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Physics and The Health Sciences

Andrew P. Whipple
Taylor University

Festschrift

Honoring

Elmer N. Nussbaum

Elmer and Ruth Ellen Nussbaum
at the naming of the
Nussbaum Science Center

Festschrift Honoring
Elmer N. Nussbaum

PHYSICS AND THE HEALTH SCIENCES

contributors

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PREFACE

"I stand on the shoulders of giants."

Sir Isaac Newton

This festshrift is assembled in honor of Professor Elmer N. Nussbaum upon the occasion of his retirement from Taylor University, and is comprised of several talks delivered at Taylor in the fall of 1984 as a symposium, "Physics and the Health Sciences". As Newton gave credit to those who preceeded him, so now do students and colleagues of Dr. Nussbaum acknowledge his shoulders - intellectual, spiritual, and personal - in this volume. The four symposium presentations recorded here evidence the impact Dr. Nussbaum has had, and continues to have, in the lives of his associates. Each paper is primarily a work in the area of the health sciences, and each is based upon the principles of physics. Each writer pays tribute to Dr. Nussbaum not only by demonstrating competence and accomplishment in his chosen area of science, but also by stating his indebtedness to Elmer spiritually and personally. Dr. Brain and Dr. D. Randall each review a portion of his own work in scientific research paper format, yet each purposefully has directed his presentation toward the undergraduate student, using original research results as a pedagogical tool to demonstrate the workings of science to the student. Dr. Lee presents an overview of certain aspects of molecular biology, an area in which he is

actively researching, and thus reminds us of Dr. Nussbaum's great interest in imparting current scientific findings to his undergraduate audience. Dr. W. Randall's talk is rather a hybrid of these approaches with the additional exposition of his understanding of the interplay of science and the Christian faith.

> "I cannot believe that God plays dice with the world."
>
> Albert Einstein

Science has its origins in a Judeo-Christian understanding of the world, in which space and time, matter and energy are consistent and predictable. That is the way God and his creation are depicted in scripture, and the methodology which is science depends on such order. Many modern scientists, seduced by the power of the scientific method, have forgotten their philosophical and in fact religious roots. Those scientists honest enough to face science's essential nature admit to there being more to reality than the physical realm, and some are even humble enough to name the creator and sustainer of the universe, even if from an incomplete understanding of whom they speak. How much more fully do those scientists who comprehend the relationship of the creator to the created truely understand the physical world as revealed through the processes of scientific inquiry, and the work in this volume exemplifies this world view.

> "Humble yourselves in the sight of the Lord, and he shall lift you up."
>
> James 4:10

This volume contains the words of men who, while laboring in the realm of science, have gone

one step further in attaining a more complete understanding of reality by personally accepting the claims of Jesus Christ as Lord and Savior upon their lives. A common thread in these scientists' Christian experience is the model that Elmer N. Nussbaum has been for them in humbling ones self before God, thus permitting the Lord a central position in their lives and work.

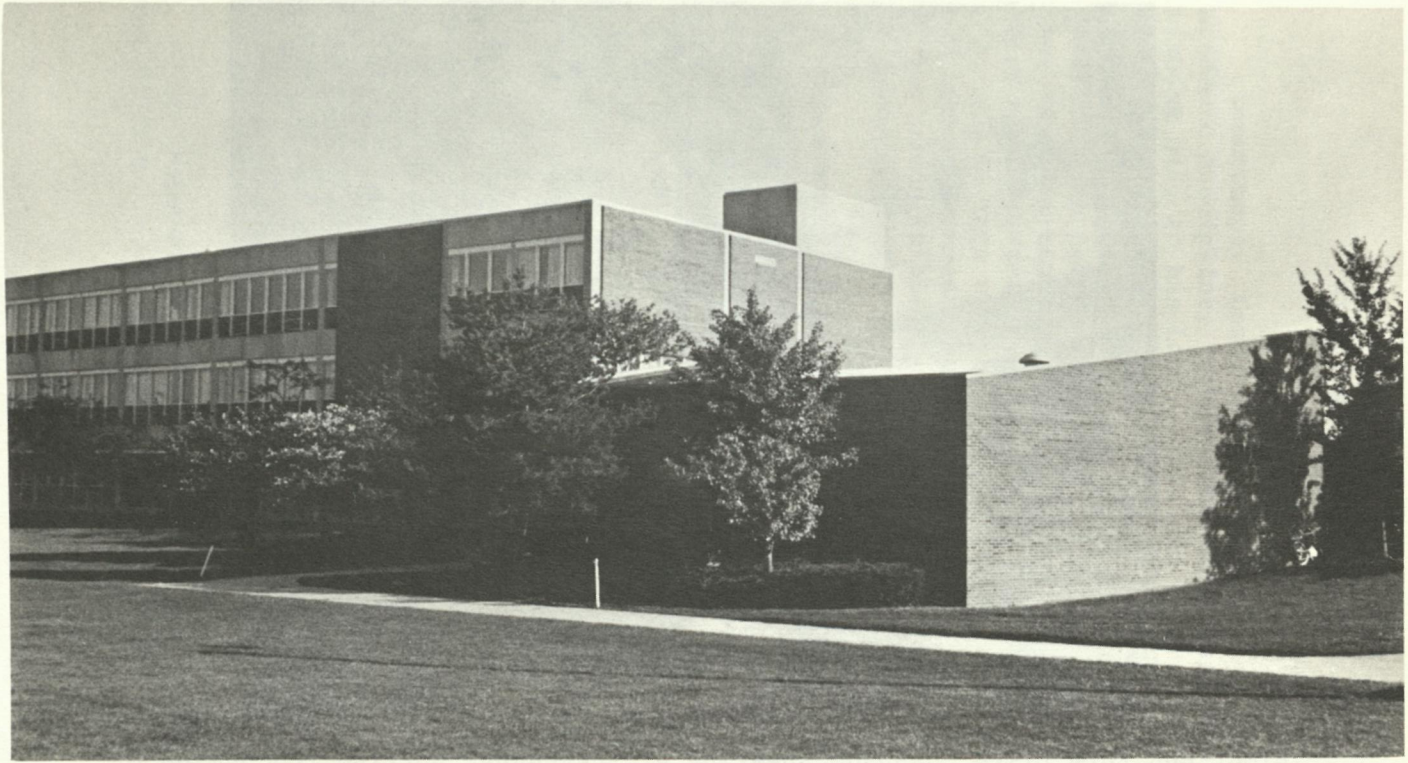
A compilation of letters from students and colleagues was assembled and presented to Dr. Nussbaum by Robert Wolfe, former student and fellow Taylor Physics professor, at a retirement dinner in the spring of 1985. Excerpts from some of these letters are also presented in this volume and the reader is directed to them for a less formal and more personal commentary on the person and career of Dr. Elmer N. Nussbaum.

It has been this editor's exceeding good fortune to be associated with Dr. Nussbaum, if only for a short period of time, and I feel confident that I would not be misrepresenting the views of the many contributors by suggesting that the tributes and accolades here presented by mortal humans might be considered a preface to our heavenly Father's ongoing and future words to Elmer,

"Well done, thou good and faithful servant."

Matthew 25:21

Andrew P. Whipple
Upland
August 1985



The Nussbaum Science Center, Taylor University.

Elmer and Ruth Ellen Nussbaum speaking at the chapel marking the naming of the Nussbaum Science Center.

Commitment. Commitment to his family, to his academic discipline, to his alma mater, and underpinning all, to his Lord. Thus can Elmer Nussbaum's long-time association with Taylor University be explained. Commensurately gifted individuals generally aim for and achieve worldly acclaim, for that is their commitment. Elmer Nussbaum has received that acclaim, probably in lesser measure than had he made that his life's goal, but his aim and his achievements have been directed towards a higher plane in his commitment to his Lord's work at Taylor University.

Born second of the seven sons of Samuel and Margaret Nussbaum, Elmer grew up on the family farm in Adams County, Indiana in the German-Swiss community centered about the town of Berne. Graduating from Monroe High School and from Taylor (BS, 1949) with his graduate degrees from Ball State (MA, 1952) and the University of Rochester (PhD, 1957) completing his formal education, Elmer returned to Taylor as Head of the Division of Natural Sciences. A 1963 world tour under the auspices of the International Atomic Energy Agency was the only significant absence from the Taylor campus since, although his role as Consultant (1960) and Senior Scientist (1962) with the Oak Ridge Associated Universities has taken him and many Taylor students to Oak Ridge repeatedly. Elmer, with the mobile nuclear science laboratory, has visited many other colleges in his role as ORAU visiting scientist.

Dr. Nussbaum's interest in things scientific was evident in his intrigue with the farm

generator and with early attempts at home wiring, and foreshadowed the electronic nature of his courtship of Ruth Ellen Shugart while both were students at Taylor. A private telephone line between their dorm rooms was one extracurricular utilization of physical principles exemplifying the whimsical and creative character of the man destined to be her husband; one Friday night in 1948 Ruth Ellen had an even more memorable demonstration that physics is fun. After being escorted to a seat at one end of the Taylor physics lab, she spotted an illuminated heart at the opposite end of the lab. A doll, suspended from a wire, popped from beneath the heart and slid across the room, delivering an engagement ring to a most surprised Miss Shugart. Many years of service at Taylor, and the auspicious occasion of groundbreaking on November 29, 1965 for the Science Building now bearing his name did not deter Elmer from again injecting an amusingly creative use of electronics on the Taylor campus. Four series of push buttons were wired to dynamite charges planted at the four corners of the building site, and as each was set off by dignitaries pushing the buttons clouds of purple and gold colored flour rose to salute Taylor's colors and the imagination of Dr. Nussbaum. The event also saluted Elmer's resourcefulness and understanding of experimental equipment, as another physics professor, Roger Roth, was secretly planted with backup firing controls in the event the primary system failed.

As a student at Taylor honors came to Elmer in several forms. He had the highest grade average in the student body and earned

the All College Scholarship in 1947 and the Alumni Scholarship in 1948. As a senior he was hired to teach general physics and Don Odle, Taylor basketball coach and history professor, recounts using Elmer's test as a key for grading the other tests. Four listings in Who's Who and 14 articles in professional journals attest to Elmer's continuing scholarship, as do his travels to 25 states and 4 countries in an official capacity to direct training in radiation biology and health physics. A recent sabbatical leave at Oak Ridge was occupied with research on the detection of single atoms. Honors continue to come Elmer's way, most recently in the naming of the science building the Nussbaum Science Center on November 4, 1984. A special chapel, as well as ceremonies at the building itself with President Lehman and other dignitaries present, marked this event, as did the symposium this festschrift records.

This volume bears witness to the many academic offspring Elmer has nurtured, and this volume would be incomplete without including four of them, Paul, Kathleen, Sonja, and Mark Nussbaum, the children of Elmer and Ruth Ellen. Paul, a graduate of the Ball State School of Journalism, works for the Philadelphia Inquirer. Kathleen, a Taylor biology graduate with a Masters in Library Science from Ball State, is reference librarian at the public library in Mansfield, Ohio. Sonja Nussbaum Oetzel graduated from Taylor, then from the University of Illinois with a Masters degree in mathematics, and presently is a math professor at the University of Northern Colorado. Mark, a Taylor chemistry graduate is currently pursuing his doctorate in chemistry at the University of Illinois.

Elmer and Ruth Ellen continue to reside just off campus in their Wright Avenue home and from there Elmer can be seen to sally forth, bicycle for transportation and Greek sailor's cap for protection from the elements, still influencing those round about him reminding us of his commitments, expecially to Taylor and to our Lord, Jesus Christ.

The honors continue: As we go to press, Dr. Nussbaum has been awarded (October 26, 1985) the Legion of Honor, the highest honor bestowed by the Taylor University Alumni Association. The four earlier recipients are Milo Rediger, Harold Ockenga, Ted Engstrom, and Don Odle, thus placing Elmer in an exceedingly select group of fine Taylor alumni to be so honored. In addition, Dr. Nussbaum was elected a Fellow of the Indiana Academy of Sciences at its annual meeting (November 15, 1985).

Ground breaking for the new science building. Elmer Nussbaum at the leftmost push button and a cloud of flour and dust in the distance as the charge goes off.

Elmer Nussbaum,
Taylor Senior, 1949

David C. Randall

Dr. Randall graduated from Taylor University in 1967 as a combined physics and chemistry major. He received his Ph.D. degree from the University of Washington in physiology and biophysics. He taught at John Hopkins University Medical School before going to the University of Kentucky where he currently is Associate Professor of Physiology at the School of Medicine. His research interests include studies of the nervous control of the heart during periods of behavioral and environmental stress.

A STUDY OF THE CARDIOVASCULAR EFFECTS OF TOLBUTAMIDE, AN ORAL HYPOGLYCEMIC AGENT FOR TREATMENT OF OF DIABETICS: ONE EXAMPLE OF HOW TO PURSUE A SCIENTIFIC PROBLEM[1]

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ABSTRACT

Tolbutamide is a drug which is given to patients with diabetes mellitus to increase secretion of insulin from the β-cells of the pancreas. In addition to this desirable therapeutic effect, we show that it also produces an unwanted side effect: increases in arterial blood pressure. This paper also tests a series of hypotheses to determine the underlying physiological mechanism responsible for this pressor effect. Our results indicate that tolbutamide potentiates the tendency of normally occurring hormones within the body to cause constriction of the

[1]Supported by NIH Grant HL 19343 to the Department of Physiology and Biophysics, University of Kentucky Medical Center.

resistance arterioles of the peripheral circulation.

ABBREVIATIONS

Blood Pressure	BP
Cardiovascular	CV
Epinephrine	E
Heart Rate	HR
Left Ventricular Pressure	LVP
Norepinephrine	NE
Total Peripheral Resistance	TPR

INTRODUCTION

Although this paper presents data on the cardiovascular (CV) effects of a drug called tolbutamide, the principal objective is to illustrate a useful method of approaching a scientific question. Science proceeds by postulating and testing hypotheses in an attempt to more fully understand the lawful relationships linking naturally occurring events (1,2). The practitioner of this art - the scientist - typically builds upon previous knowledge to solve his or her own immediate question. This paper shows the process we used to elucidate the mechanism responsible for the increase in arterial blood pressure (BP) following administration of tolbutamide into the pulmonary artery.

Individuals suffering from the disease diabetes mellitus have an inadequate blood concentration of a hormone called insulin. Insulin permits the body to utilize glucose as an energy source by facilitating

cellular absorption of this simple sugar. Consequently, diabetic patients have an elevated blood concentration of glucose because it is not taken up from the blood into the various cells. The oral hypoglycemic agents, of which tolbutamide is an example, coax β-cells of the pancreas to secrete more insulin, thus counteracting the deficit. Like many drugs tolbutamide has side effects, reactions that are not related to its desirable therapeutic actions. Intra-venous administration of tolbutamide in animals increases BP, which may be an unacceptable side effect because many diabetic patients also suffer hypertension (high BP). The BP of these individuals should not be elevated further. Patients suffering from hyptertension have high incidences of morbidity and mortality. Studying the pressor (i.e., increase in BP) effect of tolbutamide is therefore a worthwhile project.

What is BP and why is it important physiologically? BP was first measured by the Rev. Stephen Hales (1677-1761) in 1733 in a horse. Rev. Hales inserted one end of a goose trachea (which he used because it was flexible) into a cut end of the animal's carotid artery; he affixed the other end of the trachea to a glass tube. He then determined that the horse's heart forced a column of blood 8 feet up the glass tube: the animal's BP was, therefore, 8 feet of blood. Contemporary scientific practice is to use the metric, rather than English, system; this conversion is easily made as follows:

8 ft. of blood x 12 in/ft. x 25.4 mm/in = 2438 mm of blood.

Finally, modern terminology defines BP as the height a heart would force a column of mercury (Hg); this is calculated by dividing the result obtained above by

the relative density of mercury to blood, which is 13.6. The animal's BP was therefore 180 mm Hg. (The normal BP is about 100 mm Hg. The horse's blood pressure was found to be very high, which illustrates another principle of physiology: stress tends to increase BP. This may be one basis of "essential hypertension" - high blood pressure of unknown origin.)

This pressure is responsible for the flow of blood around the circulation, which can be expressed mathematically as follows:

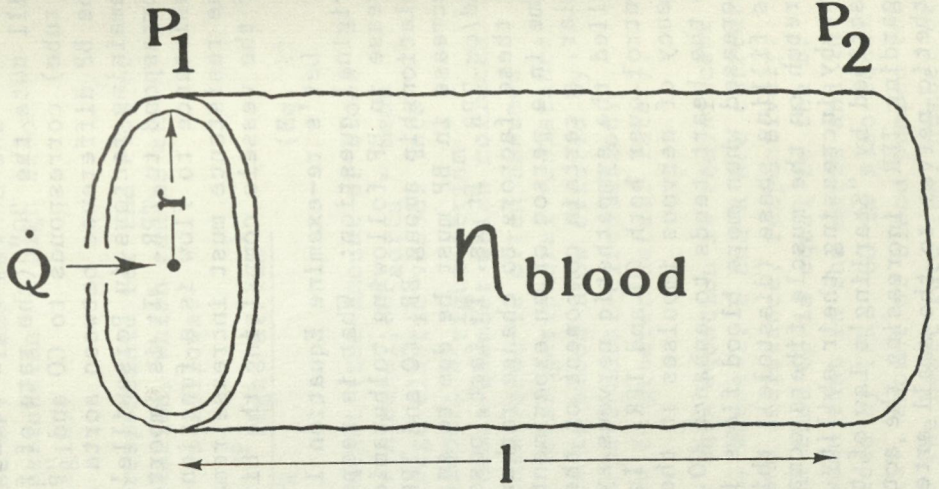
$$CO = \frac{(BP_{aorta} - BP_{right\ atrium})}{TPR} \qquad \text{(Eq. 1)}$$

where: CO = cardiac output (the amount of blood pumped by the heart per minute); BP_{aorta} = mean BP at the aorta (the large elastic vessel into which the heart pumps blood); $BP_{right\ atrium}$ = BP at the atrium (the heart chamber which collects blood from the body; this value is often assumed to be zero); and TPR = total peripheral resistance (the overall resistance to blood flow offered by all the vessels of the peripheral circulation, which will be explained in greater detail later).

You may note that this equation is reminiscent of Ohm's Law: $I = E/R$, where I, E and R are current, potential difference and resistance, respectively. Correspondingly, recall that CO is equal to the BP difference (i.e., between that in the aorta and in the right atrium) divided by TPR. CO is also equal to the stroke volume (SV, amount of blood pumped for each heart beat) times the heart rate (HR, number of heart beats per minute). TPR is the hydraulic analogue of electrical resistance. A French physio-

logist and physicist named Jean Poiseuille (1799-1869) formulated the relationship between pressure, flow (Q), resistance, viscosity of blood (η) and the length and radius of a tube; this mathematical relationship is called "Poiseuille's Law" (Figure 1). If you compare the terms of Poiseuille's equation to equation 1, you will note the "Q" (the rate of fluid flowing through a tube) corresponds to CO and "$P_1 - P_2$" corresponds to the BP difference between aorta and atrium. The remaining factors in Poiseuille's Law must, therefore, correspond to TPR. It is important to note that the resistance to flow is a function of r^{-4}; therefore, the resistance must increase remarkably as the radii of the vessels comprising the circulation decrease.

Let's re-examine Equation 1 in light of our original question: What is responsible for the increase in BP following tolbutamide injection? The relationship among BP, CO and TPR insists that an increase in BP must be due to an augmentation in CO and/or TPR. It is, in fact, possible for one or both of these factors to change rather remarkably over time in a person or an experimental animal. In particular, a certain component of the nervous system, called the sympathetic nervous system, exerts powerful control over both CO and TPR. Increasing the frequency of nervous impulses in the sympathetic nerves to the heart tends to enhance CO. CO is also increased when more blood flows into the heart during its filling phase (diastole); this increases the stretch on the muscle fibers comprising the organ, thereby increasing their ability to contract, as is described by "Starling's Law of the Heart" (3). Regarding TPR, increasing the activity in the sympathetic nerves to the small arterial vessels (called "arterioles") causes them to contract. This, in turn, tends to decrease the radii of these vessels, thereby



$$\dot{Q} = \frac{\pi}{8} \cdot \frac{(P_1 - P_2)}{\eta \, l \, r^{-4}}$$

Figure 1. Poiseuille's Law

(via the principle of Poiseuille's Law) increasing the resistance to flow. These nerves exert their effect on the vascular smooth muscle of the arterioles by releasing a chemical, or "neurotransmitter", from their endings called norepinephrine (NE). When NE is released, it diffuses to the arterioles and activates the α-receptors. This α-receptor activation causes the vascular muscle cells to contract. Administering a drug activation causes the vascular muscle cells to contract. Administering a drug which has α-blocker activity (eg., phentolamine), prevents this vasoconstrictor action of the sympathetic nervous system because the α-receptor activation is "blocked", or prevented.

We now have enough information to generate a simple possible explanation for the pressor effect of tolbutamide; this potential explanation is called an "hypothesis." We then design and perform experiments to prove or disprove the hypothesis (2). For example, we might ask if the increase in BP is due to an augmentation in CO and/or TPR. We could choose to hypothesize that "the increase in BP is due to an increase in CO with no significant change in TPR." (A more traditional procedure requires that we formulate a null hypothesis or "H_0" such as: the CO is not altered by tolbutamide administration.) We then design experiments to find out whether the CO is altered by tolbutamide administration. The most direct experiment would be to measure and compare the CO after tolbutamide, dissolved in saline, and saline (of the same volume) are injected into the subject's veins. After the hypothesis is confirmed or refuted based on the results of the experiment, we may progress to a new hypothesis and a new experiment.

Figure 2 shows the series of hypotheses that we tested; it constitutes the foundation around which this paper is built.

METHODS

Unless otherwise noted, all experiments were performed on fully conscious, adult mongrel dogs weighing between 17 and 29 kg. The animals were allowed free access to Purina Dog Chow and water. Food was removed for the period starting 12 hours prior to the surgical procedures described below. Successful pursuit of these experiments depends upon recent technological advancements for measuring the pressure inside the left ventricle (LVP) of the heart, arterial BP and the length of isolated segments of heart muscle (ie., myocardium) from small devices chronically implanted inside the subject's body. In particular, LVP was measured using an instrument (Konigsberg (P-19) containing a silicone chip that changes its ohmic resistance with changes in the applied pressure. The P-19, in turn, constitutes one arm of a Wheatstone bridge circuit. Devices of this nature have a pressure range of from ca. -300 to +300 mm Hg with a linearity and hysteresis of $\pm$0.5 (% full scale at 37°C) and a flat frequency response from DC to 2×10^5 Hz (4). The arterial BP was measured using an intravascular catheter connected to another pressure transducer located outside the animal. The segment length recordings from the myocardium were made using piezoelectric crystal pairs. One crystal is excited by a brief electrical impulse which causes it to oscillate for a short time at a very high (ca. 6 mHz) frequency. This oscillation causes a wave of

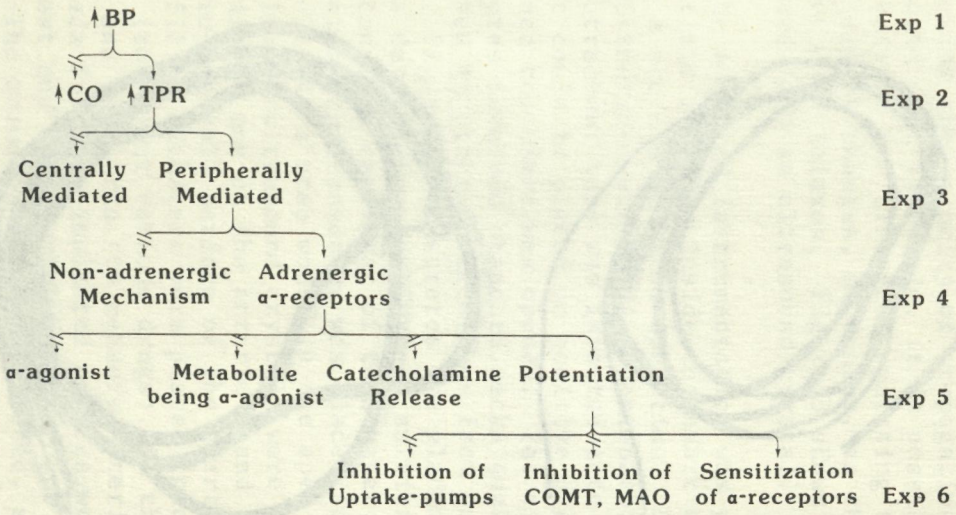


Figure 2. Schematic of hypotheses tested and results.

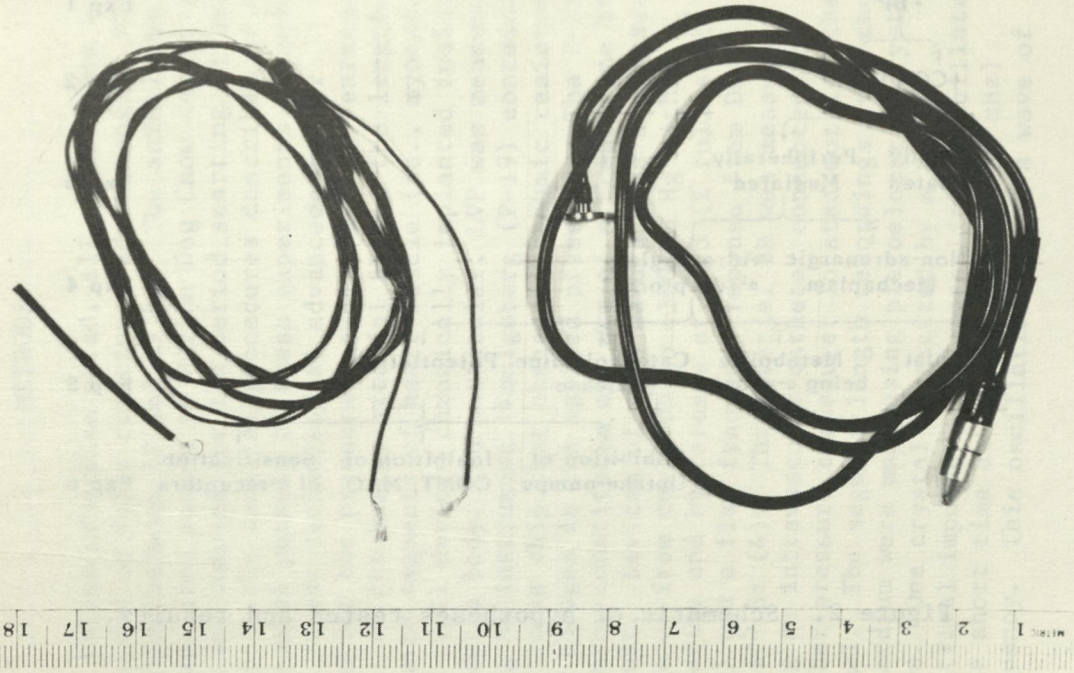


Figure 3. Konigsberg transducer and ultrasound crystal.

"ultrasound" vibration to propagate outward through the myocardium. This wave of mechanical oscillation impinges upon a second crystal located about 1 cm from the first, thereby exciting it. By measuring the time from the transmitted to received signal, and knowing the velocity of propagation of the ultrasound wave in muscle, it is possible to continuously compute the distance separating the 2 crystals (5). This distance changes, of course, as the heart muscle contracts and relaxes. Figure 3 shows the Konigsberg transducer and an ultrasound crystal.

The required instrumentation was placed in the appropriate location inside the heart and vasculature during a sterile surgical operation. Each animal was anesthetized with sodium pentobarbital (25 mg/kg). An endotracheal tube was inserted into its windpipe so that it could be placed on positive pressure ventilation once the chest was opened. The exact oeprative procedures involved standard techniques which are explained in other publications from our laboratory (6,7). Figure 4 illustrates the placement of the various devices in the heart in sufficient detail to understand the remainder of this paper. Note that the Konigsberg transducer was placed inside the left ventricle via a stab wound in the apex of the heart. Two pairs of ultrasound crystals were inserted into the myocardium: one on the anterior, and the other on the posterio-lateral, surface of the heart. In addition, fluid filled catheters were placed into the pulmonary artery (to inject various drugs), in the atrium (not shown) and the aorta (to measure arterial pressure). The leads from the implanted devices were exited from the chest and exteriorized at the nape of the animal's neck. The animal's chest was closed, sealed tightly and the normal intrathoracic negative pressure

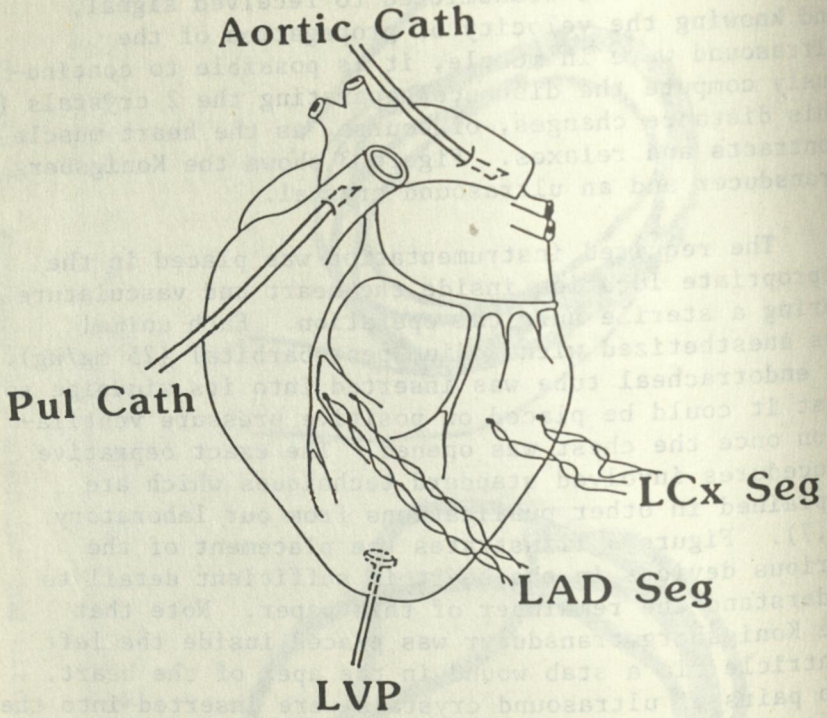


Figure 4. Instrumentation placement. Pul Cath, pulmonary catheter for drug injection; Aortic cath, aortic catheter for arterial pressure measurement; LVP, left ventricular pressure measured by a Konigsberg transducer; LAD Seg and LCx Seg, pairs of ultrasound piezoelectric crystals for measuring myocardial segment lengths.

re-established so that the dog could once again breathe naturally. The animal was then permitted to recuperate from the surgery for two weeks before being subjected to experimental manipulations. During this time the animal wore a light leather harness which protected the leads of the implanted sensors.

One important reason for using conscious animals in an experiment of this nature is because no anesthetic drugs are required. Anesthetics can otherwise interfere with the neural control mechanisms which are often the object of interest in an experiment. Conscious animals, however, do respond to even small changes in their environment; BP, CO and other CV variables may show marked variations. For this reason, all the intact animal experiments described in this paper were conducted while the dog was unanesthetized and kept in an isolation booth (8). Before any experiment was conducted, each subject was placed in the booth for two hours per day for five to seven days to adjust to the experimental environment. The various CV variables were recorded on a Beckman Model R polygraph located in another room via hard-wire electrical connections. The dog was also observed by closed circuit television.

In addition to continuous recordings of the BP, segment length and LVP, we also computed the first time derivation of LVP, or d(LVP)/dt. The d(LVP)/dt gives important information on how rapidly the heart is able to develop pressure (9). The rate of change in LVP is believed to be an index of the force of myocardial contraction, which also correlates with the SV. In addition, CO was determined by "dye dilution" techniques. More specifically, a special dye called "Cardio Green" (Hynson, Westcott and Dunning) was injected into the left atrium while blood was being continuously withdrawn from the aorta through an optical densitometer. Cardio

Green has a peak spectral absorption frequency at 800-810 millimicrons; for various reasons, this permits one to measure blood optical density changes due to differences in plasma dye concentration independently of changes in the relative balance of oxygenated vs. deoxygenated hemoglobin. The shape of the absorption curve over time changes as a function of CO. We used a commercial computer (Waters Instruments DCR 702A) to determine the CO at specific times during our study.

The exact protocols varied from experiment to experiment, and will be briefly reviewed in the "RESULTS" section where appropriate. In general, different doses of tolbutamide or saline were injected in random order after a one minute control period; the CV variables were monitored for 30 minutes after the injection. There were at least 24 hours between injections to keep the residue left in the body from the previous drug injection to a minimum. Other drugs were often given immediately before or after the tolbutamide. The dogs were removed from the chamber at the end of the experiment, fed, and returned to their home cages.

The data were recorded on a 8-channel magnetic tape as well as the strip-chart paper from the Beckman polygraph. The tape recordings were then analyzed in the computer facility of the Department of Physiology and Biophysics using a DEC PDP 11/23 for the necessary A to D conversions and computations. Using this equipment, we determined minute long averages for the value of each variable. Finally, the concentration of NE in a subject's plasma (blood with the erythrocytes removed) was determined using a radioenzymatic test (10). Appropriate statistical

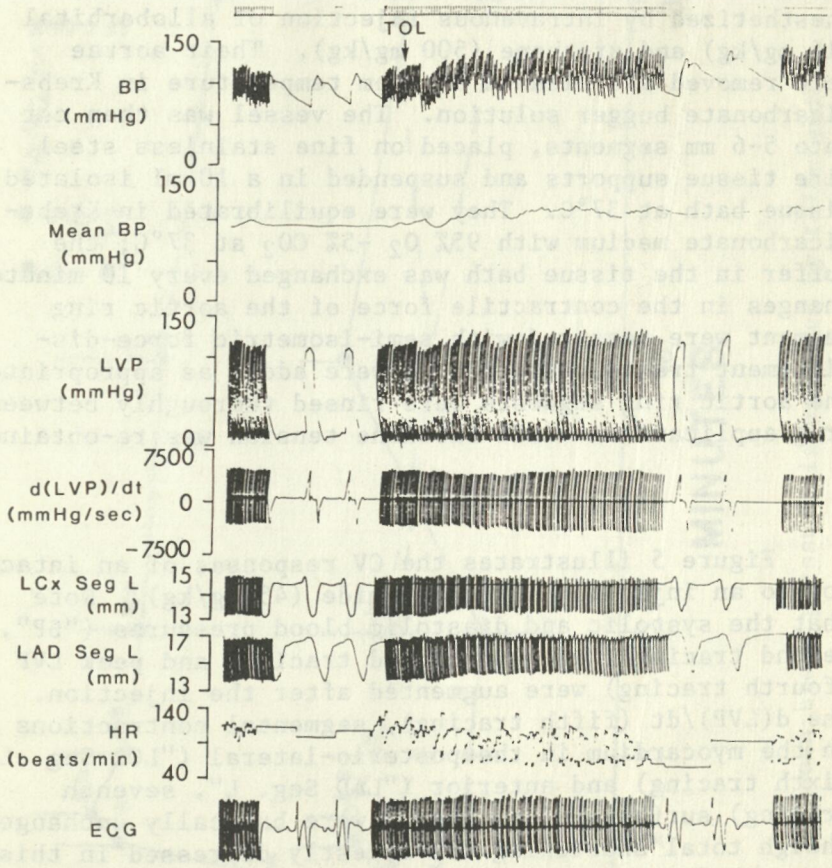


Figure 5. Cardiovascular responses to injected tolbutamide. The topmost tracing shows elapsed time.

tests, which included paired t-tests and analyses of variance, were used to analyze the results.

The paper also reports some *in vitro* studies using cat aortae. In these experiment, the animals were anesthetized by intravenous injection of allobarbital (15 mg/kg) and urethane (500 mg/kg). Their aortae were removed and cleaned at room temperature in Krebs-bicarbonate bugger solution. The vessel was then cut into 5-6 mm segments, placed on fine stainless steel wire tissue supports and suspended in a 10 ml isolated tissue bath at 37°C. They were equilibrated in Krebs-bicarbonate medium with 95% O_2 -5% CO_2 at 37°C; the buffer in the tissue bath was exchanged every 10 minutes. Changes in the contractile force of the aortic ring segment were measured with semi-isometric force-displacement transducers. Drugs were added as appropriate. The aortic ring segments were rinsed thoroughly between drug applications until baseline tension was re-obtained.

RESULTS

Figure 5 illustrates the CV responses of an intact dog to an injection of tolbutamide (45 mg/kg). Note that the systolic and diastolic blood pressures ("BP", second tracing), mean BP (third tracing) and peak LVP (fourth tracing) were augmented after the injection. The d(LVP)/dt (fifth tracing), segmental contractions in the myocardium in the posterio-lateral ("LCx Seg. L", sixth tracing) and anterior ("LAD Seg. L", seventh tracing) surfaces of the heart were basically unchanged, though total shortening was modestly depressed in this dog. HR (eighth tracing) was suppressed. There was no obvious change in the electrocardiogram pattern "ECG", ninth tracing).

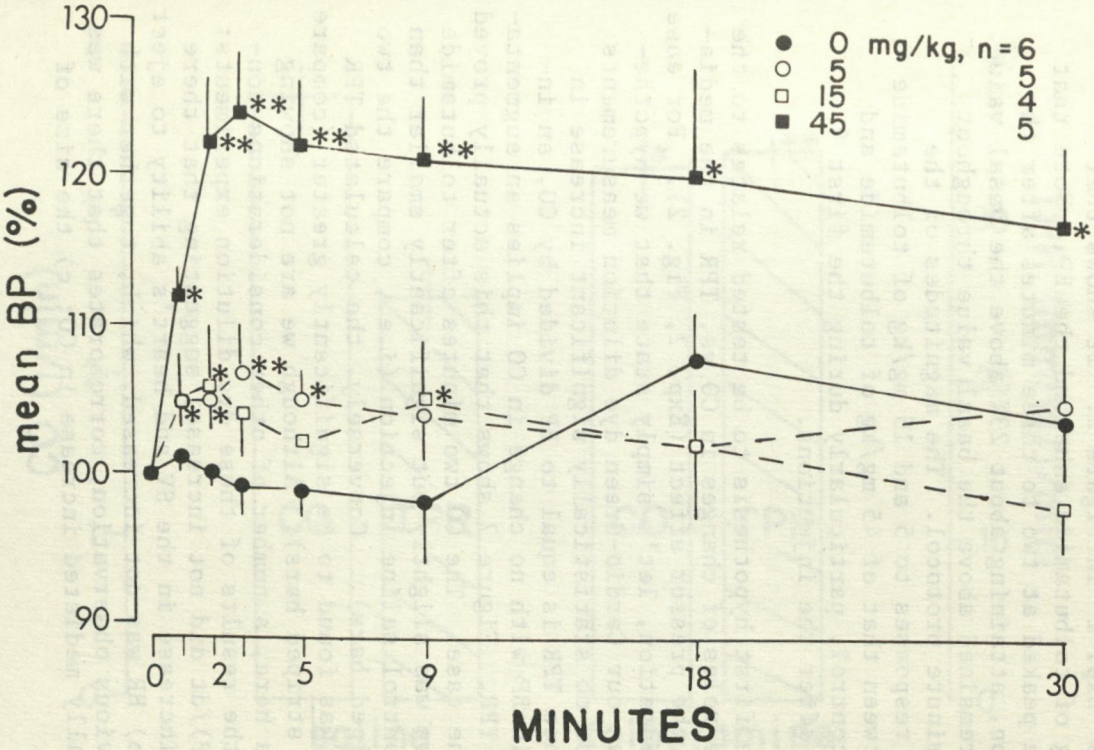


Figure 6. Mean blood pressure is enhanced by tolbutamide.

Figure 6 shows a quantitative analysis of the BP response as averaged over 4-6 dogs for each of the 3 tolbutamide doses and saline control. It represents "Exp. 1" in Figure 2. It shows that 45 mg/kg of tolbutamide enhanced the BP. Note that pressure peaked at two to three minutes after the injection, attaining about 23% above the basal value. The BP remained above the basal value throughout the 30 minute protocol. The magnitudes of the pressor responses to 5 and 15 mg/kg of tolbutamide were between that of 45 mg/kg of tolbutamide and saline control, particularly during the first 9 minutes after the injections.

The first hypothesis to be tested relates to the relative roles of changes in CO vs. TPR in the mediation of the pressor effect (Exp. 2, Fig. 2). For ease of presentation, let's simply state that we hypothesize that our Cardio-Green dye dilution measurements will show no statistically significant increase in CO. Since TPR is equal to BP divided by CO, an increase in BP with no change in CO implies an augmentation in TPR. Figure 7 shows that this actually proved to be the case. The CO two minutes after tolbutamide injection was slightly but significantly smaller than after control saline injection (i.e., compare the two non-striped bars). Conversely, the calculated TPR (BP/CO) was found to be significantly greater (compare the two striped bars). Although we are not showing the data here, a number of other considerations confirmed the results of these dye dilution experiments: a) d(LVP)/dt did not increase, suggesting that there was no increase in the SV and heart's ability to eject blood; b) HR was not increased, which, together with the previous observation, corroborates that there was no neurally mediated increase in CO; c) the size of

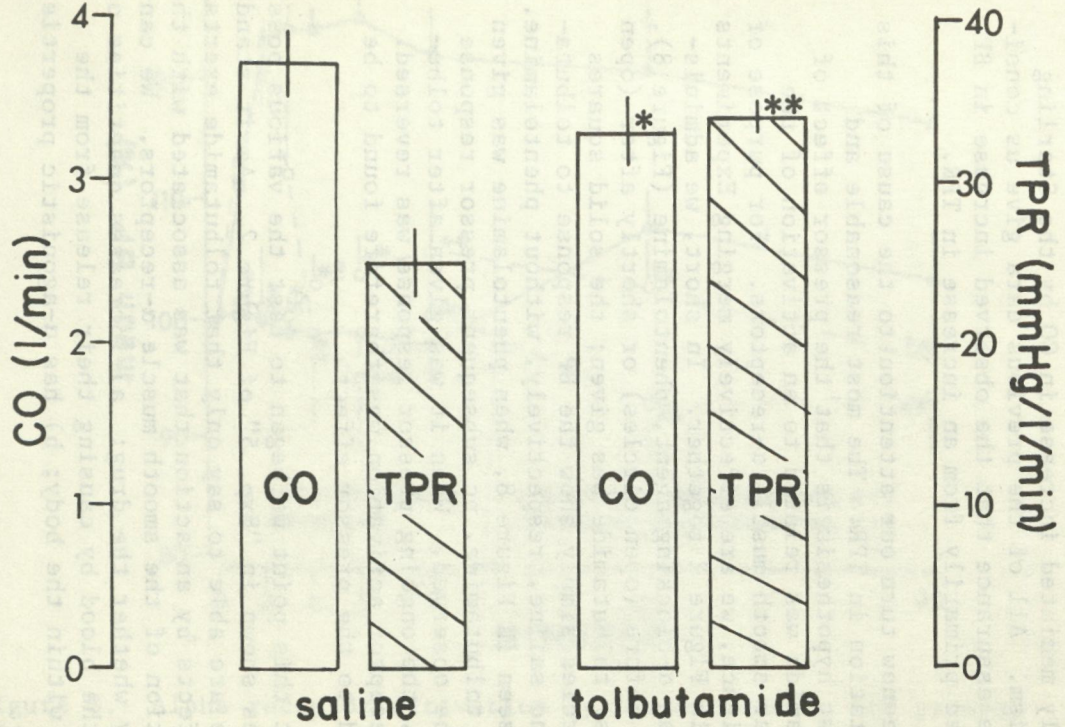


Figure 7. Total peripheral resistance is increased by tolbutamide.

the heart and the relative degree of shortening during contraction, measured by the ultrasound crystals, were not changed following tolbutamide administration; this indicates that there was no non-neurally mediated increase in CO by the Starling mechanism. All of the previous data give us considerable assurance that the observed increase in BP resulted primarily from an increase in TPR.

We now turn our attention to the cause of this augmentation in TPR. The most reasonable and simplest hypothesis is that the pressor effect of tolbutamide was related to an activation of the vascular smooth muscle α-receptors. For purpose of convenience, we are effectively merging Experiments 3 and 4 in Figure 2 together. In short, we administered an α-blocking agent, phentolamine (Figure 8), either before (open circles) or shortly after (open squares) tolbutamide was given; the solid squares and circles simply show the BP response to tolbutamide and saline, respectively, without phentolamine. As is seen in Figure 8, when phentolamine was given before tolbutamide, no subsequent pressor response could be observed. When it was given after tolbutamide, the ongoing pressor response was reversed. An α-receptor activation was therefore found to be related to the pressor effect.

At this point we began to test the various possibilities shown in "Exp. 5" of Figure 2. As it stands now, we are able to say only that tolbutamide exerts its effects by an action that was associated with the activation of the smooth muscle α-receptors. We cannot say whether the drug: a) increases quantities of NE in the blood by causing their release from the stores within the body; b) has α-agonistic properties;

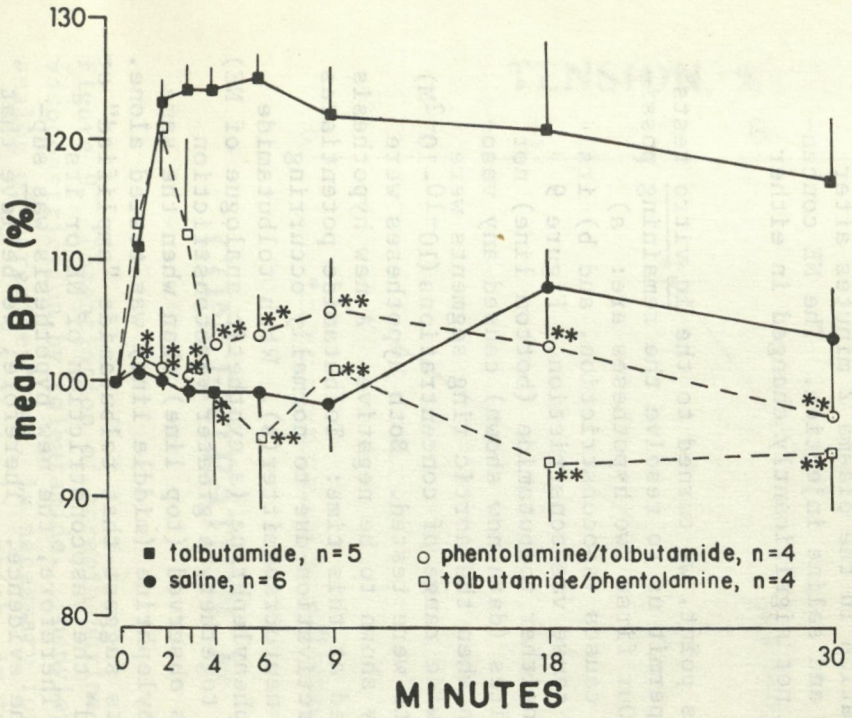


Figure 8. Alpha receptor activation by tolbutamide in the pressor effect of tolbutamide. Phentolamine, an α-blocker, blocks tolbutamide-induced increase in blood pressure when given before tolbutamide, and reverses this pressor effect when given after tolbutamide.

c) has metabolites (chemicals converted in the body from tolbutamide) which act as α-agonists; or d) potentiates α-receptor activation by the normally occurring NE. We began to eliminate these possibilities one by one. We first hypothesized that tolbutamide enhances NE release, thereby causing vasoconstriction. To test this, we measured the NE concentration in the plasma 2 minutes after tolbutamide and saline injection. The NE concentration was not significantly changed in either case.

At this point, we turned to the *in vitro* tests which will permit us to resolve the remaining possibilities. Our first two hypotheses are: a) tolbutamide causes vasoconstriction, and b) its metabolites cause vasoconstriction. Figure 9 shows that neither tolbutamide (bottom line) nor its metabolites (data now shown) caused any vasoconstriction when the aortic ring segments were tested. A wide range of concentrations (10^{-10}-10^{-2}M) ring segments were tested. Both hypotheses were consequently shown to be negative. A new hypothesis was generated at this time: Tolbutamide potentiates α-receptor activation due to normally occurring sympathetic neurotransmitter(s). When tolbutamide (10^{-2}M) and phenylephrine (a synthetic analogue of NE) were tested together, a greater vasoconstriction response was observed (top line) than when the same dose of phenylephrine (middle line) was tested alone. These results suggest that tolbutamide "amplified" or "potentiated" the vasoconstriction of NE or its analogues. Therefore, the new hypothesis *was* supported by the evidence. Therefore, we believe that these *in vitro* studies explained why the BP of a dog was enhanced after tolbutamide injection: Tolbutamide

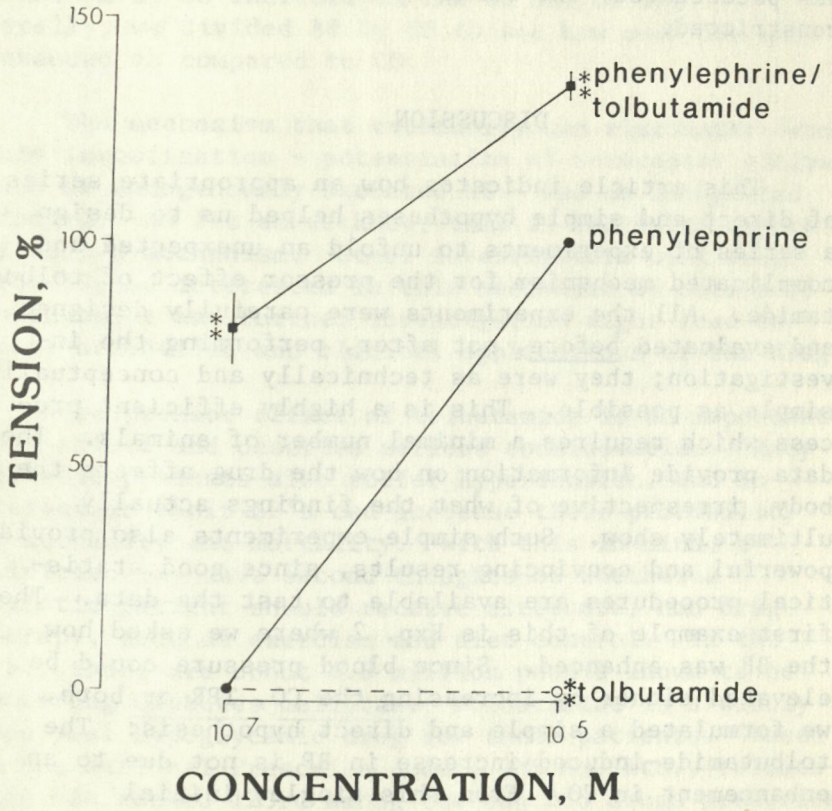


Figure 9. Potentiation of norepinephrine-mediated vasoconstriction by tolbutamide. Phenylephrine, an analog of norepinephrine, is necessary for the pressor effect of tolbutamide which, in turn, amplifies phenylephrine's intrinsic pressor activity.

potentiated the α-receptor activation of the normally occurring NE in dogs; when the α-receptor activation was potentiated, the blood vessels were further constricted.

DISCUSSION

This article indicates how an appropriate series of direct and simple hypotheses helped us to design a series of experiments to unfold an unexpected and complicated mechanism for the pressor effect of tolbutamide. All the experiments were carefully designed and evaluated before, not after, performing the investigation; they were as technically and conceptually simple as possible. This is a highly efficient process which requires a minimal number of animals. The data provide information on how the drug affects the body, irrespective of what the findings actually ultimately show. Such simple experiments also provide powerful and convincing results, since good statistical procedures are available to test the data. The first example of this is Exp. 2 where we asked how the BP was enhanced. Since blood pressure could be elevated either by increasing the CO, TPR or both, we formulated a simple and direct hypothesis: The tolbutamide-induced increase in BP is not due to an enhancement in CO. From this single, initial hypothesis, we designed experiment one: we measured the CO two minutes after tolbutamide and control saline injections. The CO's were compared using a statistical test called the "paired t-test", which is rather powerful. No matter whether the CO after tolbutamide injection was found to be significantly higher, lower or unchanged, the data would provide an answer to the question: If it were found to be

lower, BP should be enhanced by an increase in the TPR. If it were found to be higher, BP should be enhanced by an increase in the CO and/or TPR. Finally, we divided BP by CO to see how much TPR was enhanced as compared to CO.

The mechanism that eventually was elucidated from this investigation - potentiation of α-receptor activation of endogenously secreted NE - was an unexpected finding. As far as we know, this is the first report of such a mechanism. Other investigators will very probably be interested in this mechanism of action of tolbutamide and further investigation might lead to other scientific and clinical applications of the drug.

The pressor effect of tolbutamide is an important side effect and deserves serious consideration. Many diabetic patients also suffer hypertension, and increases in their BP's can increase their probability of morbidity and mortality. With this in mind, a clinician may have second thoughts on whether a diabetic patient should receive alternate, non-drug therapy, such as exercise and diet control. In the U.S., there are about 4.8 million people known to be suffering diabetes mellitus. Tolbutamide is a widely used oral hypoglycemic drug for these patients. Based on the National Prescribe Audit, IMS Am. Ltd., tolbutamide was ranked 123rd among the top 200 drugs prescribed in 1983. Based on the consumer report by Upjohn Company, there are about 2 million patients taking oral hypoglycemic drugs with 10-15% of them taking tolbutamide. A new generation of even more potent tolbutamide-like drugs (glimidine and glibenclamide) are in clinical use in Europe and elsewhere. These drugs may have an even stronger pressor action. Knowing the mechanism

of the pressor effect of tolbutamide, pharmaceutical companies may consider developing a new drug which, like tolbutamide, enhances pancreatic insulin release and yet, unlike tolbutamide, is free of the pressor effect.

The foregoing paragraph concerning the clinical applicability of our experimental findings has several implicit assumptions, one of the most obvious being that our canine data are applicable to human patients. Our dogs were not diabetic and we intend to re-examine our findings in other dogs which have been previously rendered diabetic by treatment with a substance called alloxan (11). At an even more fundamental level, however, one could ask whether any physiological findings in a dog can really be applied to man. Pragmatically, the answer to this question has been shown to be "yes" in countless experiment, though appropriate caution must always be exercised in projecting animal data to man. At a more philosophical level, however, this commonality between man and other living creatures should come as no surprise to those of us embracing the God who performed the creative acts described in the first chapters of Genesis - it surely represents the same omnipotent genius applied at multiple levels.

This paper has focused upon the process of hypothesis testing. Here, too, those of us who profess Christianity view this phenomenon from a unique philosophical perspective. That is, we assume that the same God who prescribed the moral and social laws explained throughout the Bible also established the lawful relationship between cause and effect operating in biological systems. It is this divine underpinning which, we believe, makes "hypothesis testing" possible. The apostle Paul seems to be echoing similar thoughts in his letter to the Romans (1:30; American Standard Version): "For since the creation of

the world His invisible attributes, His eternal power and divine nature, have been clearly seen, being understood through what he has made...". In this sense, the practice of science can be a worshipful experience for those who have committed their lives to the God of the Bible.

The ultimate conclusion we have drawn regarding the action of tolbutamide to potentiate the α-agonist activity of endogenous NE was, as previously indicated, unexpected. Like most scientists, we actually had other "pet" hypotheses which we really expected to verify through our experiments. The scientist is always tempted to manipulate his findings, however, slightly, to favor such preferred pre-conceptions. It requires personal discipline and scientific integrity, as well as competence in basic principles, to ultimately arrive at correct conclusions. The "scientific method", if applied in the absence of these personal characteristics, would yield results little better than those from purely superstitious beliefs. This symposium is being held in honor of Dr. Elmer Nussbuam, a long-time member of the science faculty at Taylor University. His academic career emcodies the highest expression of each of these personal attributes. Perhaps his greatest contribution to his students has not been in their learning important principles of physics, but rather in their attempting to mold their personal and professional careers after these attributes as mirrored in their instructor and friend, Dr. Elmer Nussbaum.

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You not only taught me the fundamentals of physics but also the love of science. Your dedication to Christian education and Christian living has been an inspiration to myself and many others. Your patience and kindness in all your actions has been a trait that I will always appreciate.

John C. Lee, Ph.D.
Associate Professor of Biochemistry
University of Texas
Health Science Center
San Antonio, Texas

I am sure you are aware of the depth of admiration I have for you even though I know of no words to properly express it. You are a great teacher in every respect; your attitudes, your quiet gentle manner, your concern for others (especially your students), as well as your teaching style and professional expertise have had an unmeasureable influence on all of us who have been associated with you.

Dee G. Puntenney, Ph.D.
Associate Professor of Physics
Asbury College
Wilmore, Kentucky

I am most thankful for the Christian role-model that you presented to me during my early years at Taylor as I was not a believer at the time. I really attribute your combination of Christian behavior and life-style, in combination with your academic achievement, as having made a strong impact in my life and my subsequent decision to have the same Master in my life.

Doug Dickinson, M.D.
Birmingham, Alabama

Your sense of humor and optimism have always been an inspiration to me. It is due to your own personal input that I remember your physics class as the high point of my four years at Taylor University. Since leaving Taylor, I have strived for personal excellence in the field of medicine, and you have certainly had an important contribution, with your personal inspiration.

Robert R. Schenk, M.D.
Director, Section of Hand Surgery
Rush-Presbyterian-St. Luke's Medical Center
Chicago, Illinois

The Physics Program, and, in fact, the entire Science Program, have certainly prospered during your tenure at Taylor. Almost anyone acquainted with the school would attribute much of this prosperity to your own efforts - I certainly do! We all owe you a great deal, and it will be very difficult for any series of letters, lectures - or even renaming the science building in your honor - to adequately express well-deserved gratitude.

David C. Randall, Ph.D.
Associate Professor
Department of Physiology and Biophysics
College of Medicine
University of Kentucky
Lexington, Kentucky

Many times it seems that recognition goes to those who are the most aggressive and have a tendency to "blow their own horn". Truly you have taught me that it is possible to set a good example by daily living in a quiet and forceful way that

in the end is just as an effective way of witnessing to ones beliefs as those who are more aggressive towards others. I want to thank you for the Christ-like life that you have displayed before me that has encouraged me and has challenged me in the way that I should live.

Dale Bales, Ph.D.
Chemistry and Physics Department
Mississinewa High School
Gas City, Indiana

I have always been proud of the education that I received while at Taylor University. I know that you are a key person that I have to thank for the quality of that training. You have a way of not only instilling knowledge and comprehension in your students, but you also are an example of a total or complete person. I know you to be a humble man, and with all the letters you will receive, you will probably tend to discount the much praise and many thanks. Please be assured that I (and I'm sure the others) are trying to express the way we truely feel.

Bruce Hess
Business Systems Analyst
Bell Telephone Laboratories
Piscataway, New Jersey

In addition to your fine teaching, another quality which has made an invaluable impression on me and others is your Christian testimony. It was certainly a privilege to have a Professor who was concerned with his students' spiritual welfare as well as their educational development. You have prepared us well for the everyday work world both spiritually and academically.

Bonnie Jean Rumble, M.S.
Section Head
Goodyear Atomic Corporation
Piketon, Ohio

An item which stands out in my mind about physics at Taylor is the opportunity I had to work on the Taylor accelerator. I remember well, Dr. Nussbaum, the afternoon that you and I switched on the high voltage supply for the first time. There was real excitement in the air as we worked in a darkened room illuminated only by the indicator lights on the control panel and the soft glow of the rectifier filaments in the high voltage tank. I consider that accelerator an important step in my career.

David G. Beechy, M.S.
Controls Group
Fermi National Accelerator Laboratory
Batavia, Illinois

Dr. Nussbaum, I can honestly say that most of what I am as a scientist and much of what I am and will yet become as a Christian I owe to you. I thank you so much for the impact that you have had on my life, not only through your teaching, but through the example of your personal life that showed the terms scientist and Christian are not mutually exclusive.

David A. Klopfenstein, M.S.
Systems Analyst
ITT Federal Electric Corporation
Santa Maria, California

I have often said that I went to the Harvard School of Public Health by accident. But mainly I went to Harvard because, being unwilling to spend two dollars to replace a lost transcript when I had already decided to go somewhere else, you pulled two dollars out of your pocket and sent me to the Registrar's office to send Harvard another transcript anyway. A small act with profound consequences, it illustrates your generosity and personal concern for your students beyond the classroom that means so much to us all.

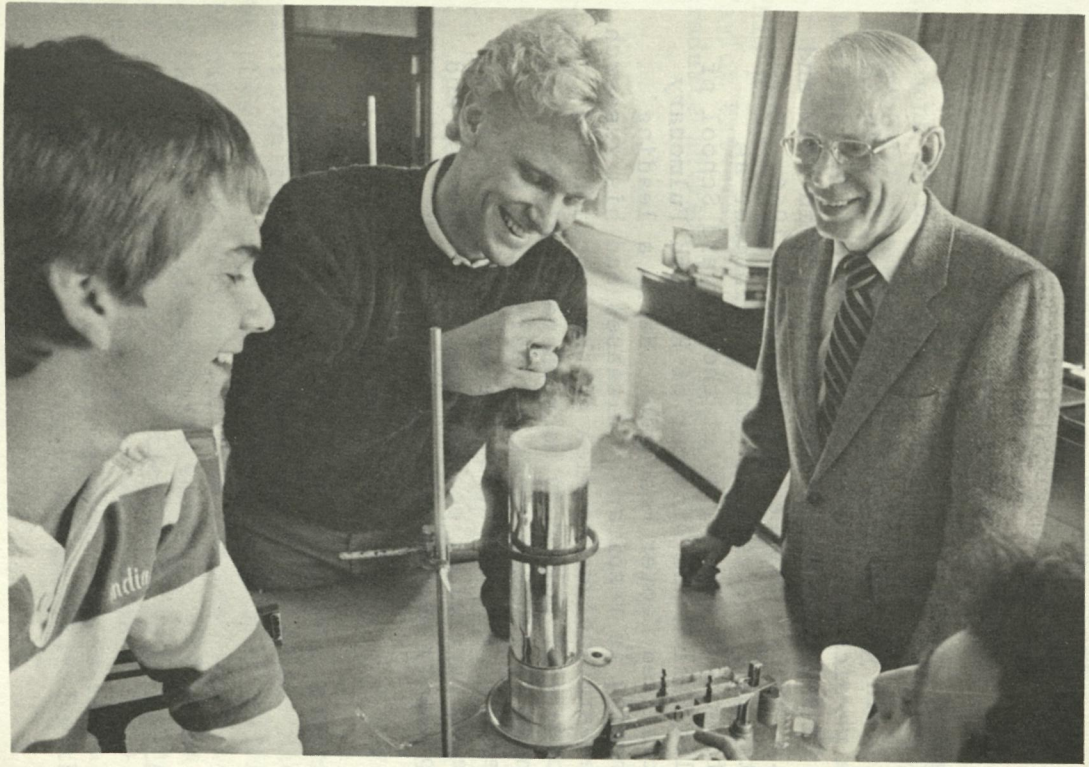
Ray C. Woodcock, Ph.D.
Corporate Industrial Hygienist
Dayco Corporation
Waynesville, North Carolina

As I was able to observe you and your colleagues and see your spiritual commitment, dedication to students and scholarship the Lord made it clear to me that He wanted me to teach at a Christian college. I trust that I have not gone too far from your example by teaching computer science rather than physics.

William Toll, M.S.
Computing Center Director
Asbury College
Wilmore, Kentucky

The best tribute I can think of is to say that there is a part of you, your ideals, your dedication and your love for science (and people) in each of us. Thank you again and God's speed.

Major Dee Friesen, M.S.
Pilot, U.S. Air Force
Albuquerque, New Mexico



Joseph D. Brain

Dr. Brain graduated from Taylor University in 1961 as a physics major under Dr. Nussbaum. He received his SM degree from Harvard University in 1962 and a S.D. Hygiene degree from Harvard in 1966. Currently he is serving a joint appointment as professor of physiology at the Harvard School of Public Health and Director of Harvard Pulmonary Specialized Center Research. He is a leading authority in respiratory diseases and his research interests include studies of the function and structure of pulmonary macrophages, pulmonary responses to inhaled gases and particles, health effects of air pollution, deposition and clearance of particles, occupational lung disease and respiratory mechanics.

BIOMAGNETISM IN THE STUDY OF LUNG FUNCTION

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This paper is dedicated to Dr. Elmer Nussbaum, Taylor University, Upland, Indiana, the undergraduate advisor of Dr. Brain and Dr. Valberg.

INTRODUCTION

A major topic in physics is magnetism. In fact, Dr. Nussbaum frequently taught an entire course in electricity and magnetism. This paper draws upon those concepts and applies them to important problems in physiology, cell biology, and toxicology.

Although magnetism has been a physical phenomena well known for millenia (the compass is an old device), the physics of magnetism was only developed during the nineteenth century. Only in the last 20 years, has the field of biomagnetism emerged. This term refers to the study of magnetic fields originating in biological systems (Williamson and Kaufman, 1981). As described in this paper, magnetic fields may also be produced by electrical currents associated with

the movement of ions in the body. About 20 years ago, Baule and McFee (1963) used induction coils to detect the magnetic field emanating from the human heart. The peak magnetic field was found to be approximately 50 picotesla (1 picotesla = 10^{-12} tesla). This is many orders of magnitude weaker than the earth's steady field of about 70 microtesla (1 microtesla = 10^{-6} tesla). These magnetic fields can be detected non-invasively at the body surface above the heart. They are associated with either the conduction of nerve impulses throughout the heart, or ion fluxes relating to the contraction of cardiac muscle (Cohen and Chandler, 1969).

Cohen et al. (1968), and Williamson and Kaufman (1981), have also observed magnetic fields near the head. These reflect ion currents in the brain and they fluctuate at a frequency similar to the alpha rhythm. They exhibit an amplitude of about 1 picotesla. Magnetic fields have also been recorded from single nerves. Other actions such as movements of the arm produce magnetic fields associated with the contraction of skeletal muscle. When the lungs contain magnetic dust (for example, that experienced by an arc welder working with iron materials), the field emanating from the chest can be as great as 1000 picotesla. Nevertheless, problems of instrumentation in biomagnetic measurements are always difficult. First, one must have adequate sensitivity to detect such small signals. On the other hand, one must overcome interference from much stronger fluctuations of the earth's magnetic field as well as the unwanted contributions from other magnetic field sources such as trains and automobiles. Both fluxgate and superconducting magnetometers (Williamson and Kaufman, 1981) have been successfully used and various shielding strategies have also proven to be important.

This paper describes experiments with inhaled magnetic dusts similar to those used to make recording tapes.

Magnetic forms of iron oxide aerosols are easily generated. When inhaled by experimental animals or humans, they are relatively non-toxic and can be easily detected non-invasively by magnetometry. This technique can be used to describe the distribution of retained particles in the respiratory tract. Repeated measurements describe clearance of particles. Since iron oxide is ingested by pulmonary macrophages, magnetometry can also be used to follow the progression of phagocytosis in vivo, to describe organelle motion in macrophages, and to estimage cytoplasmic rheology.

BIOLOGIC FATE OF IRON OXIDE

Before describing our work using magnetic forms of iron oxide as a probe of the lung, let us briefly consider its biological fate in the respiratory tract. Iron oxide can be used as a non-toxic test aerosol for studies of particle deposition and clearance in the lungs of animals and humans. It can be readily generated in various forms by combustion of iron pentacarbonyl (Brain and colleagues, 1984; Valberg and Brain, 1979). It is easily seen in the light microscope when stained by the Prussian blue reaction and in the electron microscope by virtue of its electron density (Figure 1).

We have used both of these microscopic techniques to study particle clearance in the lungs of mice after they were exposed to an aerosol of submicrometric non-magnetic hematite (Fe_2O_3) (MMAD = 0.31 um, g = 1.25) (Sorokin and Brain, 1975). The animals

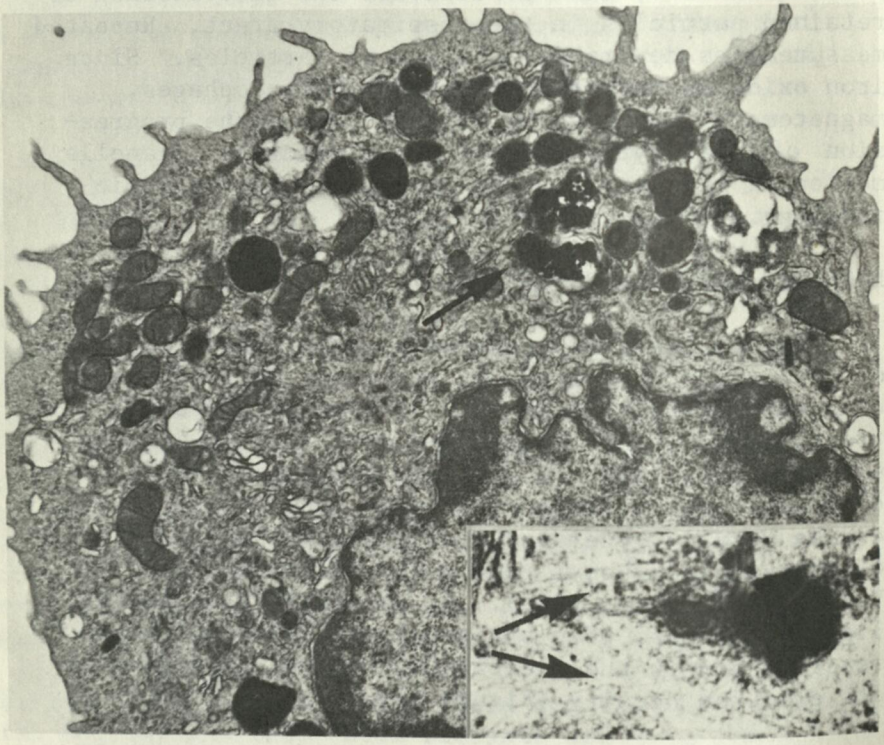

Figure 1. An alveolar macrophage lavaged from a Syrian hamster lung. The arrow indicates Fe_3O_4 particles; magnification x12,500. Inset shows Fe_3O_4 particles wrapped in a membrane in close association with microfilaments (arrows) x50,000). From Gehr and colleagues, 1983c.

were serially sacrificed up to 14 months after inhalation exposure. Acutely, particles which deposited on airways were swept toward the pharynx by mucociliary transport. Examination of the lung sections from animals serially sacrificed clearly showed three phases of clearance. Particles depositing on alveolar surfaces were rapidly ingested by alveolar macrophages. This phase was virtually complete in 24 hours. The second phase was characterized by the gradual migration of particle-laden alveolar macrophages toward ciliated bronchiolar surfeaces. These cells were also swept toward the pharynx by ciliary action, but appeared to move much more slowly than uningested particles cleared initially. Clearance by this pathway may continue for several months. Finally, the third, or chronic phase began when particles appeared within macrophages in the connective tissue of the lungs; these particles persisted for long periods of time but were slowly solubilized. We suspect that the rate of solubilization depends critically on the particle size; smaller particles with a correspondingly greater surface area-to-volume ratio dissolve faster. Light microscopy was the most useful in delineating these phases, while electron microscopy permitted the description of particles within phagosomes and phagolysosomes. Recently, Sorokin (Sorokin, 1983a, 1983b) has further characterized the dynamics of lysosomal formation and fusion following exposure to inhaled iron oxide aerosol. This same hematite aerosol was also used in experiments which described (a) altered biochemical activity of lysosomal enzymes in pulmonary macrophages from rabbits breathing iron oxide (Grant and colleagues, 1979), (b) changes in the phagocytic

behavior of pulmonary macrophages from hamsters breathing iron oxide (Kavet and colleagues, 1978), and (c) the uptake of iron oxide aerosols by the airway epithelium of normal (Watson and Brain, 1979) and sulfur-dioxide injured lungs (Watson and Brain, 1980).

We have also used iron oxide particles as a non-toxic negative control in an *in vivo* hamster bioassay designed to assess the pulmonary toxicity of inhaled particulates (Beck and colleagues, 1982). The assay utilizes bronchoalveolar lavage performed at various times after particle exposure; cellular and biochemical constituents relating to lung injury are analyzed and interpreted in order to characterize the nature and extent of lung damage (Brain and colleagues, 1983). We have used our bioassay to compare the toxicity of iron oxide with that of other dusts such as alpha-quartz, aluminum oxide, volcanic ash from Mt. St. Helens (Beck and colleagues, 1981) and emissions from coal and wood stoves. Although high doses of iron oxide caused some nonspecific inflammatory changes one day following exposure (elevated neutrophil counts and albumin levels), the response was always less than that observed for toxic particulates. Occupational exposures to pure iron oxide also appear to be innocuous. Furthermore, most of the cellular and biochemical parameters returned to control values in seven days or less after iron oxide exposure. These studies confirm the results of morphologic and epidemiologic studies which also suggest that iron oxide has low toxicity. Alpha-quartz, in contrast, caused many of the indicators of pathology to be elevated for up

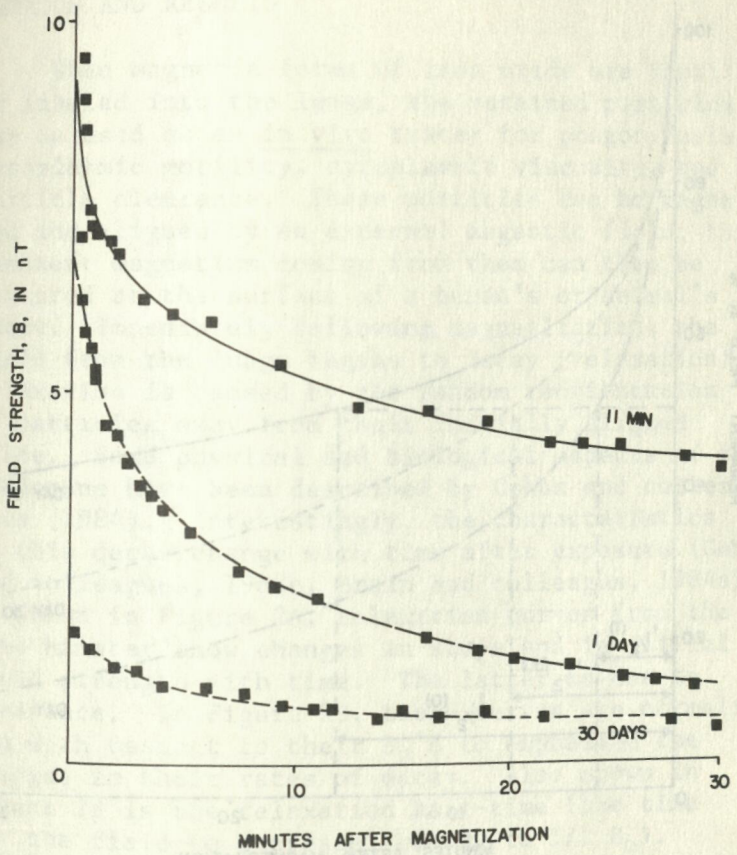

Figure 2A. Relaxation curves. Data from hamster No. 1 at 3 different times after intratracheal instillation of Fe_3O_4 particles.

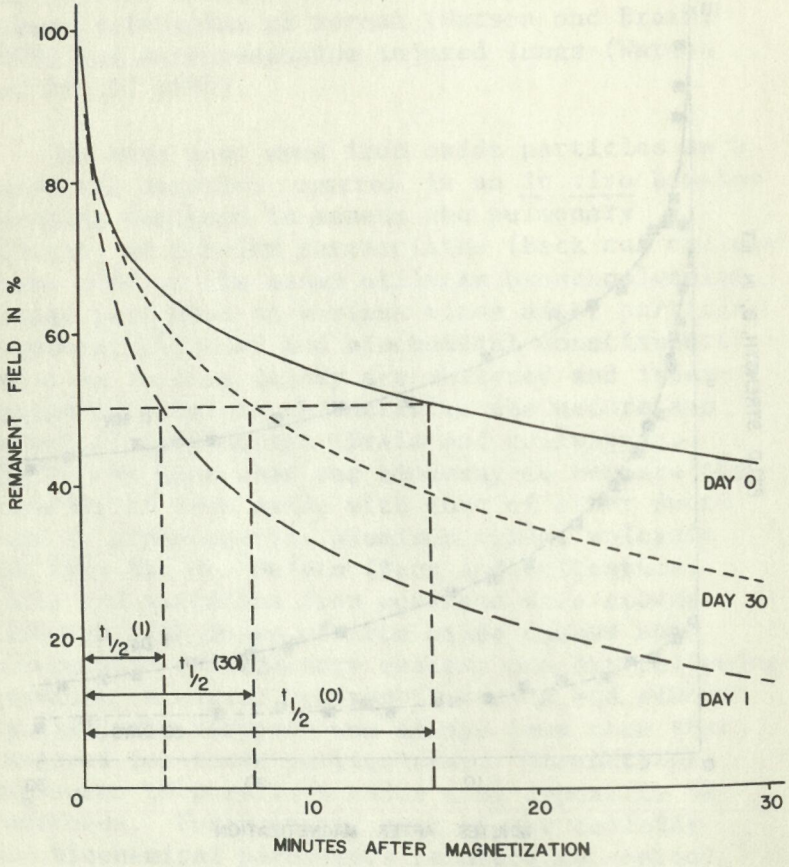

Figure 2B. Relaxation curves. Same data with initial field strength (B_o) of each curve normalized to 100%. $t_{1/2}(0)$, $t_{1/2}(1)$, and $t_{1/2}(30)$ are relaxation half times 11 min, 1 day, and 30 days after instillation, respectively. From Gehr and colleagues, 1983c.

to twenty-eight days after exposure.

METHODS AND RESULTS

When magnetic forms of iron oxide are instilled or inhaled into the lungs, the retained particles can be used as an *in vivo* tracer for phagocytosis, cytoplasmic motility, cytoplasmic viscosity, and particle clearance. These particles can be magnetized and aligned by an external magentic field; the remanent magnetism coming from them can then be measured at the surface of a human's or animal's chest. Immediately following magnetization, the field from the lungs begins to decay (relaxation). Relaxation is caused by the random reorientation of particles away from their initially aligned state. Some physical and biological aspects of this phenomena have been described by Cohen and colleagues (1984). Interestingly, the characteristics of this decay change with time after exposure (Gehr and colleagues, 1983c, Brain and colleagus, 1984a). As shown in Figure 2A, relaxation curves from the same hamster show changes in shape and in initial field strength with time. The latter is due to clearance. In Figure 2B, these curves are normalized with respect to their B_o's to emphasize the changes in their rates of decay. Also shown in Figure 2B is the relaxation half-time (the time for the field to decrease from B_o to 1/2 B_o). Similar data obtained from rabbits exposed to a gamma-Fe_2O_3 (maghemite) aerosol are shown in Figure 3. We believe that the early increase in relaxation rate (decrease in relaxation half-time) seen in our data represents the transition of free particles to phagocytized particles. Our studies suggest that ingested particles relax faster than free particles; therefore, non-invasive magnetometry might be used to follow the progression of

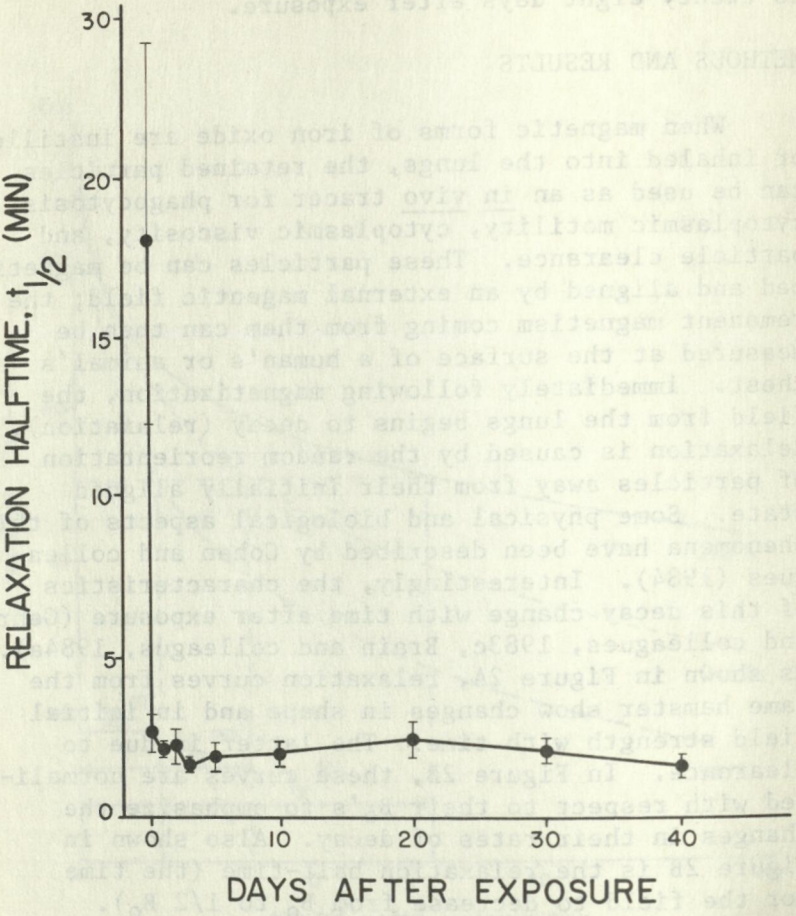

Figure 3. Relaxation half-time ($t_{1/2}$) as a function of days after exposure. Half-time decreases as time after exposure increases from 0 to 30 days. All values represent mean ± standard error based on five rabbits. From Brain and colleagues, 1984a.

in situ phagocytosis. These results correlate well with our morphologic findings showing that phagocytosis proceeds rapidly toward completion during the first twenty-four hours after aerosol deposition. In addition to the morphologic evidence for this, we have quantified the progress of phagocytosis using our lambda technique (Brain and Corkery, 1977). One hour following instillation of colloidal gold into rabbits, 27% of it had been phagocytized, while after 16 hours, 91% had been ingested (Brain et al., 1984a). Relaxation parameters, such as the half-time for the decay, continued to change for weeks after initial deposition of the particles. This may reflect changes in the proportions of the total particle burden located in various pulmonary compartments (e.g., macrophages, connective tissue) (Brain and colleagues, 1984a; Gehr and colleagues, 1983c).

Relaxation curves can be interpreted by considering the following factors. First, the phenomenon reflects actual physical movement (rotation) of the magnetic particles. If the particles are embedded in a frozen lung or a lucite block, no relaxation occurs. Thus, a decreasing magnetic field represents the physical reorientation of the dust, as the particles themselves cannot spontaneously demagnetize. Secondly, we must consider the forces available to move particles within the lungs. These forces include mucociliary action (mucus transport as well as the shearing and tumbling action of the cilia), macrophage mobility, intracellular movement within macrophages, fluid movements in the alveoli, shape and area changes associated with ventilation, cardiac motion (and arterial pressure pulses), and Brownian movement (Table 1). Thirdly, we must consider the milieu in which the particles are found. The rheologic properties of the medium surrounding the particles

at any given site will influence the effectiveness of the applied forces. The medium may either resist the applied forces or help to transmit them to the particle-containing phagosomes. Particles not only initially deposit at a number of different sites within the lungs, but change their location with time. For example, extracellular particles initially may float freely in alveolar or airway lining fluid or may be adherent to epithelial cells. With increasing time, more and more will be ingested by airway and/or alveolar macrophages; a few may be found within epithelial cells or in macrophages within connective tissue and lymph nodes.

TABLE 1 - Possible Mechanisms of Relaxation.

1. Mucociliary transport; local mixing produced by cilia and mouthward movement of airway lining fluid
2. Macrophage locomotion
3. Intracellular movement of macrophage organelles, primarily phagosomes and phagolysosomes
4. Elastic recoil of organelles in the cytoplasmic matrix
5. Fluid movements in alveoli, such as alveolar bronchiolar transport of the alveolar lining layer
6. Changes in shape and area associated with breathing
7. Cardiac-induced motion (either heart motion or arterial pressure pulse)
8. Brownian movement

Our in vivo experiments suggest that the rotational forces applied to the particles (after phagocytosis is complete) come largely from intracellular movements of phagosomes and phagolysosomes that contain the particles (Brain and colleagues, 1984a,b; Gehr and colleagues 1983b, 1984c). We believe that

these movements arise from contractions of the cytoskeleton, which orchestrates cell motion required for functions such as phagocytosis, secretion, or ameboid movement. Even in the motionless lung in a dead animal, relaxation takes place as long as the in situ alveolar macrophages are kept warm and oxygenated (Brain and colleagues, 1984b). The hypothesis that organelle motion is a dominant mechanism for relaxation has now been confirmed in studies of hamster pulmonary macrophages observed in vitro (Gehr and colleagues, 1983a; Valberg, 1983, 1984; Nemoto and colleagues, 1984). Macrophages which had previously ingested magnetic particles exhibited relaxation which was quantitatively similar to that seen in vivo, demonstrating that cardiac and respiratory movements are not essential for particle misalignment. Nemoto and colleagues (1984) demonstrated temperature dependence of relaxation over a wide range.

The interventions used in these studies shed additional light on the mechanisms of relaxation. Cytochalasin B and D, known to disintegrate the microfilament system (actin), slowed relaxation as did cold and cyanide (uncoupler of the respiratory chain in mitochondria), whereas colchicine and nocodazole (disintegrator of the microtubules) had no effect. Formalin and glutaraldehyde fixation resulted in a complete halt of relaxation. These interventions, most of which compromise the contractile capabilities of the cytoskeleton, demonstrate that organelle motions are driven by an energy dependent, actin-based mechanism (Gehr and colleagues, 1983a, 1983c; Valberg 1983, 1984).

The rheologic properties of cytoplasm can also be measured using magnetic particles and magnetometry (Crick and Hughes, 1985; Valberg, 1984). After magnetizing the particles, a magnetic field is

applied perpendicular to the axis along which the particles were aligned by the initial magnetization. The ease with which the particles realign toward this "twisting" field is related to the viscosity of the medium surrounding the particles. Valberg has shown that cooling, but not cytochalasin D, increases the viscosity of the cytoplasm of hamster pulmonary macrophages.

Clearance of particles can also be described by magnetometry. The remanent field immediately following magnetization, before relaxation occurs, is proportional to the amount of magnetic material remaining in the lungs. This measurement, repeated over weeks or months, describes a clearance curve. It requires several seconds to move an animal or subject from the magnetizing field to the probe of the measuring device, and, of course, some relaxation has ensued when the initial reading is taken. In order to estimate the field before relaxation, we fit the data from the first one or two minutes of relaxation to the equation $B = B_o e^{-\lambda t}$. B is the field strength at time t after magnetization, and λ is the decay constant. B_o is the field strength at the time the magnet was removed. We have described clearance in rabbits and hamsters (Brain and colleagues, 1984a; Gehr and colleagues, 1983). Figure 4 shows clearance of magnetic dust from rabbits. Halpern and colleagues (1981) obtained similar data in donkeys.

Experimental studies of clearance of magnetic dust have also been performed on human subjects. The magnetic properties of such minerals as magnetite (Fe_3O_4) and gamma hematite (maghemite) are suitable. Amounts as small as 0.05 mg can be detected and repeated measurements describe the clearance of

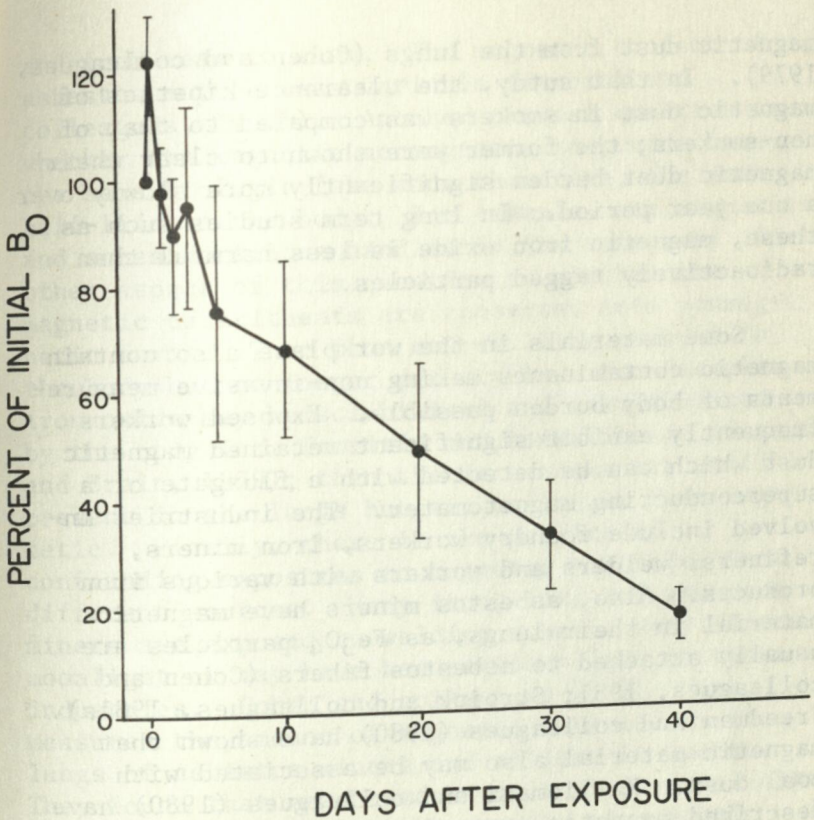

Figure 4. Disappearance of gamma-iron oxide from lungs of five rabbits as indicated by remanent magnetic field normal to chest wall immediately after magnetization. The reading, shown as a percentage of the field strength measured immediately after exposure, is plotted versus time after aerosol exposure. At each time indicated the rabbit was magnetized by an external magnetic field. The decrease in the magnetic field with time is related to physical clearance of iron oxide from the lungs and/or conversion to nonmagnetic forms. All values represent mean ± standard error. From Brain and colleagues, 1984.

magnetic dust from the lungs (Cohen and colleagues, 1979). In that sutdy, the clearance kinetics of magnetic dust in smokers was compared to that of non-smokers; the former were shown to clear their magnetic dust burden significantly more slowly over a one year period. In long term studies such as these, magnetic iron oxide is less harmful than radioactively tagged particles.

Some materials in the workplace also contain magnetic contaminants making non-invasive measurements of body burden possible. Exposed workers frequently exhibit significant retained magnetic dust which can be detected with a fluxgate or a superconducting magnetometer. The industries involved include foundry workers, iron miners, refiners, welders and workers with various iron products. Also, asbestos miners have magnetic material in their lungs, as Fe_3O_4 particles are usually attached to asbestos fibers (Cohen and colleagues, 1981; Stroink and colleagues, 1981a). Freedman and colleagues (1980) have shown that magnetic material also may be associated with coal dust. Kalliomaki and colleagues (1980) have described magnetic contamination in steel welders. Such measurements could be superior to estimates of retained dust based on air concentrations in the workplace. Magnetometric measurements reflect individual differences in collection efficiency and clearance.

Non-invasive measurements of body burden are possible. There are, however, crucial problems. It is important to know whether the magnetic component is a constant fraction of the parent material. For coal this varies from mine to mine

and from seam to seam. The magnetic content of asbestos may be less variable (Stroink and colleagues, 1981b). Another crucial question is whether the magnetic nonmagnetic compounds have the same biologic fate and, therefore, the same half-life in the body. For example, are magnetite and asbestos fibers handled in the same way? Another aspect of this question is whether the magnetic constituents are converted into nonmagnetic forms. Then iron may still be present in the body but no longer detectable. For example, iron oxide may be solubilized and resynthesized by the body into ferritin and hemosiderin (Watson and Brain, 1979); then the iron atoms are still present in the lungs but are no longer ferromagnetic. Finally, there is the problem of confounding exposures to magnetic particles from different sources. Many iron, coal and asbestos miners are exposed to welding fumes. Many miners moonlight or may have had previous jobs in these industries. Cohen and colleagues (1981) have measured the amount of magnetic material in the lungs of asbestos miners and millers in Quebec. They found that measurements at an industrial site were feasible and that the amounts of magnetic contamination in the lungs were clearly detectable. However, they had difficulty with miners who had significant welding exposures. For the non-welders, however, they found a modest correlation between the amount of magnetic material in the lungs and aerometric estimates of the dust exposure.

CONCLUSIONS

Magnetometry can be used to monitor magnetic particle clearance from the respiratory tract of

animals and humans. In addition to describing the anatomic fate of inhaled particles, we have shown that magnetometry can also be used to assess in situ particle phagocytosis and events reflecting cytoplasmic viscosity and motility. Current studies of deposited magnetic iron oxide are correlating biochemical, histological, and morphometric parameters with the magnetic phenomena. We also hope to be able to assess non-invasively the long-term effects of various environmental and pathological conditions on phagocytosis, cytoplasmic motility, cytoplasmic rheology, and clearance in living animals.

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Colleagues Through Association With The Oak Ridge Associated Universities

I can't say too many times what a pleasure it has been for me to know a man who has received the admiration and respect of his students and colleagues. Your pleasant personality, gentle manner, and dedication to the teaching profession are qualities that all of us strive for during our professional career and lifetime. Thanks again for giving me the opportunity to know and work with you over these past nineteen years.

Jo T. Tipton
Registrar/Administrative Officer
Professional Training Programs
Oak Ridge Associated Universities
Oak Ridge, Tennessee

It sometimes takes a special occasion to make people realize how much they owe to others. The occasion of your retirement has made me reflect on how much your students, coworkers, and friends are in your debt. I can only repay my debt to you by emulating your dedication to providing a quality education for young men and women in a quiet and patient manner. Your help as a supplemental staff member at ORAU has also extended your influence to a greater number of students from a large number of colleges and universities. As for us, we could not have carried out our mission without your help.

Roger J. Cloutier, M.S.
Director
Professional Training Programs
Oak Ridge Associated Universities
Oak Ridge, Tennessee

I feel that my association with such fine physicists as yourself has been invaluable in preparing me for my chosen career. For that experience, I remain eternally grateful to you for taking the time and having the patience to teach me.

Troy L. Brannon, M.S.
Radiation Physicist
Head, Medical Radiation Physics Section
Valley Sierra Health Services
Sacramento, California

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Thomas W. Stone
Radiological Health Specialist
Virginia Department of Health
Richmond, Virginia

I can think of no other person who surpasses you in several respects: professional competence, teaching ability, calm approach to all situations, as well as an open, friendly interaction with all.

Lee S. Anthony, Ph.D.
Health and radiologic Physicist
Physics Associates
Roanoke, Virginia

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Max H. Lombardi
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John C. Lee

Dr. Lee received his B.A. degree in physics from Taylor University in 1961. He received his M.S. and Ph.D. degrees from Purdue University in molecular biology in 1967. After doing post-doctoral research at MIT for two years he went to the University of Texas Medical School where he currently serves in the Department of Biochemistry. His research interests concern the function of nucleic acids and differentiation.

GENES, PSEUDOGENES, AND DESIGNER GENES

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ABSTRACT

One of the central problems of biological sciences is to discover how two cells with the same genetic information can each make a different array of proteins. Understanding how genes are controlled is essential for comprehension of normal cell differentiation and of diseases due to uncontrolled cell growth, such as cancer. In cells that have a nucleus, including human cells, the genetic information in the DNA molecule is first transcribed into messenger RNA which is then translated into proteins. A large number of events happens to the RNA between transcription and translation. Among the exciting new discoveries is that the gene for the protein is much larger than what is needed for encoding of the protein. These extra DNA sequences, called introns, split the DNA sequence coding for the protein into segments, called exons. Both the introns and the exons are transcribed as a precursor of the messenger RNA.

Introns must be first removed before the messenger RNA can be used to direct protein synthesis. This prerequisite can potentially allow production of different proteins from the same gene depending on which intron is removed. It is also beginning to seem that few genes are alone in mammalian chromosomes but are present as a family of genes. Some of these repetitive genes are non-functional pseudogenes. Analysis of pseudogenes have revealed an unmistakable homology to the functional genes but they contain structural variants which prevent them from being expressed. These discoveries have also advanced our knowledge about human genes so that it is now possible to assign many genes responsible for specific disease conditions. For example, genes for the oxygen carrier protein, hemoglobin, have been mapped to human chromosomes 11 and 16. Such information is useful not only in the prenatal diagnosis of human genetic diseases but also aid in the isolation and subsequent correction of defective genes.

GENES, PSEUDOGENES AND DESIGNER GENES

I wish to thank all the people who are involved in the organization of this symposium in honor of Dr. Nussbaum and I am particularly pleased to be included in this festive activity. I will have more to say about Dr. Nussbaum later but the fact that

one of my sons is named after him should indicate to you how I feel about him.

To understand heredity is so important to humans that investigations on its nature have continued for centuries; however, the concept of the gene has changed throughout the entire history of modern science. Gregor Mendel showed that there are certain "hereditary factors" that are responsible for the traits of an organism. Later the Danish biologist Welhelim Johannsen called these "hereditary factors" genes. In the early 20th century, genes were defined as discrete elements in the chromosomes. Only 40 years ago, Avery and his colleagues showed that DNA was the hereditary factor. In 1952, Hershey and Chase confirmed the idea that the genetic material is DNA by conducting the famous experiment showing that the DNA component of a bacteriophage T2 is sufficient for transmitting genetic information to progeny phages. The structure of the DNA, particularly the double helix, was defined by James Watson and Francis Crick in 1953 who won the Nobel Prize for their work. In the following years, molecular biologists learned how the hereditary information is encoded in the DNA structure and how this information is translated into proteins that determine the structure and function of cells and organisms. In 1958, Francis Crick enunciated a rule which has continued to be known as the central dogma of molecular biology. The central dogma states that the genetic information in nucleic acid carried by the base sequence of the nucleic acid can be transferred or perpetuated, and this information is transferred into proteins. The flow of genetic information in normal cells as described by the central dogma is illustrated below:

DNA → RNA → protein

As indicated in this scheme, DNA is not the direct template for protein synthesis. Rather, the template for protein synthesis is another type of nucleic acid, RNA. This process of synthesis of RNA according to instruction given by a DNA template is called transcription. The following process in which the RNA template specifies the synthesis of a protein is called translation and it is irreversible. All these processes depend on a multitude of enzymes and factors and obey the known laws of physics and chemistry.

Let us consider the nature of these three types of macromolecules. A DNA molecule in all higher organisms is a long double helix resembling a spiral ladder. Each DNA strand is a chain of nucleotides, which is characterized by a chemical group known as a base: adenine (A), guanine (G), cytosine (C), or thymine (T). Each nucleotide is made up of a nitrogenous base and a five carbon sugar, deoxyribose. The adjacent nucleotides are linked by a phosphate group. The two DNA strands are held together via specific base pairings: A pairs with T and G with C. Genetic information is encoded in the sequence of these bases. Precise sequences of nucleotides along one DNA strand comprise the code that dictates the arrangement of amino acids in the assembly of a protein chain. The genetic information is transferred through the intermediary RNA molecule. Like DNA, RNA is a polymer whose monomers are nucleotides. In RNA, the four bases are adenine (A), guanine (G), cytosine (C), and uracil (U). The five carbon sugar in this molecule is ribose. Only one of the DNA strands is copied and the transfer is achieved

via specific base pairing rules: an A pairs with U and G with C. The result of this process is the production of a messenger RNA molecule whose sequence is complementary to the DNA template. This strand of RNA will be used to direct protein synthesis. A protein molecule is a long chain polymer whose constituents are amino acids which are linked via peptide bonds. There are 20 amino acids. Proteins are the instruments by which the genetic information encoded in the DNA is expressed. There are thousands of different proteins in the cell, each carrying out a specific function determined by its gene.

It is clear that a discrete, continguous stretch of DNA encodes the genetic information to specify the manufacture of a single protein. Consequently, the linear sequence of bases in the DNA should correspond directly to the linear sequence of amino acids in the protein. However, to our surprise, this principle of colinearity is applicable to bacteria but not to higher organisms. In fact, many genes in mammals, birds, and amphibians are split. It means that the DNA sequences comprising the gene are interrupted and can be classified into two categories: the exons and the introns. The exons comprise the regions that are represented in the messenger RNA which is used to direct protein synthesis. The introns are missing from the messenger. In these cells, the DNA first gives rise to a precursor RNA molecule which contains all the sequence of the gene. This precursor RNA cannot be used to direct protein synthesis until the introns are removed from it to generate a messenger RNA that consists only the series of exons. The exons are always

joined together in the same order in which they are represented in the DNA. These reactions are called RNA Processing.

Genes come in all shapes and sizes. Of all the genes analyzed so far, there seem to be no rules setting the number of introns that a particular gene can have. For example, the genes coding for the alpha and beta chains of the hemoglobin molecule contain two introns, whereas the genes coding for ovalbumin and conalbumin contain 8 to 17 exons respectively. The chicken alpha collagen gene appears to contain the largest number of introns of all genes examined to date; it contains more than 50 introns. The size of the intron also varies ranging from 40 to 1000 nucleotides.

Although the physiological significance of split genes is unclear, the discovery of split genes and RNA processing in higher organisms helps us to begin to understand one of the marvels of nature, i.e. the immune response of the mammal. In response to provocation by a foreign agent, our body responds by the production of a protein, called antibody, that specifically recognizes that agent, called antigen. One of the mysterious features of this process has been the ability of our body to produce an appropriate antibody whenever it is exposed to a new antigen. How can our body be prepared to produce antibody proteins each designed specifically to recognize an antigen whose structure cannot be anticipated? One might think that our body would have to possess millions of different antibody genes, each coding for only one kind of antibody. This seems improbable. There simply is not enough DNA in our body to code for all these different types of antibodies plus the thousands

of normal structural and functional proteins in our body. One alternative would be designer genes constructed specifically for each condition. It appears that the DNA coding for the antibody molecule consists of several different kinds of genes, scattered through the entire DNA molecule. On demand, these various DNA segments, which are separated initially, are transposed and joined into a specific sequential arrangement. It is estimated that these DNA segments can be joined in different combinations to make as much as 20,000 DNA sequences for different antibodies. An analogy would be the following: If one has a large set of Tinkertoys containing numerous blocks of different shapes, colors, and sizes, one would be able to construct a great variety of models by joining them in different combinations.

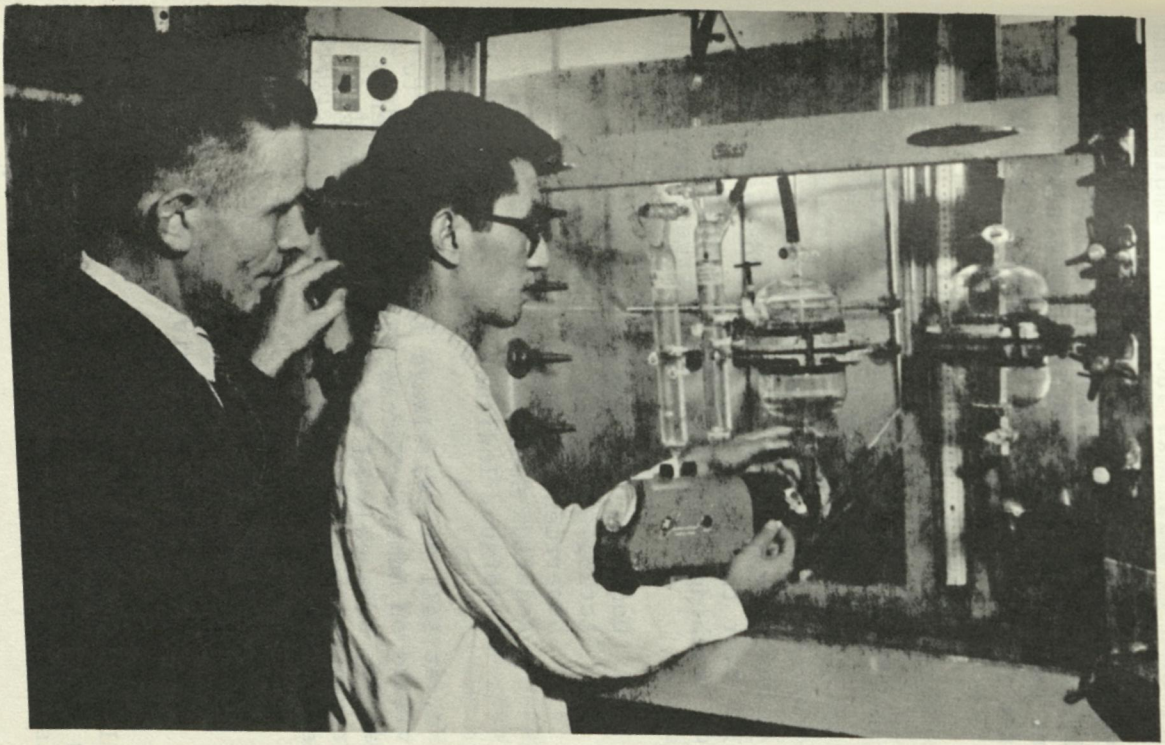
It is also beginning to seem that few genes are alone in mammalian chromosomes but rather that families of genes are present. Some of these repetitive genes are functional but some are nonfunctional pseudogenes. Analysis of these pseudogenes have revealed an unmistakable homology to the functional genes but they contain structural variants which prevent them from being expressed into proteins.

Our knowledge of genes is now being used successfully to solve a variety of medical problems, such as the diagnosis, prevention and treatment of genetic diseases. For example, one way to test for thalassemia, a form of anemia, in a fetus, is to take the DNA from the mother's amnionic fluid and treat it with a restriction enzyme to cut the DNA into pieces. If the DNA is normal, the enzyme

will cut the DNA at a specific nucleotide. If the gene is abnormal due to either a change in nucleotide sequence or deletion of a sequence, the enzyme will not be able to cut it there and the resulting pattern of DNA pieces will be different. Hence, one can tell by examining the pattern of DNA fragments generated whether the fetus is afflicted with the disease.

In an effort to solve the mysteries of the structure of DNA, we will find out about what makes genes turn on and off and find ways to fight the myriad diseases that plague mankind. As our knowledge about genes increases, our appreciation for our Designer and Creator should be heightened.

In conclusion, I wish to dedicate this seminar to Dr. Nussbaum who not only has taught me the fundamental principles of physics but also the love of science. It was also because of his suggestion that I took a course in genetics in my senior year at Taylor that initiated me into this exciting field of molecular biology. In addition, his dedication to Christian education and Christian living has been an inspiration to myself as well as hundreds of Taylor students who through his teaching career has shown how one dedicated person can make a positive impact on so many lives. He is a shining example of how one science professor can help to develop future scientists who will help mankind to understand the complexity of God's world. Dr. Nussbaum's patience and kindness in all his actions has been a trait which I will always appreciate.



Elmer Nussbaum, physics professor, and John Lee, physics student, studying the diffusion of radon in 1960.

Colleagues in the Indiana Physics
Teachers Association

Your counsel, encouragement, and enthusiasm for physics and physics teaching have always been evident and were especially valuable to me during my first few years at Marion College.

Robert J. Werking, M.S.
Division Chairman
Natural Science and Mathematics
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Donald B. Cruikshank, Jr., Ph.D.
Acting Chairman
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Anderson College
Anderson, Indiana

We, at Ball State, always looked forward to your visits on numerous occasions. Our students and faculty have enjoyed your very well thought out presentations, an obvious mark of the master teacher.

Malcom Hults, Ph.D.
Department of Physics and Astronomy
Ball State University
Muncie, Indiana

I will remember your willingness to share ideas and to listen to mine no matter how outlandish. Your gracious ways make you easy to talk

with and you are always interested in other colleges and their programs. You are always willing to share equipment and your expertise to help others in their time of need.

Robert E. Hale, M.S.
Professor of Physical Science
Huntington College
Huntington, Indiana

Perhaps most of all I recall the sessions you set up at Taylor for college physicists to meet to hear reports of doings at national meetings from those who were able to attend the national meetings. This was a great idea and sorely appreciated by all who participated.

Robert L. Henry, Ph.D.
Professor and Chairman
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Crawfordsville, Indiana

Since the Oak Ridge beginnings, it has been a joy to cross paths with you and share thoughts at short courses, A.A.P.T., and Indiana Academy of Science meetings. I've always been an admirer of your ability to carry on significant research while devoting the time to teaching that quality demands.

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Walter C. Randall

Dr. Walter Randall is a 1938 graduate of Taylor University. In 1942 he received his Ph.D. degree in physiology from Purdue University. He taught at both Purdue University and St. Louis University School of Medicine before going to Loyola University. At Loyola he was chairman of the Department of Physiology at the Stritch School of Medicine for a number of years and now is Professor of physiology there. He has served as chairman of the National Board of Medical Examiners and is a recent past-president of the American Physiological Association. His research interests include studies of sweating, temperature regulation, circulation and autonomic nervous systems and nervous control of the heart.

THE LORD GIVETH WISDOM

Walter C. Randall
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ABSTRACT

I will seek first to honor Dr. Nussbaum and to recognize qualities of excellence in the Taylor Science faculty. This will include my concept of a "great teacher", and how Dr. Nussbaum qualifies for that designation.

An important function of a university is to actively support scholarly work, and I will lift up Dr. Nussbaum's achievements as a teacher, an investigator, and as an inspiration to many students who are now either involved in or are supportive of research.

I will then attempt to illustrate how countless, individually small research accomplishments led up to the dramatic abilities of the physician to replace a worn out heart, bypass clogged coronary arteries, or to replace virtually all of your skin which may have been burned totally beyond recognition. None of these operative procedures were possible, or even dreamed of when we were at Taylor; today they are becoming commonplace, because of research and because teachers like Elmer have planted the

seeds of basic knowledge and stimulated the realization in young scientists' minds that God created much more than all of His disciples presently know.

There are those who accept the idea that serendipity plays a leading role in making new discoveries in the laboratory. I choose to believe that the Holy Spirit will direct the mind and the hands of the scientist who has a place in his life for God, and that the scientist's conscience can be informed or even trained by the Holy Spirit to be coupled to the intellect to lead in the design of his protocols, making his observations, and in the interpretation of his data. To teach us to walk by faith, God has hidden from us nearly everything we wish to know about the way our bodies function. "As thou knowest not what is the way of the wind, nor how the bones do grow in the womb of her that is with child; even so thou knowest not the work of God who doeth all." (Ecclesiastes 11:5). In a Scriptural sense, wisdom is a moral as well as an intellectual quality, more than mere intelligence or knowledge, certainly more than cleverness or cunning.... "If you accept my words and store up my commandments within you, turning your ear to

wisdom and applying your heart to understanding, and if you call out for insight, crying aloud for understanding, and if you look for it as you would for silver and search for it as for hidden treasure, then you will understand the fear of the Lord and find knowledge of God. For the Lord giveth wisdom, and from his mouth come knowledge and understanding." (Proverbs 2:1-6)

THE LORD GIVETH WISDOM

I deeply appreciate the opportunity of sharing these moments with you as we focus our attention, admiration, professional respect and love for Elmer Nussbaum. Many of you have sat in his classes, or have worked across the laboratory bench from him, matched wits with him in academic discussion, or in unraveling his questions during examinations. Many of you have fond recollections of him wheeling across campus on his two-wheeled Cadillac, vintage about 1914. We celebrate the rededication of an edifice which he helped to build with his intellect, and with his blood, sweat, and tears. Some of us were not so fortunate with respect to the bricks and mortar in which we learned our basic science disciplines, but we did profit from the critically important ingredient of a Taylor education; its thoroughly trained, completely dedicated, student oriented, and Christ-centered science faculty. While we recognize the importance of the magnificent bricks and mortar in the Nussbaum

Science Center, we insist that the important components of a Taylor education are the centricity of Christ and the quality of its faculty.

I feel comfortable in characterizing the Science faculty at Taylor: first and foremost in their personal belief in, and commitment to Christ. Secondly, they are teachers, scientists, investigators with abiding interest in students and in development and communication of knowledge. I identify with them. We consider our professional career as a Christian ministry to which we have been specifically called. Each of us has daily opportunities to extend his Christian testimony to his community, to his colleagues, and to his students. I direct a question now to each member of the faculty and focus the introspection upon myself. If a stranger were to query a former student some years after he sat in my classes, would he recall me as "an enthusiastic, committed Christian teacher", or as "just another member of the faculty in Physiology"?

There is consensus that Elmer is a good teacher. Ther are those among his nearly 100 physics majors who would argue strongly that he is a <u>great</u> teacher. But what are the attributes of a <u>great teacher</u>? Some students' view may be of one who presents his didactic material in beautifully organized outline form and then asks for its verbatim recitation back to him in his examination, with an A to the student who can do it. It does not matter to this teacher that the student hasn't reflected one iota upon the content or implications of the items; his only concern is, did the student memorize it faithfully. Of course,

some students like that kind of teacher because with little intellectual effort they may seem to perform well in the course. We encounter that kind of teacher too often and, in my opinion, he does great harm. His students may bring excellent grade point averages on their transcripts but be totally unable to hack it in medical or graduate school.

I happen to believe with Dr. Willis Hurst, Professor of Medicine at Emory University, that the student can not accurately designate a really good teacher until he has been out of school for perhaps ten years. By that time he will have forgotten many of the so-called "facts" we have taught him, but he will remember the intellectual challenges, the times we showed him how to observe and how to think critically, the times we required him to clearly analyze his laboratory results, the opportunities he had to sharply define and to defend his goals in life, and the challenge to develop his ethical and spiritual values. The great teacher's lectures are not perceived to be at arms' length, designed entirely for mass education; factually efficient but cold. His emphasis upon factual knowledge is carefully integrated with understanding and philosophic outlook. The student leaves his classroom clinging firmly to an exciting and enthusiastic conceptualization of his discipline, its proper place and function for him, and to the attractive features of his teacher's role in his learning.

Sydney J. Harris recently told about a University of Chicago Professor whose newspaper obituary ended with the bleak sentence, "He left no survivors". One of the professor's former students protested that this was not true. While the professor, a

lifelong bachelor, died without next of kin, he left hundreds of student "survivors" all over the world. A great teacher, even if he writes not a word, may be survived by endless generations of students. Jesus, like Socrates, wrote only simple messages with a stick in the sand; neither published a single word. Still, their thoughts remain eternally fresh. They acquire new disciples (students) every day. The impact of the teacher's insight and personality are far more decisive and more permanent than the facts he imparts. Those of us in scientific disciplines know how quickly so-called "facts" may change. This is what Einstein meant when he defined education as, "what is left after you have forgotten everything you learned in school". What is left is the indelible memory of your teacher's insight and spiritual commitment, his moral courage, his respect for reason, his excitement for learning, his desire to share his knowledge and know-how, his eagerness to learn as much as he imparts. Unfortunately, there are not many teachers of this sort; fortunately for Taylor, there is Elmer Nussbaum.

An important function of a University is to encourage and to actively support scholarly work. At Taylor University, Dr. Nussbaum has consistently practiced, taught, and cultivated research. His expertise in Nuclear Physics emerged at a time in history when such knowledge was at high premium, and he carried out exceptional research in his laboratory here and at Oak Ridge. He represents a magnificant "window" through which the scientific world may look in upon Taylor University. However, his personal participation in research isn't my primary target this morning. I suspect he is like me in this

regard--that he simply loves to do research--why should one be rewarded for doing exactly what he most likes to do? As Christ implied, "He has already had his reward" for that. But Elmer went far beyond that quality. He inculcated within his students an appreciation for research, and many are vigorously and creatively involved in it as a result. But even though they may not do research themselves, his students understand and are supportive of research by the nation's corps of scientists. Congress and you, the tax payer, have generously supported research, and we have seen a magnificent harvest of new knowledge, new products, new diagnoses and treatments, and even new conceptual worlds in biotechnology, medicine, and industry, much of it in the last 20 years. Do you realize that some 80% of all medical knowledge has been derived in the last 25-30 years? Permit me to illustrate a few of these advances in knowledge and what they mean to use.

Some of you know that I myself have profitted handsomely from this research, and I stand before you today only because of it. I see God's hand in each individual step along the way, and I wish to direct your attention to the way in which He has led researchers over the last 15 to 20 years to work out thousands of small and large questions, to piece together biomedical jigsaw puzzles so that physicians and surgeons can now replace your worn out heart (or other damaged organs), bypass your clogged coronary arteries, substitute an electronic device which will artificially pace your heart, automatically deliver insulin when your Islet cells fail, or replace virtually all of your skin which may have been burned totally beyond recognition.

You have read about each of these miraculous accomplishments in your daily newspaper within the past 24-48 hours; they are becoming everyday events. None of them were possible, or even dreamed of, when I (or even Elmer) were students at Taylor. They have come about through research, because teachers like Dr. Nussbaum have planted the seeds of basic knowledge and inspired the realization in the young scientist's mind that God created much more than any and all of His disciples presently know. That by using his brain and the potential creativity within him, the science student can make the world better through his carefully perceptive research.

I wish to describe briefly the evolution of the currently popular and life-prolonging coronary bypass operation, realizing that it was considered an heroic procedure only 5-6 years ago. Consider but a few of the hundreds of individual research projects which had to be worked out before this particular medical miracle could be successful. Perhaps I should start with the first catheterization of the living human heart in 1929. A young German physician, Werner Forssmann, working with a mirror, inserted a urinary catheter into his own basilic vein and pushed it on into his right heart, anchored it in place, and then walked up a flight of stairs to confirm its position by x-ray examination. He was primarily interested in injecting therapeutic drugs directly into the heart, and he had no concept of the immensely productive potential of the research field he was opening up. His Chief of Medicine repremanded him severely and forbad his ever doing it again, and to my knowledge, he never did. But he had shown that it was possible. A year later, another German physician (Klein) employed the same route to a patient's heart. The procedure became routine in

the 1950s and opened vast areas for acquisition of new information regarding cardiac function, diagnosis and treatment of disease.

In 1939 Dr. John Gibbon, a young surgical resident from the University of Pennsylvania, sat through the night with a patient suffering from pulmonary embolism, and realized that he could save her life if he could temporarily substitute a simple pump for her heart while he excised the blood clot from her lung vessels. Unfortunately, no such pump was available, and the patient, with thousands like her, died. Dr. Gibbon determined that he would design and build such a pump, and he experimented with hundreds of models between 1939 and 1954 when he finally made the first one work successfully. But before Gibbon could make his pump work, there had to be a way to prevent blood from clotting as it flowed through the pump. He was dependent upon Charles Best for the preparation of a substance (heparin) which would accomplish this. (And incidentally, that was the same Dr. Best who helped to discover and develop insulin.) Consider the individual experiments required to learn which blood vessels could be used to interconnect the aorta and the distal portions of the coronary arteries, and the experience needed simply to sew these blood vessels together. And still nothing could be accomplished for the patient with severe coronary occlusion until the precise location of the blockage could be determined within the arteries. This was, in fact, accomplished by Dr. Mason Sones during the early 1960s when he injected radio opaque dye directly into the coronary arteries under fluoroscopic visualization.

Mechanisms of oxygen and carbon dioxide transport, ability to <u>stop</u>, and then to <u>restart</u> the heart after

surgery, matching blood and tissue types, maintaining blood volume, and countless other complex problems required definitive solutions before the spectacular bypass procedures could become reality. When coronary bypass surgery was introduced in 1968, at least 95 of every 100 cardiologists believed (and I emphatically taught) that coronary vasospasm could play no role in the intense anginal pain which signaled severe coronary disease. Today there would probably be 100% agreement that coronary vasospasm is an important element in many kinds of angina. (Recall my comments regarding the validity of the so-called "facts" we teach in our science courses.) At least 300,000 aorto-coronary bypass operations were performed in the United States alone last year, and many of us who walk among you would not have been so fortunate only a few years ago.

You are all aware of the dramatic announcement of the first successful transplantation of a human heart less than 20 years ago. This occurred initially in Dr. Christian Bernard's hospital in South Africa, and it was quickly repeated some 500 times in other hospitals all over the world, but with less spectacular success. This lack of success was not because surgeons couldn't handle the cutting, sewing, and the plumbing problems, but because the body rejected the foreign heart. Within 4-5 years all but a very few hospitals stopped performing the operation. Perhaps you did not realize that many researchers worked even harder to learn why the transplanted hearts were rejected. They identified and elaborated the physiologic system responsible for the rejection, and designed new molecules that would attenuate it. This summer you have read again about heart transplants at Stanford, Pittsburg, Arizona, Minnesota, Alabama, Texas, and more recently even in Chicago, Buffalo, and

Louisville, where they were never attempted before. This time there is great hope that the patients will go home after a brief recovery period, protected by antilymphocyte globulin and Cyclosporin, and go productively back to work. Young people are prime candidates, and their chance of success is better than 80%. The remarkable change in success of these recent operations is not due to the fact that the surgeons are any better. Rather, a small corps of scientists learned through basic, fundamental research, how to counteract the immunochemical rejection problems.

But scientists and surgeons sometimes forget the Genesis story which teaches that "God created human beings, making them to be like himself" (Genesis 1:27). We have learned that when a complex instrument breaks down in the laboratory, we must send it back to the manufacturer in order to find someone who really understands it and can fix it. Shouldn't we also look to God for such understanding of the sensitive, vibrant human body which He created? I learned early as an investigator that conscientious reading of the research literature, hard work and long hours in the laboratory, careful attention to the critiques of my colleagues, topped off by thoughtful and prayerful analysis of all of these components together, generally led me to accurate interpretation of my new data. Serendipity is a term coined by Horace Walpole nearly 250 years ago after his tale of the Three Princes of Serendip, who made a series of fortunate discoveries. It is often used to identify an apparent aptitude for making fortunate discoveries, accidentally. I choose an alternative explanation for the scientist whose life includes time and room for God. If the

scientist will listen, I believe the Holy Spirit will direct his intellect as well as his hands, even in the laboratory. God has opened doors in my career as a scientist that I never dreamed of. In my student days at Taylor I could not have planned the rewarding experience I have enjoyed. I am totally convinced that He has directed the course of my life, and has led me to each of the mountain top experience I have had in research.

I see a parallelism in Paul's advice to his friends in Corinth to what I have in mind for the scientist's guidance in his laboratory: "We impart a secret and hidden wisdom of God, which God decreed for our glory before time began... what no eye has seen nor ear heard. No mind has conceived what God has prepared for those who love him, but God has revealed it to us by his Spirit. For the Spirit searches everything, even the depths of God... So also no one comprehends the thoughts of God except the Spirit of God. We have received not the spirit of the world, but the Spirit which is from God, that we might understand the gifts bestowed on us by God. And we impart this in words not taught by human wisdom but taught by the Spirit, interpreting spiritual truths to those who possess the Spirit" (I Cor. 2:7-13).

Perhaps a scientist's conscience can be coupled to his intellect, or even trained by the Holy Spirit, leading him in the design of his protocol, in making his observations and in his interpretation of results. Most researchers will agree that their best ideas often come when least expected, even in the twilight hours of wakefulness. Could this be the Spirit working within us?

To teach us to walk by faith, God originally hid from us nearly everything we would like to know about the way our bodies function. "As thou knowest not what is the way of the wind, nor how the bones do grow in the womb of her that is with child, even so thou knowest not the work of God who doeth all" (Ec. 11:5). In spite of remarkable advances during the past 2-3 decades, our understanding pales to insignificance beside the wisdom of God. In Scriptures, wisdom is a moral as well as an intellectual quality, more than mere intelligence or knowledge, certainly more than cleverness or cunning. Packer, in Knowing God, argues that to be truly wise, ones intelligence must be harnessed to the right end. Wisdom is the power to see and the inclination to choose the highest goal, together with the means of attaining it. The fruit of wisdom is Christlikeness--peace, humility, love (Jas 3:17)-- and the root of it is faith in Christ as the manifest wisdeom of God. Thus the wisdom God wants to give us is that which will bind us to himself.

As a laboratory investigator I have observed phenomena that were new. I knew the literature well enough to realize that this was the first time anyone had recognized it. I know the soaring feeling that Elmer has experienced under comparable circumstances in his laboratory. The experience is, of course, both an intellectual and a spiritual high. I realized that God elected to reveal this previously unknown portion of His Creation through me. Why did He choose me? Out of thousands of years and billions of people, He chose to show it to me first. Why? I believe the Holy Spirit led me up to, and through the experiment, and prepared my mind for the result. This experience carries deeply spiritual impacts. The old axiom, "God has no hands but my hands" becomes very real at such

moments. Certainly the researcher has responsibility to test and prove his new information, and then to communicate it accurately and effectively. But while he must document the discovery for his peers and in the scientific literature, he is also obligated to honor God who created it in the first place and then through the Holy Spirit allowed him to unveil it for the world.

I close with a quotation expressed a few years ago by Andre Cournand, a truly great cardiovascular physiologist and a Nobel Laureate who first catheterized human patients in 1942 in order to measure their cardiac output; "Knowledge is proud that it has learned so much; Wisdom is humble that is knows no more". Wisdom is one of the greatest treasures God has for us. Listen now to our scriptural text for the morning (from Proverbs, 2:1-6), "My son, if you accept my words, and store up my commandments within you, turning your ear to wisdom and applying your heart to understanding, and if you call out for insight, crying aloud for understanding, and if you look for it as you would for silver and search for it as for hidden treasure, then you will understand the fear of the Lord and find knowledge of God. For the Lord giveth wisdom, and from his mouth come knowledge and understanding."

Elmer N. Nussbaum, Alumnus of the Year, 1966, receiving the award from President Milo Rediger.

Elmer, I have observed many of your behavior patterns (your quiet nature, your love for others, always putting others before yourself, your strong leadership) which I admire very much and have made a conscious effort to incorporate into my own life-style. Thank you for the role model you have been for me in my life over the years.

Timothy J. Burkholder, Ph.D.
Professor and Chairman
Biology Department

Your total commitment to the Lord Jesus Christ has been shown so vividly in all aspects of your living. There are literally hundreds of students around the world today committed to our Lord Jesus Christ because of your influence.

Daryl E. Yost, Ed.D.
Acting President

You have been a godly example to students, faculty and staff in your service for Jesus Christ and your personal intimacy with God. You will stand through time as an example of a humble man of God and an outstanding scholar and one whom we will not only revere, but whom many will choose to emulate.

Robert R. Griffin, MRE
Campus Pastor

You are one of the "academic architects" of the University, and you are certainly one of the pillars in that architecture. Taylor people are richer for the part you have had in our lives as you have served God and your fellow man in the spirit of love and excellence.

Milo Rediger, Ph.D.
President Emeritus

Your life demonstrates how to pursue excellence in everything with quiet dignity, humility and Christian grace. Your work will never retire, Elmer. It will continue for generations as your teaching and loving Christian example will continue in the work and lives of your students for years to come.

Hilda L. Steyer, M.A.
Professor Emeritus
Music Department

I have admired and appreciated you for many reasons: your dedication to Taylor when more lucrative opportunities could have lured you away; your intelligence and common sense--when E.F. Hutton (I mean Elmer Nussbaum) talked, people listened; your gentle, courteous, and good-natured spirit; your exemplary life and commitment to Christ and Christian values.

Hazel Carruth, Ph.D.
Profssor Emeritus
English Department

My days as one of your students generated strong impressions of how a knowledgeable, considerate, Christian professor could and should relate to his students and colleagues. Working with you as a colleague has revived, strengthened and broadened those impressions. The unity in the science division under your leadership which I have experienced and the strong Christian qualities in your family which I have observed are but two witnesses to your gift for serving others which I so deeply admire and appreciate.

Stanley L. Burden, Ph.D.
Professor and Head, Chemistry Department
Chairman, Science Division

Elmer, I appreciate the way you and Ruth Ellen have been friends to Miriam and me. You have always reached out to us, cared about our family and have shown that you really do care. You both represent the Taylor tradition as well as how Christians ought to treat one another.

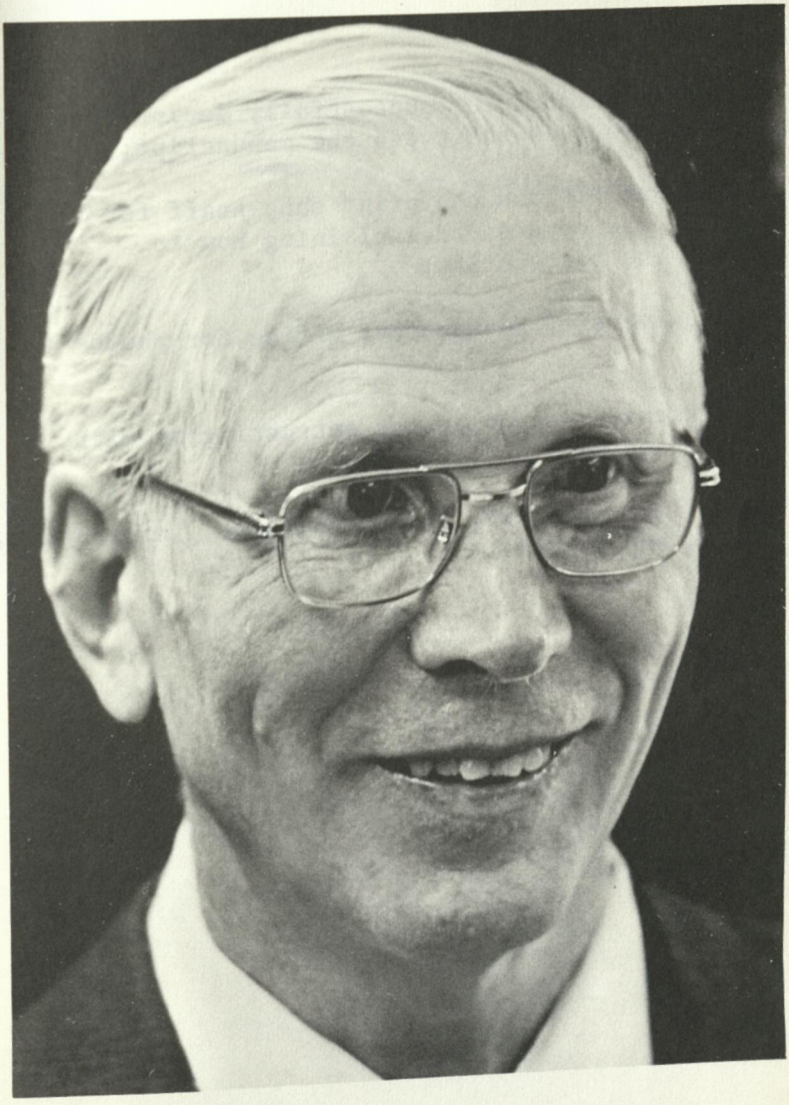
Daniel Jeran, Ed.D.
Professor and Chairman
Education Department

I admire you for your kindness and love that I see you constantly giving to everyone. I have never heard you give a cross or unkind word to anyone. This is a very special trait that very few people have. God bless you, Elmer. We will miss you as our leader.

Dale E. Wenger, M.S.
Professor of Mathematics

It has been my distinct privilege and pleasure to receive (and to read) the many letters contributed for this scrapbook by your friends, former students and colleagues. They reflect the esteem in which you and Ruth Ellen are held -- by all who know you. Perhaps the finest tribute is that of appreciation to you for your sensitivity to persons. Certainly for that reason you have had an importance in my own life surpassed by no other man. You have been a patient and helpful mentor -- a faithful and trusted friend. Truly you have been a model of Christian servanthood to us all. Pray for us that we may carry on in that tradition.

Robert Wolfe, M.S.
Professor of Physics



Elmer N. Nussbaum

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To Dr. Richard Stanislaw for entrusting me with this project; and

To Dr. Elmer Nussbaum, for photographs, information, stories, and himself.

SYMPOSIUM SCHEDULE

Monday, October 29, 1984
SL-102 4:00 p.m.

Dr. David Randall
"A Study of the Cardiovascular Effects of Tolbutamide, an Oral Hypoglycemic Agent for Treatment of Diabetics: One Example of How to Pursue a Scientific Project"

Wednesday, October 31, 1984
Rediger Auditorium 10:00 a.m.

Dr. Joseph Brain
"Science and the Christian College"

Wednesday, October 31, 1984
SL-101 4:00 p.m.

Dr. Joseph Brain
"Magnetometry: A New Tool to Study the Biology of the Lung and Liver"

Thursday, November 1, 1984
SL-102 4:00 p.m.

Dr. John Lee
"Genes, Pseudogenes and Designer Genes"

Sunday, November 4, 1984
Rediger Auditorium 10:30 a.m.

Dr. Walter Randall
"The Lord Giveth Wisdom"