

SURVEY OF THE HAZARDS OF THE CHEMICAL AGE

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ABSTRACT

The first part of this report is devoted to recalling *some very general concepts*—indispensable for the understanding of the problems involved:

1. Concerning the different kinds of toxicity, acute, subacute, short term and long term, with special consideration of the consequences, mostly very insidious, of repeated exposure to poisons with cumulative properties.
2. Concerning the processes of absorption of potentially toxic products.
3. Concerning the principal factors inherent in the nature of the subjects exposed or of the environment, which are liable, qualitatively or quantitatively, to have an effect on the toxicity and the ways in which it manifests itself.

The second part consists of the presentation of examples of risks of toxicity in a certain number of fields.

1. Utilization of chemical products in therapeutics.
2. Occupational exposure to chemical agents in industry and agriculture (pesticides).
3. Intentional or unintentional incorporation of chemical agents in food, including water.
4. Exposure of the population in general, which could result from air pollution.
5. Use of chemical products on the domestic level, including the so-called cosmetic products.

In the third section the author pays particular attention to defining the general principles of prevention against the hazards of the chemical era, the chief principle being the disclosure of the risks which necessitate the implementing of an adequate methodology for toxicological evaluation.

Among others, the following are studied:

- the laying down of standards of purity for chemical products
- labelling
- the measures to be taken in the case of individual or collective exposure to toxic chemicals, with reference to the development of centres for toxic pathology or anti-poison centres
- the problem of permissible limits for pollutants in the work environment or in the atmosphere of cities

- the problem of determining acceptable daily intake for chemical products which could be incorporated in food and which are involved in the determining tolerance levels
- the problems raised by the necessity for control, by means of adequate physical or chemical methods of analysis, of the occupational or general environment, as well as man's food.

INTRODUCTION

One of the salient features of our time is undoubtedly the prodigious development of the chemical industry and consequently the increasing expansion of the use of chemicals in the most varied fields.

It should be emphasized that the spectacular progress of the chemical sciences has been very beneficial on the combined economic and social level and has resulted in an unquestionable increase in the welfare of the population. This justifies the slogan: "Chemistry—key to better living" which appears on the emblem commemorating the 75th Anniversary of the American Chemical Society, celebrated in New York in September 1951, on the occasion of the 13th Conference and 13th Congress of the International Union of Pure and Applied Chemistry (I.U.P.A.C.).

Inevitably, however, there is the other side of the coin, and we must not forget the risks of poisoning man is running by being exposed under the modern conditions of life to a considerable and ever increasing number of chemicals; some of them are dangerous to his health and therefore present the toxicologists, hygienists, physicians, engineers, and technologists with the problem of the measures to be applied in order to safeguard the population against them.

The object of this paper is to draw attention, by means of a few suitable examples from different spheres, to the hazards which may result from the developments of the chemical age, and to some of the general preventive measures to be applied with the view to the elimination, or at least the diminishing of such hazards as far as possible.

I. GENERAL NOTIONS ON TOXICITY

In order to be able to define the problem, we thought it advisable to summarize in the first section of this paper some of the more general notions concerning toxicity.

(a) Types of toxicity

There is a regrettable tendency, still far too prevalent, to be only concerned with cases of acute or subacute poisoning as caused by the intake, in one dose or several doses in quick succession, of certain chemicals. The poisoning is revealed by spectacular symptoms, often immediate, and sometimes followed by death. Such is the case, for example, with the inhalation of toxic gases or vapours, such as chlorine, phosgene, carbon monoxide, or hydrogen cyanide, or with the ingestion of sufficiently large amounts of some chemicals to cause serious accidental, or deliberate, poisoning.

As a rule much less is known about the effects of long-term poisoning, often called chronic poisoning, which may be caused by repeated absorption of sometimes minute quantities of certain chemicals over long periods of

time. Such cases may be no less serious than the former, however, for they are often irreversible. They are particularly insidious, as they very often give no noticeable signs of warning.

The two main factors required for the occurrence of long-term poisoning are:

- (i) cumulative properties
- (ii) ability to produce so-called summation of the effects.

(i) *Cumulative properties*—Many substances possess cumulative properties, i.e. they are susceptible to being retained in the body for varying lengths of time. As a result of prolonged absorption of small quantities of such substances—which would not have any discernible consequences if their elimination was sufficiently prompt to be completed between the exposures—a threshold concentration of the poisoning is reached in a susceptible receptor after a certain time, the length of which depends on the size of the individual doses, the rate of elimination, and the length of the intervals between the doses.

This applies to substances which are soluble in lipids but not readily soluble in water, such as the organo-chlorine insecticides (DDT, lindane, aldrine, dieldrine, heptachlor, chlordane, etc.) which accumulate not only in the physiologically inert adipose reserves, but also in the organs and tissues rich in lipids (liver, brain, adrenal cortex, etc.) where they may remain for very long periods, owing to their relative chemical stability. It likewise applies in the case of inorganic fluorine and arsenic derivatives, heavy metal salts (lead, mercury, cadmium, etc.), dinitro-*o*-cresol and 'related derivatives', which form stable complexes with certain constituents of the body as a result of chemical affinity, and are therefore difficult to eliminate.

To make it quite clear, let us consider the fluorine derivatives. Considerably more than one gram of sodium fluoride is necessary to produce serious acute poisoning in a grown-up man; yet, because of the retention of fluorine due to fixation on the calcified tissues in the form of insoluble calcium fluorophosphate complexes, a few hundredths of a gram will suffice in the case of repeated daily doses to produce long-term poisoning, called fluorosis, which is characterized by dental and osseous lesions. Moreover, retention, especially in certain endocrine glands, causes—via other mechanisms—severe cases of cachexia. Similarly due to their affinity for bone tissue, some of the radioelements of the alkali-earth family (radium, radioisotopes of barium and strontium) and even of the actinide group (plutonium, etc.) are particularly dangerous because their affinity causes the retention of these sources of ionizing radiation which are then able to damage not only the bone itself, but especially the bone marrow.

It should be stressed that, in the case of such cumulative poisons, it is possible to determine the quantities which do not present any danger, on the basis of the elimination rates, the intervals between the periods of intake, and the required concentrations at the susceptible receptor level for the inducement of toxic effects.

(ii) *Ability to produce a summation of effects*—This aptitude is clearly revealed in the case of substances which are, under certain conditions, capable of

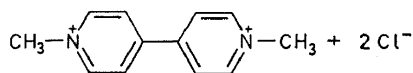
inducing cancerous lesions and are therefore called carcinogenic substances or carcinogens.

The works of Druckrey and co-workers on the dose-effect relationship of such carcinogens as *p*-dimethylaminoazobenzene (butter yellow), *p*-dimethylaminostilbene and diethylnitrosamine, seem in fact to suggest that the manifestation of the activity of such compounds is not a function of the retained fraction of the amount absorbed (as is the case with typical cumulative poisons), but a function of the total sum of the amounts absorbed, irrespective of their distribution in time and of the elimination and metabolic destruction rates. Everything happens as if there was a *complete summation of absolutely irreversible effects*, like the successive impressions upon a photographic plate or film, for example. As a result—even though in the case of carcinogenic substances, as in that of poisonous chemicals in general, there exists a relationship between the amounts absorbed and the responses obtained (percentage of induced tumours or mean time required to induce them)—it is in practice impossible, at the present state of our knowledge, to establish threshold doses below which the danger no longer exists, in the cases of repeated exposure throughout a person's life. In fact, if we admit the continuation of the effects after the disappearance of the substance responsible for them (*Cessante causa, non cessat effectus*), even very minute doses can be dangerous if their intake recurs over a sufficiently long time, or if a sufficiently long time has passed for their activity to become manifest. Exposure to carcinogenic chemicals is therefore particularly dangerous, especially where it starts in the early stages of life.

These remarks are also valid for the chemicals with a mutagenic activity. It would have been desirable, at this point of the article, to discuss the highly promising lines of research on the reactivity of some chemicals with respect to biological macromolecules, such as nucleic acids, the fundamental role of which consists of the control of cellular multiplication as well as the transmission of hereditary characters, and consequently requires the preservation of an unaltered structure which is indispensable for correct coding.

Here we have a promising field of toxicology, called molecular toxicology. In this direction some of the results already available, especially those pertaining to the carcinogenic compounds of the nitrosamine series, suggest a means of understanding what determines certain long-term effects.

In recent years, in the case of certain chemicals, delayed toxic effects have been discovered which may result from even a single absorption and only become manifest long after they have left the body. One striking example is in the delayed respiratory failure, due to a vast proliferation of cells in the



Paraquat

lung blocking the air exchange in the alveoli, which is produced by ingestion of the herbicide paraquat, a bipyridinium derivative, although this compound is poorly absorbed from the gut and that fraction which is absorbed is rapidly

excreted. It would appear that if a certain concentration of the compound is reached in the lungs, even for a short time, an irreversible process is initiated which continues remorselessly long after the stimulation ends. Analogous examples of delayed effects are: kidney tumours produced in the rat by dimethylnitrosamine, lung oedema provoked by pyrrolizidine alkaloids, damage to neurones of the central nervous system leading to paralysis caused by triorthocresylphosphate and other organo-phosphorous compounds, etc. Poisons producing such delayed toxic effects have been aptly named "Poisons that hit and run" by Barnes in *The New Scientist*. It is reasonable to consider the possibility that this type of delayed response might be more common than is generally supposed.

(b) Absorption of toxic chemicals

It should be remembered that toxic chemicals may be absorbed not only by the digestive tract, which naturally comes first to mind, but also by other routes, such as the lungs and the skin.

The pulmonary route is by far the most important, not only in the case of gases and vapours, but also of the liquid aerosols (mists) and especially of the particles minute enough not to be mechanically retained at the upper air canals.

The cutaneous pathways can be utilized by many chemicals, in particular those soluble in the lipids of the skin, e.g. aromatic nitro- or amino-derivatives, organophosphorus insecticides, the chlorinated phenolic derivatives, tetraethyl lead, and numerous solvents.

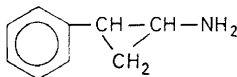
(c) Factors affecting toxic phenomena

Various factors should be taken into consideration in the conditioning of toxic phenomena. It is not possible now to enlarge on this, but we would like to mention the influence of certain genetic characters. To give but one example: the deficiency of glucose-6-phosphatedehydrogenase, an enzyme active in the aerobic catabolism of glucides in the red blood corpuscles of certain groups of people. This deficiency has been the cause of severe haemolytic cases recorded during the war in the Pacific among American Negroes after ingestion of therapeutic doses of an antimalarial drug, Primaquine; it has been responsible for similar disorders among workmen exposed to various industrial chemicals, particularly aromatic amines; and also for the poisoning, not previously understood, caused by consumption of the common bean (*Vicia faba*) among certain groups of population in the Mediterranean region. It is interesting to note at this point that genetic deficiencies of this kind can be detected by suitable tests so that the patients known to be susceptible should be able to avoid exposure. It has been written with perfect justification that the discoveries in this sphere constitute a major triumph of toxicology.

We must also mention the high sensitivity of the foetus to various chemical agents, which is the reason for the greatest caution regarding the possible exposure of pregnant women. Studies of the permeability of the placenta have consequently assumed a great importance in experimental toxicology. The recent findings of Druckrey and his team concerning long-term production of brain cancer in rats born to females that have been given a single

injection during pregnancy of a small dose of nitrosomethylurea would in no way diminish the importance of these remarks.

Lastly, it should be remembered that, under modern conditions, man is not exposed to a single chemical, but to a whole series of compounds, absorbed as drugs, with food, or with the air inhaled. Antagonistic reactions are of course possible, but there is also the likelihood of additive effects, and even of potentiation. A certain number of cases of toxic synergistic effects has already been recorded. Not all the instances are as easy to detect as the truly spectacular occurrence of hypertension, and even cerebral haemorrhage, in consumers of tyramine-rich cheese who have initially taken the psycho-tonic drug, Tranylcypromine which, by inhibiting monoaminoxidase, prevented the breakdown of the sympathomimetic amine. Here is a field of



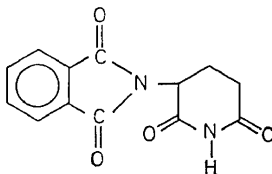
Tranylcypromine

research almost entirely unexplored. As in many other fields, toxicology must resort here to biochemical methods and data without which the secret mechanisms of the action of poisons, those chemical scalpels in the words of Claude Bernard, cannot be understood.

II. SOME EXAMPLES OF TOXIC HAZARDS IN VARIOUS FIELDS

(a) Therapeutic use of chemicals

It is a well-known fact that a chemical producing beneficial results when applied in definite doses, and for this reason used in therapeutics, may produce toxic symptoms in the receptor of the therapeutic effect if taken in larger doses. It is, however, the study of the secondary effects of drugs that occupies by far the most important position in the study of therapeutic risks. We could quote many examples of secondary toxic effects which have revealed themselves in the form of virtual medicinal diseases. They have resulted in the development of pharmacological, toxicological, and clinical tests prior to the appearance on the market of any new drug. Some of the particularly severe cases have been nevertheless unexpected. We shall mention but one, the tragic history of N-phthaloyl-glutarimide or Thalidomide.



Thalidomide

We recall that when this hypnotic with mild tranquillizer properties appeared on the market in 1957, it was considered—on the basis of toxi-

ecological tests carried out in accordance with the conventional standards of the day—to be the least toxic of all the known hypnotics. And yet, taken by a pregnant woman at the period of early differentiation of the embryo, that is during the first few weeks after conception (23rd to 40th day), it caused anatomical malformation in the foetus with the consequent birth of an abnormal baby, sometimes with the appearance of a real monster. An investigation of such teratogenic effects has subsequently been included in the design of toxicological testing of all drugs.

Among the hazards of the chemical age, the case of drugs is, however, of a very special nature, because in prescribing one, both the benefit and the risk should be carefully weighed. The latter must, however, first become known before the physicians can be wary of them.

(b) Occupational exposure to chemicals

The study of the risks of poisoning of workmen exposed to the action of the ever increasing number of chemicals occurring in their environment constitutes one of the great chapters of modern toxicology. Acute poisoning, sometimes mass poisoning, caused by accidental exposure due, for example, to failure of the sewerage system, corrosion of containers, breakage of reaction flasks containing large quantities of toxic materials, particularly those of a volatile nature, must of course be dealt with.

To mention but a few instances: poisoning with hydrogen sulphide in natural-gas scrubbing plants, or in plants for the refining of crude mineral oils rich in sulphur; poisoning by hydrogen cyanide in nitrile manufacturing plants; with chlorine, phosgene, ammonia or nitrous vapours—often recorded in various plants; lastly with dinitro-*o*-cresol used as a herbicide or defoliating agent, as well as with the organo-phosphorus insecticides which have anticholinesterase properties, for example parathion or malathion—in the case of workers assigned to the spraying of these chemicals in agriculture without using the necessary precautions, especially protective clothing.

Much more frequent is, however, the day by day exposure, under conditions of industrial operation, to small amounts of chemicals with cumulative properties which may in the long run become the source of poisoning. Already in 1703, the great precursor Bernardino Bamazzini, an Italian physician, wrote “Craftsmen often get grave diseases where they hoped to get the means for the sustenance of their families, and they die cursing the trade they chose.” And, wisely, he advised physicians attending the common people to enquire about their profession.

Since then, many occupational diseases due to exposure to industrial or agricultural poisons have been identified, such as mercurialism, saturnism, manganism, cadmosis, berylliosis, silicosis, benzenism, occupational dermatosis, as well as occupational cancer of chemical origin, produced in the skin or lung by tar, crude mineral oils, impure paraffins, and then the very long-term bladder cancer caused by certain aromatic amines, such as beta-naphthyl amine, benzidine and xenylamine.

A consequence of the appearance of these occupational diseases and poisonings has been the development of a specialized branch of medicine, the Occupational Medicine, one of its chief duties being the detection of such

diseases with the view to their treatment and compensation. In parallel, for the purpose of study and of the introduction of preventive measures which will be discussed below in general terms, a new discipline—industrial hygiene—has been created. This includes two collaborating groups: on the one hand, the toxicologists entrusted with the investigation of the toxicity of chemicals and with the development of analytical methods for their detection and dosage, both in the environment of workmen and in biological media (blood, urine, exhaled air, etc.) obtained from exposed individuals; and on the other, the technologists, sanitary engineers and the chemists whose task it is to design industrial installations, manufacturing processes, and the practical methods of application of chemicals.

(c) Incorporation of chemical agents in foodstuffs

In view of the ever-increasing application of chemistry in the spheres of agriculture and food technology, many substances may at present be incorporated in food—either as a result of treatment prior to slaughtering or harvesting, or as a result of contamination in the course of processing for consumption, storage or distribution; or else as a result of deliberate addition of chemical agents for various reasons, such as preservation, improvement of flavour and taste, improvement of the appearance and presentation.

The study of the risk of poisoning due to the presence of such substances in food is at present one of the main tasks of toxicology. It cannot be over-emphasized that man is inevitably subjected to the influence of his nourishment from birth until death, and that this offers the optimum conditions for the possible manifestation of long-term toxic effects.

It is not possible in a general review like this to go into details, and we are compelled to quote some example only to prove the reality of hazard to health inherent in a casual—deliberate or otherwise—incorporation of chemical agents in food.

Regarding the chemicals known as 'pesticides', the use of which in combating agricultural parasites and crop pests is essential for the preservation of our food resources at the time of the well-founded campaign against hunger in the world—the fundamental problem is the possible presence of such compounds or their metabolites in the form of residues in the food consumed by man. Some of the residues may in the long run produce serious toxic effects once their proportion has exceeded a certain value. In this way, the organo-chlorine insecticides, with the cumulative capacity pointed out above, may produce, among others, hepatic lesions and nervous disturbances, while the organo-mercury fungicides may cause renal lesions and serious nervous disorders. Some pesticides have even shown carcinogenic potentialities in animal experiments. Such was the case with the inorganic derivatives of arsenic and selenium, acetylamino 2-fluorene, aramite (*p*-*tert*-butyl phenoxyisopropyl and beta-chlorethyl sulphide), aminotriazole, etc.

The case of acetylamino-2-fluorene should be emphasized because, on the basis of acute and subacute toxicity tests, its commercial use as insecticide had been seriously envisaged. Fortunately, and for completely unrelated reasons, attention of specialists on chemical carcinogenesis has been drawn to this compound which has proved to possess a high carcinogenic activity in

various animal species and various organs and tissues, in the case of ingestion, external application or injection. The discovery of its noxiousness by exposure of humans in the course of its utilization was therefore averted.

A spectacular example of danger inherent in a material that has not been subjected to strict toxicological testing is that of *tri-o*-cresyl phosphate in the group of chemicals which may be imparted to foodstuffs by wrappings used for storage. This chemical had been used some time ago as plasticizer in a polyvinyl chloride, known in Germany as Igelite, and used *i.a.* as packaging material for foodstuffs. On contact with fatty materials there was considerable migration of this lipid-soluble organophosphorus compound and this was the cause of polyneuritis and paralysis, similar to the disorders observed in Morocco a few years ago as a result of consumption of edible oils fraudulently adulterated with this compound

In the group of intentional additives we shall mention a few toxic compounds, at one time recommended:

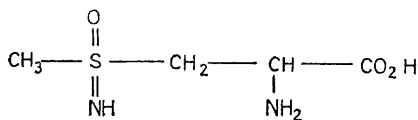
Among the preservatives, monobromacetic acid and its derivatives (sodium salt, ethyl ester, ethylglycol ester, etc.) are protoplasm poisons which bloc the thiol groups—SH indispensable for the functioning of numerous enzymes and, consequently, for metabolism and cellular growth. They possess relatively durable cardiotoxic properties.

Among the antioxidants, diphenyl-*p*-phenylene diamine (DPPD) produces, in tests on rats, the prolongation of gestation and a high mortality in the offspring; thiourea, which was proposed as a fungicide for the preservation of citrus fruits has proved a potential carcinogen of the liver and thyroid.

Among the sweetening agents, the ethyl and *n*-propyl ethers of amino-2-nitro-4-phenol (neodouxane and P.A.N.) have proved toxic to liver, thyroid and erythrocytes, while dulcine or *p*-ethoxyphenylurea and, quite recently, cyclamates have been shown by animal tests to be potential carcinogens.

Among flavourings, safrol (allyl-4-methylenedioxy-1-2-benzene), an active principle of the Sassafras oil used for a long time in the manufacture of certain non-alcoholic beverages, has been shown to cause lesions and even malignant growths in the liver.

Among the agents used for treating and/or bleaching of flour, nitrogen trichloride, Cl₃N, extensively used for some time under the name of agene, transforms methionine present in the gluten proteins into sulphoximine, which was responsible for the occurrence of epileptic convulsions in dogs



Sulphoximine

fed agenized flour. Some scientists argued that the action of sulphoximine on the central nervous system is limited to certain animal species and is not effective in man. In 1961, however, the Soviet author Krakoff, who administered this compound *per os* as an anti-cancer agent in man, recorded

phenomena of excitement accompanied by confusion and hallucinations. Let us make it clear that in the case of nitrogen trichloride it is not the additive itself that is toxic, but the product it generates by reacting with a normal and even essential constituent of food from the nutritional point of view.

To give another example, nitrosamines have been detected in foods treated with relatively high concentrations of nitrosating agents, such as nitrites, under conditions which favour their formation. This finding, the significance of which is still under discussion, created considerable concern about the use of nitrites as food additives and the problem is under active study.

Lastly, among the colouring agents—as a result of the discovery in 1935 of the hepato-carcinogenic activity in rat of an azo dye, the *p*-dimethyl-amino-azobenzene (butter yellow) used at the time in some countries for the coloration of margarine and food pastes—a number of dyes belonging to the various chemical classes, which had been proposed for the food industry, have been found after animal tests to be potential carcinogens.

Obviously, this consciousness of the various toxic potentialities has resulted in much caution in the granting of permits for the incorporation of chemicals in food. Such permits are not at present granted unless the chemical has been subjected to stringent toxicological tests and been proven innocuous to the consumer under the conditions of utilization and thus to be suitable for inclusion in the lists of acceptable products, the so-called 'positive lists'. Interpretation of the results of tests, however, inevitably involves an appraisal of value with the inherent notion of gain that may result from the use of the given substance.

We should mention in this connection, as an example, the interest which may exist in making available suitably selected fungicides for combating the proliferation on certain crops of moulds producing highly toxic substances, such as *Aspergillus flavus* which elaborates aflatoxins, by far the most active among the known hepatic carcinogens, with an activity at least a thousand times greater than that of *p*-dimethylaminoazobenzene. This remark prompts us to stress in passing that certain natural chemicals may be considerably more toxic than those obtained by chemical synthesis.

We could not leave this branch of toxicology, called food toxicology, without at least touching on the toxicological problems posed by the chemical pollution of rivers on which we depend increasingly for the supply of our growing requirements of drinking water for large cities. Obviously, river water, usually polluted with industrial effluents, is mechanically, chemically and biologically treated with the view to the elimination of micro-organisms, especially bacterial pathogens, as well as various suspended and dissolved impurities. Nevertheless, certain pollutants occurring in trace amounts may be incompletely removed, especially where they are associated with surface-active agents not susceptible to biological degradation, which maintain them in solution. Bearing in mind that water is consumed by man continuously, whether as beverage or in the preparation of various foods—we must realize that continued intake of chemical micropollutants cannot be regarded as harmless to health, unless proven to be so. In our opinion, this is a problem of extreme importance at the international level.

(d) Possible exposure of the general public due to air pollution

Air is the most essential life requirement of man who absorbs some 12 m³, or slightly more than 15 kg, of air every day of his life, from birth to death. Any encroachment on its purity is therefore of primary importance, since the chemical agents it contains, not only gases and vapours, but also aerosols and sufficiently small particles, penetrate right into the pulmonary alveoli. Once there, they may cause not only local damage, but often get into the general circulation owing to the high absorptive capacity of pulmonary epithelium, which is very thin and has a very large surface area surrounding a capillary-rich region. Respiration being the fundamental character of life, air pollution affords the optimum conditions for the manifestation of toxic effects, especially of long-term poisoning.

The recognition of the importance of the problem dates back to ancient times. For the last fifty years, however, it has been assuming ever more imperative forms, because the chemical pollution of the atmosphere has been increasing incessantly in large urban communities, as a result of numerous household fires, factories, and motor vehicles, which are the chief contributors. This is the more meaningful toxicologically because, at the same time, the number of exposed individuals keeps on increasing as a result of the concentration of population in the cities.

The principal polluting agents are the following:

Carbon monoxide evolving chiefly from domestic fires and motor vehicle engines, its proportion in the motor car exhaust fumes being from 2.5 to 7% by volume;

Sulphur dioxide emitted constantly into the urban atmosphere (180,000 tons in Paris during 1958) from hearths utilizing coal or fuels which contain a certain proportion of sulphur. Through oxidation under the influence of moist air, sometimes catalysed by certain metallic elements, it generates a sulphuric acid micromist which constitutes the famous 'acid smog' of some cities, such as London in the United Kingdom or Pittsburgh in the United States;

Nitrogen oxides occur in the exhaust fumes of motor vehicles; these compounds, especially the peroxide NO₂, play a very important part in the building up of the 'oxidizing smog' rich in ozone and organic peroxides, typical of the sunny regions such as Los Angeles in the United States and which photochemical reactions help to generate;

Unburnt hydrocarbons, discharged in the exhaust of motor vehicles;

Soot containing polycyclic aromatic hydrocarbons with benzo(a)pyrene as the most common.

Here should be added industrial fumes discarded specifically by certain factories, such as inorganic fluorine derivatives, mineral dusts in a large variety of compositions (arsenic, selenium, silicon, lead, iron, chromium, manganese, nickel, vanadium, and beryllium derivatives, etc.) and the malodorous derivatives (mercaptans, various amino compounds, etc.).

These diverse chemicals may have a toxic effect originating at a certain concentration in the air. Moreover the possibility of toxic synergistic effects is not excluded since in the final count city dwellers are treated to a pollutant-soup. Lastly, certain meteorological conditions, such as formation of fog or the phenomenon known as temperature inversion, may prevent diffusion of

pollutants and keep them near the ground in relatively high concentrations. This accounts for the occurrences of collective acute poisoning such as was recorded in the Meuse industrial basin in 1930 (some 1,000 cases of poisoning more than 60 fatal), at Donora, Pennsylvania, in October 1958 (6,000 poisoned, 20 dead), and in London in December 1952 and December 1962 (several thousand aged dead).

The most insidious danger is once more that of long-term poisoning. We shall mention but a few examples:

Sulphur dioxide and the part it plays in the induction of chronic bronchitis.

Fluorine fumes and the part they play in the etiology of fluorosis in cattle in the proximity of certain factories, particularly those manufacturing aluminium by means of electrolysis of bauxite in the presence of fluorides used as flux.

Soot. Above all, there is the highly probable role played by soot particles as carriers of carcinogenic aromatic polycyclic hydrocarbons frequently associated with light petroleum hydrocarbons, acting as eluents, in the etiology and pathogeny of bronchial cancer shown by statistics to be definitely increasing in frequency over the last decades, particularly in the urban areas. Without omitting the recognized role of tobacco, particularly in the form of cigarettes, air pollution is generally regarded as an important factor.

(e) Use of chemicals in households

For lack of space, we shall not enlarge on chemicals specifically produced for household use, though many of them (such as cleaning and maintenance materials, insecticides, etc.) are dangerous to health unless rigorous precautions are taken. Instead, we shall say a few words about cosmetics and toilet chemicals.

Though the use of such preparations with the view to the maintenance of suitable standards of hygiene is an important factor contributing to the welfare and health of the population, careless use of certain chemicals in the manufacture of cosmetics may present a danger to public health. For this reason one of the international organizations, EUROTOX has devoted one of its sessions (London 1962) to the investigation of such hazards, particularly the long-term ones, the results of which may be serious on account of the prolonged use of such preparations. Of particular importance are the compounds occurring in the preparations which could be partially ingested. For example, certain dyes in lipsticks, such as rhodamine B which is considered a potential carcinogen. Other substances may penetrate through the skin, especially in the presence of surface-active agents with which they are usually associated. For example, tri-*o*-cresyl phosphate used for the manufacture of nail polish, certain organo-mercurials, valued as preservatives of shampoos and creams, and female hormones so often incorporated in the latter.

Without describing the accidents, sometimes serious, recorded in the past with products like *p*-phenylenediamine, a constituent of some hair dyes; carbon tetrachloride, a hair-degreasing agent; thallium salts, constituents of depilatory ointments; nitrobenzene, a cheap scent for soap and toilet

lotions—the above few remarks will suffice to show why the big cosmetic manufacturers maintain large toxicological research departments.

III. SOME GENERAL PRINCIPLES FOR PREVENTION

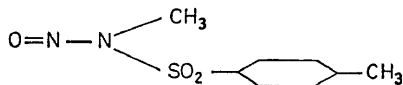
It is not possible to prevent danger unless it is recognized. The major rule of prevention against the hazards of the chemical age is to lay bare the risk of poisoning. For this purpose it is necessary to develop adequate methods of toxicological evaluation comprising sufficiently thorough and prolonged tests on suitably chosen animal species, without overlooking the possible contributions of biochemical investigation, particularly of the metabolic fate of the substances tested and their effect on the fundamental enzyme systems. It is not possible to go into details on this point, but we would like to emphasize that much attention should be given, in our view, to the investigation of the possible long-term dangers, since, as we have stressed repeatedly, man is in most cases exposed throughout his lifetime to chemical agents present in his environment and food.

We should also like to stress that, in view of the uncertainty always inherent in the extrapolation of experimental results obtained on animals to man, observation of the latter is of the utmost interest. The ideal would be to experiment on man himself; however, for reasons at once practical and moral, it cannot be done except in very special cases where it is possible to apply all the safety measures and exclude all major risks. Consequently, we are compelled in most cases to carry out surveys on exposed groups of people. These are of great value in the occupational and therapeutic fields, but less so in the case, for example, of chemical agents incorporated in food. It is in fact rather unlikely that the carcinogenic effects of some food additives could be revealed by such investigations in useful time, since even if it were a powerful carcinogen, its effects would not become apparent within less than some twenty years and, in view of the multiplicity of factors to be taken into consideration, it would still be very difficult to determine the relationship between the cause and effect.

We shall now enumerate some very general rules which are likely to contribute to the prevention of the risks detected. Their application would not of course replace the truly technical preventive measures, such as—in the field of industrial hygiene—operation of certain apparatus in closed vessels, removal of toxic fumes and dusts, application of ventilation systems, etc.—nor the measures of individual and collective hygiene. On the contrary, the general rules are meant to serve as a basis for them.

(1) The ideal rule of prevention would naturally be to exclude the chemicals which are too dangerous. It would be easily applicable in the case of such drugs as thalidomide, additives such as bromacetates or butter yellow, pesticides like the fluorine derivatives of some of the organo-phosphorus compounds, or the industrial chemicals with high carcinogenic activities such as beta-propiolactone or nitrosamines. It could not be applied so explicitly to the pollutants of urban air. We could not, for instance, eliminate completely benzo(a)pyrene from the urban atmosphere or even from areas of high-traffic density. One should, therefore, try to reduce as far as possible the volume of pollutants discharged, by implementing,

gradually, suitable technical means. In the case of industrial chemicals of high toxicity to which workmen may be exposed, the efforts should be directed, through a well-defined co-operation between chemists and toxicologists, at their replacement by functionally equivalent chemicals which, if not completely free from toxicity, then at least be much less toxic. A spectacular example is the progressive replacement of benzene as industrial solvent by such chemicals as toluene, cyclohexane, gasoline hydrocarbons and the chlorinated derivatives of ethylene, which are free from the dangerous aggressiveness towards bone marrow exhibited by the first member of the aromatic hydrocarbon series. Another example is the replacement, in various applications, of paradimethylaminobenzene by paradiethylaminobenzene which has no carcinogenic potentialities with respect to liver. More recently, the discovery of the high carcinogenic potentialities of the alkylating agents currently used in organic synthesis, such as nitrosomethylurethane, nitrosomethylurea, and diazomethane generated by the former two, has resulted in a search for substitutes. The proposed compound is N-nitroso-N-methylparatoluene sulphonamide which has been proven by animal tests to be free from carcinogenic activity.



N-nitroso-N-methylparatoluene sulphonamide

Similarly, on the basis of the well-established fact that the aromatic amines which are responsible for bladder cancer in man, lose their carcinogenic potentiality through sulphonation, it should be advisable, instead of using beta-naphthylamine as raw material for the manufacture of certain dyes, to proceed from beta-naphthol that has been sulphonated in order to produce, by the action of ammonia, Tobias acid, a sulphonated derivative of beta-naphthylamine, which can replace the latter in most industrial applications.

The problem of replacement of highly toxic chemicals by practically non-toxic ones or ones with very low toxicity, applies equally in research laboratories, because many analytical reagents, such as benzidine, or organic synthesis reagents, such as diazomethane, present great danger to the health of those who manipulate them, the more so as very often they are not aware of it.

(2) It should be remembered that very often the toxicity of a substance may be due to the impurities it contains. A well-known fact is, for example, that when it was first introduced as an industrial solvent, trichloroethylene was much more toxic than the purified and stabilized trichloroethylene at present in use. In the insecticide group, chlordane at the beginning of its commercialization contained impurities much more toxic than the active principle. Among the additives, to mention one last example, quercetin, a colouring agent of vegetable origin, produced cataract in rats subjected to repeated administration but, after thorough chromatographic purification, it lost this property.

A corollary of these remarks is obviously the need for standards of purity. These should be applied in a very rigorous manner to the various groups of additives for foodstuffs.

(3) Once the toxicity of a chemical has been discovered, it should be made known to individuals likely to be exposed to it. The problem of labelling of chemicals has preoccupied various national authorities and international organizations such as the International Labour Organization and the Council of Europe. To be effective, labelling should attract attention to the dangerous properties of the substance in a distinct and easily understandable manner. This means, in our view, that it should not be burdensome. Symbols of danger, such as the skull and cross-bones are of great value in the case of high-toxicity chemicals, not only of an immediate nature but also with long-term poisonous properties such as benzene. The remarks concerning labelling are equally valid in connection with transport and storage of dangerous chemicals. In some cases, such as seed or tubers treated with fungicides as preservatives, colouring or malodorous matter should be added as a warning against accidental consumption. Lack of such precautions has often been the cause of poisoning, e.g. severe porphyria with photosensitization recorded in Anatolia a few years ago as a consequence of the consumption of corn seed treated with hexachlorobenzene.

(4) In view of the increasing frequency of accidental poisoning, especially among children, as a result of the spreading of chemicals by man in his environment, it is necessary to gather information on first-aid measures, especially antidotes, to be applied. The awareness of the danger has resulted in the development in many countries of 'anti-poison or toxic pathology centres' which provide diagnosis and first-aid service to victims of poisoning, and are entrusted with the collection and distribution of information on chemicals with toxic potentialities.

(5) As regards toxic chemicals that may be encountered in the atmosphere of working premises, one of the major safeguards is, once the threshold of toxicity has been determined, to establish the permissible limits of concentration at which, and below which, there is practically no danger, whether in short-term exposure (ceiling values) or, in the case of long-term poisons, with repeated daily exposures under normal conditions of work in industry or agriculture (time-weighted averages). The problem of permissible limits, comprising the additional problem of permissible limits of poisons and their metabolites in biological matter specimens (blood, urine, exhaled air, etc.) from the exposed individuals, virtual poison collectors, is of the highest importance in industrial hygiene. It forms at present the subject of intensive studies at the national and international levels. Two symposia held under the joint auspices of several international organizations, one in Prague in 1959, and the other in Paris in 1963, have already been devoted to it, not to mention a whole series of colloquia, which have yielded practical resolutions and, above all, have stimulated research with the view to providing guidance based on scientific data to safety engineers responsible for the implementation of technical preventive measures.

The problem of the determination of the thresholds of toxicity and permissible limits arises likewise in the case of chemical agents of atmospheric

pollution in cities and industrial environment. It is far more subtle, at the present stage of our knowledge, and is also the subject of intensive research activities. We shall only stress that in this case the values to be applied will be considerably lower than those for the working environment. In reality, whereas the workmen are exposed intermittently (six to eight hours per day, five or six days per week), which gives an opportunity for recuperation, the general public is exposed continuously to the air it must breathe and has no choice. Moreover, workmen are nearly always adults that have undergone pre-employment examinations and are subjected to regular medical checks which permit the elimination of individuals in a poor physical condition; the general public, on the other hand does not consist of fit adults alone but also of pregnant women, children, the aged, the sick, and those afflicted with undetected ailments such as renal, hepatic pulmonary or cardiovascular deficiencies, and consequently may be much more susceptible. To get this clear, we shall quote the example of beryllium. The generally recognized tolerance limit for air in work premises is $2 \mu\text{g}/\text{m}^3$, but for industrial environments where the atmosphere may contain this highly dangerous element with toxic and even carcinogenic potentialities for pulmonary tissue, it is barely $0.01 \mu\text{g}/\text{m}^3$, e.g. 200 times less.

(6) As for the chemical agents that are likely to be incorporated, intentionally or otherwise, in our food, it is again the principle of limit concentrations, for acceptable chemicals appearing on the so-called 'positive lists', that should constitute the golden rule. In conformance with the doctrine put in 1956 before the Council of Europe Sub-committee for sanitary control of foodstuffs which has since been unanimously adopted on an international level, the basic toxicological value for each chemical is the acceptable daily intake for long-term adsorption. This value has been determined on the basis of reliable toxicological information obtained from animal laboratory tests, where possible complemented by observations on man, a safety factor always being applied to take care of the variation in sensitivity as a function of various factors.

Proceeding from this value, and taking account of the proportion of the given food consumed, it is possible to calculate the maximum permissible concentration and consequently to determine the tolerances which may be much lower wherever a high standard of food technology or sound agricultural pesticide practice permit.

In fact, at the present stage of our knowledge, many of the problems in this connection still await solution.

(7) Whether it is a question of the permissible levels of pollutants in working premises or in the urban or industrial environmental atmospheres, or the tolerance limits for chemicals in foodstuffs—it would be of no avail in practice to recommend them, unless adequate analytical control methods were available. The same applies regarding the establishment of purity criteria for the various chemicals, in particular for the food additives.

Here is an enormous field of activity where the International Union of Pure and Applied Chemistry (IUPAC) has an important part to play in conjunction with other international organizations such as the International Labour Organization, the Permanent International Commission for Occupational Diseases, the World Health Organization, the F.A.O..

International Union against Cancer and the European Economic Community. Programmes of co-operation with some of these organizations have been drawn up and their implementation has furnished results of great practical value. It is worth mentioning that a particularly fruitful factor in carrying out these programmes has been the liaison with the chemical industry whose experts are likely to contribute very valuable assistance in the investigation of the problems of analytical control.

(8) A rule which in our view is of great importance for the prevention of toxic hazards is the promotion of suitable health education not only for individuals exposed, but likewise, and perhaps particularly for those engaged in chemical industry who frequently—we must stress—are not aware of the dangers more especially the long-term dangers, involved in the exposure to some of the chemicals. We believe it highly desirable, therefore, to include in the teaching programmes of chemistry a course, even if a short one, devoted to the exposition of the basic toxicological notions and drawing attention to the hazards inherent in products of high short-term or long-term toxicity.

CONCLUSION

In this paper it has only been possible to give very general and of necessity very incomplete ideas on a subject of such enormous vastness. It is nevertheless hoped that we have succeeded in showing real hazards to health may be inherent in the development of the chemical age unless much attention is accorded to their evaluation by means of adequate toxicological investigations capable of detecting the risks and of furnishing the biological and analytical basis for the determination of preventive measures. This is the reason why it is highly desirable to develop, on a world level, toxicological research centres suitably equipped in material and staff qualified to apply multi-disciplinary methods that should be implemented in the investigations of the various aspects of toxicological problems. It is impossible to overstress in this connection the fact that, even in the most advanced countries, such as the United States, toxicology, the science of poisons, continues to be underdeveloped.

We also hope moreover to have shown that the time is past when the sole object of this discipline was the study of toxic substances in forensic medicine or in therapeutics. Its field of investigation has in fact greatly expanded with the development of the chemical age, and it has truly become, for this reason, a social science with the fundamental objective of safeguarding the health of the people and enabling them to benefit in perfect safety from the progress of modern chemistry.

That is a particularly stimulating objective to all those engaged in this sphere of research.

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