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Perspectives: How can we explain the American dominance in biomedical research and development?

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Excerpts:

Part 1: Decision making

In this paper, Europe is categorised as a linear society and the USA as chaotic or non-linear…

Linear could stand for more rational, conservative, more bureaucratic, critical, hierarchical, organised, predictive, worried, social, more passive or ordered. Chaotic is not necessarily only the opposite but may be more open-minded, flexible, free-spirited, 'just-do-it' mentality, organisationally flat, aggressive or proactive. 'Analysis paralysis' seems to be an important consciously and subconsciously well-accepted decision-making mode in certain important European countries, whereas the glass in the USA is most of the time half-full and not half-empty. *Hakuna Matata*, a Swahili expression for 'there are no problems' and *Carpe Diem*, a famous quote from Horace meaning 'seize the day', are more reflective and representative of the USA than of Europe.

If this linear/non-linear segmentation is agreed, why is it important for the innovative potential in science and technology?

Although the main messages concerning decision making in a linear versus nonlinear environment are certainly applicable to other high-technology environments, the example given here is from biomedical research. The development of a drug represents an even more complex dilemma because the time frames often span a decade and even more. In other words, it is very costly and difficult or even impossible to test different strategies to obtain a better understanding of what works or does not work in finding the next blockbuster drug.

…The go/no-go decisions in drug development are clearly much more complex than estimating the market size potential, but even for cash- and resource-rich companies, perfect information is not possible and linear thinking patterns will lead to inefficient decisions. The linearity dilemma lies in the fact that a single parameter with many unknowns, leads to the termination of a certain programme. Using probabilities to semi-quantify the different parameters is also not really possible because we do not know the odds with any reasonable precision. Biomedical research is a highly fragmented endeavour and useful statistical calculations are very difficult to do in many circumstances.

… This is where linear thinking has its limitations because if the conclusion is that, eg the market size is too small, the project will not be pursued. Using a more non-linear decision mode, the project might be moved to a point where better information is available or other options open up or are considered, eg out-licensing with buy-back options. This sounds trivial for those involved in these decisions but such flexible thinking might not be practised as often as it should be.

… The key message here should be that perfect information with forecasting is not possible and because we are dealing with chaotic systems where small changes can make a dramatic difference in the outcome, the forecasting mistakes might not only be plus or minus 20 per cent, but five- or even ten-fold. Promising programmes or projects therefore should not be terminated because the forecast value of a single parameter might suggest so.

… Part 2: From high-risk projects to groundbreaking innovations Background noise or waste is a characteristic of chaotic systems.

The USA consumes per head about twice as much as European countries and therefore generates also about twice as much waste.3 This might be one reason why they are more able to tolerate background noise, wasted resources, failed efforts and non-perfect information. The consumption-inclined attitude of the American people might also play a role. In 2003, the household saving rate as percentage of disposable income was below 2 per cent in the USA, but above 9 per cent in Europe.4 The 'noncritical, easy-going attitude' as described above might also play a role in this behaviour.

… It is almost impossible to predict the future value of funding for biomedical science or for scientific activity in any field of interest… However, because of the already described differences between Europe and the USA (linearity versus non-linearity; tolerance towards 'failed efforts'; 'easy going' attitude, etc.), it is believed here that the probability for a high-risk project to receive funding in the USA is significantly higher compared with Europe. The non-criticism attitude mode also helps in this respect. It is not trivial to define or characterise high-risk projects, especially prospectively, but they try to advance our knowledge not by small steps, they are not incremental, but by a significant move forward. High-risk projects have a higher chance to develop into quantum leaps and groundbreaking, revolutionary or paradigm-shifting technologies.

… These ideas and projects are unconventional, untested and visionary. In Europe, these projects would not survive the partially endemic bureaucratic paths to receive funding. In the USA, they would probably also not survive the normal funding paths but several alternative money resources exist (eg DARPA, NSF, NIST, HHMI and private donations). Some of them have supported such projects for decades. In addition, significant amounts of 'private' money in the form of donations flow regularly into US scientific laboratories and this money can be used for unconventional research more easily than the resources from a government-sponsored programme. A high-risk project is often not suitable for

government-based funding because, first some scientific data are required for submission and secondly, a (positive) progress-report has to be shown, to increase the likelihood of extension. High risk projects frequently tend not to deliver the necessary results.

It is important to note in this context that high-risk projects must be based on world-class science or very reasonable and logical hypotheses and basic scientific concepts. They should not incrementally advance a certain sub-domain of a certain sub-sub-field but open entirely new scientific directions. Therefore, respected world-class scientists must play an important role in the decision-making process to fund such programmes. How such a decision-making process should be organised in order to fund the most innovative project is far from trivial. The author believes that this tendency to support 'unusual' research activities is probably not planned but is a reflection of the American society — aggressiveness and daring might go hand in hand.

… Whatever the true reasons are, American laboratories take much more risk when they choose scientific projects and this attitude seems to pay-off handsomely in the long run.

… The success formula might be the following: Americans are more aggressive, more tolerant of failure because they are used to waste and chaotic systems and are more willing to fund unconventional projects, which lead to higher value creation in the long term. Many of these projects do not go anywhere but some of them do greatly advance certain scientific areas significantly. Nevertheless, almost nothing moves without fuel and one essential ingredient for research is much more 'abundant' in the USA than in Europe.

MONEY AVAILABILITY AND DISTRIBUTION

Arguably, this is the single most important factor explaining the dominant role of the USA in innovative research. The total R&D expenditure in the EU was 1.99 per cent of GDP in 2002, whereas in Japan it was 2.98 per cent (2000) and in the USA 2.80 per cent.6 In 2000, the gap between US and EU investment in R&D reached C=124bn.7 Assuming a conservative 10 per cent allocation to biomedical research, C=12.4bn less was invested in Europe compared with the USA in 2000. The average cost of a drug developed by the pharmaceutical industry is estimated to be around US$800m.8 In other words, about 15 new chemical entities could have been developed with this money. This number would even increase if one considers the cost of developing a drug by biotechnology companies. In 2002, the FDA approved 17 new molecular entities. Closing, or at least narrowing this financial gap, and not only in biomedical research, would make a tremendous difference for Europe.

… In addition to government money, funding from non-government foundations and private sources, money from biotechnology and pharmaceutical companies also flows at a significant rate into the leading research institutions. Several articles and one book have been published recently about the commercialisation of academic research and the

potential dangers involved in this recent phenomenon.10–13 It is less of a concern for basic research, but causes significant headaches when clinical investigators test a new drug on patients and at the same time receive support for their laboratories from the company attempting to receive marketing approval for the drug.

…The conversion rate of private biotechnology companies into public entities through an initial public offering is significantly higher in the USA than in Europe. It is also much easier to have a substantial secondary offering further nurturing these companies with tens of millions of dollars, the majority without revenues. It has been calculated that on a per-company-basis, at least five times more money has been available in the USA compared with Europe during the last decade (Techno Venture Management, Boston office).

In other words, using the example of drug development, if it is a pure probability game combined with some luck, US biotechnology companies have significantly higher odds compared with Europe to develop successful drugs. In addition, it should not be forgotten that drug discovery and development is not a linear process, ie five times more money does not mean five times more drugs.

… SELECTION CAUSES BRAIN BATTLES AND BRAIN DRAINS

… Individuals are very competitive and very motivated. In addition, at the prestigious universities, selection does not take place only at the student, but also at the professor level. Many professors are often recruited to these institutions only when they are well established in the scientific community and recognised worldwide. Who would not follow an offer receiving an excellent academic salary, very good financial support for research activities and in addition highly motivated students? This combination of double selection should lead to more ideas and innovative potential. The best professors filter and select the best ideas from very motivated and clever students, in addition to being able to pursue their own ideas with these students. This is an ideal win-win situation for both professors and students.

… [Based on] the worldwide ranking of Universities by the Institute of Higher Education, Shanghai Jiao Tong University…[a]mong the top 20 universities in the world only three are not from the USA.

… To compare the US and European systems, it appears that the European system is more hierarchical and the professors ‘use’ the students to advance his or her career by telling him or her what to do; whereas in the USA, the motive of the professor is probably the same, but the student has certainly more freedom to choose a topic. The increased freedom combined with the lower age when such a choice is necessary, might also lead to more unconventional, unusual or daring projects, potentially leading to concepts with higher innovative potential.

… It must be also clearly stressed that a lot of the ‘brain battles’ at US universities are

actually 'fought' by non-Americans. Europeans represent a significant percentage of all post-doctoral fellows in US biomedical research laboratories and biotechnology companies. The number of European, including former east bloc countries, Indian, Korean and Chinese computer and electrical engineers is also very substantial.

… If one combines the aggressiveness of the American society, its ability to tolerate failure and waste, with unconventional thinking patterns leading to the design of high-risk projects; fuels this explosive mixture with significant amounts of money; selects the best professors and students and gives them early responsibility and freedom and allows and nurtures a positive brain-drain, the result might be the recent very successful innovative capacity of the USA.