The System Dynamics of Bacterial Evolution and the Human Immune System

A. Introduction

Two independent discoveries were mentioned at recent Royal Society lectures which suggest that it may be useful to consider bacteria in terms of system dynamics, as well as in the usual biological and medical contexts. The first discovery was made some time ago by the nuclear physicist Szilard, who found that a single bacterium, nurtured under laboratory conditions, could apparently "evolve" (1). The second discovery made in much more recent work was that the human immune system could undergo changes "to meet a threat in a day or two" (2). This also amounted to "evolution", taking place over a surprisingly short timescale in a creature which measures even minor evolutionary changes in terms of tens of millennia i.e. ourselves. Taken together the two discoveries suggest possible hypothetical models which could shed light on these "evolutionary" systems and their interaction. The basic principles of the models are such that they can all be put to the test by experiment and measurement.

B. Model of bacterial propagation

Szilard's discovery suggests that bacteria follow a different model from the accepted view of evolution by natural selection. Natural selection depends on variation in a population, from whatever cause, which produces individuals that differ from the population at large. Such variation may have an exogenous cause, such as cosmic radiation, but it is much more frequently caused by faulty reproduction of interacting individuals; something is missed out which ought to be there, or something is added by mistake. When complex individuals produce offspring, they do not simply make clones of themselves.

Most variants which result from the process of natural selection are less suited to survival in the environment than the original, and progressively die out through competition. However, a few may be more suited and prosper to the extent that they become a distinct species in their own right. Differentiation between variants may be exaggerated by changing environmental conditions, and eventually a variant may even displace the original in the new environment. In systems terms, survival means more efficient capture of inputs and processing them to outputs as growth, energy, disposal of waste etc.

However, a single bacterium isolated in a test tube must unambiguously belong to a single species with no variation, whatever relation it bears to other bacteria outside. Feeding the bacterium allows it to divide, so as to form clones. These clones produce more clones. If we discount intervention from outer space, any variation in the population of bacteria formed from the single bacterium must have its cause in the internal processes of reproduction of the bacterium. It cannot be a process of selection by environmental conditions i.e. natural selection, because the environment is stable.

Thus if a single isolated bacterium evolves, it is because bacteria are rather erratic at cloning themselves. Some are much better than others, because they are known not to have changed over a period of a thousand years or more e.g. typhoid. Others seem to be "evolving" and producing new "species" every year. The effectiveness of the internal mechanisms which control cloning must vary from species to species.

The significance of this analysis is that we ourselves are a most suitable temperature-controlled environment for growth with plenty of inputs etc, and so it must be assumed that what happens in the laboratory medium also happens in the human body.

This is quite different from the conventional view of bacteria, for example, that they are continually probing our weaknesses to cause mischief. If the hypothesis of poor cloning is correct, it suggests that bacteria may be considered as chemical entities with the unusual properties of cloning themselves. They are no more malicious than, say, oxygen molecules which intervene to form a layer of oxide on metal surfaces because they are all bathed in it, an advantage for some processes which affect man, but a disadvantage for others e.g. soldering. Another example might be water molecules, which are immediately adsorbed onto available surfaces, a vital necessity for natural processes, but a distinct nuisance for engineers when they are trying to make adhesive bonds.

The point is that when changes occur which produce bacteria that are undesirable in humans, it is not the probing of our weaknesses, but the natural result of disturbing systems which were in equilibrium. The results may be exaggerated for us, because the systems in question are dynamic, so that apparent stability results from the balance of opposing forces. If bacteria do not multiply each time with precision, equilibria may be upset. The flaw may be only one in a million, but one bacterium soon grows to a million, given the inputs.

The process by which this could occur is shown in Figure 1. It is implicit in the preceding argument that populations of bacteria are highly likely to be heterogeneous i.e. not every bacterium is absolutely identical to every other in the population, even though they are all apparently the same "species". If a population is treated with a bactericide solution, a large proportion of its bacteria may be killed, but a proportion will remain which comprises those more resistant to the bactericide (after 1st treatment). If the more resistant bacteria are then fed with inputs, they are likely to produce a population of bacteria which is more resistant to the bactericide at the concentration used. The average resistance to bactericide has increased.

If this resistant population is treated in its turn to more concentrated bactericide solution, the process repeats itself (2nd treatment). Most bacteria will be killed, but a proportion will remain which can tolerate the higher concentration of bactericide. If these are provided with nourishment, they will produce a population which is yet more resistant to the bactericide, until eventually a population of bacteria is produced which is completely resistant to the bactericide at the concentration first used. The bactericide is in effect being used to produce "natural" selection.

Bacteria as living entities grow to fill the available space, provided there are enough inputs. However, if there are too many bacteria competing for space and inputs, they do not necessarily form a hierarchy which we would recognize. The bacteria which we consider dangerous, may be just another competitor for bacteria which do not threaten us at all. Thus the scope for colonisation and expansion may be limited by the populations of other species of bacteria which are already present. If all populations are treated with bactericide indiscriminately, and if some survive the treatment and have access to inputs, the result could be to leave the field to bacteria which are resistant, quite the opposite of what was intended. The cure would be worse than the disease.

C. Model of operation of the immune system

The human immune system appears to be a very large resource comprising different species of active entities which deal with intruders into the system by locking onto and destroying them. Each species of active entity or antibody deals with a specific species of intruder, where specificity is conferred by stereochemical linkages. Each individual antibody appears to be used only once, because it is itself destroyed in its attack on an individual of an intruder species. This is a process which is going on continuously under normal circumstances.

If this is so, there must exist a means of making more antibodies of a species as required, and the question then arises: how does the immune system know that more antibodies of a particular species need to be made? The mechanism that suggests itself is again a chemical analogy, this time of chemical equilibrium, in which chemical species A and B combine to form compound AB, but AB also decomposes to form A and B. Where the equilibrium settles depends on the rate at which the two processes occur.

$$A + B \leftrightarrow AB$$

If the concentration of one component, say B, is reduced by some exogenous source, the relative rates of formation and decomposition of AB restore the equilibrium.

In this case information is fed back to the locus of manufacture by displacement of the equilibrium, which manifests itself as a decrease of concentration of a specific antibody. So as the concentration of a specific antibody is consumed by successful attacks on intruders, more is produced to restore equilibrium. This is the body as chemical reactor with a definite size. The biological question, as opposed to the systems question, would then be how such an equilibrium came to be established in the first place.

From time to time intrusions of a species occur for which there is no ready made antibody, because the antibody system has not met that particular type of intruder before. In this case there is no equilibrium to restore, which is where the second discovery described at the beginning comes into play, the evolution of the antibody system. The immune system produces new variants in a matter of days, possibly by targeting the intruder, possibly on a stochastic basis, and they increase in number to some equilibrium concentration. In either case, after an interval of time a variant will be produced which

has the specificity required to destroy the new intruder. Its concentration will tend to grow, but it will also be continually reduced as it attacks the intruding entities. This will cause more be made, which continues the process of combating the intruder; in effect there will be a new species of antibody in the repertoire.

D. The combined model

Combining these models, it can be seen that the outcome of such encounters for the human body will depend on the relative rates of production of intruder and antibody. If the number of antibodies produced is sufficient to outstrip the number of intruders, health is maintained. However, if the number of intruders grows faster than the antibody can be discovered and produced, the intruder manifests itself as pathogenic, and ill health results. The actual ratio of antibodies to intruders required to prevent infection depends on the efficiency of the process i.e. rates of mixing may mean that it needs several antibodies to track down each intruder, even though only one actually completes the destruction.

If this model provides a reasonable working hypothesis, it suggests that most of the mutations which infect animals occur during the process of replication within animals themselves, since they are the most suitable culture media of all. Thus humans are the sources of most of the bacterial infections which are pathogenic to them. Pathogens may be transferred from other humans, or they may be produced by poor cloning within a human body during formation of a population of bacteria.

If bacteria spray off variants stochastically as they clone themselves during the course of an infection, almost all populations of bacteria are likely to be heterogeneous. They can therefore be differentiated by change of environment e.g. addition of dyes, bactericides etc. Differentiation shows that bacteria in the population have a statistical distribution of properties, which will not necessarily be the same for all additives used to discriminate between individual bacteria. The discriminant which ultimately matters is susceptibility to species of antibody in the immune system.

In these competing processes, the immune system almost always wins, which is why we are normally healthy. However, occasionally variants are produced with which the immune system cannot cope rapidly enough e.g. the delay in “evolving” a new antibody allows the bacterial variant to reproduce itself in numbers too large for the immune system to match.

These are the conditions under which an antibiotic is administered, but by the preceding argument it is unlikely that an antibiotic could kill off an entire pathogenic population, because of differentiation of resistance. The nature of the process is that there will always be some, however small a number, which are resistant to the antibiotic. These would then go on to multiply in the culture medium which is the body.

Nevertheless, there is no doubt that antibiotics produce the desired results in most circumstances, even if they may never have seen the variants before. But if they do not destroy the resistant bacteria, the question is: what does? The corollary is that there must

be a further process at work which completes elimination of resistant bacteria. This can only be the immune system. Thus the function of the antibiotic may therefore be to give the immune system time to respond, say by producing a new species of antibody.

The most encouraging aspect of this hypothesis is that the immune system can win against "resistant" bacteria, given the chance. We do not need a perpetual supply of new magic bullets, because the immune system will make them. It is a matter of controlling competing rate processes. (Not that magic bullets are without applications if they are available).

A condition such as MRSA therefore probably means that there remains too large a number of pathogenic bacteria for the immune system to cope with after antibiotic treatment. It is not that every individual bacterium in the population is of a new resistant species, just an unusually high proportion. In principle the shape of the distribution curve could be confirmed by laboratory tests. In the case of MRSA, methicillin is in effect being used as the discriminant.

"Friendly" bacteria may also play a part in limiting infection. The body may be regarded as a vessel which contains at least 500 species of bacteria, all competing for space i.e. inputs and freedom from increasing predation. This must be true in any system or it would continue to grow for ever. The result is that these bacteria co-exist in equilibrium, apparently without causing harm, and possibly performing essential functions for the body. Under normal circumstances, if something happens to disturb the equilibrium of these species, the system tends to return to a stable state again.

However, an intruder bacterium has to force its way into this system to establish itself, which could have two consequences. First, it is possible that a boost to the equilibrating system may limit the rate of growth of the intruder species by denying it "space", for example by addition of "friendly" bacteria. Secondly, antibiotics may damage the populations of equilibrating bacteria to such an extent that space is inadvertently made for the intruder.

In competing rate processes, the initial conditions are likely to determine the entire outcome. There may be induction periods which influence all subsequent development. If bacterial reproduction and immune system production occur at equivalent rates, the effect is neutral, but if the immune system has an induction period while it finds the right antibody, it can never match bacterial reproduction. To compete it has to find a faster rate from somewhere. There is the possibility that the balance can be redressed in favour of the immune system by antibiotics or other agents which cause induction periods in the onset of growth of bacteria, or reduce the rate of division of bacteria , say division every hour rather than 40 minutes, which has a considerable effect on numbers of intruders at any particular time. This is the sort of competition of which the outcome is entirely calculable, if the rate constants are known.

The model would also explain the mechanism by which vaccines protect. They provoke the evolution of the correct species of antibody to add to the collection, so that when real

infection occurs the immune system has a head start with no induction period. Antibodies passed on with mother's milk would operate in a slightly different way; they would provide cover while the offspring's own immune system found and made its own antibodies. Since antibodies in this model form such a small proportion of chemicals by weight of the human body, the concept of "overloading" the immune system would appear to be meaningless. Vaccines could also work in conjunction with antibiotics, neither being conclusive, but both contributing to the effectiveness of the immune system to finish the job.

E. Conclusions

As a working hypothesis, bacterial evolution and immune responses can be treated as systems. The elements are in place, even if the specifics are certain to be modified in the light of further research. The model is one of competition between two rate processes, which is ceaseless, because there is no let up in intruders making their way into the body in the normal course of living. Pathogens become obvious only when the balance changes in favour of the intruders.

The basic assumptions of the model can be tested e.g. by treatment of populations of bacteria in vitro with the right discriminating bactericides to determine the shape of distributions of resistance, but it is not enough merely to show visual differences, nor even the response to antibiotics. The discrimination which matters is by human antibodies.

This requires tests in vivo, which are difficult, but they may be the only way to test antibody/bacterium interactions. Cases have been documented of comparative trials where not administering antibiotic was more effective than administering one. Antibiotics appear to have hindered the ability of the immune system to fight back, which is a clear indication of interaction.

The model clarifies the various parameters which affect resistance to bacterial infection, and suggests that their effects would be cumulative i.e. they are not a series of alternative treatments which might interfere with each other. The first clear priority is to limit the number of hostile bacteria which enter the body, and there may be scope for limiting the "space" accorded to them by promoting other, less hostile bacteria. Some of these are already present. Obviously no procedures should be used which weaken the relative position of bacteria already present or impede the immune system itself.

There may be treatments which selectively slow down the rate of growth of intruder bacteria by increasing the time between divisions to form clones, which is useful both by limiting the numbers to be killed and because it is the cloning process which produces the variants causing the pathogenicity. Some types of antibiotic or similar materials might perform such a function without actually killing bacteria. The aim would be to give the immune system time to find an antibody which would perform the final act of destruction.

Other possibly relevant parameters come straight out of chemistry. For instance, reduction of temperature slows down the rate of a reaction, and it might do the same for bacterial cloning. It might even reduce the incidence of variants, though there is the danger that it might also retard beneficial reactions. The rate of mixing of antibodies and bacteria could also have an effect, if the former have a problem finding the latter. This is the efficiency of mixing and stirring, which is in effect chemical engineering.

According to the model, vaccination speeds up the response of the immune system by providing ready made antibodies which eliminate the induction periods involved in starting from scratch, and so it may be possible to engineer model templates which promote the process of the body's development of new antibodies. A well known strategy for parents is to mix small children together socially to spread a disease at an age when its consequences are much milder than in adults. This may have ramifications which spread into unexpected areas (3).

The presence of antibodies in breast milk serves a different purpose. It may simply provide cover against infection while the offspring's immune system gears itself up to respond, in which case protection would last only until all the breast milk antibodies were consumed, and it suggests that any healthy woman's breast milk would do a similar job. On the other hand there is the possibility that antibodies in a mother's milk may not only provide cover, but in some way encourage the offspring's own immune system to begin to function fully, which would be a major natural, and not entirely unexpected, advantage in a system which has evolved over many millennia.

If the model of competing rate processes is valid, it emphasises the absolute necessity of keeping the initial number of entities of pathogenic species to a minimum through cleanliness, especially if they are completely new to humans. The aims are: to reduce the opportunity for multiplication through inoculation of humans; to reduce the probability of spreading by limiting geographical scope, introducing separation barriers which should last until intruder bacteria are eliminated etc; once the pathogenic species have spread, again cleanliness to limit numbers. However for global infections this may not be enough, because even a few bacteria left rapidly increase in numbers.

Pathogenic bacteria come with humans, and they are by no means confined to hospitals. For instance, there have been claims that MRSA is widespread among the general population in the US, lying dormant until individuals fall sick. According to the model it is falling sick that tips the balance in favour of the intruders. However, it is in hospitals that the sick tend to congregate, and so this is what catches the public's attention.

Thus if the list of measures described above has failed to cure the problem, there is the question of separating the infected from the non-infected, which implies some form of hospitalisation. A major part of the treatment then becomes the architecture of hospitals, because this determines the effectiveness of processes carried out in them. Poorly designed hospitals may vitiate cures, whatever care is taken to ensure cleanliness. The architecture is a vital part of the cure by preventing re-infection, spread of infection to other patients etc

The hospital is a part of the wider national system of health care, and so the full cost to be reckoned is that borne by the community as a whole. It is no use optimizing the ostensible costs of hospitals, if real costs are inadvertently passed on to the wider community. No healthcare system can be optimized by optimizing its subsystems independently, because they interact. In this context it might be useful to consider the production curve used in economic analysis.

The lowest cost of a unit of output from a factory is achieved when it operates at about 80% of its design maximum (Figure 2). Above that level operating costs increase faster than output, because running continually flat out causes more wear and tear, more breakdowns, more mistakes, and more waste, and reduces the time available to solve problems which might ease this. Neither is there time to cope with exogenous problems such as supply or bad weather. In short there is not enough slack in the system. The norm for production should be just below that level; maximum should be reserved for special, temporary situations.

As a result, simple cost accounting may be misleading when applied to complex processes, because it is based on a static model. In the real world processes are by definition dynamic. When a factory operates, costs mount up visibly as the system begins to be overloaded. For hospitals the increases appear in the difficulty of reaching the goal of eliminating the intruder bacteria completely, in which case there is the likelihood that they will spread again. If they do, the cost falls on the wider health care system, and appears in due course in further hospitalization etc. This is the system developing positive feedback, which results in escalating costs.

The increasing incidence of MRSA is a case in point. The model of a dynamic equilibrium suggests that when it gets too far out of balance the advantage moves rapidly in favour of the pathogens. Architecture and excessively high bed occupancy may fail to eliminate, and may even increase, the incidence of infection despite the best efforts of staff and the highest standards of cleanliness. It could be that what is ultimately required to reach the goal of eliminating MRSA is more distance between patients, the equivalent of the physicists mean free path in gases. Or perhaps temporary facilities could be used for the specific purposes of isolation. A hospital system based on lowest cost, both public and private, could prove to be very expensive in the long run.

The requirement for wider understanding of the processes of infection and cure can only increase as billions more human beings from all sorts of different environments worldwide are pulled into the global socio-economic system in which all this happens.

However, there is a significant feature of the model which is most hopeful: it proposes that it is the human immune system which effects the final cure, even if it needs a little help from antibiotics along the way. The analysis suggests no reason to think that it cannot cope with almost all bacterial “intruders”, given the chance. If the hypothetical antibody process is valid, patients cured in isolation by the sorts of procedures outlined above would be immune from re-infection, having developed the appropriate antibodies,

and will not infect others if they remain isolated until cured. Properly constructed, the system would be self-righting.

Of course it is much more complicated than that, and there are similar concerns relating to the spread of viruses and fungi (4). It seems that erratic cloning is a feature of life at microbial level, which is why it is so successful. The dynamics will be different, but seems likely that similar systems analysis could be useful.

This calls into the question the whole philosophy of relying on silver bullets to solve such problems. The deeper solution requires better understanding and control of systems. For agriculture it may mean rejecting monocultures, returning to diversity and rotating crops to reduce spread of disease.

For bacterial infections it means everything described above, especially preventing outbreaks from occurring in the first place, but it also implies the whole raft of measures which complement each other and range from architecture to vaccinations and social policy. Solutions require a holistic approach, and in particular it means the elimination of the poverty in which bacterial infections thrive.

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References

1. Bacterial populations and bacterial diseases. Brian G Spratt, Professor of Molecular Biology, Department of Infectious Disease Epidemiology, Imperial College London. Royal Society Leeuwenhoek Lecture 17 November 2003.

2. Mutating DNA: protector as well as killer. Michael Neuberger of Cambridge University. Royal Society Lecture. 30 October 2003.

3. Infants in daycare may suffer less leukaemia. Guardian, James Meikle Health Correspondent, 23 April 2005. Putting your baby into daycare in its first year could mean it is less likely to develop childhood leukaemia, according to results of a 15 year study of childhood cancers in Britain. Exposure to other childhood infections among other infants might prime the immune system and sometimes prevent the second half of the "double whammy" that scientist believe is needed for the cancer to develop. There is growing consensus that the cause of the cancer is exposure to some sort of infection in infancy, perhaps a group of bacteria or viruses. Former East Germany and Costa Rica had lower levels than other industrialized countries until they ended universal child care.

4. Fungus that goes against the grain. Guardian Life, 21 April 2005. Magnaporthe grisea rice fungus can infect and blight many different varieties of the grain, because it has a knack of genetic variation even without the help of sexual recombination.

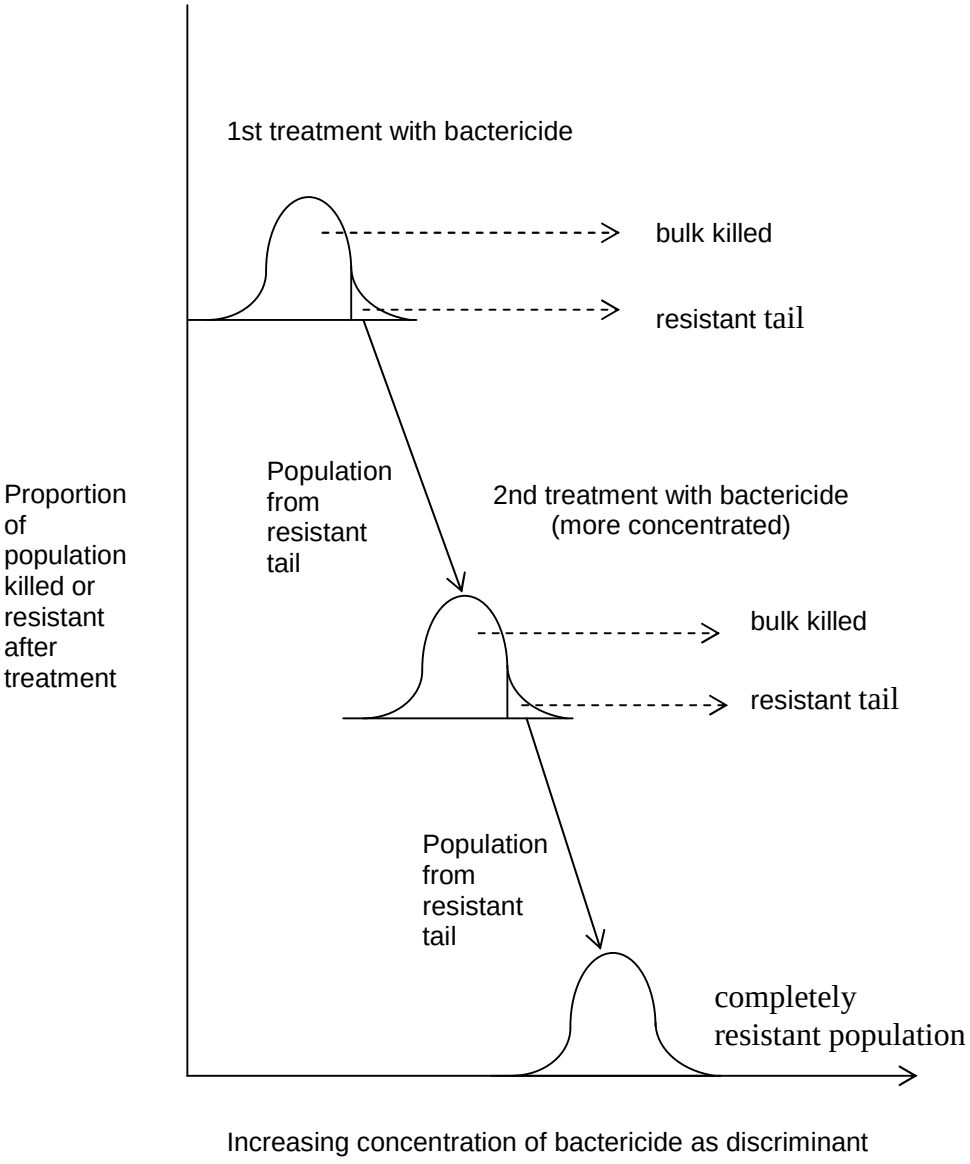

Figure 1. Increasing resistance of populations “cloned” from a single bacterium

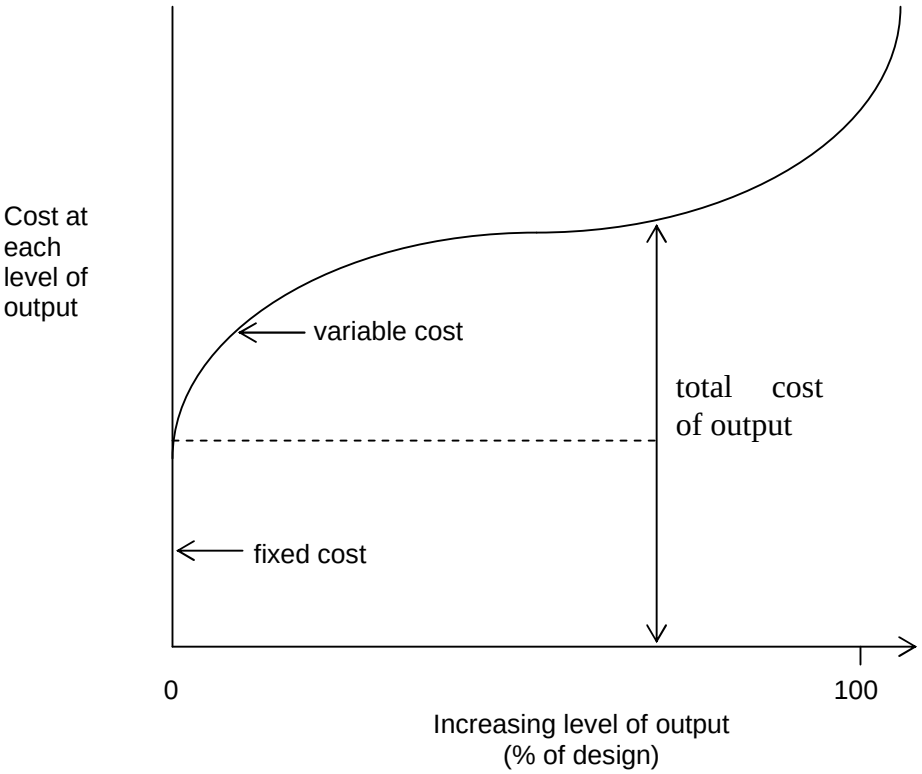

Figure 2. General Production Cost Curve

Footnote

Analysis in this field is normally medical, biochemical, microbiological or molecular biological. I thought it would be useful to consider it as a dynamic system, which may suggest a new approach. In support of this I would quote the section on Evolution in my book on systems, A Degree of Freedom (copyright 1993), which anticipates roughly the situation of the Human Genome project today i.e. the crux lies in the interaction between genes, and of course time, rather than in the genes alone. Donated a copy of the book to the Royal Society. I believe it has produced some useful insights.

In the context of the present paper:

- It may not have been noticed that I modified the meaning of the term "pathogen" from potentially harmful to causing actual harm. This is an essential part of the proposed theory of equilibrium. Potentially dangerous bacteria do not cause infection under normal conditions because they are continuously being annihilated by the immune system.

- The proposed equilibrium in antibody numbers suggests that antibodies which have already been produced and the "production line" for producing them must have a common locus, or there would be no feedback for control of the system. The locus must be stereospecific, or it would not be able to produce the right tool for the job i.e. it is not a general purpose workshop.

- The mechanism appears to be that stereospecific antibodies which have already been made are continually being adsorbed at and desorbed from this locus, thus denying space for the raw material of which the antibodies are composed to reach the production line. As antibodies are consumed from the fluid surrounding the locus of production e.g. by attacking intruders, space becomes available on the production line, and more antibodies can be produced to join the fray.

- If this is so, the equilibrium can be displaced by restricting or increasing inputs of one or other components. Furthermore, there may be a mechanism for destroying antibodies quite apart from fighting infection, ot there would seem to be the possibility of eventual overproduction.

- If resistance occurs as a result of faulty cloning during ther course of an infection, as proposed, the slow release of antibiotics would ensure no resurgence of invading bacteria resulting from incomplete treatment. The role of slowly released antibiotic would be to keep the rate of production of invading bacteria, and so resistant variants, to a minimum. Variants which got through would be annihilated as the immune system evolved to match the new stereospecificity.

- Since production of "resistant" bacteria would be confined to an individual body, given the isolation recommended, there is no way that resistance could pass into the outside world.

Much of this is new thinking, and at the very least supportive of other approaches.

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