signals, a 6 V car battery serves as power supply. The current is limited to 2A.

If the chamber is to be perfused, a reservoir (Figure 1) is needed to pre-warm the fluid before it enters the chamber. For our purposes we chose to have 2 reservoirs, thus permitting the injection of different solutions while recording bioelectrical activity.

The cells were grown on glass coverslips. For electrophysiological measurements, the coverslip bearing the culture was placed directly into the microchamber with the cells uppermost. The chamber is fixed to a rigid stage which fits between the objective and condenser of an inverted microscope.

Performance. The performance of the chamber was tested with a small thermocouple which was placed at different locations in the chamber. Relative temperature measurements could be performed with an accuracy of $\pm$ 0.1 °C. It was found that an alteration of $\pm$4 °C can be realized in about 1.5 min with the chamber being perfused at a rate of 60 ml/h. The temporal fluctuations in temperature were within $\pm$0.15 °C at any point in the chamber.

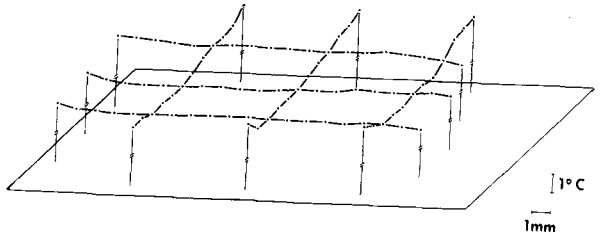

Fig. 2. Graph showing the temperature of the bathing fluid at different locations of the microchamber. The temperature measurements could not be extended all the way to the right side because of the location of the thermistor and the reference electrode.

As important as the temporal stability is the uniformity of the temperature distribution over a large area. In a schematic 3-dimensional graph, the temperature is plotted versus the dimensions of the chamber (Figure 2). The average temperature (66 data points, area = 10×18 mm) was 36 $\pm$ 0.29 °C. It is apparent that the temperature was higher in the areas adjacent to the walls. The slightly increased temperature at the rear of the chamber resulted from reduced heat loss caused by a perspex bar which holds the thermistor and the reference electrode.

The present paper demonstrates that the construction of a small temperature-controlled perfusion chamber without any hot spots or heat sinks is feasible with proper choice of materials. The chamber is easily adaptable to special needs. It proved to be reliable and mechanically stable in hundreds of experiments in which single unit recordings were successfully carried out for many hours, although the bathing solution was often changed.

Zusammenfassung. Konstruktion einer einfachen, temperaturstabilisierten ($\pm$ 0.3 °C) Durchflusskammer für elektrophysiologische Untersuchungen an Nervengewebekulturen.

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OECOLOGICA HUMANA

Man-made Chemicals and our Milieu Interieur: A Preliminary Report from the Special Commission on Internal Pollution

Editorial Note. The following contribution of the Special Commission on Internal Pollution (S.C.I.P.), London, seems to us to be of the greatest interest for the world-wide effort towards a health strategy, and we have therefore decided to publish it in 'Oecologica humana', inspite of its considerable length. M.

Almost every aspect of daily life in the industrialized countries has been touched on and transformed by the use of synthetic chemicals. The possible effect of these on our milieu interieur prompted us to write an article for these pages four years ago[1]. This publication evoked a large correspondence and stimulated the formation of a Committee to study the problems – the Special Commission on Internal Pollution. Its terms of reference were agreed as follows: To consider the present use of chemicals under four broad headings – medication, food additives and colourants, agricultural aids, and household goods; and to relate their respective use to the responsibility shared by the producers – that is, industry – the consumer, the government regulatory agencies, and the biomedical professions. Furthermore, it was resolved to examine the state of the chemical age in the last quarter of the 20th century, with special reference to the benefit: risk ratio in the different classes of compounds mentioned above, and see how this ratio can be improved. As a result of a recommendation on the political level it was also resolved to examine methods to achieve harmonization of drug safety protocols within the European Economic Community.

A report on some of our work in the field of medication, food intentional additives, and agricultural aids was given before a joint meeting of the WHO/EEC/USEPA at UNESCO headquarters in Paris last summer[2]. Our endeavours towards harmonization have been discussed a number of times with the appropriate authorities in Brussels, and a report issued[3]. Many of our proposals in this regard have become incorporated into the third EEC directive recently issued from Brussels. However, our concept of establishing a 'transnational regulatory drug agency' has not yet captured the imagination of the policy-makers at the headquarters of Europe in the rue de la Loi.

[1] P. Beaconsfield, R. Rainsbury, J. Huxley, R. Peters, J. Trefouel, J. Monod, R. Paul and H. Theorell, *Suggestion for a Study of Various Chemicals and Non-Disease Specific Drugs*; Experientia *27*, 715 (1971).

[2] P. Beaconsfield, N. Borlaug, A. Carpi, H. Krebs, R. Peters and R. Rainsbury, *Internal Pollution – Our First Priority; a Review of the Studies of the Special Commission on Internal Pollution;* Proceedings of International Symposium on Recent Advances in the Assessment of the Health Effects of Environmental Pollution, Paris (1974), p. 163.

[3] P. Beaconsfield, *Drug Safety and the Law: Harmonisation and its Obstacles in the European Economic Community*; Pharm. J. *212*, 502 (1974).

This paper comprises some of our discourse given in Paris, together with the philosophy which underlies our modus operandi in the assessment of benefits and risks encountered by 20th century man in his progression through this Chemical Age.

The ever-increasing use of man-made chemicals in every sphere of activity in the industrialized countries has been accepted almost unnoticed as we move into this last quarter of the 20th century. This use directly touches far more people and influences more aspects of daily life than any kind of revolution that has preceded it, including the atomic age, and ours could well be called the 'Chemical Age'. We have become accustomed to rely on chemicals for health, for homes, for transport, work, leisure, food and drink, and even for fertility and sterility. It is profligate use of chemicals which is the root cause of pollution – whether external pollution of the environment or internal pollution of our own bodies.

This pollution has among its principal causes over-population, over-exploitation of the world's finite natural resources, and unwillingness or inability to dispose of refuse and waste products. The industrialized nations depend on man-made chemicals for their present modus operandi and in addition to developing new chemicals we have growing populations and so manufacture greater quantities of these chemicals to serve them. It has become a vicious circle of more people demanding more goods; it can be broken only if the birth-rate is controlled, if the real need for these chemicals is assessed, and if people are told that these compounds entrain risks as well as benefits. The economic – and hence political – implications of this way of life mean that if we are really concerned to decrease pollution we have to consider making radical alterations in it – alterations which would affect the work forces and distribution of labour and perhaps change the whole direction of national industries.

In Western Europe alone about 10 million workers are presently employed directly or indirectly by the chemical industry. Over the past 10 years the production of all manufactured goods in these countries has risen by approximately 40%, whereas the production of chemical goods has risen by 90%. Entire national economies are geared to the use and availability of these compounds. If there is any doubt about the political or economic implications of our dependency on chemicals it is only necessary to consider the unemployment and redundancy caused by any limitation, run-down, or cut-back in industrial production, most of which relies completely on synthetic chemicals of one kind or another. Nevertheless, if certain aspects of the developed countries' life-style continue unchecked, it can be predicted with some certainty that they will eventually constitute a danger to the entire world, including themselves.

The advent of the Chemical Age has completely changed our attitudes to health and disease. We tend to think of medication in relation to the cure and treatment of disease, but in fact only one tenth of all drugs taken in the industrialized world are for this purpose. The rest go to maintain a new concept – that of 'positive health'. Few, if any, of these chemicals have ever before been taken regularly over such long periods of time, by people who are healthy to start with, and the long-term effects – biological, genetic, and economic – are therefore not yet apparent or appreciated. Hence another new concept is needed – that of Internal Pollution[4].

Internal pollution is brought about in three ways: by the ingestion and inhalation of the products of the already-polluted external environment; by the daily intake of chemical additives and impurities in pre-packed food; and by the vast number of medicaments taken regularly and, more often than not, unnecessarily. The last two ways could be minimized fairly easily, since it is possible to control the mechanisms involved and the economic consequences would be manageable.

Before embarking on a discussion of the specific fields of chemicals the Commission considered the terms 'safe' and 'safety', which are bandied about so freely in the chemical context. Safe is an absolute term meaning 'without danger'. Safety, on the other hand, is a real concept, but one which is relative to the current state of knowledge; is also changes and evolves with variations in the behaviour of the society concerned. It is significant that the body which checks and permits marketing of medicines in Britian is officially known as 'The Committee on Safety of Medicines', for this word 'safety' has insinuated itself into our thinking as being an absolute requirement of medication. As English has now become the scientist's *lingua franca* this crucial conceptual error seems likely to be perpetuated. In order to make a start in reversing this tendency we would suggest that the title of this Committee be changed and the change widely publicized. Other responsible bodies might take the same line instead of continuing to compound the error with the use of such mindless concepts as the recent World Health Organization publication 'Safe Use of Pesticides'. There is no such thing as a safe chemical and we have decided that the term is a misnomer and should be dropped. Instead we propose to evaluate compounds from the point of view of the benefits they confer and any hazard their use entails, and to seek to have a benefit: risk ratio commensurate with the situation concerned. Cost is another factor that has to be taken into account. Many desirable benefits are economically impracticable; experience has led us to accept certain small and limited risks for the sake of decreased costs.

Not nearly enough attention has been given to the question of benefit and risk. Three separate factors need assessing: the benefits a compound can confer; the dangers of taking it; and the consequences of withholding it. In diseases which are invariably fatal if left untreated, these factors are relatively straightforward to weigh up. But with the improvement of medical practice such extreme situations have become the exception rather than the rule, and other aspects have to be considered. One is the question of the relative dangers and benefits of alternative therapies; another is the severity of the disease which may vary from inexorably lethal, like cancer of the stomach, to fatal at a later and uncertain stage, like Hodgkin's disease and some leukaemias; from the incapacitating like the arthritides to the merely inconvenient, like some skin conditions. Other factors include how long the disease may be expected to last if untreated; is it acute and completely curable with the appropriate therapy? Is it short term chronic and curable? Or long term chronic and controllable rather than curable? How much risk is acceptable in therapy which will sufficiently control the disease to give the patient a reasonable quality of life? Which will end his life first – the disease or the drug? Is it possible that social opinion may change during the natural history of a patient's chronic disease?

These questions are still further complicated by the fact that no two human beings are identical and hence will not react identically to the same drug. In a sense, each new administering of medication is an experiment.

[4] P. BEACONSFIELD, *The Other Pollution – Internal*; New York Times 11 January (1971).

There is good reason for considerable concern over the upsurge in iatrogenic conditions[5]. A conservative estimate has it that some 5% of all patients admitted to hospital in the UK and USA are there because of the side effects of drugs they are taking: and of these patients between 2 and 3% die. The number of patients who die because of side effects of drugs in USA alone is estimated at between 6,000 and 12,000 annually[6]. 2 to 3% of congenital malformations are attributable to drugs and chemical pollutants. 18 to 30% of hospital patients suffer some side effect of their medication and this usually doubles the length of their stay in hospital. According to the U.S. Department of Health the total annual cost of treating this drug toxicity is close to 3 billion dollars.

What are the reasons for this level of apparent failure in a field supposedly as minutely researched as pharmacology? It is fashionable, especially in journalistic circles, to pin the blame on the pharmaceutical industry itself, if only because evidence of price-fixing and substantial profits induce people to look no further for a scapegoat. This attitude is not justified. Investigations show that the ethical pharmaceutical industry maintains high overall standards of manufacture and testing. Furthermore, these investigations do not support the impression common since the thalidomide tragedy that the tests carried out on new drugs are ineffective or inefficient. In fact, it can be stated categorically that the tests are as good as our present state of knowledge allows.

We found the problems to lie not with the tests, but with the testers. Many testers succumb to the human weaknesses of inefficiency and lack of conscientiousness – especially if their salaries are poor and their career-structure unestablished. They are no different from the society which produces them. In addition, we have found that many preclinical tests are not carried out by the scientists in charge of the project; he reads the results brought to him by his technicians. This is particularly true of industry, where there is rigid adherence to a hierarchical system.

The truth is that many research scientists are, by nature of their intense specialization, unqualified to correlate diverse results, to cross-transfer, or to recognize anomalies thrown up by different testing techniques. The picture is one of so many tests that no single scientist is competent to make a final assessment of the drug under examination. The pharmaceutical industry itself complains of toxicity tests so numerous that the very volume of work gives the regulating agencies an assurance of quality that could be illusory. In fact, our experience has shown that the perspicacity to pick the right animal and conduct the correct study in depth in a small group of animals is far more likely to provide the desired information than is sheer numerical weight of different tests. This fact is well recognized, yet it is still not accepted practice.

However, the testers are not the only ones at fault. In fact, there are twin culprits – the testers and also the doctors. On the medical profession's side, all is not well. Most of the adverse drug reactions are the direct result of the indiscriminate and over-indulgent prescribing habits of physicians who often rely solely on advertisers' copy for their information about the use of the drugs. In 1973 the number of drugs bought on doctor's prescriptions in the USA had doubled compared with a decade previously and cost about 12 billion dollars, which is more than the national annual budgets of half the countries of the world. And in this plethora of prescribing the specialists are more guilty than the general practitioners[7].

Most doctors are still trained to diagnose and not to prescribe. The medical curriculum for the past 100 years has been designed to elicit diagnosis, for until recent times diagnosis was all we could offer the patient apart from surgery. Drugs were few and their mode of action, even when curative, was ill-understood. Now drugs are many and potent, and their method of action and interaction must be known by the prescriber. Although this fact is recognized, few medical schools give any formal training in the subject, and fewer still have academic departments of clinical pharmacology.

Since the whole field of medication is in the hands of experts and is therefore amenable to control, the cavalier attitude of the medical professional is inexcusable. In fact, medication is the aspect of internal pollution most easily dealt with in the framework of our present technical and economic possibilities.

The use of chemicals in the food industry has had even more far-reaching effects on Western society's economy than has the concept of positive health. More people eat, and they eat a greater diversity of foods in a greater number of places than ever before. Food is produced in one place, processed in another, sold in a third, and retailed elsewhere again. No longer do the seasons dictate the menus of the developed countries. We have what we want when we want it, and without chemical help most of this would be impossible.

The economic implications of all this are immense. Whole new industries employing hundreds of thousands of people have been created; farming itself has been modified to produce a crop of maximum suitability and convenience for harvesting and packaging.

A distinction must be drawn here between those chemicals which are valuable in improving the product or in preserving it better, and those which are added purely and simply for profit. It is one thing to add a preservative to give a good product a better shelf life; but it is nothing other than sharp practice to feed a pig a chemical compound which will cause it to retain water to make it weigh more in the market place. One well-known manufacturer puts up to 20 different chemical additives into his pork pies. Nowadays this is the rule rather than the exception. We may well ask – why – when there is no price advantage to the consumer and a possible risk to his health.

At present few people realize the degree of adulteration undergone by the food they buy. In addition to the obligation of food manufacturers to put dates on their packages, which has only recently become mandatory in most countries, all the ingredients and their proportions should be detailed similarly, in understandable language. The consumer needs to be educated to understand and use this information to his best advantage.

Pesticides, fertilizers, and other agricultural or livestock improvers have now come into almost universal use. These, together with the genetically-improved crops, have produced a new concept – the farming equivalent of 'positive health' – the so-called 'green revolution'.

It now takes less manpower to produce more food from a given acreage in a greater diversity of conditions. However, all this is only with the expenditure of more energy for the same tonnage of production. And just as consumers need even greater quantities of chemicals to maintain their standard of living, so intensely-farmed soils come to rely more and more on chemicals to make up for their depleted structures.

[5] H. KREBS, *On the Overuse and Misuse of Medication*; Executive Health *9*, No. 2 (1974).

[6] N. S. IREY, *Deaths due to Adverse Drug Reactions*; J. Am. med. Ass. *231*, 22 (1975).

[7] T. D. RUCKER, *Drug Use*; J. Am. med. Ass. *230*, 888 (1974).

However, in all evaluations of 'agribusiness' it must be remembered that these 20th century farming aids have to be seen in the context of the nutritional status of the population needing to be fed. We all know about the dead fish in the Baltic and Lake Michigan, but what would happen if DDT were not used in Ceylon? We have the answer to this question. We know that in the 1950s some 2 million cases of malaria were treated there annually. With the introduction of DDT spraying the number fell to 31 cases in 1962 and was only 17 a year later. Discontinuation of DDT spraying because of financial stringency occurred soon after and by 1969 the number of malarial victims had returned to the 2 million mark.

Once again, the point is the same as in the matter of 'positive health': what benefits do we demand and what risks are we prepared to run for them? Scandinavia or parts of the United States may ban the use of DDT though Ceylon may not, but it remains far more difficult to assess permissable risk where the relative tenderness of sirloin steak for the world's overfed minority is concerned.

Up to the present, few people have understood that the comfortable life-style of the industrialized world entails its own risks, and that those risks may not be generally known. A man getting into his car to drive to work accepts – albeit subconsciously – that there is a definite statistical chance of his becoming one of the 8 million injured or 250,000 killed annually on the roads of the industrialized world. Yet the same man sitting down to dinner does not even consider that his precooked TV dinner, bought at the local supermarket, could entail any risk.

It is wrong that he should continue in this state of uninformedness. He is entitled to know so that he himself can decide whether a particular risk is worth taking, and this knowledge must be separated from the claims a manufacturer makes for his product. It is a fact that the value of many goods is overstressed by advertising. The public is conditioned just as effectively as any Pavlovian dog by the sheer weight of repetitiousness of the advertising copy thrust upon it. Over promotion and over advertising are our second pair of culprits; while the first pair – tester and prescriber – can be educated, this second pair cannot, since its only objective is to make money. The legislators' attention needs to be turned to this aspect of risk in our Chemical Age. Control in the advertising sector will of its own accord effect a considerable amelioration of behaviour in the zone of tester and prescriber.

At present the consumer is exploited through his technical ignorance. An urgent need exists for clearer understanding of the medical, social, and economic benefits and risks that accrue from the application of science and technology and the use of chemicals in today's world, and better guide lines for decision-making. Decision-making is a complex process involving assessment of an array of factors concerning benefits, risks, and costs, many of which may be unavailable or imperfectly understood. In the circumstances, it is clearly of limited value to single out particular chemicals for special control, yet that is precisely what is being done presently.

Our aim as scientists should be twofold: firstly, to keep pollution at a minimum level while we examine our continuing progress in the Chemical Age; and secondly, to inform and instruct the citizen about the causes of internal pollution and what is required from him and us in trying to remedy them. In a free society, at the end of the day it is the citizen who finally decides what kind of life he wants. It is the responsibility of scientists to see that he has the necessary knowledge to make the right decision.

P. BEACONSFIELD, H. KREBS, N. BORLAUG and REBECCA RAINSBURY

Special Commission on Internal Pollution (S.C.I.P.), Bedford College, University of London, Regent's Park, London, N.W.1 (England), 14 March 1975.

CONGRESSUS

Italy
Satellite Symposium on Function and Metabolism of Phospholipids in CNS and PNS

in Perugia, 29–31 August 1975

At the same time an International Table Discussion on Biochemical and Pharmacological Implications of Ganglioside Functions will be held. The Symposium and the Round Table is officially part of the 5th International Meeting of the International Society of Neurochemistry in Barcelona (Spain) of 2–6 September 1975.
Further Information by: Prof. G. Porcellati, Istituto di Chimica Biologica dell'Università, Policlinico Monteluce, C. P. 3, Succ. 3, I-06100 Perugia, Italy.

Italy
International Symposium on Thrombosis and Urokinase

in Roma, 30 October–1 November 1975

The Symposium is organized by the Istituto Superiore de Sanità and the chairmen are: Prof. Sol Sherry of Philadelphia, USA, and Prof. R. Paoletti of Milano, Italy. Main topics: Physiopathology of thrombosis. Chemical, biochemical and pharmacological aspects of urokinase. Effects of urokinase on thrombosis. Clinical applications of urokinase.

Registration fee will be US Dollars 30.00. Information and registration by Prof. Rodolfo Paoletti, Via A. Del Sarto 21, I–20129 Milano, Italy.