Modulation of Hormone-Induced Tumours by Dietary Factors

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Dedicated by the authors and by Hoffmann-La Roche & Co Ltd to Professor René Truhaut, in celebration of the first 50 years of his contributions to research in the field of Toxicology.

It is a truism that « there is nothing new under the sun ». Nevertheless, there are points in time when collections of old facts come together and fit into a newly-perceived pattern and this is exactly what has happened in relation to the modulation by dietary factors in the genesis of hormone-induced tumours.

It has long been known, that the amount of food consumed and its composition influence the incidence of tumours in laboratory rodents which are not deliberately exposed to carcinogens. But, in the interpretation of the results of studies in this area, emphasis has hitherto been put either on the role of calories or on the different effects of fats, proteins and carbohydrates on the metabolic profiles of animals. The demonstration in the 1940's (1) that calorific intake could modulate both spontaneous tumour incidence and the response of animals to known carcinogens was a matter of relatively little interest to those exploring the mechanism of action of known potent carcinogens such as certain polycyclic aromatic hydrocarbons, azo dyes, or aromatic amines. Similarly, the pioneering work of many investigators showing that both natural and synthetic hormones, in excessive doses, can produce cancer was regarded as a separate branch of carcinogenesis rather than as an integral ingredient in the variation in response of animals to xenobiotic agents.

Several factors have served to bring about our newly emerging understanding in this area. The most important is the switch in emphasis of biological work away from studies of the effects of known carcinogens, often administered in very high dosage, to the testing of chemicals of unknown carcinogenic potential to see whether they possess any such activity. As an integral part of this switch in emphasis, there

had to be great improvements in the standards of animal husbandry, otherwise animals under test might not live long enough to develop tumours in response to a weakly-active carcinogen. Accordingly, colonies of rodents were rendered free of parasitic and epizootic microbial diseases by rearing Caesarian-derived animals behind barriers and feeding them on pasteurized diets. At the same time, importance was attached to the need to provide animals with nutritionally adequate diets. But, unfortunately, no-one realised that overfeeding and overnutrition could produce as many disease problems, particularly in elderly animals, as nutritionally deficient diets.

Traditionally, nutritionists involved in the formulation of laboratory animal diets have seen it as their main tasks (i) to ensure that no animal is put at risk of developing any disease attributable to nutritional-deficiency, and (ii) to ensure maximum weight gain during the first part of life. At the same time, the toxicologist has traditionally taken very little interest in diet formulation, other than to suspect nutritional deficiency when anything goes wrong with his experiment. He has tended to argue that since animals in control and treated groups in carcinogenicity tests all get the same basic diet, its composition does not really matter.

It is now abundantly clear that both the nutritionists and the toxicologists have been negligent in their approaches. The nutritionist has made no attempt to study the effects of variations in quality and quantity of diet on longevity and disease incidence in later life and the toxicologist has ignored evidence that has long been staring him in the face, that most laboratory rats and mice are grossly overfed, obese and sluggish ; that in many cases rats suffer from chronic progressive renal disease and various manifestations of mineral imbalance and that many tend to be riddled with a rich variety of hormonally-mediated disease, including many different kinds of endocrine cancer (2, 3, 4).

In order to maximise the chances of detecting weak carcinogenicity, Regulatory Authorities tend to require, firstly, that sufficient animals survive for a long enough period after first exposure to a test agent and, secondly, that animals are exposed to dosage levels that greatly exceed those to which man is ordinarily exposed. The latter requirement has often been promulgated without adequate thought to the possible effects of exposure either to the test agent, or the vehicle, on the nutritional status of animals. A particular example of this has been the corn oil saga associated with the National Toxicology Program. Corn oil in doses equivalent to a human having to drink up to 1/3rd litre of oil per day was given orally by gavage or admixed with the food as a vehicle in these studies. Such treatment was found to be associated with enzyme changes and an increased incidence of tumours of the exocrine pancreas (5, 6). Earlier, Gellatly (7) reported that the incidence of liver tumours in mice can be multiplied by a factor of 3 to 9-fold merely by doubling the content of groundnut oil included in the diet.

Perhaps the most worrying observations of recent years have been those of Ross and Bras and their colleagues (8, 9) and Turnbull *et al.* (10). These workers have shown that what a rat eats just after it is weaned has a seemingly indelible imprint on its subsequent risk of developing neoplasia.

Ames (11) recently proposed a theory whereby ageing and associated progressive increase in cancer risk are due to endogenously produced oxygen radicals and lipid peroxidation. If true, then one would expect the rate of accumulation of DNA damage to relate generally to basic metabolic rate and overfeeding to be associated with an increased rate of oxygen radical production. Hormone imbalance associated with hyperplasia in particular endocrine glands and in particular hormone-responsive tissues might well then lead to increased oxygen radical generation in these

tissues and consequently to increased risk of tumour development. Thus Ames' theory might explain why prolonged hyperplasia in any tissue predisposes to increased cancer risk. The observations of Ross and Bras (8, 9) would be explained if high dietary intake in early life predisposed to high basal metabolic rate throughout life.

Apart from overfeeding, we are also concerned about the careless way in which diets are formulated in respect of mineral content, especially in respect of calcium (Ca), magnesium (Mg) and phosphorus (P). The NAS have, from time to time, set minimum levels for these minerals (12), but curiously have always underestimated the requirement of rats for Mg (13). Apart from this, the NAS have given little thought to the consequences of excessive minerals in diets. It is, in fact, quite common for diets fed to rats to contain more than 1.0 % of Ca and more than 1 % of P. These levels are not only unnecessarily high, but predispose to various forms of nephrocalcinosis especially if various carbohydrates, such as lactose, various sugar alcohols, and various chemically modified starches, which increase calcium absorption from the gut, are included in the diet in high concentrations (14, 15).

Recently, our attention has turned to yet another consequence in rats of excessive calcium absorption from the gut. Long-term studies in which rats were fed on diets containing 20 % sorbitol or xylitol led to increased incidences of adrenal medullary hyperplasia and neoplasia (16). In the light of published evidence of an association between hypocalcaemia and hypofunctioning of the adrenal medulla in terms of catecholamine and dopamine production, we postulated that hypercalcaemia or increased calcium throughput might lead to hyperactivity of the adrenal medulla. If calcium absorption was so excessive as to lead to hypercalcaemia, this might, in turn, cause changes in calcium regulating hormones which could stimulate the adrenal medulla. Experimental evidence consistent with this sequence of events has recently been obtained. In rats fed on a 20 % xylitol diet there was a rise in blood calcium, a marginal fall in blood pressure, and a rise in the level of adrenaline in the adrenal medulla. Furthermore, the level of adrenaline in the adrenal medulla was found to vary with the concentration of calcium in the diet. On the basis of this and other evidence that we review elsewhere (17) we suggest that 3 factors modulate the risk of adrenal medullary proliferative disease in rats (i) overfeeding generally (ii) excessive calcium in the diet (iii) the concentration in the diet of carbohydrates which facilitate calcium absorption. In other species, including the mouse and man, there is no evidence of any link between hypercalcaemia and risk of adrenal medullary proliferative disease.

Relevant both to the effects of overnutrition and mineral balance is the fact that chronic progressive nephropathy predisposes to parathyroid hyperplasia and neoplasia and these in turn predispose to widespread metastatic calcification, e.g. in the aorta, lungs and renal cortex. Where nephrocalcinosis from this cause coincidences with other forms of nephrocalcinosis due to dietary mineral imbalance or carbohydrate-associated increased calcium absorption, there exists a very complex puzzle for the toxicologist to untangle.

An obvious conclusion from the above considerations is that the toxicologist can no longer afford to ignore the impact of diet on hormonal status, ageing and cancer risk especially if he is investigating the long term effects of agents which modify nutritional or hormonal status. Common sense dictates that untreated control rats which, by the age of 2-2 1/2 years, have severe progressive glomerulonephritis and incidences of pituitary, mammary, testicular, adrenal medullary and other tumours in the range of 20-100 % are not suitable models for studying the long term toxicity of chemicals and provide no basis for predicting cancer risk for man. Research is urgently required to define the conditions needed to maintain

laboratory animals into old age essentially free from multiple hormonal disturbances.

Summary

Overnutrition predisposes to increased tumour incidence generally and in the endocrine tissues and hormone-responsive tissues in particular. Overnutrition early in life indelibly enhances cancer risk later in life. Excessive calcium intake predisposes to hypercalcaemia, hyperplasia and neoplasia of the adrenal medulla. Chronic progressive nephropathy secondary to overfeeding predisposes to parathyroid hyperplasia and neoplasia. Basic research is urgently needed to establish the nutritional requirements of animals in long-term tests such that excessive tumour incidence in control animals is avoided.

Résumé

La suralimentation favorise une incidence accrue de tumeurs dans l'organisme en général ainsi que dans les tissus endocriniens et les tissus réagissant aux hormones en particulier. La suralimentation à un âge précoce accroît irrévocablement le risque de cancer à un âge ultérieur. Une consommation excessive de calcium prédispose à une hypercalcémie, ainsi qu'à une hyperplasie et néoplasie médullo-surrénale. Une néphropathie chronique progressive, secondaire à une suralimentation prédispose à une hyperplasie et une néoplasie parathyroïdiennes. La recherche fondamentale doit s'employer de toute urgence à établir les besoins nutritionnels chez l'animal de manière à ce que, lors de tests à long terme, une incidence accrue de tumeurs soit prévenue chez l'animal témoin.

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