Lipids and Health

LIPIDS AND HEALTH

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Editor:

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FOREWORD

It is with great pleasure that I open this second European Symposium on 'Lipids and Health'.

Why a Symposium on the relationship between 'Lipids and Health'?

The connection between diet and cancer and diet and cardiovascular diseases has haunted the minds of epidemiologists for many years. Ever since the appearance of such famous studies like those of Doll and Peto or Hirayama in the field of cancer and Framingham in that of cardio-vascular diseases, no one doubts the fact that there is a definite relationship between how we eat and the appearance of different types of cancers or diseases.

Seventh day Adventists or Mormons have been used as controls in several research projects, however the steps from correlation to causality have not yet been surpassed. Concrete scientific evidence has yet to be found to establish an unquestionable relationship between diet and illness. This relationship is obviously indispensable.

Associations in the fight against cancer or against cardio-vascular diseases must develop a coherent and rigourous message of prevention. They demand scientific certainty: this is why the Belgian Cancer Association has taken the initiative to organise this novel meeting.

It goes without saying that in everyday life there is a lot of wide ranging lectures and information concerning the relationship between diet and cancer. Beginning with popular sayings such as 'we dig our own grave with our teeth' to best sellers, whose titles I won't mention here so as not to give them more publicity, to dogmatic arguments presented by certain vegetarian tendancies or dietary sanctuaries, the enormous amount of social discussion on the virtues of dietary preventative measures is a real phenomena. Obviously it has not only been limited to our area but it benefits from an enormous distribution because of the mass media.

Must a scholarly argument replace or oppose these popular arguments, and thus be the fact or knowledge on the relationship between cancer and diet or cardio-vascular diseases and diet?

In any case it is difficult to pin-point the truth, especially since the epistemological orientation in cancer research is largely dominated by the molecular biology model introduced by Watson and Crick's famous discovery on DNA structure. Perhaps this model blocks the passage from the microcosm to the macrocosm, from the inscription in the cell of an anomaly to the complete transformation of this cellular modification.

Or in other words, is it by studying the cell that we will have a better understanding of the irreversible disorders a dietary imbalance can cause in our cellular organisation?

What is a balanced diet anyway? Is not a balanced diet just simply that

diet which permits one to live in good health? With such a definition we can go from the individuals' level to that of the whole community: are not healthy populations those whose diet is balanced? As a result of such conclusions we enter the domain of epidemiology and more concretely social anthropology which can shed a clear light on dietary habits: rituals, anomalies, transmissions, taboos or prescriptions for example. From mini to macro, changing dimensions permit these rich epistemological meeting points which have often been at the origin of great scientific discoveries.

Isn't it about time that an organisation should have the capacity to centralize recommendations, transmitted on the basis of experts studies, which could constitute a reliable reference for all scientists in the field. This reference point would facilitate the creation of comparative studies which are severely lacking for the moment. As a result, a series of quality criteria could be created as well, so that the idea of study validity could be introduced.

Why couldn't the Belgian Cancer Association inspire such a cooperation at a European level? Wouldn't it be necessary to compare experience gained in health education throughout Europe and also to have regular meetings between specialists and actively involved people? Thinking about ways in which we can arrive at this goal is one of our priorities.

This could become a reality through the creation of a European Dietary School in which the Belgian Cancer Association would be the promotor in the field of initiatives and financial resources.

In the meantime as this idea matures, the Belgian Cancer Association, aware of the importance of the need, is more than ever, determined to support research projects implying the collaboration of different centers installed in different countries.

I can thus announce to you all, that next year's priority will be given to research in the dietary and tracer domain implicating the idea of an intraeuropean collaboration: a Belgian center, a center in another European country.

This is the corner stone of this European Symposium on 'Lipids and Health'.

This International Symposium enjoyed the esteemed patronnage of Her Majesty the Queen Fabiola, as well as that of several ministers and secretaries of State and was held under the auspices of the Commission of European Communities and the E.A.C.R. (European Association for Cancer Research). It was organised with the participation of the I.A.R.C. (International Research Center for Cancer).

The aim of this symposium is, to bring up to date current knowledge in the field of lipids and health, to permit an exchange of ideas and to establish a base for the development of strategies in dietary prevention in the fields of cancer and cardio-vascular diseases.

We have invited the most renowned specialists in the fields of lipids and cancer on the one hand and lipids and cardio-vascular diseases on the other. They have accepted to give a syntheses of the latest discoveries concerning these subjects. These specialists come from Belgium, the Nether-

lands, France, Great-Britain, the Federal Republic of Germany, Italy, Denmark, Finland and Greece.

The epidemiological and experimental aspects, and dietary profiles as well as alternatives in dietary behaviour will be successively discussed during the symposium.

The Symposium will be published in the 'Exerpta Medica' International Congress Series from Elsevier in Amsterdam.

I thank those specialists, ladies and gentlemen, who have accepted to communicate the latest scientific information in the field. Thank you for being here this morning.

Georges ZIANT, M.D.,
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Association (Belgium)

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LIPIDS IN EXPERIMENTAL CARCINOGENESIS

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INTRODUCTION

Among non-smokers, cancer of the breast and colon are the most important malignancies for which, nevertheless, treatment remains disappointing. Hence both epidemiologists and experimental researchers have worked to identify the causes of these cancers, with the hope to be able to make practical recommendations for their prevention. The strong association between modern affluence and the occurence of both breast and colon cancer and possibly others has been used to suggest that they may share important etiological factors among which dietary factors may play a leading role.

In addition to epidemiology, experimental research has also given support to hypothesis of a role of diets in the etiology of cancer mainly breast and colon cancers. It has moreover, been used to identify specific constituents of diet as prime targets for preventive recommendations. Among the various dietary factors : content of fats, fiber and micronutrients (vitamins and oligoelements such as Se) as well as calorie intake are the most frequently cited candidates (11, 40, 1, 31).

By quoting these data from epidemiologic and animal studies, health authorities both in Europe and in North America are advocating recommendations for reduction in dietary fat intake and increase in dietary fiber content as major clues for cancer prevention. However the scientific basis for such recommendations have been repeatedly questioned and controversial arguments have been developed (14, 47, 15, 31, 28, 17).

It is the objective of the present article to critically review experimental evidences pro-and con such a relationship for fat and calorie intake. However, that critical analysis cannot be made without reference to our present understanding of the patterns of neoplastic development in particular during chemical carcinogenesis which is generally used as a model process to study the influence of lows vs high fat and low vs high calorie

diets. The two stage theory of chemical carcinogenesis will be discussed in some details and the concept of modulation will be proposed (41-44, 38) with the hope that it might help clarify the debate.

PATTERNS OF NEOPLASTIC DEVELOPMENT : THE MULTISTEP HYPOTHESIS

Nearly all proposed definitions of cancer emphasize the characteristically progressive, disproportionate and seemingly purposeless overgrowth of a tissue that continues indefinitely after all known or suspected inciting stimuli have ceased to operate. But cancer is also a chronic disease tending back usually for many years before clinical signs are apparent so that the clinically recognizable lesions represent only a fraction of the history of the disease (16, pp 41).

During many years (up to the early fifties), experimental study of cancer has most exclusively been limited to either "spontaneous" tumor development (mostly mammary tumors) or, tumor induction (mostly in skin) by repeated administration of a chemical or a mixture of chemicals (i.e. tar). One important general principle emerged from these studies : both spontaneous and experimentally induced neoplasia advance by progression through stages that are qualitatively different (16, pp 41).

Since the fifties, after the pioneering works of Rous and Kidd (45), Berenblum (4, 6), Berenblum and Shubik (5), chemically induced carcinogenesis has become a reference model to study neoplastic development not only in the skin (8) but also in the liver (34), in the urinary bladder (18), in the mamma (19), in the colon (13), ... These studies have all confirmed the long lasting and progressive nature of neoplastic development as well as, in many cases, the existence of qualitatively different stages that preceed the appearance of malignancy. In addition, these studies have open the door to the identification of chemicals which, when given chronically, increase the number and hasten the emergence of neoplastic growth. Such compounds which have been identified by their effects not by the mechanism of their action (2), have been called promoter of carcinogenesis.

There is thus an overwhelming amount of experimental data which indicate that carcinogenesis is a long lasting process which progresses through stages that are qualitatively different.

Moreover, treatments do exist which accelerate the passage from one stage to an other including the ultimate passage to malignancy.

In that framework, initiation (I) is the necessary event without which neoplasia would never occur. It can even be the sufficient event since a single dose of some carcinogens induces a full neoplastic development without any other subsequent treatments (52, 49, 48). "I" is the treatment that induces latent neoplastic potentialities in cells which then advance, at varied, often extremely slow rates, towards the neoplastic state(s).

Promotion (P) which, as opposed to "I", might not be an obligatory step in neoplastic development, means selection and clonal proliferation of initiated cells induced by a chemical compound or an other factor applied repeatedly or acting chronically. According to the classical theory, such a definition applies only to treatments occuring after "I" (46). However, it must be underlined here that in many (if not most of) reports on cancer promotion, the study is limited to its effects on the number and (sometimes) the kinetic of appearance of phenotypically altered foci whithout any further reference to their progression to or simply to the number of malignant tumors to which they are supposed to give rise even tough these are the only true end points of neoplastic development.

MODULATION OF NEOPLASTIC DEVELOPMENT

As a conclusion of the preceeding discussion we see neoplastic development as a long lasting and progressive process which needs to be initiated. Beyond the initiating event which, at least in some cases, may be a single (or short lasting) hit, some cells have acquired a "neoplastic capacity" that slowly progresses through qualitatively different stages to malignancy. Promotion of neoplastic development is the consequence of any (chronic) treatment which acts on the genesis of phenotypically altered lesions that preceed but are not always the (obligatory) precursors of malignant tumors. As a consequence of promotion more of these lesions emerge earlier and, at least in some cases, this is accompanied by an increased incidence (number of animals with tumor(s)) and/or yield (number of tumor per animal bearing tumor(s)) of malignant tumors that even appear

earlier. Based on such observations, a simplified view of neoplastic development describes it as a two(-multi)-step process resulting from two fondamentally different mechanisms : initiation and promotion. This view ignores : that "spontaneous" carcinogenesis exists; that a single dose of a carcinogen is, in some cases (52, 49, 48), sufficient to induce a full neoplastic development; that most reports on so called promotion of carcinogenesis rely on the counting of phenotypically altered lesions (papilloma on skin, foci and nodules in liver ...) whithout any evaluation of incidence and/or yield of subsequent malignant tumors; that it has repeatedly been reported that the sequence "I"-"P" can be reversed and still enhances tumor yield (21,22); that treatments do exist which, even tough they reduce the incidence of phenotypically altered lesions, still shorten the latency period for malignant tumor development and increase its kinetic (36); that surgical and dietary manipulations performed before, during and/or after "I" enhance neoplastic development as evalued by incidence and yield of malignant tumors (35, 12, 3). All these treatments which are not obligatory to but can qualitatively and/or quantitavely modify the outcome of neoplastic development in experimental animals, are not stricty equivalent to promotion. They are more general because their effect(s) is (are) on the neoplastic development as a whole. Furthermore they can be applied before, during and/or after "I" and finally (and most importantly), their effects are evaluated in term of malignancy. Moreover "promotion" is only seen as a treatment which enhances neoplastic development not considering the possibility that it might hinder it by slowing down its progression or by reducing the incidence and for the yield of tumors. Expressions like "inhibition of carcinogenesis; anticarcinogenesis, antitumor promotion, chemoprevention of cancer, ..." are used to cover these aspects.

With all that in mind we have recently proposed the term modulation to account for these modifications/changes in the pattern(s) of neoplastic development as evaluated by counting histologically identified malignant tumors as end point (41, 42, 38, 43, 44).

Modulation is then defined as the effect to any treatment which given before, during and/or after "I" modifies the pattern