CHEMICAL AND BIOCHEMICAL IMPLICATIONS OF HUMAN AND ANIMAL EXPOSURE TO TOXIC SUBSTANCES IN FOOD

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ABSTRACT

The complexities of the subject of food toxicants are surveyed in regard to their qualitative and quantitative aspects. Chemical and biochemical implications are reviewed, tracing the stages in the transit through the body of chemical entities in food.

The capacity of the intestinal flora to bring about chemical transformations of ingested compounds may lead to detoxication or serve to create new and potent toxicants. The role of the intestinal mucosa in relation to food toxins is surveyed from the standpoint of recent observations.

The impact of food toxins on the liver is the most striking and general aspect of their action. Nuclear and cytoplasmic events are delineated, in terms of their repercussions on the body economy. The chemical basis of events in other organs, resulting from exposure to food toxins, is illustrated by selected examples of effects on endocrine, reproductive, nervous and renal function. Reference is made to the potential of some food toxicants for mutagenesis, teratogenesis and carcinogenesis and consideration given to the biochemical mechanisms that may be involved.

Food allergy is briefly discussed in chemical terms and an assessment made of the immunological implications of the presence of additives and residues in food.

Finally, attention is drawn to the change in outlook that has occurred in the past twenty-five years and to the need for perspective in judging the implications of exposure to toxic substances in food.

INTRODUCTION

During the past quarter-century analytical chemistry has made unprecedented progress in its ability to isolate, identify and measure minute traces of materials in food. Over the same period toxicology has sought, not very successfully, to cope with the torrent of new knowledge and techniques flooding from the multitude of scientific disciplines whose contributions are all important to our own multidisciplinary science. Taking stock of the position at the moment, we are keenly aware of the increasing difficulties that we encounter in the interpretation of the phenomena that we observe. The purpose of this lecture is to discuss these difficulties frankly, as a

basis of consideration of the manner in which chemistry and biochemistry can contribute to the solution of at least some of our problems.

Faced with a wealth of fascinating and esoteric natural components of food, as well as a multitude of additives and residues, my choice has fallen on some of the commonest, even commonplace, aspects of food. They may appear to be less worthy of attention, but their implications are often more far-reaching. Also, since a limit must be drawn somewhere, no consideration will be given to the microbiology, virology and parasitology of food as sources of hazard to the consumer.

WHAT CONSTITUTES A TOXICANT?

The nature of 'toxicity'

What renders a food ingredient toxic? As a first approximation there is the traditional judgment: "wat nie dood maak nie, maak vet" (that which does not kill, nourishes). This criterion has no doubt served well as a guide to acute toxicity in gauging the acceptability of unfamiliar foods. Tradition and culture have determined ethnic dietary customs, with little or no heed to long-term effects. Today it is these subtle consequences that are our principal concern, and in most instances they remain as difficult to detect as ever.

Another problem is that of discriminating in clinical practice between nutritional effects—which may be caused by deficiency, imbalance or excess of some nutritive factor—and toxic effects, which may in some instances be due to that same nutritive factor. Consider, for example, water, our most essential nutrient and one to whose components there is lifelong exposure. An association now appears to be established between living in an area with soft, acid drinking water and sudden death linked with cardiovascular disease, including ischaemic heart disease, cerebrovascular disease and hypertension¹. After weighing various possible toxic factors, such as cadmium and lead, opinion has settled on low serum calcium and magnesium levels as the likely link with soft water. Hence the question may now be one of nutrition rather than toxicology; but the last word has not been said on the subject.

The problem of dose

Toxicology is concerned with biological effects characterized by distinct dose-response relationships. Both aspects—dose as well as response—may be difficult to interpret when dealing with food components. The dose ingested daily, particularly of a naturally-occurring toxicant in food, is subject to so much variation that usually only the most approximate upper limit can be set. Even this estimate may ignore excessive intakes by substantial sections of consumers with ethnic, regional or individual peculiarities in their food patterns.

No component of food, whether a natural ingredient, a food additive or a residue, can be considered safe solely on the basis of traditional use without apparent adverse effect, or because it has been allocated 'generally recognized as safe' (GRAS) status by expert opinion ten or more years ago. Hence misconceptions about 'natural' and 'synthetic' food components

must be cleared away. So vast is our area of ignorance about the safety of food itself that attention should not be centred exclusively on additives and residues. Much mortality and morbidity may stem from naturally-occurring materials in food. Where, for instance, is the line of demarcation between carcinogenic polycyclic aromatic hydrocarbons synthesized by edible plants, or deposited on them from the environment or introduced into food when it is smoked or charcoal-broiled? Or what is to be done about the great and increasing intake of caffeine in coffee, tea, caffeinated beverages and foods flavoured with kola nut extract, guarana and guarana gum? The pharmacological actions of caffeine are familiar to us all, and in recent years attention has been directed to immediate responses to caffeine such as catecholamine release² and intervention of methylated xanthines in the phosphodiesterase-cyclic 3',5'-AMP mechanism. Important long-term effects under study have been the possible consequence of elevation of blood lipids by caffeine on coronary artery disease³ and the hoary old question of mutagenesis by caffeine^{4, 5}.

The first consideration is the dose to which the individual is exposed, from whatever source. The second, and hardly less important, matter of concern is the presence of other substances in the diet, again from whatever source, that may modify the biological action. Here the mycotoxins, to which so much attention is rightfully devoted at this Symposium, play an important part. Many more potential hepatotoxins and hepatocarcinogens are known to be present in food. Undoubtedly there are others awaiting discovery. The point to stress, however, is that for the most part the dose-response relationships are unknown in animals, let alone in man. Until this information becomes available, we are groping in the dark. What also complicates the question of dose is the intervention of multiple factors in the pathophysiology of a single syndrome, as in the case of beer-drinkers' cardiomyopathy elicited by synergistic action of trace amounts of cobalt, with alcohol and a protein-poor diet⁶.

The significance of 'toxicological insignificance'

Orders of magnitude are the toxicologist's business. Superimposed upon the well-nigh countless naturally-occurring components of food are about 10,000 chemical additives, residues and migrant compounds (from packaging) that may be introduced or formed between the stages of production and consumption of food. Hence the need for orders of priority in evaluating the safety of all these compounds, based on the likelihood of hazard.

Conceptually, most of us accept that there exists some finite level—albeit exceeding small—below which no chemical in food is toxic. The definition of what this level may be has great practical importance to regulatory authorities, to industry and to the consumer. However, faced with the problem of setting a figure for 'toxicological insignificance' the W.H.O. Scientific Group on 'Procedures for Investigating Intentional and Unintentional Food Additives', could only conclude that further studies should be devoted to 'criteria to be used in distinguishing biological effects that are toxicologically significant from those that are not'⁷. Since then, a Food Protection Committee Task Force of the U.S. National Academy of Sciences—

National Research Council has expressed the view that additives (other than heavy metals and their compounds) used for at least five years at a level of 0.1 ppm of the total diet are 'toxicologically insignificant'. The statement is made that most of the chemicals "present naturally and unavoidably in food . . . are assumed to be toxicologically insignificant because: (1) they are present in foods at extremely low concentrations, (2) have been consumed by man for generations without apparent harm, and (3) are not related chemically to substances of known high toxicity". Based on these criteria, "there is a body of empirical knowledge deemed sufficient on which to base a judgment of the safety of virtually all of these substances at the levels found in food. . . . The criteria are equally valid when applied to evaluation of safety for use of synthetic substances"⁸.

There is another aspect of the problem, namely what constitutes a negligible pesticide residue in food? Originally this awkward issue was more or less successfully evaded by the myth of 'zero tolerance'. Nowadays finite residue tolerances have been set for most pesticides, on the assumption that such levels represent a 'negligible' hazard. Some of the uncertainties of this situation will emerge from the discussion below.

THE NATURE OF BIOLOGICAL RESPONSE

Toxicity implies an injurious effect, that is, harm, detriment, damage, involving an alteration of structure, function or response in some living system. It is difficult enough to apply this concept on a lifetime basis to a single chemical entity to which clear-cut, definable exposure may occur, for instance under industrial conditions. How much more uncertain are we when dealing with dietary exposures, where 'toxic' effects may derive from nutritional imbalance or from individual susceptibilities, either genetically-determined or related to age, sex or disease state; or where potential toxicants may not manifest themselves in the presence of protective nutrients in a well-balanced diet.

The best we can do experimentally is to create an arbitrary set of conditions of administration of a test compound which we consider to be as relevant as possible to the conditions of intended human or animal exposure. The fact that under these circumstances a compound has elicited an injurious effect means that the resistance of the living system concerned was inadequate or that its powers of adaptation have been exceeded. But how to distinguish an effect that is adaptive, or physiological, from one that is detrimental or pathological—there is the nub of the problem. Often adaptation merges imperceptibly into injury, or the adaptive change may be beneficial in one situation, yet detrimental in another. As we seek that mirage of the toxicologist and the regulatory official, the 'no adverse effect level', we involve ourselves again and again in arbitrary interpretations and conclusions, the reason being that we do not yet know enough about the phenomena with which we are dealing. The best that we can hope to achieve, then, is the assessment of reasonable men who are fully conversant with the present state of the art.

ADAPTIVE PHENOMENA

Hepatocellular adaptation

How does mankind survive and flourish, despite the vast number of naturally-occurring toxicants that we know are present in food? In part the answer lies in the capacity for biochemical adaptation, which resides in every organ of the body. Not the least of the adaptive systems are those in the small intestine, where, to cite but one example, ingestion of sucrose or fructose produces disaccharidase (sucrase) activity in pluripotential crypt epithelial cells as they divide and migrate up to the tip of the villus⁹.

From the standpoint of toxicity the liver is the main bastion of the body's defence mechanisms. Of great current interest are the microsomal metabolizing enzymes (processing enzymes) that render more polar the lipophilic foreign and endogenous molecules reaching the liver. The increase in activity of these enzymes that occurs after birth is undoubtedly an important protective mechanism. An increase can also be induced in the adult by drugs, polycyclic aromatic hydrocarbons and pesticides¹⁰, cedrol and cedrene from cedarwood¹¹, terpenoids and other non-nutrient components of food¹², certain other terpenes¹³, as well as coffee, alcohol, nicotine and probably others of man's delights and vices.

Strangely enough, very little attention has been paid to other food components that stimulate processing enzymes. Rancid food has been found to contain inducers; peroxidative products of cholesterol and other dietary steroids formed on storing food (presumably without added antioxidant) act as enzyme inducers¹⁴. Inhibitors of processing enzymes are also present in food; so far interest has centred mainly on methylenedioxyphenyl compounds, such as piperonyl derivatives, that serve as alternative substrates for the microsomal hydroxylation system¹⁵.

Although the action of processing enzymes is usually studied with foreign compounds, the ω -oxidation of fatty acids to the corresponding hydroxy acids and the oxidation of aliphatic hydrocarbons to alcohols are also catalyzed¹⁶. The most important endogenous substrates for the liver microsomal hydroxylases, however, are steroids: androgens, estrogens, progestational steroids and glucocorticoids¹⁰.

The implications of dietary stimulation or inhibition of such endocrine balance mechanisms require no emphasis. With each passing day the significance of processing enzyme activity grows wider. For example, stimulation of hepatic microsomes increases hepatocellular binding and deiodination of *L*-thyroxine (T_4) and *L*-triiodothyronine (T_3), as well as biliary excretion¹⁷. It would be useful to study the overall effects of such stimulation in liver by constituents of a diet containing goitrogens that simultaneously interfere with T_3 and T_4 synthesis in the thyroid¹⁸. The goitrogens themselves may be processing-enzyme stimulators, an aspect of particular importance in view of their demonstrated secretion into cow's milk in areas of endemic goitre¹⁹. Perhaps somewhere in this area lies the solution to one of the epidemiological enigmas of our time: the persistence and even increase in endemic goitre, despite decades of iodine prophylaxis^{20, 21, 22}.

Another aspect of the effects of dietary components on the thyroid may be cited as an example of the complexity of interacting causes. First consider

those instances of individual susceptibility to excess iodide. These constitute a failure of normal adaptation, since most subjects respond to a prolonged iodide load with reduction of thyroid uptake; a few, however, fail to compensate in this way and iodide goitre develops²³. Even among the majority whose defence mechanisms function adequately, the large quantities of iodide provided in various additives to continuous-mix process bread²⁴ raise the question of the risk of thyrotoxicosis²⁵. In the same context should be mentioned the hyperthyroid effect of *p,p'*- and *o,p'*-DDT in mammals^{26, 27} and birds²⁸.

The lesson to be learnt is that each homoeostatic mechanism of the body embodies several adaptive phenomena. Attention needs to be focussed on all the environmental influences—particularly those in the diet—that affect the function of each form of homoeostasis by modifying adaptive responses.

Issues for consideration

What factors determine the activities of processing enzymes and the enhancement of activity in response to dietary toxicants? Is there a practical limit to this form of adaptive response and, if so, what happens when the limit is exceeded? Finally, are the consequences of processing-enzyme stimulation invariably beneficial?

The activity of processing enzymes is lowered by starvation or the consumption of low-protein diet^{29, 30} or by parenchymal liver damage of sufficient degree. In this connection, it is interesting to note that the protection afforded by a protein-free diet against the lethal and hepatotoxic effects of dimethylnitrosamine is not reversed by administering phenobarbitone or DDT³¹. Considerable species and sex differences (in the rat) are found in the response to inducing agents but the presence of pesticide residues in animal diets often renders it difficult to achieve a basal level of activity. A striking demonstration of the advantage of a 5% casein diet to the rat is the protection against the toxicity of heptachlor, by preventing the formation of heptachlor epoxide³².

A systematic study has been carried out of the capacity of phenolic compounds to stimulate processing enzymes in rat liver³³. On following the time course of enzyme induction after a single oral dose and after 6–10 daily doses, some compounds stimulated at 24 hours after a single dose but no longer did so after 6–10 daily doses; other compounds displayed the opposite effect. Structure-activity relationships within this group of compounds were found to be determined very largely by the lipid-water partition coefficient π of Hansch and Fujita³⁴, as measured by a chromatographic procedure³⁵.

This approach makes it possible to predict the biological activity of members of a closely-related series of compounds, on the basis of observations on a few of them. It might be expected to prove useful in screening groups of non-nutrient components of food.

The attainment of a limit of adaptive response was demonstrated with 2,4,6-tri-*tert.*-butylphenol in the rat^{36, 37}. A constant low level of the compound was maintained in the liver, despite an increase in dosage from 0.5 mg/kg (stimulation of processing enzymes) to 10 mg/kg (increase in relative liver weight; also decreased hepatic glucose 6-phosphatase, a sign of incipient

liver damage), up to 50 mg/kg. Beyond this dose, histopathological evidence of liver damage was manifest and at 75 mg/kg there was a steep increase in the liver concentration of the test compound. These results, together with related findings in the case of butylated hydroxytoluene³⁸ suggest that initial lack of metabolising capacity on the part of liver exposed to a compound leads to storage of the substance in adipose tissue, liver and to a small extent elsewhere in the body. Then, as processing enzymes are induced, the level in fat falls to a plateau representing an equilibrium between rate of intake and capacity for metabolism and disposal of the material. If the rate of intake continues to be excessive, liver damage may ensue as the level of the compound builds up in the liver and elsewhere.

Continued administration of dieldrin to rats (0.1–5 mg/kg daily) gave rise to a sequence similar to that described above with increasing dosage of 2,4,6-tri-*tert.*-butylphenol; unfortunately, however, tissue levels of dieldrin and related compounds were not reported^{39, 40}. Three stages of response were designated. In the stage of induction there was an increase in liver weight and microsomal protein, with proliferation of smooth endoplasmic reticulum, stimulation of processing enzymes and increase in cytochrome P-450. By 14 days the second stage, or 'steady state' had been reached; enzyme activity remained high and the animals tolerated doses of dieldrin that would have proved fatal at the start of the experiment. When the third stage, decompensation, developed at 52 days all changes were still present except that now processing-enzyme activity had declined, so that the hypertrophic endoplasmic reticulum was hypoactive. At the same time, biochemical and morphological alterations in the hepatic mitochondria heralded the onset of liver damage.

The work of Street^{41, 42} suggested the possibility that stimulation of processing enzymes by any environmental agent would tend to reduce the body burden of stored pesticides. However, a dissociation between liver and adipose tissue storage emerged from the work of Cueto and Hayes⁴³, who showed that pretreatment with phenobarbitone of rats given dieldrin results in a decreased storage of dieldrin in fat but has little effect on the level in liver. The authors considered that the rate of liver metabolism of dieldrin was not a limiting factor in liver storage, retention here being more dependent upon dosage and lipid content than upon rate of biotransformation.

Deichmann *et al.*⁴⁴ have taken the matter further, demonstrating that, in beagle dogs ingesting DDT and aldrin (and this holds presumably for dieldrin too), the retention of *p*, *p'*-DDT and DDE in fat and blood was up to 4 times greater than in animals fed DDT alone. Liver levels, however, were the same in both groups. The levels of dieldrin in fat, liver and blood were essentially unaffected by simultaneous administration of DDT, even though the dose of DDT given (12 mg/kg daily for 10 months, with follow-up for a further period of 12 months) should have induced a powerful processing-enzyme response.

The examples cited serve to illustrate the complexity of the interactions between doses of processing-enzyme stimulators and processing-enzyme substrates, and the levels of these compounds and their metabolites in adipose tissue, blood and liver.

The observations bring us to the final point: is liver adaptation always a beneficial change? The protective consequences of the process have been stressed. But the other side of the coin appears when the processing enzymes form a metabolite that is far more toxic than the parent compound, as in the case of carbon tetrachloride or diethylnitrosamine. We do not know how often such harmful potentialities are realized in practice. In acute experiments, combination of pesticides such as parathion (whose conversion to paraoxon introduces an altogether higher toxicity) with others that can act as processing-enzyme stimulators did not elicit any very striking potentiating effect⁴⁵, perhaps because only acute toxicity was studied in pairs of compounds administered in close succession. On the other hand, methylenedioxyphenyl inhibitors of processing enzymes retard the metabolic inactivation of carcinogenic aromatic hydrocarbons⁴⁶. To try to assess accurately the balance of benefit and harm from processing-enzyme stimulation, in the present state of knowledge, is akin to expecting a blindfold juggler to maintain in the air simultaneously an assortment of objects whose number is unknown and whose various shapes and sizes he has never seen nor felt.

The activity of processing enzymes in extrahepatic tissues is an aspect to which attention has recently been drawn⁴⁷, stressing particularly the effects in the kidney. Wattenberg *et al.*⁴⁸ have long emphasized the stimulation of these enzymes in the gastro-intestinal tract, lung and other sites. The body's response at portals of entry of toxicants is obviously important.

The placenta is among the least explored areas of processing-enzyme activity, despite the ready availability of human tissue. A burst of research activity may be anticipated in this area in view of the reciprocal relationships in steroid synthesis and biotransformation existing in the fetoplacental unit. These mechanisms are likely to be influenced by drugs, smoking and other stimulants of processing enzymes in the placenta^{49, 50}.

I have attempted to point out the problems of the toxicologist faced with an increasing proportion of more and more refined observations, most of which do not involve injury. A decision has to be made on the significance of adaptive changes seen in animals in the context of likely hazard to man.

CHEMICAL AND BIOCHEMICAL IMPLICATIONS

Some lessons from the past

Clinical observation and epidemiological study are blunt instruments with which to attempt to detect adverse effects brought about by toxic components of the diet. Only when a dramatic outbreak of poisoning occurs, as in the case of the 'Epping jaundice'⁵¹, is attention drawn to the possibility that a contaminant in food was responsible. The nature of most long-term toxic effects arising from food components is likely to be such as to fail to arouse suspicion and to be confused, according to the severity of the clinical condition, with psychosomatic causes or incidental 'idiopathic' disease processes. How vast an area of ignorance is covered by the term 'natural causes'!

In this situation, much can be learnt from past experience. The presence of methionine sulfoximine (MSI) in flour treated with nitrogen trichloride (so-called 'agenized' flour) provides a clear example of a toxic agent

consumed by millions in many countries over a quarter of a century before the use of the process was discontinued. MSI is a potent neurotoxin, not only in dogs, cats and other species, but also in man^{52, 53}. MSI binds to nerve endings, where its presence is associated with destruction of synaptic vesicles⁵⁴. Biochemically, the compound is a powerful irreversible inhibitor of cerebral glutamine synthetase and probably acts at the level of the structural compartment engaged in synaptic transmission. Ronzio, Rowe and Meister⁵⁵ have shown that the inhibited enzyme, when isolated, contains tightly-bound MSI, phosphorylated on the imino group. Other effects of MSI on cells of the nervous system have been reported⁵⁶.

Thus the situation is as follows: the nature of the toxicant is known; so is the level that was present in flour; so is the dose-response relationship of toxic action, at least in animals; so is the likely mechanism by which the effect is brought about. Yet we have no evidence that the presence of this highly potent neurotoxin in food harmed any human consumer. One explanation attributes the apparent human immunity to the fact that when part of the methionine in flour was converted to MSI, the remainder served to protect the consumer⁵². Ronzio *et al.*⁵⁵ found that a mixture of glutamate and ammonia prevented enzyme inhibition by MSI.

It may have been true that the majority of consumers suffered no harm from MSI; but no assurance is forthcoming regarding epileptics or other particularly-susceptible groups within the population. The lesson is clear. What is basic to safety evaluation of any compound in food is knowledge of chemical identity; knowledge of interactions with food components and changes undergone within the body; knowledge of dose-response relationships in animals; and knowledge of the mechanism of biological effects observed. Finally all this information is needed to validate studies in man, when man is the species exposed to the potential food toxicant.

A further lesson to be learnt from the 'Agen' episode concerns the importance of trying to achieve a clear understanding of the nature and proportions of various toxicants responsible for biological effects. In other words, is it sufficient to accept whole foods as safe because, when fed as a substantial part of the diet of animals they produce no apparent adverse effect? As with agenzized flour, experience teaches that this approach may be fraught with fallacies and dangers. Many foods that are wholesome for man are toxic to some other species, as for instance chicken and green beans given to dogs or beans (*Phaseolus vulgaris*) to rats, causing tissue damage whose pathogenesis we are unable to account for⁵⁷. Dalderup and Visser⁵⁸ greatly shortened the lifespan of rats, produced fatty livers and accentuated glomerulonephritis by rearing them on a human diet. Replacement of 15 calories per cent of starch by sucrose made matters considerably worse. The question of testing whole foods becomes increasingly important in view of the development of substitute foods, synthetic foods or new forms of food processing. The solution attempted for the problem of irradiated foods has proved a colossal and costly failure. Feeding irradiated fruit salad to dogs has not established safety, nor has the whole vast exercise provided an advance in fundamental knowledge to serve as a springboard for further work. Complex though these problems undoubtedly are, short-cuts will not solve them.

Besides feeding whole foods to animals, an alternative suggestion is the preparation and testing of extracts using solvents considered appropriate to the particular material being studied. Even avoiding the formation of new toxicants by interaction of the solvent with food constituents, the use of extracts is a tedious, expensive and unrewarding approach. In the long run there is no alternative to the painstaking and often laborious isolation, identification and quantitative measurement of individual compounds in food, followed by detailed study of their biological properties and mechanism of action. Until all this can be accomplished, however, there is obvious merit in screening food extracts for the presence of known categories of toxicants, such as nitrosamines.

Interactions in food and the effects of processing

Man is the only species that cooks its food and this fact has led Roe⁵⁹ to speculate whether any connection can be traced with the high and undiminishing incidence of human colonic cancer. As time goes on, an increasing proportion of dog and cat populations also live on processed foods. The reactions that occur when food is cooked have not yet yielded up all their secrets. To take one of the most commonplace, the Maillard reaction ('browning' involving interaction of carbohydrate with amino acids), Adrian⁶⁰ has studied the particular susceptibility of lysine and has shown how frying of a milk-egg mixture converts proteins in which methionine is the limiting amino acid into ones in which lysine is limiting.

Processing of foods at high temperatures produces the 'roasted-nutty' character that is so desirable in peanuts, potato crisps, coffee and cocoa. Among the volatile aroma compounds are pyrazine and its alkylated derivatives, formed by condensation of 2- and 3-carbon fragments of sugars with amino-acid nitrogen. Neither ammonia nor the ammonium ion is the common intermediate through which the nitrogen enters into pyrazine⁶¹. Nevertheless, the question of ammonia treatment of carbohydrate sources has some interesting implications. Ammoniated invert molasses and related cheap carbohydrates were investigated as possible protein substitutes for incorporation into animal feedstuffs. Despite a promising start, the products were found to be toxic, producing 'violent hysteria' in cattle and convulsions in guinea-pigs⁶². Wiggins⁶³ had shown that ammoniated molasses contained 20% of various pyrazines as well as 10% of imidazoles, of which the only one isolated and characterized was 4(5)methylimidazole (MI).

Recently Nishie *et al.*⁶⁴ have demonstrated that the toxic manifestations of ammoniated molasses can be reproduced in rabbits, mice and day-old chicks by administering MI. In the mouse, MI proved one-fourth as potent a convulsant as pentylenetetrazole, while related imidazoles had similar but lesser activity.

What lends particular interest to this observation is the fact that an important process in the manufacture of caramel, by far the most widely-used food colouring, involves heating glucose or other carbohydrate with aqueous ammonia under pressure. At least 8 imidazoles have been identified in this type of caramel, the major one present being MI⁶⁵. There is an urgent need for further investigation of caramels, as pointed out by Golberg²⁰.

Repeated heating of edible fats is one aspect of processing that has

attracted much attention. Moderate heating may be beneficial to fats by destroying toxic ingredients. Among the toxic components of certain fats are a hexachlorodibenzo-*p*-dioxin and hexachlorohexahydrophenanthrenes. The latter toxicants do not produce a state analogous to 'chick oedema' when fed to rats; instead they induce subtle ultrastructural changes in the liver⁶⁶. A great deal of emphasis has been placed on potential carcinogenicity of heated fats. In the latest study to be published, O'Gara *et al.*⁶⁷ conclude that differences between the stomach of man and those of rodent species are too great to permit meaningful conclusions to be drawn. Ending on a rather limp note, the authors merely advise against excessive re-use of cooking fats. In a study simulating practical conditions of fat frying, Nolen *et al.*⁶⁸ showed that such fats displayed levels of toxicity so low as to have no dietary significance for practical purposes. Probably the only aspect for serious consideration is the adipose tissue storage of epoxides (and perhaps other autoxidation products) present in vegetable oils heated in air and fed to rats⁶⁹. More work should be carried out on the kinetics and implications of such tissue storage, particularly in man, who has so much else stored in his body fat.

The presence of nitrites and nitrates in food and water is a source of increasing concern. The amount of nitrate present is tending to increase as a result of wider application in fertilizers, with subsequent leakage into deep wells (rather than surface water). The earlier problems of sensitivity of young children and risk of methaemoglobinemia have been added to by the problems of carcinogenic nitrosamines and possible associated teratogenicity and mutagenicity, including the risk of mutagenicity of nitrite itself. Just how great the concern ought to be remains uncertain because so much of the information on nitrosamines in food remains unpublished. Nitrites react with amines and related substances in food, particularly when the food is processed under conditions of temperature, pH and time conducive to the formation of nitroso derivatives. Nitrosamines can also be formed under the acid conditions prevailing in the human stomach⁷⁰ but to a lesser degree in the rat stomach⁷¹.

Here is a typical situation where testing whole foods by feeding them to animals is a virtually useless exercise. The individual nitrosamines and related compounds must be identified, measured quantitatively, synthesized and the dose-response relationships of their biological actions established. Only when the whole composite picture is assembled can any fully reliable assessment of hazard be made and even then evidence in man will not be available. Nevertheless, in view of the carcinogenic potency of so many nitrosamines, particularly their capacity for transplacental tumour induction in the unborn child^{72, 73} some immediate action seems necessary. This should be aimed at reducing the intake of nitrites and nitrates, from whatever dietary source, to a minimum, and at replacing nitrite and nitrite-nitrate by other preservatives, as far as possible. Foods known or suspected to contain nitrosamines should be listed and pregnant mothers advised to avoid them.

Absorption, malabsorption, persorption and sensitization

Intolerance to food is a common biological effect. From its original vague connotations and association with 'digestibility', the concept of intolerance,

particularly to mono- and disaccharides as well as to carbohydrate sources that give rise to them, has developed into a series of clearcut clinical entities in both children and adults. Intolerance involves deficiencies of intestinal mucosal enzymes, morphological alterations of the intestinal epithelium and changes in the flora, chemical composition and pH of the intestinal contents. Exciting developments are taking place in the study of racially-determined intolerance to lactose, a defect now thought to reflect a negative adaptation to low levels of exposure.

The vast topic of malabsorption syndromes is one to which it is impossible to do justice here. The development of gluten sensitivity, primary and secondary pathological states of the intestine, alterations brought about by surgery all have effects that may justifiably be classed as toxic responses to food, but their amelioration is not our concern here.

Recognition of the 'Chinese restaurant syndrome', now generally attributed to unusual individual susceptibility to monosodium glutamate (MSG) is an example of the unexpected turn of events that can occur in the use of a common food constituent and flavour enhancer, categorised as GRAS in the U.S.A. According to Schaumburg *et al.*⁷⁴ as little as 2 g of MSG given in dilute solution orally to fasting subjects sufficed to elicit minimal symptoms; by the intravenous route the threshold range was 25–125 mg. The condition is thought to result from very rapid absorption of MSG, but does not involve elevated blood levels of glutamate. The mechanism by which subsequent events develop is under investigation in our Institute, and the rapid and apparently complete recovery of affected subjects does facilitate research into a human condition that has so far not been reliably reproduced in animals.

The situation with regard to modified starches is hardly less surprising. These important thickeners may constitute a substantial proportion of certain frozen foods. This development began with mild treatments involving heat, acid, alkali, enzymes or hypochlorite. It has progressed to increasingly drastic oxidations, substitutions and cross-linking. The resulting starches continue to be introduced and accepted as minor modifications because the products of digestion in the intestine are substantially the same as those derived from the parent starch. Nevertheless there is formed from each modified starch a series of new materials whose safety to man cannot be evaluated without the most thorough tests in animals and man.

Apart from the very real possibilities of intolerance of such digestion products, and consequent upset of the balance of intestinal flora and activity, other serious dangers exist. In order to understand these, reference must be made to the rediscovery in recent years of the phenomenon of 'persorption'. By this mechanism solid particles of starch and other food components may be "kneaded" between the cells of the intestinal epithelium and enter the body. Subsequently the presence of these particles may be demonstrated in blood, urine, other body fluids and in various tissues⁷⁵. Where a modified starch is present in uncooked form, as in cold-setting puddings and even in many cooked foods, we must assume that some of the starch will be absorbed into the body in the form of solid particles.

Whether such particles of modified starch constitute a hazard is not known. The possibility of sensitization needs to be taken into account.

Lietze⁷⁶ has drawn attention to the role of particulate insoluble carbohydrates—for instance wheat and corn starch—in food allergy. Whether the modified starches are more antigenic is unknown. Whether the substituted cross-linked members of the group, or their residual low molecular weight products of intestinal digestion, can form haptens is a matter of conjecture. But it is at least conceivable that some of them might have the capacity to acylate the free amino groups of proteins, to link to sulphhydryl groups or generally to react in the manner postulated for the highly-sensitizing small degradation products of penicillin⁷⁷.

While on the subject of sensitization, mention should be made of allergy to food and to food additives. Food allergy is commonplace when it relates to fish or strawberries, but its more subtle forms may prove surprising, as in beet sensitivity to what is ostensibly 100% pure beet sugar and to monosodium glutamate derived from beet molasses⁷⁸. Allergy to particular foods is often readily recognised and the responsible items of diet avoided. In the case of food additives, preventive measures are much more difficult, both because of the problem of attributing sensitivity to its correct cause, and the virtual impossibility of avoiding all foods and other sources of the offending agent. For instance, food, drug and cosmetics colours cause allergic reactions. So do some flavourings, either when used in relatively high concentrations or when they happen to supplement natural components of food, such as salicylates, or drugs containing aspirin or other salicylates. The importance of sensitivity to benzyl salicylate has been stressed by Rothenborg and Hjorth⁷⁹.

In many areas of hypersensitivity, the relationship to dosage applies, probably accounting for the rarity of any sensitization to pesticide residues in food⁸⁰. In thinking of minute levels of exposure, however, the possibility of cross-reaction must not be overlooked. One example is that of the parabens, preservatives used in cosmetics, pharmaceuticals and, in some countries, in food and beverages. Insidious and often unrecognized paraben contact dermatitis⁸¹ may cross-react with 'para' group sensitization to hair dyes, drugs and other structurally-related chemicals. In a similar manner, there is the rapidly-growing list of photosensitizing compounds—food components, drugs, and the host of agents used in cosmetics and toiletries. Reports of photosensitization to food additives are rare and often poorly documented. In relation to the volume of use of saccharin and cyclamate, for example, the incidence of photo reactions is negligible^{82, 83, 84}, and may reflect cross-reaction to sensitization with structurally-related and much more powerful photosensitizers such as sulphonamides, thiazide diuretics or sulphones⁸⁵.

Limitations of space do not permit speculation on the wider implications of absorption-persorption-sensitization. To mention but one issue, what of the fact that a proportion of apparently normal, healthy people have antibodies to milk protein circulating in their blood, sometimes to high titres? Suggested associations with the problem of sudden death in infancy⁸⁶, with ulcerative colitis⁸⁷ and with coronary heart disease⁸⁸ leave the question open.

The intestinal flora

Preoccupation with the 'putrid poisons' manufactured in the human intestinal tract dates back for many centuries. Concern with the role of such

endogenous poisons in disease became part of orthodox medical thought late in the Victorian era, when bases like choline, putrescine and cadaverine were isolated and the toxic action of 'ptomaines' postulated. Today we are aware of numerous essential functions performed by the intestinal micro-organisms, for instance in bile acid metabolism and hence in the absorption of fat. Toxicologically, too, there are important implications: we have come to realize that those 'putrid poisons' are not a myth after all!

Chemical transformations brought about by the intestinal flora present the body with problems whose existence would not be suspected from the nature of the compounds ingested. The versatility of the intestinal milieu as a reaction vessel is illustrated by the reductive fission of azo linkages in many water-soluble colourings. In most instances sulphanilic acid or other relatively innocuous products result. With Brown FK, however, highly toxic amines are formed. In part, they condense to form phenazines, one of which—1,4,7-triaminophenazine—has been identified and synthesized. The capacity of Brown FK to cause damage to skeletal muscle and myocardium is almost certainly attributable to the action of the transformation products formed in the gut⁸⁹. They are probably also responsible for ceroid pigment formation in liver, skeletal muscle, heart, kidney and thyroid when Brown FK is incorporated in the diet of rats or miniature pigs.

Equally potentially harmful is the transformation in the intestine of *nordihydroguaiaretic acid* to the corresponding *o*-quinone, which is absorbed, then excreted in the urine and appears to be the agent responsible for cystic reticuloendotheliosis of the paracoeal lymph nodes and vacuolation of the renal tubular epithelium⁹⁰.

These two examples illustrate an important principle in toxicology. In the case of Brown FK, a dietary level of 0.1% produces no adverse effect in rats when fed for 150 days. In view of the limited use of Brown FK for colouring kippers, involving an average daily consumption of 0.5–1.0 mg/day by a 70 kg adult, there appears to be an adequate safety margin. With *nordihydroguaiaretic acid*, however, neither no-effect levels nor accurate human intake data is available, so that safe use in the human diet cannot be predicted.

A current problem of some importance concerns the conversion of cyclamate to cyclohexylamine in man, and to a lesser degree in other species⁹¹. A search for possible sites at which the action of a hitherto-unrecognized sulphamidase might be manifested has shown that in all probability intestinal anaerobic microorganisms are responsible. *Clostridium perfringens* is active in this way, and may well explain the great fluctuations in excretion of cyclohexylamine by one and the same human subject on successive days, despite constant intake of cyclamate. Even more intriguing is the excretion of N-hydroxycyclohexylamine, cyclohexanol and cyclohexanone in human urine⁹².

Recent investigations on cyclamates have had repercussions on the specifications of these sweetening agents, on the study of their breakdown products in food and in the gut and on the question of cyclamate metabolism and possible toxicity. In view of the widespread and increasing use of these agents closer attention needs to be paid to all these aspects. When research on cyclamate was intensified five years ago, softening of stools and diarrhoea

produced by high intakes appeared to be the only adverse effect. Now the central issue is the possibility of genetic damage brought about by cyclohexylamine or other compounds derived from cyclamate.

Rothe *et al.*⁹³ showed that, even in the first hour after DDT was administered orally to rats, much of it was absorbed as DDE. Only recently has attention been given to the degradation of DDT by intestinal micro-organisms in the rat⁹⁴; the activity of the human flora in this respect is unknown, but it is possible that their action accounts for a proportion of the DDE in the human body. Errors may be perpetrated through failure to take account of the role of gut bacteria; for example, in the case of aromatisation of quinic acid, the species differences found to exist between Old-World monkeys and New-World monkeys now appear to be due, at least in part, to difference in activity of gut bacteria⁹⁵. This observation emphasizes the problems that arise in attempting to study in animals, even non-human primates, the significance of toxic products formed in the human intestine.

Intolerance to certain foodstuffs, notably cheese, is displayed by patients being treated for tuberculosis or depression with drugs that inhibit monoamine oxidase⁹⁶. These incidents have recalled attention to the presence of pharmacologically-active amines, particularly tyramine, in many foodstuffs and to the production of such amines by gut bacteria. The problem probably extends far wider than this, for dietary tyramine is now thought to be involved in the pathogenesis of at least one type of migraine. Tryptamine is the most potent physiological cerebral excitant amine. Failure of the intestinal (and hepatic?) inactivation mechanism to function adequately or reduction of the activity of this mechanism by a high saturated fat diet⁹⁷ enables tyramine to reach the circulation and liberate vasoactive amines and other compounds from their storage sites, precipitating migrainous headache in susceptible subjects. The long-suspected connection between food toxicants and migraine thus begins to take shape as a definite pathogenic mechanism. Now is the time to apply modern techniques to the study of these aspects in food, in the gut and in the individual.

OTHER BIOLOGICAL EFFECTS

Acute actions

The presence of toxicants in human or animal food has been most readily apparent to man through acute effects, among the most dramatic of which are those brought about by seafood toxins. The great and increasing dependence of millions of people on the sea as a source of food demands more extensive study of this vast area of toxic components in food. Present plans for utilizing marine organisms as sources of protein concentrate are fraught with danger unless the necessary research is carried out as a basis for adequate implementation of measures of control.

Apart from episodes of acute poisoning by high levels of toxin or very powerful agents, most forms of intoxication involve prolonged intake of low levels of toxicants without overt signs of toxicity. Control here is very difficult. By and large it is the effects on domestic or farm animals, or on laboratory animals, rather than manifestations of human illness, that have revealed the existence of hazards. A typical example is the presence of potentially hepatotoxic agents in the diet. They are numerous and include coumarin,

safrole, ethanol and its aliphatic alcohol congeners in beverages⁹⁸—to mention only a few. The application of specific tests for each form of damage²⁰, study of dose-response relationships and accurate measurement of levels in food constitute the appropriate sequence of measures to be taken for scientific control.

The order of priority for such control is not, however, as great as in the case of some long-term effects, to which attention will now be drawn.

Carcinogenesis

The suggestion is increasingly heard that as much as 80–90% of human and animal cancer has environmental causes. Among these causes, food-borne carcinogens play a leading aetiological role. Suspect in this context are the elevated incidence of stomach cancer in Iceland, Japan and Korea; of oesophageal cancer in Puerto Rico, Brittany (associated with consumption of Calvados), Iran and the Transkei; and of liver cancer in parts of Africa and among the Chinese in the Philippines and Indonesia. No direct association with a particular carcinogen has yet been established in these instances, although strong candidates exist.

Surveying the field of food-borne carcinogens, pride of place must be given to nitrosamines and related compounds. Many members of this group are not only highly potent but also multipotential in their ability to induce tumours in a variety of tissues. Included among these are the tissues of the foetus, through the transplacental passage of nitrosamines given even in a single dose in late pregnancy to experimental animals (see above). The formation of nitrosamines in food was referred to above. Mycotoxins, including aflatoxins and sterigmatocystin, are also a source of concern. Much has been made of plant alkaloids, such as those of the pyrrolizidine group, that may occur in plants used in herbal remedies or 'bush teas'. The ubiquity of the polycyclic aromatic hydrocarbons in food, drinking water and the atmosphere is well known and needs no further emphasis.

In dwelling on the importance of carcinogens in food, one must not lose sight of two other aspects of the problem of human and animal carcinogenesis. The first concerns the old idea, often thought to be discredited, of formation of carcinogens within the body, derived from precursors in the diet. The observation that Refsum's syndrome stems from a genetically-determined disorder in the metabolism of phytol has drawn attention to the isoprenoid fatty acids. Phytanic acid is not only formed in the bovine but is the major branched-chain fatty acid in human milk⁹⁹. Pristane is the corresponding C₁₉ hydrocarbon and, with other saturated branched-chain hydrocarbons, is found in the unsaponifiable lipid fractions of human tissues. Pristane is a carcinogen producing plasma-cell tumours in mice¹⁰⁰. Here is one example of many that may be cited to underline the possibility of endogenous formation of carcinogens.

The second aspect of the problem is the reality, as yet relatively unexplored, of cocarcinogenesis, syncarcinogenesis and anticarcinogenesis. The available evidence cannot be reviewed in full here. Suffice it to mention the work of Roe and his colleagues^{101, 102, 103} on the tumour-promoting activity of citrus oils applied to skin pretreated with carcinogen, the suggestion of a carcinogenic action of oil of sweet orange on the urethra and the

promoting action of *D*-limonene, possibly mediated by oxidation in air to a hydroperoxide^{103a}. To add insult to injury, strongly-brewed tea and its phenolic fraction have been implicated as a cocarcinogen¹⁰⁴.

Synergistic effects between enzyme inhibitors and carcinogens as well as non-carcinogenic compounds as exemplified by the methylenedioxyphenyl group of substances present in food or used as pesticide synergists¹⁵. Heated vegetable oils have been studied in relation to carcinogenesis but the most striking demonstration of a dietary contribution of this sort to cancer has been that of Lee *et al.*¹⁰⁵ in using combinations of aflatoxin B₁ and cyclopropenoid fatty acids in the diet of rainbow trout and, more recently, of rats. In trout the cyclopropenoid acids increased hepatotoxicity and the formation of hepatomas even at 0.4 ppb of aflatoxin. Incidentally, the earlier reports of detrimental effects of cyclopropenoid fatty acids in avian species have now been supplemented by demonstration of adverse reproductive changes in the rat¹⁰⁶.

Insufficient attention has been directed to the possibilities of dietary and other environmental anticarcinogens. These include aromatic polycyclic hydrocarbons, sulphhydryl-binding compounds, adrenal inhibitors such as *o*, *p*'-DDD and dietary constituents like vitamin A, linolenic acid, vitamin E, and riboflavin.

In considering the situation with regard to human and animal cancer, one obvious difficulty lies in establishing any environmental carcinogen as the definite aetiological agent responsible for human disease. This problem is not a new one. The endeavours of the epidemiologists to relate smoking to lung cancer, emphysema and cardiovascular disease are an illustration of the inherent difficulties. One might point also to the fruitless efforts to establish, by retrospective or prospective studies, whether the widely-used drug isoniazid, a carcinogen in animals, is or is not a carcinogen to man. Such are the weaknesses of Human Biology, where we seek in vain for refinement of tests and neat numerical expression of analytical results. In the interests of public health, action must be taken on the basis of strong suspicion, without waiting for absolute proof. Measures taken to limit the aflatoxins present in food are a case in point. Where the presence of a characteristic group of carcinogens, such as *N*-nitrosamines, can be tested for, the results are of great value. Thus the discovery by Du Plessis *et al.*¹⁰⁷ of diethylnitrosamine in a Transkeian food component and the report of diethylnitrosamine in Malawi gin¹⁰⁸ are noteworthy observations.

Where such short cuts to the detection of carcinogenic potential do not exist, the old road of isolation, identification and quantification is still long and arduous, despite the availability of modern analytical tools. So much hangs on the reliability of the biological assay for carcinogenicity that some frank words on this score are not inappropriate. While there is rarely any difficulty in demonstrating the carcinogenicity of highly potent compounds, serious problems arise with weaker carcinogens or with departures from the orthodox techniques of skin-painting or oral administration. Thus the use of the subcutaneous route for testing carcinogenicity in rats and mice has perpetrated serious errors, most of which have not yet been rectified^{20, 109, 110}. Sorbic acid is the latest additive to suffer in this way¹¹¹. Similarly, failure to understand the relationship between formation of bladder stones and the

development of bladder tumours in rats and mice¹¹² led to the unjustified condemnation of food additives as carcinogens. We still do not know whether DDT, dieldrin, aldrin and maleic hydrazide are or are not carcinogenic to animals. The recent mammoth study, commissioned by the National Cancer Institute, involving 130 compounds, including 104 pesticides, administered to 20,000 newborn mice, has implicated *p,p'*-DDT and 10 other compounds producing an elevated tumour incidence¹¹³. In all probability these results cloud the issue rather than clarify it.

Effects of reproduction, including teratogenesis

The capacity to interfere with the normal reproductive process of animals has been found to reside in many of the components of, or additives to, food. Embryotoxic and embryopathic effects have been induced with salicylates, including methyl salicylate¹¹⁴, caffeine and theophylline¹¹⁵, and a variety of pesticides, including methylparathion, parathion, diazinon and carbaryl¹¹⁰.

It is difficult to assess the relevance to man of effects brought about by relatively large doses of compounds given to chick and duck embryos, rats, mice, hamsters, rabbits and dogs. Success in current studies on non-human primates will greatly clarify these issues. What has to be borne in mind is the difficulty of interpreting in terms of human hazard either a positive or a negative result obtained in animals. To elicit a teratogenic effect, a critically-correct dose must be given to a genetically-susceptible species and strain of animal at the appropriate stage of gestation, when the embryo has attained the point of organogenesis that enables that particular chemical to exercise a recognizable influence. With a sufficient effort all this can be accomplished, but it is all too easy to achieve a negative result that has doubtful validity. Even with thalidomide we have not as yet arrived at an understanding of the mechanism of action. Obviously, the extrapolation of animal results to man is fraught with uncertainty.

Production of genetic damage

In the area of mutagenesis many food components, such as caffeine, coumarin, adenine and ethanol are active chromosome breakers or have other effects on chromosomes. Nitrous acid and compounds like nitrosamines that can act as alkylating agents react with components of nucleic acids. Heavy-metal chelators, by complexing the DNA-bound metals, induce chromosomal aberrations¹¹⁶. Formaldehyde, maleic hydrazide, xanthene food colourings are among other compounds shown to be mutagenic in various organisms.

As indicators of potential hazard to man, little confidence can be placed in many of the currently-available tests of genetic damage. The more sensitive the test, the further phylogenetically removed from man the test organism is likely to be. Primitive forms of life that present virtually naked DNA to attack by a chemical yield information of little relevance to higher organisms equipped with elaborate mechanisms for detoxication or adaptation, as well as possessing capacity to repair damaged DNA. At present the only reliable screening procedure for mutagenesis is the dominant lethal test in mice, carried out according to Bateman¹¹⁷. Unless this test is used, one arrives at a situation exemplified by the case of Captan. This widely-used agricultural

fungicide has been reported to prevent mitosis and break chromosomes in cultured mammalian cells, to be mutagenic in bacteria, to increase the incidence of chromosome breaks in both meiotic and germinal cells in rats and to be highly teratogenic to the chick embryo^{117, 118}. What all these findings imply in terms of hazard from Captan residues in food is still an open question. The same may be said of findings on maleic hydrazide, which breaks chromosomes in *Vicia faba*, is mutagenic to *Drosophila* and bacteria, and greatly increases the yield of hepatomas after subcutaneous injection into newborn mice¹¹⁹.

Far from raising alarm over the hazards of genetic effects that may only become apparent in future generations, I feel that more careful work is needed in man with a few compounds to which he is already exposed. Cyclamate is a case in point, to which reference has been made. Only when direct correlations become available between the animal data and experience in man can we begin to assess realistically the hazards of other individual compounds. Only at a later stage shall we have to concern ourselves with possible synergisms in teratogenesis and mutagenesis, serious though these problems may be. Stokinger¹²⁰ has stated that combinations of teratogens, or the potentiated interaction of teratogens with altered physiological states, probably account for three-fourths of human congenital abnormalities. Whether or not this is the case, attempts at regulation of teratogens or mutagens that advance far ahead of existing scientific knowledge would create serious problems with no compensating security to the public.

ACTION AND REACTION

There are other reasons besides journeys to the moon that make this an exciting era for the scientist. In the field of nutritional toxicology also, Spring is in the air. Not very long ago interest centred almost exclusively on dietary deficiencies, the problems of vitamin balance¹²¹ and other states of frank and latent malnutrition. As far as adverse effects of food were concerned, the easy victories of the past had become less and less frequent as animal diseases became rarer clues to human hazards, as the bases of human degenerative diseases defied efforts to identify them and as the epidemiologists encountered increasing difficulty in connecting cause and effect.

The discovery of nitrosamines, the rebirth of purposeful interest in mycotoxins, the reawakening to hazards from the human bowel—these are only a few of the developments that have transformed the situation. A multitude of problems demand contributions of the chemist and the biochemist towards their solution. In the meantime, what can be done to control the hazards from food? Control must be based on knowledge:

“In full fair tide, let information flow.

That evil is half-cured whose cause we know.”

Control must discriminate between hazards, in relation to the health and welfare of man. Where man's survival is directly jeopardised, drastic action is justified. Where lesser hazards are involved, measures must be taken to prevent impairment of man's capacity for full enjoyment of health and efficient function. The most difficult problem area is that in which subtle

biochemical, physiological or psychological alterations may result from prolonged exposure to low levels of toxicants. The emotive phrase 'biochemical cripples' has been applied to such states.

The time is not far off when the refinement of analytical methods will permit a catalogue to be drawn up of all trace residues present in human tissues and especially in body fat. Wootton¹²² carried out a similar, much simpler exercise with renal dialysis fluid and discovered an amazing collection of odds and ends in human blood. By the time man lives out his lifespan, he will be found to have accumulated in his tissues a clutter of endogenous metabolites and exogenous debris—pesticide residues, other polychlorinated compounds, aliphatic and aromatic hydrocarbons and many other substances—that rivals the assortment of hardware whirling around in space.

Does such accumulation in the body really matter; are we being 'crippled' biochemically? Smyth¹²³ has drawn attention to the old adage that "every man must eat a peck of dirt in his life". We cannot create an aseptic world. Today, as much as ever before, the need exists for sufficient but not overwhelming challenge to stir up the body's adaptive responses. Only by recognizing such need can we achieve a proper sense of proportion in relation to the presence of 'chemicals' in food and the hazards that may be associated with them.

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