CANCER AND NUTRITION IN AFRICA IN THE POSTGENOMIC AND PROTEOMICS ERA

Department of General Surgery and Organ Transplantation, Urology Unit, University of Pavia, Italy*, Department of Surgery, Urology Unit, University Teaching Hospital, Lusaka, Zambia** and Department of Surgery, Urology Unit, Makerere University, Mulago Hospital, Kampala, Uganda***

INTRODUCTION

Since I taught at Makerere University in Kampala (1973-1975) and at the University Teaching Hospital in Lusaka (1977-1980), I have been concerned with the continuing clinical observation of the very impressive correlation between the type of diet of a typical population (tribe) and the prevalence of certain tumors.

In epidemiological studies carried out in the 1970's and 1980's considering the highly varied dietary regimens in each group of the population, nutrition scientists in Western Countries preferred to follow the so-called "reductionist" method by investigating a single nutrient's effects on a biological system. In that historical context, I tried to encourage several scientific institutions or associations in Europe and Northern America to perform such studies in Africa, where it was – and still is – possible to find entire population groups using a single type of food to cover up to 80% of their diet. If the "reductionists" had accepted my invitation, we would have made considerable progress, probably anticipating or facilitating the application of nutritional genomics and proteomics to molecular epidemiology and diet in cancer prevention.

Examples of population groups living off one main type of food are the Baganda in Southern Uganda, on Lake Victoria's banks, as a group whose staple food was (and is) green banana; the Acholi tribe, using cassava (a low-protein, starchy root) and millet; the Karamo-jong, the Samburu and the Masai tribes, using blood proteins to cover 80% of their nutritional requirements and a little millet; the Bemba tribe in Northern Zambia, whose staple diet consists of cassava and the Nianja tribe, in the Central and Southern Provinces of Zambia, covering over 80% of their diet using maize meal food.

Unfortunately, my cry for research in Africa was not heard.

Nowadays, reductionist scientists have lost their leading position because the discovery of the human genome and the subsequent knowledge of nutrient-gene interaction have brought an impressive research revolution in the correlated fields of carcinogenesis and nutrition. However, the progress in understanding the dietary, environmental and genetic factors affecting the process of carcinogenesis has not been fully applied to agricultural and clinical
trials. One of the major problems is how to focus on one particular aspect of a total diet, and even scarcer is the knowledge about the nutrient-nutrient interactions.

The largest epidemiological study, covering 23 countries, was conducted by Armstrong and Doll\(^2\) to correlate alimentary factors to the incidence and mortality of cancer in various parts of the body. It revealed, for instance, that fat was mainly related with the risk of cancer of the colon, rectum, breast, ovary and prostate.

In the 1970's it was thought that this apparent correlation between a specific staple food and cancer should not be taken as an evidence of causation or as a basis for preventative action, but only as a suggestion for further research.

At the beginning of the 1980's, Doll and Peto\(^3\) suggested that diet was responsible for most cancer deaths (35%), while the confidence limits were 10-70%. Therefore, they admitted that the figure of 35% was speculative and that dietary factors had not yet been reliably identified.

Since that time, genetic research has been galloping.

**POSTGENOMIC ERA**

Watson and Crick\(^4\) revealed the structure of human DNA in 1953. It took another 48 years for Celera Genomics to reveal the first complete draft of the human genome, in the year 2001\(^5\). These two events mark the beginning of the post genomic era. During the same five decades, research on carcinogenesis also remarkably progressed, both from the informational and technological point of view. Cancer is now considered a genetic disease: tumor cells result from multiple genetic defects caused by exposure to environmental, dietary and infectious agents as well as other lifestyle factors\(^6\).

Carcinogenesis is a multi-step, multi-stage process, and the progression from premalignancy of intraepithelial neoplasia to a clinical, symptomatic and invasive stage may take 20 years or more\(^7\).

While in the 1970's dietary intervention to prevent cancer development was only a speculative concept, it is a real opportunity today. Nowadays, genomic technologies, both in the human being and in plants, are excellent tools, which have made obsolete the reductionist method of investigating the effects of single nutrients on a biological system.

The monodiets adopted in most African populations are an easy research field to understand the interaction between the various nutrients on one side and between nutrients and genes on the other.

For these reasons we believe that before we present our data in Zambia and in Uganda, a modern view of nutrition has to be illustrated.

**DEFINITION OF NUTRIENTS**

In the past 30 years, the definition of nutrients has continuously evolved, parallel to the understanding of the nutrient-gene interaction.

Classically, a **nutrient** is a component of food necessary for normal physiological function, while **essential nutrients** are components required for optimal health\(^8\). **Nutrients** are chemical substances needed by the body for growth, maintenance and repair of tissue and are obtained from food; **essential nutrients** must be present in the food we ingest, because they are not formed metabolically within the cell, whereas **non essential nutrients** can be produced by the cell\(^9\).

New technologies exploring the molecular details of the effect of nutrients on an entire biological organism have become indispensable tools to any new paradigm for nutrition research in diet and cancer prevention\(^10\).

Most recently, in 2002, two major scientific institutions held a conference focusing on phytochemicals and gene regulation in cellular animal and human models, and examining the role of nutrients in cancer survivors as well as the influence of nutrients on cancer prevention throughout the life cycle\(^7\).

It may appear at least premature, if not ironical, to apply the principles of genomics, proteomics, metabolomics and metabolomics to the African dietary environment, which, in most instances, is still primitive as far as seeding, cropping, processing and storing of staple food is concerned. But the fact that nothing has changed in the African rural nutritional methods should not discourage African scientists.
and doctors to learn and adopt the application of nutritional genomics and proteomics to molecular epidemiology and diet in cancer prevention.

In the past century, our nutrition research archetype was focused on the identification of a single nutrient in its deficiency state and the role of particular single nutrients in intermediary metabolism and cell growth, development, and maintenance, which has led to the formulation of a Recommended Dietary Allowance (RDA) of each nutrient. These public policy actions have helped successfully to eradicate and to prevent recurrence of acute nutrient-deficiency diseases such as beriberi, scurvy, rickets and pellagra.

With our expanding knowledge of the role of nutrients in gene expression and the cellular response to changes in nutrient availability, various academic societies and editorializing experts have led the ongoing pursuit of a definitive meaning of the term nutrient\textsuperscript{11}, what exactly is a nutrient these days? Young\textsuperscript{12} defined a nutrient in the postgenomic era as a "fully characterized (physical, chemical, physiological) constituent of a diet, natural or designed, that serves as a significant energy yielding substrate or a precursor for the synthesis of macromolecules or of other components needed for normal cell differentiation, growth, renewal, repair, defense and/or maintenance or a required signaling molecule, co-factor or determinant of normal molecular structure/function and/or a promoter of cell and organ integrity".

A comprehensive definition along these lines is timely in the postgenomic age because nutrients can influence or regulate the transcription, translation, and post-translational metabolic processes. The nutrient-genome interaction may differ according to the life cycle of the organism and has a profound influence on health maintenance and disease prevention. Within this mechanistic definition of nutrients, it must be taken into consideration that the requirement range of a particular nutrient is contingent upon the functionality of the cell and organism, that the required amount may vary depending on whether the nutrient is needed for normal cell growth or cancer prevention, and that certain nutrients may also be harmful in supranormal doses\textsuperscript{6}.
Table 1: Levels of Gene-Nutrient Analysis for Assessment of Nutrient Requirements\textsuperscript{13,14}

<table>
<thead>
<tr>
<th>Level</th>
<th>Definition</th>
<th>Example of Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – Genome</td>
<td>Genomic imprint</td>
<td>Nucleotide sequencing</td>
</tr>
<tr>
<td>2 – Methylome</td>
<td>DNA methylation modifications</td>
<td>Microarray analysis</td>
</tr>
<tr>
<td>3 – Transcriptome</td>
<td>mRNA expression</td>
<td>Hybridization assays; temporal</td>
</tr>
<tr>
<td>4 – Proteome</td>
<td>Set(s) of cellular proteins</td>
<td>Mass spectrometry; two hybrid; 2D gel, posttranslational modifications</td>
</tr>
<tr>
<td>5 – Metabolome</td>
<td>Low molecular weight metabolites in cells / organs</td>
<td>(\mu)TAS; IR, NMR</td>
</tr>
<tr>
<td>6 – Physiome / Phenome</td>
<td>Quantitative integration of cell and organ processes</td>
<td>Viable cell, organ and whole-body systems, with focus on flux and mass balance models</td>
</tr>
<tr>
<td>7 – Populome</td>
<td>Complete nutritional characterization of a population group from data sets 1 – 6</td>
<td>The above, as relevant, plus dietary and sociocultural data</td>
</tr>
</tbody>
</table>

Note: Levels 1 and 2 are gene-centric in foci and are largely context-independent. Other levels include a supra-genome strategy and are context-dependent.

- Abbreviations: 2D = two-dimensional; \(\mu\)TAS = micrototal analytic systems; IR = infrared; NMR = nuclear magnetic resonance.\textsuperscript{1} From Young\textsuperscript{17} and modified by Oliver\textsuperscript{3}.

This new definition of nutrients can provide the appropriate mode of gene-nutrient analysis needed at the genome, transcriptome, proteome, metabolome, physiome/phenome, and populome level to generate appropriate biomarkers (Fig. 2).

With the development of novel technologies and the advent of nutritional genomics, proteomics and other so-called "omics" sciences, there is a renewed interest in dietary components that affect global gene expression and the integrative physiological and metabolic functions of an organism. Nutrition science has thus evolved into a multidisciplinary field that applies molecular biochemistry and integration of individual health to the epidemiologic investigation of population health. Therefore, there exists ample justification for creating an innovative research model to further explore the role of diet in health promotion and disease prevention, including cancer and other chronic illnesses.

NUTRIGENOMICS

Nutritional genomics has the potential to assist scientists in interpreting the complex nutrient-gene interaction and the link between genetic abnormalities and predisposition to cancer, in analyzing and integrating the vast data sets, that these techniques and studies produce and, lastly, in identifying new biomarkers\textsuperscript{13}.

The levels of nutrient-gene analysis using the various technologies are listed in Table 1\textsuperscript{12,14}. Propelled by the recent mapping of the human genome and accompanying technological developments, nutrition science has introduced an encompassing new term into our vocabulary: nutrigenomics. "Nutrigenomics" provides researchers with the tools for the exploitation of systems biology in the nutrition and health arena\textsuperscript{15}.

The principles of some of the key players in nutrigenomics — genomics, proteomics, and metabolomics — are briefly discussed below.

Genomics uses either classical DNA — sequencer technology or more advanced technologies such as DNA arrays\textsuperscript{16}. Microarrays can profile gene expression patterns containing tens of thousands of genes in a single experiment, thus allowing systemic analyses of DNA and RNA variations and providing basic genetic information and insight into any heterogeneity in the coding regions or control
elements of genes. With transcriptomics, or expression profiling, scientists use a fluores-

cence-based detection system to determine RNA expression levels in biological samples. This entails using polymerase chain reaction techniques and Northern blot analyses, or annealing an immobilized capture oligonucleotide to its corresponding fragment from tissue onto a DNA microchip in a sequence specific-
fashion. This expression profiling enables simultaneous analysis of the mRNA of a few genes up to several thousand genes. Genetic polymorphism related to cancer is now widely investigated, and it is likely that many chronic diseases in addition to cancer also result from the connection between genetic susceptibility and environmental and lifestyle factors, including diet.

Proteomics enables researchers to identify all proteins expressed in a cell or organ and to detect any posttranslational modification or change in the protein expression pattern. The pattern of protein expression can be determined by a computer–based comparison of gels.

To identify the protein of interest, the protein is isolated from the gel and digested with trypsin or other specific protease, and then the resulting peptide fragments are analyzed by matrix–

assisted laser mass spectrometry, yielding the fingerprint of the peptide massing characteristic of a given protein. Database comparison of this information with known amino acid or DNA sequences identifies the protein. Any deviations of the measured peptide fragment mass from the corresponding mass of the expected amino acid sequence may indicate posttranslational modifications such as phosphorylation, glycosylation, or myristilation.

New proteomic technologies are now being applied clinically for use in early detection, therapeutic targeting and, at long last, patient–
tailored therapy.

Functional genomics and proteomics can also be applied to enzymes involved in the metabolism of nutrients.

The multi-step pathway from genome to phenotype, along with the involved process of identifying gene function, spurs continual technological development and investigation of metabolic pathways and metabolic flux analyses, or the biochemical profiling that is known as metabolomics.

Tumor cells possess the potential for proliferation, differentiation, cell cycle arrest and apoptosis. There is a specific metabolic phenotype associated with each of these processes that is characterized by the production of energy and special substrates necessary for the cells to function at that particular state.

The development of genomics, proteomics, and metabolomics has transformed the biomarkers concept of nutrient–gene interaction from the reductionist pursuit of one ideal marker into a holistic one, in which a significant
Table 3: Prospective Studies of Dietary Fat and Prostate Cancer Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Cases</th>
<th>Relative Risk for High vs. Low Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severson et al., 1989</td>
<td>8,000</td>
<td>174</td>
<td>0.9</td>
</tr>
<tr>
<td>Mills et al., 1989</td>
<td>14,000</td>
<td>180</td>
<td>1.4 (animal fat)</td>
</tr>
<tr>
<td>Giovannucci et al., 1993</td>
<td>52,000</td>
<td>126</td>
<td>1.6</td>
</tr>
<tr>
<td>Le Marchand et al., 1994</td>
<td>20,316</td>
<td>198</td>
<td>1.6 (animal fat)</td>
</tr>
</tbody>
</table>


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![Diagram of the clinical course of epithelial tumors over time, from the intraepithelial neoplasia stage to metastases. Modified from Go et al.](image)

**Fig. 4:** Clinical course of epithelial tumors over time, from the intraepithelial neoplasia stage to metastases. Modified from Go et al.

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fraction of all regulated genes and metabolites can be quantified concurrently. Validation of these biomarkers requires that nutrition scientists understand the methodological, demographic, environmental and dietary characteristic of populations in relation to genetic damage and the molecular epidemiology of cancer.

Ideally, new nutrigenomics tools will allow nutrition researchers to effectively address the interface of diet and metabolism as well as examine the pathways and mechanisms by which diet and nutrition may prevent cancer.

Milner et al. suggest that a genomic approach to biomarker discovery can proceed along two pathways:

1) it can focus on the disease state, whereby investigators identify the earliest genes involved in disease and use them as targets, aiming to pinpoint nutritional agents capable of modifying the gene expression; or

2) it can focus on the healthy condition where researchers examine the effects of dietary components of global gene expression,
seeking links between gene expression patterns and the processes of disease development.

Milner et al. propose that a major future research effort should be to identify and validate cancer-related biomarkers that are modulated by nutrients, and they further affirm that panels of biomarkers rather than single biomarkers may provide the best approach.

DIET AND CANCER PREVENTION

Current dietary recommendations for cancer prevention largely stem from epidemiologic studies that compare dietary patterns (i.e. intake of particular food items) between countries of low and high incidence for a particular cancer (Tables 2, 3). In general, most of the recommendations from the federal governments, preventive health organizations and world bodies are in favour of an increased intake of fiber and a variety of fruit and vegetables, consumption of alcohol and salt only in moderation, and increased physical activity. Largely based on these recommendations, the National Cancer Institute (NCI) and other funding agencies have initiated and supported various prospective, large-scale dietary and cancer prevention clinical trials. Two large-scale β-carotene intervention trials within populations of smokers and asbestos-exposed individuals revealed that the risk of lung cancer had increased rather than decreased, as expected, in the group supplemented with β-carotene, which suggests that this supposedly promising chemopreventive agent had exerted a pro-oxidant activity. Although these studies had been based on strong epidemiologic evidence linking the consumption of carotenoid-rich fruit and vegetables with a reduced risk of cancer, the trial outcomes failed to support the hypothesis that carotenoids (namely β-carotene) are responsible for the beneficial effects. Our broadening biomolecular-based knowledge of cancer has opened new avenues and targets for prevention trials. Similarly, the focus on a molecular target for chemoprevention has now shifted to the intraepithelial neoplasm stage of epithelial malignancy (Fig. 4).

Genotypic and phenotypic biomarkers have been used as surrogate endpoints because they correlate with histological modulation of intraepithelial neoplasia. The goals for cancer prevention may also have to be repurposed to the in-utero and early childhood stages of the human life cycle, if nutrition programming
in relation to the cancer risk does actually occur during these stages\textsuperscript{12}.

Using genomic technologies coupled with molecular analysis, investigators have observed and subsequently documented that dietary constituents can indeed modulate carcinogenesis via one of several pathways, with different tissue specificities and potencies. The nutrient-modulated pathways presented in the conference include altering carcinogen activation by inhibiting Phase 1 drug metabolizing enzymes through the cytochrome P450 superfamily; modifying carcinogen detoxification through Phase 2 drug metabolizing enzymes; scavenging reactive DNA agents and enhancing DNA repair mechanisms; interacting with signal transduction; inhibiting angiogenesis and suppressing abnormal proliferative characteristics, either by influencing apoptosis or cell cycle checkpoint activities.

This experimental molecular evidence forms the rationale for ongoing clinical chemoprevention trials and has become the key molecular target for nutrients involved in cancer prevention\textsuperscript{18,32}. Potential cancer preventive agents from dietary constituents are available to the research community through the Rapid Access to Preventive Intervention Development (RAPID) Program of the NCi's Division of Cancer Prevention.

In any diet and cancer prevention strategy, the constantly changing food supply must be studied, monitored, and considered, because the era of functional foods has also arrived. Several recent studies serve as example projects that integrate genomics and nutrition to determine the effect of functional food components on health\textsuperscript{34,35}. Genomics for food biotechnology and genome-level DNA sequencing of whole plants, in conjunction with improved methods of profiling natural products, have made possible the combined genetic and biochemical approaches to deciphering biosynthetic pathways and engineering new pathways in transgenic plants\textsuperscript{36}.

Investigators must embrace the genetically modified foods that result, and actively pursue the effects of these foods on animal and human health and disease prevention. Combined efforts from industry, government, and academics are essential in developing a comprehensive and integrated strategy for research on nutraceuticals and functional foods in relation to cancer prevention (Fig. 5).
Table 4: Food Source of Naturally Occurring Dietary Carcinogens

<table>
<thead>
<tr>
<th>Type of Food</th>
<th>Natural Pesticides:</th>
<th>Micotoxins:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>apples, pears, plums, cherries, carrots,</td>
<td>Aflatoxins</td>
</tr>
<tr>
<td></td>
<td>celery, lettuce, potatoes, endive, grapes,</td>
<td>Ochratoxin A</td>
</tr>
<tr>
<td></td>
<td>eggplant, thyme, basil, anise, sage, dill,</td>
<td>T2 toxin</td>
</tr>
<tr>
<td></td>
<td>caraway, rosemary, tarragon, coffee beans</td>
<td>Zearalenone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fumonisins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deoxynivalenol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nivalenol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allyl isothiocyanate</td>
<td>cabbage, cauliflower, Brussels sprouts,</td>
<td></td>
</tr>
<tr>
<td>Saffrole</td>
<td>mustard, horseradish</td>
<td></td>
</tr>
<tr>
<td>Estragole</td>
<td>basil, tarragon</td>
<td></td>
</tr>
<tr>
<td>Carvacrol</td>
<td>majoram</td>
<td></td>
</tr>
<tr>
<td>Furocoumarins</td>
<td>lime, citrus oils, carrots, celery, parsley</td>
<td></td>
</tr>
<tr>
<td>Hydrazines</td>
<td>mushrooms</td>
<td></td>
</tr>
<tr>
<td>Pyrrolozidine</td>
<td>herbal teas (comfrey)</td>
<td></td>
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<td></td>
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</tbody>
</table>


THE TEMPEST OF GENETICALLY MODIFIED ORGANISMS (GMO)

In 1962 Rachel Carson wrote the book “Silent Spring” where she made the terrible accusation against “pesticides” being responsible for poisoning the environment and our food. The American Cyanamid Company, the largest pesticide industry, stated in “The New Yorker”: “if man were to follow the teaching of Mrs Carson, we would return to the Dark Ages, and the insects and diseases and vermins would once again inherit the earth”.

For the next 40 years poisonous chemicals became a major factor of agricultural development. But at what a cost for the human being! (Fig. 6) Enough to mention the disaster of the Dioxin factory in Seveso, near Milano, Italy, and the worst chemical disaster at the chemical factory in Bhopal, India. (Fig. 7)

During the past four decades the earth, its rivers, its lakes, its soil have been poisoned by all sorts of pesticides: fertilizers, herbicides, anticrittogamics. But the wealthy people in the Western World as well as the hungry people in the developing countries needed food. The demographic explosion in the poor countries required more and more food, and the only way to increase the food production was to increase the use of pesticides. But, not too late, genetic engineering scientists had the idea of creating plants with built-in resistance to pest insects, or resistance to drought or to humidity. The same giant companies, such as Monsanto, Bayer, Hoechst and Aventis diversified their production and started producing the so-called “genetically modified” (GM) plants or organisms (GMO).

Paradoxically, the same groups or associations dedicated to protecting the environment
Fig. 8: Cotton field. Cotton genetically engineered to produce the insecticidal Bt toxin thrives, while a non-Bt crop is trashed by pests insects. From: Watson, J. DNA, The secret of life. William Heinemann: London, 2003

have been the most aggressive opponents to GMO. The present “anti-global” groups, active all over the world, light GMO in the name of the anti-imperialism ideology, identified with the giant agro-industries.

At this time, any crop (corn, wheat, rice, cassava, potato, tomato, beans etc.) can get its DNA modified, using the “gene gun”, which fires the desired gene into the cell.

In this context environment has been the first winner. In 1995 the introduction of the Bacillus thuringiensis (Bt) crops resulted in an annual reduction of 2 million gallons of pesticides for the production of cotton in the USA. In 1999, Chinese farmers, planting Bt cotton, reduced their use of pesticides by an estimated 1.3 million tons.

Scientific criticism to GMO is based mainly on the potential development of resistance of pests to gene treatment. But this is the same fight man is fighting against infections by a continuing innovation of antibiotics.

Farmers will have at their disposal new strains of Bt toxin any time resistance may appear.

But can GM agriculture diminish human suffering, including famine and cancer? We do believe that GM plant revolution has an astonishing range of potential applications, although we are at the very beginning of the way, and further research is mandatory to guarantee that DNA manipulation of plants will not produce unwanted and dangerous side effects in human beings.

Let us try to summarize the advantages of GM:

- reduction and abolition of pesticides,
- increase of food production, yield and quality,
- enhancement of the nutrient profile of crop plants adding a fuller array of nutrients or amino acids essential to human life which are scarce in the population using vegetarian diets,
- reduction of the cost of crop production by reducing the use of fertilizers, herbicides, insecticides, etc.
- improvement of the quality of labour
- control of the timing of ripening and reduction of transportation and storage costs
- avoidance of fungal invasion where storage systems are still primitive
- preservation of the environment.

A good example is the story of the “golden rice”. In 1992 UNICEF estimated that some 124 million children around the world were dangerously deficient in Vitamin A and, annually, half a million would become blind or die. These deficient populations are concentrated in regions where rice is the staple diet. Therefore, the so-called “golden rice” was produced, which contained a precursor of Vitamin A, beta-carotene. Unfortunately, beta-carotene requires fat for its absorption in the gut. Here again the need for an appropriate diet is obvious.

The major disadvantage of GM crops is the fact that they develop better than non-GM crops, but they produce seeds incapable of germinating. This is the main argument of the anti-global movements against the agroindustry monopolies, accusing them of re-colonizing poor farmers, forcing them to buy seeds every year. Non-germinating seed will always be available, but the GM will provide farmers with more and continuously improving choices.

We believe that the battle against GM crop is similar to that against the sale of antiretroviral drugs to poor countries at a reasonable and affordable price. If the opponents won this battle, we would achieve a great victory against famine and HIV/AIDS in both fields.

By reducing air, soil and crop poisoning by pesticides, by controlling the nutrient-to-nutrient and the nutrient-to-gene interaction, “nutrigenomics” will, in the near future, become
Table 5: The Effect of Various Factors on the Risk of Developing Various Stages of the Adenocarcinoma Sequenc37,38

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adenoma Formation</th>
<th>Adenoma Growth</th>
<th>Colon Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>↑</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alcohol</td>
<td>±</td>
<td>↑</td>
<td>0</td>
</tr>
<tr>
<td>Physical activity</td>
<td>±</td>
<td>±</td>
<td>↓</td>
</tr>
<tr>
<td>High energy intake</td>
<td>±</td>
<td>±</td>
<td>↑</td>
</tr>
<tr>
<td>High body mass index</td>
<td>±</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

Table 6: The Epidemiology of Cancer of the Proximal Colon, Distal Colon and Rectum38,39

<table>
<thead>
<tr>
<th>Agent</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>proximal colon</td>
</tr>
<tr>
<td>Smoking</td>
<td>+</td>
</tr>
<tr>
<td>Alcohol</td>
<td>-</td>
</tr>
<tr>
<td>Familial factors</td>
<td>+</td>
</tr>
<tr>
<td>Geographic variation</td>
<td>+</td>
</tr>
</tbody>
</table>

the best tool for the prevention of dietary tumors. Dietary interventions should be established at the specific stages of carcinogenesis30.

In fact, the same dietary components do not exert the same effect throughout carcinogenic development. In studies on the effects of various factors on the risk of developing certain stages of adenocarcinoma, tobacco was found to enhance adenoma formation but not adenoma growth or colon carcinoma38,39 (Table 5), while alcohol was found to exert major effects on the rectum38,40 (Table 6).

The interactions and synergies of dietary components require further studies and, coupled with current gene array methodology may enable the precise roles of specific nutrients to be elucidated. It is well known that the tumor incidence in 48 American states varies by a factor of four or more. It is reasonable to attribute these differences to the existing dietary diversity. With all this experience and data in mind, we thought that the great diversity of diet in different African populations should explain the wide differences in the incidence of the same tumor or the incidence of different tumors.

For this reason, we have started to study the correlation of diet and cancer in Zambia and Uganda. In the following, we present our preliminary data collected in Zambia by Dr. Labib and Dr. Bowa, both Urologists at University Teaching Hospital, Lusaka.

A study of the data collected in Uganda by Dr. Watia and colleagues will follow in due course.

CANCER AND NUTRITION IN ZAMBIA

There has been an increase in cancer in Zambia for the last 10 years41. In addition, the peak cancer age has come down to 35-45 years41. The most common cancer of men in Zambia is cancer of the prostate41, while cancer of the cervix is the most common cancer in women followed by cancer of the breast41. Among the patients treated at the University Teaching Hospital (UTH) of Lusaka, cancer of the prostate is the main cancer of the urological system followed by cancer of the bladder42.
Table 7: Incidence of Cancer in Zambia by Province (No. of Cases)

<table>
<thead>
<tr>
<th>Year</th>
<th>Central</th>
<th>Copperbelt</th>
<th>Eastern</th>
<th>Luapula</th>
<th>Lusaka</th>
<th>Northern</th>
<th>North Western</th>
<th>Southern</th>
<th>Western</th>
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</thead>
<tbody>
<tr>
<td>2002</td>
<td>9</td>
<td>0</td>
<td>62</td>
<td>3</td>
<td>497</td>
<td>12</td>
<td>15</td>
<td>64</td>
<td>2</td>
</tr>
<tr>
<td>1999</td>
<td>14</td>
<td>2</td>
<td>41</td>
<td>2</td>
<td>458</td>
<td>3</td>
<td>2</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>1998</td>
<td>21</td>
<td>0</td>
<td>27</td>
<td>0</td>
<td>170</td>
<td>4</td>
<td>17</td>
<td>42</td>
<td>20</td>
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<td>115</td>
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<td>188</td>
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In a five-year review of urological malignancies at the UTH, it was found that 45% of all urological cancers developed in the prostate gland. They also make up 6% of all urological cases seen over this period. The role of diet in the etiology of cancer in Zambia has not been studied extensively. A study was, therefore, carried out to compare the pattern of cancer distribution in Zambia to the dietary patterns based on the major foods produced and consumed in the various parts of the country.

The national cancer registry in Zambia keeps data of all confirmed and reported cases of cancer in the country. The cumulative totals of all cancers in Zambia from January 1st, 1991 to December 31st, 2002 by province were obtained. These were tabulated by province (Table 7), and the per capita cancer rate for each province was recorded.

The central statistics office (CSO) of Zambia conducts a census of population and housing every 10 years. The last census was conducted from October 16th to November 15th, 2000. In this census the CSO also produced an agricultural analysis report. This report was used to assess the major crops produced in the country and the proportion of their production in various parts of the country (Table 8). The ministry of agriculture, food and fisheries in conjunction with the central statistics office produces an annual crop forecast report. This was used in addition to determine crop production by province. The authors compared the cancer patterns to the crop production/consumption pattern to see a possible association with cancer.

The results show that the cancer burden per capita (Fig. 10) closely follows the agro-ecological zones in Zambia (Fig. 9). The agro-ecological zones determined by climate dictate the main crops grown in the zones. Zone 1 has the lowest rainfall and is prone to drought. It has an annual rainfall of less than 800 mm and a short rain season. Zone 2 has rainfall of between 800-1000 mm; it is the most heavily industrialized region with major commercial farming activity. Zone 3 has the highest rainfall of over 1000 mm and a long rain season. (Fig. 9) The per capita cancer rate taken cumulatively shows Zone 1 with the highest prevalence at 80 per 100,000 people. Zone 2 with 30 per 100,000 and Zone 3 with 9 per 100,000. (Fig. 10)

Studies on quantitative estimates of avoidable cancers show that dietary causes make up the largest proportion ranging anywhere from 10-70% of all exogenous causes of cancer. Genetic factors make up only 5% of all cancer etiologies. In fact, exogenous factors are still seen as the initiators of cancer even when genetic factors are present. Also the distribution of cancer prevalence in the three zones of Zambia suggests that diet may play a significant role in the etiology of these cancers. The crops produced in these areas are dictated both by tradition and climate.
<table>
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<tr>
<th>Crop</th>
<th>Central</th>
<th>Copperbelt</th>
<th>Eastern</th>
<th>Luapula</th>
<th>Lusaka</th>
<th>Northern</th>
<th>North Western</th>
<th>Southern</th>
<th>Western</th>
<th>Total %</th>
<th>Total No. of Households</th>
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<td>12.8</td>
<td>20.4</td>
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* The base of the percentages is the total number of crop-growing households in the country.
In Zone 1 the main crop produced is maize (96% of all crops) while in Zones 2 and 3 the main crop is cassava (54% and 59%, respectively). The other crops and livestock produced are in relatively low volumes. The major foods produced and consumed are grains which have a high starch content. The results show that where cassava is produced in large volumes the per capita cancer prevalence is low.

Other confounding factors which need to be considered do not appear to tally with the figures. HIV, for instance, is known to be associated with high levels of lymphoreticular cancers. One would, therefore, expect high levels of cancer in high HIV prevalence areas such as the copperbelt. However, this study finds the copperbelt to have one of the lowest prevalence levels for cancer. Environmental pollution from paint, mining and manufacturing industries is also a major cause of cancer. This would lead one to expect high levels of cancer along the railway line which is the most industrialized area. This expectation is not borne out by the study findings, since they show high levels of cancer in Zone 1 which does not follow the railway line but, instead, the agro-ecological zone.

Cassava has traditionally been grown in Luapula and the Northern provinces. These areas have the lowest cancer prevalence. Over the last 5 or 10 years there has been a shift to encourage the growth of cassava in the Western province for reasons of food security. The prevalence of cancer in the Western province is one of the lowest now per capita. There are several reasons why cassava might be protective against cancer. The composition of cassava is mainly starch and it has little protein and therefore needs supplementation. Nonetheless, the cassava leaf is very rich in antioxidants which have strong anti-cancer activity. The leaf contains 311 mg of vitamin C, a powerful antioxidant, which mops up superoxides which are agents in carcinogenesis. Vitamin A is important for the maintenance of the epithelial surface integrity and, therefore, prevents dysplasia which may lead to cancer. The vitamin A content in the leaf is up to 3300 μg, much more than in any other crop. Cassava contains high amounts of the poison hydrocyanide which is produced in order to discourage animals from eating the plant and gives it a rather bitter taste. The housewives traditionally pound and soak the cassava in water which removes this poison. A chemical found in cassava which is responsible for the production of hydrocyanide has been shown in vitro to cause death of cancer cells by self-toxicity with hydrocyanide. Agriculture economists in addition point out that the processing and preservation of cassava requires no chemicals which may be carcinogenic, in contrast to other grain crops like maize and groundnuts. The cassava plant growth requires no fertilizer, and the root can be stored by drying.
This pilot study suggests that cassava may be important in cancer prevention. Further studies are needed to confirm these findings in view of poor reporting of cancers by the National Cancer Registry and also further breakdown into per capita prevalence by district. The agro-ecological zones are cut across provinces and, therefore, the interpretation of the cancer information by province lacks sufficient precision.

In Zambia cancer is a major problem with late presentation and high mortality. There is a notable presentation of cancer in relatively younger patients than in the developed countries with a very aggressive course. The WHO indicates that there is a co-relation between cancer and nutrition. The study of the geographical distribution of cancer in Zambia shows that cancer is more prevalent in certain regions of the country. These geographical regions follow certain agro-ecological zones determined by climate patterns. The zones have a common climatic pattern and a common livelihood. This information suggests a possible relation between the dietary patterns and cancer. The notable finding is the fact that cancer appears to be lowest in high cassava growing areas. Literature shows that cassava has certain components which have anti-cancer activity but further studies are needed to substantiate these findings.

CONCLUSIONS

Collective epidemiologic studies and preclinical studies provide rather compelling evidence that dietary components modify the incidence and the biological behavior of tumors, specifically those of the breast, prostate, colon, liver and bladder.

To date, more than 500 dietary compounds have been identified as potential modifiers of cancer. Both essential and non-essential allelochemicals in plants, as well as zochemicals occurring in animal products, may be physiologically important modifiers. Compounds encompassing such diverse categories as carotenoids, diithiothiones, flavonoids, glucosinolates, isothiocyanates, allyl sulfhydryls and fermentable fibers have been found to influence experimentally induced cancers. Numerous reviews have emerged in recent years. Nutrients are increasingly being recognized to influence genetic and epigenetic processes that determine cellular metabolism, differentiation and apoptosis. While the study of "Nutritional Genomics" is in its infancy, it is beginning to reveal that nutrient excesses and deficiencies can bring about a host of genomic and proteomic changes. Regardless of whether the molecular target is at the transcription, translation or post-translational level the net result is an up- or down-regulation of specific gene products.

Complementary and overlapping mechanisms appear to account for the response to bioactive food components. These biological responses encompass such diverse functions as serving as an antioxidant, promoting the activity of detoxification enzymes, blocking carcinogen formation (such as with nitrosoamines), shifting hormonal homeostasis, retarding cell division and inducing apoptosis. Since more than one of these responses may occur simultaneously it is difficult to determine which is most important in dictating the change in cancer risk and/or tumor behavior.

Some of the likely mechanisms by which dietary components may suppress the cancer process are:

1. Inhibition of genetic damage due to endogenous and exogenous agents by:
   - inhibiting carcinogen uptake
   - retarding activation
   - enhancing detoxification
   - scavenging oxygen radicals
   - preventing DNA binding

2. Influencing repair of structure / functional genetic defects by:
   - enhancing endogenous repair
   - restoring proper methylation

3. Elimination of damaged cells or clones by:
   - inducing apoptosis
   - promoting differentiation
   - enhancing immunosurveillance

4. Suppression of growth and clonal evolution by:
   - Slowing or stopping proliferation
   - Retarding angiogenesis
   - Inhibiting invasion
It is clear that some nutrients can bring about the opposite effect and thereby enhance carcinogenesis. The ability of several nutrients to influence the same biological processes raises issues about possible synergy, as well as antagonistic interactions, among dietary components.

The future of nutrition and cancer research resides in the ability to move beyond observational studies to a molecular approach that will allow for tailored recommendations. The study of nutritional genomics has the potential to identify definitively which components in food bring about either cancer-inhibitory or cancer-enhancing effects and to clarify their relevant mechanism of action; this should lead to the identification of a molecular target that can be manipulated for cancer prevention. About 26000 to 38000 genes are found in the first draft of the human genome, which is about double that found in the fruit fly and worm. A website (gov/ncicgap), part of the recently launched Cancer Genome Anatomy Project (CGAP) that was developed jointly by the National Cancer Institute (NCI) and National Library of Medicine, offers scientists a powerful new tool to study diet and cancer interrelationships. Scientists can literally click on the CGAP website and submit queries about genes expressed during the development of cancer. In response, the CGAP database will sort through its gene index in seconds and provide a list of genes relevant to the query; data that a few years ago might have taken years or even lifetimes to compile.

A fundamental action of a nutrient is to serve as a regulator of gene expression and/or a modulator of a gene product. Thus nutrients have specific sites of action which can best be described as molecular targets. These molecular targets may be individual genes, molecules that either result from gene expression or are otherwise affected by gene expression, or any other molecular events that are relevant to the process of carcinogenesis. The increasing recognition of the diversity of molecular targets demonstrates the complexity and breadth of actions that nutrients can have in increasing or decreasing cancer risk.

Some of the most compelling evidence that diet can influence the cancer process comes from the intervention study by Clark et al. with selenium yeast as a supplement. (Fig. 11) Most of the current evidence suggests that while supplemental selenium may retard the cancer risk, classical selenium deficiency per se may not be a prerequisite for an increased risk.
Another nutrient with apparent significance in the cancer process is folate (folic acid). Its essential role in de novo biosynthesis of purines and pyrimidines, and thus DNA replication and cell division, and for the synthesis of S-adenosylmethionine (SAM), a methyl donor for more than 100 biochemical reactions including methylation of DNA, places it in a unique position relative to DNA stability. These biosynthetic pathways, each of which is important to DNA metabolism, appear to compete when the dietary methyl supply is inadequate, as in folate deficiency, possibly resulting in altered DNA methylation (an epigenetic event), disruption of DNA integrity and disruption of DNA repair, and, consequently, in an increased risk for carcinogenesis. Some of the most compelling evidence linking folate deficiency and cancer comes from the colorectal risk, although evidence does exist that a risk of cancer of the lung, uterine cervix, esophagus, stomach, pancreas, liver, breast and colon/rectum may also be associated. Hypomethylation and DNA stand breaks arising from folate inadequacy may actually promote the incorporation of viruses such as human papilloma virus (HPV) into human DNA. In humans, folate administration has significantly reversed hypomethylation in patients with chronic atrophic gastritis and colorectal cancer.

A number of nonessential phynutrients have also been found to impact the cancer process. Diethiolethione represents one class of nutrients that has been reported to influence a variety of molecular targets associated with cancer.

One of the major mechanisms of protection against carcinogenesis, mutagenesis, and other forms of toxicity mediated by carcinogens is the induction of enzymes involved in their metabolism, particularly phase-2 enzymes such as glutathione S-transferases, UDP-glucuronosyl transferases, and quinone reductases.

The hypothesis that fiber might decrease the cancer risk, especially in the colon, has been a topic of discussion for well over a quarter of a century. Several mechanisms, such as: increasing the stool bulk, decreasing the transit time, binding to bile acids and salts, fermenting to volatile fatty acids, binding to carcinogens and altering the colonic microflora, have been proposed to account for the epidemiological findings and the ability of selected fibers to alter the risk in animal models. Unfortunately, recent intervention studies raise real issues about which role fibers have in cancer prevention, if any. A 4-year study performed by Schatzkin et al. revealed that an increased ingestion of fruits, vegetable and fibers was not accompanied by a change in the risk of recurrence of polyps. It is, however, conceivable that for fibers to have an impact they have to be introduced earlier in the cancer process and thus examining individuals who are highly susceptible to the recurrence of polyps may not be the most appropriate target group.

Using the molecular epidemiology of genomics, proteomics, and metabolomics in this postgenomic era will enable complex nutrient-gene interactions to be investigated in clinical and dietary intervention studies at different stages of the life cycle (e.g. in utero, adolescence, adulthood or advanced age). Furthermore, researchers will be able to determine the effects of timing in the continuum of various cancer phases, from nutrition programming in utero to the intraepithelial neoplasia phase and to the invasive stage and metastasis. The resulting robust data bases of information should be sufficient to yield information on whether a particular nutrient, food, or diet intervention is appropriate for health at a particular point in the life cycle or at a specific stage of carcinogenesis of a given cancer.

In this postgenomic age, the nutrition sciences are undergoing a renaissance that serves as a catalyst for the study and understanding of the integrative biology of living organisms. Consequently, the complexities of the interactions among genotype, diet, and environment will unravel, and personalized nutrition recommendations for individuals will become a feasible and long-term challenge. In the near future, diet, nutrition and cancer prevention will have a dual focus on public health programs that target cancer risk management in the population at large and on individual programs that will focus on particular cancer risk profiles.

Nutritional genomics, proteomics, and metabolic profiling use highly sophisticated technologies that enable researchers to analyze thousands of genes and their complex expression simultaneously.

Increasing evidence substantiating the beneficial effects of certain nutrients in the carcinogenesis pathways pave the way for an eventual modification of nutritional require-
ments as a cancer prevention strategy. Concurrent with the rapid progression in the field of human genomics, agricultural industries have developed genomic-assisted plant improvement and now produce flora enriched with certain nutrients. As the nutrition sciences unfold at the levels of molecular genetics and nutrient-gene interactions, new knowledge will emerge on how nutrients may modify cancer risk and how food (functional or nutraceutical) that is altered with agronomic approaches and biotechnology may be used in cancer prevention. An effective multidisciplinary approach to these developments and the ever-widening knowledge base is paramount because our efforts will ultimately affect clinical applications in health promotion and disease prevention. Plainly stated 50 years ago, it is more true today than ever that nutrition remains the cornerstone of preventive medicine, the handmaiden of curative medicine, and the responsibility of us all.

It appears to us that the figure of 60-70% of cancer in sub-Saharan Africa, induced by poor nutrition and inappropriate diets is not far from the truth and we hope that the Medical African Societies will soon get interested in studying the dietary habits of their people and their correlation with cancer, instead of adopting slavishly the Western principles of oncology treatment.

Information and education should be part of African Medicine commitments. The abuse of ethnic beers, of tobacco and the life-long diets based on a single staple food will probably be found in all social levels.

REFERENCES


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