Mathematical Relationship of "Probacent'-Probability Equation among Exogenous Stressor, Stress and Response in Biological Phenomena

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ABSTRACT

The author studied mathematical relationships among stressor, stress and response in various biological phenomena in humans and other living organisms. He constructed a mathematical model of "probacent"-probability equation that would be applicable as a general approximation method to calculate probabilities of outcomes of biological response as a function of intensity of exogenous stressor and duration of exposure. In this study, the author reviewed and summarized findings in his researches. An underlying, unifying equation, **Eq. 28**is found to exist from which various forms of "probacent"-probability equations are possibly derived. A correlation between the "probacent"-probability equation and the Selye's stress theory is presented. The probacent"-probability equation may be hopefully helpful in biomedical researchfor predicting outcomes as a function of intensity of stressor and duration of exposure in various biological phenomena.

Keywords: "Probacent"-Probability Equation;Formulas of Survival and Mortality Probability; Formula of $LD_{50;}$ US Life Tables; Radiation Hazard, Carbon Monoxide Poisoning; Formula of Drug Toxicity; Selye's Stress Theory, Computer Programs of Nonlinear and Linear Regressions; Cancer.

1. INTRODUCTION

Selye (1936) [1, 2] introduced the idea of stressor to harmful stimuli, noxious agents for living bodies; e. g. cold, heat, trauma, burn, radiation, fatigue, bacterial infection and intoxication etc. These various stressors induce biological stress as common reactions to injury and for defense of the body. Stress reactions were named general adaptation syndrome (a stress theory). Since the Selye's stress theory was published, various bodily responses to stressors were investigated.

In general, marked variations are found in percentages of response occurring in the body, depending upon intensity of stressor, duration of exposure and individual sensitivity. A clear and exact quantitative mathematical relationship among three factors, namely, intensity of stressor, duration of exposure and percentage of occurrence of response in biological phenomena such as human tolerance to total body irradiation is still not known[3]. The time factor is often not taken into account in response. Biological phenomena are often observed and investigated after states of equilibrium have been attained.

The author defines stressors like heat, cold and radiation as "exogenous stressors" which can be arbitrarily given to living bodies with a definite constant intensity for a definite duration. Drugs and toxic chemicals are included in the exogenous stressor. Biological stress is induced by exogenous stressors. Cause-unknown cancer and metabolic disorders are defined as "endogenous stress".

The author and his coworkers began a study of mechanical exogenous stressor on mice and thereafter studied other exogenous stressors and responses in living organisms to search a mathematical model[4, 5].

1. 1. 1. Study of Mouse Tolerance toPositive Radial Acceleration of*G*-force

The author presented his study of positive *g*-force radial acceleration on mice on November 29, 1956 at the 5th Semi-Annual Medical Conference of the U. S. Far East Air Force, Baguio, Philippines. It seemed to the author that there were no articles in the literature that published a mathematical model predicting tolerance to *g*- force as a function of magnitude of acceleration and duration of exposure [6-10].
One hundred ninety one mice were subjected to positive radial acceleration from 3 to 85 *g* for periods of 5 seconds to 80 minutes. Data on mortality, electrocardiogram and pathology were studied [4, 5].
A formula, **Eq. 1**was constructed from the mortality data to express mortality probability as a function of magnitude of acceleration and duration of exposure.

$$P = [(g - 7)t - 5.3] / (0.025t + 0.173) \quad (1)$$

Where g = magnitude of positive acceleration in units of gravity; t = duration of exposure in minutes; P = mortality in percentage.
Formula-predicted mortalities approximately agreed with observed mortality data.
Eq. 1 is rewritten in a general form, **Eq. 2** for further consideration**.**

$$P = [(g - a)\, t - c] / (bt + d) \quad (2)$$

Where *a, b, c* and *d* are constants.
Results are shown in Figure 1 in which two curves expressing zero and 100 percent mortalities are plotted as strength-duration curves in a graphic representation. The two curves seem to reveal two rectangular hyperbolas having asymptotes which are of significance. For the zero percent mortality curve, it seems to exist a *g*-force of magnitude of the constant *a* at which the time factor ceases to be significant in the response unless other factors than *g*-force begin to operate. Cranmore [8] designated this value *a* as infinite survival (author's note: a threshold to induce a response). **Eq. 1** and **2** are constructed from the experimental data and also seem to be possibly derivable as described in the following section.

Place Figure 1 here.

Figure 1. Mortality of mice exposed to *g*-force. Curves fitted visually to delineate100% survival and 100% fatality. All deaths occurred prior to removal of animal from its cylinder. No animal died under later observation if alive when removed from the centrifuge cylinder. No significant sexual differences were found in resistance to positive *g*. The calibration of time plotted in abscissa is accurate up to 3 min., thereafter only adequate to represent time and is not logarithm of time.

1. 1. 2. Deductive Derivation of Eq. 1 and 2

(1) Derivation of Eqs. 1 and 2 of "probacent" [4]

If a certain exogenous stressoracts on living bodies with a certain constant intensity *i*fora period oftime *t*, it could be guessed that a certain percentage of occurrence of response might be determined

by a relative amount of biological stress (reaction) induced in the body by the action of exogenous stressor. The amount of biologic stress is expressed by "probacent" *P* that is a relative biological amount of stress that represents the sum of induced internal bodily reactions. The biologic stress might be in proportion to the amount *D* of damaging action of stressor, and inversely proportional to the amount *R* of repair and recovery in resistance. It might be expressed by **Eq.3.**

$$P = D/R \qquad (3)$$

A definite amount *c* of action of stressor corresponding to a critical threshold might be required to induce biological stress in the body, that is, when the total amount *E* of action exceeds *c*. Therefore, the remaining effective amount*D*of damaging action is expressed by **Eq. 4.**

$$D = E - c \qquad (4)$$

It has been recognized that there is in general a threshold intensity "*a"*of stimulus causing reaction or response in a biological system. For example, rheobase is known as threshold in electric stimulation of single nerve or muscle fiber. It is impossible to give rise to a response by stimuli weaker than " *a* " even for a long duration. The author considers the excessive intensity over "*a*", namely *i* minus *a*as the effective active injuriousintensity**. Eq. 5** is obtained:

$$E = (i - a)\, t \qquad (5)$$

Where *E* = total amount of exogenous stressor that has accumulated as a sum during of exposure time *t*. The total amount of energy *E* of stressor in a physical standpoint is represented by **Eq. 6** in the physical world.

$$E = it \qquad (6)$$

Eq. 4is expressed as follows:

$$D = (i - a)\, t - c \qquad (7)$$

The amount *R* of bodily repair and recovery is the sum of always existing readily available certain amount *d* of repair and recovery and amount *r* of repair and recovery which is automatically mobilized in the body with a velocity *b*. *R*of amount of repair and recovery is expressed by **Eq. 8.**

$$R = r + d = bt + d \qquad (8)$$

If **Eqs. 7**and **8**are substituted in **Eq. 3,** then**Eq. 9**that is same as **Eqs. 1** and **2** is obtained.**Eq. 2** is thus derivable [4].

$$P = [(i - a)t - c] / (bt + d) \qquad (9)$$

In some biological phenomena such as goldfish tolerance to methanol, survival probability in man, and mouse tolerance to Metrazol toxicity, "probacent" is time dependent (t^n), so **Eq. 10** is a general formula of**Eq. 9.**

$$P = [(i - a)\, t^n - c] / (bt^n + d) \qquad (10)$$

(2) Derivation of Eq. 10 of Mortality Probability and 14 of Survival Probability of Integral Equation

"Probacent" expresses relative biological amount of stress, sum of reactions associated with exogenous stressor or loss of relative biological reserve for survival. The final response in an exhaustion period such as respiratory arrest and death may occur, depending on individual sensitivities to stress.

The author assumes that the distribution of sensitivities in a population is in the Gaussian normal distribution (Figure 2). The percentage of occurrence of response would be expressed by the Gaussian normal integrated frequency curve (Figure 3). "Probacent" can be expressed by mean and standard deviation (SD) along x-axis; "probacents" of 0, 50 and 100 correspond to mean - 5 SD, mean and mean + 5 SD, respectively as shown in Figure3; one "probacent" is eaqual to 0.1 SD.
Moreover, the "probacent"-probability equation can be applied to mathematical prediction problems in general biological phenomena.
The form of the normal distribution curve is illustrated in Figure 2. It can be expressed by **Eq. 11.**

$$y = [N/(s\sqrt{2\pi})] \exp[-(x-m)^2/2s^2] \quad (11)$$

Where x is a value of the variable,
$y$is a value of the corresponding ordinate (frequency)
m *is the population mean,*
$s$is the population standard deviation (SD],
N is the number of cases in the distribution, therefore, the number of area
units under the curve.

The integral of the normal curve equation (12) giving values of the area under the curve for various values of x is illustrated in Figure 3.

$$q = [N/(s\sqrt{2\pi})]\int_{-\infty}^{x} \exp[-(x-m)^2/2s^2]\, dx \quad (12)$$

If N is 100 in case of percent probability, **Eq. 12** becomes **Eq. 13** that is similar to **Eq. 10b** [4]**.**

$$Q = (10/\sqrt{2\pi}) \int_{-\infty}^{p} \exp[-(P-50)^2/200]\, dP \quad (13)$$

Consequently, mortality probability (%) Q is expressed by **Eq. 10** and survival probability (%) S by **Eq.14**.by incorporating "probacent" value P into the integral form.

$$P = [(i-a)t^n - c]/(bt+d) \quad (10a)$$

$$Q = (10/\sqrt{2\pi})\int_{-\infty}^{p} \exp[-(P-50)^2]\, dP \quad (10b)$$

"Probacent" P_1 of survival probability S is equal to 100 minus "probacent" P of mortality probability Q (see Figure 3).P_1 is in inverse relation to P. Therefore, Svalue can be obtained by incorporating P_1value into **Eq. 14b. Eq. 14** is the equation that expresses survival probability.

$$P_1 = 100 - P.$$

$$P_1 = 100 - [(i-a)\, t^n - c]/(b\,t+d) \quad (14a)$$

$$S = (10/\sqrt{2\pi}) \int_{-\infty}^{p} \exp[-(P-50)^2/200]\, dP \quad (14b)$$

More detail correlations between probability and "probacent" are shown in Table 1.a, b, c, d and n are constants but vary, depending upon sorts of animals, stressors, responses, units and so on.

Eqs. 10 and **14** may be considered to represent the velocity of biological response to exogenous stressors [4].

Place Figure 2 here.

Figure 2. Normal frequency curve.

Place Figure 3 here.

Figure 3. Integrated frequency curve from normal frequency curve.
Comparison of "probacent" of Chung with standard deviation (s).
"Probacent" of 0, 50 and 100 corresponds to mean – 5 SD, mean and mean + 5 SD.

1. 1. 3. Correlation between "Probacent"-Probability Equation and the Selye's Stress Theory

It seems to the author that there might be possibly a correlation between the "probacent"-probability equation and the Selye's stress theory of general adaptation syndrome (GAS) as follows:

(1) The early Period of alarm stage of Selye Corresponding to "Probacent" of *P*< 0 or = 0.

$$P = [(i - a)\, t^n - c] \,/\, (b\, t^n + d) \qquad (10a)$$

When the *P*-value is zero, *D* in Eq. 3 is 0; it means no damage caused by exogenous stressor.

$$(i - a)\, t^n - c = 0$$

$$t = [(c/(i - a)]^{1/n}$$

Time *t* seems to represent the early period corresponding to the alarm stage.

(2) The Later Period of Resistance Stage of SelyeCorresponding to "Probacent" of 0 <*P* > 100

The period of resistance correspond to period of *P* value between 0 and 100.
During this period, there would be biological stress consisting of damage (*D*) with concomitant repair and recover (*R*) expressed by **Eq. 3,** $P = D/R$;and $0 < P < 100$.

(3) The Final Period of Exhaustion Stage of Selye Corresponding to "Probacent" of *P* Increasing toward 100 and Greater than 100

Exhaustion in biological stress may occur soon or later, depending on individual sensitivity to stress when *P* value is approaching to 100 or > 100. Therefore, there seems to be roughly a possible correlation between the "probacent"-probability equation and the Selye's general adaptation syndrome of three stages.

1. 2. 1. Study of Carbon Monoxide versus Carboxyhemoglobin

General formulas, **Eqs.15**and**16**are constructed from the data published by Forbes, Sargent and Roughton [11, 12, 13] and express a mathematical relationship between carbon monoxide concentration of air and carboxyhemoglobin level of blood in men exposed to carbon monoxide at rest or at light activity, respectively [12].

$P = [(C - 0.00001)\ t^{0.957} - 0.00623] / (0.000318\ t^{0,957} + 0.254)$ (15)

$P = [(C - 0.00001)\ t^{0.713} - 0.0012] / (0.00000785\ t^{0.713} + 0.06)$ (16)

Where C = carbon monoxide concentration (CO) of air (%) = ppm/10^4 (parts per million); t = duration of exposure in minutes; P = "probacent" = percent carboxyhemoglobin (COHb) of blood. **Eq. 15**is for men at rest and **Eq. 16**for men at light activity.

Figure 8 illustrates the above relationship expressed by **Eq. 15**. Analysis of data shows no statistical difference between formula-calculated-predicted and the reported percent COHb values at rest or at light activity (p> 0.1). Analysis also reveals a correlation coefficient greater than 0.9 (r = 0.966 at rest and r = 0.979 at light activity). The results of this study seem to indicate that the "probacent" value may express a relative amount of biological stress as percentages of COHb in carbon monoxide exposure in air in men and further that the "probacent" value could express in general the relative amount of biological stress.

1. 2. 2. Deductive Derivation of Eqs. 15and 16

Eqs. 15 and 16 can be derived as described in the section 1. 1. 2 of the study of g-force.

1. 3. 1. Study of Goldfish Tolerance to Methanol in Water

Kim and Chung [14] published goldfish tolerance to methanol in water.**Eq.17**that expresses a relationship among methanol concentration of water, duration of exposure and mortality probability (onset of respiratory arrest) was constructed from their data.

$P = [(C - 0.1)\ t^{1.2} - 3.16] / (0.046\ t^{1.2} + 7.31)$ (17a)

$Q = (10/\sqrt{2\pi}) \int_{-\infty}^{p} \exp\ [-(P - 50)^2/200]\ dP$ (17b)

Where C = methanol concentration of water (temperature: 21 ± 1° C); t = duration of exposure in minutes; P = "probacent"'; and Q = percent mortality probability (%) indicated byonset of respiratory arrest.

Figure 9 illustrates results of experiments of goldfish tolerance to methanol intoxication. A good agreement is found between formula-predicted and observed mortalities in goldfish (p > 0.05).

1. 3. 2. Deductive Derivation of Eq. 17

Eq. 17can be derived as described in the section ofthestudy of g-force.

1. 4. 1. Study of Human Tolerance to Ionizing Total Body Irradiation

A clear and exact quantitative relationship between dose of radiation and mortality in humans is still not known because of lack of human data in ionizing total body irradiation. A general formula, **Eqs. 18** and **19**[3, 15] that predicts mortality probability of LD_{50} as a function of dose rate and duration of exposure was constructed from the data based on animal-model-predictions published by Cerveny, MacVittie and Young [16].

$\text{Log}\ D_{50} = 2.21767 - 0.9013 \text{x} \log T$ (18)

$LD_{50} = 10^{2.21769 - 0.90913\ \text{x}\ \log T}\ \text{x}\ T$ (19)

Where T = duration of exposure in minutes;D = dose rate in rad/min. D_{50} is a dose rate with which a 50% fatality occurs. LD_{50} is a radiation dose that causes a 50% fatality in humans exposed to total body irradiation.

1. 4. 2. Deductuve Derivation of Eq. .

$$P = [(i - a)\ t^n - c] / (b\ t^n + d) \quad (10a)$$

$$P\ b\ t^n + P\ d = i t^n - a\ t^n - c$$

$$P\ b\ t^n + a\ t^n + P\ d + c = i t^n$$

$$(P\ b + a) + (P\ d + c) / t^n = i \quad (20)$$

If $P$is a certain number like 0, 50 or 100, then $(P\ b + a)$ and $(P\ d + c)$ become constants, then **Eq. 21**can be writtenas **Eq. 22.**

$$i = A + B/t^n \quad (21)$$

$$\log (i - A) = \log B - n \log t$$

If a is negligibly small (see Figure 10 and Ref. 3), then

$$\text{Log } i = B' - n \log t \quad (22)$$

Eq. 22 is a form similarto **Eq. 18;Eqs. 18**and **19**are derived.

1. 5. 1. Study of Survival Probability, Life Expectancy and Death Rate in US Adults

The National Center for Health Statistics (NCHS) published the United States life tables, 2001 for US total, male and female populations on the basis of 2001 mortality, the 2000 decennial census and the data from the Medicare program [17]. The author constructed formulas that express survival probability, life expectancy and death rate in US adults, men and women from the data of the NCHS. A model of "probacent"-probability was employed in this study [18].
Eqs. 23and **24**are formulas expressing survival probability in US adults of 20 – 60 years of age, and death rate in US elderly population of 60 - 85 years of age, respectively.

$$P^{12.7} = 4.67677 \times 71.002^{12.7} - 3.67677 \times 61.605^{12.7}$$

$$- 2.63013 \times (71.002^{12.7} - 61.605^{12.7}) \times \log t \quad (23a)$$

$$S = (10/\sqrt{2\pi}) \int_{-\infty}^{p} \exp [- (P - 50)^2 / 200]\ dP \quad (23b)$$

$$(\log D)^{0.82} = 12.75481 \times 0.00655^{0.82} - 11.75481 \times 0.97102^{0.82}$$

$$+ 6.6107 \times (0.97102^{0.82} - 0.00655^{0.82}) \times \log t \quad (24)$$

Where t = age;;P = "probacent"; S = survival probability (%); D = death rate (%).
Figures 11 and 12 illustrate relationships between age and survival probability and death rate, respectively. Analysis of the data shows that there are statistically no significant differences between

formula-predicted and NCHS-reported values in survival probability and death rate (p >0.05). The formulas are accurate and reliable with a remarkable agreement (p>0.995).

1. 5. 2. Deductive Derivation of Eq. 23 of Survival Probability and Eq. 24of Death Rate

(1) Derivation of **Eq. 23** of Survival Probability

$P = [(i - a)\ t^n - c] \ / \ (b\ t^n + d)$ (10a and 14a)

Where i= intensity of stimulus (exogenous stressor, noxious agent)
a= threshold of intensity of stimulus,
c= minimal critical amount of stimulus (exogenous stressor) above which biological stress starts to be induced, and so stimulus becomes to be effective to induce bodily reaction (stress),
b = velocity of repair and recovery,
d = initially existing and available certain amount of reserve for repair and recovery.

$P\ (bt^n + d\ ) + Pd = (i - a)t^n - c$

$Pd + c = (i - a - bP)t^n$

In the context of life for a population, total sum of exogenous stressors such as work load of job, performance of duties,provision of food, movements against gravity,causes of fatigue and diseases etc. Total sum of exogenous stressors ($\sum i$) is assumed to be undetermined but unchangeable along time and constant for the population under observations in this study.

$Pd + c = (\sum i - a - bP)\ t^n$

If P is a certain value ,like 0, 50 or 100 and assumed to be constant, then

$Pd + c = k_1; \sum i - a - bP = k_2$

$k_1 = k_2\ t^n$

$\log k_1 = \log k_2 + n \cdot \log t$ (25)

$k_3 = k_4 + n \cdot \log t$ (26)

If a mortality probability (%) at a given time t is $Q$and a corresponding "probacent" is P_1, then **Eq. 27** would be obtained with an assumption of $k_3 = P_1$.

$P_1 = k_4 + n \cdot \log t$ (27)

Eq. 27 is "probacent" of mortality probability. This assumption is supported and verified by results of the author and his coworkers' experimental studies and clinical applications as shown in this study. **Eq. 28** is a general formula of mortality probability.**Eq. 28** is furtherconsidered to be an underlying, unifying general formula of "probacent"- probability equation from which various forms of "probacent"-probability equations can be derived.

$P^r = [(i - a)\ t^n - c] \ / \ (bt^n + d)$ (28a)

$Q = (10/\sqrt{2\pi}) \int_{-\infty}^{p} [-(P - 50)^2 / 200]\ dP$ (28b)

Survival probability (%) = 100 – mortality probability (%)
"Probacent" $P_2$of survival probability (%) = 100 – "probacent" P_1 of mortality probability."Probacent" P_2 of survival probability is expressed as follows:

$P_2 = 100 - P_1 = 100 - (k_4 + n \cdot \log t)$ (29)

$P_2 = k_5 - n \cdot \log t$ (30)

Eq. 30 is similar to **Eqs. 23a,**representing "probacent" of survival probability.
If observations arecarried out during a life span of subjects (or species), effects of aging, i. e. young or old chronological effects would show up in biological stress. For example, the period of observations of a study is decades or 100 years of a life span in humans [18] or 600 days in mice [19, 29], " another parameter, constant *r*or *c*would be needed as seen in **Eqs.23a and 28a**ofsurvival probability and mortality probabilityexpressed by "probacent" P^r instead of P,and $(\log D)^c$in **Eq. 24**of death rate**.**A new parameter *r* and *c* represent the aging factor that is dependent on age in observations for a long time of life span. In short time observations like days to months in humans, hours to days in mice, the values *r* and *c* value would be one.
If P_2 is generalized with time *t* as observed in experimental and clinical data, **Eq.31** can be obtained from **Eq. 30.**.

$P_2^r = k_5 - n \cdot \log t$ (31)

Eq 31is an equation of form similar to **Eq. 32a**of "probacent" of survival probability. Survival probability (%) is expressed by **Eq. 32.** Mortality probability (%) is expressed by **Eq. 33.Eq. 33**with*c* = 1 is similar to the equation of hazard rate known in statistics.

$P^r = A - B \times \log t$ (32a**)**

$S = [10/\sqrt{2\pi}] \int_{-\infty}^{P} \exp [- (P - 50)^2 / 200] \, dP$ (32b)

$(\log D)^c = a + b \cdot \log t$ (33)

Where *t* = time after biomedical insult or duration of exposure; *P* = "probacent" (abbreviation of probability percentage) = "relative biological amount of reserve for survival; *S* = survival probability in percentages; *r, A* and *B* in **Eq. 32a** are constants; *A* is an intercept and*B* a slope; *r represents a curvature* (a shape of curve).
D = death rate (%);*c, a* and *b* in **Eq. 33** are constants; *c* represents a curvature, *a* is an intercept and *b* a slope.

(2) Derivation of Equation of Death Rate, Eq. 33

Formula of mortality probability or death rate, **Eq. 33**is derivable from **Eq.28** of survival probability by differential as shown in the author's previous publication [21].

1. 6. 1. Study of Mouse Tolerance to Metrazol Drug Toxicity

Formulas, **Eq. 34** expressing tolerance of mice to Metrazol, a central nervous system stimulant and predicting mortality probability as a function of dose and time after administration was constructed from experimental data [22]. applying "probacent"-probability equation.

Analysis of the data on mortalities shows that the formula is fairly accurate and reliable with a good agreement between formula-predicted and experimentally observed mortalities.

$$P = 100 \times [\log D - \log (0.1 + 2.61/t^{1.455})]$$

$$/ [\log(5.5 + 173.61/t^{1.455}) - \log (0.1 + 2.61/t^{1.455})] \quad (34a)$$

or

$$P = [(D - 0.1)t^{1.455} - 2.61] / (0.054t^{1.455} + 1.71) \quad (34aa)$$

$$Q = (10/\sqrt{2\pi}) \int_{-\infty}^{p} \exp[- (P - 50)^2 / 200] \, dP \quad (34b)$$

Where D = dose ofMetrazol *(mg/*10 gm body weight),
t = time in minutes after administration of Metrazol,
P = "probacent"
Q = predicted mortality probability in percentages.
Figures 4 and 13 illustrate the experimental results in mice regarding tolerance to Metrazol.

1. 6. 2. Deductuve Derivation of Eqs. 34 [4]

$$P = [(i - a)t^n - c] / (bt^n + d)$$

When $P = 0$,

$$i = a + c/t^n$$

IfDrepresents$i$, then

$$D_0 = a + c/t^n$$

Where D_0 is a dose of "probacent" 0.

When $P = 100$, then

$$D_{100} = (a + 100b) + (c + 100d) / t^n$$

Unknown "probacent" P of Metrazol dose D is calculatedfrom **Eq. 35**on the basis of the "probacent"-probability relation as described in the section of 1. 1 of the study of$g$-force on mice (Figures 4 and 13).**Eq. 34a**is similar to **Eq. 35** andderived.

$$P = 100 \times (\log D - \log D_0) / (\log_{100} - \log D_0) \quad (35)$$

Where $a = 0.1$, $c = 2.61$, $b = 0.054$, $d = 1.71$, $n = 1.455$ (see Eq. 34aa) ,substituting these values in the equations of D_0 and D_{100} (**Eqs, 38** and **40**), , then **Eq. 35** becomes the following equation,**Eq. 34a**, substituting the values of constants.

$$P = 100 \times (\log D - \log (0.1+2.61/T^{1.455})$$

$$/ (\log (5.5+173.61/T^{1.455}) - \log (0.1+2.61/T^{1.455}) \quad (34a)$$

Mortality probability, Q can be obtained by incorporating "probacent" *P* value in **Eq. 34b.**

To my knowledge, there seem to be no articles in the literature that clarify an unifying mathematical model underlying quantitative relationships among intensity of exogenous stressor, biological stress induced and occurrence of response in biological phenomena. The author feels that it is a good time to review and summarize findings of the author and his coworkers' researches for the last five decadeson general mathematical relationships in the above described and attempts to find a general unifying equation in this study.

2. MATERIALS AND METHODS

2. 1. Materials of Studies

2. 1. 1. Study of *g*-force

One hundred ninety one mice were used in the study; they were centrifuged at various radial positive *g*-force from 3 to 85 *g* until the minimum time was determined at which 100% fatality occurred. The criterion of death was absence of visible respiration. Mortality, electrocardiogram and pathology were studied. A formula was constructed from the results to express the mortality as a function of magnitude of *g*-force and duration of exposure [5].

2. 1.2. Study of Carbon Monoxide versus Carboxyhemoglobin

Forbes et al. [11] published data on carboxyhemoglobin levels of blood resulting from exposure to carbon monoxide in aircontaining 0.01 to 2.0 % of CO for various durationsin normal healthy men at rest and light activity at sea level.

Formulas predicting carboxyhemoglobin levels of blood resulting from CO exposure as a function of CO concentration and duration of exposure at rest and light activity were constructed from the data [12].

2. 1. 3. Study of Goldfish Tolerance to Methanol in Water

Kim and Chung [14] published data on tolerance of goldfish to various kinds of exogenous stressors of chemicals: methanol, urea, ammonium sulfate etc. in water. Their data on methanol toxicity were used to construct a formula predicting mortality as a function of methanol concentration and duration of exposure. The criterion of death was respiratory arrest.

2. 1. 4. Study of Human Tolerance to Ionizing Total Body Irradiation

Data on human tolerance based on animal-model predictions published byCerveny, MacVittie and Young [16] were used to construct formulas to predict mortality as a function of radiation dose rate and duration of exposure in humans in total body irradiation (3). The data are based on an extensive studies of mortality resulting from radiation exposure and a compilation of animal experimental data published by Jones, Morris, Wells and Young at the Oak Ridge National Laboratory [23].

2. 1. 5. Study of Survival Probability, Life Expectancy and Death Rate in US Adults

The National Center for Health Statistics (NCHS) [17] published the United States life tables, 2001 for US total, male and female populations on the basis of 2001 mortality statistics, the 2000 census and the data from the Medicare program. Formulas predicting survival probability, life expectancy and death rate were constructed from the data of the NCHS [15, 18].

2. 1. 6. Study of Mouse Tolerance to MetrazolDrug Toxicity

The author and Hur [22] used 150 mice to study their tolerance to Metrazol, a central nerve system stimulant. Metrazol was subcutaneously injected to the back of mice. After injection, mice were observed until respiratory arrest occurred as a sign of death. Formulas predicting mortality as a function of Metrazol dose and time after administration were constructed from the data [24].

2. 2. Methods of Studies

2. 2. 1. Conversion of Percent Probability into "Probacent"

In general, data from experiments or reports in the literature are used to construct a "probacent"-probability equation by determining values of constants in the "probacent" equation, **Eq. 10a**. For this calculation, conversion of percent probability into "probacent' is needed first. Table 1 [24] can be used for this conversion.

Place Table 1 here.

(1) Determining the Constant *n* in Eq. 10a

Various doses of drugs are given to animals by a certain mode of administration. Thereafter, percentages of occurrence of certain response are measured at various given times. Results are plotted on a log-log scale graph paper. Doses of drugs are taken along the ordinate and times after administration along the abscissa. If points indicating 50% responses at each dosage level are connected, they reveal approximately a linear straight line with a definite declination (ø) at higher dosages. Three lines indicating specific percentages of occurrence of response, e. g. 0, 50 and 100%, may be likewise parallel to each other at higher doses as shown in Figure 4.

The value of the constant *n* in **Eq. 10a** relating to "probacent" can be obtained from the declination (ø) as shown in Figure 4 [24] as follows:

$$n = \tan ø \qquad (12)$$

For instance, the declination of the line of 50% response to Metrazol reveals $55^{o}30'$, so the value of *n* is:

$$n = \tan 55^{o}\ 30' = 1.455$$

Place Figure 4 here.

(2) Determining the Constants, a, b, c and d in Eq. 10 a [24]

Results are plotted on a "probacent"-probability"semi-log graph paper for 10 and 25 mg dosage level of the drug. The time is taken along the abscissa of logarithmic scale as shown in Figure 5. Percent probability of mortality and corresponding "probacent" are taken along the ordinate on the left and right side, respectively. The distribution is overall linear for each dosage level [24].

The value of the constant *a* in **Eq. 10a**(*i= D* here)can be obtained from D_0 at the infinite time, that represents the asymptote along the abscissa in Figure 4. Substituting $t = \infty$ and $P = 0$in the **Eq. 10a**, the following equation is derived:

$$a = D_0 \qquad (36)$$

The above described D_0 may be determined graphically as shown in Figures 4and 13 for Metrazol. Results of the longest period of observation, e. g. 1440 minutes for Metrazol, are plotted on the "probacent"- probabilitygraph paper. Doses are taken along the abscissa of logarithmic scale, giving D_0 = 0.1 mg/10g body weight and $a = D_0 = 0.1$.

The value of the constant *c* in **Eq. 10a** can be calculated from one set of data with a condition of $P = 0$, by substituting values of *D, t, P, n* and*d a.*

For example, D = 10 mg, t = 0.4 min, P= 0, n = 1.455 and a = 0.1 (the value of 0.4 min is determined graphically from the "probacent"-probability paper as shown in Figure 5, c = 2.61.

The values of the constants *b* and *d*in Eq. **10a** can be determined from two sets of data by substituting values of *D, t, P, n, a* and *c* in **Eq. 10a.**

For example:

(1) D = 25 mg, t = 4.5 min, P = 100, n = 1.455, a = 0.1 and c = 2.61

(2) D = 10 mg, t = 12.3 min, P = 100, n = 1.455, a = 0.1 and c = 2.61

The values of 4.5 min for the dose of 25 mg and 12.3 min for the dose of 10 mg are determined from the "probacent"- probability graph paper a shown in Figure 5. Values of *b* and *d* are calculated from Eq. **10a** as: b = 0.054 and d = 1,71.

Eq. 37 of "probacent"are finally constructed.

$$P = [(D - 0.1)t^{1.455} - 2.61] / (0.054\, t^{1.455} + 1.71) \qquad (37)$$

The following three equations express D_0, D_{50} and D_{100}that correspond to P = 0, 50 and 100, respectively.

$$D_0 = a + c / t^n$$

$$= 0.1 + 2.61 / t^{1.455} \qquad (38)$$

$$D_{50} = \sqrt{[(a + 100 \cdot b + (c + 100 \cdot d) / t^n)(a + c / t^n)]}$$

$$= \sqrt{[(5.5 + 173.61 / t^{1.455})(0.1 + 2.61 / t^{1.455})]} \qquad (39)$$

$$D_{100} = a + 100 \cdot b + (c + 100 \cdot d) / t^{1.455}$$

$$= 5.5 + 173..61 / t^{1.455} \quad (40)$$

Eqs. 38, 39 and 40 can be substitutedin **Eq. 35.**

Place Figure 5 here

Figure 5. Results of tolerance of mice to Metrazol are plotted on a"probacent"- probability semi-graph paper. The ordinate represents percent probability (*Q*) of response (mortality) on the left scale, and the corresponding"probacent" (*P*) on the right scale. The dashed line connects points of data observed at 1440 min after injection of Metrazol. Doses of Metrazolare taken along the abscissa (upper). The two solid lines connect points of data observed with the doses of 25 mg(closed circles) and 10 mg (open circles) ofMetrazol. Time after injection is taken along the abscissa (lower) [24].

(3) Determining Values of Constants in Eqs. 10b and 14b of "Probacent"

Methods of determining values of constants in **Eqs. 10a**and **14a** of "probacent" are described in Methods and Appendix of the author's previous publications [4, 25, 26, and online: 3, 12, 15, 20, 28, 29].

2. 3. Description of the Computer Program

The computer program is written in UBASIC for IBM PC microcomputer and compatibles for **Eqs 10** and **14** and other various forms of "probacent"-probability equation. The computer program uses a formula, **Eq. 42** of approximation [30] instead of integral of **Eq. 10b** and **14b** because the computer cannot perform integral [15, 30, 31].

$$Ø(X) = (2/\sqrt{\pi})\int_0^x \exp[-t^2]\, dt \qquad (41)$$

The digital computer uses the following equation, **Eq. 41** as an approximation for **Eqs. 10b** and **14b** of integral for $0 \le X < \infty$ in this study. Eq. 42 is an approximation formula for **Eq. 41**[20]**.**

$$Ø(X) = 1 - 1/(1 + A_1 \cdot X + A_2 \cdot X^2 + A_3 \cdot X^3 + A_4 \cdot X^4)^4 \qquad (42)$$

$A_1 = 0.278393$
$A_2 = 0.230389$
$A_3 = 0.000972$
$A_4 = 0.078108$

Mathematical transformation of integral, **Eqs 10b** and **14b** to the formula of approximation, **Eq. 42**is described in detail in the author's book [31].

A representative computer program for nonlinear, curved regression for "probacent"-probability equation predicting survival probability as a function of age in US total adult population is illustrated in Figure 6. This program includes the formula of approximation, **Eq. 42** and calculates the sum of squares.

A representative computer program of linear regression for "probacent" model predicting human tolerance to total body irradiation is illustrated in Figure 7, calculating the sum of squares [28].

Place Figure 6 here.

```
10 lprint "Sum of square differences in curved regression for 'probacent'-"
20 lprint "probability equation expressing survival probabilities in US"
30 lprint "total adult population. This program is for gamma value, G=12.8"
40 lprint "and the age group of 20-60 years."
50 read T, R
60 'R stands for NCHS-reported survival probability at age T.
70 G=12.8
80 DeffnQ=4.67677*71.002^G-3.67677*61.605^G-2.63013*(71.002^G-
61.605^G)*log(T)/log(10)
90  P=DeffnQ^(1/G)
100 A1=0.278393
110 A2=0.230389
120 A3=0.000972
130 A4=0.078108
140 if (P-50)<0 then 150 else 180
150 X=(50-P)/sqrt (200)
160 S=50/(1+A1*X+A2*X^2+A3*X^3+A4*X^4)^4
170 goto 200
180 X=(P-50)/sqrt (200)
190 S=100-50/(1+A1*X+A2*X^2+A3*X^3+A4*X^4)^4
200 Z=S-R
210 ZZ1=ZZ1+Z^2
220 ' ZZ1 stands for sums of square differences at the age T.
230 lprint G,T,S,ZZ1
240 goto 50
250 data 20,98.682,25,98.214,30,97.743,35,97.189,40,96.388,45,95.234
260 data 50,93.552,55,91.179,60,87.705
```

Figure 6.

The computer program to calculate the sum of squares, $\sum (E\text{-}O)^2$ as a function of *r* value and age (*T*) in the US total adult population. This program is for *r* value of 12.8 in **Eq**.**23a** for the age group of 20-60 years**.**

Place Figure 7 here.

```
 10   lprint
 20   lprint "Sum of squares in linear regression for Eq. 6."
 30   lprint "This program is for B=-0.909089."
 40   lprint
 50   lprint "B",tab(16);"Dose rate",tab(28);"Time",tab(56);"Sum of squares"
 60   lprint tab(16);"rad/min",tab(28);"min",
 70   lprint
 80   read D,R
 90   B=-0.909089
100   T=10^((log(D)/log(10)-2.21766)/B)
110   Z=T-R
120   'Z stands for differenc at dose rate D.
130   ZZ1=ZZ1+Z^2
140   'ZZ1 stands for sum of squares added up at dose rate D.
150   lprint B,tab(15);D,tab(27);T,tab(55);ZZ1
160   goto 80
170   data 50,3.72,20,10.2,10,21.8,5,46.8,2,128.5,1,275
```

```
Sum of squares in linear regression for Eq. 6.
This program is for B=-0.909089.

B               Dose rate   Time                          Sum of squares
                rad/min     min
-0.909089       50          3.7201477900139159843         0.00000002184188821 32
-0.909089       20          10.1928380090917450155        0.00005131595565814 03
-0.909089       10          21.8488615559384267376        0.00243876760438214 54
-0.909089       5           46.8341349940772252481        0.00360396542503434 82
-0.909089       2           128.3209104143624407212       0.03567704510886702 68
-0.909089       1           275.0623333633464816954       0.03956249329495153 45
```

Figure 7 illustrates the computer program of linear regression for "probacent" model in which LD_{50} is a function of dose rate *D* and duration of exposure *T* in total body irradiation in humans.

2. 4. Statistical Analysis

A Chi square goodness-of-fit test (logrank test) is used to test the fit of mathematical models to reported data [32]. The differences are considered statistically significant when $p < 0.05$. A correlation coefficient is used in some studies for comparison of formula-derived and reported values.

3. RESULTS

3. 1. Study of *g*-force

Figure 1 illustrates the relationship among magnitude of radial acceleration, duration of exposure and mortality in mice exposed positive *g*-force of exogenous stressor. It suggests an overall close agreement between formula-predicted and experimentally observed mortality.

3. 2. Study of Carbon Monoxide versus Carboxyhemoglobin

Tables 2 and 3, and Figure 8show the relationship among carbon monoxide concentration of air, duration of exposureand carboxyhemoglobin level of blood in men exposed to CO at rest or at light activity. Differences between formula-predicted and reported carboxyhemoglobin levels in both cases of men at rest or at light activity are statistically not significant ($p > 0.1$).

Place Table 2 here.

Table 2. Percent carboxyhemoglobin (COHb) of blood in relation to carbon monoxideconcentration in air and time of exposure in men at rest.

Carbon monoxide Concentration (%)	Time of exposure (min)	Formula-derived % COHb*	Reported % COHb*
1	5.5	20	20
1	7	25.1	25
0.5	5.5	10	10
0.5	11	19.3	20
0.5	15	25.8	26
0.3	4.5	4.9	5
0.3	9	9.5	10
0.3	18	18.4	20
0.3	27	26.9	27

0.2	7	5	5
0.2	14	9.7	10
0.2	30	19.7	20
0.2	50	31.6	30
0.15	9	4.8	5
0.15	18	9.2	10
0.15	42	20.2	20
0.15	72	32.9	30
0.12	12	5	5
0.12	25	10	10
0.12	54	20.3	20
0.12	92	32.7	30
0.1	15	5.1	5
0.1	30	9.9	10
0.1	68	20.8	20
0.1	80	24.1	23
0.08	20	5.4	5
0.08	40	10.3	10
0.08	87	20.7	20
0.08	135	30.3	28
0.06	25	5	5
0.06	52	9.8	10
0.06	120	20.5	20
0.06	200	31.3	28
0.06	218	33.6	30

0.05	30	4.9	5
0.05	65	10	10
0.05	150	20.6	20
0.05	200	26.1	24
0.05	235	29.7	27
0.04	40	5.1	5
0.04	80	9.6	10
0.04	200	20.9	20
0.04	245	24.5	23
0.03	50	4.7	5
0.03	110	9.5	10
0.03	200	15.7	15
0.03	260	19.2	18
0.02	80	4.8	5
0.02	190	10	10
0.02	300	14.3	14
0.01	190	5	5
0.01	290	6.9	7

* Differences between values of both columns of each level are statistically not significant (p >0.1). Correlation coefficient r = 0.966.

Place Table 3 here

Table 3. Percent carboxyhemoglobin (COHb) of blood in relation to carbon monoxide in air and time of exposure in men at light activity

Carbon monoxide	Time of	Formula-derived	Reported

concentration (%)	exposure (min)	% COHb*	% COHb*
0.02	60	6.1	6
0.02	120	10.1	10.7
0.02	180	13.4	14.3
0.02	240	16.5	17.2
0.02	300	19.3	19.6
0.02	360	21.9	21
0.03	60	9.2	9
0.03	120	15.1	15
0.03	180	20.1	20
0.03	240	24.7	25
0.03	300	28.9	26, 26.5, 26.3**
0.04	60	12.3	11.3
0.04	120	20.1	20
0.04	180	26.9	26.3
0.04	240	32.9	31
0.06	60	18.5	16,4, 19.2, 17.8**
0.08	60	24.6	21.3, 29.9, 25.6**
0.1	60	30.8	26.0, 38, 32**

* Differences between values of both columns on each level are statistically not significant ($p > 0.1$). Correlation coefficient r = 0.979.

** Average value.

Place Figure 8 here.

Figure 8. Percent carboxyheemoglobin of blood in men at rest, exposed to carbon monoxide, in relation to CO concentration in air and time of exposure [11]. Abscissa: time of exposure in minutes. Ordinate: CO concentration in air in percentages. A log-log scale is used. A closed circle indicates a plot of a result representing a specific percent carboxyhemoglobin of 5, 10, 20 and 30% in relation to CO concentration and time. The five solid and/or dashed lines indicate the concentration-time curves of 5, 10, 20 and 30% COHb. The solid lines are based on reported data. The dashed lines are extrapolated and assumed lines (see text).

3.. 3. Study of Goldfish Tolerance to Methanol in Water

Figure 9 illustrates the relationship among methanol concentration of water, duration of exposure and mortality (respiratory arrest) in goldfish. Differences between formula-predicted and experimentally-observed mortalities are statistically not significant (p>0.05).

Place Figure 9 here.

Figure 9. Tolerance of goldfish to methanol, determined by onset of response of respiratory arrest at 21 ± 1 C. Concentration-time curves of 100, 50 and 0 “probacents” of onset of respiratory arrest are shown. Abscissa: duration of exposure in minutes. Ordinate: concentration of methanol in water.

3. 4. Study of Human Tolerance to Ionizing Total Body Irradiation

Figure 10 illustrates the relationship among dose rate, duration of exposure and lethal radiation dose of LD_0, LD_{50} and LD_{100} in humans exposed to ionizing total body irradiation. A remarkable agreement is present between formula-predicted and reported-estimated LD_{50} (p> 0.995). More detail data on comparison of mortality are presented in the author’s previous online publication [3].

Place Figure 10 here.

Figure 10.Relationship among dose rate of radiation, duration of exposure andlethal radiation dose (LD) in total body irradiation to humans. The abscissa represents duration of exposure in minutes (log scale). The ordinate represents dose rate in rad/min (log scale). Data points indicate lethal doses of LD_{5-95} and appear to fall on the five formula-predicted straight lines in each group, respectively (see text).

3. 5. Study of Survival Probability, Life Expectancy and Death Rate in US Adults

Figures 11 and 12 illustrate the relationship between age and survival probability or death rate in US total adult and elderly population, respectively. A remarkable agreement is found between formula-predicted and the NCHS-reported survival probability, life expectancy or death rate (p > 0.995) [15, 18].

The study suggested that the mathematical model of “probacent”-probability equation better fit the US national mortality data of the elderly populationthan the Gompertz, exponential, the Weibull and the lognormal distribution [18].

Place Figure 11 here.

Figure 11. Relationship between age and percent survival probability in the US total adult population of age 20-100 years for 2001. The abscissa represents age in years (log scale) and the ordinate percent probability (*S*) (normal probability scale) on the right scale and "probacent" (*P*) on the left scale. Data points of open circles indicating survival probabilities at different ages appear to fall overall on a solid curved line. The solid line can be expressed**Eq. 23**for the age group of 20-60 years and two other constructed equations for age groups of 60-85 and 85-100 years [18}.

Place Figure 12 here.

Figure 12. Relationship between age and death rate in the US total elderly population of 60-100 years for 2001.The abscissa represents age in years and the ordinate death rate (*D*) in percentages (log scale). Data points of closed circles indicate US national life table death rates reported by the National Center for Health Statistics (NCHS) for 2001. The dashed straight line represents death rates predicited by the Gompertz mortality model expressed by equation, $D = 10^{(-2.2674+0.03779t)}$. The solid curved line represents death rates predicted by the "probacent"-probability model of death rate (*D*) expressed by "probacent"-proability equations, **Eq. 24** for the age group of 60-85 years andanother equation for ages of 85 -100 years) [18]. Data points of NCHS appear to fall overall on the solid death-rate line predicted the formula The maximum predictive error of the "probacent" model is ± 0.3% and that of the Gompertz model ± 3.2%.

3. 6. Study of Mouse Tolerance to Metrazol Drug Toxicity

Figure 13 illustrates the relationship amongMetrazol dose and time after administration by subcutaneous injection and mortality in mice. A considerable agreement was overall present between constructed-formula-predicted and experimentally-observed mortality in mice ($p > 0.05$). The predicted values were based on calculation of **Eq. 34** by the first computer program designed in the author's research(1962) [31].

More detail data on comparison of constructed-formula-derived and experimentally-observed or reported values in the above described researches are published in the author and his coworkers' previous publications.

Place Figure 13 here.

Figure 13. Tolerance of mice to subcutaneously administered Metrazol, determined by onset of respiratory arrest (mortality). Abscissa: time in minutes after injectionof Metrazol. Ordinate: dose in mg/10gm body weight of Metrazol. A log-log scale is used. Aclosed circle indicates a 100% actual mortality point. A half closed circle indicates an actual mortality between 0 and 100%.

An open circle indicates a 0% actual mortality point. The three solid lines show the dose-time curves of LD_{100}, LD_{50} and LD_{0}. The dashed line indicates *Dm* (dose: 25 mg/10g).

4. DISCUSSION

Figures 1, 4 and 8 -13; and tables 2 and 3 seem to reveal an overall close to remarkable agreement between constructed-formula-derived and experimentally-observed or reported data in the above described six categories of biological phenomena: study of mouse tolerance to *g*-force, study of goldfish tolerance to methanol in water, study of carbon monoxide versus carboxyhemoglobin, study of human tolerance to ionizing total body irradiation, study of survival probability, life expectancy and death rate in US adults and study of mouse tolerance to Metrazol drug toxicity, respectively ($p > 0.05$ to 0.995).

In this study, a "probacent"-probability equation that could express a relationship among CO concentration of air, duration of exposure and mortality probability in men could not be constructed because of lack of sufficient human data. However, an approximate probability of symptoms would be possibly predicted by the *P* value expressing % carboxyhemoglobin levels of blood resulting from carbon monoxide exposure in air as shown in Table 4 though there could be variations in occurrences of response due to presence of different individual sensitivities to the stress of carboxyhemoglobin levels[33, 34] In the United Sates, OSHA limits long-term workplace exposure levels to less than 50 ppm averaged over an 8-hour period [35]. The percent carboxyhemglobinlevel derived from **Eq. 16** after an 8-hours-exposure is less than6.7 % limit. The air quality guidelines of World Health Organization for Europe is 2.5 % carboxyhemoglobin level after exposure to carbon monoxide in air, corresponding to 1.1 % of COHb calculated by **Eq. 16.**Carbon monoxide poisoning is the most common cause of injury and death due to poisoning worldwide [36].

Place Table 4 here.

Table 4. Correlation between reported symptoms of carboxyhemglobin levels and "probacent" values in carbon monoxides poisoning.

Carbon monoxide Concentration (%)	Time of exposure (min)	Symptoms*	Carboxyhemoglobin** level (%)
0.0035	360-480 (6-8 hrs)	Headache, dizziness	4 – 5 %
0.01	120-180 (2-3hrs)	Slight headache	5 – 7 %
0.02	120-180 (2-3 hrs)	Slight headache	10 -13 %
0.04 (1-2 hrs)	60-120	Frontal headache	12 – 20 %

0.08	< 45	Dizziness, nausea, convulsion	< 20 %
0.08 (<2 hrs)	< 120	insensible	< 40 %
0.16	20	Headache, dizziness, nausea	23 %
0.16	< 120 (< 2 hrs)	Death	< 81 %
0.32	5-10	Headache, dizziness, nausea	17 – 28 %
0.32	< 30	Death	< 60 %
0.64	1-2	Headache, dizziness	11 – 17 %
0.64	< 20	Convulsion, respiratory arrest, death	< 90 %
1.28	< 3	Death	< 47 %

*Ref. 33, 34.

** “Probacent” values expressing percent carboxyhemoglobin levels calculated by **Eq. 16** of the current study. There seems to be an apparent good correlation between symptoms and carboxyhemoglobin levels (%) in carbon monoxide poisoning.

Place Figure 14 here.

Figure 14.Semilogarithmic plot of plasma acetaminophen levels with or withouthepatotoxicity reported in the literature. A closed circle indicates a plot with hepatotoxicity. An open circle indicates a plot without hepatotoxicity.

Three solid lines show the 100 (TC_{100}), 50 (TC_{50}) and 0 (TC_0)% toxic concentration-time lines of plasma acetaminophen.

In this study, an underlying and unifying equation, **Eq. 28** seems to be found for the "probacent"-probability equations of various forms that are possibly derivable from it. The "probacent" model is also found to better fit the observed survival times in mice exposed to total body irradiation of daily different dose rates than the Gompertz model [19, 20].

The first mathematical model of "probacent" equation, **Eq. 1**was constructed from experimental data on mortality in mice exposed to exogenous mechanical stressor of positive *g*-force [5]. The "probacent" value expressed by **Eqs.15** and **16**seems to be proved to express the relative biological amount of stress induced by exogenous stressor in the study of carbon monoxide versus carboxyhemoglobin [12]. The general model of "probacent"- probability equation, **Eq. 10** is further constructed from the other subsequent studies [14, 22, 24-27, 38-40]

Exogenous stressors used in the author and his coworkers' researches are mechanical (acceleration) [5, 14, 37], thermal stressor (heat, cold)[14, 38], chemicals (drug [22, 24,], acetylcholine [39,40], ether and chloroform of anesthetics [41], hydrogen sulfide [42], quinacrine hydrochloride [43], carbon monoxide [26], pH [44], radiation [3, 20, 29], electric current [14, 25, 45] and osmotic stimulus [14,46].

Animals used in the above studies are mammalian (mice, rats, rabbits),birds (pigeon, cocks), fish (goldfish, loaches), insects (house flies), protozoa (*Paramecium caudatum*[14, 22, 24-27,38, 39, 41-46]. Studies of sensationwere done in humans [41].

The model of 'probacent"-probability equation was applied to clinical data published in the literature to express carboxyhemoglobin levels of blood as a function of carbon monoxide concentration of air and duration of exposure in men at rest and light activity [12]; to express a relationship as illustrated in Figure 14 among plasma acetaminophen concentration, time after ingestion and occurrence of hepatotoxicity in man that is encountered in the emergency room of medicine as shown in Figure 14[47, 48]. Figure 14 was useful in the author's medical practice in a hospital.**Eq. 34**seems to be applicable to drug toxicity research as shown in Metrazol and acetaminophen toxicity studies [24, 48].

The "probacent" model was employed to construct **Eqs. 43**for PVR of 2.5 units/m^2 and**44** for PVR of 5 units/m^2 that may predict survival provability in patients with heart transplantation that is a major surgery considered as an exogenous stressor of trauma (Figure 15)[49, 50]. There is a complete agreement between the reported survival probabilities and the formula-predicted values as shown in Table 5 and Figure 15.

$$P_{3.3} = 637029 - 252356 \cdot \log t \quad (43a)$$

$$S = (10/\sqrt{2\pi}) \int_{-\infty}^{P} \exp [- (P - 50)^2/200] \, dP \quad (43b)$$

$$P_{3.3} = 533920 - 250077 \cdot \log t \quad (44a)$$

$$S = (10/\sqrt{2\pi}) \int_{-\infty}^{P} \exp [- (P - 50)^2/200] \, dP \quad (44b)$$

Where t = time in years after heart transplantation in patients whose PVR (pulmonary vascular resistance) is 2.5 units/m^2 (**Eq**. **43**), and 5 units/m^2(**Eq**. **44**); P = "probacent" = relative biological amount of reserve for survival; S= survivalprobability in percentages.

Place Table 5 here.

Table 5. Comparison of formula-derived survival probability at different times after

Heart transplantation whose PVR* was 2.5 or 5 units/m^2 with reported values

[49]**

PVR* (%)	Survival probability	Time after heart transplantation (year)				
		1/12	1	2	3	5
2.5	Formula-derived	92	77	70	65	58
	Reported	92	77	70	65	58
5	Formula-derived	88	67	58	52	43
	Reported	88	67	58	52	43

* PVR: pulmonary vascular resistance.

** Ref. (49): Kirklin, J. R. et al.

A complete agreement is present between formula-derived and reported survival probability (%).

Place Figure 15 here.

Figuren15. Relation between time after transplantation and survival probability in patients with heart transplantation. The ordinate represents survival probability (*S*) on the right scale and the corresponding "probacent" (*P*) on the left scale. The abscissa of log scale represents time in years after transplantation. The two solid and dashed lines connect points of data observed in the two groups of patients whose PVR was 2.5 and 5 units /m^2, respectively. The two lines can be expressed by **Eqs. 43** and **44**, respectively (see text].

The "probacent"-probability equation was applied to express a relationship among age, height and weight, and percentile in Saudi and US children of 6 – 16 years of age [51, 52].The "probacent" model was applied to predict the percentile of heart weight by body weight from birth to 19 years of age [53, 54].The comparison disclosed discrepancies between the formula-predicted values and the heart weights versus the body weight in the first report by Scholz and his coworkers (Mayo Clinic Proceedings, 1988). The author wrote a letter to one of the coworkers, notifying him that there were discrepancies between their data on heart weights and the author's formula-calculated values as shown in the table accompanying the letter. He mentioned in his reply that they recognized an error and would publish their corrected data in the same journal [53], and commented that the author's calculation wasso accurate. A remarkable agreement was found between their corrected data on heart weights and the author's formula-derived values as shown in the author's subsequently published article in 1990 [54].

The "probacent"-probability equation was applied to predict the percentile of serum cholesterol levels by age in adults [55, 56] and to express survival probability, death rate and life expectancy in US adults, men and women [18, 21];

and to express human tolerance to ionizing total body irradiation [3]as afore-mentioned. The values of LD_{50}, 1.860-2.751 Gyin total body irradiation in humans found in the author's study are considerably close to LD_{50} published in the literature: 2.45 Gy (Lushbaugh et al (1967) [57], 2.65-2.70 Gy (Bond and Robertson, 1957 [57], 2.3-2.6 Gy (Fujita, Kato and Schull, 1989) [58]. If it is taken into consideration that $LD_{50}$is a function of dose rate and time, there seems to be a remarkable agreement between formula-derived and reported, estimated LD_{50} values [3]

In addition to studies of exogenous-stressor-induced stress and response, the "probacent" model was applied to data on cause-unknown endogenous stress of cancer: chronic leukemia [59], malignant melanoma [60] and acute myelogenous leukemia [61]

The model was applied to experimental data on animals reported in the literature to predict survival probability in mice inoculated with leukemic cells [62], and to predict carcinoma-free probability in rats exposed to carcinogen DMBA [63].

The author feels that in the variety of biological phenomena, the constants *r* and *c* in **Eqs**.**32**and **33** are, if applicable, generally greater or les than one but not one (r or$c \neq 1$), indicating a curved line when plotted on a X-Y graph paper. The r and c values are relatively rarely one, indicating a straight line on a graph paper or otherwise approximately straight as seen in Figure 10. The phenomena seem to be analogous to the light path in physics that light path is actually curved when passing through a gravitational field of space but appears straight [64, 65].

If the value of constant *r* becomesequal to one, **Eq. 32**represents a lognormal distribution. If the *c* value in **Eq. 33** that is derivable from **Eq. 28** [21] becomes one.**Eq. 33** is essentially similar to the Weibull distribution that is a generalized exponential distribution [66]. If the base of logarithm is one, the lognormal distribution becomesa normal distribution as shown below [31, 67]:

$\text{Log}_1 1^0 = 0$
$\text{Log}_1 1^1 = 1$
$\text{Log}_1 1^2 = 2$
$\text{Log}_1 1^3 = 3$
$\text{Log}_1 1^n = n$

If the logarithm of one as its base is taken for X-axis of time, the Gompertz distribution might be similar to the Wibulldistribution. Therefore, it seems to the author that the Gompertz distribution might be a specific form of "probacent"-probability equation. A normal distribution is likewise a specific form of the "probacent"-probability equation.

"Pobacent" can be a dependent variable versus an independent variablesuch as time or age as seen in survival probability and life expectancy in US adult population (NCHS). [18, 21]."Probacent" can be a dependent variable versus two independent variables such as intensity of stimulus or harmful agent and duration of exposure like dose rate of radiation and duration of exposure in total body irradiation in humans [3], like dose of drug and time after administration [22, 48]. In case oftwo independent variables, **Eqs. 10, 14, 28**and **34**can make a prediction of probability ofoccurrence of response in subjects in various biological phenomena. The original and ultimate purpose of the author's studies has been to find a general mathematical model, possibly a mathematical law hidden in nature that might calculate the probability of safe survival in humans and other living organisms exposed to any harmful or adverse circumstances or conditions, overcoming the risk [4, 31].

It seems to the author on the basis of experimental observations, clinical applications and theoretical reasoning that the computer-assisted general mathematical model of "probacent"-probability equation may be applicable as an approximation method to make useful predictions of probable outcomes of response in a variety of biomedical phenomena [4, 31], and that the model may be employed in mathematical analysis of not only biostatic (bioststistics) but also "biodynamic" ("biodynamics") phenomena in which certain biomedical events occurring along time would be mathematically determined.

The “probacent”-probability does not predict a single definite result or response for an individual observation in dynamic biological phenomena. Instead, if the same observations are made on a large number of similar population, each of whom had the same condition at the start, the model would predict the possible outcomes, the approximate biomedical events in quantities under observations, but it could not predict the occurrence of the specific event in an individual. Thus, the “probacent” probability would introduce an unpredictabilityin biomedicine like an uncertainty principle of Werner Heisenberg in quantum mechanics [64, 65].

The smaller the number of subjects under observations, the less accurate and less continuous (zigzag) is the predicted result as in Kaplan-Meier’s method [66]. The largerthe number of subjects, the more accurate and continuous is the probability predicted by the model as seen in “probacent”-probability model applicable to the life tables of US total, men and women in the national vital statistics [18].

However, if the probability predicted by the model is 0 or 100%, it might be able to predict that an individual exposed to a harmful or adverse circumstance under observations would be most likely safe or risky with a considerable certainty. In carbon monoxide poisoning, “probacent” values may give approximate probabilities of occurrence of symptoms as suggested in Table 4.

The computer program of nonlinear, curved regression for **Eqs. 23, 28 and 32**enables users easily calculate sums of least squares by using a formula of approximation, eliminating a need for consultation of table of normal frequency or percentile in books of statistics and mathematics.

A general mathematical model of “probacent”-probability equation developed in the author’s studies would need further research for its verification and/or improvement, specially with more data on human tolerance to exogenous stressors such as radiation, toxic chemicals like carbon monoxide in order to establish LD_{50}.[3, 12, 68].

5. CONCLUSIONS

In this study, findings in the author’s researches on mathematical relationships among exogenous stressor, stress and response in a variety of biological phenomena are reviewed and summarized. Researches included animal experiments, clinical applications and theoretical reasoning.

1. The author classifies stress into two categories: one exogenous-stressor-induced stress and cause-unknown endogenous stress.Heat, cold, trauma, radiation, toxic chemical, bacterial infection etc. belong to the exogenous stressors. Cancer, metabolic disorder etc. are considered endogenous stress.
2. “ Various forms of “probacent”-probability equations are constructed from experimental results or reported data in the literature that express mathematical quantitative relationships among intensity of exogenous stressor, induced stress and occurrence of response in various biological phenomena.
3. **Eq. 28**expressing a general mathematical model of “probacent”-probabilityequation seems to be found to be ageneral unifying equation from which various forms of “probacent”-probability equations are derivable in a variety of biological phenomena.
4. A possible correlation between the “probacent”-probability equation and the Selye’s stress theory is presented in this study.
5. “Probacent”-probability equation seems to be as an approximation method to possibly calculate probabilities of outcomes of safe survival or mortality probability in humans and other living organisms exposed to harmful environment or noxious agents, overcoming the risk.

Further research would be required for its verification and/or improvement of the “probacent”-probability equation;especially ongoing investigation would be needed for more data to studyhuman tolerance to exogenous stressors such as radiation, toxic chemicals like carbon monoxide [3, 12, 68].

6. ACKNOWLEDGEMENTS

The author is thankful to Dr. C. W. Sheppard, Karl Friedrich Gauss and my teachers in mathematics, not named in my papers, for their shared knowledge that made my articles possibly published to the academic world. I would like to express my deep gratitude to Dr. Chung Chin Kim for his valuable contributions and achievements in our biomedical research.

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