PROGRESS IN ENVIRONMENTAL MUTAGENESIS

M. ALAČEVIĆ

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PROGRESS IN ENVIRONMENTAL MUTAGENESIS

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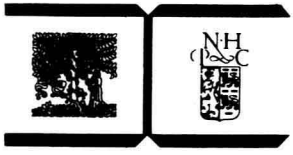

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Volume 7

Volume 1	Clinical Chemistry and Chemical Toxicology of Metals S.S. Brown editor, 1977
Volume 2	Progress in Genetic Toxicology D. Scott, B.A. Bridges and F.H. Sobels editors, 1977
Volume 3	Chemical Toxicology of Food C.L. Galli, R. Paoletti and G. Vettorazzi editors, 1978
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Volume 6	The Scientific Basis of Toxicity Assessment H.R. Witschi editor, 1980
Volume 7	Progress in Environmental Mutagenesis M. Alačević editor, 1980

PREFACE

The ninth Annual Meeting of the European Environmental Mutagen Society was held at Makarska - Tucepi, Jugoslavia from September 30th to October 5th, 1979. Following the tradition of previous meetings, most of the scientific communications were in the form of posters, abstracts of which are published elsewhere. A particular feature was the emphasis given to the plenary sessions, the proceedings of many of which constitute the substance of this book. The two major sessions were on the subjects of molecular mechanisms of genetic changes and a comparison of chemical and radiation mutagenesis. The importance of this comparison lies in the fact that it must influence the extent to which the philosophies and concepts of radiation protection can be applied to protection against chemical mutagens. It is hoped that these Proceedings will reflect the intellectual quality of the meeting although they can do nothing to communicate the warmth of Jugoslavian hospitality or the intense informal scientific discussions that were facilitated by the relaxing atmosphere of the Adriatic coast and islands.

B. A. BRIDGES

on behalf of the Programme Committee

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We also wish to emphasize the unselfish assistance of our students whose youth and enthousiasm brought a particular atmosphere to the Meeting.

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COMPARATIVE MUTAGENESIS: CHEMICAL *VERSUS* RADIATION

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Progress in Environmental Mutagenesis
M. Alačević, editor

HOW EFFECTS OF CHEMICALS MIGHT DIFFER FROM THOSE OF RADIATIONS IN GIVING RISE TO GENETIC ILL-HEALTH IN MAN

H.J. EVANS
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INTRODUCTION

The title to which I have been asked to speak is in the form of a rather formidable and important question which is not of my own choosing. It is *formidable* because we can by no means claim to have a clear understanding of how exposure to radiations induces genetic ill-health in man, let alone ask how the consequences of exposure to chemicals might differ from exposure to radiations! It is *important* because, in addition to the very wide range of naturally occurring biologically reactive compounds present in our environment, man has already made and introduced into his environment some 70,000 or so new or unnatural synthetic chemicals and is currently introducing a further 1,000 or so new compounds per annum. Our concern naturally follows from the fact that many of these chemicals, or their derivatives, are highly reactive, and a significant proportion of them are mutagenic in bacterial or eukaryotic cell systems. Our interest in the effects of these chemicals and of radiations on genetic ill-health in man is therefore a consequence of the mutational properties of these agents.

In any attempt to consider possible differences between the effects of these two groups of agents, we need first to arrive at some estimate of the contribution that the mutational process currently makes to ill-health in man - in other words that are the "spontaneous" rates of mutations that result in what we loosely define as ill-health or disease? For these are the rates that we expect to be altered if we expose ourselves to radiations or chemical pollutants. But before considering these numbers, we should first note that there are two kinds of genetic damage relevant to our discussion:

(i) The first type, which is often considered to be *the* genetic damage of importance, involves mutational changes induced in germ

cells or germ cell precursors which are then transmitted to the products of conception and to any resultant offspring and their descendants. This kind of damage we can refer to as *heritable genetic damage*.

(ii) The second kind of genetic damage that is often glossed over, ignored, or not considered to be relevant under the general heading of genetic damage, is that damage sustained by the genome in somatic cells which is transmitted to daughter cells. Such *somatic mutations* are of course not heritable in the familial sense, but they are transmitted to descendant cells within the body.

A. SOMATIC MUTATIONS

In so far as genetic ill-health in man is concerned, virtually nothing is known about the consequences of somatic mutations, although we do know that they exist and indeed for certain type of mutation, for example some of those which involve chromosomal structural changes, we can even provide some data on the frequencies of these events in blood lymphocytes or bone marrow cells[1]. What is worth bearing in mind is the fact that each day within our own bodies some hundreds of thousands or millions of cell divisions take place in the bone marrow, in the skin and the epithelial linings of the body cavities, and that each of us continually produces a large mass of replacement new tissue that is required for a normal healthy status. Considering this over the lifetime of an individual, then it is clear that there are many billions of cell divisions involved and if any mutational event at any given locus occurs at a frequency of 1 in 10^5 or 10^6 cell divisions, then each day in our lives each of us produces a few score mutant cells. Many of these mutations will be quite irrelevant, but others may be very important, depending on the type of mutation and the kind of cell in which it occurs: for example, a mutation at an immune system gene that is not transcribed in a differentiated nerve cell may be immaterial, but such a mutation in a lymphocyte precursor could have dire consequences.

We like to speculate that some of the most important somatic mutations in relation to human health are those that result in neoplastic change and there is a very considerable body of indirect

evidence that points to a mutational process as being important in the development of most human cancers[2]. I am not going to discuss this, but I want to briefly refer to the fact that some individuals have a heritable predisposition to the development of early cancer, which in some cases can be shown to be inherited as an autosomal recessive condition. In one such example, that of ataxia telangiectasia, cells of these individuals are ultrasensitive to the mutational and chromosome damaging effects of X-rays and the individuals themselves are ultrasensitive to the induction of tumours by X-rays[3]. Cells from other 'cancer-prone' individuals in which there may be a defect in the machinery for repairing DNA damage, have been shown to be ultrasensitive to the induction of mutation and chromosome damage following exposure to UV-light and/or a variety of chemical mutagens (table 1).

TABLE 1

INHERITED CONDITIONS IN MAN PREDISPOSING TO EARLY DEVELOPMENT OF NEOPLASIA AND IN ULTRASENSITIVITY (+) TO CANCER INDUCTION, CELL KILLING, MUTATION AND CHROMOSOME ABERRATIONS FOLLOWING EXPOSURE TO MUTAGENS

Phenotype	Mutagens	Cell killing	Mutation	Chrom. aberr.	Cancer induction
Ataxia telangiectasia	X-rays various chems.	+	+	+	+ (X-rays)
Xeroderma pigmentosum	UV-light various chems.	+	+	+	+ (UV-light)
Fanconi anaemia	various chems.	+	+	+	?
Blooms syndrome	UV-light various chems.	+	+	+	?
Retinoblastoma	X-rays	+	?	?	?

Individuals with xeroderma pigmentosum are ultrasensitive to the induction of skin cancer by UV-light and their cells to the induction of mutations and chromosome aberrations by this agent and by

various chemical mutagens[4]. Cells from patients with Fanconi's anaemia or with Bloom's syndrome are also ultrasensitive to damage induced by a variety of chemical mutagens[5,6] and, although we have no direct evidence, it seems not improbable that at least a part of the increased cancer incidence in such individuals[7,8] may be a consequence of their exposure to chemical mutagens.

What of course is clear is that ionising radiations and certain of the chemical agents known to be mutagenic to human cells in culture, are human carcinogens and in that context we might consider that exposure to these agents contributes towards induced genetic ill-health in man. In comparative terms, we would of course expect that differences in metabolism and tissue distribution on the part of chemical mutagens will result not only in differences between the distribution and types of neoplasm induced, or promoted, by chemical mutagens on the one hand and radiations on the other, but also in differences between the different chemical agents.

Before leaving the topic of somatic mutations, I think we should note that a wide spectrum of different mutations over a range of loci in the human genome could result in producing non-malignant cell lines or clones within the body which are less efficient than the normal. These mutations could contribute to lowered efficiency of cells, tissues, organs, or enzyme systems and so to ill-health and life shortening. It may be very difficult to detect such mutations, but they surely must exist and indeed, it has been suggested[9,10] that atherosclerotic plaques on the walls of blood vessels may represent just one such class of mutant clones contributing to ill-health. However, at present we really have no means whatsoever of measuring the consequences of somatic mutations to health - but we musn't forget that they exist.

B. HERITABLE MUTATIONS

We could consider that our heritable mutations may be grouped into five convenient phenotypic classes including conditions inherited as; (i) dominant, (ii) recessive, (iii) sex-linked effects showing simple Mendelian inheritance, and, (iv) chromosome abnormalities and (v) multifactorial - or polygenic - states.

Dominant, recessive and sex-linked conditions

In his most recent catalogue of phenotypes (or genetic loci) in man, McKusick[11] lists around 1,700 dominantly inherited conditions, about 1,200 recessives and some 200 or so X-linked conditions. All of these by no means reflect serious disabilities or disease states on the parts of the individuals carrying them, but some of them do and this catalogue as yet of course can list only a fraction of those genetic states in man that are associated with ill-health. Our deleterious genes may affect the whole spectrum of body systems and the frequencies of some of the more common autosomal dominant, recessive and sex-linked conditions are given in tables 2, 3 and 4[12].

TABLE 2
ESTIMATES OF BIRTH FREQUENCIES OF SOME MORE COMMON DOMINANT CONDITIONS IN EUROPEAN DERIVED POPULATIONS PER 1000 LIVE BIRTHS*

Nervous system	Huntington's chorea	0.5
	Neurofibromatosis	0.4
	Myotonic dystrophy	0.2
Intestines	Multiple polyposis coli	0.1
Kidney	Polycystic disease of the kidneys	0.8
Skeleton	Diaphysial aclasis	0.5
Sight	Dominant forms of blindness	0.1
Hearing	Dominant forms of early childhood onset deafness	0.1
	Dominant otosclerosis (adult onset)	3.0
Circulation	Monogenic hypercholesterolaemia	2.0
Teeth	Dentinogenesis imperfecta	0.1
Blood	Congenital spherocytosis	0.2

* After Carter[12]

Amongst the autosomal dominants we might well have included α-1-anti-trypsin deficiency, with an incidence of around 1 in 2,000, where some 10-20% of people with this gene develop severe hepatitis as neonates and up to 30% may develop emphysema as adults. It is also worth noting that there are other more common autosomal dominant disorders of lipid metabolism, and that individuals homo-