A THEORY OF RADIATION RISK BASED ON MICRODOSIMETRY

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Abstract

This paper demonstrates how microdosimetry can be applied to a theory of radiation risk. Many recent radiobiological experiments show that the relative biological effect (RBE) between two different radiations increases as the dose decreases. The historically developed quantities of radiation dosimetry, the absorbed dose and the dose equivalent, fail to account for this phenomenon. Also, because the absorbed dose is an averaged quantity, it provides no physical basis for other than linear extrapolation of biological data to the small radiation exposures encountered in radiation protection. Microdosimetry suggests that a consistent theory of radiation risk can not be linear for all radiations.

Several models which fit the distributions of microdosimetry to biological data are possible. Because none of them can be linear, it is necessary to process the individual datum of a microdosimetric distribution in order to produce an index of risk. As a demonstration of the feasibility of the procedure, a Rossi-type tissue equivalent proportional counter was interconnected with a PDP-8I computer and exposed to several different types of radiation. The results show that single-valued indices of radiation risk can be directly measured and, thus, one of the hurdles to the application of microdosimetry to radiation protection appears to be solvable.

Introduction

Perhaps the central issue in radiation protection is how biological effect data obtained at high doses should be extrapolated to the low dose range of maximum permissible limits and radiation protection guides. If the important biological effects of radiation occurred with statistically sufficient frequency at the doses of interest, it would be possible to investigate the dose-effect relation experimentally. However, the important effects, such as the induction of neoplastic disease and genetic mutation, occur with low probability even at high dose rates.[1] It has not been possible to date to reliably estimate the shape of the dose-effect curve below dose levels at least ten times greater than present guide lines. Furthermore, as Rossi[2] has pointed out, the experimental approach is usually self-defeating. There is an understandable tendency to reduce permissible doses well below the level where biological effects can be observed. Consequently, the radiobiological experimenter is always pursuing the retreating mirage of lower dose effects. It is therefore clear that extrapolations must be made on some theoretical basis.

Most extrapolations to the low dose range have a biological basis. Dose response schemes[1,3] which make use of thresholds are based on the accepted notions of biological repair processes and sublesion damage. The well-known sigmoid LD_{50} curve for experimental whole-body irradiation of mammals is a simple example.

Linear and curvilinear relationships have been proposed[1,3] which are derived from physical and molecular considerations. At sufficiently low doses and dose rates the linear model has been attractive to many workers because the spatial and temporal separation of ionizing particles is large enough so that effects are caused principally by single tracks through cells. Since interactions between tracks in this case would be negligible and the density of tracks is linear with dose, a linear dose-effect relationship is a necessary result. The major difficulty with this reasoning is that the estimates of risk which are linearly extrapolated to low doses are based on biomedical evidence obtained at high doses where, for low LET radiations, there are multiple traversals of ionizing electrons through cells and cell nuclei.

The linear non-threshold hypothesis has been used in radiation protection standards because it is easy to apply, gives clear-cut estimates of risk and is generally thought to be conservative. However, Baum[4] has presented evidence that linear extrapolations are not necessarily conservative for heterogeneous human populations. He shows how a dose-effect relation represented by a simple power function of dose with an exponent of less than one can occur when subdivisions of a population have differing sensitivities. An important result of a power function with an exponent less than one is that the effectiveness per rad is greater at low doses than at high doses. However, Baum assumes a linear dose-effect relation for each of his subdivisions of the considered population with different thresholds for each subdivision, and consequently, even in his hypothesis, the linear dose-effect relation is fundamental.

Inherent in existing radiation protection guides is the assumption of linearity of effect with dose for all radiations. This is a consequence of a constant quality factor for all doses of a given radiation. But, increasing evidence shows that the relative biological effect (RBE) of any type of radiation is not a constant, but increases with decreasing dose. Furthermore, consideration of microdosimetry data suggests that the risk of effect can not be linear for all radiations. For example, the dose-effect curves for neutron and gamma radiation cannot both be linear. If the curve is linear for neutrons, it cannot be linear for gamma radiation over the entire dose range of biological interest.

This paper presents the biological and physical evidence that supports linearity of dose-effect for densely ionizing radiations (i.e., high LET-radiation) and decreasing effectiveness with decreasing doses of sparsely ionizing radiations (i.e., low-LET radiation). It also reviews the potential uses of microdosimetry in radiation protection and discusses how microdosimetric indices of risk may be measured directly.

RBE as a Function of Dose

The ICRP[5,6] originally intended the LET-QF relation to follow the LET-RBE relation. But this intention was shown to be in error when results of track segment experiments began to appear. In these experiments[7,8,9] accelerated heavy particles pass through monolayers of cells. By adjusting the amount of absorber in front of the target cells, the experimenter could select the portion of the heavy particle track (and thus the LET) he wished for irradiation. These experiments, pioneered by Barendsen, are ideally designed to test the

efficacy of LET as a quality factor. The results offered little support for the LET-QF relation. RBE-LET curves differed from one biological system to another. RBE did not always increase with increasing LET; for lower organisms, the RBE decreased with high LET radiation. For mammalian cell killing the RBE does increase at high LET, but not linearly. Furthermore, the RBE-LET curve for cell killing goes through a maximum at about 100 keV/micron and falls off at higher LET values. Similar experiments with chromosome abnormalities as an end point[10] showed a similar RBE-LET curve with a maximum.

By itself, the RBE-LET track segment evidence only appears to place the QF conservatively high as a function of LET. This is not a serious problem, since the risk from radiation exposure would never be under estimated. However, the difficulty with constant quality factors became more significant when a number of radiobiological experiments indicated that RBE was a function of dose over the whole range of LET. Barendsen's now classic, track segment experiments were the first to show this. The peak RBE had a value of 7.5 for 80% cell survival, 4.5 for 20% survival, 3.5 for 5% survival and 3.0 for 1% survival. Neither the shape of the curves or the location of the maxima (110 keV/micron) vary, but the RBE increases for all values of LET when the survival increases (and thus when the dose decreases).

Barendsen's finding on the dose-dependence of the RBE was soon supported by other workers. Bateman,[11] measuring opacities in mouse eye lens for neutrons of different energies, also found the RBE varying inversely with dose. The slope of the RBE-LET curve increases as the neutron energy is decreased from 14.3 MeV to a maximum at about 340 keV and then decreases for lower energies. The dependence of RBE on dose was extended to the induction of mammary cancer in Sprague-Dawley rats by Vogel[12] and Shellabarger.[13] An apparent difference in their results can be attributed to differences in neutron energy spectrum.[13] Otherwise, their results are consistent with those of other workers for cell killing, chromosome aberrations and cataracts. The same increase in RBE occurs as the dose is decreased and the slope of the RBE-dose curve for mammary cancer data on a log-log plot is similar to and consistent with the data on other effects. The significance of Vogel's and Shellabarger's data cannot be over emphasized. Neoplastic disease constitutes the major concern of those setting radiation protection standards. Cell killing and chromosome aberrations clearly originate with damage within a single cell, while cancer can not so readily be traced to an alteration of a single cell. The similar RBE-dose kinetics for cell killing and mammary cancer suggest that neoplastic disease may also originate within a single cell. Even if this simplication does not actually occur, the results may still be used in an empiric fashion so that the impact on radiation protection will remain in any case. Kellerer and Rossi[14] have summarized the available data which show the RBE-dose dependence. They used the data to support an hypothesis that biological effects originate in cellular lesions which are produced by one high LET particle but which require at least two electrons. Recently, Hall, et. al.,[15] have reported exhaustive studies on the RBE-dose dependence for effects on Vicia faba. These studies completely confirm all aspects of the other studies quoted.

What is to be made of these data? They show that RBE is unity, or close to it, at high doses over the range of LET. Then for a variety of effects (cell survival, lens opacification and cancer induction) as the dose decreases, the RBE begins to increase, at different rates for radiations of different LET. Does the RBE increase indefinitely at lower doses? If so, what does that mean for radiation protection? Would this imply drastically lowered limits for densely ionizing radiations? Or does one re-evaluate limits for x-and gamma radiation?

A report by Sparrow, et. al.[16] suggests a possible resolution of this problem. They obtained dose-response curves for somatic mutation in Tradescantia stamen hairs exposed to 0.43 MeV neutrons and 250 kvp x-rays. All the neutron data fit a linear plot. The x-ray data was curvilinear down to five rads. From 5 to 100 rads the RBE (neutron/gamma) decreased with increasing dose from about 50 to about 15. Below x-ray doses of 5 rads, the RBE remained constant because the x-ray data were linear. Both the neutron and gamma curves peak and decline at higher doses so that the RBE does not approach unity as other RBE-dose data. The study shows, admittedly for a non-mammalian cell, but nevertheless for a eucaryotic cell, that the RBE does not increase indefinitely. Furthermore, since the neutron response is linear throughout the range, while the x-ray response is only linear at very low doses, it appears that x-rays are less effective per rad at low doses.

Some Concepts of Microdosimetry

If the biological effectiveness between different radiations did not vary with dose, the absorbed dose, and with an appropriate quality factor, the dose equivalent, would serve the purpose of radiation protection without difficulty. Since the dose-dependence of RBE is now well established, it is apparent that the physical parameters now used for the estimation of risk, the absorbed dose and linear energy transfer, need to be re-examined.

When a small animal, e.g., a mouse, is irradiated, the absorbed dose is constant over the whole animal (neglecting, of course, the differences in atomic composition and density of bone, fat, etc.). This constancy of dose remains for any tissue mass larger than several milligrams. Thus, if our mouse received 100 rads, every gram absorbs 10,000 ergs, every 100 milligrams very close to 1000 ergs and every 10 milligrams about 100 ergs. But when the sample of mouse gets down to the size of the cell (micrograms), or the cell nucleus (tenths of ug), the energy density (E/m) will seldom equal the absorbed dose. This results from the discontinuous nature of radiation energy deposition; matter exposed to ionizing radiation receives its energy from charged particles which dissipate their kinetic energy in discrete tracks of ionization and excitation. While a gram of tissue may be traversed by a vast number of charged particles when absorbing a dose of one rad, a cell nucleus in that gram of tissue might be traversed by only a few particles, or even none at all. Since it is widely supposed that biological effects originate in cells, it would seem prudent to investigate the deposition of energy on a microscopic scale. Any given amount of energy absorbed in a material will, if the sample size is small enough, produce distributions of microscopic values of the energy density. The study of these microscopic distributions has come to be called microdosimetry.

Historically, microdosimetry orginated with Rossi's use of tissue equivalent, spherical proportional counters to determine LET distributions.[17] He soon realized that the proportional counter spectra were interesting in themselves.[18,19] The counter, operating with tissue equivalent gas at pressures of a few millimeters of mercury, could simulate very small volumes of tissue. For example, a 7.5 inch counter can simulate a volume of effective diameter of 6 microns when operated at 40 mm Hg, 3 microns at 20 mm Hg and 1.5 microns at 10 mm Hg. In each case the mass of the gas is equal to that of the small simulated tissue sphere at unit density. The practical limit to which this technique has been pushed is about 0.1 micron.[20]

Of course there is a magnification of the particle fluence in the simulated sphere because the number of particles crossing the cavity is proportional to the cross-sectional area of the cavity. Corrections for this effect and other technical details have been extensively discussed by Rossi.[21]

Pulses can be sorted as they are produced in the counter (i.e., sent directly to a pulse height analyzer) or collected for a given time and then sorted. In the first case, a distribution of single events is generated, and in the second case, distributions of multiple events occur.

When a charged particle traverses the proportional counter and is detected, the process is called an event. Hopefully, this experimental event mimes the microscopic event, the passage of a charged particle through a biological structure. To determine the magnitude of an event, the size of the biological structure must be specified. The quantity of energy, E, deposited in a single event, divided by the microscopic diameter was first called the event size, Y, and later redefined as the lineal energy density, y.[22]

Single event distributions do not have to be limited to the lineal energy density. The event energy can also be divided by the volume or mass of the biological structure. The ratio of E/m has been defined as the specific energy, z.[22] $f_1(z)$ is the differential distribution of single events in specific energy z.

Another single event distribution is the event frequency, $\phi(y)$, the mean number of events with size in excess of y per unit absorbed dose. $\phi(0)$ is the frequency of events of all sizes per unit absorbed dose.

Single event distributions are unique for each type of radiation. The range of magnitude included in the distribution is a characteristic of each radiation type. For example, ^{60}Co radiation produces an $f_1(z)$ distribution in one micron spheres which includes events from 1 to 200 rads, while Pu-Be neutrons produce events from 80 to 7000 rads. Single event distributions increasingly overlap as the sample size is increased and increasingly separate as the sample size is decreased. The ability to "fingerprint" the radiation type had led to attempts, unsuccessful to date, to use the single event distributions of microdosimetry as an index of radiation quality.

It is widely accepted that energy is responsible for biological changes. Work must be done on a biological system to cause any change. This acceptance of energy's role accounts for the fundamental position that the absorbed dose holds in radiation science.

Microdosimetry does not abdicate the fundamental concept of energy input into a biological system as being a necessary condition for radiation effect. Rather, it requires that the energy input be known with more detail. Instead of the energy input to a body organ, averaged over the whole organ, the question asked is: what is the distribution of energy inputs to the microscopic structures in the cell?

The absorbed dose is a single valued quantity, while the specific energy, z, is random valued and must always be known in its complete distribution. The absorbed dose is thus the mean value of the differential distribution of z. The symbol for the z distribution is $f(z;D)$ indicating that the distribution is also a function of absorbed dose.

The event frequency must exceed one for any sphere size, provided the dose is high enough. The smaller the sphere size or the higher the LET, the greater the dose must be for multiple events to occur. It also follows that for any combination of radiation type and sphere size that the event frequency can be less than one. This means that no event occurs in some fraction of the samples. When this zero component is large, the $f(z;D)$ distribution is nearly equivalent to the $f_1(z)$ distribution. All energy depositions come from single events in this case. This occurs at low doses, but at different absolute absorbed

doses for different radiations. Generally, densely ionizing radiations, such as alphas, protons and neutrons, produce single event distributions in the absorbed dose range of interest for radiation protection. Electron and photon radiation usually produces multiple event distributions. At very low doses, or also with very small sphere sizes, electrons and photons can produce single event energy density distributions. The dose below which this occurs for 250 kVp x-rays in one micron spheres is 20 rad, in 3.5 micron spheres two rads. For the same spheres, 0.34 MeV neutrons produce single event distributions up to 1430 rads and 143 rads, respectively.

Comparing specific energy distributions for various doses of low LET and high LET radiations shows that high LET spectra increase in area with increasing dose but do not shift in value because multiple events have low probability. Low LET radiation spectra on the other hand show strong shifts up the scale with increasing dose because of multiple events. At sufficiently high doses the low LET and high LET spectra overlap completely. It's this phenomenon that appears to account for the dependence of the RBE on dose.

The Microdosimetric Implications of the Absorbed Dose

As a single valued, averaged quantity, the absorbed dose concept assumes that ionizations are distributed homogeneously and randomly throughout the irradiated material. As a consequence, when the dose is lowered, the concentration of ionizations is assumed to be lowered. Each ionization would, in this case, have the same probability of contributing risk at low doses that it did at high doses. Thus, only linear extrapolation is possible as long as the absorbed dose is believed to be fundamental.

Of course, ionizations are not randomly distributed in irradiated material. They are associated with ionizing particles which are randomly distributed. Recognizing the reality of microscopic energy distributions, the ICRU[23] provided an alternative definition of the absorbed dose:

$$D = \bar{z} = \int_0^\infty z f(z) dz$$

If the absorbed dose were the correct quantity with which to correlate biological effect, then this non-uniform deposition of energy in biological structures must be reflected logically and consistently in the biological effects of radiation. Since effects originate within cells, then the absorbed dose concept presumes that the probability of an effect occurring in a cell is linearly related to the energy density in the cell. However, if this were true, there would be no RBE between different radiations and no RBE dependence on dose. Furthermore, the results of track segment experiments cited earlier are consistent with a linear z-effect relation. These experiments show that a limit of effectiveness is reached with increasing energy density. More important, the effectiveness per rad falls off rapidly with decreasing energy density.

The deficiencies of the absorbed dose are not fully compensated for by multiplication with LET-related quality factors. Because of the RBE dependence on dose, it is clear that a non-linear function must be found to weight the energy density distribution.

A Model for the Extrapolation of Risk to Low Doses

Consider two types of radiation which have quite different $f_1(z)$ distributions, say fast neutrons and gamma radiation. Recall that the $f(z;D)$ distribution for fast neutrons was similar to the $f_1(z)$ distribution over most of the dose range of biological interest. That is, the z values remain constant with dose, and only the probability of each z increases with increasing dose. Because the area under the $zf(z;D)$ distribution in this case is directly proportional to the dose, you would expect the dose effect curve to be linear over that range of dose, no matter what the z-effect function was. The $f(z;D)$ distribution for gamma radiation can also approximate its $f_1(z)$ distribution, but at much smaller doses. At very small doses, the gamma dose effect curve would be linear but reduced in effectiveness per rad, provided that the z-effect function had values greater than zero within the range of values included in the $f_1(z)$ distribution for gamma radiation. This is likely to be the case since the $f_1(z)$ distributions for fast neutrons and gamma radiation overlap for sphere sizes such as the cell nucleus and since all fast neutron events appear to be effective in cell killing experiments and to be linearly proportional for cataract and cancer induction. For an absolute dose threshold to exist, an effective energy density threshold in the particular cellular target, e.g. the cell nucleus, must occur.

A great deal of evidence exists to show that the cell nucleus is the appropriate sphere size for microdosimetry. For example, the cell killing experiments with track segments show probability cross-sections which are geometrically equivalent to the cell nucleus cross-section. Other evidence includes kinetic analysis by Kellerer and Rossi.[24] A typical diameter for a mammalian cell nucleus is 3.5 microns. For a sphere of this diameter there is considerable overlap of $f_1(z)$ distributions for low LET and high LET radiations. To provide enough separation to account for the RBE's of 50 or more which appear to be reached at low doses, it is necessary to assume very diminished effectiveness for low values of specific energy, so that an effective threshold of energy density in the mammalian cell nucleus appears to be required for biological effect.

The significance of this model is far reaching. It demonstrates that it is not physically or biologically feasible to extrapolate linearly from high doses of gamma or x-radiation to low doses. It also gives support to the conclusion that risk for low doses of radiation may be significantly over estimated.

Two of the important features of the extrapolation need numerical values: Firstly, the dose at which the RBE becomes constant is the dose where the reference radiation, 250 kVp x-rays, becomes a single event distribution. For target volumes 3.5 microns in diameter single event distribution occur at doses less than 2 rads. Secondly, if one made use of Kellerer and Rossi's equation for the RBE,[14] one would project a maximum RBE of about 400. This maximum RBE, because it occurs at low doses, is of obvious significance for estimating risk to populations. This value of the RBE should not be used to reduce the neutron fluence to which a population should be exposed. Rather, since electron and photon radiation is so much less efficient than previously assumed from linear extrapolations from high doses, the permissible photon fluence may be increased substantially.

The Direct Measurement of Indices of Risk

If, as suggested here, the measurement of cell nuclei energy density distributions is important, it will become necessary to perform on-line processing of the large amount of data contained in a microdosimetric

distribution. Conceptually, this offers no barrier. Miltenberger[25] has interconnected a TE proportional counter to a PDP-8I computer and obtained single-valued indices of risk from a variety of radiations and doses. There are, however, some difficult obstacles, not the least of which is the fluence magnification mentioned earlier. In a sense the dose reduction phenomenon, caused by the density differences in the TE gas and counter wall allows accumulation of microdosimetric distributions within reasonable times. However, high intensity fields may not be measureable since the counting time, already below the millisecond range for low dose rates, will be too short even for electronic timing. Because the technique is most important for low dose levels, this fundamental deficiency may not inhibit the practical use of the technique.

The procedure used by Miltenberger was as follows: The TE proportional counter was connected to a pulse amplifier. From there the amplified pulse was directed to an analog to digital converter. The numerical value from the converter was then fed into a Digial PDP-8I computer. The numerical value was then weighted by the computer according to the function assumed and added as an increment of risk to the sum index.

It should be possible to develop analog circuits to perform the weighting function and thus allow the eventual development of a reasonably sized and priced instrument.

References

1. Report of the Advisory Committee on the Biological Effect of Ionizing Radiations, The Effects on Populations of Exposure to Low-Levels of Ionizing Radiation, National Academy of Sciences/National Research Council, Washington, D.C. 20006, November, 1972.

2. Rossi, H.H., The Effects of Small Doses of Ionizing Radiation, Phys. Med. Biol., Vol. 15, No. 2, pp. 255-262, 1970.

3. International Commission on Radiological Protection, Publication 14, Radiosensitivity and Spatial Distribution of Dose, Oxford, Pergamon Press, 1969.

4. Baum, J.W., Population Heterogeneity Hypothesis on Radiation Induced Cancer, Health Physics, Vol. 25, pp. 97-104, 1973.

5. International Commission on Radiological Protection, Report of the RBE Committee to the International Commissions on Radiological Protection and on Radiological Units and Measurements, Health Physics Vol. 9, p. 357, 1963.

6. International Commission on Radiological Protection, Recommendation of the International Commission on Radiological Protection, 1965, ICRP Publication 9, Pergamon Press, Oxford, 1966.

7. Barendsen, G.W., Impairment of the Proliferative Capacity of Human Cells in Culture by Particles with Differing Linear-energy Transfer, Int. J. Rad. Biol. Vol. 5, p. 453, 1964.

8. Barendsen, G.W., Relative Biological Effectiveness as a Function of Linear Energy Transfer, Proceeding of the First Symposium on Microdosimetry, Ispra (Italy), Euratom, 1967.

9. Todd, P.W., Heavy-Ion Irradiation of Cultured Human, Rad. Res. Supp. 7, p. 196, 1967.

10. Skarsgard, L.D., B.A. Kihlman, C.M. Pujara and S. Richardson, Survival, chromosome abnormalities and Recovery in Heavy-Ion and X-irradiated Mammalian Cells, Rad. Res. Supp. 7, p. 208, 1967.

11. Bateman, J.L. and M.R.S. Snead, Current Research in Neutron RBE on Mouse Lens Opacity, in Symposium on Neutrons in Radiobiology, CONF-691106, 1969.

12. Vogel, H.H. and R. Zaldiver, Experimental Mammary Neoplasms: A Comparison of Effectiveness between Neutrons, x- and Gamma-radiation, in Symposium on Neutrons in Radiobiology, CONF-691106, 1969.

13. Shellabarger, C.J., Unpublished data, given in Radiation Carcinogenesis at Low Doses by H.H. Rossi and A. Kellerer, Science, Vol. 175, pp. 200-202, 14 Jan. 1972.

14. Kellerer, A.M., and H.H. Rossi, RBE and the Primary Mechanism of Radiation Action, Rad. Res. Vol. 47, pp. 15-34, 1971.

15. Hall, E.J., H.H. Rossi, A.M. Kellerer, L. Goodman and S. Marino, Radiobiological Studies with Monoenergetic Neutrons, Rad. Res. Vol. 54, pp. 431-443, 1973.

16. Sparrow, A.H., A.G. Unterbrink and H.H. Rossi, Mutations Induced in Tradescantia by Small Doses of X-rays and Neutrons: Analysis of Dose-Response Curves, Science, Vol. 176, pp. 916-1918, 26 May, 1972.

17. Rossi, H.H. and W. Rosenzweig, Advice for the Measurement of Dose as a Function of Specific Ionization, Radiology, Vol. 64, pp. 404-410, 1955.

18. Rossi, H.H., Specification of Radiation Quality, Rad. Res., Vol. 10, p. 522, 1959.

19. Rossi, H.H., M.H. Biavati and W. Gross, Local Energy Density in Irradiated Tissues. I. Radiobiological Significance, Rad. Res. Vol. 15, p. 431, 1961.

20. Rossi, H.H., Experimental Limitations of Microdosimetry, Second Symposium on Microdosimetry, Stresa, Italy, EUR 4452.

21. Rossi, H.H., Microscopic Energy Distributions in Irradiated Matter in Radiation Dosimetry, Volume 1, F.H. Attix and W.C. Roesch, eds., Academic Press, 1967.

22. Rossi, H.H. and A.M. Kellerer, Summary of Quantities and Functions Employed in Microdosimetry, Second Symposium on Microdosimetry, Stresa, Italy, EUR 4452.

23. International Commission on Radiological Units and Measurements, Radiation Quantities and Units, ICRU Report 19, Washington, D.C., 1971.

24. Kellerer, A.M., and H.H. Rossi, The Theory of Dual Radiation Action, Current Topics in Radiation Research, Volume 8, No. 2, October, 1972.

25. Miltenberger, R.P., Measurement of the Microdosimetric Quantities $\bar{z}_e$ and $\phi(zT)$, Masters Thesis, University of Pittsburgh, Graduate School of Public Health, 1973.