three years, although we are gradually moving towards five-year grants. Translational research is increasing, and we are building a new research hospital on the Karolinska campus in Stockholm, with a more translational and supportive structure.

Finally, Sweden has a strong pharmaceutical and biotech industry that supports its own clinical trials quite well, but supports very few

investigator-driven clinical trials. Our government, therefore, should devote half-a-billion Swedish crowns a year to support the latter. To successfully implement medical research for better health, we need university medical centers (UMC) that are truly integrated, with an equal emphasis on research, education and healthcare, all under one leadership. (In Sweden the federal government is responsible for education and research; and the County Council, for healthcare.) We are now trying to promote our integrated model to better facilitate collaboration between Swedish academia, healthcare and industry.

Comments

(Unidentified): I was struck by your four-year budgeting process. Does that lead to discontinuity, or have investments and priorities over time been consistently and smoothly evolving?

Prof. Olle Stendahl: The four-year periods can actually promote funding continuity and financial stability. For example, a few months before the current financial crisis, our government approved increasing our research budget by €200 million, a very large increase. And they didn't back out, once the economy sort of collapsed. However, the long-term strategy can change every fourth year, depending on the political situation.

(Unidentified): When money goes from the County Councils to the university hospitals to support medical research, is it the hospital that decides what research to fund?

Prof. Olle Stendahl: Yes. The big issue at the moment is whether all six university hospitals should receive their money automatically, or whether it should be allocated according to research performance. We support a more activity and quality-driven allocation, based on a more national perspective.

Biomedical Research and Development in Israel

Policy Support and Funding of R&D in Israel: An Overview

Mr. Yigal Erlich

Deputy Chairperson, Israel National Council for R&D

I will speak mainly about financing and government policy, and the special problems that biomedical and biotechnology R&D startups have in those areas. I will address only two of the five elements that constitute that ecosystem in Israel, namely government and venture capital.

In an area like Information and Communications Technology (ICT) the ecosystem is more or less complete. Israel has active companies of all sizes – small, big and medium. There are research institutions, defense institutions, and multinational companies. All contribute to the emergence of new companies. There is also a full range of financial tools: venture capital, private equity, and programs run by the Office of the Chief Scientist (OCS) of the Ministry of Industry and Trade (MIT). Most of that is non-existent or barely active in the biotech realm; and capital investment is much higher in the high-tech sector. International companies, one of the major builders of the ecosystem, invest about 90% in ICT, but only about 10% in life-science related initiatives.

Venture capital funds, of which Israel has many (post-1993), have invested a lot in high-tech but almost nothing in biomedical ventures. In the 90s, the venture capital and financial markets began to be very effective, and a few years later some big international companies started acquiring local companies. Within fifteen years, more than 200 companies had come here by acquiring small Israeli companies and their technology; and, in turn, they also contributed

a lot to the economy. Although Israel often questions whether it should sell technology instead of growing its own big companies, in those years, at least, it was a very positive move. However, we don't have many such international companies in the pharmaceutical and biotech sectors – less than ten and almost all in medical devices.

Israel's biotech industry is also very fragmented. A recent study by Ernst and Young (2008), showed that we have about 798 biotech companies, about 90% of them small, so they must continue to do R&D or disappear. Again, the most advanced area is medical devices, in which we had 406 companies in 2007 (12 with over 100 employees). So, when we talk about biomedical companies to Israel's financial community and government, they first think about medical devices rather than drugs.

More generally, Israel does have efficient resources for new companies. All universities have technology-transfer organizations (TTOs) that know how to operate (the Weizmann Institute's Yeda is the third most profitable TTO in the world. All have had their successes – unfortunately, more past ones than new ones. Hadassah, which works through Hadassit, is now trying to establish their own companies, a different model than most other TTOs which concentrate on giving licenses and collecting royalties. Hadassit has already built a cluster of about twelve companies in different areas; but life is very difficult for them because there is almost no financing. The only thing that rescued them (and many other small biomed companies) three years ago was the Tel-Aviv Stock Exchange, a rather temporary phenomena, that is not consistent – one cannot depend on it. Still, more than twenty small companies were able to raise money and survive.

As for the Israeli government's industrial research and development policy, there have been three main elements for the last forty years.

The Ministry of Finance acts according to economic principles; and if there is a market failure they do not hesitate to intervene. The MIT/OCS engages in risk-sharing and catalysis. They get a lot of funds, not only because the applications and companies they fund are indeed good, but also because they get major matching funds from industry. That is easy in the private sector, but not in the universities.

The government follows several principles when trying to cooperate with the private sector (business). One is matching funds. The other is neutrality. The MIT/OCS does not intervene or tell our companies what R&D to do. It will fund any project that has a demonstrably good innovation and the potential to grow. Only in the last 2-3 years has there been a policy shift that has created some proactive, preferential activity in nanotechnology and biotechnology; but mostly the MIT/OCS is still highly neutral. A third principle is for the government not to accept control, but to only make indirect investments, as it did when it established Yozma in 1992 (which created ten venture capital funds, that in turn invested in specific companies).

If the government ever does abandon neutrality, it will need someone to set national priorities for allocating capital. There is a National Council for Research and Development (NCRD); but, unfortunately, it doesn't have the right position to be influential. It belongs to the Ministry of Science, which has too little power. Still, some such body should help define such priorities, and also balance the allocations going to universities, hospitals, clinical research, industry, etc. Nobody really does that now (although the Ministry of Finance is, of course, technically responsible). To do it correctly, the Prime Minister must become the chairman of a modified, more powerful NCRD. That's a key to pushing many of the things we have been talking about, but I'm not sure that it will happen.

What are the existing mechanisms for financing R&D? The MIT/OCS has an annual budget of about $400 million for industrial R&D in companies. Some private individuals also invest in companies. Israel's Teva Pharmaceuticals has made more than fifteen investments in small bio-companies. That Israel has only one such company in this field. There are also the Tel-Aviv Stock Exchange and venture capital funds (which invest mainly in ICT and medical devices). Venture capital financing is relatively short-term, not more than ten years from investment to anticipated returns. If you see in advance that it will take longer, you don't start. This is the main reason for the government's decision to help attract funding to the biomedical industry by allocating about $80 million to new funds. They expect that leveraging will create a market, and that another $300 million will be invested in biomed companies if their initiative is successful.

MIT/OCS does fund some biotech collaboration with academia. Only Nofar is devoted to biotechnology. It provides $100,000 per project; and 90% of its funds are from the government and only 10% are from the private sector. It had only fourteen projects in 2008. There are also some innovative bio-companies in the MIT/OCS technology incubator programs. But, as a whole, the MIT/OCS invests less in biomed than in other fields: about 25% of the total, and not more than $90 million a year (2008 figures). Only about $13 million of the MIT/OCS's money went to pharmaceuticals, most – again – was in medical devices. In the venture capital community also, bio-investment (2008) was very low; about $30 million compared to $185 million for devices.

Here's what happened when the government, in 1992, invested $100 million in its Yozma fund, to establish a venture capital market. Yozma established another ten funds and, after four years, was privatized (the government now is not involved in venture capital).

Some $60 billion has been raised since then, but only 10% went to life sciences and most of that went to devices. The management and acquisition movement that started in the mid-90s saw a turnover of $23 billion, but only $2.4 billion was bio-deals, again most involved devices. So this initiative greatly affected the ICT market, but did little for biotech.

The Israel biotechnology industry is, thus, not yet a major national player. Of its 160 companies, 106 have less than 10 employees. Its total of about 2,500 employees is dwarfed by the about 100,000 employees in the high-tech sector. Six Israeli biotech companies are listed on the NASDAQ exchange, compared to 70 high-tech ones (GlenRock, 2007).

Ernst & Young's research concludes that Israeli venture capital, as now structured, is not suited for the biomedical investment. Of course, they do offer some suggestions, which perhaps none of you have seen.

The main question is whether biotechnology is a national priority or not. We can ask the same question about the biomedical sector. It is a good macro-economic question. If you look at the government's total investment in universities, the life sciences garner 30-40% of the total budget. But if nothing happens on the other side of the pipeline, we have a problem. We train ever more people as experts in these areas, but once trained they cannot find a job. We need to fix this imbalance by increasing money for new biomed companies and by promoting more successes, rather than by cutting our universities.

So there is a capital shortage; and there are challenges; and everybody talks about the IP problems. In the case of government hospitals, our government hasn't done anything about it for the last five years. All this slows the potential we have for developing new ideas and

innovations. We also have a shortage of experienced managers. The government should try to bring more biomed-oriented multinational companies here. We need more balances in future R&D and that could be done under a NCRD headed by the Prime Minister. We need to attract two or three big biomedical companies immediately, strengthen our clinical research, and create more capital for companies in this vital, but undercapitalized, sector.

Comments

(Unidentified): Recently the founder of Medical VC Fund, in an interview in Haaretz, said that the biotech industry in Israel is a pipe dream. He put the blame on the quality of researchers in Israel, except for a very few outstanding exceptions. Is this really the problem?

Prof. Benny Geiger: People find many excuses to explain what they don't do. There is a structural problem in funding; it's not a question of quality, it's a question of being a financial non-starter. Investors don't look at biomedical companies, because they know quite well that it is going to take longer to realize returns. So, if they have other alternatives, they quite rightly go there. It's very simple.

Prof. Christopher Kennard: Some of the problems that you mentioned may be of national origin; but others are international – for example, the lack of capital for growing small companies.

Prof. Benny Geiger: As you say there is no financing in the market; and when the private money is decreasing, the government must play a more active role. In the U.K. there is a plan to put at least £500 million into a fund to raise such money. The government also has to decide its priorities. Today industrial biotechnology, in general (i.e., not only biomed or devices), is stronger than it was in the past, so when you think about allocating a limited budget,

this must be taken into account. On the other hand, Israel's great potential in the biomedical sector is obviously not being fully exploited. The question is whether we can really be a successful player there or not.

Biomedical Funding by the Israel Science Foundation (ISF)

Prof. Benny Geiger

Area Chairperson, Life Sciences and Medicine, ISF

The mission of the Israel Science Foundation (ISF) is to fund, on a competitive basis, meritorious basic research, without earmarks or priorities in any particular field, to provide a foundation for the generation of new knowledge in Israel. For convenience, its activities are divided into the Exact Sciences and Technology Division, Life Sciences and Medicine Division and Humanities and Social Sciences Division. The ISF started in 1972 as Israel's Basic Research Foundation (BRF), with just $300,000. By 1995, its budget had greatly increased to $22.6 million, and it became an independent body with its own Council, Executive Committee, and Academic Board. Its administration is still small, but extremely effective. The ISF is respected by the scientific community for its high-quality evaluations, which involves both international mail reviews and local study sections.

The ISF's largest program provides individual research grants for up to four years. In addition, there are Centers of Excellence grants and a unique Bikura (FIRST) program for high-risk, high-promise research proposal, which are rarely funded by regular programs because the likelihood of their success is unclear. There are also some research workshops and equipment grants. The latter fare poorly when we have budget cuts or limitations, which is sad, because they are extremely important for conducting good research. The ISF also encourages international interactions. For example, we collaborate with foundations abroad to facilitate joint research by providing small complementary grants, covering mostly travel

costs. This "glue money" can also help these groups submit serious joint grant proposals to international bodies.

All these years, the ISF (but not FIRST) has funded only excellence and not topic-oriented research. We always felt that it is not our job to tell researchers what to do or to set topic-related limits. Excellent researchers will make the right decisions. Originality, creativity, excellence – all such criteria play the major role.

As for our funding, you can easily transform everything from the Israeli scale to the American scale by simply changing "millions" to "billions." The ISF budget increased during the 90s, to $48.8 million in 2001, although a projected target of $80 million per year was not reached. In fact, thereafter, the main budget, most of which comes from the Planning and Budgeting Committee (PBC, VATAT) of the Israel Council for Higher Education (CHE), has remained quite flat, until the last few years. Various additions from major donors recently increased the total budget to about $70 million.

Our annual budget, everything included, is now about $78 million and we receive about 1,700 new research proposals a year, about a third of which are funded. So, last year, we funded 1,564 grants: about 1,000 ongoing and 500 new. The average grant is usually about $48,000 a year in the Exact and Life Sciences, ranging from $30,000-70,000 a year. Of course, in the United States and Europe, similar grant proposals receive about $100,000 to $300,000 per year for individual grants, and investigators can submit several applications. That is what our researchers have to compete with. Grants in the Humanities and Social Sciences are typically smaller because they require less infrastructure and equipment.

Several very interesting recent innovations are due to cooperation between the ISF and the U.S.-based Legacy Heritage Foundation

(Morasha). One of our joint programs deals with Israel's brain-drain problem by providing returning Israelis attractive recruitment packages (including equipment). Two other joint programs are specifically related to biomedical research. One provides young clinical investigators in hospitals grants which buy them "protected time," at least two more days beyond what the hospital gives them. The program also provides research support. The second program (Legacy Biomed Project) currently proactively focuses on neurodegenerative and genetic disorders. This deviates from our tradition of undirected funding, by selecting just two preferred topics. Both were already funded, but needed a lot more investment, allowing us to help some excellent groups already working in these fields in a much more generous way. Biomed grants are about double our regular grants. Here too, scientific excellence remains our only criterion for evaluation (within the selected fields).

The ISF's portfolio of grants in the Life Sciences and Medicine (2003-2009) can be divided by topics (review committees) or combined into three broader groups (which characterize our typical landscape): biomedical research (467 projects, 531 including Morasha), in which there is a direct relationship to a human disease; biological research (345), which has potential biomedical implications but is not directly related to a medical application; and basic research (122), in which we cannot foresee (without intellectual acrobatics) a direct relationship to biomedicine. The latter includes such fields as botany, ecology and environmental research. Much of the research we currently support is potentially related to biomedical research, although funding is sporadic, limited, and extremely low relative to the existing potential and needs.

In passing, I would note that it is very difficult for part-time researchers in hospitals to compete for these ISF grants. They submit fewer proposals (only about 9% of the total) and their success is

significantly lower (19% compared to 31%) than that of full-time researchers in academia. We need to change that.

The Morasha Biomedical Program has contributed more submissions, more awards and higher acceptance rates in its chosen areas. This program has also yielded some interesting trends and insights. For example, 130 preproposals were received in the first year. Half were approved for further examination and 23 of them were awarded grants (about $100,000 each), a success rate of about 18%. The number of submissions decreased in the second year (89); and, in the third year (now), the number of submissions was lower still (59). So, by focusing on a specific topic, we seem to have slowly exhausted the number of potential, high-quality applications that are still unfunded. We need to sit down with the Legacy Heritage Foundation to think about how to broaden the program's scope or to include other fields within biomedicine.

Of the 109 physician-researchers funded to do research in 2003-09, fifty were directly due to the Legacy Heritage Foundation's involvement, a significant impact indeed. Thanks to such efforts, we are beginning to see more people moving from the clinical environment to more basic research. An earlier Batsheva de Rothschild Foundation (prototype) series of Physician-Researcher Awards also covered "protected time" plus a research grant to physicians. Although our new program has received only 13 applicants a year for the first two years, the number of submissions doubled in the third year, an indication that clinical researchers and hospitals are beginning to internalize this concept. We don't know what will happen next, but all these grantees – and we do monitor them – are indeed establishing themselves as clinical researchers. Hearing their enthusiasm I think that this is exactly where we can invest heavily and wisely. It will require strong collaboration with the hospitals, but the promise is huge.

For the future, we need to drastically increase the ISF budget; and several committees have already recommended that. To be competitive, we must fund research at levels comparable to those at the best places abroad. We need to better support excellent biomedical research, in the spirit of the recommendations of the Arnon Committee; and we need to continue and extend clinical investigator programs. The existing Legacy Heritage Program for supporting outstanding returning Israeli scientists is ending shortly; and we need alternative sources of funding. Finally, we need to involve groups in the Exact Sciences and Social Sciences and Humanities that can contribute cross-disciplinary research activity. In a way, the ISF is a "one-stop shop," where we can create these new interactions that can contribute so much to the future of Israeli biomedical research.

The State of Clinical Research in Israel

Prof. Gabriel Barbash

Director, Tel Aviv Sourasky Medical Center

I would like to share with you a hospital's perspective on the promise and problems of biomedical research. The promise includes recent advances in biomedical science, molecular biology, advanced treatment and diagnostic procedures, etc. In Israel we have excellent medical care, usually provided by an elite group of professionals exposed to the latest science. They are an excellent source of innovation for healthcare, and they can act as a bridge between advanced medical fields and Israel's biomedical industry. These slides, from the Chief Scientist of the Ministry of Industry and Trade, show Israel's competitive advantage in both research and patents. Israel ranks first in the number of medical device patents; and fifth in the number of all patents. We also spend an exemplary amount on R&D per GDP and per capita.

Our hospital's research network, like that of many other major hospitals, has a clinical research arm (the largest and most industry-driven) and a basic research arm. We currently have forty distinct research groups (centers of excellence), although some consist of only one person, and a medical-device technology incubator. We do industry-initiated research partly to get the funds to support our other research arms.

Of our 1,000 physicians, 25% are involved in some kind of (mostly clinical) research. In 2008 we received 39 competitive grants which provided over NIS100,000 (each). However, these involved only 14 MDs (five of them MD/PhDs) and six PhDs. So there is only a small core of investigators doing truly competitive research.

A recent study of Israeli patent applications registered with the U.S. Patent Office (Roll and Lerner, Tel Aviv University) shows that the contribution of hospitals increasing, compared to universities, during 2004-2008. The number of hospital-related applications is increasing every year, as are patent families, joint patent applications (with other institutions) and projects opened for license.

Given all this, why are Israeli physician-researchers so rare? First, there is the long training period: seven years of medical school plus more years to get the necessary scientific skills. They need to master two distinct professions: a good physician cannot automatically do good research; and there is very intense competition for resources. They never have just one project or career to develop; and developing both creates an inferior situation for them, as compared to full-time scientists. Then there is the very real temptation of higher paying private practice, which takes some of our best physicians out of research. When they move from the public system to the private one, we lose valuable human resources. You have to catch them when they first come back from their research fellowship, before they go into private practice; later it is a lost cause. This is partly why we see so few surgeons involved in research. They have less time to invest while doing their demanding clinical work, and the outside temptation is much higher.

On another issue, we have had a ten-year discussion with the Ministry of Finance about the intellectual property management of government hospitals, particularly the need to give royalties to their researchers (all Israeli academic institutions give 40-50% royalties to their researchers). The Israeli government can't seem to allow that. The Ministry holds: Your physicians are paid to do clinical work not research. So they ask: Can't we limit the number? Can't we have a percentage? These questions reflect a basic misunderstanding at the mid-level of the Ministry of Finance. We

think that we are starting to overcome that, but we thought so ten years ago too!

Returning to hospital administration, why do we invest in biomedical research? First, clinical excellence goes hand-in-hand with scientific excellence. Second, to develop leadership in medicine, you need people strongly based in research. It is becoming increasingly difficult to find people who have both excellent clinical and research capabilities. Also, people increasingly want to invest more time in their families, which, while laudable, also competes with public service. Finally, maybe, sometime someone will come up with an innovation that would allow us to disconnect from the government and expand our research component.

What other dilemmas do we face, when dealing with biomedical research? First, priorities. How do we allocate funds between topics? Strategies are less important, because we cannot develop a research strategy for our institutions. What we develop is based on people, going after excellent people, not after subjects. Second, is the issue of applicable versus basic research. I personally believe in letting anyone do whatever he or she is really good at and wants to do, because, if he is an excellent researcher, he will come up with results. But, in practice, because of the scarcity of resources, we often limit our support to applicable research. We have collaborated with the Weizmann Institute for ten years now on applicable research projects. What about a bright researcher who is a poor clinician, particularly if he wants to practice? I remember two researchers being let go, because we couldn't hire them as physicians; so this is an issue. There are also ethical issues, and issues of quality assurance. This is comparatively simple in clinical studies; but how can you assure the quality of basic research?

How do we promote research? First, research is required for promotion. Hospital physicians know that they cannot get a permanent position or head a unit or department, without significant academic background. Hospitals also may have "excellence" funds (Talpiot, Ofek=Horizon) that provide protected time for physicians. We encourage and fund some training of physicians to become MD-PhDs (we have such a collaboration with the Weizmann Institute). We collaborate with other institutions to complement our clinical capabilities with their basic science capability. We also have a technology incubator and compulsory GCP training (Good Clinical Practice).

In our view, when research money comes in, it should be allocated to three pillars. One is dedicated time for research. Second, laboratory support, not only infrastructure but also manpower support. And finally collaborations, which are an important tool to get centers and researchers to work together. For example, Israel has been considering establishing a central national tissue bank, a potentially important tool for supporting advanced research. Once these issues are resolved, Israel is going to move ten steps ahead; and I think this is what we should concentrate on.

Comments

(Unidentified): Do any Israeli clinical academics work in hospitals as university employees under a university contract, or are they all hospital employees?

Prof. Gabriel Barbash: They are all employed by the hospitals, except at Hadassah where there are joint appointments. During a recent two-month sabbatical at Columbia, I saw the bizarre situation which arises when you are running a hospital, but you are not really running your university-employed physicians. If the Dean of the university and the CEO of the hospital don't talk to each other, they are lost.

(Unidentified): Our hospitals have a lot of university-employed clinical academics. They have joint appraisal, joint planning, etc. So you need a clear agreement between the university and the hospital about what that individual does. The accepted norm is 50% research and 50% clinical work, typically (for a physician) two outpatient clinics a week.

(Unidentified): In our country, professors of medicine are paid half by their hospital, and half by their university. They have to go before the committees of both organizations. All hospital physicians must now work full-time for the public (formerly they had some time for private practice), divided between teaching or research, on one hand, and clinical work. This big change was taken in ’59; but now there is more need for physicians than for teachers/researchers. So now, in addition to the professors (both hospital and university paid), there is a large number of clinical physicians, paid only by the hospital, who do almost no research.

Prof. Uri Seligsohn: If there were one thing that you could change to enhance your ability to pursue a research agenda, what would you change?

Prof. Gabriel Barbash: I would pick more funding for more allocated time. We can manage the other issues. Regretfully, I must add that we do not have too many physicians waiting in line, but once a critical mass is created, we can attract more such physicians to come, and more youngsters will join.

(Unidentified): What proportion of your research physicians do basic science and what proportion do clinical research? Laboratory-based research can be done by non-physicians; but only physician-researchers can do high-quality inquiry-based clinical research.

Prof. Gabriel Barbash: Only about 5-10% of our physicians do really basic science and work in laboratories.

Prof. Uri Seligsohn: Please don't get the impression that all Israeli medical centers have such a dynamic director who is interested in the research. Prof. Arnon will discuss her committee's broader findings about that tomorrow.

Findings and Recommendations of the Committee for the Assessment of The State of Biomedical Research in Israel

Prof. Ruth Arnon

Vice-President, Israel Academy of Sciences and Humanities and Chairperson of the Committee

Let me start with some background. Why did we decide to delve into this whole issue? Israel has several sources of funding for general basic research (all fields) – the Israel Science Foundation (ISF), the Ministry of Science, the Chief Scientist of the Ministry of Industry and Trade – but there is no major national institution that allocates specific, targeted funding for biomedical research. This is in sharp contrast to other developed countries. For example, the U.S. has a thriving National Institutes of Health (NIH), separate from its National Science Foundation (NSF). In France there is ISERM, which is distinct from its CNRS. The U.K. has a Medical Research Council (MRC) distinct from all other research councils; and in Sweden, the Karolinska Institute de facto plays a comparable role. So we thought, shouldn't Israel be considering its own need for specifically earmarked biomedical research, particularly since there is a widely perceived need to improve Israeli clinical research (i.e., the current system does not seem to be working). After further discussions the president of the Israel Academy, Prof. Menahem Yaari, decided to form a special committee to examine the situation and to make specific recommendations.

How should we approach this rather general task? We began by collecting information, both within Israel and abroad, in three major categories of research: basic research, clinical research and translational research. All three categories exist in Israel and all three

combine to constitute a complete biomedical research system; you cannot focus on one issue while neglecting the others.

We also decided, from the very beginning to seek the advice of experts from other developed countries, particularly from the U.S. and Europe; so we invited an international visiting committee of three to four people for each of the three aspects we were studying. We provided the visiting committees considerable background information and helped them interview anybody that they wanted to speak to in Israel. We also asked them to write an independent final report. The three committees were formed and operated consecutively, so the whole process was somewhat lengthy (about 1½ years). Then we took another 2-3 months to prepare our own final report.

Both we and the visiting committees conducted many dozens of meetings and interviews. Our committee included high-powered representatives from various levels of research – from academic institutions, hospitals, industry, technology-transfer companies, etc. We wanted to have representative opinions from every actor involved.

What were our major findings? First, and this is not new, there is a lack of funding in all three areas. We cannot efficiently utilize our wonderful human resources this way. We have fantastic researchers and clinicians; but, because of the lack of funds and their distribution, we don't make the best use of them. Since human resources are Israel's main resources, we should not waste them. We really need to make things much more efficient.

Basic research was the category least affected by a lack of funds, mainly because we have an ISF that allocates about 40% of its funds to the life sciences and to biomedical research (although that

is also not enough). The most severely affected category is clinical research. Interviews with quite a few clinicians revealed that the most critical missing factor was the lack of "protected time." Their time is completely consumed by the clinical tasks, and without protected time for research, they really don't have enough research time to be competitive. This is true both for young clinician/researchers and for more established ones. We also don't have sufficient mentors among our more advanced physicians for our young clinicians, to attract them and to guide them in their clinical research within the hospital setting. Solving this problem (which also requires more funding) should be a very important part of our future efforts.

Actually, the Israel Academy recognized this difficulty some five or six years ago. We then established an experimental Batsheva de Rothschild Clinician-Researcher Fellowship Program to provide young physicians (immediately after their postdocs) a chance to devote half of their time to research for three years. The Program refunded half of the clinician's salary to their hospital, allowing it to hire a half-time replacement. This test of this concept was very successful. The ISF, together with the Morasha (Legacy) Foundation, has now extended this approach. This should really help Israel in the future.

There are several stages of translational research. There is bottom-up research in which a basic researcher in a research institute or university stumbles on a project that can be applied – not applied research but rather "applicable" research. But it is only applicable if you invest more time and money in it to (possibly) convert it into applied research. Regrettably only a very small proportion of such "applicable" projects actually become applied projects in industry. Still, if we don't pay due attention to applicable projects, we will never get applied ones; and if we don't do basic research, we will not have research to apply. So we should focus on all three stages:

basic, applicable, and applied research. The scientific community can handle applicable research, but applied research can require orders of magnitude more money, which must be supplied funded by industry, venture capital, or private funds earmarked for this purpose.

Our committee had six recommendations. First and foremost was to establish a national fund for biomedical research, something similar to the MRC in England, a research fund earmarked only for biomedical research. It should eventually be separate from the ISF and it should aim at promoting both basic, clinical and translational research. Meanwhile, the fund should start (as a practical matter) as a joint effort of the Israel Academy and the ISF. In the beginning it would be administered by the ISF; and once it grows enough to be self-sufficient, it will become independent (three to five years later). Actually, the ISF itself was started this way. It began as the Basic Research Fund (BRF, 1972) of the Israel Academy with really small sums; and it was administered by the Israel Academy. Then, when it grew sufficiently to justify an administration of its own, it became a legally independent organization (1995).

Our goal is an annual budget of $100 million. After making many comparisons to other countries and considering many other factors, I think this is a highly reasonable goal. Some people here regard it as an astronomical sum, but I believe that eventually we will reach it.

The second recommendation is to provide more funding for basic biomedical research. Although this aspect suffers the least, we need considerably more funds to take full advantage of our human resources. Our scientists now spend about a third of their time on writing grant proposal and reports. This would be much easier and more efficient if more funds were centrally available. The additional funds should be allocated by the new foundation, as (conceptually) an expansion of Israel's ISF.

The third recommendation is to strengthen clinical research in Israel's medical centers and to develop appropriate career structures for clinical researchers. We want to promote research by clinicians in hospitals who both attend to patients and who have enough funds and time to do high-quality clinical research. The number of Israeli clinical research papers has long been high, but their citation index and impact have long been quite low. To increase the quality of this research, we must provide clinical researchers with more time, funds and equipment for research. Prof. Seligsohn's detailed working proposal can help us meet this goal. In the beginning, institutional efforts should be directed towards Israel's six larger clinical research centers; but even smaller medical centers will be able to apply for center-of-excellence grants.

The fourth recommendation is to support university-based translational research that can lead to biomedical and biotechnological applications. Israeli universities already have incentives to do applicable research; and our idea is to further encourage university applicable and translational research (but not applied research in industry). Some of our experts have offered suggestions on how to raise the much larger sums needed for applied industrial research; and, as a separate matter, we intend to discuss these with our government.

The fifth recommendation is to establish a permanent mechanism to evaluate Israeli biomedical research in comparison with that of other countries. We also recommend that the Israel Academy of Sciences monitor biomedical research worldwide to identify important new research directions and trends that Israel should not miss. The new national fund should be able to develop new directions of research and to integrate emerging new technologies into research.

The sixth recommendation addresses the intellectual property and patent rights of researchers in Israel's government-owned medical centers. Most Israeli universities provide their researchers part of the royalties or profits the university receives for their inventions. This does not exist in government hospitals or institutes, since all intellectual property now belongs to the government, a serious negative incentive for clinician-researchers. The Committee urges our government to essentially adopt the American model, as embodied in their highly successful Bayh-Dole Act, and apply this to clinicians working in government hospitals. We will make efforts to help promote this important change. So, taken as a whole, this is how we see the road ahead.

Comments

Prof. Benjamin Sredni: At present, about the only place that that is devoted solely to grants for biomedical and translational research is a small program run by the MOH Chief Scientist. Our former Director-General, Prof. Avi Israeli, understood that clinical research was important and he almost doubled our (admittedly small) budget. You are right. We do need a lot more money devoted to this. Even so, our grants are now almost the size of ISF grants, over $40,000 a year. We also have two large programs (over $100,000 and $270,000) for doing clinical trials. So things are being done – albeit not at the level we need. Your report suggested that the MOH join the ISF and the Israel Academy on these grants; and we are very happy to contribute to and to be part of that.

Prof. Ruth Arnon: We think that it's fantastic that the MOH has grants. Although the sums available are not too high, we hope to increase them. But, still, it is not good for research to compete with health services under the same umbrella, because, in any competition between a research grant and an old lady dying in the

corridor, research will lose. However, when the funds are earmarked for research, it is fantastic.

Prof. Jean-Francois Bach: The lack of protected research time is very important indeed. But the patients are still there; and trying to do both jobs also poses problems of split interests and identification. Research requires real devotion, so the way to make this work needs more discussion.

Prof. Ruth Arnon: That is a very important point; because good research can be done only by somebody who really wants to do good research. Otherwise, the research may be of no benefit whatsoever. We are taking for granted that a reasonable number of clinicians want to be interested in research and want to do it.

Dr. Yaacov Bergman: There are two ways to deal with a lack of adequate funding. One is to demand more money; the other is to see how existing funding can be better allocated and used. Your committee's report emphasizes the first, but says little about the second, the evaluation of the quality of research that is now being funded and done in Israel. A recent report by Eisen and Fritz recommended that the funding for the one-third of all researchers, whom they found to be suboptimal, be stopped. Giving that money to the upper-third of all researchers would provide enough money for scientific excellence without further ado. The Israel Academy of Sciences would have to take the lead on this.

Prof. Reinhard Kurth: Prof. Arnon, what are the chances that what you describe can be implemented in Israel in the mid-term future, and how can we from abroad help?

Prof. Ruth Arnon: I hope it can be implemented. We will work very hard on it; and part of that effort is this workshop. Everything

is recorded; and we will print our discussions and send each of you a copy, so you can go over them and make corrections. This workshop and your participation are part of our strategy for working towards implementation.

We can learn so much from what is being done in other countries; and we hope very much to implement some of your successful ideas here. So this workshop is really extremely helpful to us. Also, when I looked at the sums mentioned in your presentations, it further strengthened my belief that our goal of $100 million is not only desirable, but truly needed. It seems comparable per capita to what is being done in other developed countries. So that gives us much more incentive to try and achieve that goal. I think that eventually it will be achieved. I certainly hope so.

National Support of Biomedical Research: Expert Panel and Open Discussion

- The Influence of Public Opinion on Political Decision-making
- Investigator-Initiated versus Directed Research
- The Special Needs of Clinical Research

The Influence of Public Opinion on Political Decision-making

The following discussions have been edited and shortened.

Prof. Alex Keynan: Yesterday provided a fascinating description of how several important advanced countries, of various sizes, support biomedical research. I believe that this is a first and that these proceedings could be a useful, if not landmark, reference in this field. The many common problems that all such funding systems face, and their potential solutions, are the focus of this discussion session. Israel is also facing and debating these issues, and we can use input and advice from those of you with more experience.

Let's start with the question of the influence of public opinion on political decisionmaking. In democracies, national budgets often reflect the wishes, interests, and opposition of the population (voters). So biomedical research needs a certain amount of public support. Just how important is public opinion? Are there specific sensitive points we must address? We scientists already believe that what we are doing is in the public interest, but does the public need to be convinced of that?

Prof. Harvey Fineberg: I am speaking from a personal and U.S. perspective, so I cannot assume relevance to other settings. All democracies share a certain dependence on public sentiment, yet national culture, history, tradition and experience add a very important layer of particularity to that general statement. America is characterized by an abiding sense of optimism and progress, a faith in the capacity of people to solve both their own problems and the world's problems. Historically, based in a frontier mentality and in progressive movement across a vast continent, this attitude is still a profound undercurrent in American sentiment.

On the structural level, the U.S. has a bicameral (two-chambered) legislature, separate from the executive branch. Most important, there is direct representation of specific communities and populations in the legislature. When you live in a given town, you automatically know who your representatives in the national legislature are. In the House of Representatives (lower chamber), these are reelected every two years! Although many incumbents do get reelected regularly, if not indefinitely, they get reelected only because their services seem valuable to their constituents. Thus, responsiveness to constituents is a very important part of our legislative structure. There is relatively little party discipline, compared to a typical parliament. It must seem strange, from a parliamentary perspective, to see how much tension and uncertainty there is about how legislators will vote on a given U.S. government proposal. So constituent (voter) support is important when seeking money for science or any other activity in the U.S. legislature.

Second, volunteerism – gathering into voluntary associations to accomplish specific objectives – is another deeply embedded American tradition. Some associations are very local, others have a larger geographic reach; some are national or even international in scope. The U.S. has literally thousands of independent, self-organized entities that work because they share a common cause.

That combination of strongly constituency-based legislators and highly organized volunteer organizations has a profound influence on the shape of national policy, including science policy, in the United States. For example, today's NIH represents such a legislative commitment driven by public support, embodied historically in a single highly committed individual, Mary Lasker. She persuaded legislators that solving health problems through research was important for the U.S. after the Second World War. Her movement created legislative momentum within the U.S. Congress for an

anomalously high government investment in biomedical research, compared to other scientific research.

More recently, consider the National Institute of Allergy and Infectious Diseases (NIAID). Interest groups devoted to HIV/AIDS profoundly altered the interaction of the public and scientific community in defining research direction, and even its decision-making processes. Breast cancer advocates, following their lead, have had the same kind of profound influence on national health policy. We even have a major breast cancer research program organized through the Department of Defense, because that was the most convenient legislation to use at the time (it could not be easily rejected). Unusual, but it worked.

All this has its wonderful side: we have enthusiasm, focus, energy and commitment that align government action with public interest. However, it also has a darker side: a potential for distortion, undue individual interest, and distraction from more important or more promising mainstream targets of scientific inquiry. Political earmarking may also introduce projects which particularly benefit a particular legislator's locale and constituency.

In brief, advocacy groups can be noisier than their problems are significant in the larger scheme of things; but such distortions are balanced by Americans' optimism and belief in progress. Some 70% of the public wants to invest more than we currently do in biomedical research. Of course, such surveys can be designed to evoke the answers their sponsors favor; but the organization which carried out that one, Research!America, is emblematic of the good that comes from organized public participation. It was started by a former legislator who is very committed to research; and it is a powerful force for mobilizing U.S. public opinion in favor of biomedical research. In the U.S. model, one cannot separate national

investment in biomedical research from the support, interest, and continued commitment of the public to progress in science and their government's investment therein.

Prof. Alex Keynan: America is very special in that regard. Although **we cannot clone Mary Lasker, it would be nice!**

Prof. Harvey Fineberg: Actually, the situation is very different now. There are many Mary Laskers in America today; but few have her global view. Although she was most committed to cancer research, she really wanted all of U.S. biomedical science to be better supported.

Prof. Alex Keynan: Israel has many disease-oriented organizations which can mobilize resources; but even they are not always supporters of research. They are certainly not organized to influence legislation. Many believe that Israel is too small to solve medical problems pursued by the whole world. So they doubt that Israel biomedical research is the answer to their problem. Everybody is basically involved in a local program.

Prof. Harvey Fineberg: Paul Rogers, the legislator I referred to, was famous for saying that without research there is no hope. Research!America looked at getting research funding the same way that Pepsi Cola looks at promoting a new soft drink. They tried to think about what would resonate with the public, how they could best make their case. They worked hard to mobilize scientists in every legislative district to speak to their legislators, explain things to them, invite them to their laboratories. Their method alone is very valuable. Even if it cannot be transplanted here directly, you have to recognize that public sentiment does influence policy, and how it achieves influence.

Prof. Jean-Francois Bach: I was surprised to hear how difficult it is to convince the Israeli government to support medical research, because politically it should be very popular. I would have assumed that the public would have been very receptive to the government providing major help to medical research, because this is usually at the top of their lists of what they want achieved.

More broadly, European public opinion is somewhat conflicted. There is an anti-science movement among a minority of the population, who rarely know what science is about, and among the media. But medical research advocates and patients' associations in our country (France), and in many others, all accept that research is the main long-term objective (although, of course, they also help patients directly). For example, we have a weekend telethon that collects about 100 to 110 million Euros – not bad! It's obvious that much of the money goes to research, and people accept that. It is repeated many times during the 30 hours of live broadcasting on one of the major public channels. So the public will help medical research, in spite of its questions about science. This distinction should be conveyed to the public and politicians. They should understand that it is much easier to do popular things in medical research, than in physics or chemistry, which people understand less and fear more.

Prof. Ruth Arnon: I would agree that parts of the Israeli government are not particularly interested in supporting the much larger national biomedical research budgets that were presented to us by other countries yesterday, although those numbers were very informative. However, what is the role of the media in promoting the public understanding and awareness of biomedical research in, say, the United States? The importance of having legislators who depend on public support is pretty obvious. But even without that, how much could be achieved by working on and through the media?

Prof. Harvey Fineberg: The media can be both a tremendously important ally and a somewhat risky source of distortion and distraction. As Jean-Francois reminded us, certain elements in the public are anti-science or anti-vaccine or anti-government; and the media, by its nature, prefers to report controversy. Consensus and happy agreement are not front-page news. Instead, they tend to run a story quoting one renegade who represents 0.1% of scientific opinion and one expert who represents 99.9% as if they were equal. You see a quotation from one and a quotation from the other, and that's a news story. Still, especially if you include the electronic media, we scientists are slow in thinking strategically about the media, the way we would if we were a business marketing a product – the mentality that we should bring to the table.

For example, think very hard about Israeli media personalities who could take up this cause. In the U.S., having an Oprah Winfrey on your side is a big advantage. Or a man like Danny Thomas, who raised hundreds of millions of dollars for St. Jude Hospital alone. Or a comedian like Jerry Lewis, whose annual telethons regularly raised tens of millions of dollars for research on specific muscular-skeletal problems, within 24-hours. I think there is tremendous opportunity. Yes, the media is a two-edged sword, but it can persuasively inform large segments of the public about the potential opportunities in biomedical research, what it would take to grasp them, and what it could achieve for health, for economic development and for the competitive positioning of Israeli research in a global environment. There is an opportunity here.

Prof. Alex Keynan: Unfortunately, our scientists are not very eager to appear in the mass media. We have very few people with the ability to explain those opportunities and needs. It is a problem.

Prof. Harvey Fineberg: Well, it's true that when a scientist becomes too popular, he becomes suspect amongst his peers. It is not particularly becoming to be a media star; but some are willing to choose this. If they can do it in a responsible way that reaches the public, they are certainly doing a very important service. It could be enough to have one or two prominent newspaper people adopt your cause. We tried to do this. There was even a three-year NIH program to educate science writers, although it was a flop.

Prof. Michael Sela: We cannot always rely on public opinion and lobbies. For example, pancreatic cancer is bad, cruel, and one dies within nine months; but there are few, if any families that would create lobbies for research on it. Sometimes you have to find another alternative.

Prof. Jean-Francois Bach: I'm not sure that we have to be all that specific about a need for medical research; the general idea might suffice. Then again, people are not very open to abstractions. So it is a complicated problem.

Prof. Ruth Arnon: I personally think that, in Israel, we have missed out on harnessing public opinion. Instead, we have tried to go to the Knesset (Parliament) and speak to the Committee for Science and Technology. The Committee convenes, they invite some experts, you come there, only the chairman shows up, and the secretary takes notes. None of the other members come or are interested. I usually have the feeling that I am talking to myself; and nothing happens. We did not consider going directly to the public and harnessing public opinion. When the government approves a basket of health services, there is strong public input, because people feel that they are directly affected by it. In general, our population does not feel directly affected by research. So I am writing your ideas down, because this is something that we did not even try to use before. Thank you for your suggestion.

Prof. Harvey Fineberg: By the way, in the U.S., when I go testify, it is the same as here. There's a chairperson, and not even the secretary, since they record it automatically. But if Oprah Winfrey comes to testify, they will all be there!

Prof. Alex Keynan: I would like to ask Avi Israeli, Director-General of the Ministry of Health (MOH) for many years, if there was ever any public pressure on the MOH to carry out research on the causes and ways to control disease.

Prof. Avi Israeli: Not really, although Israeli public opinion is pro-biomedical research, and everyone knows that. The problem is more structural. For example, every year, the government decides to cut a fixed percentage of the budget of all the ministries, say 2%. So, in July, I have to cut not 2% but 4% of my budget, because half of the year has passed already. The only easy place to cut is research. Why? Because that cuts no patient services, no drugs, no employees, no nothing. For many years this was where all ministries cut their budgets. When I came into the MOH, I said that is the only place I won't cut; but such a decision depends on the view of whoever is in charge.

Second, Israel's Ministry of Finance never gives money for research, because it sees research as a waste of money. I will give you a real example. When Obama and Sarkozy decided to pour huge amounts of money into biomedical research, I stupidly sent people in the Ministry of Finance an Economist article to tell them: You see, even the U.S. and France want to do more biomedical research. They sent me back a letter that said basically: Great! Let's enjoy the fruits of their additional research. Now we don't need to invest anything. Maybe we can even cut more! That's the situation here in Israel.

Under such circumstances, how could I increase our research budget? Only by giving it very, very high priority on the agenda and compromising on other things. The Treasury says, "We will give you more budget for research; but forget about all these other things." Or sometimes they want to do something and I refuse; so they say, "If you will agree, then we will give you money for research." That was how we doubled our small budget for medical research, and now nobody even dares to ask if we can cut it; but this is a very small amount of money, just $2 million a year! Other institutions get much more research money than that.

As for our ministers, since they cannot see the fruits of research during their limited tenures, most are simply not interested. Sometimes we have someone who is pro-research, but that is not common. The Ministers of Health and Finance were personally involved in the issue of intellectual property in government hospitals; but since ministers change rapidly – something that also changes state comptrollers and auditors, etc. – it takes a long time to solve such issues. We have dealt with this issue for at least ten years now, and we still have not finished it! And this is an important issue for facilitating applicable research.

The Knesset is also pro-research and they often pass recommendations – because that is the level of their decisions – for the government to increase the research budget; but it amounts to nothing at the end. This is one big difference between the U.S. and Israel.

Prof. Alex Keynan: These are all good reasons why biomedical research cannot be done in or through the Israel Ministry of Health. The primacy of patient care is too strong – one can never get enough care – so there is no room for research. We saw a separation of the two in each of the other countries that presented here. None of them put their Ministry of Health or healthcare delivery organization in charge of long-term biomedical research.

Prof. Jean-Francois Bach: In practice, the quality of medical care is conditioned by the existence of good research. A country without research cannot have really top-level medical care. It's the same for universities. Research is absolutely necessary to support top-level education. This is not easy to prove with indicators; but one observes that, in university hospitals without research, medical care may be adequate but not at a high-level. It is not able to follow the evolution of modern medicine.

Dr. Meir Zadok: For years, we at the Academy have been trying to avoid politicians, lobbyists and the media. This is the first time that we have had both a conference and committee, headed by Professors Ruth Arnon and Alex Keynan, which have done things differently. Yesterday we had a parade of politicians, and three Treasury people attended our meetings. The Committee agreed that these were straightforward, sensible things to do; and I thought O.K.; but what am I supposed to do next week to follow-up this departure from prior unwritten policy? Harvey spoke about Oprah. Like it or not, we have to start considering this kind of thing, scientifically. It will take a lot of personal effort – maybe brain transplantation! – but I think we have to do it. We have already seen encouraging signs, all too rare in the past, that politicians and Treasury people are willing to help us. We need are two things. One is a consistent Israeli effort and the second is your support. Yesterday was an excellent survey of how many advanced Western countries – and we are part of that group – are dealing with this. We will need the help of our distinguished foreign guests in the future. We might even need to ask you to come again and testify for us.

Prof. Reinhard Kurth: Scientists have their language, politicians have their language, and journalists have their own language; our professional aims are quite different. We think about publications, professorships and long time periods. Politicians think about

elections, public opinion and, usually, short-term projects. They also often have to decide very rapidly, whereas scientists have time to arrive at their decisions.

It's been my experience, as the chief scientific advisor to the German government, that we have to use a very understandable, transparent common language, one that can be sustained over years not months. When I was a young scientist at the Max Planck Institute for Virology, whenever my boss saw a journalist appearing over the horizon he told us: O.K. Bring up the bridges, close the doors and forget about him! Things have changed totally over the past twenty years. We now approach both politicians and journalists to get our ideas across and, of course, to lobby for financial support. And we have to admit what we don't know when they ask us. That is also very, very important. With swine flu and SARS there was a time when we didn't know what to expect in the future; and we had to say that explicitly. That helps to establish confidence. When politicians and influential journalists ask us, they have to be confident that we will give them the best possible scientific answer to their problem.

Once we gain their confidence, we can point out the economic consequences of our research – and I think that is a very important point for Israel. We can talk to them about intellectual property, we can talk about population benefits, etc. In Germany and Western Europe, public opinion is pro-biomedical research because we are all growing older, massively older, than in the past. We can and must "sell" our cause; and if we do so consistently, we will be successful. We have greatly increased biomedical research budgets in Germany over the last fifteen years, although competition for funds has been tough.

Prof. Christopher Kennard: Pointing out the economic gains of biomedical research is important and clearly there are some very

good exemplars in Israel. A document that really spelled this out for politicians would be useful. In a country like Israel or the U.K., with a relatively small industrial base, the intellectual base becomes the important part; and in biomedicine this is the key to developing new products and intellectual property that can benefit the country. That is one important justification for biomedical research.

Second, U.K. patient groups have been very effective in lobbying politicians for increased biomedical research funding; and they have done so in several different ways. They have gone directly to parliamentarians in Westminster to lobby them; and they've used all sorts of modern techniques. For example, Prime Minister Tony Blair had a public email address at No. 10 Downing Street to which people could write. Suddenly 15,000 people from the motor-neuron disease community emailed Tony Blair to ask why was there so little funding for this particular disease. Now that clearly has the positive aspect of raising the profile of biomedical research. It also has negative aspects, because that was a highly specific lobby group and message. Although it is a terrible disease, it is a small one in relation to many others.

Most of the charities I know actually spend most of their money on improved services for patients, because the National Health Service doesn't provide all that is required. However, most of the patients themselves – when you actually talk to them and their caregivers – want a cure. That comes only from biomedical research. So I think that one can harness those groups. Although some Israeli disease-oriented charities apparently are not interested in research, U.K. charities have come together into larger groupings that have become effective lobbying organizations for biomedical research.

Prof. Benjamin Sredni: Last year the Israel Ministry of Health formally earmarked all of its research grants money, excluding it

from its regular budget. Prof. Avi Israeli started this change, and we are continuing from there. It is the right way to go. The public wants biomedical research, the politicians want it, everyone wants it; but we have a problem. The number of publications from our small budget is incredibly high, the citations are wonderful, the partners are working. So, when the politicians and Treasury see how well we are doing with so little money, they say: We should probably cut a bit more! They don't understand that what we are missing is high-quality clinical research. We need to convince the Treasury that investing in biomedical research is not throwing away money, but making an important national investment. Right here in this room are Michael Sela and Ruth Arnon, who developed the multiple-sclerosis drug Copoxane, based on their research. It benefited science, benefited patients, and brought an incredible amount of money into the Treasury. They do understand money; so we need to help them understand the financial importance of this kind of investment. If we can translate our good science into new medicines and treatments for our biopharmaceutical sector, then we will be successful both scientifically and in terms the Treasury can more readily respect.

Prof. William Paul: U.S. advocacy groups, as Harvey pointed out, have been incredibly effective. The HIV lobby had an enormous impact; and it set the stage for other disease-specific lobbies. They were effective even when they were not themselves very popular with legislators. They used to tell me that they needed more people without holes in their ears to talk to the legislators! But, despite all that, they revolutionized how advocacy groups dealt with government.

Alex Keynan made a very telling point regarding Israel and other countries its size. No matter how effective you are, your detractors can easily say: If you didn't do it, the big gorillas would have done it anyway and you could have had a free ride. The question is: What impact can you have when your research budget is 1% or 2% that

of the NIH? The answer is plenty. The NIH is very large, and thus a rather inflexible, organization. It is very difficult to get the flywheel going, although once moving it continues very well. In contrast, a small country or organization is nimble. It can respond quickly; and if you have sufficient intellect, you can make a difference.

The general population must be persuaded that what you do can make a difference for them and for the people they know who are ill. If they feel that your research is insignificant, they will naturally want services instead. But, if they are persuaded that your research will make a real difference, you will have support; and later the Treasury will respond automatically to dollars and cents.

This is not easy to do; but one could emphasize the great creativity of Israel. Israelis must go to the world confident that they can do important things quickly and nimbly, that their work can stimulate and leverage the efforts of other nations, who can devote much larger sums of money to the new ideas they pioneer. In short, you can be instigators. If you can get that message across, you can persuade key actors that small investments here can have enormous impacts elsewhere. It is not easy, but people will respond to that. I know a group of people whose daughters have lupus erythematosus, and who mobilize about $4-5 million a year for research. The NIH budget for lupus is fifty times greater, yet these people are absolutely devoted to spending their modest sum of money, because they believe that their resources will determine how the NIH's much larger resources will be spent. If there is any way you can get that message across, do it.

Prof. Raphael Mechoulam: Israel always tries to have people from abroad come to tell us, "You are doing well, and please do more." Yet we rarely take full advantage of them. For example, here is a very distinguished group of visitors, yet not one of them has appeared on local TV, the newspapers, or other public media to help make our

case. It is all our mistake. We could have had the President of the Institute of Medicine of the U.S. National Academies publicly tell our country, "Well, you are doing good work, but you need more money, etc." Maybe we should try to do that in the future.

Prof. Reinhard Kurth: The public responds to "well-known faces," and science also needs "well-known faces." That requires a major change of attitude among scientists. I have been on TV, over the last twenty years, over three thousand times. Then you can move things, because people associate medical news with your face and message. As you said, Raphael, if Harvey had appeared on Israeli TV, it would have helped your cause here. We have to use these instruments, without jealousy among scientists (a problem in Germany). Although some scientists will be more in the public limelight than others, it helps our joint cause.

Dr. Yaacov Bergman: We notice that research quality assurance was not discussed in the Committee's report; that should be addressed. Furthermore, the relationship between the quality of Israeli clinical research and the quality of Israeli medical care, while often stated, is not obvious. Until these issues can be resolved, "free-riding" on research done elsewhere and using those resources to improve local healthcare would not seem obviously counterproductive.

Prof. Alex Keynan: That is an important issue and it can be discussed later; but to conclude the present topic of discussion, there seems general agreement that the public image of biomedical research is important. Without public support it will be difficult, if not impossible, to get much done. In Israel, there is little clear public understanding of the impact of such research on medical care. Since research cannot compete with patient care, in all the cases presented here, the central national medical research agencies are not part of the Ministry of Health. The Ministry of Health may be represented

on it and have a say; but it cannot control that agency's budget, because if there is a health emergency without enough hospital beds, research will be the first thing to be cut. We need to develop the skills to convince the public about the importance of research in curing disease; and we can learn a lot from our colleagues abroad about this.

Investigator-Initiated Versus Directed Research

Prof. Alex Keynan: Within research organizations that try to do more than just enlarge our understanding, there is always a conflict between investigator-initiated research and call-for-proposals-initiated research. The first is the best way to harness the best talent: let the scientists tell you what they want to do and judge it according to international scientific standards. But sometimes we have to proactively help solve an urgent problem. Scientists usually don't like such directed research; it is against the scientific ethos. However, society often cannot live without it. Prof. William Paul will introduce this dilemma, because he deals with this problem daily at the NIH.

Prof. William Paul: Alex has already presented this dilemma quite clearly. Public resources are given to biomedical research, because the public believes that this will eventually improve their health. That is also why they support biomedical research more generously than composing symphonies. Thus, when an epidemic arises – be it SARS, a new influenza, or HIV – the public expects that the scientific community will devote itself to finding a solution. For example, when HIV/AIDS appeared, the scientific community responded rapidly. This was orchestrated both by generous government investment and by the spontaneous recognition of individual researchers that this was a problem of great health and intellectual importance. Governments did make explicit decisions to invest considerable resources in that area in a "directed" manner. There are, however, different types of directed research; and those decisions usually did not specify what experiments were to be done. Mostly our government said, "We will support research relevant to HIV/AIDS. Tell us what you want to do." So it was directed research and yet, within that, it still fell within the accepted canon of investigator-initiated work.

Tighter direction can be dangerous. I remember once deciding to list all the research being supported by the NCI on HIV/AIDS to find clear examples where money was being used for projects that had nothing to do with AIDS. The first thing I came across was somebody studying chemoreceptors. I said, "What in the world do chemo-receptors have to do with HIV research?" Of course, three years later, it was discovered that chemoreceptors were the mechanisms by which the HIV virus entered cells. I would have told Bob Gallo, don't do this; it's silly! So centrally micromanaging ideas can be dangerous. Nonetheless, we do have a responsibility to respond to pressing needs. The best way is to direct money to the problems to be solved. Sometimes we also must spend money in a more tightly directed way: building tissue banks and vast databanks of sequences, and other things that cannot possibly be done by individuals responding to their own intellectual challenges.

NIH makes much use of requests-for-applications (RFAs). If you identify an area of science which is under-represented but critically important, you devote a special sum of money just to that area. You send out a notice, encourage applications, and judge them by merit. In theory this is a good idea, but in reality it often doesn't help much. Between the time the idea is considered and the time that the bureaucracy issues an RFA, the scientific community has already figured out that it's important; and there is really no need for the RFA. If it was a good idea, scientists will respond much more nimbly and promptly than any administrative entity can.

Still, I am convinced that sometimes even very directed research can be absolutely essential. Often that can be handled by contracts in which the NIH spells out in great detail what it wants done, e.g., to determine what certain T-cells are specific for. Science administrators tend to push for more directed research, not for any

evil reason, but because they are convinced it can respond promptly to challenges. They can often be correct; but more often than not, one has to resist.

Prof. Alex Keynan: What part of the NIH budget is used for directed research?

Prof. William Paul: When I came into the Office of AIDS research, about half of the budget went to contracts and RFAs (RFPs, requests for proposals, are somewhat different in the NIH jargon). It was far too much. I think the number is now more like a quarter of the overall budget. One has to distinguish contracts from an RFA, which is directed research in the sense that it is problem-specific, but which still utilizes peer-reviewed, investigator-initiated applications. So an RFA is still really a grant. In a contract, you simply say: This is what I want done. So there is a continuum. More broadly, all of our work is "directed" in the sense that it is biomedical; I can't take NIH money and go to my garret and write a novel. There is a place for each approach; and we need to find the right balance. Since administrators and scientists tend to push the balance in opposite directions, that tension will continue.

Prof. Ruth Arnon: The key word is balance. Every investigator will do best what they are interested in doing. However, pressing needs must sometimes dictate at least the overall direction.

Prof. Reinhard Kurth: There are two situations that require directed action. One is medical emergencies, like SARS. Politicians immediately wanted to find out what it was; we didn't even know whether it was a virus. In such a case, a funding agency has no time to allocate money by normal channels. An agency has to react quickly, although it will probably be too late anyway.

The second situation is a serious health problem that is also a serious scientific problem, one which cannot be resolved rapidly and which requires concerted action. For example, the U.S. alone pumps about $600 million into the HIV/AIDS vaccine development every year. Here we need some sort of small, highly coordinated "Manhattan Project." The NIH now has one consortium that develops neutralizing antiviral antibodies and another consortium that develops better T-cell immune responses against HIV. Whether they will be successful is another story; but the RO1-type request-for-proposal hasn't led us anywhere over the past twenty years, and there is no vaccine on the horizon. So we need a strategy to involve the best talents available to tackle the problem. We also have to tell the public, politicians and media, that there is no guarantee of success, because otherwise we lose all credibility. But except from those two situations, we really should rely on RFPs.

Prof. Christopher Kennard: Directed research in the UK model is not as specific as that at the NIH. Our Medical Research Council identifies areas where there are opportunities to bring in new talent and they put out a call for proposals in that particular area; but it is up to the individual applicants to direct their research. It would be very rare to actually use as much as 25% of the MRC's funds in a highly directed way. The only example of that was Creutzfeld Jakob Disease (CJD), a serious British disease which required the rapid investment of large amounts of money for research.

Prof. Olle Stendahl: I can give you two Swedish examples of directed research. About twenty years ago Sweden rheumatology was a very weak area. So our Research Council decided to proactively recruit young immunologists and other people from stronger areas into that field, which is now the strongest (highest impact) area of Swedish research. True, the field itself has really exploded, but still I think you can say that the system works. It works by identifying the necessary

people, rather than projects. The important thing is not to specify specific research targets, because the scientists themselves usually find the important areas. Also, in Sweden, isolated basic research has little chance of being funded. We talk more about translational and clinical research, about driving the overall process not just interesting basic scientific research. We need hypothesis-driven research plus the idea of going further (even if not all the way to use).

Prof. Jean-Francois Bach: The French government originally wanted our new National Research Agency (ANR), which gives out most of our scientific research grants, to be directed around specific themes and disciplines, while the scientific community, including the Academy, would prefer to free the money from any specific goal. Initially 80% of the money was directed to specific disciplines/ topics, and now that has been reduced to 50%. We are now fighting to reduce it to 20%, to fund the best scientific projects, independent of the needs of the nation.

It is obvious that a small country like Israel cannot be excellent in all disciplines. The important thing is to have a scientific community ready to react when problems appear. Still, creativity is not equally distributed in all sectors. Thus, Israel should encourage domains of excellence, probably close to basic research, even if some fields will be left out.

Prof. Alex Keynan: So France is moving towards more undirected, investigator-initiated research?

Prof. Jean-Francois Bach: Yes, absolutely. French politicians want money to be used where it best meets French health needs. This is probably correct to a certain degree, but dangerous if exaggerated. We try to convince the government that investigators should be free to select what they do, up to a certain limit. On the other hand, it is

unacceptable, in a middle-sized country like France, to totally lack scientific research in any specific domain that could induce serious long-term effects.

Prof. Uri Seligsohn: I wasn't clear about the NIH decisionmaking process. Are targeted projects initiated by each institute? Who makes the decision?

Prof. William Paul: In the case of HIV/AIDS, a national emergency, much of the decisionmaking came from the legislature, as well as the NIH leadership. As for SARS, the public health agencies didn't need to be provoked. They understood that they had to respond. Often, the institute director has a great deal of flexibility in determining what should be emphasized, although he will have to go to Congress every year to testify and defend it. There Congressional staff members are very important, because they are usually the ones who actually know what is happening. The Congressman is far too busy to see you. So if you see the right staffer, you can have much more impact. So it is a complex process. No one individual can make that decision alone; but the institute director and his senior staff probably play as important a role as any.

Prof. Giora Simchen: We in Israel also have several such examples. For instance, fifteen years ago, we realized that Israeli genome research was dangerously underdeveloped. We didn't take part in the Human Genome Project, etc. So the ISF earmarked a certain amount of grants money for genome research. I'm not sure that it succeeded. So my question is whether any of you evaluate, in retrospect, how successful such directed-research interventions were. It is really justified in retrospect? Can we learn from those experiences how to do it better?

Prof. William Paul: HIV/AIDS is one good place to look, because it represented an enormous investment in France, the United States, and other countries. Of course, evaluation is not easy, because there is no control experiment; there is no simple way to know what would have happened if you had done things differently. So people usually just list what was actually accomplished. In the case of HIV, one great research accomplishment was giving virologists the capacity to take the virus apart, to understand its detailed life cycle with precision, to point out where the choke-points might be, and then to help others design drugs that actually work. The first set of rationally designed anti-viral drugs came out of this. So, we did something that we had never done before. Would it have been done anyway? That I cannot answer. I wish I could.

The money also focused a large fraction of the biomedical research community onto this area. Some said that this attracted second-rate scientists, that only those people who couldn't get money to do something else moved in. The reality was quite different. Brilliant work was done. It took time to create a cadre of people who were really terrific; but in the end the quality was outstanding. I don't think that this would have occurred at that pace without directed investment. Was it useful? Probably. Was it efficient? Was the amount of money the right amount? Could it have been done with less or more? I cannot sensibly answer those questions.

Prof. Michael Sela: Many years ago I wrote an editorial for Lancet about HIV/AIDS. I pleaded for work en masse on HIV vaccines, saying that, in the middle of a battle, a general cannot stop and say, "Let's go home for a couple of years to prepare better weapons and then come back." Therefore, your strategy of greatly increasing the number of laboratories involved in HIV research, in the hope that it would help, was the right approach, whether it was ultimately successful or not.

Prof. William Paul: There are two situations that justify defining priority areas. One, indeed, is emergency situations; in a "war" situation you do have to respond. The other involves emerging fields. People do not always fully appreciate such fields, since they don't know which will be important in the long run. What will happen to systems biology in fifteen years? I can't say. You also have a problem finding the right experts to evaluate proposals. So such fields must be dealt with separately, otherwise pioneering work will die before it's born. Balance between directed and undirected funding mechanisms is critical, but there are two major checks that can help. One is freedom. People must be able to choose. So, if you have an emerging field, you advertise it. If you have an emergency situation, you advertise it. But people cannot be simply assigned to do something. Second, we cannot compromise on quality. Even in an emerging field, try to get an objective evaluation and let only absolutely excellent work be funded, otherwise you make mediocre research your benchmark. It is very important to keep these checks and balances installed at all times.

Prof. Giora Simchen: To me, directed research means contracts: this is what we want and this is what we get. That should be distinguished from policy. For example, the Ministry of Health might adopt a policy to fund mostly grants related to translational medicine. That is our purpose as an organization. We are not able to compete with the ISF in basic research, so we have a policy to do something else, to look for excellence in translational medicine. I also want to ask Bill if the NIH also has a policy to encourage people to do more translational research, instead of just basic research?

Prof. William Paul: Obviously, different mechanisms are better suited to different kinds of research, thus clinical research and translational research can be hard to fund through RO1s. The NIH's institutes will have to make decisions that they want to support

translational work and set aside resources accordingly. Also, consider the world's epidemic of diabetes and metabolic disease. It's not an under-researched area, but there is still probably a desperate need to invest more; it is a public health emergency of high order. How to do this properly we can debate; but I would like to see more money used to attract people to do such work, even though I probably could not spell out exactly what I wanted done.

Dr. Yaacov Bergman: Francois Jacobs once said "What the politician must do is to determine the importance of science to the nation in setting the total budget for science. What the bureaucrat must do is to determine the relative importance of the different areas within that budget." What he had in mind is a grid that gets finer and finer through a political and bureaucratic process. But, once it gets down to that, scientists have the freedom to work as they like within these areas. For example, both the U.S. and U.K. set national priorities. A recent FDA white paper on "Innovation or Stagnation (2004)" noted that the U.S. was far behind in translational and clinical research. The NIH took up the challenge and shifted billions of dollars from basic research into translational and clinical research. However, in the end, that effort was not very successful because the scientists in charge of allocating the money still continued to emphasize basic research. Of course, many basic research scientists were opposed to it, because it withdrew resources from their own research.

Prof. William Paul: I can't respond in any detailed way, although there were many flaws. It was not clear that the money would be well spent, but there is still great feeling that translational research is important, if difficult, to do.

Prof. Alex Keynan: Nothing can replace the creativity of individual scientists. So the best response to a pressing problem is to try to convince good minds to take it on.

The Special Needs of Clinical Research

Prof. Alex Keynan: Our next topic is clinical research. Israel doesn't have a national system of clinical research. There is some good clinical research here; but, as a system, it doesn't exist. No one mandates or demands that hospitals carry out clinical research; there is no career development ladder in clinical research; there is no specific budget allocation for clinical research. Prof. Seligsohn, within the framework of our committee, has suggested building an Israeli system of clinical research. But before discussing this, Jean-Francois has volunteered to say a few words about what clinical research is.

Prof. Jean-Francois Bach: I want to describe briefly the many, very different activities that fall within clinical research. The best known involve therapeutic trials, themselves divided into Phase I (safety), Phase II, and Phase III (efficacy). Phase III studies may not be all that intellectually stimulating, but they bring in money and allow a country to participate in an important international effort. Phase I and Phase II trials are not easy to perform, and more methodological and biological work is needed. Some diseases are more common in a given part of the world; thus there is some medical specificity in each country.

We need to understand disease mechanisms better to produce new treatments and diagnostic tools. Another aspect of clinical research involves case reports. Too many papers in the medical literature contribute little to medical progress. High-quality analysis of a specific disease in a large set of patients requires considerable time, whereas clinicians can write individual case reports rapidly. Good clinical studies also require considerable methodological training and truly good clinicians.

Another aspect is of clinical research involves epidemiological studies of public health problems. They are important for studying country-specific diseases.

Who conducts such research? Physicians, of course; but also non-MDs, such as PhDs studying the mechanisms of specific diseases. Mechanistic studies on patient samples are also clinical research, even if done in laboratories by people who never see the patient. They are based on direct interaction between the biologist and the clinician.

Such projects also need highly trained support staff. Unfortunately, physicians and nurses usually have little time to spend on clinical research. Thus, we need a few people devoted precisely to that activity. The best example of what this looks like at the largest scale is the NIH hospital, which is totally devoted to clinical research. That is a very big and expensive operation. Many countries have smaller clinical research centers with a few beds, say 3-5, where the NIH hospital concept can be applied. We do that in France. We don't have big research hospitals; but rather, smaller units for clinical research, which are supported by their hospitals. But, as Alex mentioned, hospital directors are usually overwhelmed. They have neither the money nor time to spend on such research, which they often think should be supported by other organizations. So, rather than push for money, we encourage hospitals to consider research and "medical progress" as one of their core objectives.

Last, the training of clinical scientists is absolutely crucial. One cannot ask a physician, without scientific research exposure, to suddenly do high-quality clinical research (a few exceptionally gifted exceptions exist, but they are rare by definition). The best solution is for them to undertake a research fellowship in a research laboratory for a year or two, at the beginning of their career. They have to be exposed to

how research works. Ideally, they could continue to be associated with experimental research, but that is often difficult in practice. Clinical research should not be done by scientifically inexperienced clinicians, even if they think it important for their career or image. Clinical research is not a mark of excellence, unless one does the job behind it in a rigorous and creative fashion.

Prof. Uri Seligsohn: The Arnon Committee included six physicians who helped identify several major problems that discourage Israeli clinicians from engaging in clinical research. One, of course, is protected time, which is almost completely absent. Second, in Israel, physicians usually serve three years in the army before going into medical school. After residency, most are already married and have children to support. Israel's low salaries do not allow them to engage in research without outside support (some do research in the afternoons, and then moonlight at night to make money). Third, there is a lack of sufficient grants, and those that are available are too small in any case. Fourth, there is a lack of infrastructure in the medical centers; and, fifth, over the years, the clinical-research atmosphere in most Israeli hospitals has slowly faded, with a few exceptions (e.g., the Hadassah and Sheba Medical Centers). Last, there is a lack of mentors. To address these problems, we formulated the following objectives.

Boost the quality of clinical research in Israeli medical centers. We must support physician-researchers at all levels, starting with second-year medical students because, once they engage in additional work, they usually do not go back to research. We would start with the six large medical centers already doing good clinical and basic research and, after the first three years, open the program to additional centers. Groups of established investigators at all hospitals could apply for "centers of excellence" grants, from the start.

Support for students. The program would include stipends for second year medical students, and would target those that join research laboratories and work there during the summers and/or at night. The program would also target the several dozen students pursuing an MD-PhD track, who can influence the course of Israeli clinical research in the future. Private foundations already provide a few stipends; but this would provide these opportunities to a wider spectrum of students. Israeli students still must submit a thesis at the end of medical school, although some simply review hospital charts or do theoretical work. But those who wish to do their thesis work in a research laboratory with a clinical investigator particularly deserve our support.

Support for physicians in training. Israeli doctors must, by law, train for five to six years to become "specialists." This includes at least six months of basic science. Most physicians simply collect some cases, engage in some epidemiology exercises, or analyze laboratory results to put together a report. To achieve a better yield from those six months, we would support physicians who, instead, work in a research laboratory, encouraging them to go on to develop a research career.

Support for career development. Major support would be given to a five year research-career development program. Physicians could receive 70% of their salary from the new foundation and 30% from their hospitals. They would spend eight months a year in a research laboratory and four months on the wards. If each of the initial six target hospitals employ at least one new career development grantee each year, in five years Israel would have thirty such people spread all over the country.

Support for competitive grants. The other major component of our proposal is a competitive research grants program. This would target

specialists who wish to engage in innovative clinical research. Grants of $50,000 for three years ($150,000 total) would be awarded by peer-review, at first by the ISF and, perhaps later, by a separate body. We are talking about fifty grants a year. Thus, the first year would require $2.5 million, growing three-fold within three years.

Support for returning physician-researchers. This new foundation would provide returning physician grants of about $75,000 a year (for three years) for post-docs returning to Israel, and about $100,000 per year (for two years) for returning associate professors. Of course, we would not be able to fund too many.

Support for centers of excellence. These grants help develop the infrastructure of centers of excellence comprising two or three outstanding research groups. They would provide about $800,000, with an additional $200,000 of matching funds from the host medical centers.

Clinical Research Society. Finally, we would like to start a society of clinical researchers, something new for Israel.

We look forward to comments and constructive criticism from our visitors from abroad, but first I would ask what incentives or support are currently given MD-PhD researchers in your respective countries.

Prof. Olle Stendahl: I think your proposed activities are very good. The problems you presented are not unique to Israel. They are the same in Europe. The European Science Foundation conducted a large survey which looked at the clinical research problem. Recruitment, research time for clinical investigators, and the lack of incentives were the three major problems. Although Sweden has some unique sources for supporting clinical researchers, such as the government

and county councils, we still have the same problems – not so much recruiting people to start clinical research, but giving them a chance to continue it. We have a lot of MD PhDs – more than 25% of all Swedish doctors! But they are often too old, and don't have time to continue their research. The big challenge is to find meaningful incentives. Competitive grants and centers of excellence will help, but building the right atmosphere in the universities and hospitals is also essential. It's not enough to give a few people a chance to go back to a laboratory now and then. You have to build your system in a more integrated and long-term way.

Prof. Christopher Kennard: We have exactly the same problems in the U.K. I like the idea of centers of excellence, which our National Institute of Health Research (NIHR) has already set up. One type is a "comprehensive" biomedical research center, which involves big university hospitals to pursue a wide range of high-quality research in a sizable number of different clinical specialties. These hospitals are chosen by an external (international) scientific review committee that reviews a portfolio of what each hospital does, visits each of them, and then announces their decision. This helps dampen the reactions of the hospitals not selected. The other type is "topic-specific" biomedical research centers. They receive less money than the comprehensive ones, but could provide useful models when hospitals have excellence in specific areas. In any case, peer review is very important.

I quite agree with your five-year schemes for developing clinical scientists. In the U.K. we found the mentoring of these individuals to be of great importance. Theirs is a difficult, relatively unknown path and they need mentors, including mentors external to their institution (even if they meet with them only once or twice a year). Sometimes it's more difficult to have frank discussions with someone from your own institution, so that's actually worked out very well. We've also

tried to get younger medical students and the trainees interested in research through summer schools, workshops, etc.

Prof. Jean-Francois Bach: I also think that your proposal is very good, particularly the centers of excellence and the career development awards for young clinicians. One missing partner in your presentation is the university. Many clinical scientists are professors of medicine, and good clinical research activity should be an important factor in their promotion. Second, regarding your proposed clinical research society, we tried that in France. It was good for the first year or so, and then there was a lack of attendance. So don't expect too much from that, although maybe it will work better here.

Prof. William Paul: In the U.S., the relationship between the medical schools and research hospitals is very close. In fact, the university hospitals are often owned by the medical schools, and often virtually all senior physicians in the central hospital are faculty members. Our institute has started a five-year Clinical Transition Program that takes postdoctoral fellows in science or medicine, who are not yet regarded as "competitive" for tenure-track positions, and gives them research support, a technician, and perhaps a postdoctoral fellow. They are associated with a senior figure, usually a clinical scientist, to help prepare them for positions that may become available in our own institute or elsewhere. The goal is to increase the cadre of good U.S. clinical researchers. In the U.S., as elsewhere, this is becoming increasingly difficult.

One problem is the almost prohibitive time required. They need to finish an MD, a PhD, a postdoctoral fellowship, etc. People are almost ready to retire by the time they have their own laboratory! Much of that training is redundant. In the U.K., a PhD often takes three years; in the U.S. that's often 5½ years. We are just making

old people. In Israel, I think, the Masters degree is beginning to be phased out. We have to find ways to shorten such things, particularly since people have such enormous financial obligations. When I grew up, you could finish your training by your early thirties and then launch your research career. Today, the mean age of an MD at the NIH is an amazingly old 44!

Prof. Reinhard Kurth: Germany was not able to establish significant, internationally competitive, clinical research, until the 1970s. A few people, such as doctors returning from the U.S., received small grants and were fighting to do some research in the evenings and over the weekends. In the 1980s, the German Research Foundation (DFG) asked the medical schools (we have about 34) and university faculties to define specific topics, and then form and apply as networks. Those grantees worked full-time in clinical laboratory research, although that interrupted their clinical career. That program is quite successful. The medical people move in and out of their clinical positions, and do really competitive research. About four years ago, an additional "centers of excellence" program (about €20-30 million over five years) was started. Virtually all universities submitted proposals but only five medical faculties were funded. They can now really invest in equipment and people, but we won't know the results until 2012. We may now be on a better path, but for decades we had the same problems you mentioned.

Prof. Harvey Fineberg: Uri's summary presents many important and, I think, valuable ideas. I hope you'll be able to act upon them. Even if we do nothing but reinforce what you have in mind, it would be a fantastic direction for building on the initial Committee report. On the broader question of what constitutes clinical research, I see that as more than training and funding research by scientist-clinicians who spend part of their time in clinical care and part of their time

in laboratory research. This is an important model, but it doesn't capture the whole array of Israel's opportunities.

You have to ask, what is Israel's advantage? Why go in any of these directions? Why not just wait for others? One of Israel's distinctive advantages is its great genetic diversity within such a concentrated geographic area. No other place in the world has that particular combination. Second, you have universal health coverage, and considerable ability to manage clinical practice and patient care for a sustained period within a rather uniform system. There's not that much movement, and you can track patients pretty well. Third, in large components, you have an electronically-based data system with a tremendous bank of clinical information relevant to learning about clinical care.

Now this does not diminish the potential value of disease-specific centers of excellence, but it does suggest that you could involve many more clinicians in a concerted national strategy to achieve a leadership position in comparative-effectiveness or clinical-evaluation research. This would also give every Israeli involved in clinical care an opportunity to be part of a learning community, whose results would benefit the next pool of Israeli patients. It would also make Israel a leader in answering those critical questions that every country faces, but for which data is so lacking. What works best? What doesn't? What are the consequences? How do we judge? All of those things. You have a unique potential, I think, to answer these questions.

Now what would that require? In addition to what you've already described, you would need to commit national resources to clinical research design and data analysis. A national center might be established by one of the universities or teaching hospitals to serve as a central resource for any clinical research group, so the ability

to conduct high-quality randomized trials and to design studies effectively from the first patient on would be readily available. In addition to the usual MD-PhD training, another educational track would be available to clinicians, one which would reinforce their analytic approach to clinical care itself. This line of research could be very important both for patient care and for Israel's strategy for biomedical research. I would add this other dimension to your thinking, and reinforce the idea of always going back to ask: What can we offer that is really distinctive, if not unique?

Dr. Yaacov Bergman: The Arnon report's complaint about clinical research is not about the quantity of research, but about its quality. Indeed, about 25% of all Israeli scientific papers are in medicine. Two solutions could be offered. One is to allocate more money; the other is to see whether the money could be better utilized. The report emphasizes the first solution, but the second could be even more important. For example, in Israeli promotion decisions, the length of one's publication list (not its quality) is of primary importance. In contrast, at the Harvard University Medical School, one submits a list of only five papers, one's best five papers.

Prof. Alex Keynan: Since there is no established system of clinical research in Israel, and no central funding, there is also no peer-review system for hospital-based clinical research. In fact, many doctors get private money from donations and fund themselves. Things are not peer-reviewed and they can publish whatever they want. The level of such publications can be quite low. To ensure high-quality research, we need more peer review; but that would require changing and institutionalizing the whole system. The Committee addressed that, but it will be a long road.

Prof. Gabriel Barbash: We have been seeing, in several hospitals, a new generation of young people who are genuinely interested in

doing research. Not everybody is in this business for the money. Some people see it as a satisfying, interesting career. We have to make sure that such people can flourish in research without completely leaving their clinical careers. How do we encourage that? Buying "secure time" is, of course, critical. Improving the hospital research infrastructure is also critical. Grants enable us to fund several such people within the hospital; but what happens when that soft money runs out? What is the long-term solution?

It took 2-3 years for many hospitals to even consider such programs, simply because it's not trivial to replace the researcher. A whole system has to be created within the hospital to offer these people long-term careers in both research and clinical work. It will never be a large track. It will not engage even 20% of the hospital's physicians. But that small, very specific population will make a huge difference to what Israeli clinical research can look like. And it will improve the quality of clinical work in a way you can never get by piggybacking on research done elsewhere. We will see big advances, if the money is there and the hospital infrastructure is there.

I have met numerous young MDs who have done clinical-related research abroad and who, upon coming back, cannot find suitable research positions here in Israel. They can find positions only as full-time MDs in a hospital. The hospitals simply don't have the funds to support research, so your suggestion of a limited number of positions where the hospital pays only 50% is an excellent one. It could be the most important thing we have discussed. There were many other good conclusions that I fully support, but we should try to focus our pressure on this one thing and then slowly expand it. Let's give these returnees the opportunity to do both clinical work and clinical research. That is the most important point.

Prof. Ruth Arnon: That is indeed important. We actually started working on that six or seven years ago, although there is still much to do.

Prof. Shlomo Mor-Yosef: The main problem is how to take the Committee's excellent report and turn it into reality. Israeli hospital-based research is now largely up to the CEO. Some of them do think that research is important, so they do have research. The Hadassah Medical Center, which I direct, has had a culture of research for many years; and at least three CEOs have thought that research is important. Still, where can the necessary resources come from? Donations are soft money, and many grants funds do not fund hospitals, so their affiliated universities must apply. The additional money you propose should be earmarked for research in hospitals; if it is just "biomedical research," we will see little of it. Also, when physicians come back from abroad, they don't ask about their salaries, they ask about the available infrastructure. This is another concern.

Biomedical research and translational research should be led by physician-scientists, because physicians bring a different point of view. I don't see a huge benefit in having MD-PhD programs in medical schools. I see more benefits in an MD who starts his residency in orthopedic surgery and in the second or third year does his PhD. A medical student still doesn't know what he wants to be; but if a resident tells the head of his department, "I would like to do my PhD with the hospital's support," it is going to be much more relevant than a typical MD-PhD program.

At Hadassah, we have already tried to implement the report's proposed incentives on a smaller scale. It is all rather dependent on the philanthropy market, which is now quite depressed. In any case, such an important and fundamental issue for the State of Israel

should not be left to foreign philanthropy. Our challenge is to take this report and move it forward.

Prof. Benjamin Sredni: Actually over 45% of our [MOH] grants are to hospitals. There is outstanding research being done. When I was appointed Chief Scientist of the Ministry of Health, I visited almost all of the hospitals in Israel. There is, however, a big difference between the hospitals in the center of Israel and those in the periphery. One of the biggest problems is that part of the periphery also wants to do research, but they simply don't have the infrastructure.

Dr. Arik Tzukert: What we have done at Hadassah actually constitutes a small pile of control studies on many of the Committee's recommendations. Hadassah has long had an R&D division, and other structured mechanisms to enhance research within the hospital. Its research infrastructure includes personnel, space and interdepartmental equipment, a gene therapy institute, experimental surgery, etc.; and every single department has its own research laboratory. We are now building a biotech industrial park on our premises.

Our intramural research funds include very small amounts of money to help young physicians start research. Our physician-scientist program gives protected time for one year and uses another six months from our "specialist" program. To get these funds requires submitting a very structured research program with a mentor, so mentoring is built into the system. Other programs help higher levels of faculty. All these institutional funds are distributed only by peer-review, usually outside the hospital. In all, we directly invest about $1.3 million a year in these programs. Our researchers bring in almost 300 competitive grants per year. In fact, they received twelve new ISF grants (for more basic research) in 2008. Our overall institutional investment in research is about $25 million a year.

What can be done to actually apply this model all over Israel? First, allow unaffiliated hospitals, like any other academic institution, to compete for ISF and other grants, which should include indirect costs, equipment and infrastructure. Second, provide funds by academic merit, without regard to institutional affiliation.

Prof. Alex Keynan: Thanks to all our participants. One main point is that it is possible to do biomedical and clinical research in Israel at a high level compared with other countries; but that will require considerable structural, infrastructural and financial improvements.

Prof. Ruth Arnon: In conclusion, yesterday we heard from our guests about the strategies and funding of biomedical research in other countries, countries with whom we would like to be compared. I really learned a lot. We also heard from some of our Israeli colleagues, first about the state of ISF and other research funding in Israel, and about the challenges and opportunities facing Israeli biomedical and clinical research.

I was afraid that today would be an anticlimax, but how wrong I was! I think we have had a wonderful discussion. The three issues that Alex raised are extremely important. In particular, the power of public opinion is something that we have largely neglected. We have purposely avoided contacts with politicians and the media, but in today's world we may need to change our attitude and approach. I hope that we will do better in the future.

We also discussed the balance between directed and investigator-initiated research. I think that a researcher will do his best research on something that he initiates, however, sometimes we also need to work on pre-defined needs, especially during an emergency. Balance is indeed the key word. Finally, the issue of clinical research requires particular attention and I particularly want to thank Uri Seligsohn

for his detailed proposals. The remarks of all of our guests are very important, and we will try to follow them up, if possible.

We will continue to work on this. It is benafsheinu, a question of "to be or not to be," for clinical and biomedical research in Israel, so we will work on it very hard, and we hope that, with your help, we will succeed.

Appendices

Workshop Schedule

An International Comparative Workshop:
Strategies for the National Support of Biomedical Research

Jerusalem, December 2-3, 2009
at The Israel Academy of Sciences and Humanities

Wednesday, December 2nd 2009

09.00–09.30 **Opening Remarks and Greetings**
Prof. Menahem Yaari, President of the Israel Academy Sciences and Humanities (IASH)
MK Yakov Litzman (Israel), Deputy Minister of Health
MK Meir Sheetrit (Israel), Chairperson, Science and Technology Committee, Knesset
Prof. Manuel Trajtenberg, Chairman of Planning & Budgeting Committee, Council for Higher Education
Prof. Ruth Arnon, Vice-President IASH and Chairperson, Committee for the Assessment of the State of Biomedical Research in Israel

09.30–11.00 **The National Policy for the Support and Funding of Biomedical Research; Basic, Clinical and Translational**
Chair: Prof. Michael Sela, Weizmann Institute of Science, IASH Member
Prof. H. Fineberg, (USA) President of the Institute of Medicine of the National Academies
Prof. Willam Paul, (USA) National Institutes of Health (NIH), NIAID
Prof. Christopher Kennard, (UK) Oxford University and Medical Research Council

11.30–13.00 **The National Policy for the Support and Funding of Biomedical Research** (continued)
Chair: Prof. Raphael Mechoulam, Hebrew University, IASH Member.
Prof. Jean-Francois Bach, (France) Permanent Secretary, Academie des Sciences, former Director Institute for Immunology, INSERM
Prof. Reinard Kurth, (Germany) Chairman of Ernst Schering Foundation, Former President of the Robert Koch Institute and Paul Ehrlich Institute
Prof. Olle Stendahl, (Sweden) Linkoping University, Former Secretary General of the Swedish Medical Research Council

14.00–15.30 **Biomedical R & D in Israel**
Chair: Prof. Uri Seligsohn, Sheba Medical Center and TA University, IASH Member
Policy, Support and Funding of R&D in Israel - Overview
Mr. Yigal Erlich, Deputy Chair of The National Council for R&D
Findings and Recommendations of the Committee for the Assessment of the State of Biomedical Research in Israel
Prof. Ruth Arnon, Vice-President of the Israel Academy of Sciences and Humanities and Chairperson of the Committee
The State of Clinical Research in Israel
Prof. Gabi Barabash, Tel Aviv Medical Center and TA University
Biomedical Funding by the Israel Science Foundation (ISF)
Prof. Benny Geiger, Weizmann Institute; Area Chairperson, Life Sciences and Medicine, ISF

16.00–17.00 **Summary and Discussion**

Thursday, December 3rd, 2009

09.00–10.30 **National Support of Biomedical Research** - Expert panel of all presenters
Chair: Prof. Alex Keynan, Israel Academy of Sciences and Humanities

11.00–12.30 **Expert Panel** (continued)

12.30–13.00 **Summary and Conclusion**
Prof. Ruth Arnon

The Workshop was made possible by the generous support of the Charles H. Revson Foundation, the Yad Hanadiv Foundation, and by the Eli and Marilyn Goldfarb Grant.

Annotated List of Speakers

Prof. Ruth Arnon (Israel)

Prof. Jean Francois Bach (France)

Prof. Gabriel Barbash (Israel)

Mr. Yigal Erlich (Israel)

Prof. Harvey Fineberg (USA)

Prof. Benjamin Geiger (Israel)

Prof. Christopher Kennard (UK)

Prof. Alex Keynan (Israel)

Prof. Reinhard Kurth (Germany)

Prof. William Paul (USA)

Prof. Olle Stendhal (Sweden)

Prof. Ruth Arnon, the newly appointed President of the Israel Academy of Sciences and Humanities, has served Israeli science in many senior positions, including Chairperson of the Israel Academy's Science Division, Vice-President of the Israel Academy (2008-2010) and Vice-President of the Weizmann Institute of Science (1988-1997). A noted immunologist, she joined the Weizmann Institute in 1960, where she has also served as Head of the Department of Chemical Immunology, Dean of the Faculty of Biology, and Director of the Institute's MacArthur Center for Molecular Biology of Tropical Diseases (1985-1994) and incumbent of the Paul Ehrlich Chair in Immunochemistry. Her research has made significant contributions to vaccine development, cancer research and the study of parasitic diseases. Along with Prof. Michael Sela, she developed Copaxone, a drug for the treatment of multiple sclerosis which was approved by the U.S. Food and Drug Administration and is presently marketed worldwide. She has served as President of the European Federation of Immunological Societies (EFIS), Secretary-General of the International Union of Immunological Societies (IUIS), and President of the Asian Association of Science Academies. She is the Advisor for Science to the President of Israel. Her awards include the Robert Koch Prize in Medical Sciences, Jiminez Diaz Memorial Prize (Spain), France's Legion of Honor, Wolf Prize for Medicine, the Rothschild Prize for Biology and the Israel Prize.

Prof. Jean-François Bach is Professor of Immunology at Necker Hospital in Paris. He has had a long standing interest in organ transplantation, autoimmune diseases notably insulin-dependent diabetes mellitus (IDDM) and systemic lupus erythematosus. His main contributions include the description of E rosettes, the discovery of thymulin, the description and characterization of regulatory T cells in the non-obese diabetic mouse, and the first demonstration of the therapeutic effect of cyclosporin A in recently diagnosed diabetic patients. He is a Member of the French Academy

of Sciences, Academy of Medicine and Academy of Pharmacy. He is also Member of the British Academy of Medical Sciences. Since January 1, 2006, he has been the "Secrétaire perpétuel de l'Académie des sciences."

Prof. Gabriel Barbash, MD, MPH, has been Director General of the Tel Aviv Sourasky Medical Center since 1993. From 1996 to 1999, he served as the Director General (Surgeon General) of the Ministry of Health. Since 1995, he has been the Chairman of a national project to develop and implement a SAP management and clinical information system for Israel's eleven governmental medical centers, with more than 14,000 users. From 1989 through 2000, he was Israel's national coordinator and principal investigator for numerous multi-center, International Cardiology studies. He has published more than 80 original papers mainly in the fields of diagnosis, risk assessment, and treatment of acute myocardial infarction. Dr. Barbash is a graduate of the Hadassah Medical School of the Hebrew University of Jerusalem, and is board-certified in Internal Medicine, Medical Management and Occupational Medicine. He also holds a master degree in Public Health specializing in Health Policy and Management, from the School of Public Health at Harvard University. Dr. Barbash was appointed Professor of Epidemiology and Preventive Medicine in the Sackler School of Medicine, Tel Aviv University, in 2001.

Mr. Yigal Erlich is the founder and managing partner of the Yozma Group, an Israeli venture capital company, and a founding father of the Israeli venture capital industry. In the early 1990s, he established Yozma, the first VC fund sponsored by the Israeli government. Following its privatization in 1997, Yozma joined forces with the Ofer Group to establish Yozma II and Yozma III. The group managed over US $ 200 million, invested in over 45 companies. Between 1984 and 1992, he served as the Chief Scientist of Israel's Ministry of Industry and Trade, where he started the Technology Incubator

Program that led to the creation of 24 incubation centers throughout Israel. He currently is the deputy chairman of the National R&D Council of Israel and former Chairman of MATIMOP, Israeli Industry Center for R&D, and the former Chairman of the Israel Venture Association. Mr. Erlich serves as a board member in several high tech companies as well as on Hadasit – the Technology Transfer Center of Hadassah Medical Center in Jerusalem. He holds a B.Sc. and a M.Sc. in Chemistry and an MBA from the Hebrew University of Jerusalem.

Prof. Harvey V. Fineberg is President of the U.S. Institute of Medicine. He previously served Harvard University as provost and as dean of the School of Public Health. He also has served as president of the Society for Medical Decision Making and as a consultant to the World Health Organization. His research has included assessment of medical technology, evaluation of vaccines and dissemination of medical innovations. He is the author or co-author of numerous books and articles on subjects ranging from AIDS prevention to medical education. He holds four degrees from Harvard, including an M.D. and Ph.D. in Public Policy.

Prof. Benjamin Geiger received his B.Sc. from Tel Aviv University, his M.Sc. from the Hebrew University of Jerusalem, and a Ph.D. from the Weizmann Institute of Science (1977). After Chaim Weizmann Fellowship-funded postdoctoral research at the University of California at San Diego, he returned to the Weizmann Institute's Department of Chemical Immunology, where he was appointed Associate Professor (1983) and then Full Professor (1988). He chaired the Board of Studies in Biology at the Institute's Feinberg Graduate School, and later served as its Dean (1989-1995) and was Dean of the Faculty of Biology (2003-09). He headed its Department of Molecular Cell Biology (1995-2003) and has also served as Director of the Yad Abraham Research Center for

Cancer Diagnostics and Therapy (since 1998), the Clore Center for Biological Physics (2000-09), and the Kirk Center for Childhood Cancer and Immunological Disorders (2007-present). Prof. Geiger is the incumbent of the Professor Erwin Neter Chair in Cell and Tumor Biology. He currently chairs the Israel Science Foundation (ISF), the primary competitive research-funding foundation in Israel. His research, which focuses mainly on the mechanisms of cell communication has yielded several patents, which are currently being implemented by industry.

Prof. Christopher Kennard is Head of the Department of Clinical Neurology in the University of Oxford and is Honorary Consultant Neurologist in the Oxford Radcliffe Hospital's NHS Trust. Before this he was Deputy Principal of the Faculty of Medicine, Professor of Clinical Neurology and Head of the Department of Clinical Neuroscience at Imperial College London (2003-2008). A medical graduate of the University of London, he obtained his PhD at the MRC's National Institute of Medical Research (London) and received his neurological training in Oxford and the University of California at San Francisco. He has served on both MRC and Wellcome Trust Boards, and has held a variety of national and international positions. He was editor of the Journal of Neurology, Neurosurgery and Psychiatry from 1997-2003. He is currently Chairman of the Medical Research Council's Neuroscience and Mental Health Board and a member of the MRC Strategy Board. His research includes cognitive neuroscience and visual sciences, particularly using the analysis of abnormalities of visual perception and eye movements to further understanding of brain function.

Prof. Alex Keynan is Professor of Microbiology (Emeritus) at the Hebrew University of Jerusalem, and has served since 1990 as Special Advisor to the President of the Israel Academy of Sciences and Humanities, and to the President of the Hebrew

University of Jerusalem, where he was formerly Vice President for Research (1967–1990). He has taught or carried out research in the Departments of Biology and Biochemistry at Harvard University, The Massachusetts Institute of Technology, Brandeis University, the University of Illinois, the University of Wisconsin, Oxford University, The Rockefeller University, and Memorial Sloan Kettering Cancer Research Center, and he has spent almost every summer since 1961 at the Marine Biological Laboratory in Woods Hole, Massachusetts. He has been Scientific Director of the Israeli Institute of Biological Research (1952–1962); Director of the Institute of Life Sciences at Hebrew University; Advisor for International Scientific Relations to Israel's Minister of Foreign Affairs (1965–1974); and Chairman of the Committee for Scientific Cooperation between Israel and Egypt (1979–1984); and he has been a member of the advisory board of the Pugwash Conference on Science and World Affairs (1964–1988); the Advisory Committee on Science and Technology for Development to the Secretary of the United Nations (1965–1979); The Max Planck Institute for Cell Biology (1979–1988); and the World Health Organization (1983–1986 and 1996–1999). In 1997–1998, he chaired the Carnegie Corporation's project on "Scientific Cooperation and Conflict Resolution" (published by the New York Academy of Sciences in 1998).

Prof. Dr. h.c. Reinhard Kurth has served as Director of the Robert Koch Institute (Berlin, 1996-2008), Acting Head of the Federal Institute for Drugs and Medical Devices (Bonn, 2004-2007), and Director of the Paul Ehrlich Institute (Langen, 1986-1999). All three Federal Institutes are involved in basic, applied and commissioned research relevant to public health and health protection. His scientific work, published in more than 350 publications, is focussed on retroviruses and their interactions with animals and humans. The recipient of many scientific awards, he was (in 1998), appointed a member of the Berlin-Brandenburg Academy of Sciences, in 2005,

he was awarded the Commander's Cross of the Order of Merit of the Federal Republic of Germany by the German President for his exceptional service in the virology and immunology and for his successful development of Germany's three major Federal Institutes, which he has directed. In 2008 he was appointed a member of the German Academy of Sciences Leopoldina, and in 2009 he became the first Robert Koch Fellow of the Robert Koch Institute.

Prof. William E. Paul is an immunologist best known for his discovery of interleukin-4 (IL-4), a critical regulator of allergic inflammatory diseases. He is Chief of the NIH/NIAID Laboratory of Immunology and a NIH Distinguished Investigator. From 1994 to 1997, he directed the NIH Office of the AIDS Research. He is a fellow of the American Academy of Arts and Sciences and a member of the U.S. National Academy of Sciences and of its Institute of Medicine and a Raymond and Beverly Sackler Senior Professor by Special Appointment at Tel Aviv University. He is the founding editor-in-chief of the Annual Review of Immunology, now in its 29th volume, and is the editor of Fundamental Immunology, now in its sixth edition.

Prof. Olle I. Stendahl is a Professor of Medical Microbiology at the Faculty of Health Sciences, Linköping University, Sweden. He received his MD and PhD from Linköping University Medical School (1973), where he then served as an Assistant Professor in Medical Microbiology, Dean of the Medical School (1984-87) and Vice-President (1989-95). He was Secretary General of the Swedish Medical Research Council (1994-2001), President of the Swedish Society of Medicine (2002-05) and a member of the European Medical Research Councils' Standing and Executive Committees (1994-2001) and the board of the Swedish International Developing Agency (SIDA) research committee (2004-09), Chair, the Swedish Research Council's Committee for Polar Research (2003-05) and

the board of the Swedish Defence Research Agency (2005-present), and of the board of the Karolinska Institute (2007-present). For more than 35 years he has been involved in research on microbial pathogenesis, host defense and inflammation, particularly the function and role of phagocytic cells. His current interest is tuberculosis and innate immunity. He has published more than 180 scientific articles, reviews and books.