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INTRODUCTION

Currently, predictions of possible risk of heritable mutations in human beings are based on inferences, or "extrapolating" results, of mutagenicity tests in other organisms or in laboratory cell cultures. One of the key problems in genetic extrapolation is that, while there is no shortage of mutagenicity tests using a variety of organisms and cell types, researchers have just begun the painstaking work of drawing out relationships among results of different tests, and of eventually validating models for extrapolating to heritable effects in human beings (see fig. 14). This chapter reviews the basic constructs that have been devised for framing genetic extrapolations and then presents some efforts that have been made to carry out specific extrapolations.

The Aims of Extrapolation

For many years, the emphasis in mutagenicity testing has been on developing individual tests and learning about their properties. Test development has not been targeted exclusively toward developing predictive models for heritable mutations in human beings and in fact the quest for tests that could be used to predict carcinogenicity through somatic mutation has predominated. This being the case, the test systems vary tremendously and include, for example, tests in bacteria, insects, animal somatic and germ cells in culture, whole mammals, and human somatic cells. Efforts to relate results from one test system to another or from various tests to human beings, even on a qualitative level, have been relatively recent and have not progressed very far to date. Bridges (15) summarized this situation:

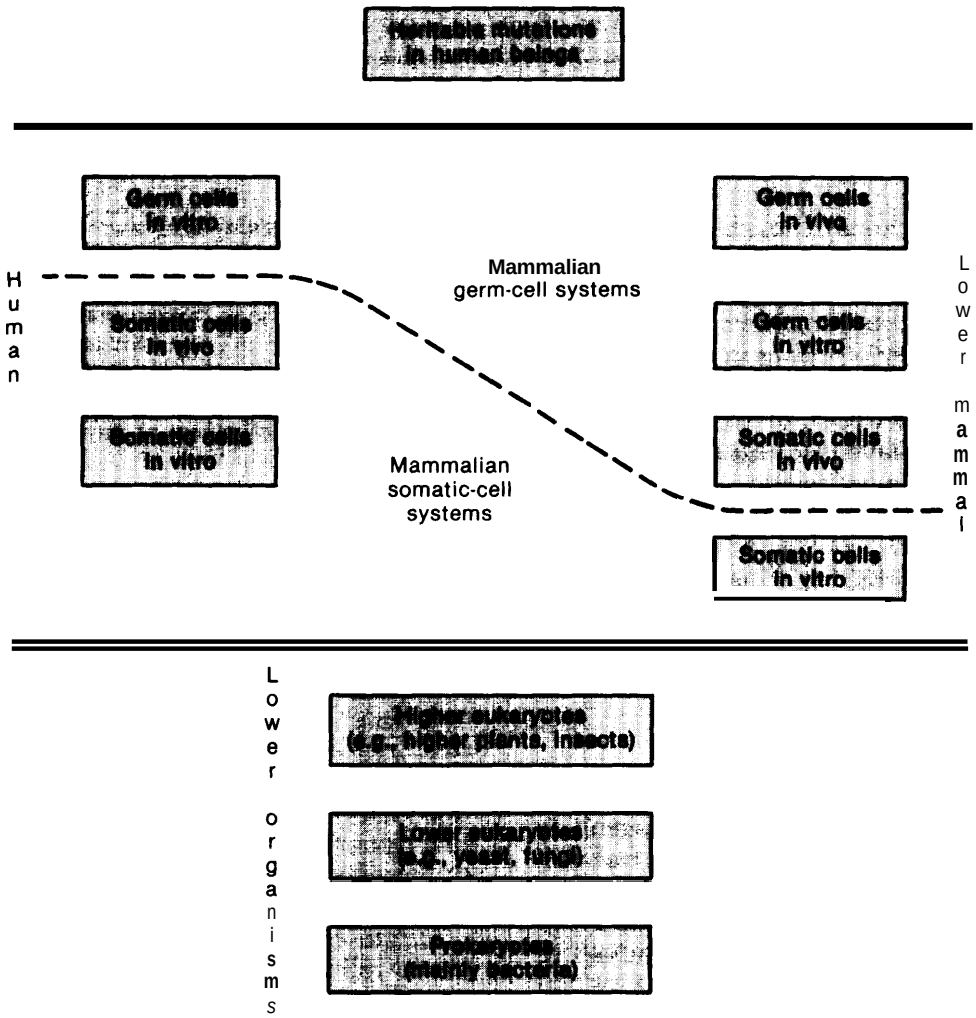
> Despite the extremely large number of screening tests that have been performed, remarkably little rational thought **has** been devoted to the use that should be made of the results of such tests. Mutagenicity tests in lower organisms[1] are essentially screening tests warning of a possible human hazard. They do not give any quantitative indication of the level of risk to man, not so much because of differences in the organization of DNA in man and lower organisms, but because of the complex metabolic capabilities of man which may greatly enhance or diminish the mutagenic effectiveness of an agent.

In recent years, scientists who use different experimental approaches to study mutations have begun to discuss methods to correlate results from various test systems. The first consideration is whether results from one system are qualitatively predictive of results in another, i.e., are appropriate endpoints being considered and do the results agree in whether they are positive or negative. This is called "biologic extrapolation. " The second type of extrapolation is *quantitative,* which deals with the relationship between the quantitative response in a test to a quantitative estimate of the likely effect in human beings.

Examples of questions posed in extrapolation are the following: If experiments demonstrate that a single exposure to a high dose of a chemical induces heritable mutations in mice, what would be the result of a single exposure to a lower realistic dose or of a long-term exposure to a lower dose of that chemical in humans? How do results of mutagenesis experiments on rodent somatic cells in a test tube cell culture (e. g., Chinese hamster ovary cells "in vitro") relate to the issue of mutation rates inhuman somatic cells, or mutation rates in human germ cells? What are appropriate dose conversions between various experimental systems and human beings? If a worker in a chemical plant has a tenfold increase in mutation frequencies in his or her somatic cells, what are the long-term health implications? Is that worker at increased risk of having a child with a new mutation? These types of questions illustrate the complex issues that arise in using results from one system to make predictions of risks to human health.

[1] "'Lower organisms" refers to bacteria, yeast, Drosophila, etc., and *not to* whole mammals.

Figure 14.-Biological Test Systems for Studying Mutations



Test **systems for studying mutations, arrayed according to biological similarity to the endpoint of interest—heritable mutations in human beings. Some test systems can be used to measure a single endpoint; more than one type of endpoint (e.g., both chromosomal and gene mutations) can be measured in other systems. Extrapolation from any system to human germ cells in vivo involves many, mostly untested, assumptions.**

SOURCE: Office of Technology Assessment,

In translating results from one system to another (using similar genetic endpoints), a number of separate extrapolations may have to be made: 1) from species to species; 2) from experimental doses to actual environmental doses; 3) from one cell type to another; 4) from in vitro to in vivo physiological conditions; and 5) the biggest and most uncertain leap, from estimates of mutation frequencies to estimates of genetic disease in humans. The kind of information that would give the biggest boost to the ability to predict effects in humans with information from other test systems is knowing exactly what kinds of mutations (e.g., point mutations, chromosomal rearrangements, etc.) each of the tests detects. The new technologies discussed in this report may provide this type of information.

EXTRAPOLATION MODELS

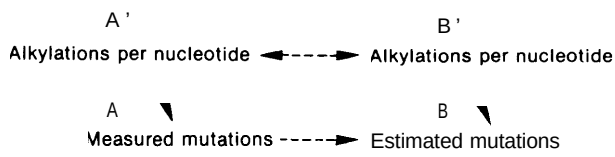
Several researchers have begun developing models for extrapolating from one test system to another (14,15,46,49,61,64,106, 129,130,138). one of the key features common to all the extrapolation models developed is that a result from a single test system would not be used alone to predict a result in another test system. Instead, results from several related test systems are correlated and used together.

Several of the methods described are extensions or rearrangements of the first extrapolation method developed by Sobels (1290)—the parallelogram (130):

> The underlying principle is to obtain information on genetic damage that is hard to measure directly, for example mutation in mouse germ cells, by comparison with endpoints that can be determined experimentally, e.g., alkylation per nucleotide in mammalian cells in vitro and in mouse germ cells, and mutation induction in mammalian cells in vitro.

Sobels' parallelogram is illustrated in figure 15. It is relatively easy to determine the mutation frequency in mouse somatic cells (a quantity called "A") upon exposure to a particular chemical mutagen in culture. With certain types of chemicals. (alkylating agents), it is also possible to derive a measure of the interaction of the mutagen with the DNA of those cells, which is quantified as "alkylations per nucleotide" (a quantity called "A"). Alkylations per nucleotide can also be measured in mouse germ cells after exposure to the same mutagen (B'). The relationship of these different values is then used to calculate the expected mutation frequency in mouse germ cells (B) on exposure to the same mutagen. A major, untested assumption is that the ratio of A to A' is proportional to the ratio of B to B', i.e., A/A = B/B If that is true, it is then a matter of simple algebra to predict the mutation frequency in mouse germ cells (B) by solving the equation for B, which is the only unknown quantity.

Figure 15.—An Example of a Parallelogram



(Note that the same test system is represented in the vertical dimension and the same genetic endpoint in the horizontal dimension.)

SOURCE: F.H. Sobels, "The Parallelogram: An Indirect Approach for the Assessment of Genetic Risks from Chemical Mutagens, " pp. 323-327 in K.C. Born et al. (eds.), *Progress in Mutation Research, vol. 3* (Amsterdam: Elsevier, 1982).

A similar parallelogram can be used to extrapolate results from mouse germ cells to human germ cells. Mutation frequencies are measured in somatic cells of both humans and mice. Germ-cell mutation frequencies are measured in the mouse and compared to somatic-cell mutation frequencies in the mouse. Assuming that the ratio of germ-cell to somatic-cell mutation frequencies is the same in mice and human beings, germ-cell mutation frequencies in human beings can be predicted from the measured human somatic-cell mutation frequencies (64).

Streisinger (138) has proposed a more complex extrapolation method using two sequential paral-

lelograms. In the first parallelogram, a measure of chemical interaction with human germ cell DNA is estimated from measurements of the effects of the chemical in human and animal (e.g., monkey) somatic cells, and a measure of interaction of the same chemical with germ-cell DNA in the same animal. In the second parallelogram, the ratio of a measure of chemical interaction with mouse germ-cell DNA to mouse germ-cell mutation rates (from the specific locus test) is used to predict the human germ-cell mutation rate using the estimated value of chemical interaction with human germ-cell DNA from the first parallelogram. This construct embodies several untested assumptions.

Bridges (1980) also developed a more complex extrapolation model based on the original parallelogram model of Sobels. Based on his approach, Bridges outlined the types of results needed to fill information gaps, ultimately to assess the impact of mutagens at the: 1) molecular; 2) cellular; and 3) whole organism levels in both animals and man. He suggested studies to determine: 1) the presence of an effective dose of mutagen at the molecular level by measuring the concentration of mutagen in the gonads or blood or the extent of reaction with DNA; 2) whether there appears to be a relationship between the presence of the mutagen and a biological response at the cellular level by measuring somatic mutation frequencies or chromosomal changes in lymphocytes; and 3) whether there is an effect at the whole organism level by measuring the frequency of heritable genetic defects, congenital malformations, or fetal loss.

The values Bridges specifies are obtainable in animal systems. To obtain such values for man, Bridges suggests that use be made of certain otherwise normal human populations that are exposed to large doses of mutagens. Examples of such populations are patients treated for diseases, such as cancer, with drugs that are known to be mutagenic, and certain occupational cohorts in which there are known excesses of cancer (1,155). Simultaneous studies using the same mutagens could be carried out in experimental mice to determine the relative sensitivities of mouse and man to these mutagens.

Parallelogram models are attractive for their simplicity and inherent logic. They are appropriate starting points for exploring relationships among test results when sufficient data become available to do so. However, the assumptions embodied in parallelogram models—consistent, predictable relationships among various cell types, translatable among species—are almost entirely untested. The great differences among species make it unlikely that these parallelogram models will survive validation studies intact. While they may continue to be useful research tools for posing logical questions, they may or may not prove practical for predicting risks of heritable mutations in human beings.

ATTEMPTS AT QUALITATIVE EXTRAPOLATION

L. Russell and colleagues (106) compared the results of mutagenicity tests carried out in a variety of systems other than whole mammals with results from specific locus tests (SLTs) and heritable translocation tests (HTTs) in mice (see ch. 6 for descriptions of these two tests). The purpose of the comparison was to find out how well results of the nongerm-cell tests corresponded to the qualitative results (positive or negative) of the two germ-cell tests. The analysis was limited by the relatively small number of chemicals that have been tested in either the SLT or the HLT. About 35 chemicals have been tested in one or both of the germ-cell assays, out of a total of about 2,000 chemicals for which some test results are available from any system.[2]

The comparison tests were grouped into 18 categories and the categories given relative weights according to their biological relationship to one of the germ-cell tests. The categories and their weights are given in table 9. The lowest weighted category includes tests using prokaryotes, such as bacteria, directly treated by the suspected mutagen. Higher scores signify moving toward higher

[2]These test systems are not the focus of this report and are not described here in detail. Descriptions of these tests can be found in **(88).**

Table 9.—Weighting of Test Results for Presumption of Germ-Line Mutagenicity

	Exposure not within mammalian body	Weight	Exposure within mammalian body	Weight	Germ cells	Weight
Prokaryotes, all endpoints	SAL WP–	1	BFT HMA	2		
Lower eukaryotes, all endpoints	YEA YEP ASP NEU	2				
Higher eukaryotes, chromosome aberrations	PYC	3			DAN DHT	8
Higher eukaryotes, gene mutations	PGM	3				8
Mammals, genetically nondefined endpoints	SC1 SC2 UDH UDP	4	SC3 SC4	6		4 8
Mammals, chromosome aberrations	CYC	5	MNT CYE CYB CY5 CY8 }	7 10	DLT CY9 CYO	15
Mammals, gene mutations	CHO V79 L51	5	MST	10	SPF	15

NOTE' In general, the weights increase from top to bottom and from left to right in the table, From top to bottom, the tests progress from lower to higher organisms and from more general endpoints to endpoints of direct relevance to human heritable mutations. From left to right, the categories progress from in vitro tests in both somatic and germ cells, to in vivo germ-cell tests

Explanation of test symbols.

ASP Aspergillus, all tests
BFT Body fluid tests, all assays
CHO Chinese hamster ovary cells in culture
CYB Mammalian cytogenetics, in vivo, animal bone marrow
CYC Mammalian cytogenetics, in vitro, all cell types
CYE Mammalian cytogenetics, in vivo, animal lymphocytes or leukocytes
CYO Mammalian cytogenetics, in vivo, oocyte or early embryo studies
CY5 Mammalian cytogenetics, in vivo, human bone marrow
CY8 Mammalian cytogenetics, in vivo, human lymphocytes or leukocytes
CY9 Mammalian cytogenetics, all male germ-cell studies
DAN Drosophila aneuploidy studies, all tests
DHT Drosophila heritable translocation test
DLT Dominant-lethal test in rodents
HMA Host-mediated assay studies
L51 Mouse lymphoma cells in culture, gene mutations at TK locus
MNT Micronucleus test, all species
MST Mouse spot test
NEU *Neurospora crassa*, all tests
PGM Plant gene mutations, all tests
PYC Plant chromosome studies, all tests
SAL Salmonella histidine reversion tests
SC1 Sister-chromatid exchange, human cells in vitro
SC2 Sister-chromatid exchange, animal cells in vitro
SC3 Sister-chromatid exchange, animals in vivo
SC4 Sister-chromatid exchange, human cells in vivo
SPF Sperm abnormalities in F1 males
SPM Sperm abnormalities in treated animals
SRL Drosophila sex-linked recessive lethal test
UDH Unscheduled DNA synthesis, human diploid fibroblasts
UDP Unscheduled DNA synthesis, rat primary hepatocytes
UDT Unscheduled DNA synthesis, testis in vivo
V79 Chinese hamster lung (V79) cells in culture, all gene mutation studies
WP *E. coli* reverse mutation studies
YEA *Saccharomyces cerevisiae*, all tests
YEP *Schizosaccharomyces pombe*, all tests

SOURCE L.B Russell, C S Aaron, F de Serres, et al , "Evaluation of Mutagenicity Assays for Purposes of Genetic Risk Assessment," *Mutation Research* 134:143-157, *1984*

mammals, toward germ cells, and toward treatment with the chemical in a whole mammal.

A single composite score was calculated for each chemical tested, adding together scores from each category in which there were test results. There is only one score per category regardless of the number of tests. Positive results are scored as positive numbers; negative results as negative numbers, e.g., an in-vitro somatic-cell chromosome aberration test with a positive result yields a score of +5, one with a negative result, a score of —5.

Russell and colleagues found that nearly all chemicals that tested positive in either or both the SLT and HTT had high composite scores from other tests. A number of chemicals with negative SLT and HTT results also had high, positive composite scores, representing "false positives" in the comparison tests.

Similar analyses looked separately at the SLT and HTT and the comparison tests that specifically detect gene mutations or chromosome aberrations, respectively. The results are similar to those matching the results in all comparison tests against both mammalian germ-cell assays: high scores for most chemicals positive in the germ-cell tests, and a number of false positives.

In an additional analysis, the comparison tests are ranked according to how well each predicts the results of the two germ-cell tests. In general, the tests in **higher** numbered categories in the earlier analyses, i.e., those that are closer biologically to whole mammal germ-cell tests, had better correlations with the SLT and HTT. For the SLT, the best predictors overall were the mouse spot test, unscheduled DNA synthesis in mouse testis, and the micronucleus test. For the HTT, unscheduled DNA synthesis in testis, the dominant-lethal test, and one lower ranked test, sister-chromatid exchange in cultured animal cells, were the strongest predictors.

While it appears that the results of some of the comparison tests correlate relatively well with the mammalian germ-cell tests, in fact, not *one* of these correlations reaches conventional statistical significance, meaning that the tests do not predict reliability better than chance. The lack of significant results is due, in large part, to the small number of comparisons for many tests, and in part because of the process for selecting chemicals for SLT and HTT. From a practical, public policy standpoint, this is an important finding. The lack of statistically significant results does not mean that these comparisons are without value. The study provides a status report on the quality and quantity of existing data.

Since the two whole mammal tests (the SLT and HTT) are relatively expensive and time-consuming, they are usually reserved for testing chemicals highly suspected of causing heritable mutations. The suspicion is based on results of other tests, specifically the comparison tests examined in Russell and colleagues' analysis. It is hardly surprising, therefore, that the comparison test results are largely positive for chemicals eventually tested in the mammalian germ-cell assays. Russell and colleagues took the preponderance of positive results into account in their analyses.

Many chemicals have been tested in mutagenicity assays because, for reasons of chemical structure or other properties, there is a high likelihood that they will be mutagenic. While these chemicals have proved useful as laboratory tools, they are not necessarily useful for drawing conclusions about what people are actually exposed to. W. Russell (111), using the same database used by L. Russell and colleagues (106), looked exclusively at the 11 "environmental chemicals" (those found in the home or workplace) that have been tested in the SLT and examined the results. All 11 are positive in the Drosophila sex-linked lethal test, the 10 that have been tested are positive in mammalian somatic-cell tests, and there are a variety of positive results in other test systems. None of the 11, each of which was tested at very high doses, is positive in the SLT, suggesting no increase in mutations in spermatogonia (the pre-meiotic male germ-cell stage) although several have positive results in tests of later sperm developmental stages.

What conclusions can be drawn about the validity of qualitative extrapolation from various mutagenicity tests to a risk of heritable mutations in human beings? The available data give no direct information about mutagenic effects of chemicals on human germ cells in vivo. Application to humans rests on a series of assumptions about the response of human germ cells in relation to responses in other types of cells and in other species.

The analysis of the these test results does allow some generalizations about biologic extrapolation and about the nature of the available test database. On the first point, there is evidence suggesting that chemicals that test positive in some comparison tests for gene mutations or chromosomal aberrations have a likelihood of being positive in the SLT or HTT, respectively, but are not invariably so. To date, chemicals testing negative in the comparison tests have not produced clear positives in whole mammal germ-cell tests, but the database supporting this comparison is limited. Biologically, it seems unlikely that chemicals that are consistently negative in comparison tests would, in fact, be germ-cell mutagens in whole animals. But it is unlikely also that very many chemicals with negative results in one or two tests will have been tested in enough systems to allow an empirical test of that hypothesis.

Both L. Russell's and W. Russell's analyses described above suggest that a number of chemicals that test positive in the simpler comparison tests will be not be shown to cause mutations in spermatogonial germ cells. At present, however, it is impossible to know based on comparison test results, which chemicals are true human germ-cell mutagens and which are not.

A major limitation of the database is that nearly all tests have been in exposed male animals. Two strong animal mutagens—radiation and a chemical agent, ethylnitrosourea—do not appear to cause heritable mutations in the immature germ cells of female mice, but the data for females are not sufficient to draw firm conclusions.

The new technologies described in this report, which could be used to provide information on the types of mutations detected by the various tests, may improve our ability to apply the results of simpler tests to predicting human risk.

ATTEMPTS AT QUANTITATIVE EXTRAPOLATION

Not surprisingly, quantitative extrapolation is even less advanced than is qualitative extrapolation. However, there are some data bearing on quantitative relationships that may eventually be useful in predicting effects in human beings. First, there is some information about dose-response relationships. Second, some preliminary attempts are being made to determine relationships among certain corners of the parallelogram models described earlier in this chapter. One such effort is described below.

In an ongoing effort, a group of investigators is using a parallelogram approach to evaluate the effects of gamma radiation, cyclophosphamide (a medical drug) and benzo[a]pyrene (an environmental chemical) on mouse and human cells by assaying chromosomal aberrations and sister chromatid exchanges in mitogen-stimulated peripheral blood lymphocytes (PBLs). While these investigators have as yet little data, a paper presenting some preliminary results (170) lays out the rigorous procedures necessary for proper extrapolation of results from different studies of just one substance to predictions in untested systems. For instance, in the case of radiation, the authors relate an experimental result in irradiated cultured human PBLs to reports from the literature of the same chromosomal endpoint (dicentrics) in PBLs from patients who have received therapeutic radiation. Thus far, these authors have not presented any conclusions about the relationships they are studying.

Dose= Response Relationships

Extrapolation from high to low dose, and from high to low dose rate, requires knowledge of dose-response relationships. For heritable gene mutations, adequate data on dose-response relationships is limited to the effects of ionizing radiation and one chemical, ethylnitrosourea (ENU), in male mice. The available information comes from results of SLTs in mice, most of the work being done in a small number of laboratories in different parts of the world. Radiation and ENU have also been assayed in many short-term in vivo and in vitro tests in human somatic cells, so some generalizations may be drawn about the nature of dose-response relationships for these two agents. In both cases, there are independent effects of dose rate and of total dose. This means that a fixed dose may cause a different rate of mutations depending on the intensity of the dose, i.e., a more protracted administration may result in fewer mutations than if the total dose is administered at one time.

Radiation

Specific-Locus Test. —In a series of experiments from the mid-195@ to the present, a range of radiation doses, delivered at a range of dose rates, has been tested in male mice. Results are available for both spermatogonial and postspermatogonial stages. In spermatids and spermatozoa (postspermatogonial stages), the dose-response relationship is generally linear, and there is no effect of dose rate. This means that approximately the same mutation rate results from a short, high-dose exposure and from a chronic, low-dose exposure when the same total dose is given.

In spermatogonia, the early, pre-meiotic stage, for equal total exposure, radiation given at high dose rates causes more mutations per unit of dose than radiation at lower dose rates. At a high dose rate of 90 Roentgens per minute (R/rein) or intermediate dose rate of 8 R/rein (work cited in 111),

the mutation rate decreases with decreasing dose faster than would be predicted by a linear relationship. At dose rates of 0.8 R/rein or below, however, the rate of mutations per unit dose appears to be constant, and without a threshold. At low dose rates, the dose-response relationship is linear, and above about 0.8 R/rein, the mutation rate per unit of dose rises more quickly than would be predicted by a linear relationship. Above a total dose of between 600 and 1,000 rem, the mutation rate begins to decline rapidly.

Investigators using the SLT offer an explanation for the observed dose-response patterns (111, 114,115). They postulate that the difference in dose-rate response between spermatogonia and postspermatogonial stages is a function of an active repair mechanism in metabolically active spermatogonial cells, which does not function at later stages. In the earlier, spermatogonial stages, a larger percentage of changes can be repaired before the spermatogonia complete meiosis when exposure is at a lower dose rate than is the case with an acute, high-dose-rate exposure. In post-spermatogonial stages when capacity for repair is low, the total radiation dose, irrespective of dose rate, is the determinant of the mutation rate.

Heritable Translocation Test.—Generoso and co-workers (135) have investigated heritable translocations induced by high-dose rate (96 R/rein) irradiation of spermatogonial stem cells of mice. They report a linear dose-response relation between O and 600 R of total irradiation, and repetition of doses in this range gave additive effects up to 2,000 R. From these data, the expected increase in heritable translocations at high-dose-rates is calculated to be about 0.00004 per R.

Cytogenetics.— Waters and colleagues (170) describe a dose-response relationship for gamma radiation after both in vitro and in vivo irradiation, using as an endpoint a certain type of chromosomal mutation, dicentrics, in PBLs. The in vivo dose-response, which was derived from reports in the literature, is linear at lower dose rates, and quadratic at higher dose rates, meaning that the increase in the number of dicentrics rises faster than it would if the relation continued to be linear. The quadratic component may be explained by an interaction of mutational events causing some dicentrics, and the interactions being increasingly more likely as the dose rate increases.

Ethylnitrosourea (ENU)

Specific Locus Test.—As is the case with radiation, both total dose of ENU and dose-rate independently affect the mutation rate in mouse spermatogonia. Experimental data indicate that the response at doses below 100 mg/kg of body weight is "infralinear," meaning that as the dose is lowered, the mutation rate drops faster than would be predicted by a linear relationship. At doses between 100 and 400 mg/kg, the response appears to be linear (4 I). No threshold was detected over the range of doses tested, but the possibility of a threshold at a dose lower than 25 mg/kg (the lowest single dose tested) is not excluded by the data.

In an experiment examining mutational responses at different dose rates, the mutation rate was measured in mice that were given 10 weekly doses of 10 mg/kg of ENU, and compared with the mutation rate for a single dose of 100 mg/kg of ENU. The mutation rate for the fractionated dose was only about 15 percent of the rate for a single dose (112).

Russell (111) notes that, in light of information indicating that ENU reaches germ cells in doses proportional to injected amounts (see next section), these results cannot be explained by differences in metabolic processes. He interprets the infralinear portion of the dose-response curve and lower mutation rate that follows dose fractionation to be the result of effective mutational repair systems in spermatogonia, the same reasoning as in the case of radiation.

Unscheduled DNA Synthesis in Mouse Spermatids.—Carricarte and Sega (cited in 111) found the dose-response of "unscheduled DNA synthesis" in mouse spermatids to be linear over the range from 10 to 100 mg/kg, the same range over which W. Russell (111) found an infralinear relationship in the SLT. Sega (cited in 111) also measured "adduct formation" after injections of ENU, and found a linear response in the range from 5 to 100 mg/kg. One conclusion from these observations is that chemical interaction with DNA may not always be directly related to the rate of mutation, and

this presents a major difficulty for Sobels' parallelogram, described earlier in this chapter.

Sister-Chromatid Exchange **and** Thioguanine Resistance.–Jones and colleagues (54) investigated the dose-response relationship for two somatic-cell endpoints in whole mice exposed to ENU. The frequency of sister-chromatid exchange (SCE) and the frequency of thioguanine resistant (TG^r) cells were measured in white blood cells in the spleen. Corresponding endpoints exist in human beings, which makes them potentially useful for extrapolating to human responses. The investigators measured both the response over time at several dose levels, and the response to a range of doses at several points in time after exposure.

Linear relationships were discovered between dose and reponse for both SCEs and TG^r cells, but the timing of these responses was quite different. For all dose levels, the highest SCE levels were measured on the first day after exposure, and SCE levels decreased back to baseline after about 70 days, whereas the TG^r response rose linearly over time to a peak after about 80 days for each dose level.

Generalizations About Dose-Response

While dose-response relationships cannot be generally and simply described some generalizations can be made. It appears that mutations in somatic cells are more predictable from the various experimental test systems available than are mutations germ-cell. Repair of mutations in germ cells may explain this difference. Both a better understanding of the mechanisms of mutation and repair at the molecular level, and empirical comparisons of test data on more substances will contribute to a better understanding of dose-response relationships. Once again, the new technologies may contribute to this understanding.

LIMITS OF EXTRAPOLATION

The main limitation to validating extrapolation models is a virtual lack of data to complete the parallelogram models. Until there is enough empirical information to determine whether qualitative and quantitative generalizations can be made, it is impossible to know how useful extrapolation could be. At present, qualitative extrapolation is at least a tentative guide for identification of mutagenic agents.

Even when data are available, many questions bedevil the use of experimental animal data to extrapolate risks to humans. In particular, little is known about the comparability of species with respect to activation, detoxification, and tissue distribution of specific chemicals, as well as other interspecies differences in metabolism. In addition, mutational responses of germ cells at different stages of development can differ for different types of mutagens. Many of these gaps in information could be filled by studies that are now technically feasible.

In using test results from somatic cell systems, there are differences in the sensitivities of various types of somatic cells and germ cells to different mutagens. Even within a single cell type, different gene loci can respond very differently to a specific mutagen. In making comparisons, for instance, between somatic and germ cells, if the same locus (or set of loci) cannot be tested, any differences in outcome cannot necessarily be attributed solely to a difference in cell type. These are a few of the many uncertainties in extrapolations from somatic to germ cells.

An organizational problem that affects extrapolation in a practical way is that collaborations have been rare among researchers working with different systems, and are particularly rare among scientists working in different laboratories. In addition, the test systems are not necessarily standardized among laboratories working with the same systems, so results from different laboratories cannot always be combined or directly compared.

Even relatively simple aspects of experimental procedures, for instance, the conditions under which cells or organisms are exposed to radiation or chemicals, vary enough among laboratories to render results incomparable to varying degrees.

Overall, the development of methods to extrapolate from different experimental test systems to the risk of heritable mutations in human beings is still in its infancy. While the various parallelogram models are appealing because of their potential usefulness, some of the data already available suggest that they may never broadly applicable. Both qualitative and quantitative improvements in the database of experimental results will be necessary before the usefulness of extrapolation can be reasonably assessed.