Royal Society of Medicine

President Sir John Stallworthy FRCOG

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Jephcott Lecture

Future Invention in a Harsher World

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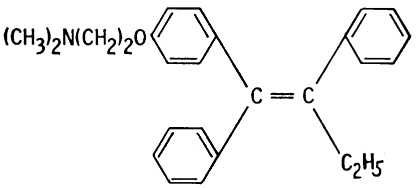
An invitation to give the Jephcott Lecture is a great honour, and particularly for someone with a pharmaceutical background. Everyone who has worked in that industry admires Glaxo, where Jephcott created one of the world's finest pharmaceutical companies by steadfast encouragement of invention, and courageous investment in it. Such innovative companies in many industries have done more than anyone else to increase the world's prosperity.

Up to a year or two ago, most of us expected this technological miracle to continue. Then one blow after another fell. Some were predicted in 1972 by the Club of Rome in 'The Limits to Growth' (Meadows *et al.* 1972) and subsequently the Club's argument on resources was brutally reinforced by severe shortages of oil, metals, grain, and so on. Their general argument has been strengthened by escalating social unrest and raging inflation. None of this seems sufficiently irreversible to precipitate the catastrophes predicted in 'The Limits to Growth', but they must eventually come if we do nothing to prevent them.

My object is to consider how invention might neutralize the most dangerous constraints. I shall then consider whether social, economic and political skills, such as they are, would allow a solution even if we could achieve it technically. To consider every point made by the Club of Rome would be intolerably mournful, and I shall discuss only the major problems of population growth, food supply, carbon, hydrogen and energy resources, and pollution. So broad a canvas can only be filled quickly with a coarse brush. It is a personal picture, drawn from my current interests, which cover ICI's total research. This ranges over drugs, pesticides, protein, plastics, fibres, fine chemicals, fertilizers and so on. If I refer mainly to it, it is because I know it best, not because it is exceptional.

The biggest problem facing the world is excessive population: our numbers will double to about seven thousand million by the year 2000, and may double again by 2030 unless effective action prevents it, or catastrophe occurs earlier. We need not wait so long to feel miserable. How delightful Britain would be if there were only thirty million of us. We could feed ourselves and have space to breathe and move and avoid each other. Even the mindless belligerence now lethally metastasizing through our society should decline. Therefore, of all future inventions, I put improved contraceptives first. Some might say that what we have are good enough, but there are two arguments against this. The first is the wide diversity of methods used by the presumably well advised – the wives of gynæcologists (Wassertheil-Smoller *et al.* 1973). This hardly suggests that the supreme contraceptive has been found. Second, in spite of the dedicated promotion of every known method, the population of India is rising by nearly 20 million a year. We need better contraceptives, and many current researches have a chance of finding them. I have selected modification of the usual pill, progesterone antagonism, œstrogen antagonism, antagonism of the luteinizing hormone releasing factor, prostaglandins and immunological methods for brief mention.

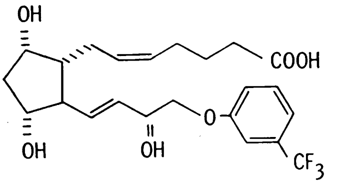
Newer pills have lowered œstrogen and, later, progestogen dosage until what we now have can perhaps go no further. If the improved pill were cheap, and if the modest sophistication required



TAMOXIFEN

Glu. His. Trp. Ser. Tyr. Gly. Leu. Arg. Pro. Gly. NH_2

LRF



ICI 81,008

Fig 1 *Top, tamoxifen. Centre, LRF. Bottom, ICI 1008*

and the willpower to use it were ubiquitous, it could usefully retard population growth. Unfortunately, these ifs may be unattainable, and further simplification and cheapening of the pill seems essential. Continual progestational treatment, and implants, have caused irregular cycling and seem unpromising (Swyer 1973). Studies of the pericoital effects of single doses of megestrol or clogesten acetate have been reported as promising, but little more has been heard. I have thought for a long time that we need a completely fresh approach.

Speaking as a former physiologist, I find it odd that the best pill is a mixture of progestogen and œstrogen, whereas obvious theory would point to an antagonist of either. So far as I know, anti-progestational action has been claimed, only for the Roussell compound R2323 (Swyer 1973). It was said to be effective in a single weekly dose but little has been heard of it recently. Progesterone antagonism probably deserves more effort.

Because implantation of the fertilized ovum in the rat is œstrogen-primed, we in ICI have sought œstrogen antagonists, mostly basic arylethylenes. The best of them, tamoxifen (Fig 1) (Harper & Walpole 1967), prevented implantation in the rat in a single low dose given around the fourth day of pregnancy. We hoped human implantation might also be œstrogen-primed, but so far our scanty evidence has failed to prove an anti-implantation effect in women. On the other hand, human œstrogen antagonism has been fully demonstrated and it has been useful in breast cancer (Cole *et al.* 1971). We know from premenopausal patients that menstruation can be suppressed by continuous dosage, and there is a fair possibility that tamoxifen would be contraceptive if used daily. Total suppression seems unnatural to most women we have consulted, yet menstruation must be a rare event in a state of nature, and it is arguable that the œstrogen surges associated with it could be harmful.

Another interesting possibility is antagonism of the luteinizing hormone releasing factor, LRF. This opinion led us to spend several years' work and about a hundred thousand sheep brains on its isolation. Unfortunately, just as we were sequencing it, we were pipped at the post by the University of New Orleans who published its structure (Matsuo *et al.* 1971) (Fig 1). Antagonists have been described (Monahan *et al.* 1972) and should block ovulation, though there is risk of other effects. Peptides of this size are fairly readily absorbed so that oral administration might be possible.

The luteolytic and oxytocic effects of the natural F prostaglandins make them contraceptive and abortifacient. Unfortunately they also have gastrointestinal actions and are bronchoconstrictor. Several years' work in our laboratories has partly separated the desirable luteolytic effect from the gastrointestinal effect, and we are about to market the first novel synthetic prostaglandin, ICI 81008 (Equimate, Fig 1) for the control of fertility in horses (Binder *et al.* 1974). This and related compounds are under study in other species. A single monthly dose should be contraceptive by turning off the corpus luteum, either just before, or within a few days of failed menstruation. Something of this sort might be the preferred invention for sophisticated communities, if side-effects can be completely eliminated. There is a reasonable chance of this.

The immunological possibility is speculative though immunization against spermatazoa has been tried. Other possibilities include immunization against a unique peptide sequence in human chorionic gonadatrophin, or against LRF. If a safe, specific antibody or antigen could be developed it might well be preferred for huge populations.

Unfortunately it takes many years to complete contraceptive research and development, and neither of my preferred inventions could be ready soon: one has to fear continued failure to control birth adequately, though effort to do so is increasing and improving.

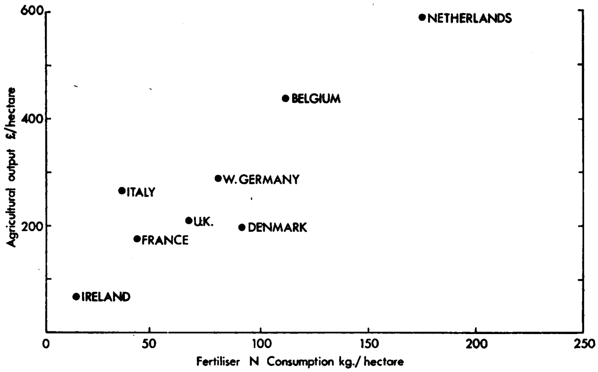


Fig 2 *Total value of agricultural output and fertilizer N consumption per hectare in the European Economic Community, 1971*

Thus the other side of the disaster equation, the production of more food, has to be given high priority. A great deal remains to be done in Britain, since within the European Economic Community we do not yet lead in growth of agricultural output, use of fertilizers, yield from them (Fig 2), or use of agricultural machinery. All this relates to familiar inventions, and increased use of them is mainly an economic and resource problem. Use over most of the underdeveloped world is quite inadequate (Table 1). It is essential that much more nitrogen, phosphate, and potash should be available, not only to increase present crop yields but to serve the far higher yields that inventions of the future will allow. These inventions can be classified into better crop plants, yield promoters, herbicides, pesticides and anti-infectives.

The first question about plants is whether millennia of empiricism have selected the best species. A diligent search for new crop species might be worth while. However, everyone knows that the new hybrids of the green revolution have much increased yields of wheat and rice. Hybridization has also improved protein content and amino acid balance. This work is of the utmost value and further big advances will be made.

Another target is yield promotion. Some years ago (Curtis & Cross 1954), we isolated a promoter from the fungus *Gibberella fujikuri*, which infects rice plants, and makes them tall and straggly. This was caused by the ubiquitous plant hormone gibberellic acid which increases internode length. Its obvious use would be to increase grass yield, but in spite of manufacture by large-scale fermentation, its use on grass has never proved economic. Its main practical success has been on fruit crops.

Table 1

Consumption of fertilizers (NPK, nutrient content)

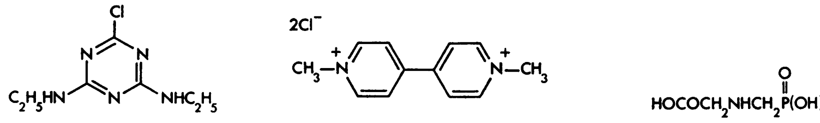
	Consumption/hectare of arable land (kg) 1949–51	1966–68
Developed countries	22.3	68.5
Developing countries ●	1.4	10.2
World ●	12.4	39.7

● Excluding mainland China

We are working intensively, as are many other companies, on other chemicals that increase crop yields. Theoretically any part or physiological process of a plant could be specifically stimulated, so that root, stem or fruit crops might need different products. I have no doubt that many will be found and will have a significant effect on world food production.

Another research has already proved its worth: that on selective herbicides. The first major breakthrough came in 1945 when my colleagues Slade, Sexton & Templeman developed the first selective herbicide, methoxychlorophenoxyacetic acid. Such compounds are analogues of a plant hormone, and as such are growth promoters, but have a well-known ability to exhaust and kill dicotyledonous weeds in monocots such as lawns or cereal crops. Ever since, search for selective weed killers has gone on energetically throughout the world and many have been discovered. We are currently interested in selective herbicides for use on cereal or grass weeds in cereal crops. A wide variety of valuable selective herbicides will be developed.

Total herbicides are also useful. The known types include triazines developed by Geigy (Gast *et al.* 1956), bipyridyls developed by ICI (reviewed by Bradbury *et al.* 1972), and the new compound glyphosate developed by Monsanto (Baird *et al.*



Simazine Paraquat dichloride Glyphosate

Fig 3 *Simazine. Paraquat dichloride. Glyphosate*

1971) (Fig 3). The triazines are sparingly soluble, and most of us use them to keep garden paths free of weeds for a year or so. But they also sterilize the top few millimetres of soil below woody perennials, so reducing weeds and increasing yield. Bipyridyl herbicides such as paraquat kill green tissues by an action on photosynthesis. Treated ground can immediately be sown without ploughing, since paraquat is inactivated by adsorption on clay, which all useful soils contain. Subsequently it is destroyed by soil microflora. There are three advantages of this no-plough cultivation: saving of labour, saving of tractor fuel, and reduced soil erosion. Although paraquat was first marketed about twenty years ago, use is still increasing at over 20% annually, and requires large tonnages of synthetic pyridine, since available coal-tar pyridine is insufficient: an example of the replacement by chemists of an inadequate fossil resource. The Monsanto total herbicide glyphosate is a derivative of glycine, and probably acts by inhibiting protein synthesis in any part of the plant. Hence it kills underground organs as well as green tissue, and may have special value because of this. Research continues strongly in this field, and valuable inventions are certain. They will increase general agricultural productivity.

Compounds acting on insects and other pests of food crops are too well known for me to spend much time on them. The persistence of DDT, discovered by Geigy, and BHC, discovered by ICI, even though they have not been shown to harm man, has evoked distrust, and the trend is towards more specific and less persistent insecticides. Most so far discovered are cholinesterase inhibitors, but toxicity to mammals, or useful insects, can be low. One of our most recent discoveries, pirimicarb (Barangovits & Ghosh 1969) (Fig 4), is very effective on aphids but

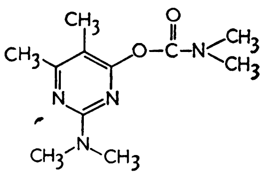
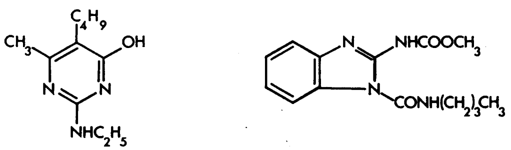


Fig 4 *Pirimicarb*

relatively harmless to ladybirds, bees and similar useful insects. Many laboratories are seeking better insecticides, nematocides and acaricides, and will find them.

We are all looking for new anti-infectives, particularly fungicides. Those exciting most attention act systemically, spreading throughout the plant from the point of application. Du Pont's compound benomyl (Delp & Klopping 1968) (Fig 5) is a broad-spectrum systemic fungicide. The ICI systemic pyrimidine ethirimol (Fig 5) (Bebbington *et al.* 1969) is specific against cereal mildew, a disease that costs British farmers about £30 million a year. Most fungal diseases of food crops will undoubtedly be defeated by the invention of new fungicides, and nearly all the successful compounds will be systemic.



Ethirimol Benomyl

Fig 5 *Ethirimol. Benomyl*

There are many diseases of food crops for which no adequate treatment yet exists, for example viral infections. My colleagues have established virucidal tests, but knowledge of the structure and action of plant and animal viruses is discouraging to a chemist who wants to design a successful structure and to a biologist who hopes to detect activity. I do not think I can predict rapid advance in this field.

Most of the science described so far may seem superficially to be a mixture of organic chemistry with a biological specialty, but to make an invention work, much excellent supportive invention is required. One thinks immediately of chemical engineering and other process invention, but a wide variety of other sciences is essential. For example, to get many plant protection products into intimate contact with the leaf of a plant much sophisticated physical chemistry is needed.

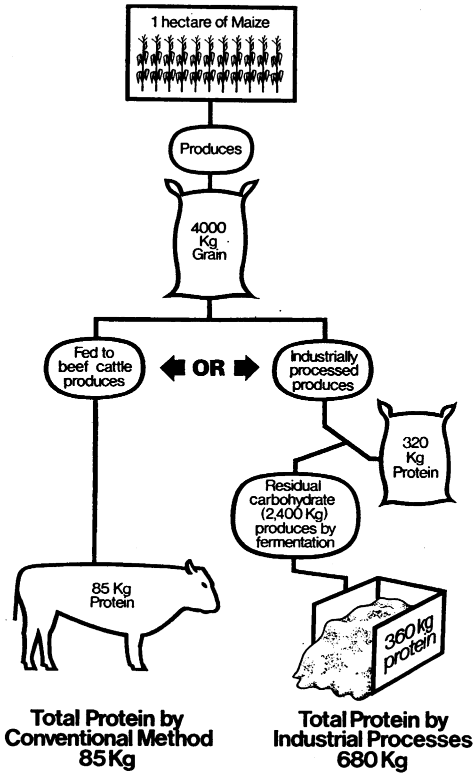


Fig 6 *Comparison of protein production by conventional/unconventional methods. (Reproduced from 'New Protein', ICI, 1973, by kind permission)*

If all the approaches to improved crop yield that I have described are developed, proved to be safe – a huge problem – and used in a concerted way with irrigational and other nonchemical aids, one could hope to increase primitive agricultural yields 10–15 times. There are several examples already of 5–10 times improvement. Thus, if we can make sufficient inventions in time, and apply them, we could exceed the Club of Rome's postulated sevenfold increase. Even this, with some other achievements, could theoretically lead to collapse around 2075 (Meadows *et al.* 1972). A reasonable assumption is that we shall need to do still more. What of factory food? Synthesis of carbohydrate is imaginable and synthesis of fat is possible, but the relative economics of agriculture and industry have hitherto encouraged the use of fat or carbohydrate as chemical intermediates. This situation could reverse and make synthesis of fat from petroleum economic. Industrial protein will be needed and made many years earlier. The need was clearly displayed in 'The Limits to Growth' (Meadows *et al.* 1972). The major causes of protein deficiency are the low concentration of protein in food grains, and the deficiency of various cereal proteins in lysine, methionine or tryptophane. The affluent supplement their cereal protein by meat, but this is an inefficient solution. The yield of protein from cereal fed to bullocks or cows is extremely poor, and industrial processing of the same cereal could give a vastly higher yield (Fig 6). Many animals convert food more efficiently than cattle, and human meat consumption and prices over the past twenty years reflect this, by favouring pigs and poultry, even though cattle have the additional advantages of using grass and of producing dairy products. Also, simple nitrogen compounds can enhance bacterial synthesis of protein and its availability to a ruminant. Urea is most often fed, but is hydrolysed too rapidly by bacterial ureases, and the ammonia thus liberated can be toxic. An invention that would reduce the rate of release of ammonia from urea would therefore be valuable. We have worked on coated pellets of urea, but our colleagues in South Africa have had more success with biuret, essentially a dimer of urea; this is hydrolysed only very slowly to urea by a bacterial biuretase. Such inventions are valuable but a harsher world could barely afford widespread use of beef protein. Increasingly we must turn for our animal protein to industrially housed chickens and pigs. Chickens and pigs are fed cereal, and need protein supplements such as soya and fish meal, and sometimes amino acids. Here is an immediate market for industrial protein. There is an economic case because industrial fishing grounds are limited, though there is scope for increased growth and yield of soya.

Chemical synthesis of protein from individually manufactured amino acids is improbable and one turns to biological methods. Filamentous fungi, yeasts and bacteria have received most attention, and organic substrates have included alkanes, methanol, ethanol, sugars, starches and cellulose. Permutation among these alone gives eighteen possible projects, and not all of them have been adequately examined. They should be, since the best route is not yet defined. The earliest work was on yeast from molasses, or cellulose waste liquors. After that most of us think of the pioneering work of BP in France and Scotland (Shacklady 1972). They have skilfully grown aerobic yeasts on the alkanes of oil. The product 'Toprina' is nutritious and apparently harmless, and is already test marketed. A one-hundred-thousand ton plant is being constructed in Sardinia. We began some years after BP at a time when North Sea methane seemed an attractive substrate. The other advantage of natural gas was the large amount, perhaps 100 million tons a year, wasted by flaring in remote oil fields.

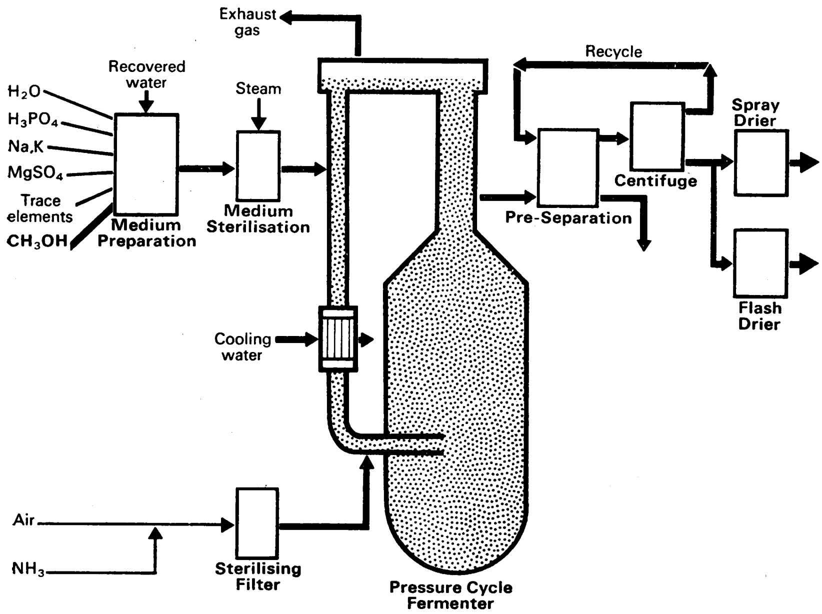


Fig 7 *The ICI plant for producing microbial protein*

Eventually we thought this work unpromising for three reasons: the poor productivity of the few organisms that would grow on methane, the explosion hazard from methane in air, and the severe mass transfer problem. We therefore turned to methanol, having a world lead in its manufacture from methane. This research proved more tractable (MacLennan *et al.* 1973) and we now have bacteria capable of converting over half the carbon of methanol into their structure. The project was helped by a fermenter invention. High pressure at the base of a very tall fermenter favours oxygen absorption. Lower pressure at the top of the tower favours CO_2 elimination. The pressure of the delivered air drives liquid up the tower, and round a loop back to the base (Fig 7). A fermenter some 30 metres high, producing a thousand tons dry weight of bacteria a year, has worked satisfactorily for nearly two years, and we have designed a single stream fermenter that should produce a hundred thousand tons of bacteria a year. Protein, lysine and methionine contents of the product compare very favourably with those of conventional sources (Slater 1974), and nutritional results in calves, pigs and poultry confirm this. Toxicological results are also encouraging. The economics depend on the relationship between the price of a natural protein, such as soya, and that of the carbon feedstock. However, these have usually kept broadly in step, and probably will continue to. Another problem is the capital cost and this is inflating severely at the present time. Nevertheless, I think that some process of this kind will succeed, because it will make within one hectare as much protein as 15 000 hectares of soya, or a beef farm of 100 000 hectares.

It is convenient now to consider the effect of present and future inventions on our catastrophe equation. My opinion is that we in ICI alone have the capability to make inventions that could turn this equation from technically hopeless to technically hopeful, with the sole exception of plant breeding, in which we are not expert. Many other companies throughout the world have an equal capability. Assuming that the social environment allows us to make the inventions, and facilitates their use, the world should be able to limit its numbers, and increase its food production to a point that prevents famine. The chief technical problem is the time necessary to bring the inventions to success, even after discovery: all the inventions we need are unlikely to be available by the end of the century, and it is essential that what we now have are vigorously used until then – particularly contraceptive methods.

Of course, we cannot live by food alone. We also need clothing and shelter. Both can be provided by existing technology, and future invention is required mainly to replace disappearing resources, and to increase productivity and maintain living standards as planned populations age, and fewer work. Textiles, either for clothing, or houses, illustrate this and also the resource problem. For most of recorded history, man wore the same materials of cotton, wool, linen or skin, fabricated by the same methods, weaving and stitching, seen in preclassical tombs. In the last forty years major change has begun: three groups of totally synthetic fibres from petroleum sources, polyesters, polyamides and acrylics, have secured over half the total fibre market in advanced countries. The processes used to make them into fabric have not yet changed, except in speed. They are still labour intensive, and only the newest, large plants have seemed likely to survive in advanced countries with high wages. Now there is a chance that this situation may be reversed. We have spent several years on an invention to make fabric directly from chemicals: fibres are spun concentrically from two polymers to form a heterofilament, in which the core is higher melting and the sheath lower melting. The fibres can be sprayed directly from the spinning machine on to a moving belt that passes under a heated roller. The fibres then fuse together but retain their integrity because of the unsoftened core. A fabric is thus formed from the polymers in a single integrated almost unmanned process, and has exceptional strength for its weight (West 1971). It is now being used for upholstery and carpets, and apparel uses are being developed. Because of the fusion of fibres the cut fabric does not fray, and no hem is necessary. It might be cut by a computer-controlled laser beam, and the pieces then fabricated into garments automatically by heat welding. A future garment factory might be automated all the way from simple chemicals to finished garments.

Inventions of this sort would allow us to support the increasing proportion of elderly in a planned population by the work of fewer young.

Synthetic fibres used in these new fabrics, or most conventional fabrics, are petroleum derived and their continued use will depend on the availability of oil or an alternative, as will plastics used for floor coverings or table tops, and contraceptives, herbicides, plant growth promoters, dyes and detergents – all the huge variety of organic chemicals that make our lives longer and pleasanter. Even the ammonia that is an important intermediate for many of them has to be made from hydrogen, most easily obtained from methane or oil. It is the ample hydrogen in oil, not just its price, that makes it uniquely valuable to the chemical industry and justifies priority of chemical use over energy as resources decline. Therefore, vigorous studies of new energy sources now beginning in oil companies and elsewhere are very welcome. The most important early supplementary source will be improved fission technology, but shale oils or tar sands might help. Their neglect hitherto is because they only become competitive when oil reaches about $10 a barrel: oil should therefore be temporarily buffered to about this price as they come into use. The snag is perhaps the use of much of the available energy in winning the remainder. Coal will also act as a buffer where it is plentiful and near the surface, or capable of automated mining. When the total of all these energy sources becomes inadequate, and that may never occur if fusion power becomes feasible within a century, solar and geothermal energy seem the likeliest alternatives.

We must also save what energy we can by better insulation, and by avoiding waste in the chemical industry and elsewhere. Petrochemical processes distil and crack oil fractions to give hydrogen, ethylene, propylene, benzene, xylene and so on, which serve as building blocks for secondary chemical processes. The scale of all such plants is now huge: half a million tons a year is common. Engineering research and design naturally seek to use valuable surplus heat in all such plants, but high thermal efficiency is not achieved because some heat eventually appears at too low a temperature to be economically recoverable. The height of a plant's cooling tower is proportional to its waste of this low grade heat. It could be used for district heating or growing melons, but novel means of recovery might now be justified by high energy prices. Research is going on, with possible applications outside large-scale plants, and may lead to valuable inventions.

We believe that oil will be available as a chemical feedstock in most countries for at least half a century, probably more. After it is exhausted our second choice will be coal, as it often is already in places like South Africa, which have plentiful cheap coal and no oil. We already have most of the necessary technology: coal can be distilled to yield aromatics; it can be reacted with water to yield hydrogen, carbon monoxide, and various hydrocarbons; it can be reacted with lime to yield carbide and then acetylene, which is a versatile though expensive building block. These technologies, which research will improve, should ensure the availability of synthetic fibres and plastics for some centuries, but much more expensively than from oil. What then? There could be some return to cotton and wool for clothing, and to wood from plastics, but if civilization continues man will retain his diverse comforts by further industrial invention. The two obvious directions of that invention will be use of CO_2 and water as carbon and hydrogen sources, and replacement of organic materials and scarce metals by readily available inorganics.

Ample energy would produce ample hydrogen by electrolysis, and thence ammonia for fertilizers and chemical feedstock. New processes will produce hydrocarbons from hydrogen and the CO_2 of limestone. If these inventions are not made early enough, cellulose, wood, and other plant products should return to favour for clothing and for shelter, but in sophisticated ways. Cellulose, sugars, plant gums, resins and oils, and particularly ethanol, would be used as chemical intermediates rather than directly. We made the world's first batches of polythene from fermentation ethanol, and still use this route in India. Plants will be hybridized and selected for all these purposes. Microbiological, including algal, processes will proliferate, and could be facilitated by genetic technologies. Slow growing northern trees could be replaced by herbaceous tropical cellulose producers, but this will depend on the success of birth control, and the availability of tropical land for nonfood uses.

In any event there will be great increase in the diversity of inorganic materials. Even now we use an average of several hundred kilograms of cement and bricks a year each, against 30 or so of organic polymers. We also use several hundred kilograms of wood, but wood will be scarce and expensive before plastics. I therefore expect early replacement of wood by proliferation of sophisticated composites of inorganic and organic components. Such composites could replace not only wood but also copper or other scarce metals as extrudable or mouldable recipes are developed. We might get back to something looking like the durable water pipes at Knossos or Ephesus.

We are working on such inorganic composites and on inorganic fibres. We have made some progress and are test-marketing Saffil, which is a fibre of alumina or zirconia. One research objective was avoidance of asbestosis, and toxicity tests so far done are promising. The suitability of such fibres, or of glass fibres, for clothing is doubtful, but they could be turned into unburnable and virtually unmeltable household or industrial cloths.

To summarize, the chemical industry undoubtedly has the science and ingenuity to make the inventions that could protect us from a harsher world, and continue to increase our comfort and prosperity. ICI alone is working on almost every current project I have mentioned and is studying many of the others.

The next question is whether the factors wil hinder or encourage chemical invention, and in particular environmental, economic and political constraints.

Pollution of air and water is not too difficult a problem. A determined attack on aerial pollution at one of our major chemical sites on Teesside has reduced emissions of particulate matter and sulphur dioxide by over 95% (Department of the Environment 1973). Almost as good results are being achieved for already slight ammonia leakage. Eventually, replacement of fossil fuels by nuclear, solar or geothermal power will produce similar achievements everywhere. Less use of coal in Britain has already had predictably good effects in city centres and on bronchitis. Pollution of rivers is still grossly excessive, but technical solutions are available, though very expensive because each 10% of pollutant removed costs far more than the previous 10%. Inorganic pollutants, and particularly heavy metals, can usually be removed by precipitation, and organic effluents by microbiological destruction. We have a number of research projects on microbiological destruction of organic pollutants, and have inventions under development. They will be useful for domestic sewage as well as industrial effluent. In total, I do not regard pollution of the environment as more than a severe economic problem, and it should not retard chemical invention.

The related problem of toxicity is more dangerous. Thalidomide was a great shock to all of us, and so are findings that long-used chemicals are carcinogenic. Very recently the chemical industry has discovered that vinyl chloride monomer used for forty years in Germany and America and thirty in Britain as an intermediate in the manufacture of PVC can cause hepatic angiosarcomata in animals and man. There must be other carcinogens, both natural and industrial, lurking unsuspected around us. Indeed I know scientists who think that most cancer is environmental. It will take many long years to prove whether this is true, and to discover all the existing environmental carcinogens, but the developer of a new compound to which the public may be exposed, whether it be a drug, herbicide, pesticide, or new industrial chemical, has an increasing duty to carry out elaborate toxicity tests. These take a vast amount of time and a great deal of money, and an intractable dilemma results. Many useful inventions could not possibly earn the money to pay for the toxicity tests that ought to be done before their introduction. This serious restraint on invention can be most clearly quantified for drugs. Twenty years ago, the world's drug industries spent about £60 million a year on drug

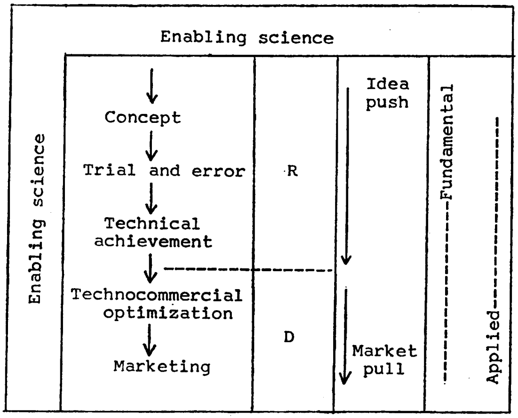


Fig 8 *The flow of invention*

research, and marketed about forty distinctive drugs a year. I am not counting mixtures or novel formulations – just new chemicals. Since then there has been a large increase in difficulty and cost of innovation, partly because of good existing drugs, but more because of elaborate toxicity tests, long clinical investigations, and long and bureaucratic regulatory delays. The consequence is that last year the international drug industry increased its annual spending to about £600 million, and introduced only nineteen distinctive new drugs, an average of over £30 million a drug (Spinks 1973). Only very skilful and large multinational companies can hope to recover expenditure of this size, and many companies may founder, diversify or reduce research severely. Obviously we cannot cut sensible toxicological or clinical evaluation, but something might be done about excessive official protocols and bureaucratic delays. One recent marketing application for a new drug in America consisted of a pile of 456 volumes 75 ft high and weighing more than a ton. This is ludicrous. No one wants to return to a dangerous free-for-all, but there is a happy regulatory medium – a willingness to use professional judgment of the balance between benefit and risk, on the basis of a reasonable volume of evidence from a modest number of capable investigators. These remarks about drugs apply with almost equal force to products for use on food crops, and to plastic additives and other products that touch our daily lives. We shall not get all the inventions we need unless common sense becomes commoner.

The rapidly increasing cost of proving safety is part of a more general phenomenon that I define as the Concorde syndrome: the likelihood that high costs of development will make useful products unavailable because the profit motive that has produced most of the world's innovations fails, or because a mixture of taxpayers, politicians, press and television concludes that the project does not deserve public aid.

At the moment it seems very doubtful whether any of us will ever ride in a hovertrain, be pulled by a linear motor, go on a public service to the moon, see humans landing on Mars in the same way that we watched Armstrong land on the moon. Perhaps these losses do not matter very much, but it will be literally catastrophic if the inventions outlined in this lecture are not made. Therefore we must finally consider whether they will be. We must hope for continued adequacy of the profit motive, since noncapitalist organizations have produced few significant inventions in any of the critical areas that I have discussed. The reason may lie in the complexity of the interrelated factors favouring effective invention. Fig 8 gives my view of the innovative process: it

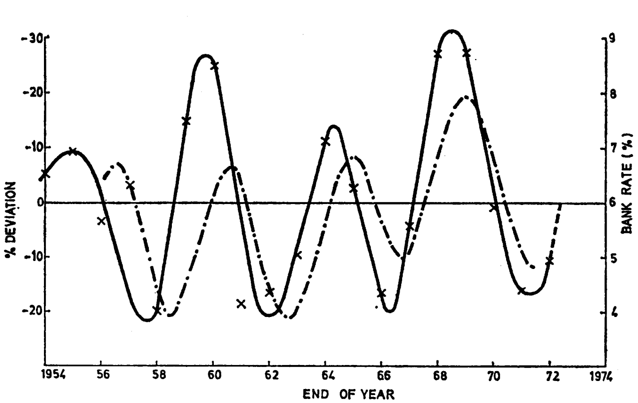


Fig 9 *Trading profit of ICI, from Annual Reports, expressed as a deviation from the smoothed growth curve (——) and British bank rate (— · —). (Reproduced from Spinks 1973, by kind permission)*

emphasizes idea-push and market-pull working together, and initiated and backed by effective enabling science, fundamental and applied. I know of no socialist organization that mobilizes these forces, notably market-pull, efficiently.

Fortunately most of the inventions a harsher world needs (rather than wants) can be based on science of fairly modest size and cost, unlike aerospace or nuclear power. I believe that continuation of free enterprise could produce them. But, if the public are taught to expect cheap drugs, and politicians force extreme price reductions, then the private drug industry will soon stop research: the taxpayer will then be compelled to support it, and it could only be cheapened by combining several research organizations, so eliminating the powerful innovative selection that comes from competitive diversity.

There is yet another danger. The world economy is now inflating at a rate that brings back memories of the events that led to the 1939 war. Nearly all ills of this kind seem to me to derive from one serious social flaw – inadequate homeostasis. To paraphrase Claude Bernard: homeostasis of the *milieu politique* is a condition of free enterprise. The wretched quality of our economic homeostasis, even in good years, is illustrated by curves that I published a year or so ago (Fig 9) (Spinks 1973). ICI's profit is seen to oscillate wildly, slightly out of phase with bank rate. The bearable instability of those years was achieved by deliberate negative feedback loops deriving in considerable part from Lord Keynes. But how inferior they are to those that keep our blood potassium so constant. Nothing in the economic or political world seems capable of being finely tuned or, once tuned, of being left undisturbed by politicians intent on excessive hurry or on confrontation. One party has no sooner set the country on a reasonably consistent set of paths than another replaces it and immediately does the opposite. Worse, it claims credit for what has taken two years to work through from all opposite actions. Lying over this is a deteriorating social environment in which the Victorian virtues have fallen into sad disrepute. In these circumstances, the confidence in the economic and social environment that long-term research and worth-while innovation require is seriously weakened.

So, my final judgment must be a balance between technical confidence and social, economic and political pessimism. It is an exceedingly fallible judgment, but on balance optimistic. I think the human race will muddle through.

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