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A MATHEMATICAL MODEL FOR OXYGEN TOXICITY IN MAN

by

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A Mathematical Model for Oxygen Toxicity in Man

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ABSTRACT

In this thesis, mathematical models are established for the development of oxygen toxicity in divers. The study endeavors to derive the shape of the oxygen tolerance curve in terms of depth-time limitations by statistical analysis of existing data. By assuming a known distribution for the time-to-serious-symptom, mathematically predictive models are developed which allow a greater degree of predictability in mission profiles and allow the associated risk to divers to be evaluated.

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I. INTRODUCTION

Priestly, upon discovering oxygen in 1775 philosophized whether, "it might exhaust the animal powers too soon, and as a candle we may burn too fast if used in our normal state of health" [Ref. 1]. It is known today that oxygen consumption in animals and man differs from Priestly's burning candle in that increases in tissue oxygen pressure do not accelerate oxidative metabolism. However, Priestly's suspicion, that oxygen might have a toxic or deleterious effect, has proven to be correct.

The toxic effects of oxygen on the central nervous system (CNS) have been recognized since the later half of the 19th century. Paul Bert is given credit for the earliest investigations in this area [Ref. 2]. In his work "La Pression Barometrique" he described in detail the incidence of convulsions in various animal species exposed to high pressures of oxygen. In 1878 he subjected larks to 15 to 20 atmospheres of air and noted that they first convulsed and then died. Further studies by Bert showed that it was the oxygen rather than the nitrogen in air that caused this phenomenon. Lorrain Smith [Ref. 3] is another early pioneer (1899) in the field of oxygen toxicity. He carried out the first extensive investigations of the toxic effects of oxygen on the lungs (pulmonary pathology).

Since these early investigations, oxygen has been shown to have toxic effects on many tissues in the body when present in abnormally high partial pressures. For a detailed account of the studies up to the early 1940's, the reader is referred to Stadie, Riggs and Haugaard 1944 [Ref. 4] and Bean 1945 [Ref. 5].

During the last few decades, research in the area of oxygen toxicity has reached a high level of activity in response to increased applications in medical therapy and in diving operations. The use of oxygen to decrease the duration and increase the effectiveness of decompression procedures in military and commercial diving operations has resulted in the exposure of a large number of healthy men to high pressures of oxygen, seemingly without any harmful consequences. Moreover, with research and experimentation a better understanding has evolved of the universal dependence of vital biological processes on oxygen, and on the opposing cellular antioxidant defense mechanism that balance the toxic effects of oxygen [Ref. 6]. It is now known that the same oxygen pressure required to sustain life would cause lethal oxygen poisoning in the absence of these defense mechanisms [Ref. 7].

The severity of oxygen poisoning appears to increase progressively with the increase in the partial pressure of oxygen and with greater exposure time. At sufficient pressure and exposure duration, oxygen will cause initial functional impairment and ultimate destruction of any living cell [Ref. 8].

The precise mechanism through which oxygen exerts its detrimental effects on the tissues and organs of the body is the subject of continuing research and controversy. Among the numerous biochemical and biophysical explanations which investigators have identified as possible causes are:

(1) Inactivation of enzymes, especially those containing sulfhydryl groups.

(2) The formation of powerful oxidizing radicals.

(3) Reduction of the amount of gamma amino butyric acid (GABA), a transmitter at CNS inhibitory synapses.

(4) Disruption of cellular membrane functions.

The United States Navy's interest in the effects of hyperbaric oxygen stems largely from the following applications of oxygen in the conduct of diving operations:

(1) As a breathing medium employed alone in the conduct of closed-circuit clandestine SCUBA operations. When used in this manner, oxygen has several distinct advantages over compressed air--it leaves no trail of bubbles by which a diver could be detected, and the absence of inert gas allows all the gas carried by the diver in his cylinder to be utilized, thus prolonging the operating time available.

(2) As a component of the atmosphere in mixed gas breathing systems that enable the Navy's divers to operate at deeper depths and for longer periods of time than is possible with compressed air diving.

(3) As an adjunct to decompression when used by divers who have incurred a decompression obligation breathing air, helium-oxygen or other mixtures. The divers are able to shorten their decompression time by breathing 100% oxygen at their decompression stops and thus increase inert gas removal from body tissues.

(4) As a component of the breathing mixture in saturation diving where oxygen is employed at higher than normal partial pressures to decrease the adverse effect of inert gas and to shorten decompression time.

(5) Hyperbaric oxygen used in the treatment of decompression sickness and air embolism, either as prescribed in the standard Treatment Tables 5 and 6 or as part of an individualized saturation treatment used for cases which fail to respond to conventional therapy (U.S. Navy Diving Manual) [Ref. 9].

The guidelines for oxygen diving in the U.S. Navy are published in the U.S. Navy Diving Manual. The maximum depth for closed circuit pure oxygen SCUBA diving during normal operations is 25 feet. The current depths and times for 100% oxygen are shown in Table 1.

If one studies the existing data or Table 1, one observes that as the depth of the oxygen exposure increases, the duration of allowed exposure decreases. This relationship reflects the fact that CNS oxygen toxicity is directly related to the partial pressure at which oxygen is breathed. A list

TABLE 1

OXYGEN DEPTH-TIME LIMITS

1. Normal Operations -	Depth (Ft)	Time (Min)
	10	240
	15	150
	20	110
	25	75
2. Exceptional Operations -	Depth (Ft)	Time (Min)
	30	45
	35	25
	40	10

Source: U.S. Navy Diving Manual

of the factors which are known to affect the onset of oxygen toxicity is presented below. This list and much of the background information on experiments was provided by Dr. Frank K. Butler of the Navy Experimental Diving Unit (NEDU) in Panama City, Florida:

(1) Partial pressure of oxygen--the greater the depth or pressure, the greater the likelihood of developing oxygen toxicity.

(2) Duration of exposure--increases toxicity with increasing time of exposure.

(3) Individual variations in susceptibility--this variation applies not only to the difference in susceptibility

between individuals but also for differences in the same individual at different times.

(4) Immersion in water--increases the onset of toxicity. Divers being treated for air embolism or decompression sickness routinely breathe oxygen in a recompression chamber at 60 feet. Breathing oxygen at a depth of 60 feet in the water would result in the fairly rapid onset of CNS oxygen toxicity.

(5) Hypercarbia--divers breathing an increased partial pressure of carbon dioxide appear to be much more susceptible to CNS oxygen toxicity.

(6) Exercise--even in the absence of an exercise-induced hypercarbia, the exercising diver is more likely to incur toxic symptoms than the diver at rest.

The most dramatic sign of oxygen toxicity is the grand mal convulsion. Convulsions may occur after other signs or symptoms have been experienced or they may be the first indication of oxygen toxicity. If the hyperbaric exposure to oxygen is stopped, the convulsions subside after a variable period of time and are not thought to be associated with any permanent neurological damage. The diver must however, be protected against physical trauma secondary to the convulsions and possible air embolism as a result of being brought to the surface while unable to carry on normal breathing. And of course, any military mission in which this would occur would be jeopardized. A variety of other CNS symptoms may be

encountered. The mnemonic acronym suggested by the Navy Diving Manual is "Ventid":

VISION. Visual abnormalities, especially "tunnel vision", which is a decrease in the peripheral field of vision.

EARS. Auditory disturbances, especially tinnitus which refers to a sound perceived by the ears but not originating from an external source. The sound may be described as a ringing, buzzing, or machinery type of sound.

NAUSEA.

TWITCHING. The facial muscles are especially prone to twitching but it may occur in other groups of muscles.

IRRITABILITY. A change in mental status which may be experienced by the diver as anxiety, confusion, or inability to focus his thoughts.

DIZZINESS.

In 1942 and 1943, a British investigator, H.K. Donald, conducted over 2000 man-dives for the purpose of establishing guidelines regarding oxygen toxicity for British frogmen in World War II. His research remains the largest dive series conducted to date investigating CNS oxygen toxicity. Some of his results and those of other earlier experimenters will be recounted.

Donald immersed 100 volunteers suited in Davis Submarine escape apparatus in a wet chamber at 50 feet of sea water (FSW) for a maximum time of 30 minutes. 30 FSW is about two atmospheres absolute (ATA). The water temperature was about 65 degrees F. Of these 100 divers, 26 convulsed, 24 had other symptoms of oxygen toxicity and 50 had no signs or symptoms. Donald also attempted to find the depth at or about which convulsions would not be observed. He conducted many such similar experiments at varing depths [Ref. 10].

An NEDU study was published in 1947 by Yarborough, Behnke et al [Ref. 11]. They tested various depths ranging from 30 to 100 FSW. In a resting dive underwater at 60 feet, 32 out of 107 exposures were terminated prior to 60 minutes, which was the maximum time for the dive. The average time to termination was 32 minutes (ranging from 8 to 58 minutes). Two convulsions were noted: one at 13 minutes and the other at 24 minutes. Another interesting observation from this study was that subjects immersed in water to their necks tolerated oxygen for periods similar to those of subjects in a dry chamber.

Another study was conducted at NEDU in 1953 by Lamphier [Ref. 12]. He used a continuous flow oxygen facemask apparatus in 80 degree F. water. Work rate was set at "greater than a man would voluntarily sustain under diving conditions, although less than the maximum possible." No convulsions were observed at depths less than 35 feet. One convulsion occurred at 35

feet after 42 minutes (out of a total of 5 dives to a maximum time of 43 minutes). One convulsion was also noted at 40 feet after 31 minutes (total of 13 dives to a maximum time of 30 minutes). This convulsion at 31 minutes is as reported by Lanphier indicating that at least one dive went beyond 30 minutes maximum. No convulsions were noted in 5 dives at 45 feet for a maximum time of 19 minutes.

In 1980 an NEDU study was published by Piantadosi, Clinton and Thalmann [Ref. 13]. Twenty-four oxygen exposures lasting from 80 to 271 minutes were performed by six immersed exercising divers at 25 FSW (1.76 ATA) in both warm and cold water. In this experiment two types of work were performed, moderate work (50 watts) for long periods of time, and graded (25-150 watts) lasting 85 minutes. CNS oxygen toxicity was not observed during these experiments although two divers had clinical evidence of early pulmonary oxygen toxicity.

The latest series of oxygen studies conducted at NEDU were directed by Butler and Thalman (1982-1983). These experiments were conducted in the NEDU Ocean Simulation Facility under rigorous experimental conditions. Divers were exercised on a horizontal bicycle ergometer placed on a platform four to five feet below the water level. A series of variable depth dive profiles were conducted to probe the tolerance curve for reasonable profiles which allow for moderate depth excursions. The results of these experiments were not published as of the writing of this thesis but will be available through the Navy Experimental Diving Unit, Panama City, Florida.

In order to make the best use of oxygen, it is clearly necessary to have accurate information about safe durations of exposure to various partial pressures. Rules such as the old 30-foot for 30-minute limitation on the use of 100% oxygen in closed circuit diving are not very useful even if perfectly valid. Such rules give no information about the possibility of spending a shorter time at a deeper depth or a longer time at a shallower depth or the probability of an occurrence of a serious symptom which could abort a sensitive military diving operation. The basic need is limit curves of partial pressure versus permissible exposure times, showing the limits which apply to specific diving conditions for the degrees of safety desired expressed as probabilities. For this, the phenomena of oxygen toxicity must be mathematically modeled.

Although the duration of exposure required to produce CNS oxygen toxicity is basically a function of the partial pressure of oxygen in the atmosphere--the higher the partial pressure the less time is required to produce symptoms--other factors are also very important. While the basic relationship of partial pressure and time hold for any specific situation, it could be overshadowed by the importance of these other variables which can greatly modify the tolerance curve. Of these, physical exertion and excess carbon dioxide appear to be the most important. Temperature, anxiety and a number of physiological factors might also be significant, but less

strikingly so. The situation is further complicated by the fact that individual variations are large and almost entirely unpredictable [Ref. 10]. Not only do individuals differ from each other, but their tolerance changes from dive to dive for reasons which are unknown. This factor in concert with the lack of control in the experiments which have been conducted thus far result in confusion and difficulties in handling the existing recorded data.

Studies conducted in the past have established the significance of factors such as exertion [Ref. 10] but have not provided sufficient quantitative data to permit establishing a tolerance limit under the specified condition with any degree of confidence. In setting such a limit, all of the relevant conditions likely to be encountered deserve consideration. Individual variations in tolerance must be taken into account. The limits must be very safe because oxygen convulsions in SCUBA diving could easily end in death, or abort a sensitive military diving operation. However, making it 100% safe for all individual and all conditions is too restrictive and is out of the question.

An ideal study of oxygen tolerance would include investigation of all significant variables, their degrees, and their combinations. A very large number of subjects would be employed to illuminate the question of individual variability, and all exposures would be carried to convulsion, which is the only unequivocal end-point of oxygen toxicity.

An ideal study would also include determination of oxygen tolerance using a variety of gas mixtures at appropriate depths, since the toxicity of oxygen may be modified by the presence of other gases. Studies have indicated that increased nitrogen pressure can suppress the convulsive manifestations of oxygen toxicity in animals. However, later NEDU studies have indicated that the presence of nitrogen may decrease oxygen tolerance in man [Ref. 12].

A. NATURE, SOURCES AND AVAILABILITY OF DATA

This investigative effort was undertaken to explore the feasibility of developing mathematical models which characterize the oxygen tolerance of human beings. Therefore, a survey of the scientific literature was performed to locate experimental data on time limits for human exposures to various partial pressures of oxygen. Unfortunately, data on human experiments published in the literature is extremely variable and is subject to influences, both physiological and environmental. Each scientist used a different approach to his experiments. Different breathing apparatus were used, different temperatures of the water, different work loads and depths, and other variants were explored by each scientist. This fact makes it extremely difficult and risky to compare the findings of the various experimenters.

Raw data from the early experiments which were conducted by the Royal Navy Experimental Diving Unit during World War

II is very difficult to acquire and some important experimental runs are only available as summaries of the results. A summary of the findings such as Reference 10 is readily available but the raw data is unavailable, being lost or buried in a mound of information in London, England.

Most of the raw data on U.S. Navy experiments is available through the NEDU library in Panama City, Florida. This data is in the form of the actual log books and is generally available in micro-fische. The result is the raw data is extremely tedious to work with and is often sketchy or unreadable. Fortunately, good summaries of the raw data are available in the form of NEDU reports such as References 11, 12, and 13.

During the last few decades, with the increased interest in oxygen toxicity, a great deal of information has become available. Most of this information is of a theoretical or clinical nature and is not applicable to statistical analysis. It is very time consuming but informative to sort out the theoretical data from the empirical data and it is obvious that improved human data on oxygen exposure limits is sorely needed if statistical analysis is to develop a model with any high degree of confidence.

II. MATHEMATICAL MODELS

In making a mathematical model for a real-world phenomenon it is necessary to make certain simplifying assumptions so as to render the mathematics tractable. Many different types of mathematical functions can be used to model a response that is a function of one or more independent variables. A mathematical model is merely a mathematical representation of a phenomenon or process. Ideally, we want a model to incorporate everything that is important and significant about the phenomenon and ignore everything else. This buys the simplicity needed to provide a convenient method for performing certain computations.

On the other hand, we cannot make too many simplifying assumptions, for then our conclusion or predictions obtained from the mathematical model would not be applicable to the real-world phenomena. A mathematical model is an abstraction which associates parameters and processes of the real-world with expressions and operations in a mathematical structure. Thus, we must make enough simplifying assumptions to enable us to handle the mathematics but not so many that the mathematical model is no longer tractable.

Keeping in mind that a density function is a theoretical model for a population of real data that occurs in the real-world, how do we know which model to use, and to what extent

does it matter if we have an erroneous model? Any fitted model we could develop is merely an approximation, either because some variables are not recorded or incorrectly measured, or because the functional form used is not exactly correct. The mathematical model is merely a useful fiction suggested so that straightforward techniques can be used for the description of a relationship or the prediction of future values. It is unlikely that one would find a density function that provides a perfect fit, which would represent a perfect fit of the density function to nature. The purpose of a probabilistic model is to provide the mechanism for making inferences about the real-world; therefore a good model is one that yields good inferences about the real-world phenomena of interest.

A. MODEL FOR THE DISTRIBUTION OF TIME TO SYMPTOM

A reasonable selection of a model is sometimes implied by theoretical considerations. A second way to select a model is to form frequency histograms or empirical distributions of the raw data and choose a density function that would visually appear to give a similar frequency curve. One simplifying assumption that mathematicians are particularly fond of and that is often made is to assume that the random variables are exponentially distributed. The reason for this is that the exponential distribution is both relatively easy to work with and is often a very good approximation to the actual distribution.

Figure 1 shows the empirical density function for Donald's experiments [Ref. 10], at 103, 93, 83 and 73 FSW as computed by an APL function which smoothes the raw data into an empirical distribution [Ref. 14]. These experiments were chosen because they were carried to decisive end-points. These empirical density functions look approximately gamma. If one truncates these graphs on the left to account for the fact that some time is required to press the divers to depth, the time-to-symptom is plausibly exponential. For those non-divers, the time of the dive begins and is calculated from the time the diver leaves the surface and it takes some variable amount of time depending on the individual diver to descend to the desired depth. Even with this limited number of data points there is a conspicuous build-up of hits followed by a long drawn-out tail. These graphs suggest that the exponential distribution could be used as a reasonable approximation to the real-world phenomenon of oxygen toxicity. Future analysis could explore the possibility of fitting gamma distributions to the times-to-symptom at depth and attempt to integrate these distributions in terms of a simple formula.

The approach taken in this thesis will be to analyze the available data with existing mathematical models. For this effort certain mathematical tools will be necessary. Fortunately, many of the tools used in systems test and evaluation and systems reliability are applicable.

In the study of the reliability of systems it is customary to think of the time-to-failure, up-time or lifetime of an item

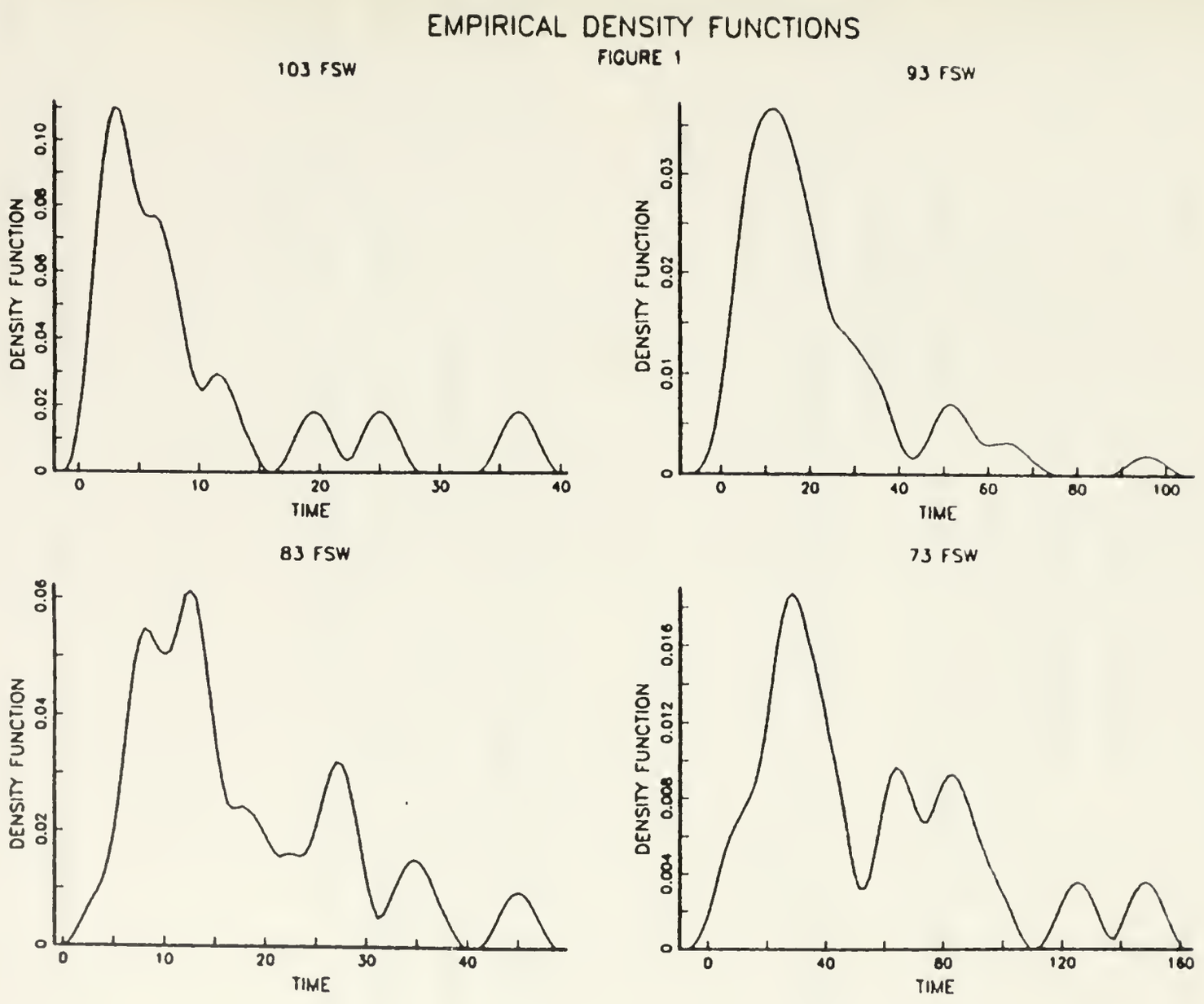
EMPIRICAL DENSITY FUNCTIONS
FIGURE 1
103 FSW
93 FSW
83 FSW
73 FSW
DENSITY FUNCTION
TIME
0
0.02
0.04
0.06
0.08
0.10
0.01
0.03
0.012
0.016
0.004
0.008
10
20
30
40
60
80
100
120
160

FIGURE 1

as a random variable, T. Fundamental to this concept is the idea that the time-to-failure varies randomly from individual item to item and failure is a well defined notion. As an example, failure in a human lifetime could be defined as death which, with respect to diving, is an unambiguous concept. In oxygen toxicity studies failure could be defined as the time-to-convulsion or the time-to-symptom. In this thesis we will work with the time-to-serious-symptom. This is because serious symptoms have been more accurately recorded and such toxic episodes usually resulted in the experimenter terminating the experiment.

Let T equal the time-to-serious-symptom, then given that T is a random variable, reliability has the following definition:

$$R(t) = P(T > t)$$

That is, R(t) is the probability that T, which is the time-to-serious-symptom, is greater than t, where t is the duration of a particular mission or mission time. If such a phenomenon is stable then such a measure has meaning in terms of a distribution function of T, $F_T(t)$:

$$R(t) = P(T > t) = 1 - F_T(t) = \bar{F}_T(t)$$

$\bar{F}_T(t)$ is often considered as a function of the mission time, t, and is called the survivor function. Accordingly, mission reliability is the probability that a diver will <u>not</u> have a

serious symptom or convulsion during a specified period of time under specified environmental conditions.

According to the above definition of mission reliability, the probability that a diver will not incur a serious symptom or convulsion which would cause the abortion of a diving operation, depends on the length of time a diver is at depth on pure oxygen. Thus of fundamental importance is the distribution of the times to failure (serious symptom or convulsion). A useful way to characterize this distribution is by means of its associated hazard rate of instantaneous failure rate.

Suppose that a distribution function $F_T(t)$ exists and is stable over time. This implies that:

$$F_T(t) = P(T < t) = \int_0^t f_T(t)dt$$

Now suppose that diver X has survived (no serious symptom or convulsion) for some time T, and we wish to know the probability that he will not survive for an additional time dt, i.e., he will have a serious symptom or convulsion in the subsequent small time interval dt. Let $\lambda(t)$ equal this hazard rate. Then:

$$\lambda(t) = P(T \epsilon (t, t+dt) \mid T > t)$$

This says that $\lambda(t)$ is the probability that T is an element of the interval from t to t plus dt, given that T is greater than t. By definition:

$$\lambda(t) = \frac{P(T_\epsilon(t,t+dt), T > t)}{P(T > t)}$$

But since $T > t$ is included in the time interval $(t,t+dt)$, it follows that:

$$= \frac{f_T(t)}{\bar{F}_T(t)}$$

$$= \frac{-d/dt\ F_T(t)}{\bar{F}_T(t)}$$

$$= \frac{-[F_T(t)]'}{\bar{F}_T(t)}$$

From the formula $\frac{du}{u} = d(\ln u)$, the solution to this differential equation is:

$$= \frac{-d(\ln \bar{F}_T(t))}{dt}$$

Solving for $\ln \bar{F}_T(t)$ by integrating both sides:

$$-\int_0^t \lambda(t)dt = \ln \bar{F}_T(t)$$

$$\bar{F}_T(t) = e^{-\int_0^t \lambda(t)dt}$$

Take the exponential of both sides

Now $R(t) = \bar{F}_T(t) = e^{-\Lambda(t)}$

where $\Lambda(t) = \int_0^t \lambda(t')dt'$ is the integrated hazard rate, and the distribution of failure times is:

$$f_T(t) = \lambda(t)e^{-\int_0^t \lambda(t)dt}$$

since $f_T(t) = \lambda(t)R(t)$ Ref. [15]

We know that the survival of diver X is a function of the partial pressure of oxygen (PPO2), duration of exposure, metabolic rate, partial pressure of carbon dioxide (PPCO2), anxiety, and other variables. Thus the integrated hazard could be written as:

$$\Lambda(t) = \Lambda(\nu_1, \nu_2, \ldots, \nu_n)$$

Mission reliability can then be written as:

$$R(t) = e^{-\Lambda(\nu_1, \nu_2, \ldots, \nu_n)}$$

The probability that diver X gets a hit (here hit means the occurrence of a serious symptom or convulsion) is 1-R(t). The question is what is $\Lambda(\nu_1, \nu_2, \ldots, \nu_n)$? Since an ideal study of oxygen toxicity has not been conducted, one must deal with those variables for which data is available namely, duration of exposure and depth, or depth as expressed as PPO2. To some extent metabolic rate has been explored in working versus non-working dives. These variables are of limited value due to the lack of commonality in control of different experiments and by the fact that PPO2, PPCO2 and duration of exposure at depth were not precisely measured in past experiments.

B. EXPECTATION AND THE PROBLEM OF CENSORING

The mean-time-to-failure (MTTF) is a quantitative assessment of the failure times.

$$\hat{MTTF} = \frac{T_1 + T_2 + \ldots + T_n}{n}$$

MTTF is an estimator of the expectation of the mean-time-to-failure. In oxygen toxicity studies there are problems in calculating the expected value of T, E(T), which result from the termination of experiments prior to all the divers reaching their individual end-points (convulsion or serious symptom).

Suppose that n divers are tested simultaneously in a chamber for a fixed depth and fixed time T, and that the times to serious symptom or convulsion are recorded. Since T is a fixed time, say 60 minutes, all of the divers will not reach their individual end-points (some will complete the entire experiment without incident). How does one calculate the mean-time-to-failure (mean-time-to-symptom). Let's assume, since the data suggests, that MTTF is exponential.

Let

$$X_i^t = \min[X_i, T]$$

where:

T = Fixed time of chamber run or experiment

X_i = Time to end-point of ith diver

The maximum likelihood estimator for $\hat{MTTS} = \hat{\lambda}$ is:

$$L(\lambda, \underline{X}) = e^{-\lambda[X_1\delta_1 + T(1-\delta_1)]} \lambda^{\delta_1} e^{-\lambda[X_2\delta_2 + T(1-\delta_2)]} \lambda^{\delta_2} \ldots e^{-\lambda[X_n\delta_n + T(1-\delta_n)]} \lambda^{\delta_n}$$

$$= \prod_{i=1}^{n} e^{-\lambda[X_i\delta_i + T(1-\delta_i)]} \lambda^{\delta_i}$$

where:

$$\delta_i = \begin{cases} 1 & \text{if} \quad X_i \leq T \\ 0 & \text{if} \quad X_i > T \end{cases}$$

$$\ell(\lambda, \underline{X}) = -\lambda \sum_{i=1}^{n} [X_i \delta_i + T(1-\delta_i)] + S \log \lambda - \lambda X_t' + S \log \lambda$$

where:

$$\ell n(\lambda, \underline{X}) = \log L(\lambda, \underline{X})$$

$$S = \sum_{i=1}^{n} \delta_i$$

Now differentiate:

$$\frac{\partial \ell}{\partial \lambda} = - X_t' + \frac{S}{\lambda}$$

$$\frac{\partial^2 \ell}{\partial \lambda^2} = - \frac{S}{\lambda^2}$$

This leads to:

$$\hat{\lambda} = \frac{S}{X_t'}$$

$$= \frac{\text{Number of failures observed in the interval } (0,T)}{\text{The total cumulative exposure time of all divers}}$$

The variance of $\hat{\lambda}$ is:

$$\text{Var}(\hat{\lambda}) \cong (E[\frac{S}{\lambda^2}])^{-1}$$

$$\cong [\frac{1}{\lambda^2} E(S)]^{-1}$$

$$\cong [\frac{1}{\lambda^2} n[1 - e^{-\lambda t}]]^{-1}$$

$$\cong \frac{\lambda^2}{n[1 - e^{-\lambda T}]}$$

Note that as

1. $T \to \infty$, $\text{Var}(\hat{\lambda}) \to \frac{\lambda^2}{n}$ which is the same as uncensored.

2. $T \to 0$, $\text{Var}(\hat{\lambda}) \simeq \frac{\lambda^2}{n} \frac{1}{\lambda T} \to \infty$, for n fixed.

3. If λT is "small," $1 - e^{-\lambda T}$ is small and the precision of the maximum likelihood estimator is small. $\text{Var}(\hat{\lambda})$ is very large, unless n is large. [Ref. 17]

This complicated mathematical path reduces to a simple ratio which is intuitively clear and simple.

$$\frac{\text{Number of Serious Symptoms Observed in Experiment}}{\text{Total Cumulative Exposure Time of All Divers}}$$

[Ref. 16]

C. CONFIDENCE LIMITS FOR THE EXPONENTIAL PARAMETER

Suppose that data is available that one wishes to refer to an exponential distribution. Let $t_1, t_2, \ldots, t_n$ denote the observed "times" to symptom or convulsion. Assuming that the

times are distributed exponentially one can establish confidence limits for the rate parameter λ, or for $1/\lambda = E[T]$, the mean-time-to-convulsion or symptom. Procedure for two-sided confidence limit:

a. Compute $\bar{t} = \frac{1}{n} \sum_{i=1}^{n} t_i$

b. Decide upon the significance level α.

c. Confidence limits for λ (failure rate): with confidence $(1-\alpha)100\%$:

$$\frac{1}{\bar{t}}\left[\frac{\chi^2_{df,\alpha/2}}{df}\right] < \lambda < \frac{1}{\bar{t}}\left[\frac{\chi^2_{df,1-(\alpha/2)}}{df}\right]$$

d. Confidence limits for the Mean-time-to-symptom:

$$\bar{t}\left[\frac{\chi^2_{2n,1-(\alpha/2)}}{2n}\right]^{-1} < E[T] = \frac{1}{\lambda} < \bar{t}\left[\frac{\chi^2_{2n,\alpha/2}}{2n}\right]^{-1}$$

[Ref. 17]

D. PARAMETER ESTIMATION

The probability density of the time to serious symptom has been defined as:

$$f_T(t) = \lambda(t) e^{-\int_0^t \lambda(t)dt}$$

For the moment let us denote $\lambda(t)$ as a constant failure rate γ, for a given depth, where $\gamma > 0$ and substitute γ into the

above equation.

$$f_T(t) = \gamma e^{-\gamma t} \qquad \gamma > 0, \quad t > 0$$

Thus we observe that the distribution of failure times is an exponential distribution when it can be assumed that the failure rate is constant. For this reason, the assumption of a constant failure rate is often called the "exponential assumption" in reliability models. Now the mean-time-to-symptom (MTTS) equals $1/\gamma$. Of course, in this situation γ is not a constant but is a function of depth, PPO2, PPCO2, work rate and perhaps several other variables. We can however, calculate $\hat{MTTS}$ for those experiments that have been conducted. Then with those experiments that have commonality (wet no-work, wet working, dry, etc.), project a curve and try to discover meaningful relationships from the curve. First, using Donald's data since his experiments have the most data points, one observes that if the depth is held constant, the time-to-symptom is plausibly exponential for any given depth. Moreover, using the censoring expectation technique we can compute $\hat{MTTS}$ for each experiment. Table 2 tabulates the MTTS for Donald's wet resting dives.

Since $\gamma = 1/MTTS$, $\hat{\gamma}$ can be approximated by $1/\hat{MTTS}$. Figure 2 is a plot of MTTS as a function of depth and time. Taking into account the variability of these averages, a smoothed curve of mean-times-to-symptom for non-working divers can be

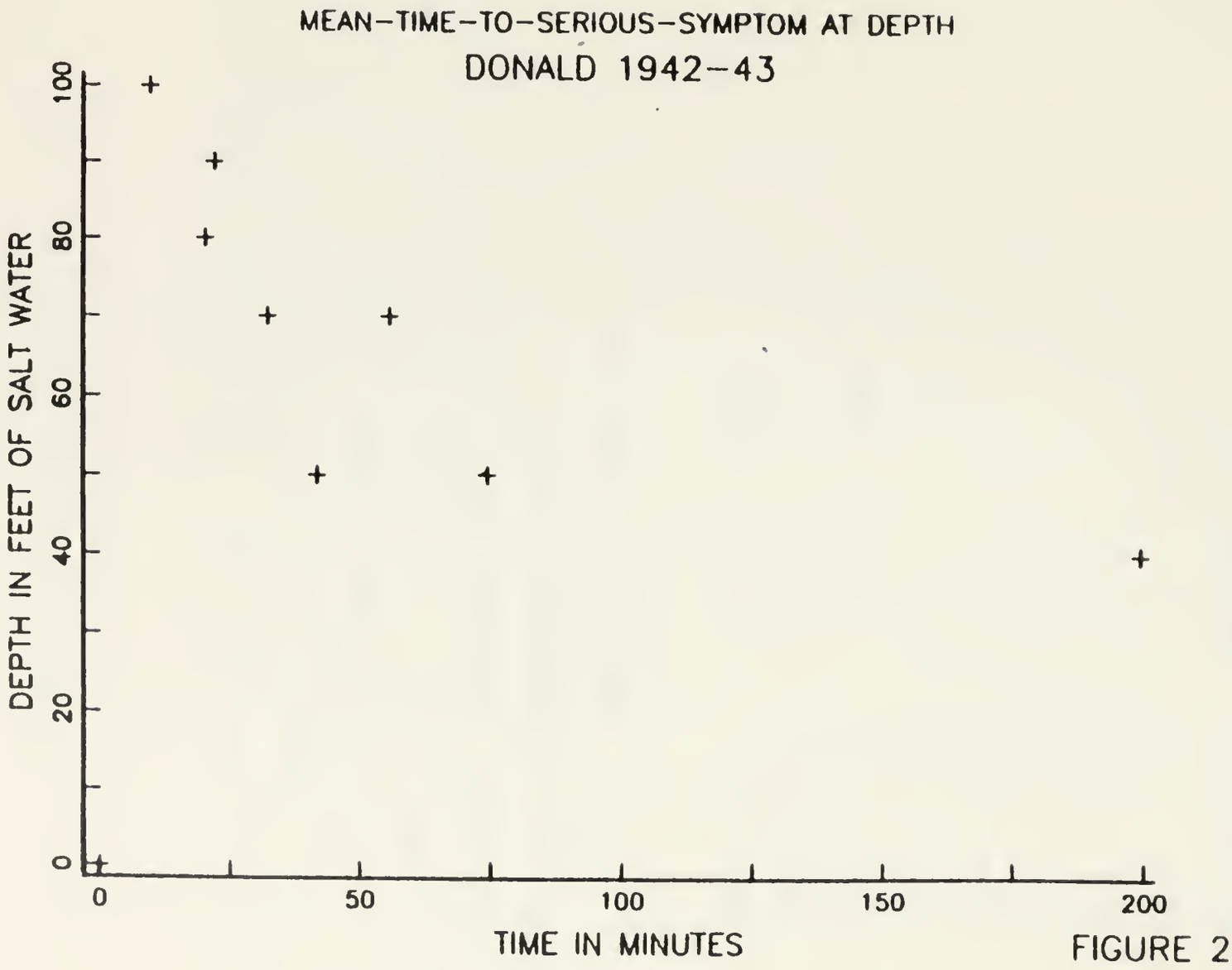
MEAN-TIME-TO-SERIOUS-SYMPTOM AT DEPTH
DONALD 1942-43
DEPTH IN FEET OF SALT WATER
0
20
40
60
80
100
0
50
100
150
200
TIME IN MINUTES
FIGURE 2

FIGURE 2

TABLE 2

MEAN-TIME-TO-SYMPTOM USING THE CENSORING TECHNIQUE FOR RESTING DIVERS UNDERWATER AS REPORTED BY DONALD [REF. 10]. $\alpha = .05$

FSW	$\hat{MTTS}$	n	2n	$\chi^2_{2n(\alpha/2)}$	$\chi^2_{2n(1-\alpha/2)}$	95% CONFIDENCE LIMIT
40	199.3	31	62	.675	1.39	134.5 < MTTS < 277.0
50	74.2	41	82	.714	1.33	53.0 < MTTS < 98.7
	41.5	40	80	.714	1.33	29.6 < MTTS < 55.2
70	32.1	15	30	.560	1.57	18.0 < MTTS < 50.4
	55.4	20	40	.611	1.48	33.9 < MTTS < 82.9
80	20.1	26	52	.647	1.43	13.0 < MTTS < 28.7
90	21.8	55	110	.742	1.30	16.2 < MTTS < 28.3
100	9.5	16	32	.560	1.57	5.3 < MTTS < 14.9

projected. Such a projected curve is provided at Figure 3. Using this curve one can calculate a conservative estimate of what the mean-time-to-symptom is for any depth, and therefore calculate a reasonable approximation to γ. This composite value of γ is a function of depth, duration of exposure, PPO2, PPCO2, and the other variables, so in some respects γ is a point quantitative value of $f_T(t)$. Now making use of the fact that:

$$R(t) = 1-F(t) = 1 - \int_0^t f_T(t)dt$$

$$= 1 - \int_0^t \gamma e^{-\gamma t} dt$$

$$= e^{-\gamma t}$$

DONALD 1942–43 AND PROJECTED CURVE

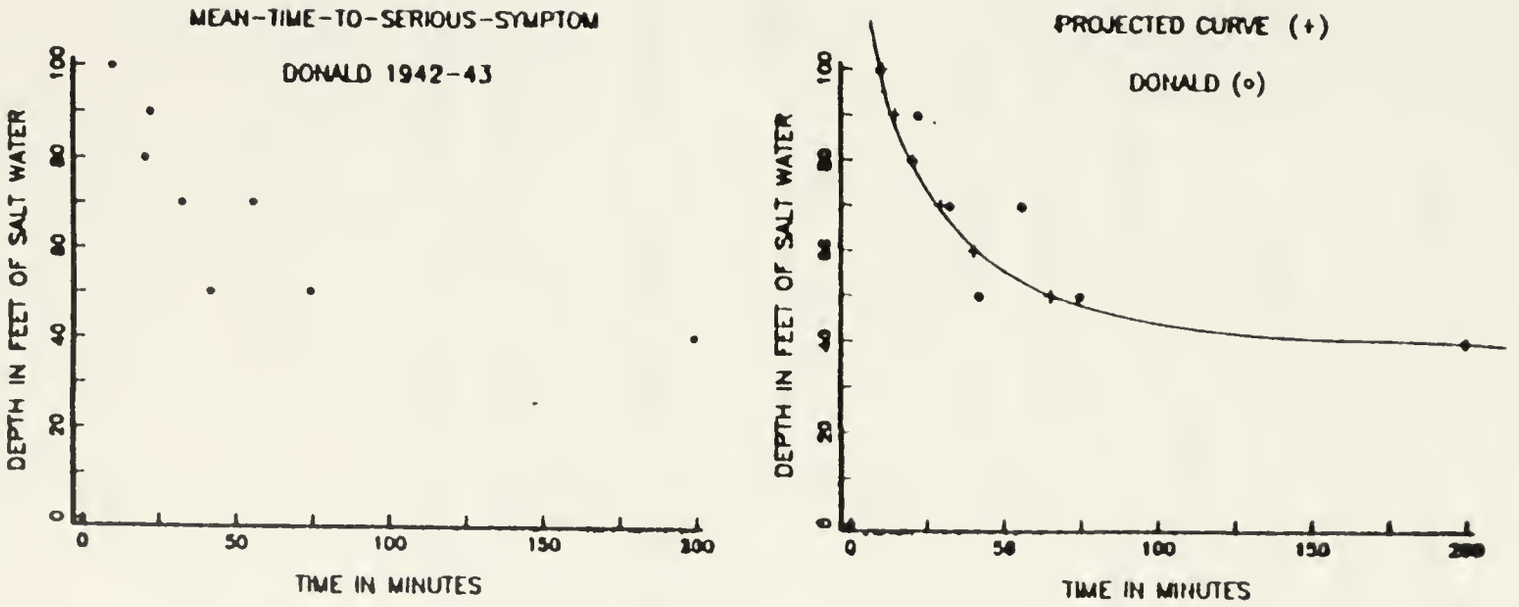

FIGURE 3

FIGURE 3

R(t) is the reliability function of an exponential model. Thus from the projected curve we can calculate $\hat{\gamma}$ for any depth based on the projected $\hat{MTTS}$ suggested by the curve.

E. MODELS

If one ponders Figure 3, one can see several approaches to model the shape of the curve in the given range. First of all it looks exponential or hyperbolic. Now, what we are seeking is a simple formula in terms of depth and time which yields reasonable probabilities for mission success or mission failure or the probability that the diver will get a hit. One such simple formula that yields a conservative value for MTTS in terms of depth is the hyperbolic function:

$$\hat{MTTS}_{(DEPTH)} = C/(depth - D_0)$$

where C and D_0 are constants. Two curves generated by this function are shown in Figure 4. This formula allows us to express the reliability function of a wet non-working diver (a diver in an SDV for example) in terms of depth and time:

$$R(t) = \begin{cases} EXP\left[\frac{-(D-D_0)^{\nu}}{D}(t)\right] & \text{for} \quad D > D_0 \\ \text{undefined} & \text{for} \quad D < D_0 \end{cases}$$

where D is depth and ν is a constant. The relationship between such a function and that of a working diver will be explored later in this thesis.

PROJECTED CURVE WITH FITTED CURVES

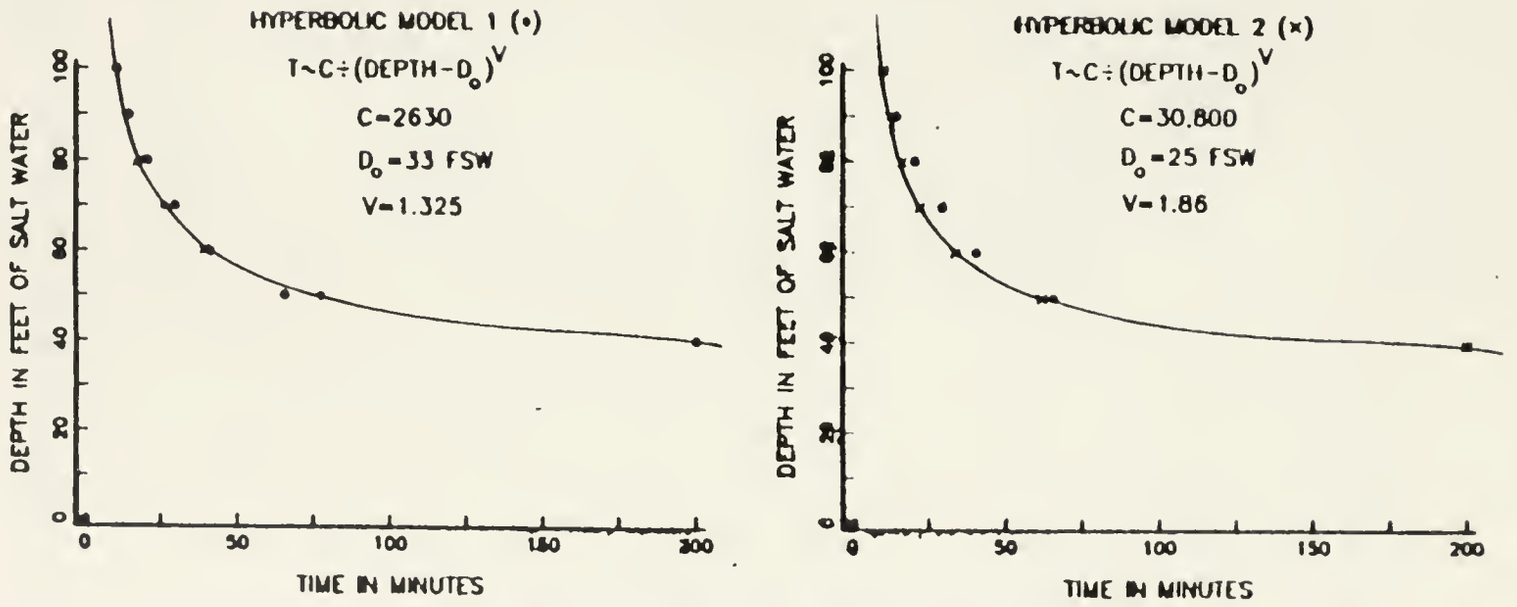

FIGURE 4

FIGURE 4

1. Hyperbolic Model 1

Let:

$$D = 33FSW$$

$$\nu = 1.325$$

$$C = 2630$$

The following values can be obtained from the formula:

$$T = \frac{C}{(D - D_0)^{\nu}} \qquad \hat{\gamma} = \frac{1}{\overline{T}}$$

FSW	$\hat{MTTS} = \overline{T}$	$\hat{\gamma}$
110	8.32	.1200
100	10.00	.1000
90	12.39	.0807
80	16.01	.0625
70	21.98	.0456
60	33.37	.0300
50	61.60	.0162
40	200.00	.0050
30	--	--

Now:

$$R(t) = EXP\left[\frac{-(D - D_0)^{\nu}}{C} t\right]$$

= Mission Reliability of a wet non-working diver

Let:

$$t = 20 \text{ minutes and depth} = 85\text{FSW}$$

$$R(t) = \text{EXP}\left[\frac{-(85-33)^{1.325}}{2630}(20)\right]$$

$$= e^{-.0714(20)}$$

$$= .24$$

So the probability of mission success under these circumstances (say a diver in a wet submersible (SDV) at 85FSW for 20 minutes) is 24% and accordingly, the probability diver X incurs a serious symptom is 76%.

2. Hyperbolic Model 2

Let:

$D = 25\text{FSW}$

$\nu = 1.86$

$C = 30,800$

FSW	MTTS = T	$\hat{\lambda}$
100	10.00	.1000
90	13.07	.0765
80	17.85	.0560
70	25.90	.0386
60	41.00	.0244
50	77.00	.0130
40	200.00	.0050
30	1543.35	.00065

Let:

$$t = 20 \text{ minutes and depth} = 85\text{FSW}$$

$$R(t) = \text{EXP}\left[\frac{-(85-25)^{1.86}}{30,800}(20)\right]$$

$$= e^{-.0659(20)}$$

$$= .27$$

Mission success is 27% and the probability that diver X gets a hit is 73%.

3. Exponential Model 1

Another approach to modeling the smoothed projected curve is to fit an exponential.

$$T = \text{MTTS}_{(\text{depth})} = ke^{-\alpha(D-D_0)}$$

Figure 5 projects such a fit. Let:

$$k = 425$$

$$D = 25\text{FSW}$$

$$\alpha = .05$$

FSW	$\hat{\text{MTTS}}$	$\hat{\alpha}$
100	9.99	.1001
90	16.48	.0607
80	27.17	.0368
70	44.79	.0223
60	73.85	.0135
50	121.76	.0082
40	200.75	.0050
30	330.99	.0030

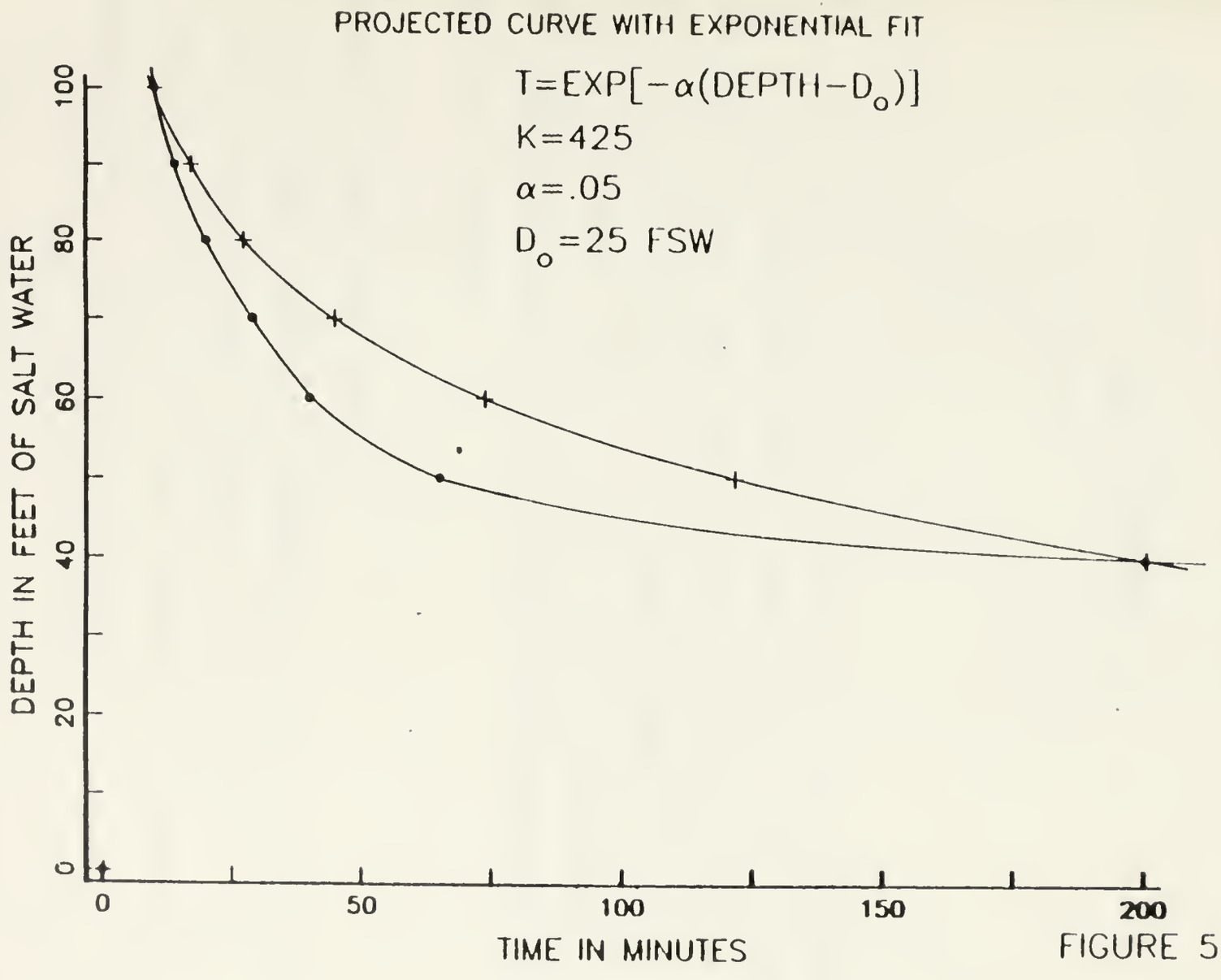

FIGURE 5

FIGURE 5

$$R(t) = EXP\left[-\frac{1}{ke^{-\alpha(D-D_0)}}(t)\right]$$

Let:

t = 20 minutes and depth = 85FSW

$$R(t) = EXP\left[-\frac{1}{425e^{-.05(85-25)}}(20)\right]$$

$$= e^{-.0473(20)}$$

$$= .39$$

So the probability of mission success under these conditions is 39% and the probability diver X gets a hit is 61%. Given the dangers involved with oxygen diving, Hyperbolic Model 1 provides the most conservative estimates in favor of diver X, given Donald's data. Figure 7 shows both the exponential fit and the hyperbolic models with the mean-time-to-serious-symptom as reported by Donald.

F. VARIABLE DEPTH DIVE PROFILE

If we make the exponential assumption about the distribution of the failure times (times-to-serious-symptom), some very useful results can be derived concerning the mean-time-to-symptom (MTTS). Making use of the fact:

$$R(t) = 1 - F_T(t) = 1 - \int_0^t f_T(t)\,dt$$

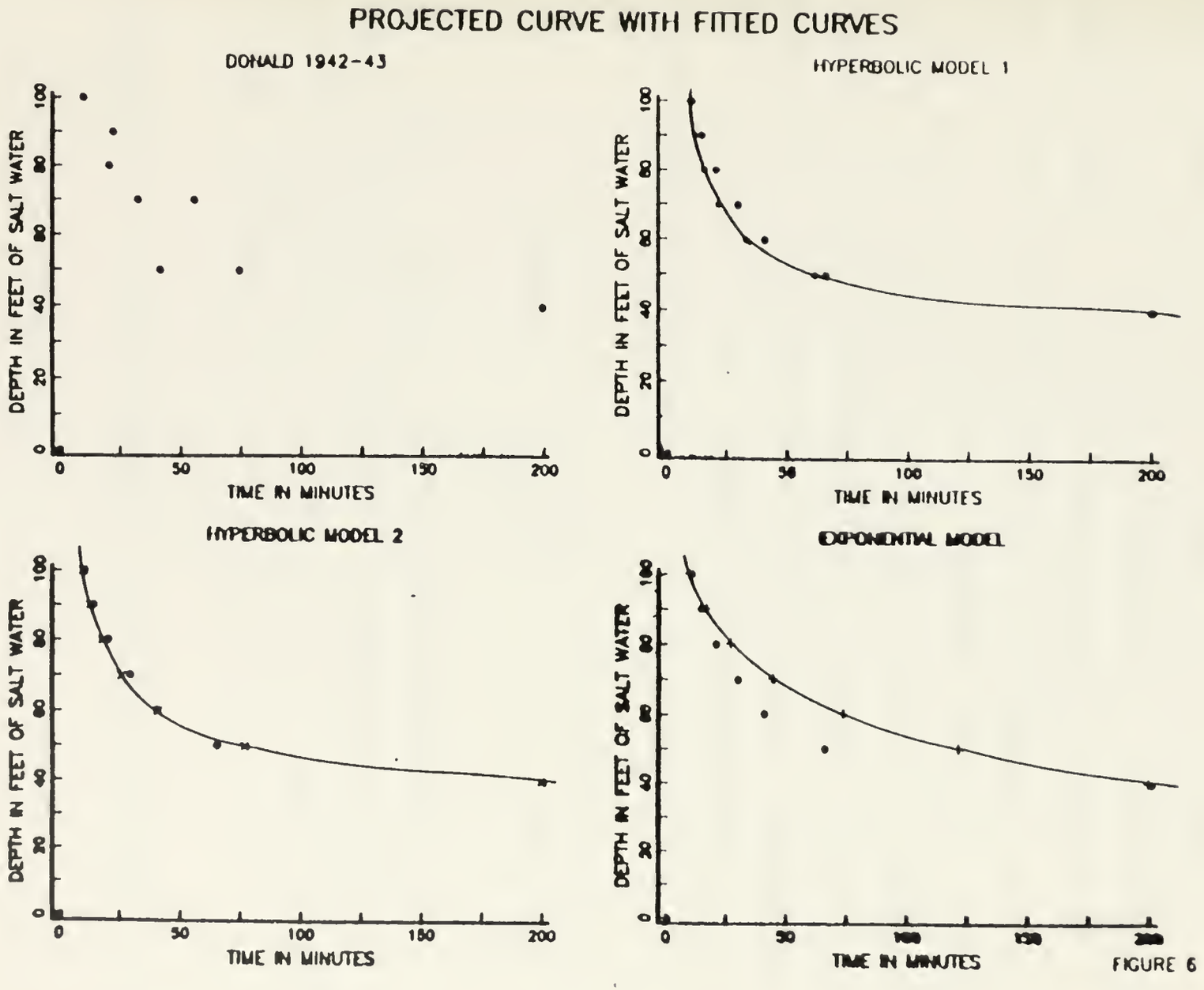
PROJECTED CURVE WITH FITTED CURVES
DONALD 1942-43
HYPERBOLIC MODEL 1
HYPERBOLIC MODEL 2
EXPONENTIAL MODEL
DEPTH IN FEET OF SALT WATER
TIME IN MINUTES
0
50
100
150
200
FIGURE 6

FIGURE 6

we obtain

$$R(t) = 1 - \int_0^t \gamma e^{-\gamma t} dt = e^{-\gamma t}$$

for the reliability function of the exponential model.

Suppose that a dive profile consists of n component dives at various depths. Consider these dives as connected in a series and that the component dives have respective failure rates of $\gamma_1, \gamma_2, \ldots, \gamma_n$. If the n component dives are thought of as a series, namely the performance of any one component dive does not affect the probability of success of any other component dive, then under these conditions the probability that the dive profile is a success will be the product of the component dive reliabilities.

$$R_{(PROFILE)} = \prod_{i=1}^{n} R_i \qquad \text{[Ref. 18]}$$

For example, suppose a dive profile consists of 200 minutes at 40FSW with an excursion to 60FSW for 15 minutes. What is the probability of success of the dive profile? Using model one to determine the value of the γ's,

$$R_{(PROFILE)} = EXP\left[-\frac{(40-33)^{1.325}}{2630}(200)\right] EXP\left[-\frac{(60-33)^{1.325}}{2630}(15)\right]$$

$$= .669 \times .638$$

$$= .427$$

The probability of mission success with this dive profile is 42.7% and the probability that diver X gets a hit is 57.3%. These are not very good odds for the SDV pilot who must make such an excursion.

1. The Effect of Work on the Oxygen Tolerance Curve

It has been generally accepted that work diminishes tolerance to oxygen at increased partial pressures. This was demonstrated by Donald [Ref. 10] in the first large series of experiments on human beings. His subjects worked vigorously underwater by lifting a large bag of weights by means of a pulley. He conducted experiments at 50, 40, 35, and 25 FSW. These experiments show conclusively that oxygen tolerance is markedly diminished by work. This author was unfortunately only able to acquire the data from the experiments at 50 and 40 FSW. The corresponding means are 41.5 minutes for 40 FSW and 21.9 for 50 FSW. Although this provides only two data points, one could hypothesize from the previous analysis and project a curve based on the projected curve of the resting divers, and fit a model similar to the models proposed earlier in this thesis. Figure 7 is an attempt to develop such a model. Consider the curve to be asymptotic to 20 FSW. Then we have:

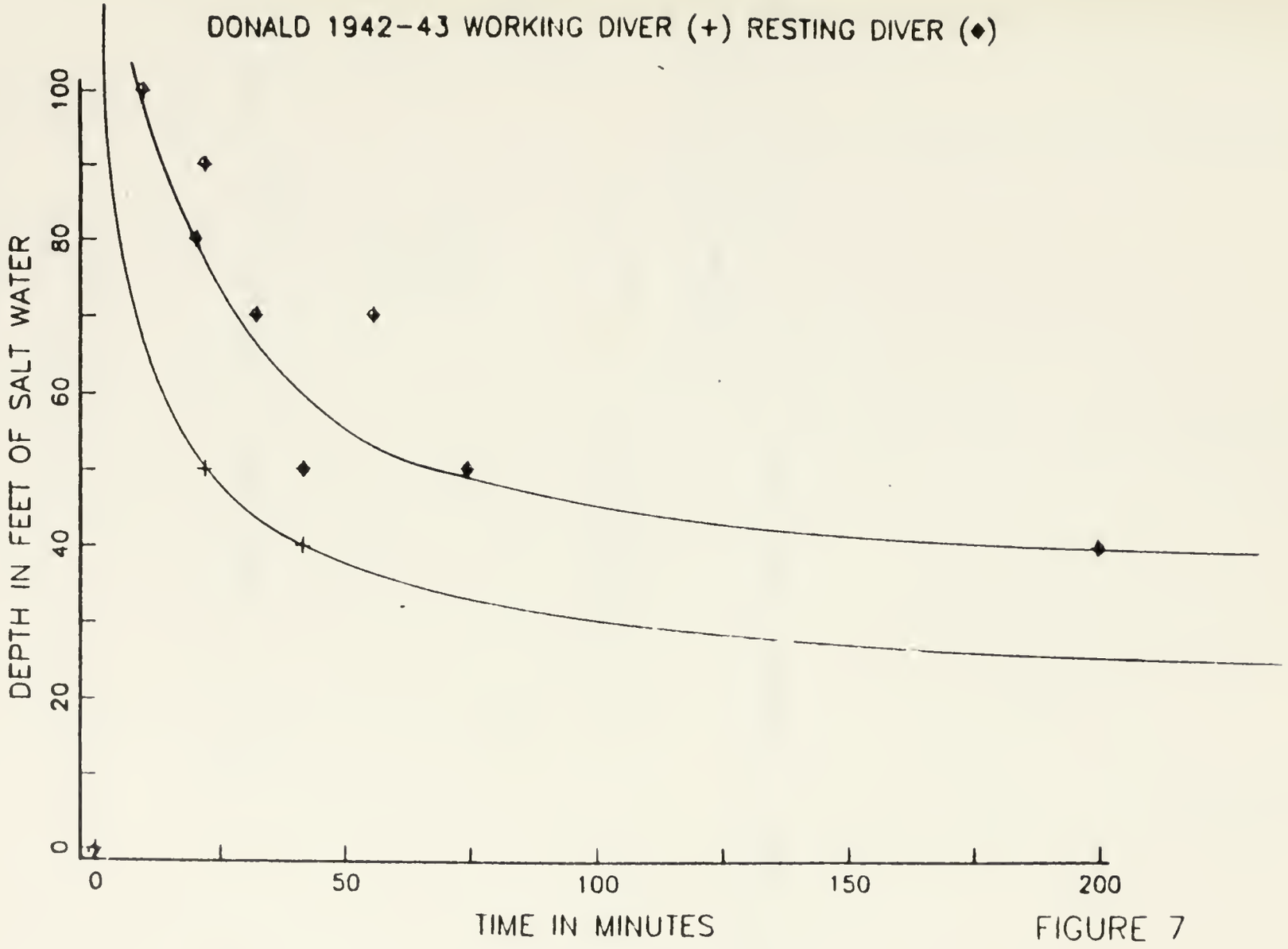

FIGURE 7

FIGURE 7

FSW	PROJECTED CURVE	FITTED CURVE
20	---	---
30	113.0	160.0
40	42.0	42.0
50	22.0	19.3
60	12.0	11.0
70	7.2	7.2
80	5.0	5.0
90	3.5	3.8
100	3.0	2.9

Figure 8 is a plot of the old and new projected curves with the fitted curve based on

$$\overline{T}(\text{depth}) = C/(\text{depth}-D_0)$$

where:

$C = 13{,}655$

$D = 20$ FSW

$\nu = 1.93$

Let's compare the results of this model with that for a non-working diver. Let:

$D = 20$ FSW

$\nu = 1.93$

$C = 13{,}655$

$t = 20$ minutes

depth = 85 FSW

FITTED CURVE FOR THE WORKING DIVER

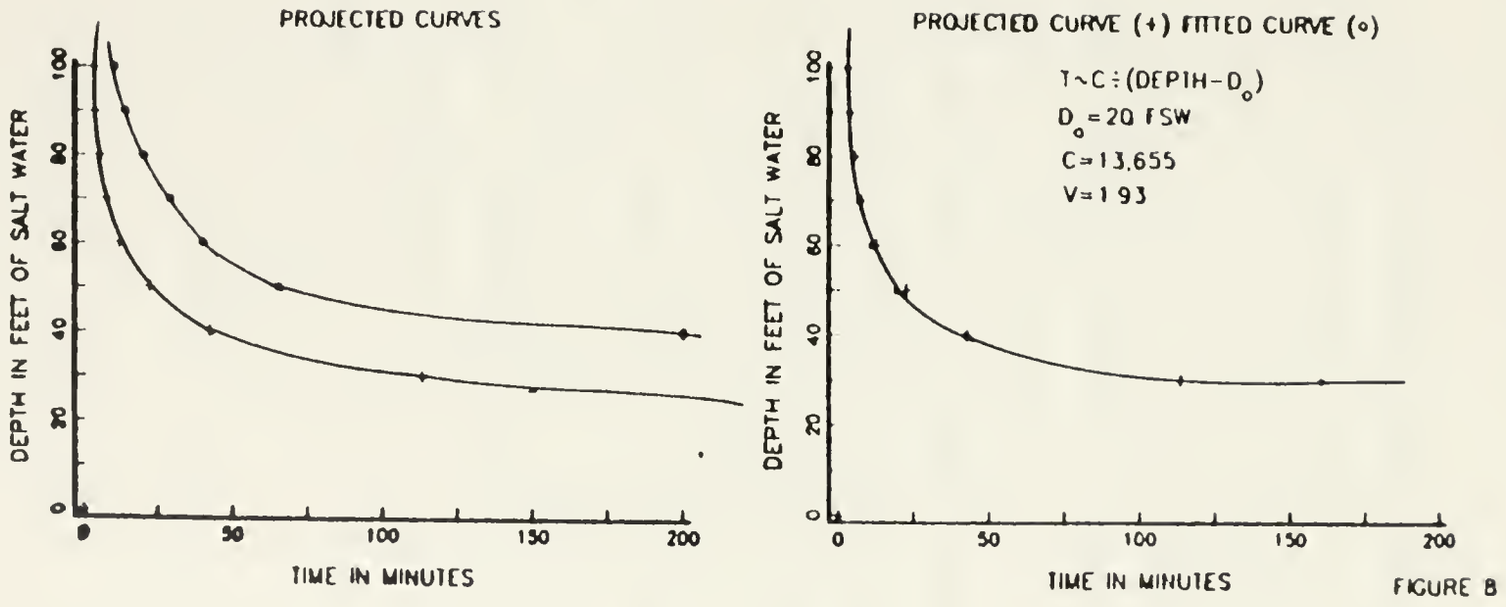

FIGURE 8

$$R(20) = EXP[-\frac{(85-20)^{1.93}}{13,655}(20)]$$

$$= e^{-.231(20)}$$

$$= .0098$$

So the probability of mission success under these conditions is .98% and the probability the diver X gets a hit is about 99%. This compares to $R_{85}(20)$ = 24% for the resting diver.

To this point the analysis and subsequently the predictive models have been based on Donald's experiments conducted in the early 1940's. This is due to the fact that Donald conducted the largest series of human experiments to date. Since that time the Navy Experimental Diving Unit has conducted human experiments but nothing on the scale of those conducted by Donald. In the main, experiments since Donald have been attempts to probe the limits of the tolerance curve of working divers and as seen from Table 3 have not produced results similar to Donald. Most $\hat{MTTS}$ values are considerably larger indicating the tolerance curve is not so restrictive as those we have developed thus far. The question arises, "What could account for such a disparity?" One possibility to be considered is that the breathing apparatus used by Donald was not as efficient as those used in later experiments and accordingly the PPO2, PPCO2, PPN2 and breathing resistance were not equivalent to those of later experiments. Higher levels of CO2, N2 and more breathing resistance might account

TABLE 3

MEAN-TIME-TO-SYMPTOM USING THE CENSORING TECHNIQUE FOR DIVERS UNDERWATER PERFORMING WORK

FSW	EXPERIMENTER	$\hat{MTTS}$	AVERAGE	MOST RESTRICTIVE
20	BUTLER	1016	1447	1016
		1850		
		1475		
25	BUTLER	471	780.2	405
		732		
	LANPHIER	405		
	PIANTADOSI	1318		
		975		
30	BUTLER	3322 min., no hits		
	YARBROUGH	2151	2458.5	627
		2007		
	LANPHIER	627		
35	BUTLER	470.1	254.95	39.8
	LANPHIER	39.8		
40	BUTLER	593	231.4	41.5
		83.6		
		72.0		
	YARBROUGH	294		
		447.67		
	LANPHIER	88.25		
	DONALD	41.5		
45	LANPHIER	37.5	37.5	37.5
50	LANPHIER	29.6	305.2	21.9
	BUTLER	864		
	DONALD	21.9		

for this disparity. This hints at the need for human experiments with elevated levels of CO2, N2, increased breathing resistance, and other introduced variables to isolate the major factors. The huge variation in MTTS across experimenters indicate that some unstudied variable is indeed very important. Moreover, Donald's experiments are consistent as a group implying the type apparatus and its associated effects, temperature, CO2, N2 or metabolic rate as a function of work rate and temperature are the prime candidates for study. At face value the major variables appear to be PPO2, PPCO2, PPN2, and metabolic rate, where metabolic rate is a function of work rate, apprehension, water temperature and other variables. Such factors as breathing resistance, age of the diver, body fat, blood factors, urine factors, exact time to symptom, and seriousness of symptom should be recorded. Ideally all dives should be carried to a decisive end-point.

Table 4 is an attempt to find the asymptote for the tolerance curve for working divers (50 watts). Many of the dives conducted by Butler were variable profile dives, many of which involved long dives at 20 FSW prior to an excursion to a deeper depth. If one aggregates these dives (using the initial part of the variable depth profile) an MTTS = 2641.88 minutes can be derived. This is well beyond the limits of pulmonary toxicity but serves as an ideal anchor for projecting a curve and gives credibility to the assumption that the asymptote is approximately 20 FSW. It follows that $\hat{\gamma}$ = .0003785 and accordingly the probability of a hit at 20 FSW is

TABLE 4

AGGREGATED EXPOSURES AT 20 FSW FOR EXPERIMENTS CARRIED OUT BY BUTLER AT NEDU

DIVERS		TIME OF DIVE		TIME OF HIT		TOTAL TIME	NUMBER OF HITS
19	×	120 min	+	5	=	2285	1
11	×	240	+	30+147+45+236	=	3098	4
16	×	120			=	1920	0
19	×	120			=	2280	0
16	×	240			=	3840	0
18	×	120			=	2160	0
22	×	240	+	24+138+110	=	5552	3
						21,135	8

The aggregated total exposure at 20 FSW equals 21,135 minutes during which 8 toxic episodes occurred.

$$\overline{T}_{(censored)} = 2641.88$$

$$1 - R_{20}(t) = e^{-.0003785(t)}$$

time	PROBABILITY OF A HIT AT 20 FSW
60	2.2%
120	4.4%
180	6.5%
240	8.6%
300	10.7%

Hit in this case does not mean convulsion but the symptoms as reported by Butler as probable and definite toxic episodes. Although not precursors of a convulsion these symptoms are indicative of the imbalance in the oxygen processes of the human body induced by the changes in atmosphere. A conservative curve would certainly pass through this point.

Let us develop one more model using the best guess hypothesis. Postulate that the diver's apparatus (SCUBA) is working efficiently and that divers control their work rate perfectly (a smooth even work rate of about 50 watts). From Table 3 our best guess of what the divers could reasonably attain might be as follows:

FSW	OBTAINABLE MTTS	FITTED CURVE
20	2641	---
30	1000	939.9
40	350	357.0
50	150	168.0
60	85	91.5
70	50	54.43
80	35	34.82
90	25	23.44
100	17	16.45

Figure 9 is a plot of these new curves where DEPTH = slope $\times \hat{MTTS}$ to the power of m, i.e.,

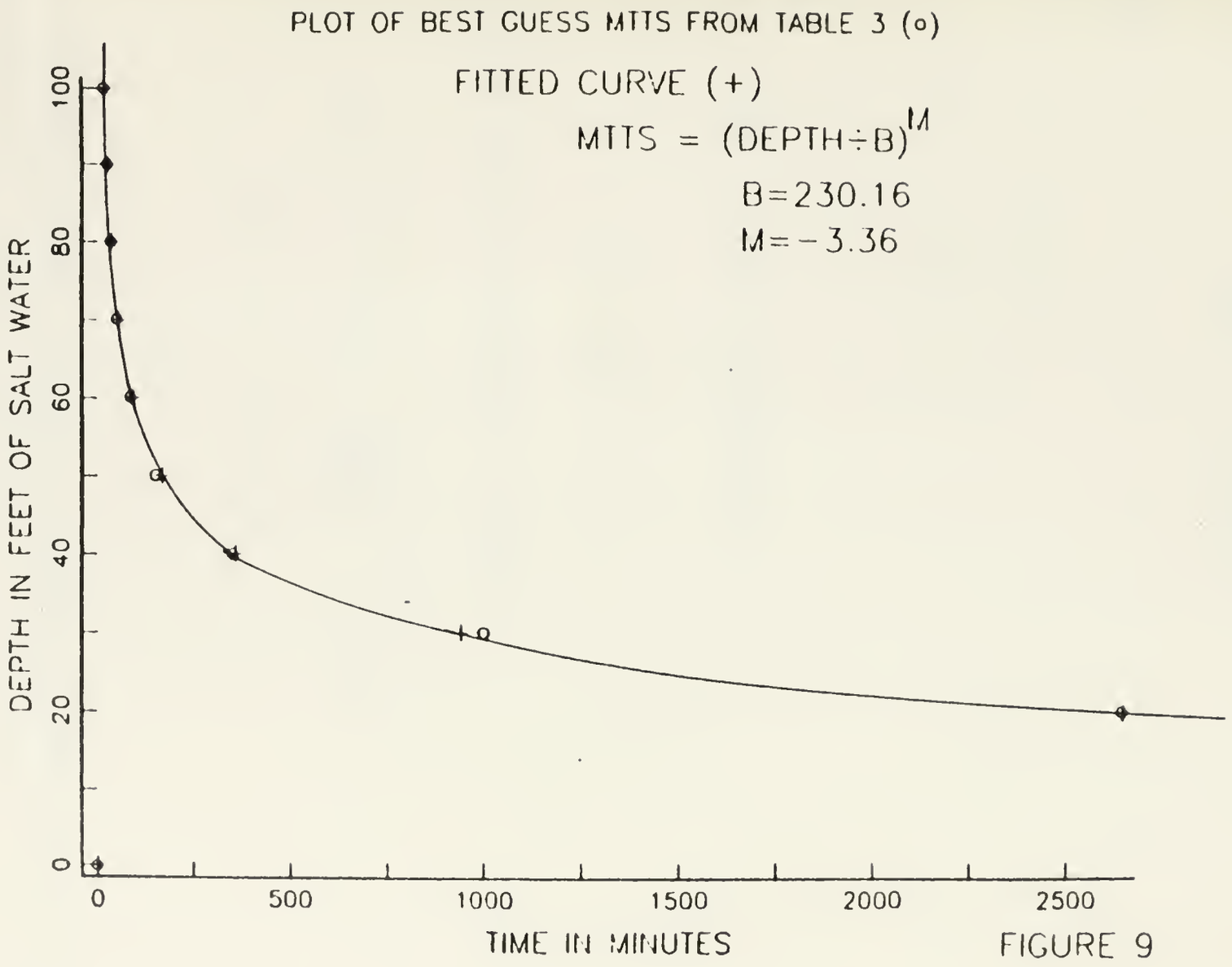
PLOT OF BEST GUESS MTTS FROM TABLE 3 (o)
FITTED CURVE (+)
MTTS = (DEPTH÷B)^M
B=230.16
M=-3.36
DEPTH IN FEET OF SALT WATER
0
20
40
60
80
100
0
500
1000
1500
2000
2500
TIME IN MINUTES

FIGURE 9

$$D = b(\hat{MTTS})^{m}$$

has been fitted to the projected curve. It follows that,

$$\hat{MTTS} = (D/b)^{1/m}$$

where:

$$b = 230.16$$

$$1/m = -3.36$$

Now

$$R(t) = EXP[-\frac{1}{(D/b)^{1/m}}(t)]$$

$$= EXP[-(\frac{b}{D})^{1/m}(t)]$$

Let t = 20 minutes and depth = 85 FSW.

$$R_{85}(20) = EXP[-(\frac{230.16}{85})^{-3.36}(20)]$$

$$= e^{-.03519(20)}$$

$$= .4946$$

Thus the probability of mission success is about 49% and the probability that diver X gets a hit is about 51%. Let t = 60 minutes at a depth of 30 FSW. Then

$$R_{30}(60) = EXP[-(\frac{230.16}{30})^{-3.36}(60)]$$

$$= e^{-.00106(60)}$$

$$= .938$$

Here we have the probability of a successful mission for one hour at 30 FSW at 93.8%. This curve is for a well trained diver whose equipment is working perfectly. His chances of a hit is only about 6.2% including symptoms which are not abortive.

Let's examine 120 minutes at 30 FSW.

$$R_{30}(120) = EXP[-(\frac{230.16}{30})^{-3.36}(120)]$$

$$= e^{-.00106(120)}$$

$$= .88$$

III. DISCUSSION

Observation is the basis of our understanding of the world around us. But observation only provides information about the specific events which we observe: alone, it provides little help for dealing with new situations. Useful knowledge results from our ability to recognize similarities in different events, isolate the important factors, and generalize from our experience. Roughly speaking, a model is an analogy for some real-world phenomenon or process we wish to characterize. Based on our observations a mathematical model characterizes the phenomenon in a mathematical structure which ideally represents everything that is important about the phenomenon or process and ignores everything else. It is difficult to realize this ideal because often we are not sure what aspects of the real-world are important. Our goal has been to provide a basis for a reasonable and fruitful correspondence between the observed phenomenon of oxygen toxicity in man and the mathematical structure which we have used to represent the phenomenon. The objective of this study was to integrate the known data points to generate oxygen tolerance curves in terms of depth-time limitations. This was done by applying a known mathematical model and extrapolating to new conditions. To accomplish this, certain simplifying assumptions were made to make the mathematics tractable and

understandable. For the sake of clarity these assumptions are listed below.

A. ASSUMPTIONS

1. There is a distribution of times-to-serious-symptom. This distribution looks gamma with a conspicuous build-up of hits followed by a long drawn-out tail. If one considers the time required to press the diver to depth and truncates this part of the empirical distribution curve, then the times-to-serious-symptom is plausibly exponential. Therefore, the exponential distribution provides a reasonable fit to the failure time distribution for a fixed depth.
2. Given that the exponential distribution is assumed as the distribution of times to serious symptom, then for a given depth the parameter for this distribution can be estimated by $1/\hat{MTTS} = \hat{\gamma}$, which is a composite value of the effects exerted by all the variables important to the distribution. By computing $\hat{MTTS}$ for the experiments which have been performed, and grouping those experiments for which commonality can be assumed, one can project a curve from which a value of $\hat{\gamma}$ can be predicted for any depth.
3. We have assumed that the phenomenon of oxygen toxicity is well behaved allowing us to hypothesize about the shape of the curve between data points. This

assumption allowed us to project the curves used in this study.

4. We have assumed that the integration of the distribution of times-to-serious-symptom for a given depth is too complicated a process for a model based on the given data, and that we could develop a simple formula in terms of depth and time which is equivalent to this integration, the value of which is a composite value of all the variables expressed in the curve. Such a formula provides a reasonable approximation to the value that would be obtained from the integration of this unknown distribution.

5. We have assumed that the major factors in the oxygen toxicity phenomenon are depth, time and work. The major factors are probably PPO2, time and metabolic rate. However, past experiments have not provided data precise enough to derive these factors from depth and work rate. Moreover, values for PPCO2, PPN2, and work rate were unfortunately not always recorded. At the very least, future experimenters should attempt to measure and record these variables.

6. By serious symptom we mean a toxic episode which would lead to the abortion of a dive. Many of the symptoms used in this study may not have been this serious. However, not knowing the degree of impairment associated with the reported hit, this author chose to be

conservative and use the symptom that ended the experiment as a serious symptom. Being a Naval Special Warfare diver the author is fully aware of the conservative nature of this approach. When the dive is long and cold, and many dives have already been performed, sometimes the fastest way to the bar is not the best way for the experimenter or statistician. This builds a conservative factor into the models automatically.

7. We have assumed that a dive profile can be thought of and modeled as a dive to a specified depth followed instantaneously by a dive to another specified depth and so on, thereby suggesting that a dive profile can be modeled as a series of connected, but independent dives. This assumption may be hard for some to accept, namely that the performance of any one component dive does not affect the probability of success of any other component dive. The feeling is that there must be some sort of cumulative oxygen dose that one builds up. However, if one assumes a series of dives, as we have, there is indeed a cumulative effect in that the probability of a successful dive profile is the product of the individual component dive probabilities.
8. Individual variation can be described by the normal distribution. Statistical theoreticians have noticed that the variance associated with complex behavioral and biological phenomena is often approximately normally

distributed. Moreover, any time a phenomenon is dependent upon a number of underlying factors, the phenomenon itself will be normally distributed, regardless of the shape of the underlying distributions. This appears to be the case in oxygen toxicity. Donald tested the same man on 20 separate occasions and found a huge variation in the time-to-symptom. What the underlying factors are remain to be discovered and are probably the key to developing an accurate tolerance curve. However, if one assumes that there is a time about which there are equally distributed, the same number of hits for a given depth, then normality is plausible, and indeed more than likely. What we see in the aggregate of individuals does not look normal but gamma. We can still assume normality for individual variation and exponentiality for the aggregation of all divers because some individuals appear to be more tolerant than others to higher than normal partial pressures of oxygen.

B. RESULTS

We were able, given the above assumptions, to mathematically model the reported incidence of oxygen toxicity. The probability of mission success, which here is defined as the probability the diver can accomplish the dive profile without a toxic episode of such a degree as to abort the dive, was

modeled as

$$R(t) = e^{-\int_0^t f_T(t)\,dt}$$

where $f_T(t)$ is the distribution of times to symptom. The models developed herein were not cross validated: testing and further development of this approach must await further studies in oxygen toxicity.

Many investigators will feel uncomfortable with this statistical black-box approach to oxygen toxicity, and it is understandable that one desires a precise physical concept as an anchor. These preliminary results merely show that the use of a mathematical model may provide a means to deal with the variance associated with oxygen toxicity. Such models transcend the tested profiles and should improve the precision of estimating toxic episodes and allow the associated risk to be evaluated.

It is stressed that the applicability of probability theory to oxygen toxicity has not herein been proven, but a serious study based on animals treated in such a fashion could demonstrate the usefulness of such models and could provide some useful parallels. Moreover, if future researchers test for and record all the major variables, statistical analysis may provide more accurate models incorporating water temperature, work rate, PPN2, PPO2, PPCO2, and human factors such as age, percent of body fat, experience, etc. Until such time as the

physical concept is discovered or an accurate mathematical model is developed, we will continue to operate on trial and error tables which are rules analogous to the old 30-feet for 30-minute rule. Moreover, a few chance hits, due to the variability involved, may preclude the use of profiles which are useful, to the prescribed degree of safety, and which are needed by the fleet.

IV. CONCLUSIONS

Central Nervous System (CNS) oxygen toxicity in man is characterized by wide individual variation and diverse symptoms. And although the deleterious effect of oxygen under pressure has been recognized for almost a century, the mechanism(s) by which high pressure oxygen produces convulsions or other toxic manifestations remains unresolved. Several theories have been suggested to explain the cause of CNS oxygen toxicity, but no single hypothesis has received universal acceptance. This study attempts to determine the shape of the tolerance curve by statistical analysis of the existing data base.

Statistical theoreticians have noticed that the variance associated with complex behavioral and biological phenomena is often approximately normally distributed. Moreover, any time phenomena are dependent upon a number of underlying factors (which appears to be the case with oxygen toxicity). The phenomenon itself will be normally distributed, regardless of the shape of the underlying distributions. With this normality assumption applied to individual variability, and the time-to-serious-symptom assumed to be exponentially distributed, this study develops oxygen tolerance curves in terms of depth-time limitations.

By applying a known distribution to the time-to-serious-symptom, mathematically predictive models have been developed

which allow a greater degree of predictability in mission profiles while concomitantly allowing the associated risk to be evaluated in terms of probability. This is one of the major objectives of mathematically modeling any phenomenon.

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