expansion may be regarded as an extremely slow continental drifting, this process is quite distinct from the Atlantic and Gondwanaland continental drift in the Mesozoic. This latter may be simply explained by the reversal of flow of convection currents beneath the Interior lobe fold-belts of the Early Grenville régime.

In this work the convection current systems postulated by Runcorn[8], and the geotectonic groupings proposed by Sutton[35], are brought together, modified and considerably elaborated in a synthesis of Earth evolution based on geotectonic evidence from earliest Precambrian times onwards. Continental drift and Earth expansion are necessary corollaries of this synthesis. In order to account for the known fold-belt trends, convection currents of fairly well defined, but changing, systems must have been active throughout the Earth's history.

The model therefore is that of an expanding Earth, having a 'cold' accretionary origin, in which a gradual growth of the core promotes changes in the convection current systems in the mantle. This Earth model[3] constitutes a working hypothesis in which the major features of the Earth's crust and the activity of the mantle are related in a systematic way: the alternative is that the relationships described are a series of most unexpected and remarkable coincidences.

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WHENCE AND WHITHER CHEMOTHERAPY?

Substance of a Friday Evening Discourse delivered at the Royal Institution on March 12

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As an introduction, I should like to touch on something which is not a unique feature of the subject of discourse. However, this is as good an excuse as any to look at the disturbing fact that communications between scientist and scientist are in a state of overgrowth or 'overpublication', while in contrast to this the writings, especially of the scientific and medical fraternity, addressed to the non-expert are, so some believe, somewhat neglected or 'underpublished'. Of course, one does not condemn the vastly increased potentialities (5–10 times that of 1945) for scientific printing space, but the sometimes indiscriminate multiplication of the printed words, formulae and illustrations leads to overburdening of libraries, to a nightmarish frustration of the research worker who never catches up with his reading, and willy-nilly to an encouragement of unfinished and mediocre material to be published.

On the other hand, the communication line from the world of science and medicine to the man and woman in the street (and everyone belongs to this species outside his own training and doings) is too thin or sometimes of the wrong kind. True, one has semi-popular magazines such as the *New Scientist* and others published in Britain and the *Scientific American* published in the United States and possibly a number of continental publications. True, one has paper-back editions on certain topics and—leaving aside the splendid efforts of the Royal Institution, the Royal Society of Arts and others—good programmes on television and radio which convey the gist of efforts and progress of researches. The newspapers give some space to their science or medical correspondents, but who can blame them if sometimes the news value overrides other considerations? No complete answer, if any, is available to this dilemma of information, which is a three-fold one and comprises donor, vehicle and recipient. Maybe if scientists and medical people as donors, instead of editing or writing another review, could spare some of their time to write about their tasks, hopes, failures and successes in comprehensible terms, particularly if newspapers and magazines as vehicles would give much more space to original reports, attractively arranged and illustrated, say, in their colour magazines or as an additional double-page extra, everyone as a member of the recipient public could deservedly enjoy, in addition to political, industrial, business, sports and art sections, some continuous reading material on various aspects of medical, scientific and technological progress.

Such enlightened information is highly desirable in matters of treatment, palliation and cure of diseases. Of all the treatments medical art and science has devised over long periods of time and to a very large extent more recently, to name a few: surgery, physiotherapy, radiotherapy and chemotherapy, the last one (together with the related pharmacotherapy) has carried with it the greatest mystery outside the initiated, possibly because of the proximity of poisons. Recent events illustrate the extreme and uncertain stand which the public and those in charge of mass communication media take when tragedy strikes like the thalidomide effects on some unborn babies or quackery is perpetrated on desperate parents with leukaemic children. The average citizen should be taken into the confidence of the experienced, and be aware of advances, changes of opinion, and prolonged struggles in the field of treatment. As a patient he should not stand in awe of the preparations of a sophisticated pharmaceutical industry but know of their history, potentials and limitations.

Chemical remedies can be arranged into three main divisions (Table 1), two of which are the subject of this article. These are chemotherapeutics and restitutional

Table 1. PHARMACEUTICAL AGENTS OR DRUGS

Chemotherapeutic	Restitutional	Symptomatic
Anthelmintics	Metabolic products such as proteins, amino-acids, nucleosides,	Central nervous system depressing and stimulating
Anti-protozoal	Vitamins, minerals	'Psychotropic'
Anti-bacterial (antibiotics)	Holo- and co-enzymes	Acting on automatic effectors
Anti-tumour	Enzymomimetics	Acting on organs: heart, blood vessels, bladder, kidney, digestive system, etc.
Anti-leukaemic	Nucleic acids	
Antiviral (interferons)	Hormones	
	Immunological products	

agents; the former used in the treatment of diseases brought about by invaders such as worms (helminths), protozoal organisms, bacteria, viruses and (as internal invaders) neoplastic and leukaemic cells; the latter applied in deficiency diseases and disturbances of somatic homoeostasis but lately also, in the main experimentally, in cancer and related morbid states. The third group will not be discussed here.

Skipping the anthelmintics and going over to the anti-protozoal drugs, one ought to remember that a great number of the chemotherapeutic agents came originally from plant or animal products.

They carried a great amount of ballast from which they were freed by the chemists of the nineteenth century. After isolation and elucidation of the structure of the active principles, the synthesis of these substances was carried out. Simpler molecules, representing parts of the total structure, were also made. A brief history of anti-malarials should serve as a representative example. It started with the South American cinchona bark and a Chinese root ch'ang shan. Both materials contain active alkaloids, quinine and febrifugine, with nitrogen heterocyclic moieties. Quinine, which was totally synthesized not before 1944, by Woodward and Doering, and febrifugine, even later, in 1952 by Baker *et al.*, were the forerunners of simpler analogues carrying similar nitrogen ring systems. The first useful synthetic drugs of pre-war days, 'Plasmochin' (pamaquine) and 'Atabrine' or mepacrine, carry one moiety of the quinine molecule, namely, the methoxy-quinoline ring. During testing, mainly in birds, a problem arose which has occurred in nearly all chemotherapeutic work (of course, also in many other fields of medical research), namely, 'species specificity' *vis-à-vis* drugs. This amounts approximately to this question: Are the results obtained in one kind of animal with one kind of invading organism relevant to the possible effects in another animal species or in man? Extrapolation of general properties of effective drugs for the patient is not only permissible but also necessary, although, as one knows, specific properties can only be assessed in man.

These and other questions prompted intensive search, particularly during the Second World War, for anti-malarials, with different activity spectra. Rose *et al.* produced 'Paludrine' or proguanil, a novel type of molecule, with a special prophylactic kind of activity. In the host it is transformed into an active metabolite which shows some similarity with the pyrimidine derivative 'Daraprim' made in the United States by Hitchings *et al.*

With all these drugs and several related ones experts thought malaria could be wiped out altogether. This scourge has befallen 300 million people every year with 3 million deaths. However, pamaquine and related quinoline derivatives are the only compounds achieving radical cures in certain forms of malaria. Unfortunately, these drugs have been found to be extremely toxic to some individuals, causing destruction of their red blood corpuscles, due to an inherited or inheritable biochemical lesion of the sugar and sulphur metabolism of the individual involved. This emphasizes the triangular relationship between hosts, parasites and drugs. Thus the words spoken in 1954 by one of the combatants against the battle of malaria: "With these synthetic remedies one can nowadays consider the problem of the chemotherapy of malaria as being solved", have proved to be only partly true. This is the more so, as the use of pesticides against the carriers of infection has also created its own difficulties.

Looking at another group of chemotherapeutic agents —those effective against bacterial infections—one notes that originally there were no potent natural products except those of an immunological type, acting prophylactically. This situation altered dramatically at the beginning of the 1930s, when Domagk *et al.*, marching along the lines laid down by Ehrlich, successfully tested the red azo-dye, later called 'Prontosil', and when Trefouël and the Bovets recognized the sulphanilamide moiety as the bacteriostatic principle. About the same time the first active concentrates of the first antibiotic, penicillin, were prepared.

Much has been said and published about the family of 'sulphonamides or sulphadrugs'; the most important concept (intellectual more than practical) which they helped to create is 'antagonism to essential metabolites'. This was put forward by Woods and Fildes in 1940 and means that certain chemicals, called antimetabolites and often very similar to the essential agonist, are capable of interfering with cellular compounds which are vital for the well-being of the cell or the organism. In the case of most of the sulphadrugs their anti-bacterial effects can be neutralized by *p*-aminobenzoic acid (PABA) which is therefore their agonist.

The era of antibiotics, active materials from moulds and micro-organisms, also began in the 1930s and reached its peak during and after the Second World War, with the isolation of penicillin, cephalosporins, streptomycin, chloramphenicol, tetracyclines and many others. Apart from a very sustained search over many years for new antibiotics with novel effects, intensive investigations have been made of their mechanism of action or, trivially expressed, of 'how they work'. This led to the recognition of the importance of the bacterial cell wall as a target of penicillin action. The key to the puzzle, according to Pollock, Richmond and others, is a mucoprotein moiety *N*-acetylmuramic acid, the three-dimensional structure of which shows convincing similarity to penicillin, in difference from *N*-acetyl neuraminic or sialic acid derivatives which form an essential part of the mammalian cell membrane. If one allows for the fact that cephalosporins (see 'Ceporin' of recent news fame) may function in the same or a similar manner, namely, by interfering with the building up of the cell wall, where acetylmuramic acid is normally used, then the principle of metabolic antagonists which arose from the examination of sulphonamides may play a part in the mode of action of materials discovered more or less by accident.

With nearly all groups of chemotherapeutic drugs, and certainly with those effective against bacterial diseases, a phenomenon has worried everybody concerned: inherent or natural and acquired resistance. The former is carried by the invading cell, whether it is of exogenous or endogenous origin, from its 'beginning'; the other kind develops over a period during its existence in the host and exposure to drugs. The causes, direct or indirect, for such therapeutic collapse are manifold (Table 2).

All this represents a serious challenge to the clinician and, via the experimental chemotherapist, down the line

Table 2

Possible modes of drug resistance

Acquired / Inherent	Counteractions
(i) Induction or increase of activity levels of drug-destroying enzymes	Enzyme resistant variants of drugs
(ii) Adaptation of invader's metabolism ≈ mutations; selection	Combination therapy
(iia) Loss of enzymes in host and/or invader for activation of drugs to effective forms	Combination therapy
(iii) Development of repair mechanism of drug—damaged parts of invader	?
(iv) Change in permeability and interactions with irrelevant constituents of invader or host	Application of 'inert compounds' neutralizing-drug-wasting interactions

to the medicinal chemist. Considerable progress in counteractions to resistance has been achieved in the fields of penicillins (and more recently cephalosporins), when the core of the molecule 6-aminopenicillanic acid was made available by the elegant work of Batchelor, Doyle *et al.*, so that a 'theme and variations' could be played. Some of these variations have greater resistance to the destructive enzyme penicillinase and show different degrees of anti-bacterial activities.

A different approach to overcome dangers of bacterial resistance was made with remedies against acid-fast bacilli causing tuberculosis. There the early application of a combination of drugs PAS (see PABA), isoniazid (see vitamin nicotinamide) and streptomycin (antibiotic) has helped in the eradication of tuberculosis (recently, similar principles have been applied in the field of leukaemias).

A number of antibiotics have been encountered which are also capable of destroying what was called 'internal intruders', namely, cancerous or neoplastic cells in their manifold forms, or leukaemic ones. One of them, actinomycin *D*, isolated by Waksman *et al.*, who also discovered streptomycin, illustrates usefully the present state of cancer chemotherapy: like other remedies such as alkylating agents or antimetabolites which were mentioned before as analogues of essential metabolites, its selectivity of action, or its specificity as a carcinolytic agent, is relatively low when compared with the activities of modern drugs against infectious diseases. The reason is that it is easier to achieve selective toxicity against exogenous invaders than against cells which in some way have arisen from the host's own tissues. But, like parasites, some cancers and leukaemias are inherently resistant, say, against actinomycin, alkylating agents or antimetabolites, or acquire such resistance during treatment. This shows that cancer is not one disease but represents a considerable number of diseases which, apart from different sites in different parts of the body and other biological or biochemical differences, may behave differently *vis-à-vis* all forms of therapy. The mechanism of action of actinomycin, like that of other remedies, especially alkylating agents, rests with its interfering in nucleic acid functions vital to the cell.

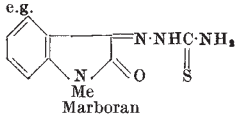
Into what new directions is carcino-chemotherapy now moving? The subject can be roughly divided into the research tendencies as given on Table 3. Some are at present fundamental and exploratory, such as the investigation of inherent and acquired resistance and the possibilities of overcoming it. Others depend on the discovery and development of new experimental systems such as those for probing chemotherapeutic agents active against secondaries or, so-called, metastatic growth. The successful search for greater selectivity of action depends on favourable metabolic changes of the drug, when entering the tumour tissue or maybe on the size of the molecule, which could be large. Homoeostatic regulators could be restitutional remedies which instead of destroying the delinquent cells and tissues may re-establish to some extent their orderly behaviour or eliminate the existing disturbances. This, together with biological forms of treatment (Table 3 (v)), rests on a number of indications that in some cancers, at least, certain items of the inventory of the aberrant cells or tissues are 'missing' and others are *de trop*. Search for the right constituents is going on continuously, in addition to that for the manner by which

Table 3

Recent directions in carcino-chemotherapy

(i) Study and conquest of all forms of resistance	(ii) Attack on metastases	(iii) Selectivity of action	(iv) Search for homoeostatic regulators	(v) Biological methods: immunology, virology, etc.
		Biochemical differences	Large molecules (cell penetration)	

Table 4. Anti-viral Agents

Chemicals	Interferons	Vaccines, etc.
5-Iododeoxy-uridine Benzimidazoles Thiosemicarbazones e.g.  Marboran	Proteins produced by virus-infected host	Attenuated or killed viruses; serum with preformed antibody

Triazines. Steroids. Macromolecules

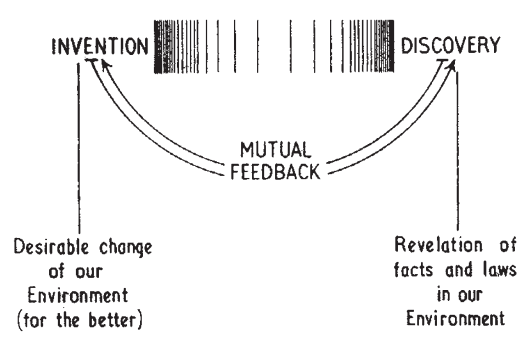
these materials could be brought back into the cell from outside.

Increasing the size of items which are not present in a well-brought-up cell under ordinary conditions, one arrives at abnormal cellular particles and finally at special viruses. The virus- and bacteria-like mycoplasmas or PPLOs are here included; they have been in and out of fashion for the past 30 years, but at the moment with respect to leukaemias and rheumatism they appear to be in. In some instances viruses destroy the cells and hosts which they inhabit, in others as demonstrated unambiguously so far only in animals (mainly birds and rodents), they apparently transform normal cells into malignant ones. There is no clear evidence, as yet, that viruses are the cause of human malignant diseases, although certain tissue changes, such as non-malignant warts, are virus-produced. Whether or not viruses are or will be found to have connexions with human tumours, their destruction or the prevention of the diseases they cause can be achieved by various means: the chemotherapeutic one is the youngest and so far the weakest (Table 4). Other biological approaches led to the interferons, discovered by Isaacs; they are a class of proteins usually produced by cells that have been acted on by virus or viral components. So far as human medicine goes they are still experimental. Vaccines (attenuated or killed viruses) have been in use for a long time against smallpox (Jenner), while more recent ones were developed against poliomyelitis (Enders–Salk–Sabin) and measles (Enders).

Another group of constituents which apart from viruses (or mycoplasmas) may appear in tumour cells, over and above their normal collection of chemical constituents and cellular particles, are 'tumour specific antigens' which are not detectable in every type of tumour and which are usually weak in eliciting the formation of their immunological counterparts, the antibodies. Nevertheless, the observation by Haddow, Delorme, Alexander and others that injections of lymphocytes from animals carrying tumour implants favourably affected the primary tumours induced by carcinogens means that a kind of potential immunotherapy of certain experimental tumours has arrived.

To a considerable extent old stuff has been dug over in the hope that it may have yielded some nuggets left behind. The main points were these: the problem of communications (printed and otherwise) between scientist and scientist and research workers and laymen; secondly, out of the subject-matter of this review arose the old question of the similarity or otherwise between the effects

Table 5



of drugs on animal and man and the danger of jumping to general conclusions from observations on a single species with respect to all the others including human organisms. This brought out the interdependence of host–invader–drug reactions generally and led further to the principle of metabolic antagonism and the problem of drug resistance. The latter one can consider to be one of the most pressing problems of chemotherapy. A relatively novel principle, that of control of homoeostasis, was touched on and the possible future role of biological methods, such as immunological and anti-viral ones, mentioned. There is one other matter which goes beyond chemotherapy and which one might jokingly call a 'metabolic by-product' of scientific and medical research: it concerns an often silent and sometimes loud controversy about the role and status of pure and applied research. Recently, Dr. P. Medawar discussed the two conceptions of science and, last year, Prof. Rattee, on the occasion of his inaugural lecture, contrasted 'discovery' as large or small revelations of what exists in our environment and the laws which condition it, with 'invention' which utilizes the results of discovery (often forgotten ones) to change the environment for the better (Table 5). What is wrong with one or the other? If scientists were rational people (which they are only to the same extent as other people) they would not deepen a 'class distinction' between so-called high and low science but solely recognize the existence of mutually beneficial feedback mechanisms. If one would freely allow these to take place, then the overall successes will be even more sustained than they are at the moment.

TURNING SCIENTISTS INTO FREE THINKERS

By A. J. KIRKMAN

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THE hall-mark of the thinking of many young scientists these days is inflexibility. They handle ideas dully and mechanically: they try to express all their thoughts in the rigid, ponderous, formal sentence structures and vocabulary in which they learn their specialist subjects.

Here, for example, are the opening paragraphs of two young scientists' efforts to formulate an opinion on the value of freedom of speech:

(Essay 1) "Man is an individual. Therefore each man thinks and decides independently for himself. Therefore freedom of belief, speech and expression is one of the basic 'laws' to which man has the right.

"What makes one man superior to another? All men are superior to all other men in some way. Therefore all men are basically equal. Thus man has the right to speak freely and express himself freely as he thinks fit. There is, however, a corollary to this statement. No man has the right to abuse the right to abuse his right or the right of others to free speech and expression. Thus drawing the arguement to its logical conclusion—no laws, whatsoever, should be passed limiting the freedom of speech and expression of any member of society. This arguement is not valid however since many men abuse the corollary and some even abuse the first fundamental fact. In such cases then laws are necessary (depending upon the circumstances) limiting the complete freedom of expression and speech in order to safeguard the basic individual."

[The students were given several quotations, to prompt their ideas and opinions. The two referred to in the next extract were:

"If all mankind minus one were of one opinion, and only one person were of the contrary opinion, mankind would be no more justified in silencing that one person, than he, if he had the power, would be justified in silencing mankind."—J. S. Mill.

"And though all the winds of doctrine were let loose to play upon the earth, so Truth be in the field, we do injuriously, by licensing and prohibiting, to misdoubt her strength. Let her and Falsehood grapple; who ever knew Truth put to the worse, in a free and open encounter?"—John Milton.]

(Essay 2) "The freedom of speech is a necessary part of our lives. Without it we cannot learn as much as we are able to do with it. By this I mean that there are two ways of looking at one thing. If we have no freedom of speech, then we can only appreciate one side of it, and that is the one which we understand. However if there is freedom of speech then we can argue and discuss the second way of looking at this point. By doing this we may learn both points of view and so our knowledge has increased and we have benifitted from it. As J. S. Mill says you may have a thousand people agreeing on one point and one man disagreeing. Then with the freedom of speech both groups can tell each other their ideas and so benifitt from it. However if that one man is not allowed to talk freely then the harm done is the same as surpressing the ideas of the one thousand men. This is so obviously bad and harmfull that nobody would dream of doing it. However it is exactly the same if the one man is silenced. It was said by John Milton that the Truth and Falsehood should be allowed grapple. In doing this the Truth should always win. All as John Milton was saying was that without freedom of speech the truth cannot be had all the time."

This is the thinking and self-expression of young men who presented themselves as potential university entrants. I do not know if they obtained university places. I do know that many students who have obtained university places show standards of thought and writing approaching this confusion and incoherence.

Weaknesses of thought and expression which students show at 18+ are accentuated during their university cram-courses in science and technology. These courses involve much rote-learning of pre-digested information, and much 'application' of set formulae or rigid procedures in solving standard problems. This may be useful for passing examinations; but, as one of the industrial witnesses before the Leverhulme Study Group on the Education of Graduate Scientists said: "I am not satisfied that technical subjects at the present time are taught in such a manner as will develop clear thinking and ability to express oneself".

Given few opportunities for practice, students soon lose what skill they once had at finding their own ways of giving order and clear expression to what they know. The result is that they emerge from ten years of secondary and higher education with much lower standards of articulacy and cogency in proportion to their knowledge and experience than they had at 11+.

I believe a university education should do more than cram students with factual knowledge: it should also equip them with processes of thought and a command of language which will fit them for the sophisticated social and professional contexts in which they will spend their lives.

There was a time, so I am told by scientists and technologists who graduated thirty or forty years ago, when students picked up sophisticated habits of thought and expression by imitation of their teachers during residence at university. Dons showed concern for thoughtful appraisal of ideas, and for articulate and unambiguous