metabolic rate while sitting is so variable, and I think that that is part of the explanation and not the whole explanation. I think that there are a whole lot of different things which integrate to make up total calorie requirements.

Chairman: Rather like individual personalities.

FOOD ADDITIVES

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I have been asked to talk about a subject which is somewhat outside the usual field of nutrition, namely, the subject of food additives. The extraneous chemicals which get into food have caused, and up to a point still cause, a certain amount of anxiety in people's minds, so I think it may be quite a good idea to tell you something about the food additive problem from a toxicological point of view and about some of the difficulties which exist in this field, because the doctor may be asked about some of these problems by anxious patients who wonder if they are being poisoned.

The occurrence of extraneous chemicals in food is related, as everyone knows, to the absolute necessity for making the best use of the world's food supplies. This is done in a great number of different ways; all sorts of devices are employed to produce more food, to prevent wastage, to get better distribution of food, and also to get more suitable foods for individual needs which are palatable. They often involve technological processes or the use of chemical substances, which now and then give rise to the question whether their use is accompanied by some risk to the health of the consumer.

If we take for the moment the broader issue of the extraneous chemicals in food, we can divide them fairly arbitrarily into three groups: the first two are straightforward contaminants of ordinary foodstuffs. You can divide these contaminants into two groups, one of which may be called " primary ", since it involves raw materials (e.g., pesticide residues, hormones used in the treatment of animals, and other substances of this description which may remain in food) and a second group of " secondary " contaminants, which get into manufactured food materials in technological processes of one sort

or another (e.g., lubricants or plasticizing agents used in making wrappers, or lacquers inside cans which may be extracted into food).

The third group, the one that I am going to talk about mainly, is commonly called " intentional food additives "—substances added to food for some particular reason or purpose. These food additives may be buffering agents, preservatives, anti-oxidants, emulsifiers, stabilizers, or colouring or flavouring agents, and they are used intentionally to alter the properties of the food in some way.

I have mentioned these three groups to get the whole picture into perspective, because the way of handling the possible risks which arise from the use of these substances differs in these three groups. The approach to the problem of primary contaminants on raw materials, such as pesticide residues, which are mostly substances with some potent biological effect, often poisonous, is a straightforward toxicological one. The safe dose can be estimated and the properties of the substance studied so that it may be used in a particular way and will not be present in the food in significant amounts. The method of protection is proper control of use. It is rather important for doctors to have some knowledge of the possible effects of these substances and the antidotes necessary. Quite a number of documents are now being circulated to hospitals, casualty departments and so on, giving information about chemicals which may be used in agriculture and in other ways. This is a toxicological problem with which we need not concern ourselves further for the moment.

The problem of the secondary type of contaminant, such as lubricants and packaging material, is solved by choosing only relatively harmless materials for use in food technology. There is a large range of possible plasticizers, for example, and there is no need to choose highly poisonous substances to put into food wrappers; again, lacquers can be chosen which are not extracted into food. Thus, there is a wide choice of substances which may usefully and relatively safely be used in association with food.

There is a large number of intentional food additives. All sorts of substances are used and can be used, and new substances are likely to be introduced which may have some application in food. It is fairly obvious, of course, that there is some element of risk in using any additives of this sort. It would be wrong, however, to imagine for a moment that this is anything new. Food additives have been used from prehistoric times, and various types of processing have been employed in making food more acceptable. All sorts of things have been added to food, including common salt and vinegar, which has been used as a preservative for centuries, but there has been rather a big increase in the number of these substances

in recent years, because the chemical industry has produced many new materials with applications in this field.

The first question is: What are the risks? The first risk is one of damage to the nutritional properties of food, by altering the protein or the vitamin content, or doing various things which alter the normal nutritional value of the food. Milling is well known to alter the nutritional value of flour, and the method of milling can have a considerable influence on the nutritional properties of the latter. Oxidizing agents can obviously alter constituents of the diet, such as oxidizable vitamins, which are likely to be destroyed.

Secondly, there is a risk of causing tissue damage, or damage to particular organs. Obviously the liver, the kidney, and the gastro-intestinal tract are likely sites of damage, because they are the possible sites of metabolism or excretion of these chemical substances or their products. Examples of food additives that were used until found to be organ-damaging agents are the coumarols, which have a vanilla flavour; some of them are liable to cause liver damage, although only in doses considerably higher than those actually used in food. However, for this reason they were voluntarily withdrawn from the list of food additives. Incidentally, they are a natural product, which reminds one of that wonderful myth that it is safe to use natural products and very unsafe to use synthetic chemicals. This is nonsense, of course. Some of the most potent poisons, such as botulinus toxin, are natural products, and a great many poisonous plants are known. There is no need, therefore, to suppose that a thing is going to be more poisonous because it is a synthetic material.

Carcinogenesis is the next risk, and a very serious one. Indeed, the possibility of producing cancer is probably the main worry some people have with regard to the use of food additives. We know that there are some colouring materials, especially those related to beta-naphthylamine, which can produce cancer. None of the common ones used in food in this country are carcinogenic, but this is always a risk to be considered.

The fourth possibility is the production of anti-metabolites. This simply means that a very small alteration in the structure of a molecule may occur, such as the addition of a small amino- or hydroxy-group, and this changed molecule may interfere in the metabolic processes in which the normal substance takes part. As we now know, anti-metabolites can be produced which do not stand much chance, because their effect is a competitive phenomenon, and if there is still plenty of the normal metabolite present the anti-metabolite is at a disadvantage. One well-known example of anti-metabolite formation was the production of methionine sulphoxi-

mine by the action of nitrogen trichloride (agene). Nitrogen trichloride forms methionine sulphoximine, which is an anti-metabolite to methionine. This interferes with the use of methionine by certain bacteria, and it also interferes with the normal functioning of the nervous system in dogs and some other animals, which get running fits when they are fed large amounts of this type of treated flour. For this reason, although no ill effect from agene-treated flour has ever been demonstrated in man, this type of treatment of flour has been discontinued.

Fifthly, there is the difficult question of hypersensitivity. Hypersensitivity in general is really idiosyncratic, a very individual thing, and as a rule one takes the view that people who have these peculiarities have to make the best of it and learn to live with them. There has never been great alarm because a few people are sensitive to lobster or to strawberries; these people usually find out fairly quickly and don't eat them any more. One has to take this view about these idiosyncratic reactions peculiar to the individual, but can hypersensitivity be more widespread? You may have heard about the trouble in Holland, where an agent put into margarine was said to have caused the illness of several thousands of people. The effect reported was largely a skin reaction and has been alleged to be due to hypersensitivity, but full details are not yet available and exactly what did happen is still a matter of controversy. There is, therefore, some possibility that hypersensitivity reactions and sensitization of this sort may occur on a much wider scale, and this might be a serious problem if it were true.

Finally, there are changes that might occur from the use of antibiotics which may alter the natural body flora and cause a certain amount of disturbance. Hypersensitivity to antibiotics might also cause difficulties. On the whole, antibiotics are not generally accepted for use in foods in this country, but there are great possibilities here. For example, the keeping properties of fish can be greatly improved by putting tetracyclines into the ice in the holds in which the fish are stored and the use of various types of antibiotics to give microbiological control may make a big difference to quite a number of food processes. A more serious problem might be the induction of widespread resistance to important therapeutic antibiotics. Considerations of this sort have made people chary about any wide use of antibiotics in relation to foods.

I now want to consider what safeguards there are against these risks and what can be done to give a reasonable guarantee of safety. We must say straight away that there is no hundred per cent guarantee. There is nothing in life with a hundred per cent guarantee and you cannot have it here: what you can do is to ensure that the

substances used in food are reasonably safe and not likely to cause serious difficulties. The safeguards used are a combination of studies in animals, with possibly some studies in man, and consideration of the known facts of the chemistry and biochemistry of the substances concerned; all of this, of course, is coupled to effective legislation which enables the matter to be handled administratively.

The legislation mainly used nowadays, as most people know, is the system of the Permitted List. In the old days, you could put anything into food unless somebody could show in a Court of Law that it was harmful. The matter was relatively simple in the past, when one was dealing mainly with adulteration, and trying to stop people from putting poisonous adulterants into food. This sort of law worked then, but in these days, when a wide number of different chemicals are being used, many of which are difficult to detect and of low toxic potential, the whole approach has had to be changed. There is now a much greater tendency to establish a list of permitted substances and new substances are admitted into the Permitted List only when there is reasonable evidence that they are safe in use. Thus, the legislative machinery has been modified and it is now much more effective to deal with current problems. If this machinery is linked to an effective testing organization, the health of the consumer should be adequately safeguarded.

I shall now say something about some of the investigations needed to ensure that a food additive is safe in use. First of all, nutritional value can be assessed directly by suitable methods. It is possible to see whether the food which has been treated has been changed, and this can be dealt with by direct measurement of nutrients before and after the treatment has been applied. This does not take account of unknown nutrients, but these will be checked by other types of tests, and so I think that direct study provides quite an adequate safeguard against loss of nutrients. Supposing nutrients are lost, this still does not mean that you need necessarily ban the material; the whole essence of the safeguard is adequate knowledge on which an opinion can be soundly based. What is done turns entirely on whether the nutrient concerned is important and whether the food involved is an important source of that nutrient. It is obvious that you need not take any action if the food material treated is not a significant source of the particular nutrient.

An example of this is the question of tocopherols in flour. There is a change in the tocopherol content of flour when certain oxidizing agents are used. It is quite definitely reduced, but it is also reduced by storage or by baking; the tocopherol content of flour is, in fact, rather labile. It also happens that it only contributes something

like ten per cent of the total tocopherol intake in the diet. I think it can, therefore, be reasonably argued that the reduction of tocopherol in flour by such things as oxidizing agents is not very important from a nutritional point of view. Indeed, the importance of that nutrient in human nutrition is controversial; but even assuming that it is important, this particular reduction is not one that we need be seriously worried about. On the other hand, the reduction of thiamine (vitamin B_1) by certain types of milling is an important question, and this is dealt with by putting a certain amount of vitamin B_1 back into the flour in those circumstances where this is considered to be necessary.

The next question is how to ensure safety from a toxicological point of view. This entails investigation in animals. The animals are fed on the material itself or food treated with the material and it is important to do both. When agene is used in flour, the toxic material is actually produced in the flour, so that the additive material itself may be harmless, but may produce some poisonous substance in the treated food. In the case of non-residual food additives, it may not be possible to test the additive itself and complete reliance must be placed on feeding treated food materials.

The sort of investigation which can be carried out in rats or other animals may involve three generations. In the first generation, studies are done with fairly general indices like the clinical state of the animal, weight gain, fertility rate, and eventually life-span measurement. The first study is carried out right through the life-span of the animal and a careful assessment is made of tumour incidence. This is an important step in the safeguard against carcinogenesis. The second study covers a much shorter period of not more than a year; otherwise there is trouble about senile changes in the rats; nobody knows enough about the geriatrics of rats to interpret results in these old animals, but in younger animals various types of organ function can be studied. One of the great difficulties here is that little is known about the sensitivity of the various tests of renal function, hepatic function and so on. Some of my colleagues have been studying this sort of problem using various methods of assessing organ function, and studying the sensitivity of these with graded doses of known toxic agents. The importance of knowing the sensitivity turns on the fact that so often in these investigations the results are negative. Negative results have little meaning if the sensitivity of the tests used is unknown. For assessing renal damage, liver damage, and various other types of organ damage, certain tests are more sensitive than others. On the whole, function tests tend, as might be expected, to be rather troublesome, because there is a tendency for compensatory hypertrophy to obscure

the situation, especially with low-grade damage which slowly accumulates. Many function tests are, therefore, unreliable for these purposes, but histopathological studies, a few selected function tests, and certain enzyme studies are quite valuable. After getting the results of these organ studies, a more detailed study can be done, if necessary, to see whether a significant risk exists. These investigations are time-consuming, expensive and difficult, but they can yield answers which have some meaning in terms of safety.

The cancer risk is assessed in much the same way. It must be done over the life-span in rats and mice by an assessment of tumour incidence after feeding a number of dosage levels of the additive and treated food materials. Injection is troublesome, because many substances, including some well-known food materials, cause local sarcomas to form at the injection site. The rat is very inclined to form local sarcomas at the site of injection, and I think, personally, that parenteral injection is not a help in attempting to assess the cancer risk.

The whole essence of our problem is to know whether a substance is safe on feeding. I believe that the dog studies insisted on in America are a waste of time, so far as assessment of the cancer risk is concerned. If they are positive they may have some meaning, but as a negative test they are useless because the number of animals involved is too small and statistical evaluation is impossible. The amount of the life-span one can study in a dog is only about ten to twenty per cent, because the life-span of a dog is about 15 years, and naturally enough these tests are usually run for not more than two to three years.

After these investigations a reasonable conclusion can be drawn about safety in rats or mice and various other animals tested, but the major problem is, of course, the application of the results to man. Their applicability to man has to be assumed and considerable margin of safety is left as regards acceptable levels of use, to cover this transfer of data obtained in animals to man. Now and again, investigations may be carried out in human subjects with reference to some particular point, but on the whole most people are against the idea of routine human studies to establish the safety of these substances. The hypersensitivity question is a special case, and if the damage said to be caused by the Dutch margarine turns out to be a human-specific sensitivity reaction, something may have to be done about suitable tests in human subjects in future. Hypersensitivity tests in animals are, on the whole, rather unsatisfactory; in order to check this point, animal studies can certainly be done, but it may then be necessary to consider control studies in volunteers and possibly even a distribution of the substance in the first place

to a control population. It is a matter of considerable interest to doctors, whether in practice an effect of this sort brought about by some particular new food additive would be detected. In the outbreak of alleged margarine poisoning there were, apparently, thousands of people involved, but the evidence so far suggests that it was detected more or less by chance. A considerable amount of trouble could arise from a particular food additive without its necessarily being detected unless there was a rather carefully zoned distribution and the doctors in the area were made aware of the possibility of something happening. This is not an easy thing to decide and there are all sorts of ethical questions involved. However, there is no other way of testing for a human species-specific reaction except in the human species, and therefore, some means of this sort must be devised if it is really thought to be necessary.

I have gone rather quickly through the question of safeguards, and I have hinted that there are places where considerable improvement is possible; one improvement would be to make safety testing shorter and less costly. Quite a lot of substances in food, and quite a lot of food that we normally eat, has not been adequately tested from the toxicological point of view. However, one does not want to load food scientists with a large amount of work yielding largely negative results unless it is really necessary. It is possible to waste a lot of scientific man-hours which could be much better employed doing something else. Any safeguard that is better and involves less work is welcome.

To summarize the way things may be handled at the present time. First, it is usual to start with a short-term test, which is not quite like an acute toxicity test, but really tells you whether the substance is absorbed and what happens to it, thus giving the biochemical background. The next step is to do a 100-day test, which will give all the information needed about weight gain, organ effects, and so on. Thirdly, a life-span study is essential for assessment of the cancer risk. Finally, there is sensitivity testing, which may require studies in man, and possibly a few confirmatory tests of special points which might be checked up in suitable human volunteers. This is the present plan of investigation of a food additive and it gives a reasonable safeguard against the sort of risks that are involved.