PRO NATURA INTEGRA

Editorial remark. The Contergan catastrophe has demonstrated the difficulties in predicting long range effects of drugs on the basis of conventional pharmacological testing. But what about the long range effects of chemicals and non-disease specific drugs used in ever increasing numbers, such as food additives, etc.? Do we have to wait for chance discoveries of effects such as those of the cyclamates?

The problem of adequate testing methods for these chemicals which are put in increasing quantities on the market has been spelled out frequently but no steps have been taken so far to really do something about it!

In the following paper leading scientists from different countries have taken the initiative to suggest inclusion of additional testing methods which are now routinely employed in specialized laboratories, namely the testing of effects of compounds at the body's ultrastructure both, functionally and structurally. This appeal of leading scientists comes at the right time to improve our environmental protection and should be seriously considered. H. M.

Suggestion For a Study on the Implications of Various Chemicals and Non-Disease Specific Drugs[1]

PETER BEACONSFIELD, REBECCA RAINSBURY, JULIAN HUXLEY, *London*. RUDOLPH PETERS, *Cambridge*. JACQUES TRÉFOUËL, JACQUES MONOD, RAYMOND PAUL, *Paris*. HUGO THEORELL, *Stockholm*.
17 May 1971.

If the present trend continues, within the next decade almost every person in the technologically developed countries will – according to the pharmaceutical industry – be on some type of daily drug regimen for the improvement or maintenance of his positive health. This habit is becoming modern Man's response to his over anxiety, over weight, over indulgence, and over population. In addition, it is inevitable that he will be consuming an ever increasing number of food additives and substitutes the use of which is the result, in large measure, of modern economic dictates concerning demand and supply, storage and distribution.

The problem of this continuous ingestion of synthetic products, their possible effects on Man, on his disease patterns, and on his physiological adaptability to the ever increasing demands of environmental change are beginning to be recognized. Environmental pollution's effect on the human organism, together with iatrogenesis[2,3] and the diseases of civilisation,[4] are among the monumental issues of our day, and they are also among the few that are capable of a solution within the framework of our economic possibilities. In sharp contrast to the difficulties of halting and correcting pollution of the external environment and the astronomical cost this will incur, preventing further internal pollution is not only relatively inexpensive but also feasible if cognizance of the problem is taken now. These are causes for concern not only to the specialist but also to the general biologist and all those having any responsibility for the physical and psychological well being of mankind.

Safety of compounds

Tests for most compounds taken by Man – irrelevant of their usage – sprang originally from the necessity to evaluate drugs in relation to disease. Therapeutic efficacy was the foremost consideration, and in the main, undesirable effects have been equated strictly with this factor. This disease-orientated fashion in testing still holds sway in classical pharmacology, despite the fact that we have now reached a stage in our attitude to health and wellbeing for which we demand aids to maintain and improve activity and appearance. The vast majority of compounds being consumed today are for non-disease related purposes and must, therefore, be considered in the context of health.

Society has reached a stage of development where the stresses and strains produced by its own speed of technological advance are not only overtaking Man's powers of adaptability – both physical and mental – but are endangering his very survival. The response of a living organism to the constantly changing environment has to be a continuous process of adaptation otherwise the inevitable consequence is breakdown into a disease state. In addition to the obvious danger from physical destruction there are an ever-increasing number of man-made forces that bend our adaptabiltity to such an extent that selection soon will be no longer simply 'natural', and mutations no longer unpredictable occurrences. Chemicals made by Man for his economic enrichment and physical well being are the primary offenders, because they are ubiquitous and being exploited to the limits of their possibilities. And yet these are the very forces which are to a large extent within the realm of the scientists' control, in particular as we already have most of the knowledge needed to eliminate their dangers and substitute inoffensive ones in their

[1] Comments and suggestions are welcomed and should be sent: In English to Prof. P. Beaconsfield, Royal Free Hospital, Liverpool Road, London N.1 (England), in French to Prof. J. Tréfouël, Institut Pasteur, Paris 15 (France).

[2] L. G. SEIDEL, G. F. THORNTON, J. W. SMITH and L. E. CLUFF, Bull. Johns Hopkins Hosp., *119*, 299 (1966).

[3] S. SHAPIRO, D. SLONE, G. P. LEWIS and H. JICK, J. Am. med. Ass. *216*, 467 (1971).

[4] J. SÓS, T. GÁTI, L. CSALAY and I. DÉSI, *Pathology of Civilization Diseases* (Akadémiai Kidaó, Budapest 1971).

stead. This is not a research project to be initiated, but conversion into practical terms of erudition already esoterically disseminated around many specialized laboratories.

In evaluating the safety of chemical compounds the purpose for which they were developed, once satisfactorily established, must be temporarily disregarded, and instead their effect on the rest of the body investigated – particularly at the cellular level in the vital organs. It is not only the final state of the compound in the body – its ultimate metabolism – that counts; but also, and in some instances even more importantly, the compound's effect on the body's ultrastructure, both functionally and architecturally.

To investigate the primary effect of any compound at the cell and tissue level in vital organs and determine whether any damage is caused by short or long term exposure to it does not require a whole new global battery of testing techniques, but rather an intelligent application of our existing technical knowledge. In various scientific disciplines not immediately related to pharmacology, such as tissue, cell, and molecular biology, biophysical and biochemical experimentation is routinely performed which ,when suitably adapted, could give much of the information needed.

A certain number of the basic tests now done to evaluate compounds for use by Man will probably continue to be employed for a long time to come, but in addition there will have to be a second tier of testing[5,6] and this will depend on the type of compound and its formulation, the length of time it is to be taken for, and the reason for its use. Most of the knowledge to evolve testing on these lines we already have; it has simply to be transferred to a different context.

Introducing this kind of testing into traditional pharmacology will have a number of advantages. It will increase the safety of all compounds, improve their efficacy, and make it possible to predict in advance with a high degreee of accuracy the majority of side and deleterious effects. This in turn will make satisfactory clinical trials easier to design and the interpretation of the results more accurate.

Safety of compounds is a problem of our technological age, and its solution must come from our advanced technology and from those who can look at a 20th century problem with the methods and equipment of today and tomorrow. Application of the expertise of other scientific disciplines to the field of traditional pharmacology, starting with a new classification and going logically therefrom to a new testing procedure, is the obvious way to proceed. Thus, what is the next step?

[5] P. BEACONSFIELD, Annali Ist. sup. Sanità *5*, 536 (1969)
[6] P. BEACONSFIELD, New Scient. *49*, 600 (1971).

The responsibility

Somehow between the identification of a problem and its solution there lies a no-mans-land which no one is willing to be first to step across. In the domain of public health there are always areas of vacua of responsibility, and these seem to occur particularly in the train of any innovation. Questions such as who should take the initial responsibility, who should incur the cost, where the venue should be, and under whose auspices should be the continuing work are disputed endlessly and unproductively; in fact, their very discussion seems to be an end in itself.

Suggestions for a solution

The purpose in setting out all the foregoing is to state a case, and then to see whether something can be done about formulating a new set of regulations for the safety of the various compounds we have been discussing.

To do this requires the setting up of a working party, which to accomplish its work completely and within a reasonable time framework should be as small as practicable. If the work of this group is to be meaningful and to the point the members should be men with a multidisciplinary orientation, having long laboratory or clinical experience, and of a broad and flexible intellect. Super specialists would serve best in a consultant capacity and the members of the working party would draw on such specialized knowledge as and when required. For a project of this importance the best brains available have to be harnessed, irrespective of their geographic origin, and they must not be in a position to be subjected to any sort of pressures.

Objects of the working party

1. To define problem areas relating to long-term effects of various chemical compounds with regard to their different categories and usage.

2. To consider a new classification of such compounds. This would put medicinal and non-medicinal compounds into specific categories relating to their origin – synthetic or biological; the purpose for which they are used – prophylactic, therapeutic, or other; and the period for which they will be taken – short, limited, or relatively indefinite. There would have to be a clear differentiation between disease-related drugs, whether taken for short or long periods, and compounds related to the concept of better positive health.

3. To define new safety criteria leading to the adoption of values and measurements on the basis of which it would begin to be possible to state that certain effects are within 'normal biochemical limits' or within 'normal biophysical limits' in the same sense as at present physiological data are accepted and interpreted.

4. To clarify and decide the experimental profiles necessary to reflect the new dimensions relative to the

effects of chemical compounds on the vital organs at the cellular level.

5. As much of the foregoing is still in the realm of limited knowledge, it would be desirable to identify and encourage active liason and cooperation between workers in research centres already concerned with these types of study.

Programme timing

All the objectives just mentioned fall broadly speaking into three phases of work.

The first phase would be to appraise present systems of compound classification, and make revised recommendations in this regard on the basis of the points outlined under section (2) on 'objects of the Working Party'. This leads logically to a consideration and selection of the crucial experimental profiles of the vital organs on which new safety criteria should be based.

The second phase would involve the setting up of studies to determine the primary effects of selected examples of various classes of compounds on the biological activity and function of different tissues, having appraised the techniques available to obtain such measurements and values. The results of these studies will provide some of the data essential for working out the basis of the new safety criteria discussed as part of the first phase.

The third phase would comprise an analysis and critical evaluation of all the data thus far obtained, their relevance to the objectives of the working party's study, and, on the basis of this, the formulation of recommendations to revise regulations pertaining to safety, particularly of chemicals and non-disease related compounds.

A programme carried through on the lines suggested above would be a first step in the protection of the public health, and a safeguard against the irreversibility of internal pollution. It would help the pharmaceutical industry, which presently feels some of the restraints imposed on it by government agencies to be useless and hampering, while in other fields industry would like more guidance and tighter controls. It would streamline production and research and allow for the introduction of more efficient safer products in a shorter period of time. Finally, it would provide guidelines for justifiably proposing changes in existing legislation.

CONGRESSUS

India
8th International Symposium on the Chemistry of Natural Products

in New Delhi, 6–12 February 1972

The Symposium will be devoted mainly to the following topics for which it is proposed to organize separate sections: 1. Alkaloids. 2. Polyphenolics. 3. Terpenoids and steroids. 4. Macromolecules of biological interest (proteins, peptides, nucleic acids, etc.). 5. Carbohydrates, lipids and related substances. 6. Other topics in natural products chemistry including physical methods of structure and determination.
The deadline for sending in abstracts is 1 September 1971. Further information by Prof. S. Rangaswami, Secretary, 8th IUPAC Symposium, Indian National Science Academy, Bahadur Shah Zafar Marg, New Delhi 1 (India).

Switzerland
Third International Congress for Stereology

in Berne 26–31 August 1971

Under the auspices of the International Society for Stereology the meeting shall comprise interdisciplinary sessions on basic stereological methods, their mathematical foundations and their application to various disciplines. Analysis of shape, topological properties, size distribution and number of particles on microscopic sections shall receive special attention. Further topics include sampling problems and instrumentation, particularly automatic image analysis and data processing. Information and provisional program by: Third International Congress for Stereology, Anatomisches Institut der Universität, Bühlstrasse 26, CH-3000 Bern (Switzerland).

ACTUALITAS

International Cell Research Organization (ICRO)

1. *Training Courses.* One of the main activities of ICRO is the organization of training courses on topics of high novelty and on modern techniques in cellular and molecular biology: Principles and techniques of tissue and organ culture; Genetics and Physiology of Bacterial viruses; Energy transducing systems on the sub-cellular level; Methods in mammalian cytogenetics; Membrane Biophysics; DNA-RNA Hybridization; Biogenesis of Mitochondria; Embryology and Epigenetics; Interaction between Animal Viruses and host cells, application of computers to experimental work in biology and chemistry; Methods in molecular biology, etc. The courses generally last 3–5 weeks, and include 16–20 young participants (sometimes more). The ICRO courses are fully international, both the teaching staff and the participants coming from the largest possible number of countries.

2. *The Problem of Developing Countries.* Most of the past ICRO courses have been organizing in European countries – east and west – but the demand from developing countries is increasing steadily. ICRO activities in developing countries may tend to give preference to topics of potential economic usefulness, such as applied microbiology, microbial protein production, fermentation industries, soil microbiology, plant genetics, etc.

Inquiries for more information should be addressed to: Dr. Adam Kepes, International Cell Research Organization, c/o Unesco – AVS, Place de Fontenoy, 75 Paris 7e, France.