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ESSENTIALS The entire health system seeks to prevent disease, or diagnose and intervene effectively to limit its impact. The goal of most funders of medically related research in the developed world is to support re- search that is upstream of that which is relevant and attractive to health providers or pharmaceutical companies, and to work syner- gistically in the health research ecosystem with these and other com- plementary organizations when appropriate. It is often impossible to predict which advances in basic science will lead to breakthroughs, but if this upstream work is not done, then in the mid and long term, the flow of medical advances will dry up. The central problem for the funder of medical research is how to choose the best use for the next Dollar, Pound, or Euro. This is essentially a problem in prediction, but as Yogi Berra said: 'It's tough to make predictions, especially about the future.' Introduction 'And over them triumphant Death his dart Shook, but delay'd to strike, though oft invok'd.' (Milton, J., Paradise Lost) A recent estimate is that current annual global spending on research and development is in the region of (US) $1.5 trillion (c.2012), of which roughly $270 billion (or about 18%) goes to medically re- lated research. Thus, in the 19 years since satirical online publication The Onion reported that the death rate remained at 100% despite huge efforts from health workers and doctors worldwide, roughly $5 trillion has been spent research work with the objective of health benefit. Yet the death rate has not been affected. Furthermore, over the next five years, the Wellcome Trust intends to spend another $7.5 billion with the same goal! So why do we do it? How do we attempt to do it well? Because, while Death cannot be denied, life can be improved through better health and Death itself can at least be delayed and premature Death prevented. Health economists might state this as an effort to maxi- mize the global number of Disability Adjusted Life Years. While the entire health system seeks to prevent, diagnose, and intervene effectively, the goal of health research is upstream of that, to deepen our understanding of the biological and social determinants that underlie health and the processes that undermine it to develop better interventions for prevention, cures, and palliative interventions. Time scales The goal at the Wellcome Trust, alongside most other funders of medically related research in the developed world, is to support research that might be upstream of that which is relevant and at- tractive to health providers (such as the National Health Service in the United Kingdom) or to pharmaceutical companies, and also to work

synergistically in the health research ecosystem with these and other complementary organizations when appropriate. We seek to support the best work throughout the research-to-implementation cycle mostly in academic institutions (universities and institutes), some of which will be too far from application or of too great a risk of failure to be justifiable in the budget of a pro- vider or a for-profit company. However, we are confident that if this upstream work is not done, then in the mid and long term the flow of medical advances will dry up. The Wellcome Trust also offers extensive funding to encourage public engagement and involve- ment with science and to research work in the humanities, ethics, and public policy. We believe that this approach ensures that the best science remains integrated within the context of the societies in which it operates and has the greatest opportunity to impact on human health whether that impact is to be in the short, medium, or long term. At the Wellcome Trust, we choose to target our funds to a range of time scales. Some investments are made in work that we estimate to be very far upstream, such as our funding of parts of the human genome-sequencing project (with the US National Institutes of Health (NIH) and others) in the 1990s. That work was clearly then of little immediate utility, but now accelerates much more targeted work in genetic testing, gene therapy, and the identification of gene products that may be useful targets for drug development. Genomics is now becoming widely useful, with larger scale genome projects in both humans and pathogens, and the beginnings of attempts to link sequence data to medical records. 2.17 Research in the developed world (a view from the Wellcome Trust) Jeremy Farrar

178 section 2 Background to medicine Some of our funds are targeted even further upstream. A signifi- cant example is our funding (with the Gatsby Foundation) of the Sainsbury-Wellcome Centre for Neural Circuits and Behaviour. This Institute is focused on the study of basic neuroscience, by the study of the behaviour and activity of neurons and their circuits in the brains of living animals (rodents and fish) while they engage in solving mazes and similar tasks. A dozen years ago techniques were developed to target genes to neural cells that express proteins which can reveal the activity of those cells by emitting specific colours of light: almost literally putting light-bulbs in the head of an animal as it thinks about its work. At roughly the same time light-activated channels were adapted from bacteria for expression in animals, so that now specific neurons can be switched on, or off, by the appli- cation of light. Taken together these new technologies are broadly known as ‘optogenetics’. And at the same time people have devel- oped better methods for mapping the synaptic connections of neural cells using light and electron microscopy, to elucidate the precise wiring diagrams of neural circuits. So that now, scientists can map the neural networks, see the ac- tivity and control specific cells, all while the animal is behaving. In an analogy to the London Underground: suddenly we can see the tracks, the trains as they move along them and even through some switches to see what happens to the paths of the trains. The clock- work of the mouse or fly mind is being revealed. One hopes that in a few decades a similar understanding of the human brain could be developed (a much bigger task). But now the science is jumping ahead again, with the discovery and engineering of proteins to control nerve cells not by light, but by small molecules (designer receptors exclusively activated by de- signer drugs, DREADDs) or by ultrasound. Work that seemed to be decades away from the clinic is now possibly only a few years away and we stand at the brink of major progress in the understanding and treatment of diseases of the brain. Perhaps conditions like epi- lepsy will be the first that are amendable to this sort of intervention, but we are increasingly confident that these new technologies will be applicable to highly complex conditions, including mental illnesses and dementia in the medium to long term. It is often impossible to predict which advances in basic

science will lead to such breakthroughs. For example, study of channel rhod- opsin in bacteria and fluorescent proteins in jellyfish leading to the understanding of and then control of the brain, or the work in fun- damental discovery science of over 50 years ago which had led to today's opportunities for treatment with stem cells and monoclonal antibodies. Such cases are the justification for funding research all along the path from the very fundamental to the very applied. But which or- ganizations should work to support which stages along the path? Health services and pharmaceutical and medical engineering com- panies are motivated towards research that is close to clinical utility or medical products. But there are gaps at this end of the spectrum for diseases where there is 'market failure'. Bluntly put; situations for which there are no financial incentives to develop interventions, dis- eases which predominantly affect the poor or diseases of poor coun- tries. Funders in wealthy countries often support work on neglected tropical diseases, for example, through genuine humanitarianism. This is sometimes augmented by enlightened self-interest: most ob- viously in the case of emerging infections that become epidemic in poor countries (such as Ebola virus). Developing vaccines or cures for these illnesses is clearly in the interest of all, as such epidemics can have a devastating and destabilizing impact on the whole of a society, country, or region and many outbreaks are only the length of a jetliner's flight from the rest of the world. Another reason why organizations in high-income countries might fund research in low- and middle-income ones is simply the power of studying a disease where it is common. One clear example of this is HIV disease and tuberculosis in Southern Africa. With the prevalence of HIV in parts of South Africa at 60%, there are imme- diate benefits to all for research to be conducted where the need is greatest. Governments fund research all along the path from basic science to applied work, but there is increasing pressure to spend tax-payers' money on research that will bring health or economic benefit in the short term. We can see this in the pressure for demonstrable 'im- pact' in the United Kingdom and in the United States, in the reduced budget for basic research in Australia, and the level-funding of the NIH in the United States, while the National Science Foundation (NSF) is actually in decline. Types of funders Government funding mechanisms in developed countries are di- verse. The largest single funder in the world is the NIH's USA extramural programme. In total the NIH funds over $30 billion a year, mostly in the United States and mostly through universities, although a significant fraction (about 17%) is spent at the intra- mural programmes (mostly at the various Institutes of the National Institutes of Health in Bethesda Maryland). The US National Science Foundation covers a broader range of science, but spends only about a quarter of the sum that the NIH does. The NSF runs no directly funded institutes. Other US federal agencies also contribute to the broad biomedical research agenda including the Department of Energy, Federal Drug Administration, and many others. As a result, the total government funding available in the United States for bio- medical research amounts to over $50 billion a year. The European Union's European Research Council (ERC) funds roughly €13 billion per year. In addition, individual European coun- tries fund science themselves. Germany funds biomedical research through both the Deutsche Forshungsgemeinschaft (DFG, or German Research Foundation), which funds mostly through universities, and the Max Planck Society, which works by funding its own insti- tutes. In the United Kingdom the Medical Research Council (MRC) runs a mixed model, with funding both through grants to academic research leaders in universities as well as its own units and institutes. The largest MRC sole-funded institute now is the Laboratory of Molecular Biology (the 'LMB') in Cambridge, although the MRC is also a founding partner in the Francis Crick Institute, which opened in 2016 and will host 1200 researchers. Some nongovernment funders have been set up as charities that specifically fund work on specific diseases or areas, such as the American Cancer Society, the British Heart Foundation, the Fragile-X Association, and many

others. These organizations gen- erally raise funds from donors in the community and with specific disease interests, and many do not accumulate large endowments. Traditionally it has not been attractive for disease-motivated donors to fund fundamental research with a long-term perspective because

2.17 Research in the developed world 179 they are mostly focused on short term progress in the disease areas of interest. These pressures often turn these charities away from basic research. However, this is changing and increasingly some of these philanthropic organizations including, for instance, Cancer Research UK and Paul Allen Foundation, are supporting extensive programmes in discovery science and taking a much longer-term perspective. Other private charities are funded by one (or a very few) living donors. The largest of these now is the Bill and Melinda Gates Foundation, which is focused on the interests of the donors: for impact on global health during their lifetimes. Another example is the Gatsby Foundation, in the United Kingdom, which is funded by Lord Sainsbury of Turville and is focused on research into food sus- tainability and neuroscience areas of interest to the donor. Some of these personal foundations are directed to spend out their funds during the lives of the donors, whereas others are organized on large endowments left by the original donors or corporations to be- come perpetual foundations or charities. These organizations invest the endowment and spend a defined fraction of the value towards the charitable activities, mostly research. The two largest of these are the Wellcome Trust, in the United Kingdom, with an endowment of over £18 billion at the last financial report, and the Howard Hughes Medical Institute (HHMI), with an endowment of roughly $18 bil- lion. Neither the Wellcome Trust nor the HHMI focus on specific diseases, but fund research broadly across the biomedical science and health area. What is the ‘unit of funding’ Most noncommercial biomedical research funding in developed countries goes towards work done by academics in universities. This is for historical reasons (that is where most of the basic and clinical scientists are), but also because universities have evolved to provide a comprehensive academic infrastructure, based on scholarship and teaching, that includes key resources (buildings, libraries, vivaria, and more). Most important is the support of the academics them- selves, through salaries and a career structure. In serious research intense universities, academic freedom is assured, at least at the level of the independent group leader (often but not always some variant of ‘professor’). Thus independent research group leaders are free to pursue their interests as far as they can find funding to do so. While they may (or usually these days do not) have ‘tenure’ (permanent employment), today they very rarely have long-term institutional re- search funding and must therefore secure grants from government or private funders. These academics are overwhelmingly dedicated, imaginative, creative, hard-working, and competitive. Because they must continuously run a permanent marathon cycle of research, publication, and grant-winning, the benefits of this dedication come to us at far too cheap a price (academic salaries do not impress bankers). While there are very great advantages to funding into univer- sities, there are also drawbacks. The academic competitive structure is based (usually) on the ‘brand identity’ of the individual group leader/professor. This is most often scored as senior-authored papers. This culture can be a major inhibitor of collaboration between research groups. As science moves forwards it is often crucial for fields to meet, for new technologies to be developed and adopted and for ideas and theories to cross boundaries. The very reward-culture system of the academic university thus incen- tivizes individual achievement and success, but at the same time dis-incentivizes interdisciplinary collaboration. While there are some university structures that are also barriers (departments and schools), the real barriers are inherent to the system of credit-by-authorship, the competitive cycle of short-term funding and the increasing pressure for ‘impact’. In

addition to the independent group leader/professor, it is also critical to support the training and career-progression of more junior researchers, through doctoral programmes and various forms of fellowships designed for basic scientists as well as clinicians. In most disruptive and creative industries, it is these individuals who have provided most of the breakthrough innovations that have led to major changes in the way we live and work. We, and our com- munity are too conservative in the freedom and support we give to this group. In our current system, at least in the United Kingdom and the United States, there is a very great excess of the number of junior people entering training over the number of professorial jobs that might await them. In the United Kingdom a study by the Royal Society in 2010 showed that only 0.45% of those entering PhD students are likely to end up as professors. While there are many other useful and productive paths for many people other than research independence, this ratio is clearly too great and is disheartening to young people. Many undergraduates sample research through pro- jects of vacation scholarships and are driven away to other fields when they see the odds for themselves. We are losing a great many talented people. The main alternative to funding research in universities is to sup- port science in institutes. These range from small ‘centres’ or ‘units’ within universities, sometimes in their own buildings, to larger or free-standing ‘institutes’, usually on their own land, such as the NIH campus, HHMI’s Janelia Farm, or the Wellcome Trust’s Genome Campus at Hinxton. In such places it is possible to rewrite some or all of the normal ‘rules’ of academic research in an attempt to over- come some of the barriers. Commonly there is no tenure. Research focus can be required. Often, resources are controlled centrally by a director. Thus, the diffuse power of the university can be concen- trated to some specific goal or purpose. Some have even attempted to abolish publication as an outcome metric. The risk is that academic freedom maybe impinged upon and creative energy suppressed. At their best, core-funded institutes bring together dedicated commu- nities that work synergistically around particular problems or technologies, are liberated from the constraints of the short-term grant cycle to take on big long-term questions and take risks. Historical examples include, in their best years, the MRC’s LMB, the Institut Pasteur in Paris, or the Institute for Advanced Studies at Princeton. At their worst, core-funded institutes can become ossified, bureau- cratic, and stultifying. How to choose Whether funding is to be devoted to training, to individual fellows or professors, or larger centres or institutes, a central problem for the funder is how to choose the best use for the next Dollar, Pound, or Euro. This is essentially a problem in prediction. As Yogi Berra said: ‘It’s tough to make predictions, especially about the future.’

 Another way to consider this is to distinguish orthogonal dimen- sions. One dimension is the fit to the strategic goals of the funder. For example, for the Wellcome Trust a grant proposal on astronomy is outside the remit and is a nonstarter. On the other hand, spe- cific goals are often developed (such as the President’s BRAIN ini- tiative in the United States) and then proposals that align to these are favoured. The strategy may be politically driven, by the focus areas of the funder or by objective realities such as the burden of disease. Getting the balance between supporting the top-down de- fined priority areas of the funder and the bottom-up ideas from the community is a constant challenge and a point of discussion among all funders. In the end, no single funder can support everything it is asked to support and a mixed economy of top-down and bottom-up funding approaches are how most organizations work.
A common problem is that just wishing to make progress in a disease area and defining a goal does not make the research tractable. One example would be Nixon’s National Cancer Act 1971—the technologies re- quired were just not yet available when he made the statement and the Act was signed into law with a view to eradicate cancer Likewise, despite many years of effort, a vaccine for

HIV has not yet been de- veloped despite being critically needed and despite the very best ef- forts of many people. The overriding dimension is clearly scientific quality. If one could somehow perfectly rank all available proposals across all the areas of interest at any one time from best to worst, then the funder could just support down the list until the money ran out. Of course, there are problems with this as well. Aside from Yogi Berra's problem, it can be very difficult to quantify quality. As Ottoline Leyser recently pointed out 'Quality is qualitative'. This does not stop many, many attempts to derive numerical metrics of research quality and im- pact. Some approach objective truth, such as citation analysis: at least it is apparent that some people are interested in a paper. But unfortunately it usually takes many years before the relative import- ance of a discovery becomes clear; much too late for any funding decision, and citation analysis can just reflect the inherent conser- vatism of the modern science environment. People work, are cited, get funded, and promoted by working on projects which others also work on. At present, almost all funders rely heavily on the opinions of sci- entific advisors. This can be by written peer-review, discussion in committees, or by direct face-to-face interviews of applicants before committees. All of these are attempts to rank applications or appli- cants to allow for funding decisions to be made. All of these tech- niques contain possible artefacts and are rarely truly quantitative. It is also difficult to show that these processes are actually accurate in predicting success. The deepest problem for funders is to judge quality and oppor- tunity across different fields. Most avoid the problem by preallocating funds by area. Some (HHMI and the Wellcome Trust) do rank appli- cations and applicants across widely different fields. This is done by a series of screens: first of many applications for technical feasibility and broad promise. Thus field-experts can remove proposals that are technically totally flawed, but these are increasingly rare. But the later stages converge on a smaller number of (mostly by this stage exceptional) candidates interviewed by a group of scientific advisors drawn from across many disciplines. Inevitably it can be difficult to ensure all disciplines are equally represented and all equal in how they judge their own discipline and other disciplines. There can also be the challenge of decision by committee which can lead to conser- vative judgements, or a single negative view ending the prospects of an application. In the end, judgements must be made. Lastly, an important principle has become acknowledged by most funders of research: that a grant is not a contract. In other words, if a scientist proposes a project, that project should be considered as an intellectual exercise: can the candidate state a clear and important question, can they think through the problems, can they work out how many people and years and dollars will be needed. But once they have succeeded and been awarded the funds, then they must be free to follow their path freely towards the best results. In addition, these may have very little to do with the original proposal. If the scientist discovers something important, or solves a big problem, or makes a breakthrough, no one will ask if it was in the proposal from five years before. If they are wise, neither will they care too much which journal it was published in. FURTHER READING Milton J (1667). Paradise lost. Book xi. The Onion (1997). World Death Rate Holding Steady at 100 Percent. https://www.theonion.com/world-death-rate-holding-steady-at-100-percent-1819564171

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