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# Biological Effects of Static Magnetic Fields: A Selective Review with Emphasis on Risk Assessment

C. E. Easterly

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HEALTH AND SAFETY RESEARCH DIVISION
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National Technical Information Service
U.S. Department of Commerce
5285 Port Royal Road, Springfield, Virginia 22161
NTIS price codes—Printed Copy: A05; Microfiche A01

ORNL/TM--7860

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Contract No. W-7405-eng-26

Health and Safety Research Division

# BIOLOGICAL EFFECTS OF STATIC MAGNETIC FIELDS: A SELECTIVE REVIEW WITH EMPHASIS ON RISK ASSESSMENT

C. E. Easterly

Date Published - April 1982

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# ACKNOWLEDGEMENT

The author would like to acknowledge J. B. Cannon for his unending support throughout the entire process of producing this document.

# HIGHLIGHTS

The increasing potential for exposures to static magnetic fields in the scientific, industrial and public sectors requires an assessment of the attendant potential biological consequences. At present, no model exists for such an assessment. While several reviews of the literature have occurred, none have led to approaches suitable for risk assessment application. As a consequence, the present work was undertaken with an expressly different perspective from that of previous reviews. Rather than focusing on literature *per se*, the current study set out to determine the status of magnetic field information that is applicable to risk assessment. Hence, an attempt is made to identify both the literature that is useful to the goal of risk assessment and a framework within which risk assessment methodologies can be derived.

From this selected review, it is concluded that three areas exist for which adequate information can be found to begin modelling: disease induction, reproduction and development, and cardiovascular response. The first two are supported by a combination of positive and negative findings and the last by a calculational technique which utilizes the physically well-known principle of flow retardation for a conducting fluid moving through a magnetic field.

# 1. INTRODUCTION

The question of the biological effectiveness of magnetic fields has been the subject of man's curiosity since ancient times. The literature on related subjects has recently increased quite dramatically, especially during the last decade. Many studies have observed subjective effects such as fatigue, irritability, and changes in appetite, and these effects are difficult to assess quantitatively. Other studies show a lack of concern for dosimetry, replication, or other important experimental characteristics; few literature references appear to meet all the necessary standards for reliable scientific reporting.

The diverse literature on biological effects of magnetic fields is extensive and is often in apparent contradiction. Some studies purport to demonstrate influences on the physical state of, or on chemical reactions that occur in cellular membranes, enzyme systems, liquid crystals, and other biologically important systems. Other studies fail to find the same results. Magnetic fields have been reported to influence and not to influence such measures as growth and viability for both tissue culture and animal systems. In addition, some experimental exposures to high magnetic field strengths have produced no reported change, while others have shown changes following exposures to low-field strengths.

Several comprehensive reviews of the experimental literature are available (Aceto, Tobias, and Silver 1970; Beischer and Reno 1971; Silver and Tobias 1974; Mahlum 1976, 1977; St. Lorant 1977; Schiff 1978; Ketchen, Porter and Bolten 1978; Nakhil'nitskaya 1975; and Busby 1967). Of these reviews, Ketchen, Porter and Bolten (1978) alone have attempted to postulate human exposure limits; they recommend a level of 0.02 T (Tesla) for continuous exposure to static magnetic fields. (The earth's natural field is approximately 0.05 milli-Tesla.) The apparent basis for the 0.02 T recommendation is the fact that the lowest exposure level experiment of those reviewed (for which no effect was reported) was 0.008 to 0.01 T of continuous exposure. The remaining reviews concluded explicitly or implicitly that data inadequacies do not allow informed statements regarding permissible levels of exposures to static magnetic fields.

## 1.1 Recent Epidemiological Studies

Three recent epidemiological studies sought to identify effects from exposures to magnetic fields. Two dealt with 60-Hz fields and one, with static fields. The results of these studies are, although inconclusive, noteworthy.

Wertheimer and Leeper (1979) associate childhood cancer data in the Denver area with residence proximity to different sizes of 60-Hz electrical distribution wires. They argue that unbalanced currents due to faulty connections result in ground currents and, hence, in the induction of magnetic fields which are noncancelling. Magnetic fields also radiate from the electrical distribution wires in which the resulting unbalanced current exists. The current difference is expected to be greatest for distribution wires carrying the most current and hence the magnetic field strength would also be greatest near these wires. Field strengths were measured near the main types of distribution wires, but no attempt was made to perform systematic measurements of the residences in question. Wertheimer and Leeper (1979) also allude to a range of 0.1 to 1 μT within the residences although no explicit measurements were presented. A factor of 2 to 3 increase in rate for childhood leukemia and other cancers are implicated by the authors to result from exposure to 60-Hz magnetic fields of some low level. Important questions have been raised by Miller (1980) about the relative effects of magnetic fields originating within the home compared with those penetrating the home from outside. These questions have been addressed (Wertheimer and Leeper 1980b) by qualitative arguments.

In an attempt to duplicate the study of Wertheimer and Leeper (1979), Fulton et al. (1980) performed a similar study in Rhode Island by using the incidence of childhood leukemia as a point of reference. They attempted to replicate the "dosimetry" methodology of Wertheimer and Leeper (1979) but were unable to find the type of relationship between childhood leukemia and electrical power line configuration that was reported for the Denver area. The dosimetric assumptions of Fulton et al, (1980) were examined by Bryan (1980), who deprecated the Rhode Island conclusions, although such action may not be fully warranted.

The accurate replication of their methodology was questioned by Wertheimer and Leeper (1980a) who reanalyzed the data of Fulton et al. (1980). Wertheimer and Leeper (1980a) used a procedure they felt to be more tenable for controlling migration habits and adjusted for the differences in electrical distribution wire configurations. As a consequence of the after-the-fact reanalysis by Wertheimer and Leeper (1980a) of the Rhode Island data, only a slight association of childhood cancer was found with the configuration of the electrical distribution wires. They concluded that it was probably not fruitful to pursue the magnetic field-cancer relationship through such crude ecological studies.

The positive findings for the case of children contrasts with results of previous studies involving primarily occupational personnel exposed at electrical substations or as linemen. These latter studies have recently been reviewed by Michaelson (1979), who concluded that 60 Hz electric fields of up to 20 KV/m and magnetic fields of up to 0.3 mT do not pose any chronic threat to health. The magnetic fields to which the children in Denver were exposed are on the average 100 to 1,000 times less intense than those for the populations reviewed by Michaelson (1979).

The possible interaction of low-level radiation and static magnetic fields was examined Polednak and Frome (1980), who studied the mortality rate among men employed between 1943 and 1947 at a uranium-processing plant. Of particular interest are the calutron—related processes. The calutrons are electromagnetic devices used to separate $^{235}U$ from $^{238}U$. The magnetic field strengths and worker residence times are not known with precision, although nominal fields were probably 100-1000 times greater than the earth's natural field (assuming 0.05 MT). Table 1 presents standardized mortality ratios for the study population and indicates the average uranium air concentrations for the different processes. The standardized mortality ratio is the number of deaths occurring in a given age group of a study population divided by the number of deaths expected for the same age group in the U.S. population. Inspection of the data suggests no increased cancer mortality in workers exposed to magnetic fields as compared with workers not exposed to

Table 1. Standardized mortality ratios for lung cancer (for white males employed at the uranium enrichment plant at Oak Ridge, Tennessee, between 1943 and 1947)

| Job group | Average concentration of uranium dust (μg/m³ of air) | Age-at-hire group (yrs) 25-34 SMR[a] (95% confidence limit) | 35-44 SMR (95% confidence limit) | 45 SMR (95% confidence limit) |
|---|---|---|---|---|
| Alpha chemistry<br>(not magnetic field exposed) | 300 | 1.13<br>(0.21-2.9) | 0.55<br>(0.12-3.6) | 3.02<br>(0.40-2.1) |
| Beta chemistry<br>(not magnetic field exposed) | 50 | 1.26<br>(0.37-2.2) | 0.86<br>(0.27-2.6) | 0.38<br>(0.03-5.6) |
| Alpha process<br>(magnetic field exposed) | 25 | 0.87<br>(0.55-1.7) | 0.78<br>(0.61-1.5) | 1.03<br>(0.56-1.7) |
| Beta process<br>(magnetic field exposed) | 25 | 1.25<br>(0.53-1.7) | 1.10<br>(0.56-1.7) | 1.51<br>(0.50-1.8) |
| Electrical<br>(magnetic field exposed) | 25 | 1.23<br>(0.37-2.2) | 1.61<br>(0.53-1.7) | 1.55<br>(0.40-2.1) |
| Not exposed | 0 | 1.51<br>(0.73-1.3) | 1.15<br>(0.79-1.3) | 0.85<br>(0.76-1.3) |

[a] SMR,--standardized mortality ratios.
Adapted from Polednak and Frome, 1981.

magnetic fields although these data have not been adjusted for potentially confounding factors such as smoking history.

In addition to the studies completed, an additional ongoing study seeks to determine the effects of occupational exposures to static magnetic fields. This study (Budinger, Wong, and Yen 1979) is also retrospective: it is designed to uncover changes in the health of workers previously exposed to elevated magnetic fields for extended periods of time. Plans are also under way to quantify these exposure levels so that the data can be divided into gradients (Colanias 1979). Exposure estimates will be made using measurements when possible or calculated when the facilities no longer exist.

## 1.2 Objectives of Review

Exposures to magnetic fields are clearly increasing in industry, science, and the public sector, and no methodology currently exists to assess the consequences of these exposures. Although an epidemiological study is under way to examine the consequences to such occupationally exposed individuals (Budinger, Wong, and Yen 1979), no hypothesis has been suggested for testing. Furthermore, the population size of this study is small. Consequently, in order to detect effects, a more significant response to magnetic field exposure would be required than has been experienced to date. Because of the overall situation of magnetic field effects, this review of the literature was undertaken with an expressly different perspective from that of many previous reviews, which have focused on identifying the literature. Rather than focusing on literature per se, the current study set out to determine the status of magnetic field information that is applicable to risk assessment.

The objective of this study is to move toward the assessment of human health risk; therefore, human epidemiology literature is the preferred source of information. The paucity of this type of data, however, dictates that other sources be examined to determine their suitability; these include predictive mathematical-physical formulations and nonhuman biological data. In contrast to the situation of scarce quantitative human data, an overwhelming quantity of physical and nonhuman biological data exist. These data are scattered in almost every aspect of science and rarely include attempts to repeat previous experiments. Hence, the risk assessment researcher is faced with a large amount of diverse information from which to draw but with no clear unifying perspective upon which to build an assessment model.

None of the previous reviews have offered direction leading to the formulation of risk assessment models, although the need for specific experiments has been noted. This review attempts to identify some of the literature that is useful to the goal of risk assessment and a framework within which risk assessment methodologies can be derived. Not all literature is therefore cited, and some potentially important areas such as muscle and nerve responses and behavioral modifications are not included.

### 1.3 Recommendations Relating to Risk Assessment

From a selected review of the literature on magnetic field effects, it is concluded that two areas exist for which a moderately consistent literature can be found and that a third area exists for which a calculational technique can be utilized. The first two areas are supported by a combination of positive and negative findings: one is coupled with a cancer model and the other is related to embryonic and fetal development. The calculational technique utilizes the physically well-known principle of flow retardation for a conducting fluid moving through a magnetic field. This flow retardation principle is used in conjunction with epidemiological information on cardiovascular disease to provide a perspective on risk.

These three areas are considered to be useful bases for the development of risk analyses, although additional types of effects should not be excluded. On the contrary, efforts should continue in the attempt to rationalize the diverse data on experimental endpoints other than those examined in this document. The literature describing effects of magnetic fields is abundant, and many biological events are modified to some degree for some period of time by static magnetic fields. When better elucidated by experimental methods, a variety of effects can therefore be used as a basis for defining human risk estimates from exposures to magnetic fields.

### 1.3.1 Cardiovascular Risk

Cardiovascular risk assessment is based on the fact that blood, a conducting fluid, experiences a pressure drop when passing through magnetic field lines. For arteries of adequate size (about 1 cm), this pressure drop can then be related to an increase in pressure in these arteries and those upstream, to the heart. Calculations indicate that this small added pressure varies directly with the magnetic field strength.

Epidemiologic studies of large populations have related absolute blood pressure to mortality rates. A monotonic relationship, beginning at low blood pressures, indicates increasing mortality rates with increasing blood pressures. In addition, other studies have determined that blood pressure is a strong risk factor in cardiovascular disease. By coupling the epidemiologic information with the calculations relating blood pressure to magnetic fields, it seems possible to develop risk analyses by using a linear no—threshold approach.

### 1.3.2 Disease

Of major concern in the assessment of occupational and environmental insults is the potential for disease induction. A promising technique for one set of diseases — cancer — is the application of magnetic field effects data to a cancer model. The cancer model chosen, described in terms of initiation and promotion, is not new, but has recently been receiving increased attention. Initiation occurs when an insult causes a cell to undergo a modification such that it possesses the capacity to develop into a tumor by subsequent treatment with a nonspecific tumor—enhancing agent. The production of a tumor from reproductive stimulation of these latent tumor cells is described by the term promotion.

Essentially all of the pertinent information indicates that static magnetic fields are not initiators. Evidence for this conclusion comes from cellular studies that have failed to stimulate transformations and from animal studies which have shown no evidence of permanent genetic transformations. Hence, it is not likely that magnetic fields could cause initiating events. On the other hand, a reasonable body of evidence indicates that magnetic fields might function as weak promotors. Evidence for this is found in alterations of mitosis, of development rates and sizes, and of tissue respiration. In developing an assessment model, additional efforts would be required to extend current initiation-promotion models from one based on cell—killing as a proliferative stimulus to one based on a direct modification of normal cell turnover consequent to magnetic field exposures.

### 1.3.3 Embryonic and fetal development

Much of the literature, that supports the unlikelihood of magnetic fields being initiators, also supports the unlikelihood of their causing genetic malformations in developing animal systems. Most experiments that have found positive consequences of magnetic field exposures in the developmental realm have dealt with exposures continuously received over generations or exposures received during a sensitive stage of development. Exposures of adult organisms have, by and large, failed to yield positive experimental results.

# 2. STUDIES OF PHYSICAL EFFECTS

Physical models have, for the most part, been unsuccessful in the past in relating observed biological responses to exposure conditions. Two general types of effects from exposures to magnetic fields are postulated (Nurath 1964) as a result of theoretical calculations: electromagnetic and magnetomechanical. Electromagnetic forces are the consequences of a moving conductive fluid in a magnetic field and result in induced voltages and flow modifications. Magnetomechanical forces could produce translation and rotation of particles (e.g., molecules, cells, etc.).

## 2.1 Electromagnetic Interactions

Electromagnetic interactions are usually described through an application of the basic laws of electricity and magnetism. Results are measured in terms of forces and induced voltages. Magnetohydrodynamic (MHD) studies describe the motion of an electrically conducting fluid in the presence of electromagnetic fields. The moving fluid in the presence of a magnetic field produces electric currents (and voltages). A major medical application of this phenomenon is the noninvasive measurement of blood flow. This application has been used for a number of years and appears to be reasonably accurate and reliable (Salles-Chuna, Battacletti, and Sances 1980).

Induced voltages have also been detected in the electrocardiograms of animals exposed to static magnetic fields. Experimental evidence has recently been presented by Gaffey and Tenforde (1979) for the dog and rat showing increased T-wave amplitude with increased magnetic field (Fig. 1). These data show a linear dependence with magnetic field strength up to about 1 T, as would be expected if field strength was the only parameter subject to variation. Above 1 T, the T-wave response becomes more complicated. Recently, similar data have been presented for the baboon (Gaffey and Tenforde 1980). The earlier work of Beischer and Knepton (1964) with squirrel monkeys also demonstrated increased T-wave amplitude with magnetic field exposure but was less quantitative than the recent work.

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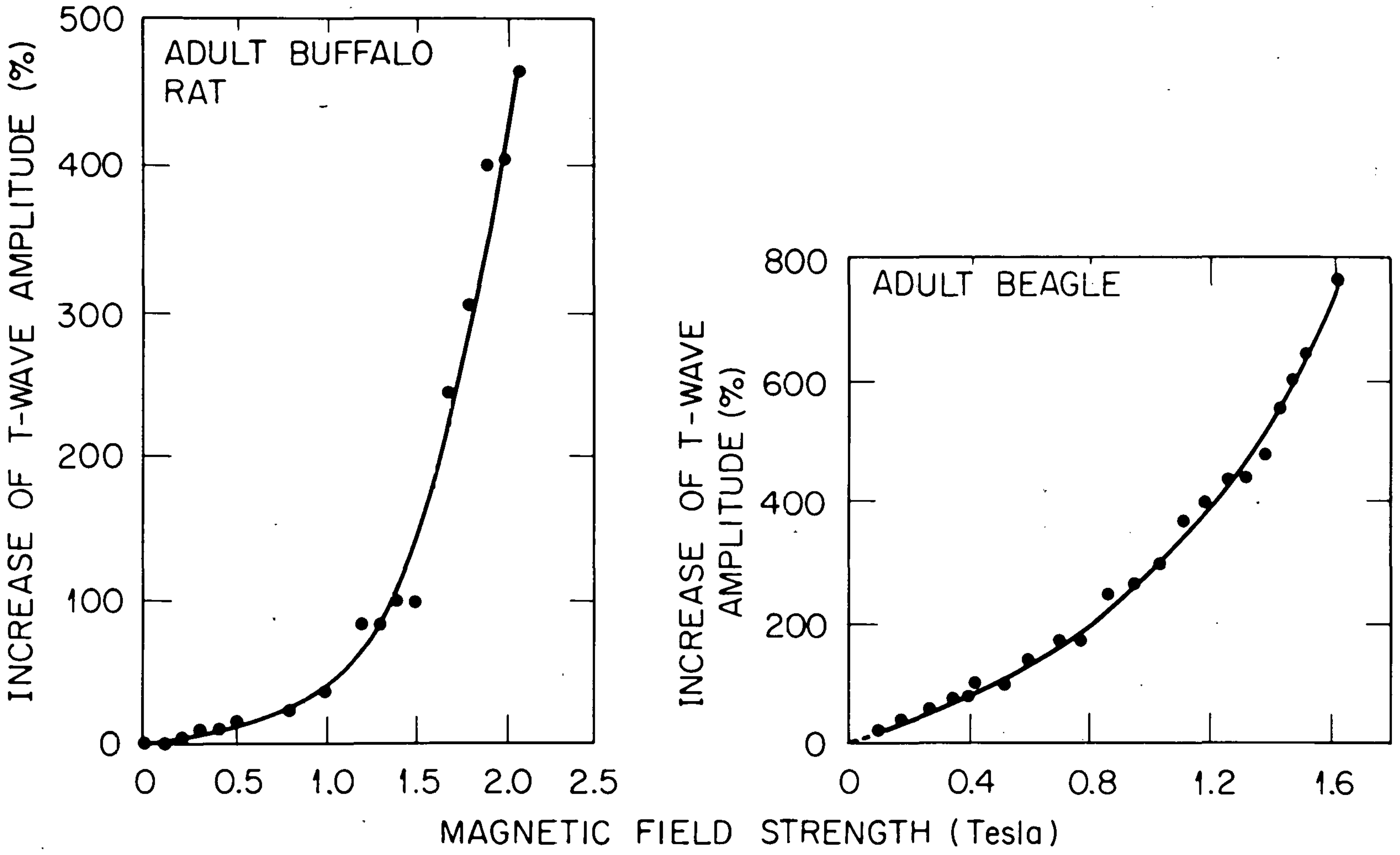

Fig. 1 Increase of T-wave amplitude as a function of magnetic field strength.
Source: Gaffey, C. T. and Tenforde, T. S., LBL-9085 (1979).

The interaction of the magnetic field and the electric current produces a body, or Lorentz force, that opposes or accelerates the movement of the fluid, depending on whether the speed of the moving magnetic field is more or less than that of the liquid. For the case of static magnetic fields and blood flow, the movement will be retarded.

Initially, the flow of a conducting fluid through a magnetic field was addressed by Hartmann (1937) for the case of liquid mercury moving between two parallel plates. The analogous problem for the circular pipe, where the uniformly applied magnetic field is in the radial direction, was treated by Pai (1954). This latter problem reduces to a two-dimensional flow very similar to MHD Poiseuille flow. Exact analyses have only been made for the case of an insulated pipe with an incompressible Newtonian fluid undergoing steady laminar flow.

Analysis of the MHD effect for the circulatory system has been attempted by several authors (Belousova 1965; Korchevskii and Marochnik 1965; Vardanyan 1973; Abashin and Yevtushenko 1974 and 1975; Sud, Suri, and Mishra 1974 and 1978; Kumar 1978). Most notably, Sud, Suri, and Mishra (1978) and Kumar (1978) have attempted to provide exact solutions for a pulsating flow. They have been more or less successful; however, the dimensionless parameters chosen reduce the potential for the direct application of results and their dissimilarity precludes direct comparison. The velocity profiles of all analyses, however are quite similar, and all predict a similar qualitative effect of the magnetic field which is to reduce the blood flow rate as the magnetic field increases. For pulsed flows, this effect increases in magnitude as the pulse rate increases.

Evaluation of the effects of a homogeneous static magnetic field on a viscous electrically conducting fluid is made by solving the Bernoulli equation. For mathematical convenience, it is assumed that:

1. the artery is a rigid right-circular cylinder of uniform diameter and electrically insulated;
2. the blood flow is laminar; and
3. the magnetic field is uniform, stationary, and constant and is directed perpendicular to the artery.

The requirements of uniform, cylindrical geometry and laminar flow (implying steady state continuous flow) are recognized not to be completely present anywhere in the vascular system, however, these assumptions are used in the application of Poiseuille's equation which has proven to be experimentally useful in many situations (Cox 1979). The effect of varying wall conductivities has been examined for the similar case of MHD channel flow (Chang and Yen 1962). The results of this study show that the primary effect in having a conductive wall as compared to a non-conducting wall is to simulate the effect of a slight increase in Hartmann number (see below). For small values of the Hartman number, as in the situation being examined in this study, the added pressure loss for perfectly conducting walls over perfectly insulating walls is in the order of 5% or less (Chang and Yen 1962). The last assumption defines a specific exposure geometry which maximizes the effect calculated. By limiting the solution to steady state conditions, an expression is arrived at (Vardanyan 1973) relating the change in the value of the pressure gradient in a magnetic field $\frac{\partial P}{\partial Z}$ to an initial (no magnetic field) pressure drop $\left.\frac{\partial P}{\partial Z}\right|_o$ and the Hartmann number, Ha,

$$\frac{\partial P}{\partial Z} = \left.\frac{\partial P}{\partial Z}\right|_o \cdot \frac{Ha^2}{8} \; \frac{I_o(Ha)}{I_2(Ha)} = \left.\frac{\partial P}{\partial Z}\right|_o f(Ha) \quad , \tag{1}$$

where $I_o(Ha)$ and $I_2(Ha)$ are modified cylindrical Bessel functions described by $I_v(Ha) = \left(\frac{Ha}{2}\right)^v \sum_{j=0}^{\infty} \frac{\left(\frac{Ha}{2}\right)^{2j}}{j!\Gamma(v+j+1)}$ . The Hartman number is given by

$$Ha = \frac{rH}{c} \sqrt{\sigma/\eta} \; ,$$

where r is the vessel radius, c is the velocity of light, σ is the electrical conductivity, η is the kinematic viscosity, and H is the magnetic field strength. This magnetically enhanced pressure drop is present during both systolic and diastolic flows, i.e., whenever the blood is moving. Values for electrical conductivity and kinematic viscosity of blood are both affected by the concentration of red blood cells. The normal (95% of the population) range of red blood cell concentrations (Cartwright 1963) is 4.5 to 6.3 million per $mm^3$ for males, with an average of 5.4, and 4.2 to 5.5 million per $mm^3$ for females, with an average of 4.8. Hematocrit levels (Cartwright 1963) average 48 for males with a 95% range of 40 to 56, and average 42 for females with a 95% range of 37 to 47. Electrical conductivity values used in this study are derived by evaluating an experimentally verified theoretical relationship (Hirsch et al., 1950) [corrected to 37°C] for the 95% range of red blood cell concentrations. Viscosity values used are taken from viscosity vs. hematocrit data (Guyton 1971). In evaluating $\sqrt{\sigma/\eta}$ , a consistent set of values is used. That is, both $\sigma$ and $\eta$ correspond to the same blood conditions, i.e., upper or lower limit of red blood cell concentration, or hematocrit. Extreme values for $\sigma$ and $\eta$ correspond to red blood cell levels in persons experiencing anemia or polycythemia (Guyton 1971). Specific values used in the following analysis are given in Table 2.

Table 2. Range of electrical conductivity and kinematic viscosity values for blood[a]

| | Male | | Female | | | |
|---|---|---|---|---|---|---|
| | -95% | +95% | -95% | +95% | Anemic | Polycythemic |
| Electrical conductivity | | | | | | |
| $\sigma$ ($sec^{-1} \times 10^9$) | 6.26 | 3.81 | 6.67 | 4.90 | 10.2 | 1.36 |
| Kinematic viscosity | | | | | | |
| $\eta$ (poise $\times 10^2$) | 2.29 | 3.54 | 2.08 | 2.78 | 1.39 | 6.25 |

[a] Adapted from Cartwright (1963), Hirsch et al. (1950), and Guyton (1971).

Evaluation of the Hartmann number for values of the magnetic field as high as 1 to 10 T, using normal blood parameters (Albritton 1952), demonstrates that the vessel radius r must be about 1 cm for Ha to appreciably affect the pressure gradient. Only the largest arteries, such as the aorta and the femoral arteries, are of this order. In the absence of analytic information on r as a function of distance along the aorta, physiological data from Guyton (1971) are used in conjunction with Poiseuille's law to evaluate Eq. (1). The data indicate that when arteries reach a radius of a few millimeters, systolic pressure is down to about 3 to 5 mm mercury from the initial pressure where the size is about 1 cm radius. As an independent check, from Poiseuille's Law, a value of 1 mm mercury pressure drop is estimated for the major arteries which are about 1 cm radius. These major arteries, the aorta and femoral arteries, are estimated to be of the order of 1 m in total length.

Integration of Eq. (1) with r = 1 cm along Z so that $\int_{Z_1}^{Z_2} \left.\frac{dP}{dZ}\right|_o dZ = 1.0$ mm mercury results in the expression

$$\Delta P = 1.0 \text{ mm Hg } f(Ha) \qquad (2)$$

where $\Delta P$ is the pressure drop in the blood vessels in the presence of a magnetic field for the distance which, without the presence of the field, would result in 1.0 mm mercury. The pressure drop due to the magnetic field, $\delta P$, is then

$$\delta P = \Delta P - 1 \text{ mm} . \qquad (3)$$

One approach for integrating Eq. (1), taken in the past, (Vardanyan 1973) is not appropriate since it required integration over a distance Z from the arteries to the arterioles where the diastolic pressure equals systolic pressure. This integration neglected the fact that the vessel radius used in the Hartmann number, changes from 1 cm in the main arteries to less than 0.01 cm in the arterioles.

Equation (3) has been plotted in Fig. 2 for the normal range of $\sigma$ and $\eta$ values (which is represented by error upper and lower bounds). The overall effect of the magnetic field can be thought of as augmenting the viscous force and, according to Sud, Suri, and Mishra (1978), as slightly retarding the timing of the pressure pulses as they travel down an artery. The pressure loss is confined to the major arteries of approximately 1 cm diameter, therefore, there will be a slightly elevated

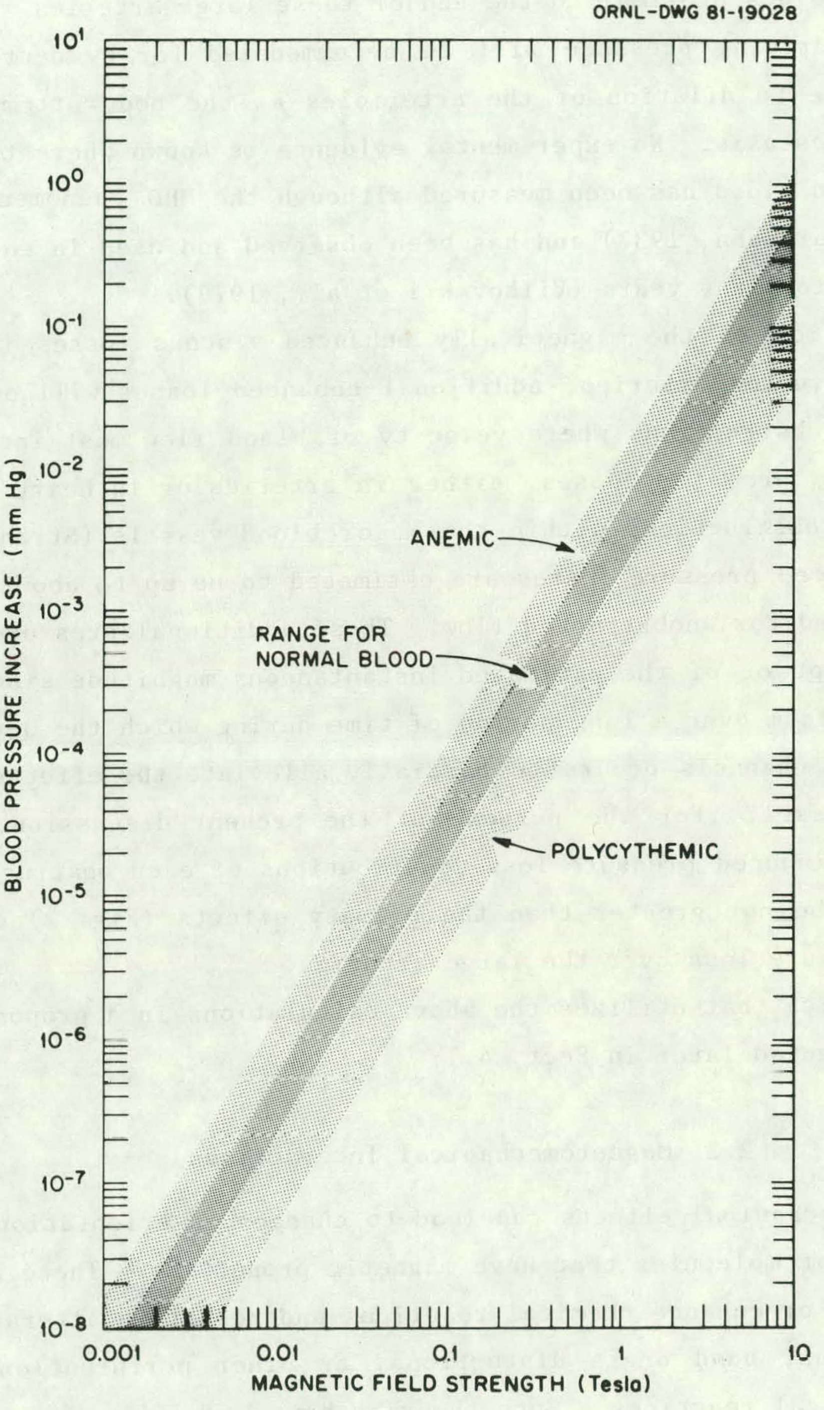

Fig. 2 Upper limit blood pressure increase for systolic or diastolic flow as a function of magnetic field strength.

pressure at points proximal to the end of these large arteries. Distally, the reduced driving pressure will be accommodated for by decreased resistance due to dilation of the arterioles as the body attempts to maintain homeostasis. No experimental evidence is known where this flow retardation in blood has been measured although the MHD phenomenon is well known (Hartmann, 1937) and has been observed and used in engineering applications for many years (Vilkovskii et al., 1979).

In addition to the magnetically enhanced viscous losses in the normal unobstructed arteries, additional enhanced losses will occur at locations of obstructions where velocity of blood flow must increase. Such locations are at stenoses, either in arteries or in heart valves and at other obstructions within the major blood vessels (Strandness, 1977). Enhanced pressure losses are estimated to be up to about 50% of that calculated for unobstructed flow. These additional pressures would never be abrupt or of the estimated instantaneous magnitude since most obstructions form over a long period of time during which the development of collateral channels occurs to partially alleviate the effects of an obstructed vessel. For the purpose of the present discussion, the magnetically induced pressure loss contributions of each obstruction is estimated to be not greater than the primary effects (Fig. 2) of the Hartmann pressure loss over the large arteries.

An approach that utilizes the above calculations in a proposed risk model is presented later in Sect. 4.1.

## 2.2 Magnetomechanical Interactions

Magnetomechanical effects can lead to changes in orientation and/or displacement of molecules that have magnetic properties. These actions could inhibit or enhance chemical reactions and result in alteration of bond formations, bond angle distortions, or other perturbations to physical-chemical reactions. Such theories have been advanced by Dorfman (1962), Gross (1964), Valentinuzzi (1964), Knox and Davidovich (1978), and others.

The question of magnetic field influence on chemical and biological reactions has been, and continues to be, subject to disagreement in the literature. This disagreement is more about the magnitude of effects likely to be seen consequent to field exposures at levels below 10 T than it is about the potential for such effects. For example, calculations and arguments by Abashin and Yevtushenko (1975) led them to conclude that permanent magnetic fields of less than 10 T do not have an appreciable influence on biological systems at the microscopic level. Their examination included ferromagnetic, diamagnetic, and paramagnetic effects, (i.e., alignment, orientation, bond angle deformation, Zeeman effects, etc). Specific examples based on theories offered by Valentinuzzi (1964) and by Gross (1964) were examined to show the insignificance of anticipated effects. In addition, Abashin and Yevtushenko (1975) cited several investigations in which they conclude that magnetic fields are ineffective in influencing chemical and biochemical reactions. They did leave an avenue of recourse, however, in that they admitted to not allowing for the specifics of biological processes and their continuous and highly ordered progress within their calculations. Similarly, Ragel (1964) has presented arguments leading to an estimate of 10 T as being required for a magnetic field to cause significant biochemical responses.

In spite of claims of unimportance, experimental reports of the influence of magnetic fields, significantly less than 10 T, on chemical and biochemical processes continue to be published (e.g. Miroschnichenko and Stadnik 1976; Vanier et al. 1978; Ahmed et al. 1975; Blankenship, Schaafsma, and Parson 1977; Hoff et al. 1977; and Yelfimov et al., 1980). Three causes for the apparent disparity between predicted and observed effects are suggested:

1. the calculational parameters are not representative of the actual process,

2. systems examined may respond by increases _or_ decreases in measured parameters, and/or

3. observed effects are not subject to influences by single calculable physical forces (e.g., account is normally not taken of collective effects).

The primary experimental vehicle for biochemical effects has been changes in enzyme activity. Vainer et al. (1978) examined the effect of a uniform magnetic field on the rate of decomposition of $H_2O_2$ by catalase and by the dimeric EDTA complex with $Fe^{3+}$. They observed that the increased production rate of $O_2$ in the fields, compared with controls, were similar functions of field strength. This is confirmed by the curve fits presented in Fig. 3. A field-dependent rate was not observed, however, for the monomeric form of EDTA. Since the reaction of $H_2O_2$ with $[Fe^{3+}(EDTA)]_1$ proceeds by a radical reaction, the authors concluded that the magnetic effects seen with $[Fe^{3+}(EDTA)]_2$ were due to a Zeeman type response, in which the weak magnetic fields removed the degeneracy present and allowed for changes in transition rates for states of different multiplicity. Hence, a change in the number of reactive states occurred. This same phenomenon was offered to explain the data for the catalase activity, since its dependence was similar in form to that of the EDTA complex. At 0.8 T the reaction rate increase is 20 ± 5% for catalase and 24 ± 5% for $[Fe^{3+}(EDTA)]_2$. In this carefully performed experiment, using optical end points, a regular monotonic increase in reaction rate was observed as a function of increased magnetic field strength.

Similar results were observed earlier by Haberditzl (1967), who also examined the reduction of $H_2O_2$ by catalase. He found that for a uniform 1.5-T field, the percentage change over controls was 12 to 15% and that, for a uniform 6-T field, the percentage change was 5 to 9%. In a nonuniform field of 6 T and 0.45 T/cm, the rate increased 40% over control values.

The enzyme system L-glutamic dehydrogenase (LGDH) exhibited a dissimilar behavior in that a reduction in activity was observed by Haberditzl (1967) for exposure to a magnetic field. A similarity in degree, however was present: for uniform fields of 5 to 7 T a 10% decrease was observed, whereas, for nonuniform fields of 6 to 8 T and of 0.45 to 0.6 T/cm, the reduction in enzyme activity averaged 60% of the control values.

Trypsin activity, as determined spectrophotometrically by the rate of benzoyl-DL-arginine-p-nitro-anilide hydrochloride hydrolysis, was

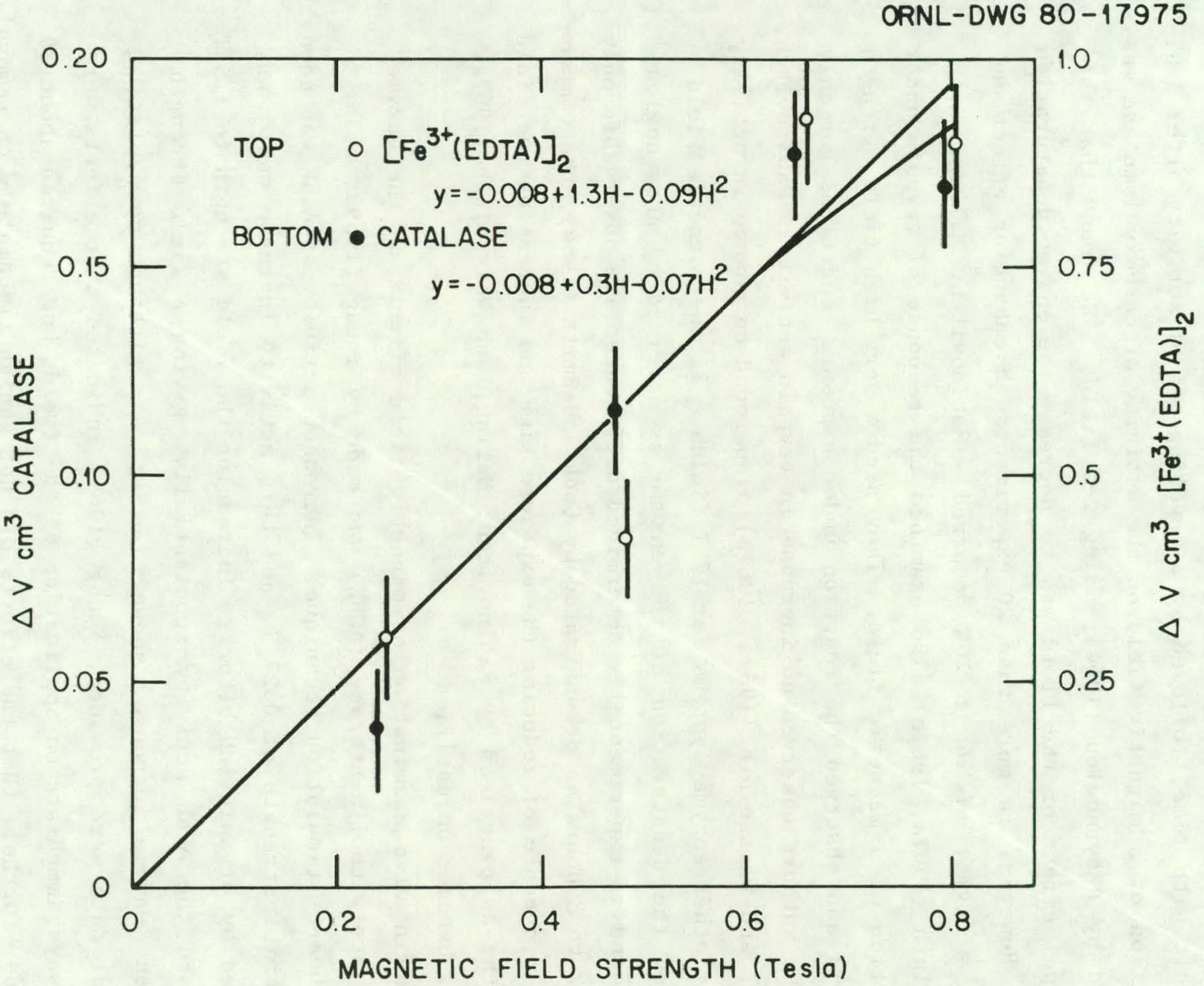

Fig. 3 Dependence of ΔV (difference in $O_2$ produced in and out of the magnetic field) on strength of magnetic field in decomposition reaction of $H_2O_2$ by: catalase and $[Fe^{3+}(EDTA)]_2$.

observed by Cook and Smith (1964). The reaction began to show differences from controls between 1 and 2h of exposure, giving a reproducible trend of about 10 to 20% increase in activity over controls, monotonic with time, followed by a leveling off of activity after 3 h. The action of a magnetic field on the activity of carboxydismutase was studied by Akoyunoglou (1964), using 2-T fields. He found that the principal effect of the field was to decrease the enzyme denaturation rate. However, in more than 20 experiments an enhancing effect on enzyme activity of 14 to 20% occurred. Rabinovitch, Maling, and Weissbluth (1967a, 1967b) also examined the response of trypsin under the action of a magnetic field. They used a very high field strength (20.8 T) and observed the reaction under exposure conditions for only 1h. The authors observed no increase in trypsin activity. Rabinovitch, Maling, and Weissbluth (1967a, 1967b) also found no change in activity of four other enzyme systems for 17 T fields. If the magnetic field modifies the denaturation of the enzyme as observed by Akoyunoglou (1964) and if experimentally determined differences are observable only after 2 to 3 hours as demonstrated by Cook and Smith (1964), the compensation procedure of reducing the exposure time and increasing the field strength, as practiced by Rabinovitch, Maling, and Weissbluth (1967a, 1967b), becomes unjustified.

An in vivo examination of magnetic field effects on the enzyme system acetylcholinesterase (AChE) was made by Young (1969), using a vagal heart stimulation technique. Increased activity of AChE was seen at a field strength of 0.27 T, and this activity increase could be reversed by organic inhibitors. Increasing the field strength to 1.5 T increased the AChE activity substantially, giving a field strength dependent enzyme response, shown, in Fig. 4. Although no explicit temporal data were provided, Young (1969) indicated that effects were not always immediate on application of the fields but required about 30 min. and, further, that the effects did not vanish immediately on removal from the field; in some cases hours were required.

Cooperative orientation in weak magnetic fields is postulated by Ahmed et al. (1975) for the increase in the diamagnetic susceptibility of solutions of lysozyme. They observed that, on exposing water solutions

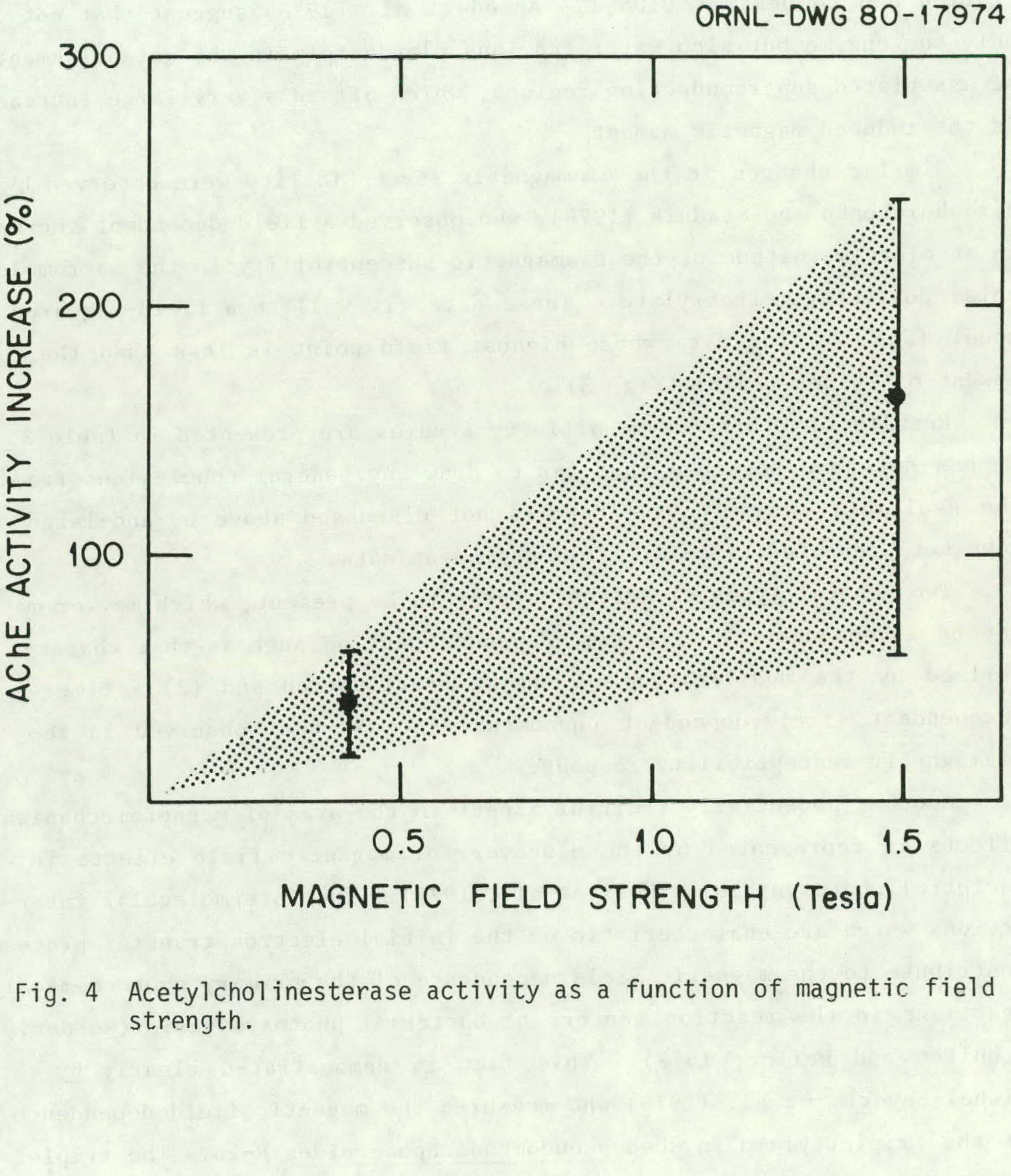

Fig. 4 Acetylcholinesterase activity as a function of magnetic field strength.

(0.011 wt %) of lysozyme to magnetic fields of about 0.06 T, the absolute magnitude of the diamagnetic susceptibility increased by $1.5 \times 10^{-6}$ over low field measurements. This is 104 times higher per molecule than would normally be expected for conditions without cooperative effects. The increase in susceptibility was found to be nonlinear with concentration and to peak at 0.06 T. Ahmed et al. (1975) suggest that not only the enzyme but also water and ions play a role in the establishment of associated superconducting regions, which afford a very large increase in the induced magnetic moment.

Similar changes in the diamagnetic susceptibility were observed by Miroshnichenko and Stadnik (1976), who observed a field-dependent increase in absolute magnitude of the diamagnetic susceptibility in the macromolecule, polymethylmethacrylate. These data fit well to a field- squared model (Fig. 5) for data whose highest field point is less than the lowest of Vainer (1978) (Fig. 3).

Results of other enzyme activity studies are presented in Table 3. It has not been possible thus far to draw any general conclusions from the available enzyme data. Reports not discussed above by-and-large have not presented time- or field-dependent data.

Two general types of actions appear to be present, which may or may not be independent: (1) a time dependent action such as that characterized by the modification of enzyme deactivation and (2) a time-independent, field-dependent phenomena, such as that observed in the diamagnetic susceptibility responses.

Another potentially fruitful aspect in the area of magnetomechanical effects is represented by the discovery of magnetic field effects in bacterial photosynthesis (Hoff et al., 1977). The intermolecular interactions which are characteristic of the initial electron transfer process contribute to the magnetic field dependence of the primary photochemical reactions in the reaction centers of bacterial photosynthesis (Werner, Schulten and Weller, 1978). This fact is demonstrated clearly by Michel-Beyerle et al. (1979) who measured the magnetic field dependence of the triplet yield in Rhodopseudomonas Sphaeroides R-26. The triplet yield decayed monotonically with increasing magnetic field and saturated at field strengths $\geq$0.03T. An explanation of the magnetically induced

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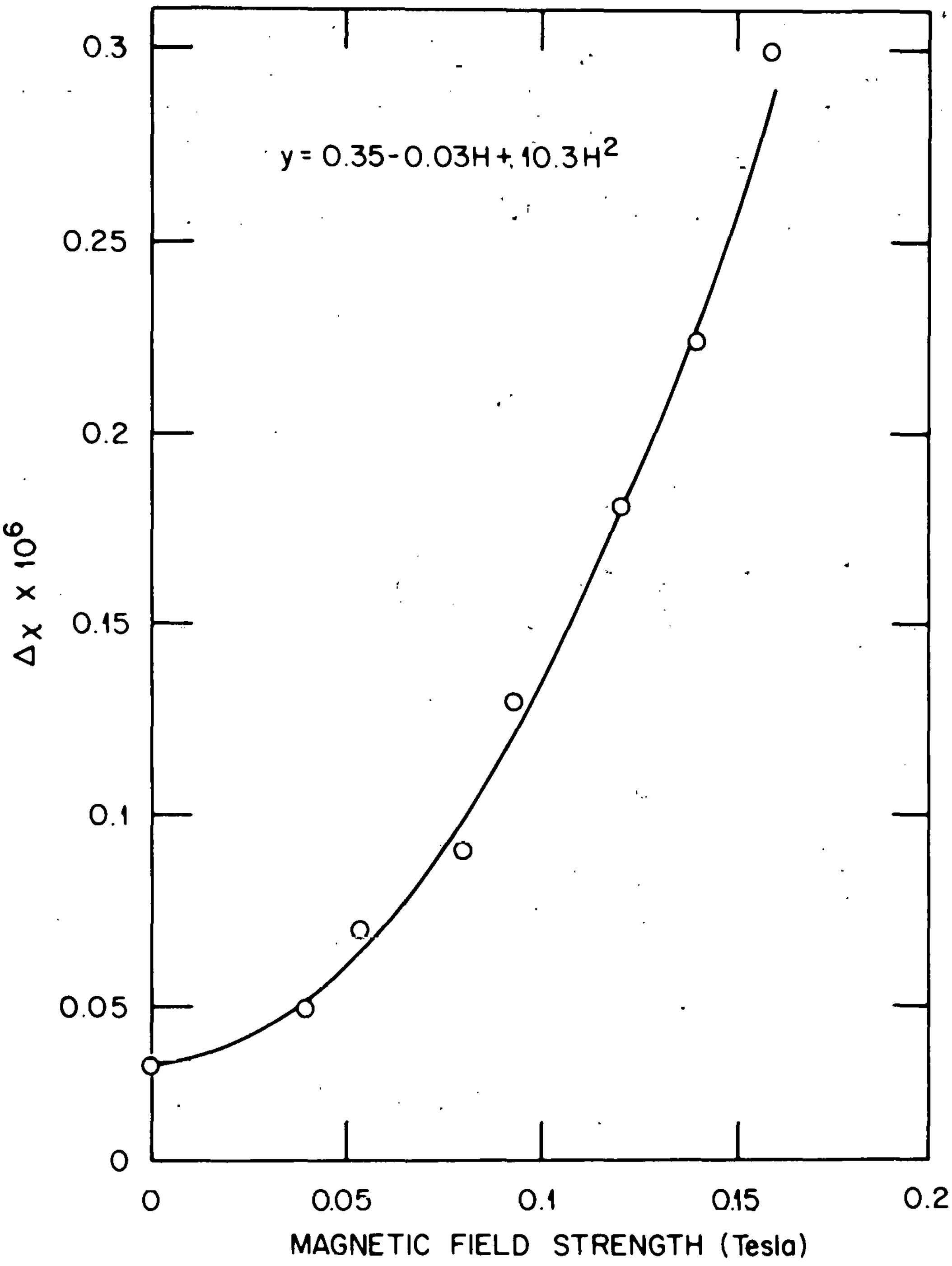

Fig. 5 Change in magnetic susceptibility ($\Delta\chi$) of polymethylmethacrylate as a function of magnetic field strength.

Table 3. Enzyme systems activity response to magnetic field exposure

| Enzyme | Field | | % Change | | Reference |
|---|---|---|---|---|---|
| | Uniform (T) | Non-Uniform (T/cm) | Increase | Decrease | |
| Acetylcholinesterase | 0.11, 1.5 | 0.083, 0.49 | 40,170 | | Young, 1969 |
| Catalase | Background-0.5 | | 0-20 (continuous) | | Vainer et al., 1978 |
| Catalase | 65,6.0<br>6.0 | <br>0.45 | 12-15, 5-9<br>(40) av | | Haberditzl, 1967<br>Haberditzl, 1967 |
| GDH | 5.0-7.0<br>6.0-8.0 | <br>0.45-0.6 | | 10<br>60 | Haberditzl, 1967<br>Haberditzl, 1967 |
| Trypsin | 0.8 | 0.022 | 10-20 | | Cook and Smith, 1964 |
| Trypsin | 20.8 | | None | None | Rabinovitch, Maling, and Weissbluth, 1967b |
| Carboxydismutase | 2.0 | | 14-20 | | Akoyunoglou, 1964 |
| RNase | 5.0 | | None | None | Maling, Weissbluth, and Jacobs, 1965 |
| RNase | 0.32 | | None | | Komolova et al., 1972 |
| RNase | 1.4 | | None | None | Muller, Haberditz, and Pritze, 1971 |
| RNase | 17.0 | | None | None | Rabinovitch, Maling, and |

Table 3. (continued)

| Enzyme | Field | | % Change | | Reference |
|---|---|---|---|---|---|
| | Uniform (T) | Non-Uniform (T/cm) | Increase | Decrease | |
| DNase | 0.32 | | 30 | | Komolova et al., 1972 |
| Succinate-cytochrome | 5.0 | | None | None | Maling, Weissbluth, and Jacobs, 1965 |
| c-reductase | 5.0 | | None | None | Maling, Weissbluth, and Jacobs, 1965 |
| Asparaginase | 1.7 | | 25 | | Shishlo, 1974 |
| Histidase | 1.7 | | | 25 | Shishlo, 1974 |
| Alcohol dehydrogenase | 1.4 | | None | None | Muller, Haberditz, and Pritze, 1971 |
| Lactic dehydrogenase | 1.4 | | None | None | Muller, Haberditz, and Pritze, 1971 |
| Polyphenol oxidase | 17.0 | | None | None | Rabinovitch, Maling, and Weissbluth, 1967a |
| Peroxidase | 17.0 | | None | None | Rabinovitch, Maling, and Weissbluth, 1967a |
| Adolase | 17.0 | | None | None | Rabinovitch, Maling, and Weissbluth, 1967a |

effects observed is offered by Haberkorn and Michel-Beyerle (1979) who provide analytic expressions of a simplified model designed to study the influence of the rates of the primary electron transfer reactions and the exchange interactions on the yield of excited triplet states. This explanation proceeds via the radical pair mechanism of chemically induced dynamic nuclear and electron polarization in which transitions between singlet and triplet states of a radical pair are induced by the magnetic hyperfine interaction of the unpaired electrons with the nucleus. An external magnetic field partially impedes this spin motion and thus has an influence on the combination product yields. The temperature dependent fluorescence studies of Yelfimov, Voznyak and Kazantsev (1980) also suggest a hyperfine interaction as the means for reducing the triplet population. This radical pair mechanism is different from triplet formation caused by intersystem crossing which is induced by spin-orbit coupling.

Clearly, biological effects at the microscopic level are ultimately important to the understanding of magnetic field interactions with humans. However, there does not, at this time, appear to be a sufficiently comprehensive level of understanding of potential microscopic mechanisms to allow extrapolation for purposes of risk assessment. The area of microscopic studies is beginning to show some useful progress in terms of mechanistic knowledge specifically for the very specialized case of charge exchange interactions involved in bacterial photosynthesis. The degree to which the human function relies on similar hyperfine interactions sensitive at the 0.01 T level and below is undetermined at this time. Hence, the potential for this mechanism to influence human response is not known.

# 3. STUDIES OF TOXIC, DEVELOPMENTAL, AND SYNERGISTIC (WITH RADIATION) EFFECTS

## 3.1 Toxic Effects

The literature does not contain a well-characterized set of biological responses which could be classed in terms of toxic effects. Animal effects chosen for this category are related to changes in growth and modification in normal cell kinetics. Effects reported vary from growth stimulation to inhibition, with varying degrees of modified cellular morphology. Many reports have found no effects attributable to the presence of magnetic fields.

### 3.1.1 Animals

A rather interesting set of in vivo experiments, using corneal epithelium and bone marrow cells of mice exposed to constant magnetic fields, was performed by Strzhizhovsky et al. (1977). The end point measured was mitotic activity immediately after terminating magnetic field exposure. The characteristic response is described by Fig. 6, where at short times a loss of activity is seen, followed by an overshoot and a gradual return to normalcy. The degree of difference from normal activity, (100%), increased as the field strength increased. This type of response is suggestive of compensative mechanisms responding to the stress effects of the magnetic field.

Orientation of the field with respect to the long axis of the mouse was important in producing the mitotic change. In order to produce the same change, fields horizontal to the long axes of the mice were required to be much greater than fields vertical to the long axes. The minimum horizontal field strength for which a change in mitotic index was seen was 1 T, whereas 0.1-T vertical fields were adequate to produce significant mitotic activity changes. This difference is perhaps understandable because the corneal epithelium consists of several layers of cells that are well oriented in space. A 15-d exposure to a vertical 0.1-T field was accompanied by activation of regenerative processes; when exposure

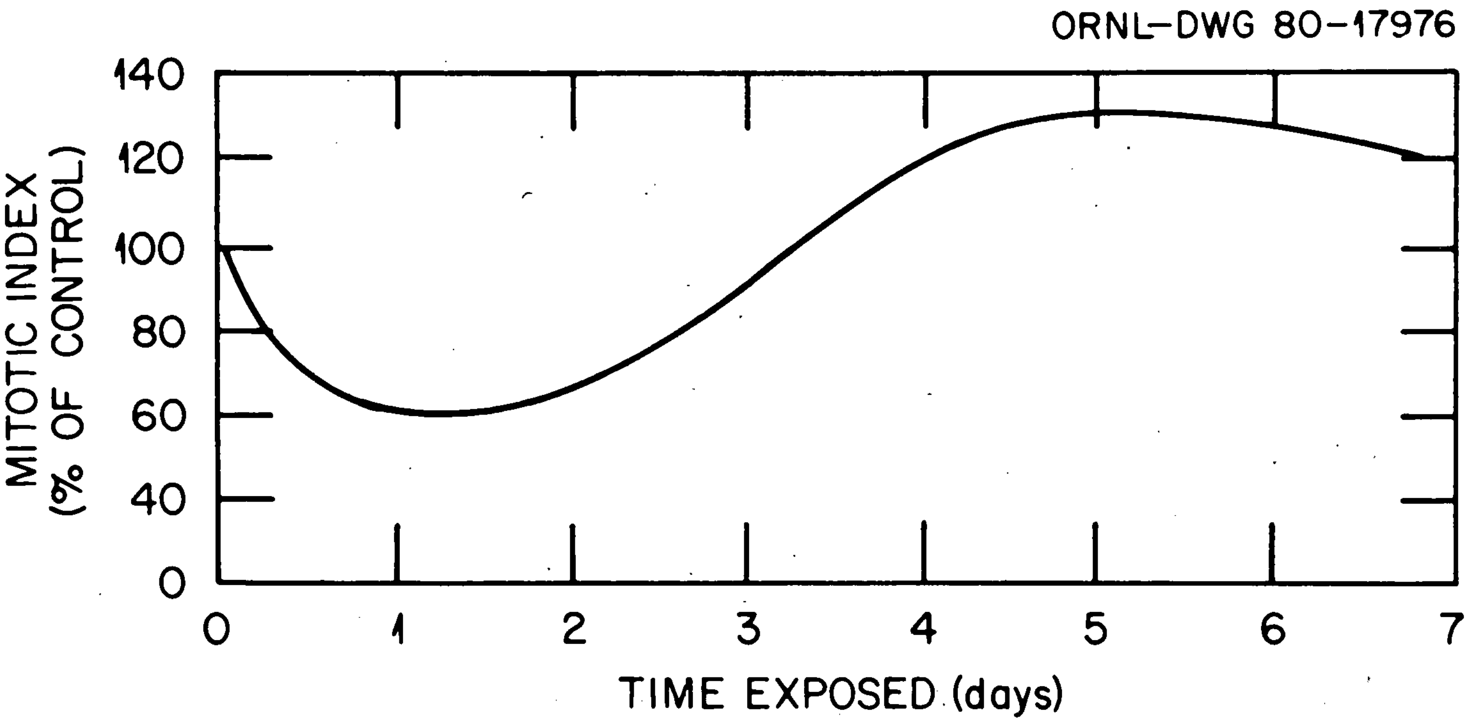

Fig. 6 Response of mitotic index over exposure time for a constant magnetic field.

to the field ceased, the increased mitotic activity continued at 20% above normal (for an unreported length of time).

Experiments repeated with a very low frequency field (period 30 s) showed that, in the corneal epithelium, the biological effectiveness in retarding mitotic activity increased substantially over the static field situation. This difference was more pronounced for low field strengths.

Experiments of the above type were also performed for bone marrow cells. Effects seen were much less pronounced, although some indications of qualitative similarity were present.

In addition to the mitotic studies, Strzhizhovsky et al. (1977) also examined the cells for degenerative changes and found none. Further, the frequency of aberrant mitoses in both cell types did not increase when recorded for gross chromosome aberrations.

Rats exposed to homogeneous 0.02- to 0.1-T static fields for one month were examined by Nahas et al. (1975) for possible histopathological and vascular effects. A single nonpathological congestion of the spleen was the only effect seen from examination of blood chemistry and body and organ weights and from the histopathological examination of vascular tissues and ten organs. The exposed young rats experienced higher increased organ and body weights than controls, but the population size was too small for statistical certainty.

In order to determine the physiological effects of magnetic fields on organisms, Toroptsev et al. (1974) examined 204 mature guinea pigs after they had been exposed to 50 Hz, 0.02-T fields, and static magnetic fields of 0.002 and 0.7 T. Exposure times varied from one-time 6.5-hr exposures to a chronic continuous exposure (500 h). Microscopic studies were performed on more than a dozen organs.

These studies revealed numerous morphological changes, which exhibited a definite tendency toward renormalization of the disturbed structures upon termination of exposure. The effectiveness of alternating fields was said to be greater than the static field. Although the 0.02-T exposures showed a lowered degree of morphological changes, the types were the same as for the higher field strength exposures. The fields were generally found to have a disturbing effect on mitosis with the attendant presence of giant multinuclear cells in the testes, liver, kidneys, suprarenal glands, and the epithelium of the crystalline lens. The highest sensitivity of the organs studied was reported to be the male gonads. For several days after termination of the exposures, the morphological changes were preserved; however, they tended to disappear after one month.

Rather pronounced differences occur within an intact animal on exposure to magnetic fields; that is, some functions appear to increase and others, decrease. Barnothy and Sumegi (1969) have examined organ changes in Swiss mice subsequent to magnetic field exposure. The effects seen included disorganization and narrowing of the zona fasciculata of the adrenal cortex, changes in the number of megakaryocytes in the bone marrow and spleen, and changes in the mitotic index of liver tissue. Exposures of adult mice to 0.22 T and greater resulted in an increasing degree of disorganization of the zona fascicula with increasing field. In addition, mice exposed during gestation showed a 66% increase in adrenal lesions. An increase in megakaryocytes in the spleen was found, in contrast to a decrease in the bone marrow. Finally, the mitotic index for liver tissue showed a distinct increase with field strength. The types of morphological changes and proliferation responses seen in the liver tissues are reported to be similar to those observed for other types of injuries. The data reported by Barnothy and Sumegi (1969) unfortunately represent three different experiments at different field strengths. This confounding factor must be kept in mind when examining a summary of their data as depicted in Fig. 7. General trends, however, indicate that the biological responses are related to field strength and duration of exposure.

Except for the mitotic index of the liver tissues, which increased on exposure in a manner similar to that which would be expected for a nonspecific stress agent, the other observations are not consistent with the concept of a nonspecific stresser (Barnothy and Sumegi 1969).

### 3.1.2 Plants

The development of root structure after prolonged exposure to magnetic fields for three species, Allium, Narcissus, and Coleus, was

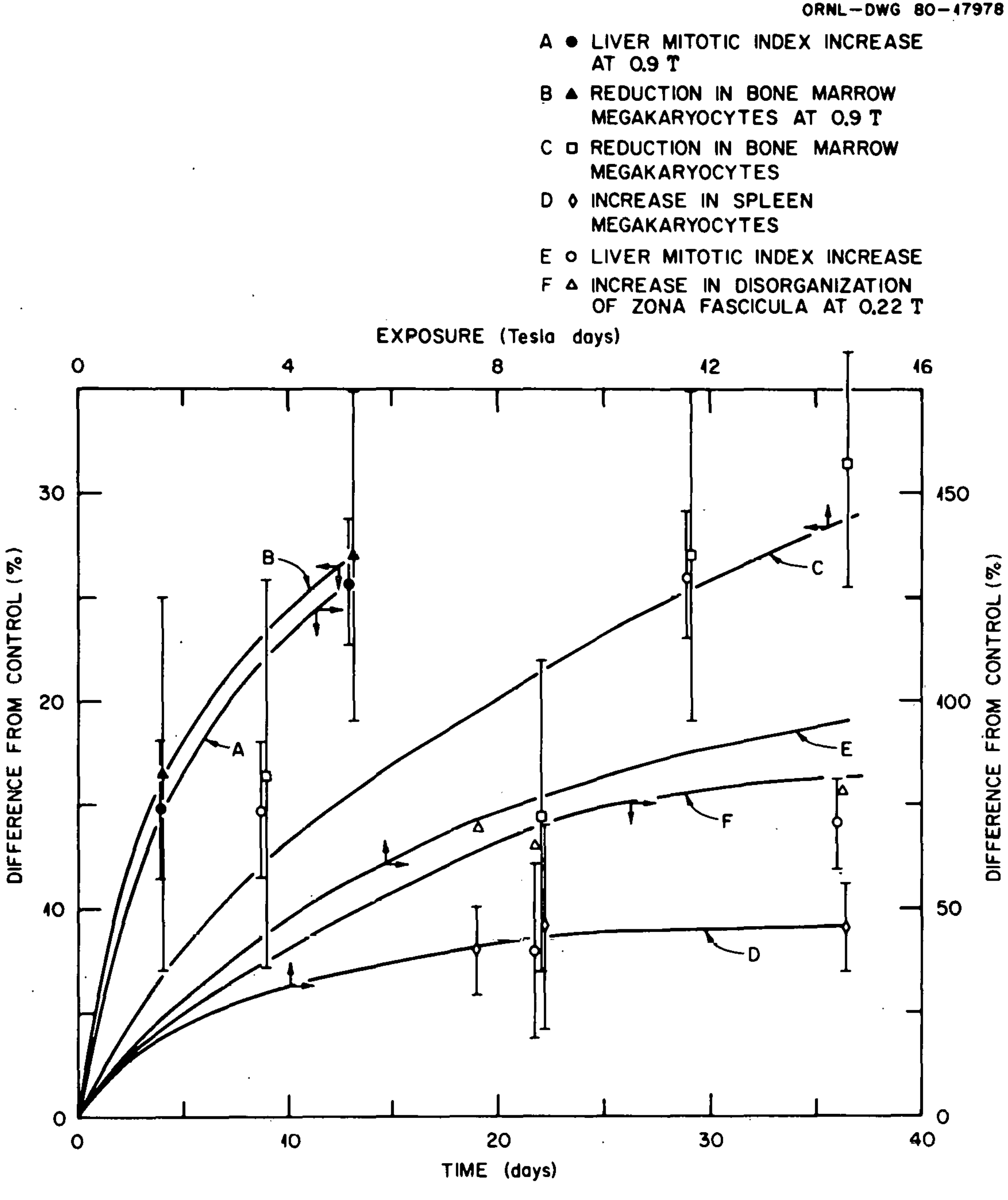

Fig. 7 Physiological changes in mouse organs as a function of magnetic field exposure conditions.

studied by Dunlop and Schmidt (1969). They used heterogeneous fields of 0.05 to 0.45 T. Basic responses of the adventitious roots were inhibition of cell reproduction, followed by death of embryonic tissue and early senescence of all root tissue. In addition, anomalous development of certain cells and tissues was observed, including nuclear, cytoplasmic, and cell wall abnormalities and omission of some normal developmental cell types. A plot of the data on Coleus rooting (Fig. 8) indicates a depressed effect and the familiar stress pattern of cyclic response of the organism's attempting to find an appropriate equilibrium value.

The repression effect seen by Dunlop and Schmidt (1969) contrasts with the results of Mericle et al. (1964), who looked at the growth of barley seeds under the influence of magnetic fields. They found initial increases of growth in both shoots and roots. The absolute magnitude was less than that experienced by Dunlop and Schmidt (1969), and the difference from controls decreased with time (Fig. 8).

### 3.1.3 Cell lines

Morphological effects. One recent experiment, which did report morphological and physiological transformations of cultured cells, was reported by Malinin et al. (1976), who exposed cell cultures at 4.2°K to 0.5 T static fields. In an attempt to reproduce these effects, Fraizer, Andrews, and Thompson (1979) exposed frozen cells (77°K) of the same type to 0.5- to 1-T fields but were unable to reproduce any of the effects seen by Malinin et al. (1976). However, by using control cultures and growing them without passage from 28 to 45 d and without the aid of magnetic fields, Fraizer, Andrews, and Thompson (1979) were able to reproduce the reported "transformations."

Two tumor cell lines (Raji, a lymphoblastoid culture derived from a Burkitt lymphoma, and AT-264, derived from a human bronchogenic carcinoma) were exposed in vitro by Chandra and Stefani (1979), to constant magnetic fields of strengths from 0.23 to 1 T. Exposed cells passaged and maintained for eight weeks exhibited no altered morphology nor ultrastructure changes, nor were regression or retardation in growth observed.

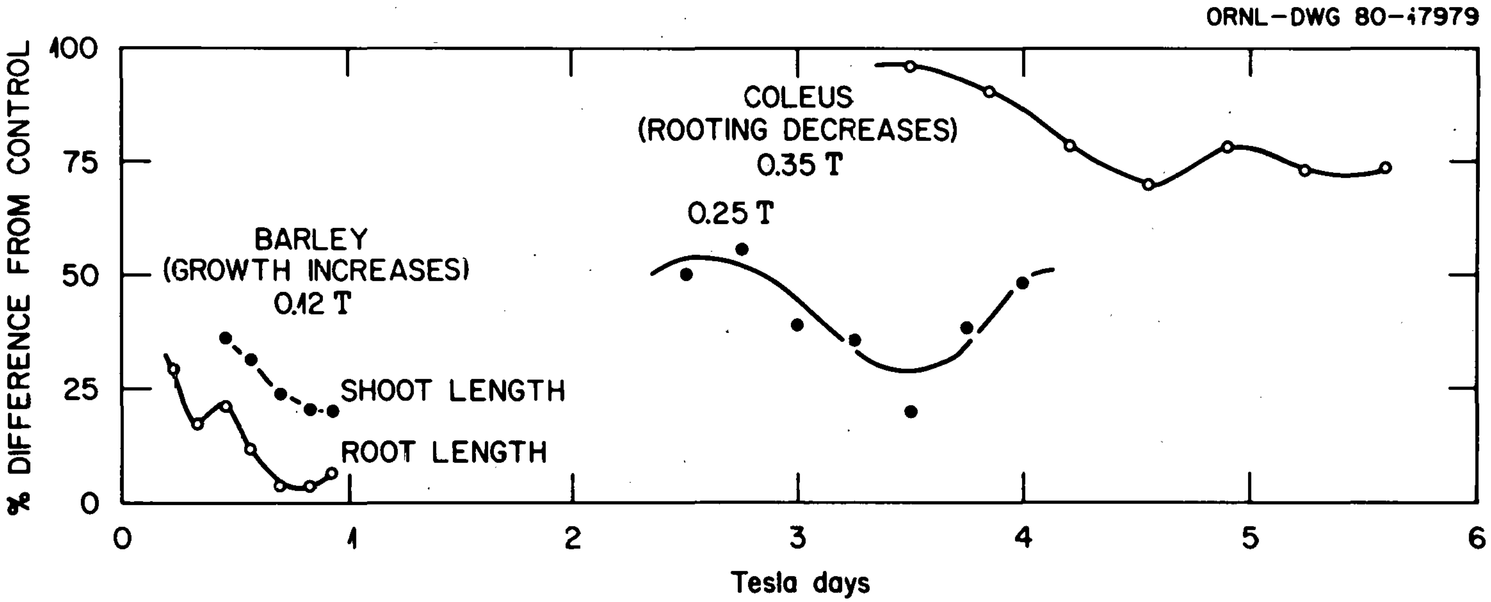

Fig. 8 Modifications of plant growth characteristics as a function of magnetic field exposure conditions.

Mulay and Mulay (1964) examined the effect of varying magnetic field intensity on ascites tumor (S-37) cells in vitro. They used magnetic field intensities of 0.01, 0.06, 0.15, 0.2, 0.44, 0.7, and 0.8 T, each with about 20% gradient per centimeter. Up to 0.44 T, normal differentiation was observed after 18 h of slide culture; however, in the 0.44- to 0.8-T group, tumor cells exhibited significant degeneration. Degeneration consisted mainly of pycnosis (shrinkage and darker staining of the nucleus), rhexis (dark staining and breakage of the nucleus into several pieces) and cytolysis (scattering of the nuclus outside of the cell and a complete breakdown of the cell membrane). At 0.8 T over 80% of the cells exhibited some form of degeneration. The authors attempted to use a different strain of host mice to reproduce the observed effects but were unable to do so. The effects observed are thought to have been very dependent on certain conditions of the tumor used as a cell source.

*Growth and function*. The effect of a magnetic field on DNA synthesis by ascites sarcoma S-37 cells was investigated by D'Souza et al. (1969), using tritiated thymidine uptake. For a 0.73-T field intensity, a depression of 20 to 30% in DNA synthesis was observed which did not appear to depend on the exposure time for 1-, 2- or 3-h exposures. A similar time-independent depression of 20 to 30% was observed for respiration of the S-37 cells in 0.73-T fields by Cook, Fardon, and Nutini (1969). In addition, Cook, Fardon, and Nutini (1969) and Pereira et al. (1967) examined the effect of intermittent magnetic fields on respiration of mouse tissues and yeast. They found a 20 to 30% decrease in respiration for embryo kidney tissue and embryo and early neonatal liver tissue but no effect for adult or older neonatal kidney and liver tissues. They concluded that the more actively proliferating cells are most responsive to the fields, whereas older tissues are not. Yeast cells responded to the fields by stimulation at an approximate 40% level. For all the systems studied by Cook, Fardon, and Nutini (1969) the threshold for response was near 0.008 T.

A more detailed examination of the effects of age on tissue respiration was performed by Reno and Nutini (1963, 1964) for mouse kidneys. They determined the respiration pattern of embryo mouse kidneys as a function of embryo length for a static 0.73-T magnetic field. Respiration was measured after 1, 2, 3, and 4 h of exposure. Since no apparent difference is present in these temporal data, they were combined to yield Fig. 9, which provides a very distinctive picture of the effect of age on magnetic field response.

The mitotic indices of Chinese hamster (subline 237) and L cell lines were examined by Sushkov, Vnukova, and Cheremnykh (1977) for effects on exposure to magnetic fields. They employed fields of from 0.1 to 8.0 T, with the field lines perpendicular to the monolayer of cells in culture. While some temporary effects in growth rate were observed, no irreversible changes were found in the indices tested. Short-term exposures to 0.1 and 0.4 T produced a 10 to 30% decrease in the mitotic index, which returned to normal after 12 h following a brief overshoot. The initial degree of mitotic inhibition (at 1 h) was found to be dependent on the field strength and reached over 80% at 8 T. Prolonged exposures (1 to 3 passages) at 0.1 T did not result in changes in cell proliferation or in forms of mitotic abnormalities. Further, no changes in the genetic constitution was observed.

Hall, Bedford, and Leask (1964) examined the effects of 0.5-, 2.7-, and 7.7-T static magnetic fields on HeLa cells; exposure times were 10 d, 1 h, and 15 min for two experimental and two control flasks at each field strength, respectively. They found no differences in the number of colonies formed compared with controls, and no morphological alterations were observed. Similar results were obtained by Halpern and Green (1964), who also used HeLa cells, exposing them from 2 to 7 d to a 0.12-T field. They found that the growth index of exposed cells was not significantly different from that of the controls.

Evidence that in vitro cell cultures can maintain apparently normal growth characteristics in magnetic fields appears to be greater than had been thought. This normalcy, at least for several systems, results after an initial adjustment to the magnetic field stress. The ascites sarcoma 37 line appears to respond with reduction in both DNA synthesis and respiration at roughly equal levels (20 to 30%) for 0.73-T fields. Finally, tissues from the embryo stage appear to be sensitive to the effects of magnetic fields in terms of decrease in respiration.

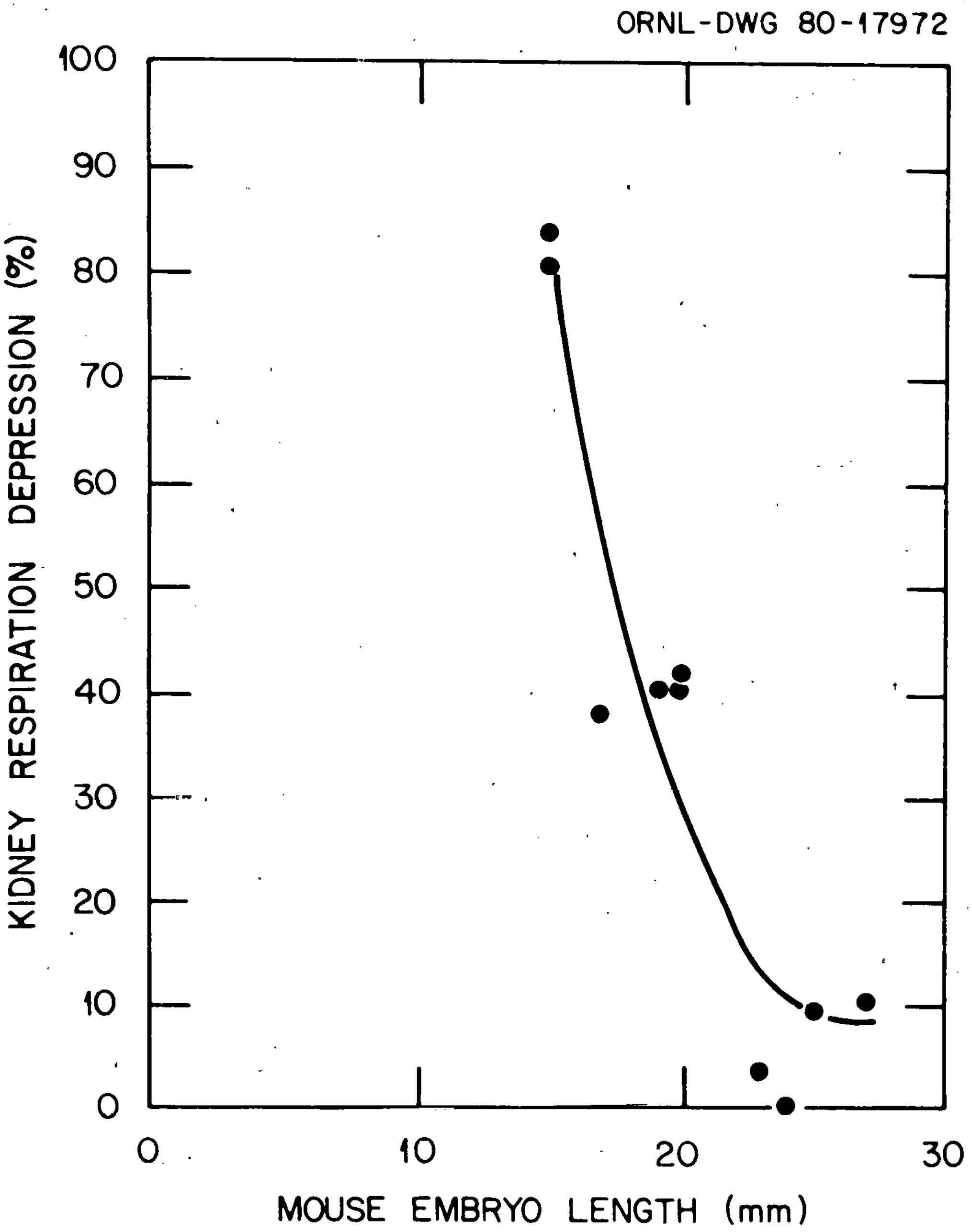

Fig. 9 Percent respiration depression of embryo mouse kidney in a 0.73 T magnetic field.

## 3.2 Genetic and Developmental Effects

### 3.2.1 Animals

The effects of magnetic field exposure on prenatal or postnatal development of intrauterine mice were examined by Sikov et al. (1979) for uniform 1-T or gradient (2.5 T/m) 1-T fields. Only occasional differences occurred between the exposed and control groups (in spleen and kidney weights) and, no differences were replicated. No statistically significant effects were detected for the end points and observations chosen, and the number of experimental animals was too small to enable Sikov et al. (1979) to draw firm conclusions.

The induction of genetic changes in mice as detected by dominant lethal assay was investigated by Mahlum, Sikov, and Decker (1979). They exposed male mice to homogeneous 1-T fields, gradient (2.5 T/m) 1-T fields, and ramped gradient fields (period approximately 100 sec) for 28 d before initiation of a breeding series. (The induction of dominant lethal mutation would be reflected by preimplantation losses and by the number of dead implants or early absorptions.) The incidence of dominant lethal mutations was not affected by exposure to fields, although there were slight differences in total sired offspring. Differences in offspring were the result of differences in the number of pregnant females, although the population size was small enough that this difference could be caused by normal variability.

Kale and Baum (1980) used 1.3- and 3.7-T static homogeneous fields in an attempt to induce mutations in Drosophila melanogaster males by exposing eggs, larvae, pupae, and adults. Eggs were exposed from just after being layed until 7 d for the 3.7-T and 10 d for the 1.3-T fields. After exposure, males were mated to 12 virgins. Five such broods to successive virgin females were cultured for the 3.7-T field and six, for the 1.3-T fields. Sex-linked recessive lethals were scored in the $F_2$ generation. By means of the experimental design, these lethals were scored in chromosomes exposed as spermatozoa, spermatids, and spermatocytes. The resultant data presented below (Table 4) indicate that the mutation frequency is not significantly changed by the presence of the magnetic fields. These data are in agreement with that for 1-T exposures of male adults obtained by Diebolt (1978) and for 1.1-T fields obtained by Mittler (1971).

Table 4. Magnetic field-induced mutations in Drosophila melanogaster

| Field (T) | Control mutations/chromosomes | Experimental mutations/chromosomes | Expected mutations |
|---|---|---|---|
| 1.3 | 4/5310 | 3/5840 | 4.4 |
| 3.7 | 5/5594 | 4/6127 | 5.5 |

An attempt was made by Mulay and Mulay (1964) to provide a quantitative relationship for developmental effects of magnetic field exposures. They mated wild type fruit flies (Drosophila melanogaster) in magnetic fields and the subsequent progeny remained in the designated fields for three generations. No abnormalities were observed during the first generation for fields of 0.01, 0.06, 0.15, 0.3, and 0.44 T. Deformities significantly in excess of controls were observed for both the second and third generations (Fig. 10). Curve-fitting of the data to second-order polynomials indicates that, at low fields, the data do approach the cumulative range of background data in a regular fashion. Further, the effect of increasing the field strength is a regular increase in observed deformities. By the use of standard techniques, Mulay and Mulay (1964) ruled out the possibility of dominant, recessive, recessive lethal, sex-linked recessive, and sex-linked recessive lethal mutations in the flies that had abnormalities.

Another low field study of the effects on reproduction was performed by Tegenkamp (1969), who used the fruit fly (Drosophilia melanogaster). He found significant changes in sex ratio (a predominance of male flies) both for high-gradient, 0- to 0.01-T fields, and for nearly uniform fields of 0.05 T. No clear relationship between exposure time (24 to 72 h) prior to mating, field intensity, and alteration of sex ratio is apparent. Exposure of flies in a 0- 0.05-T (high gradient) field, from

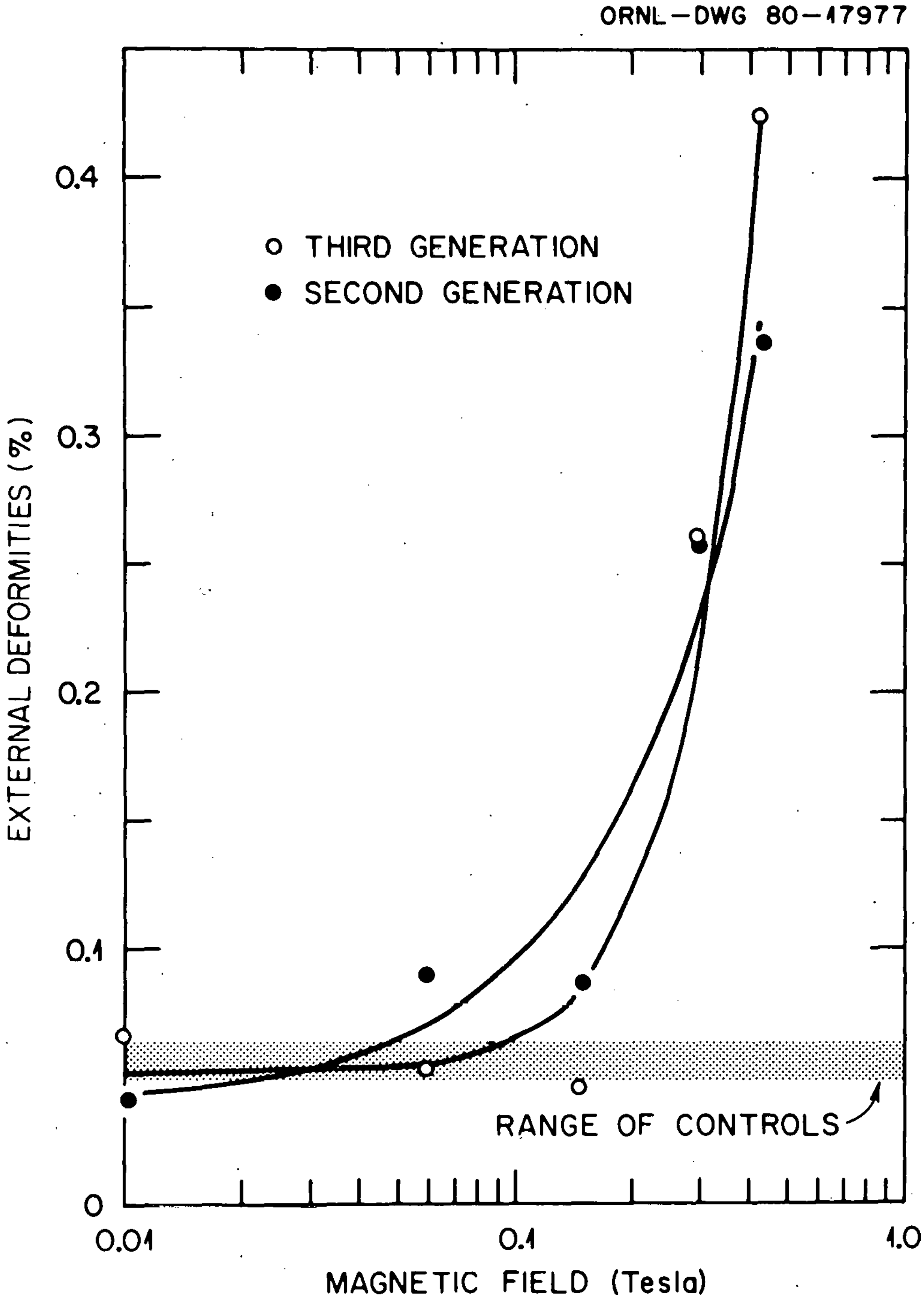

Fig. 10 Total external deformities in second and third generation of exposed Drosophila melanogaster.

mating until the appearance of their first offspring, resulted in the appearance of a single mutant fly with withered wings. The progeny of this fly underwent examination for five generations, and it was determined that the withered wings resulted from a recessive gene. These five generations also displayed a predominance of female offspring; this occurence was explained on the basis of a sex-linked recessive lethal gene. Tegenkamp (1969) took exception to the conclusions of Mulay and Mulay (1964) about the nature of effects seen: he produced evidence from a single mutant indicating that the change in sex ratio was a sex-linked recessive lethal gene that resulted in a predominance of female offspring. That the single mutant may or may not have resulted from the magnetic field was not considered. In the light of such dependence on the progeny of a single mutant, these results should not be considered to have much weight. Of interest, though, is the predominance of male flies resulting from exposure of normal flies from 0.01- to 0.05-T fields prior to mating.

Earlier studies by Levengood (1966, 1967) also used Drosophilia melanogaster and gave evidence of an alteration in their development sequence. Pupae were exposed to 15-mT fields with 5.5 mT/mm gradients, and the consequences were observed through generations. The main features observed were increased development time, decreased number of progeny, and a slight sex ratio imbalance. These factors gradually returned to normalcy by the 30th generation. The sex ratio imbalance differed in direction between Tegenkamp (1969) and Levengood (1966, 1967); however, the developmental status of the exposed organisms also differed.

Several researchers have noted that magnetic effects appear to be evidenced more frequently in juvenile organisms or during the reproductive stage. These qualitative observations have been given reinforcement by the recent work of Brewer (1979), who studied the magnetic field effects on the life cycle of the guppy. Her study observed the responses of three generations of the Lebistes reticulatus to continuous exposures to a 0.5-T homogeneous field: (1) the first generation (parents exposed prior to and following mating) exhibited a gestation period shortened by 30% but had a normal number of brood; (2) the second generation exhibited a 30% shortening of the average gestation period and had an average reduction in spawning rate of 50%; (3) the third generation experienced complete inhibition of reproduction; (4) fish reared to maturity in the field experienced accelerated growth and development with an average weight two to three times that of the controls for the female and a lesser amount for the males; and (5) on removal of the third-generation fish from the field, reproduction resumed by 180 d, and the sizes of broods, gestation times, and growth patterns returned to normalcy by the second generation. The normal patterns of reproduction and growth appear to be modified by continuous exposure to the magnetic field, with an inhibiting effect on fertilization or initial growth and an enhancing effect on subsequent growth.

The picture of developmental effects consequent to magnetic field exposures is currently ambiguous. However, the preponderance of positive effects points to changes in morphology that are nongenetic in character. These non-Mendelian occurrences are normally attributed to cytoplasmic inheritance (Levengood 1966, 1967) and would be expected to be subject to dilution with wild stock breeding, as has been observed. Further, if the hypothesis of non-Mendelian inheritance as amplified over generations of exposure is the cause for the morphological changes seen in _Drosophila_ and _Lebistes_ (Tegenkamp 1969; Levengood 1966, 1967; and Brewer, 1979), conflict would not necessarily exist with the negative dominant lethal findings of Mahlum, Sikov, and Decker (1979) for mice nor with those of Sikov et al. (1979) on the development of mice exposed for one generation or less.

### 3.2.2 _Plants_

An attempt to determine the exposure-effect relationship on the sensitive plant _Tradescantia_ was made by Baum, Schairer, and Lindahl (1978). They examined stamen hairs for mutation inductions as a function of static magnetic field strength. These data are presented in Table 5.

Table 5. Mutagenicity tests with *Tradescantia*

| Field strength (T) | Number of hairs scored | Exposure (d) | Pink mutations | Expected | Chi-squared value |
|---|---|---|---|---|---|
| 0.067 | 16,800 | 6 | 31 | 54.0 | 9.80[b] |
| Control | 14,921 | | 48 | | |
| 0.07 | 29,100 | 6 | 91 | 83.9 | 0.60 |
| Control | 37,100 | | 107 | | |
| 0.8 | 9,330 | 6 | 24 | 28.0 | 0.57[b] |
| Control | 8,996 | | 27 | | |
| 0.94 | 26,784 | 6 | 63 | 50.3 | 3.21 |
| Control | 21,294 | | 40 | | |
| 3.7 | 37,571 | 2 | 81 | 67.6 | 2.66 |
| Control | 28,916 | | 52 | | |

[a] Data (for clone 4430) according to J. W. Baum, Brookhaven National Laboratory (personal communication to C. E. Easterly) and Baum, Schairer, and Lindahl (1978), LBL-452.

[b] Expected greater than observed.

A weighted linear least–squares fit of mutation frequency versus tesla and tesla-days (Fig. 11) indicate slight positive slopes which go below the expected no effect level at the zero abscissa point. The range of data at the low exposure levels is quite large, however, and suggests that the non–zero values of the slopes calculated may lack statistical meaning.

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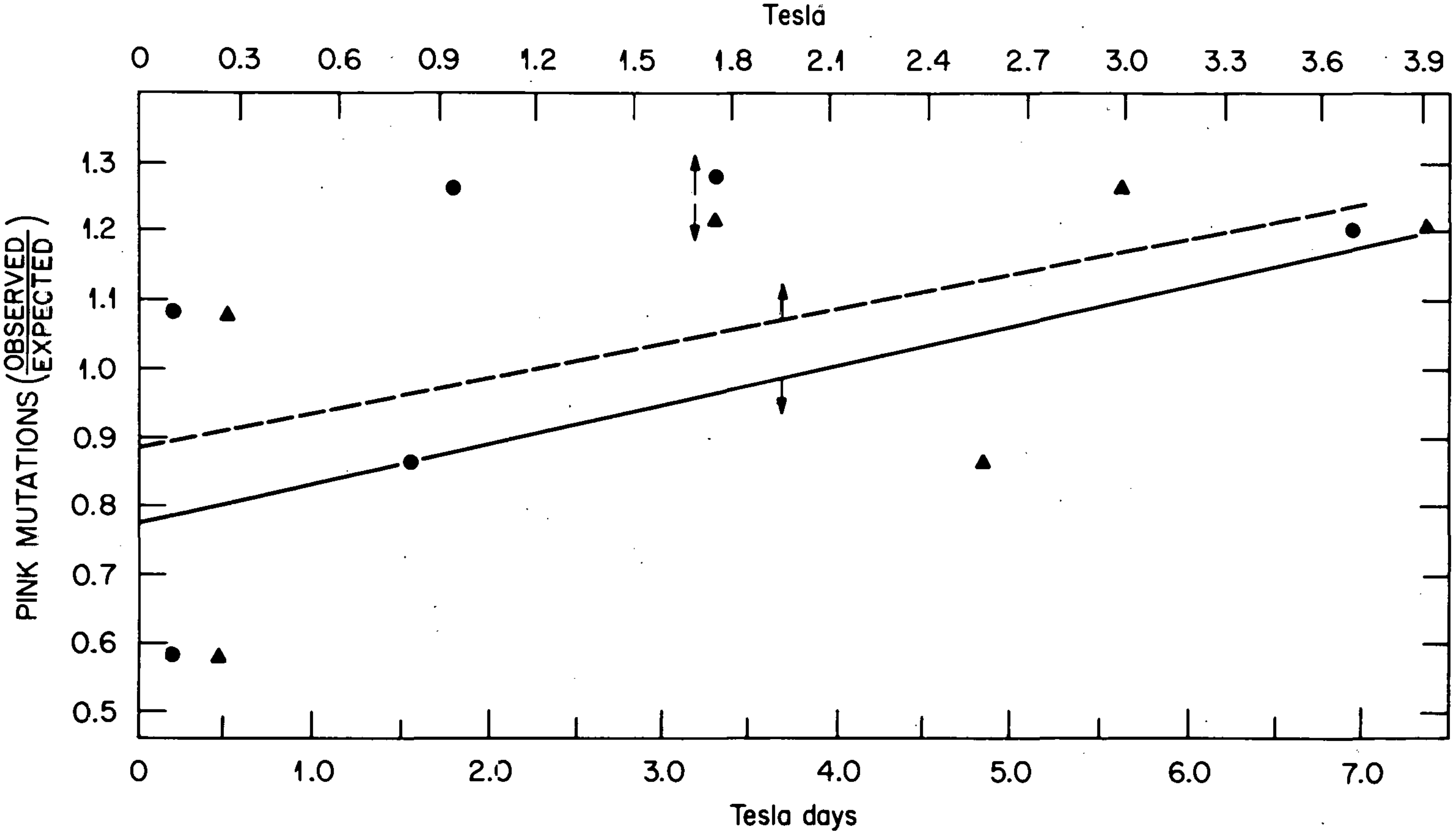

Fig 11 Pink mutation frequency of *Tradescantia* as a function of magnetic field exposure conditions.

## 3.3 Synergism with Radiation

### 3.3.1 Animals

Wordsworth (1974) subjected rats to fractionated x-ray doses of 6000 rads in and not in the presence of 0.6–T static magnetic fields. He analyzed serum concentrations of alanine aminotransferase, aspartate aminotransferase, and total hemolytic complement as a function of time after exposure. For each of these three serum components, magnetic field exposures caused similar, though reduced, levels of effects as measured by increases in the above serum components compared with the only irradiated mice. Evidence indicates that combined radiation and magnetic fields are additive and possibly slightly synergistic. These results of Wordsworth (1974) are qualititatively in support of the evidence presented by Barnothy and Sumegi (1969).

Evidence of stimulated changes in mouse leukocyte levels was presented by Barnothy (1964a), using static magnetic fields of 0.42 T. Within the first two weeks of exposure, the number of circulating leukocytes decreased by 20 to 40% and then surpassed the normal by 20% if the mice were removed from the fields at the end of the initial two weeks. A similar experiment was performed by Eiselein, Boutell and Biggs (1961) who did not see any change in total white blood count. Barnothy (1964a) noted the importance of timing in her experiment and this may be responsible for the negative results of Eiselein, Boutell and Biggs (1961) who did not reproduce the timing in their experiment.

A reduction of gamma-irradiation mortality through pretreatment of mice with static magnetic fields was demonstrated by Barnothy (1964b). The mice were pretreated by a two-week exposure to 0.42-T fields and irradiated with potentially lethal gamma-ray doses. The mice irradiated within a few days after magnetic field exposure demonstrated a 20 to 30% decrease in death rate. The reduction was attributed to the increased leukocyte levels at approximately two weeks past the magnetic field exposure, a time when the intestinal and bone marrow radiation syndrome takes its toll as a result of decreased leukocyte levels.

Modification of radiation injury with magnetic fields was reported by Amer (1965), who irradiated pupae of *Tribolium confusum* with 1200 rads of 250-kVp x rays. Following irradiation, one group of pupae was exposed to a magnetic field for 7 d and the other to a dummy magnet. The group not exposed to the magnetic field experienced a 93.4 ± 1.4% incidence of abnormal wing development, and the magnet group experienced 54.1 ± 5.3%. In addition, the magnet group was reported to have a reduced degree of wing abnormality. Qualitatively different results were reported by Forsberg (1940), who exposed eggs of Drosophila melanogaster to 165 rads of gamma rays. The simultaneous presence of a 0.6T magnetic field was said to decrease the hatchibility, compared with no field.

Adult fruit flies were irradiated with 3690 rads of x rays, and one group was subsequently exposed to a field of 1.0 T throughout their life. Close and Beischer (1962) reported no change in the life span between the two groups. Another experiment on adult Drosophila melanogaster was performed by Mittler (1971), who simultaneously exposed 3-d old males to 3300 rads of x rays and an 1.1–T magnetic field. No difference was seen when compared with the nonmagnetic field exposed group by means of the sex-linked recessive lethal mutation test.

Kale and Baum (1980b) investigated damage to all three germ cell types in treating male fruit flies with 166 h of magnetic field exposure at 3.7 T while simultaneously receiving 180, 310, or 508 rads of mixed gamma-neutron irradiation. Treated males were mated with untreated females, and the progeny were examined for lethal mutations. No difference was found between mutation induction in the experimental or control populations using sex-linked recessive lethal test in Drosophila melanogaster. By sequence of matings, Kale and Baum (1980b) were able to score mutations in spermatoza, spermatids, and spermatocytes. No evidence was found of an interaction between the two types of chronic exposure in causing genetic damage in any of the three cell types. A similar, but less detailed study of the spermatocyte stage was performed by Mittler (1971), who also found no additional mutations as a result of the magnetic fields.

### 3.3.2 Cells

Using Chinese hamster cells (subline 237) in vitro, Sushkov, Vnukova, and Cheremnykh (1977) exposed cells to 200 and 400 rads of $^{137}Cs$ gamma rays in a 0.1–T field. In all the temporal variants, the combined effects of magnetic fields and radiation did not affect the quantitative parameters of the radiation effects examined, which were chromosome aberrations and cell survival. Similarly, Rockwell (1977) exposed EMT6 mouse mammary tumor cells in vitro to mixtures of 12–kV x rays and 0.14–T static fields. Continuous exposure for 0 to 40 h had little effect on cell survival, although after 5 h there was a 10% decrease, followed by a slight overshoot (2 to 5%) for the 8 h exposures, and a return to normalcy for 40-h exposures. The percent of clonogenic cells was affected in an opposite way, with an initial decrease of 30% below normal between 5- and 8-h exposure, followed by a slight overshoot to normalcy at 40 h of exposure. Survival curves were plotted from 0 to 1200 rads for magnetically and nonmagnetically exposed cells; no difference is indicated. In addition, recovery from sublethal (500 rads) and potentially-lethal (1000 rads) radiation doses was similar in magnitude and time course for control cells and for cells incubated in the magnetic field during the recovery period.

Experiments of a similar nature were performed by Nath, Schultz and Bongiorni (1980) using Chinese hamster lung cells. They used 30 MeV x rays for the irradiation with static homogeneous fields of 2.1 T and inhomogeneous fields of 1.7 T with a 0.2 T/cm gradient. Effects of the magnetic field alone were measured by cell survival. For two hour exposures, no effect on survival was noted. A series of experiments was used to determine the mean lethal radiation dose with and without the magnetic field. The data suggest no significant change in the survival when the cells were irradiated in the presence of strong magnetic fields. Finally, over the dose range of 400 to 3000 rads, a non-parametric analysis was performed to determine the presence or absence of a magnetic field induced dose modifying factor. The results, within 95% confidence limits, indicate that the data are consistent with a modifying factor of unity. In summary, within the margins of experimental uncertainty, no modification of effects of high-energy x rays on the survival of mammalian cells by 2.1 T field was observed.

## 4. DIRECTIONS FOR RISK ASSESSMENT

The Department of Energy recently formed an ad hoc committee to establish exposure guidelines for technologies that utilize magnetic fields. The guidelines that were developed (Table 6) are not intended to be standards or legal limits but are to serve as an interim measure for regulating exposures to occupational workers (Alpin 1979). Further, the committee has reported that it is not prepared to offer exposure guidelines for the general population.

Table 6. Guidelines for occupational exposure to constant magnetic fields.

| | 8-h workday (tesla) | 1-h or less (tesla) | 10-min or less (tesla) |
|---|---|---|---|
| Whole body or head | 0.01 | 0.1 | 0.5 |
| Extremities | 0.1 | 1 | 2 |

Inspection of the committee's recomendations (Table 5) indicates a consistency with the exposure guidelines used for the past several years at the Stanford Linear Accelerator Center (Kaufman and Michaelson 1974). Exposure limits, however, are reduced by a factor of 2.

It does not appear appropriate to attempt to utilize the above recommended limits in performing a health risk assessment of occupationally exposed personnel. This end was not explicitly pursued by the ad hoc committee; consequently, they did not formalize the methodology used to arrive at the recommendations. This committee is currently disbanded, and there is no indication that the committee will be reformed in the immediate future (Alpin 1980).

Although the exposure guidelines currently represent the closest approximation to a consensus on adequate level of protection, a methodology or set of methodologies that could be applied to exposure situations in order to arrive at risk level estimates would be useful. In the preceding pages, ample evidence is presented demonstrating that static magnetic fields, even at relatively low strengths, have observable effects on biological systems. The major task remaining is to synthesize the information in order to arrive at an algorithm for relating some combination of field strength and exposure conditions with estimates of human health risk. In light of the available data, the following areas are suggested for analysis of risk: (1) cardiovascular response, (2) disease (cancer induction), and (3) reproduction and development.

## 4.1 Cardiovascular Response

The magnitude of anticipated physical forces is addressed in Sect. 2.1. It is shown that magnetic fields could cause an increased pressure drop in large arteries. The effects of pressure losses in the major arteries due to the influence of magnetic fields are expected to be similar to those for arterial obstructions due to a diseased condition since the magnetic field enhanced pressure loss would give rise to a pressure load for the left ventricle, the coronary artery tree and other vessels proximal to the small end of the large arteries. Regardless the cause of an increase in pressure on the proximal side of a point of resistance, such as a stenotic segment, or a coarctation of the aorta, the consequences of the induced hypertension will be similar. For example, a coarctation of the aorta (which is a narrowing of the descending aorta at the level of attachment of the ligamentum Botalli) results in a restriction of the blood flow to the lower body and an elevation of the pressure in the upper half of the body (Van Der Werf, 1980). The blood pressure in the lower part of the body is decreased although flow is mediated through the narrowed descending aorta and also through the development of collaterals. The requirement for homeostasis is normally met by a reduction in the distal pressure by the dilation in the arteriole lowering the arteriovenous pressure difference. Coarctation or blockage of the aorta thus forms a pressure load for the left ventricle in the same way as systemic hypertension does, although this particular form of hypertension is only present in the upper part of the body. The elevated pressure is generated by the left ventricular myocardium using the mechanism of hypertrophy (enlargement of the heart). Such a cause for hypertension would not affect the preload as in the case of a volume-dependent hypertension (Van Der Werf, 1980).

The exact effect of increased blood pressure does not lend itself to simple elucidation; however, the effects of blood pressure, as a risk factor, on mortality experience are quite well documented. The 1960-1962 National Health Survey (Lew, 1973) indicates that about 15% of the population suffers from definite hypertension (systolic pressure 160 mm Hg or higher) and that a like proportion has borderline hypertension (systolic pressure 140 to 159 mm Hg). The summarized results (Lew, 1973) of the Build and Blood Pressure Survey of 1959 indicate a monotonic relationship between systolic pressure (for all diastolic pressures) and mortality ratio, Fig. 12. Followup studies of insured persons carried out over nearly 50 years have shown that untreated blood pressures in excess of 140/90 are associated with significant extra mortality over a period of years.

The relationship betweeen hypertension and mortality was examined (Deubner et al., 1975) in a ten year study. This relationship was characterized by the parameter, population attributable fraction, which they found to be 0.26 to 0.54 for systolic hypertension, indicating that 26 to 54 percent of all deaths were excess deaths associated with hypertension. In addition, evidence from the Framingham Study (Kannel et al., 1971) indicates that hypertension as a risk factor has a different relation to overall mortality than to coronary heart disease morbidity. That study points to the fact that not only does the overall incidence of coronary heart disease increase with blood pressure, but that the proportion of coronary heart disease cases which are identified initially by a fatal episode also increases with increased blood pressure.

Thus far, four prospective studies in the United States, two in Europe and one in Israel have shown with remarkable consistency that close to or more than half of the new events of coronary heart disease occur among men falling within the upper 20% of the risk function of a multivariate analysis, with serum cholesterol, blood pressure and smoking contributing the most to the predictive function (Epstein, 1978). This in itself and the consistency of the relationship despite

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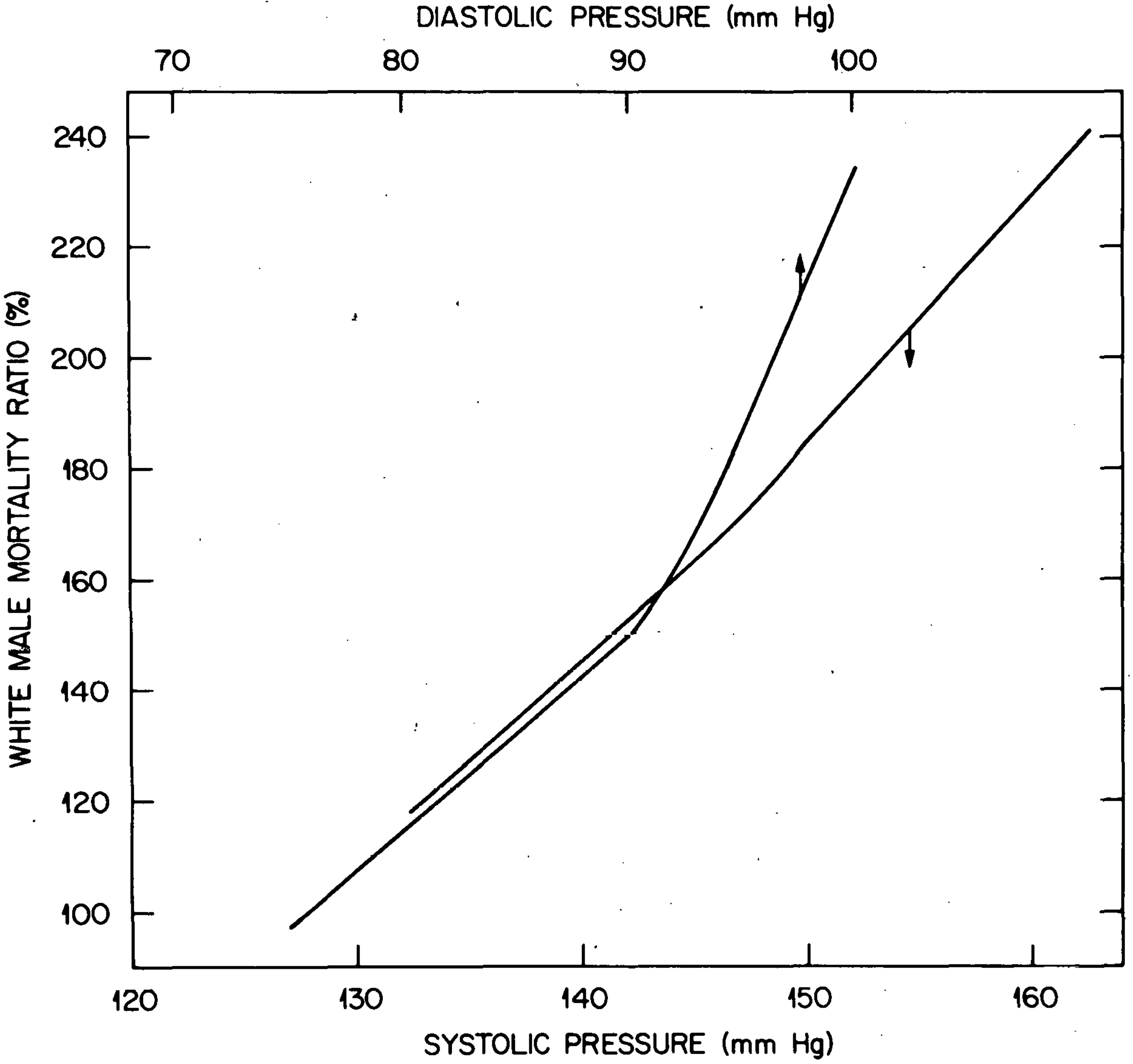

Fig. 12 Dependence of white male mortality ratio on systolic and diastolic pressure.

considerable interstudy differences in absolute risk (incidence), strongly suggest a casual connection between the risk factors and risk.

Multiple logistic functions can effectively account for enhancement of risk by the simultaneous presence of more than one risk factor and especially for the potentiating effect of multiple borderline elevations. However such a function partly obscures the long-recognized, well-known relationship between a single risk factor and disease risk. The dose-response feature provides additional presumptive evidence for a cause-effect association. An illustration of this can be seen for serum cholesterol and systolic blood pressure from the data in the final report of the Pooling Project, (1978) of the American Heart Association (Table 7).

Table 7. Risk of myocardial infarction and sudden death*

| | Serum cholesterol | | Systolic blood pressure | |
|---|---|---|---|---|
| Quintile | % of events | Relative risk | % of events | Relative risk |
| I | 13 | 72 | 13 | 70 |
| II | 12 | 61 | 17 | 86 |
| III | 16 | 78 | 17 | 87 |
| IV | 26 | 129 | 21 | 102 |
| V | 33 | 158 | 32 | 150 |

Data from the Pooling Project (1978).
*Subjects were 8,284 men aged 40 to 64 years.

As can be seen, serum cholesterol and blood pressure can concentrate, each by itself, a third of the new events into the top quintile of the distribution. This predictive power even of single risk factors compares favorably with the preformance of the multiple logistic function, (Epstein, 1978) which achieves a concentration of half of the future events within the upper fifth of the distribution.

In arriving at a procedure for estimating an upper limit of mortality increase for exposure to magnetic fields, it is assumed that:

1. The major response of a flow restriction is an increase in blood pressure in the vessels proximal to the termination of the large vessels.

2. The person works a normal 8 hr day, i.e., spends 24% of the total time in the field and is employed continuously.

3. Increases in mortality and mobidity for this artificial stimulus are in a manner similar to normal hypertension, subject to the fraction of exposure time.

The additional component of the mortality ratio can be found by multiplying the pressure addition from Fig. 2 by the fraction of time exposed, times the fraction of excess deaths attributable to hypertension, times the slope of the systolic mortality curve (Fig. 12), (i.e., $\delta P \times 0.24 \times 0.3 \times 0.04 = 0.003\ \delta P$). The fraction of excess deaths attributable to hypertension is not a precisely fixed number but 0.3 is chosen as a quantity representative of data presented in Deubner, et al., 1975 and The Pooling Project Research Group 1978. Therefore, the mortality ratio increase can be found by multiplying the increase in blood pressure in mm Hg found in Fig. 2 by 0.003.

Estimates of cardiovascular related consequences from exposure to magnetic fields can now be made. From Fig. 2, the blood pressure increase, $\delta P$, for a 1-T field is $2 \times 10^{-3}$ mm. Assuming a normal death rate of 950 per $10^5$ persons per year, the increase in mortality rate for an average occupationally exposed individual would be $5.7 \times 10^{-8}$ deaths per year. This is compared to an annual risk for safe industries of $10^{-4}$ deaths per person. For a 50 year period at risk, the lifetime risk would be $2.9 \times 10^{-6}$ deaths per person. These low values clearly indicate that an individual's cardiovascular disease risk resulting from exposure to static magnetic fields should not be a serious problem.

In addition to uncertainties in the viscosity and conductivity which have a range of variability (as reflected by the error range in Fig. 2) items not specifically accounted for are the effect of the magnetic field on the turbulent blood flow within the heart, and the magnetic enhancement of pressure losses at points of constriction. These two considerations are not expected to contribute more than a factor of two to additional uncertainty.

While the individual risk appears to be low, future technology may result in large populations exposed to magnetic fields. The relationship between some detriment and the distribution of dose in an exposed population is not simple and probably no single quantity can adequately represent the detriment for the purpose of assessing risk. Nonetheless, there are many situations in which valuable use can be made of a collective dose. The collective dose (D) is defined by the expression

$$D = \sum_i d_i p_i \ ,$$

where $d_i$ is the magnetic field dose (the pressure drop $\delta P$ due to the magnetic field) of the $p_i$ members of the subgroup (i) of the exposed population. For fields below 1 Tesla, $\delta P$ reduces to $\frac{Ha^2}{4}$ ; hence the pressure drop enhancement is related to the square of the magnetic field strength. Since the risk model is linear with exposure time, the unit of dose would need to be (field strength)$^2$ x time. Application of the collective dose concept requires that effects follow a linear dose-effect relationship. While the data of Fig. 12 are not perfectly linear, a linear relationship could be approximated. Following the calculation of a population or collective dose, application of known, quantitative "risk factor" relationships between blood pressure and morbidity/mortality, can be made. For example, consider a population of $10^6$ commuters utilizing a future magnetically levitated train two hours per day with a field exposure of 0.5 Tesla. The annual collective dose would be 50 mm-yr. This would result in an annual risk of 0.005 deaths per year per $10^6$ persons. In addition to the mortality ratio presented earlier, estimates of loss of years of life as a function of age and diastolic blood pressure could be made using recently derived relationships (Whooler 1979). This quantity, loss of years of life, could be related to both economic and social costs.

The magnitude of anticipated physical forces due to magnetic field exposure has been examined in light of modifications to normal circulation. In question is the actual human response to resultant resistance to flow associated with magnetic field exposure. In the sense that the increased resistance is perceived by the heart muscle and actually exists in the artery system to the point where the vessel diameter becomes quite small, the action of the magnetic field on the blood flow can mimic certain disease conditions and contribute to effects caused by hypertension for a portion of the cardiovascular system. It is well established that cardiovascular related morbidity and mortality are strongly associated, in the epidemiological sense, with blood pressure. As such, the preferred direction in risk estimation for this agent is in a population, or collective, sense; that is, as a statistical phenomemon, utilizing established relationships between blood pressure and morbidity/mortality to determine upper bound estimates of risk. In this case, a simple dosimetric device or methodology, integrating field strength squared and time (e.g., $\text{Tesla}^2$-days) similar to that described by Tenforde, Fujita and Goulding (1981) would be sufficient for personnel monitoring when field strengths are anticipated to be below 1 Tesla.

## 4.2 Disease

### 4.2.1 Existing risk model for carcinogenesis

One of the major concepts of cancer induction follows the lines of initiation-promotion, that is, a two-stage process (Farber and Solt 1978; Peraino, Fry, and Grube 1978; Berenblum 1954). Initiation is believed to occur when an insult causes a cell to undergo a nonreversible modification of its nuclear makeup such that it possesses the capacity to develop into a tumor by subsequent treatment with a nonspecific tumor-enhancing agent (Rous and Kidd 1941; Hennings and Boutwell 1970; Bertram 1977). The awakening or stimulation of these latent tumor cells is described by the term promotion. This process of promotion enables the transformed cells to develop into neoplasia, which may be accompanied by malignant conversion (Boutwell 1974; Farber 1980; Haddow 1974).

Transformed cells may be produced by a variety of insults, including radiation, chemicals, and random misreplication. Once a transformed cell is replicated, the "error" is fixed and the initiation stage is said to be complete. Altered cells may remain subject to normal cell kinetics for a substantial period of time (latent period), until a clone of a specific size is reached, allowing independent growth. Adequate stimulation of mitosis, either by chemical or physical means, is sufficient to promote these cells into a visible tumor.

The concept of promotion via a proliferative stimulus is not new and is supported by recent studies (Columbono, Rajalakshmi and Sarma 1981; Ying, Sarma and Farber 1981; Farber 1980) as well as by earlier observations (Acros 1974; Haddow 1974; Raik, Thumm, and Chivers 1972; Burch 1960; Salaman and Roe 1964). Numerous factors have been known, or suspected, to affect cancer rates, including the long- recognized agents radiation (Arcos 1974), chemicals (Redmond 1970; Yamagiwa 1918) and mechanical irritants (Arcos 1974; Salaman and Roe 1964), as well as hormonal balance (Arcos 1974), surgical wounding and organ removal (Pullinger 1945; Rajewsky 1972), lactation interval (Zeilmaker 1968), antiinflammatory steroids (Belman and Troll 1972), and vitamin treatment (Mossman, Craighead, and Macpherson 1980). Each of these agents possesses features modifying cellular growth (Belman and Troll 1972; Berenblum 1944; Viaje et al. 1977; Reddy et al. 1979; Slaga 1977).

Assessment models for carcinogenesis should eventually contain a time-dependent character because many time-dependent variables are involved in the sequence of tumor formation relating to the initiating and promoting insults, the time duration of synthesis inhibition processes, and the time to hyperplastic state. However, the primary data base for this time sequence is comprised of experiments with laboratory animals that possess reaction times different from those of humans. Therefore, an attempt to include the temporal sequence in a carcinogenic model does not appear to be appropriate at this time. Instead, a simple model relating cancer occurrence to cytotoxicity, a measure of promotion, seems to be more in order.

Cell survival has been proposed (Walsh 1976) as a key for risk modeling, based on the potential for growth of altered cells exposed to ionizing radiation. This proposal has been made because of the fact that the parameters describing cell survival as a function of dose are also important in describing cell alterations as a function of dose. Such model development relating cancer to cytotoxicity has been pursued by Jones et al. (1979) for ionizing radiation and Cayama et al. (1978), Griffin, Jones, and Walsh (1979) and Jones et al. (1980a) for chemical insults. These studies have demonstrated direct relationships relating cytotoxicity to a variety of neoplastic disorders. Cytotoxicity based on degree of cell killing is used by Jones et al. (1979), Griffin, Jones, and Walsh (1979), and Jones et al. (1980a) because it is directly related to a profileration stimulus. This concept of cellular proliferation as a driving force for the second stage of the initiation-promotion scheme of cancer induction has been generalized by Jones, Griffin, and Walsh (1980b). This unifying concept for carcinogenesis derives from a common-index quantity, which is quantified in terms of the degree of cytotoxicity induced by a specific exposure.

### 4.2.2 Application to magnetic fields

Examination of the literature has failed to uncover evidence that static magnetic fields possess fully carcinogenic properties similar to radiation and certain chemicals. That is, on the basis of the extant data, exposure to magnetic fields alone would not be expected to give rise to malignant tumors. Using the initiation-promotion concept, experiments with static magnetic fields have provided only marginal evidence that magnetic field exposures could result in genetic alterations. Notable evidence in that regard was the cell transformation report by Malinin et al. (1976). These data have been refuted strongly by Fraizer, Andrews, and Thompson (1979), who demonstrated that the cell transformations were a consequence of the cell culture techniques and could be produced without the presence of magnetic fields. The other piece of data that could possibly be used to support the initiation concept is that of Baum, Schairer, and Lindahl (1978), who used mutagenesis tests for the plant Tradescantia. A slight, positive slope is obtained by plotting their data on mutation frequency versus tesla or tesla - days. For the data of Baum, Schairer, and Lindahl 1978, these two units are almost directly proportional. The range of data at the low exposure levels is quite large, however, and suggests that the calculated nonzero values of the slopes may lack statistical meaning. In any case, Tradescantia is one of the more sensitive indicators for studying mutagenic effects of both physical and chemical substances (Sparrow, Underbrink, and Rossi 1972; Underbrink, Shairer, and Sparrow 1973). As such, perhaps additional work will clarify the data of Baum, Shairer, and Lindahl (1978) for mutation induction via static magnetic fields.

Looking from the other direction, a substantial body of literature exists, which contains negative results for attempts to induce mutations by means of magnetic fields or combinations of magnetic fields and radiation (see Mahlum, Sikov, and Decker 1979; Kale and Baum 1980b; Diebolt 1978; Mittler 1971; Mulay and Mulay 1964; Levengood 1966, 1967; Brewer, 1979). In light of the nature of the data available (virtually all of which negates the mutagenic effects of magnetic fields) static magnetic fields are not taken to be strong initiators, if at all. Rather, more data are available indicating that magnetic fields might function as weak stimulators of cellular proliferation and perhaps as weak promotors. Evidence such as modifications of the mitotic index, (D'Souza et al. 1969; Strzhizhovsky et al. 1977; Sushkov, Vnukova, and Cheremnykh 1977; Barnothy and Sumegi 1969) of development rates and sizes (Levengood 1967; Brewer 1979) and of tissue respiration (Cook, Fardon, and Nutini 1969; Reno and Nutini 1964) is recalled to support the premise of magnetic field modifications of normal cellular function and proliferation. Not all of the data examined gave indication of changes in growth or mitotic activity. If the action of magnetic fields is one of a general nonspecific stressor, as indicated by Barnothy and Sumegi (1969) for mitosis alternations in the liver, the differences observed may be only a reflection of differing cell type, organ, or organism responses.

Clearly, substantial additional effort would be necessary to extend the initiation-promotion model proposed by Jones et al. (1979), Griffin, Jones, and Walsh (1979), and Jones et al. (1980a) from one based on cell-killing as a proliferative stimulus to one based on a direct modification of normal cell turn-over. In addition, a more detailed examination of the extant literature would be required to better quantify altered mitosis as a function of magnetic field exposure. The altered mitosis appears to vary at least from organ to organ (Barnothy and Sumegi 1969; Strzhizhovsky et al. 1977; Sushkov, Vnukova, and Cheremnykh 1977), in temporal response (Barnothy 1964), and in level of response (Strzhizhovsky et al. 1977), depending on the orientation relative to the magnetic field. Dosimetry for this aspect of magnetic fields would be expected to be difficult, in that a complex temporal aspect might be required to follow the time-lagged, damped response that is reported (Barnothy 1964a; Barnothy and Sumegi 1969; Strzhizhovsky et al. 1977).

### 4.3 Reproduction and Development

Reproduction and development effects can be caused by a variety of factors, including inherited genetic (Mendelian), inherited cytoplasmic (non-Mendelian), teratologic insults from conception through development, and toxic insults that could affect development at any stage. Of the literature examined, no substantial evidence was found to support the concept of transmitted generic mutations associated with magnetic field exposures. In fact, a substantial body of literature suggests that there are no mutagenic effects (Sect. 4.2.2).

The concern for reproductive and development effects derives from observations of reduced progeny and morphological changes in progeny of organisms exposed to magnetic fields. The observed effects are often seen more clearly in generations other than the first, and the gradual loss of the effects over generations after exposure indicates morphological alterations of non-Mendelian character (Levengood 1967). Cytoplasmic inheritance is suggested by Levengood (1967), who offered a kinetic hypothesis for this phenonmenon.

No clear evidence was uncovered that would implicate magnetic fields with direct teratologic effects. A rather substantial data base indicates the absence of mutagenic properties of magnetic fields both alone, and in combination with radiation (Mahlum, Sikov, and Decker 1979; Kale and Baum 1980b; Diebolt 1978; Mittler 1971; Mulay and Mulay 1964; Levengood 1966, 1967; Brewer 1979). Since many teratologic effects derive from essentially mutagenic phenonema occurring on the somatic level, the arguments of Sect. 4.2.2 are invoked to indicate the unlikelihood of teratologic events occurring subsequent to exposure to magnetic fields.

The mitosis modification-related data presented earlier (D'Souza et al. 1969; Strzhizhovsky et al. 1977; Sushkov, Vnukova, and Cheremnykh

1977; Barnothy and Sumegi 1969; and Toroptsev et al. 1974) might give rise to concern in terms of growth modification because the majority of developmental defects can be explained on the basis of too few cells, or cell products, to permit the completion of morphogenesis or functional maturation (Wilson 1973). Franz (1971) has shown that slowed mitotic rate can contribute significantly to growth retardation independent of cellular death. Only indirect evidence for this type of action has been found for magnetic field insults; this evidence is the increased development time of Drosophila reported by Levengood (1966, 1967). Increased mitotic rate is implicated in the decreased development time of the guppy (Brewer 1979). Finally, although mitotic changes caused by physical and chemical agents have been implicated in teratogenic events (Wilson 1973), no evidence has yet been identified that links magnetic field exposures to teratogenic occurrences.

Both tissue culture and whole animal data indicate a potential for effects on immature organs and organisms. Especially interesting are the respiration inhibition of certain embryonic tissues and the age relationship of this inhibition (Reno and Nutini 1964). Although the in vitro respiration data may not be strictly indicative of in vivo conditions, the qualitive relationship gives rise to concern about growth and development with reduced oxygen availability. Reduced oxygen availability as occurs in high altitudes is suspected by McCullough, Reeves, and Liljegren (1977) to be a primary contributor to the increased levels of perinatal mortality experienced at such locations. This work indicates that high altitude, possibly through the mechanism of exaggerated fetal hypoxia, retards fetal growth and increases the mortality rate of preterm infants. Only minor evidence for this type of effect is available for animals exposed to magnetic fields, this evidence being the few nonreplicated reduced organ weights seen by Sikov et al. (1979).

Most experiments that have found deleterious consequences of magnetic field exposures have been associated with continuous exposures over generations or exposures during a sensitive stage of development (e.g., organogenesis). Exposures of adult organisms have, by and large, failed to exhibit effects.

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