COMPARISON OF SEVERAL TESTS OF BLOOD PRESSURE REACTIVITY

by
Richard D. Remington

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in the
University of Michigan
1958

Doctoral Committee:

Associate Professor Fay M. Hemphill, Chairman
Professor Paul S. Dwyer
Associate Professor Sibley W. Hoobler
Professor Robert J.M. Horton
Associate Professor Charles A. Metzner
Professor Clarence J. Velz

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A series of blood pressure stimuli are studied in an attempt to measure susceptibility to the development of hypertension (high blood pressure). Stimuli which are considered include the stress of initial measurement, cold applied to a hand, breath holding, exercise, CO_2 inhalation, and postural change.

The literature concerning these and several other tests is reviewed and criticized from a statistical point of view.

A standard series of stimuli is developed and applied to a group of four medical students. Stimuli in this series include cold, breath holding, CO_2 inhalation and exercise. In an attempt to determine the significance of various sources of variation including variation between subjects, between tests, between various orders of administration of the tests, and variation from day to day, an experiment designed in the form of six randomly selected Latin Squares is carried out. The procedure does not show such extreme or capricious variation to make it unsuitable for further study.

A similar test series substituting a postural change for CO_2 inhalation is applied to 2 groups of children between the ages of 8 and 18, with 50 children in each group. One group is composed of children of hypertensive parents treated at the University of Michigan Hyper-

tension Unit and the other a matching group of school children enrolled in the University of Michigan grade and high schools. The test series is composed of 32 determinations of blood pressure and 31 determinations of pulse rate on each subject.

The children of hypertensive parents show uniformly and significantly higher mean systolic blood pressure levels than the school children, both for stimulated and unstimulated readings. The mean diastolic blood pressure levels for the 2 groups are quite similar throughout the test procedure. The mean pulse rates for the children of hypertensive parents are uniformly lower than for the control group.

Analysis of the differences between stimulated and pre-stimulation readings reveals no significant differences between the 2 groups for the stimuli of cold, breath holding, exercise or initial reading. Postural change results in a difference between the groups with respect to change in systolic blood pressure. The fact that a more nearly basal blood pressure level was attained prior to the postural stimulus than for the other stimuli might be in part responsible for this finding. Techniques of linear discriminant analysis are used in analyzing the differences between the 2 groups.

ACKNOWLEDGMENT

The author is indebted to Dr. S.W. Hoobler for suggesting this investigation, for his constant guidance and help with the clinical aspects of the study, and for the use of the facilities of the Hypertension Unit of the University of Michigan Hospital. He is also indebted to Dr. P.S. Dwyer for consultation regarding statistical phases of the project, to Dr. F.M. Hemphill for his constant encouragement and counsel throughout the course of the study, and to the remaining members of the doctoral committee for their cooperation. Finally, the author expresses his indebtedness to the many people who gave assistance in the collection and reduction of the data and in the preparation of the manuscript.

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CHAPTER I

STATEMENT OF THE PROBLEM

General

Hypertension in man is an important condition in many parts of the world. This importance is not only reflected directly by cause of death statistics, but also indirectly by the immeasurable contribution of elevated blood pressure to the total load of sickness and disability in the world.

Cause of death statistics in the case of hypertension are of limited usefulness in assessing its burden on a population. Hypertension is a condition which can pass unnoticed either by patient or physician for many years. It is very often symptom free and frequently is diagnosed only by the capricious occurrence of an insurance or selective service examination. Certainly many cases go entirely undetected.

The prime diagnostic tool in hypertension is measurement of the blood pressure, almost always by an indirect estimate of the pressure in either a brachial or femoral artery. Two different blood pressures are routinely estimated. These are the systolic or maximum pressure within the artery and the diastolic or minimum pressure. Thus a blood pressure estimated and recorded as 120/80 generally means that the maximum intra-arterial pressure is estimated to be 120 millimeters of mercury and that the minimum pressure is estimated to be 80 millimeters of mercury. The history of medical practice regarding hypertension has

been marked by disagreement about the interpretation of a given level of blood pressure. Most authors have adhered to the practice of considering some fixed point of demarcation between "normotension" and "hypertension," although this point is frequently considered to vary for different ages, sexes, or races. The range of suggested demarcation pressures has been very great--at least from 120/80 to 180/110. (The unit for all blood pressures given in this study is one millimeter of mercury.) For a good discussion of the interpretation of a given blood pressure see Pickering (52), pages 170-183. Pickering also points out the disagreement which has existed regarding the effect of aging on blood pressure. Such disagreement regarding basic definitions certainly affects vital statistics on hypertension and emphasizes the need for clarification.

An even more crucial and basic problem lies in the decision on the part of the attending physician to assign a given death to hypertension. If his patient has a history of mild essential hypertension, how, for example, should he interpret a death directly resulting from a cerebral vascular accident? Cause of death statistics cannot accurately reflect the contribution of elevated blood pressure to total cardiac, renal, or cerebral deaths.

It is thus only with grave reservations that one can quote current vital statistics as indicating the magnitude of the hypertension problem in this country. Recognizing these deficiencies, the magnitude of the problem is indicated by the report (73) that for the United States in 1955, of a total death rate of 930.4 per 100,000, the rate for hypertensive disease was 51.8. In addition, elevated blood pressure is irretrievably enmeshed as a complicating factor in the rates

for many other conditions. The contribution of hypertension to these rates cannot be directly estimated.

Only a small proportion of cases of elevated blood pressure can be assigned to a specific etiology. Apparently no good estimate has been made of the exact proportion of secondary hypertension in a population, but clinicians agree that it is small--probably of an order less than 5%.

In the absence of good information regarding etiology, medical practitioners have been forced to try to reduce blood pressure without fundamental understanding of the basic disease process or processes. Thus, while it seems most reasonable to regard elevated blood pressure as a clinical sign, no one is yet really sure just what it is a sign of. Therapeutic efforts to lower blood pressure are becoming increasingly successful and practical with the discovery of new hypotensive agents. In fact, study of the action of drugs may eventually clarify the pathogenesis of what today must be called essential hypertension.

The influence of heredity will be discussed in the next chapter when the historical background of the topic is given. In summary most observers agree that there is a familial factor in hypertension. There is considerable disagreement regarding the specific nature of this association. For example, the proportionate role of hereditary and environmental factors is not understood. The mode of genetic transmission, if any, has not as yet been explained. However, it can be said with some assurance that children of hypertensives run a higher risk of developing the condition than do children of normotensives.

Statement of the Problem

Assuming the existence of a familial factor or factors influencing development of hypertension, is it possible to devise a simple procedure or sequence of procedures which will discriminate between children of hypertensives and children of normotensives? That is, is there available a simple method for describing and quantitating the increased risk inherent in having a hypertensive parent? If a really clear-cut discrimination were possible, a powerful diagnostic tool would be available. At least one could possibly say, "This individual reacts to these tests more like a child with a hypertensive parent than like a child with normotensive parents." The reason for stating the problem in terms of children seems obvious. Here is a health problem whose onset and course is not well understood. It is apparently time-connected, i.e., "runs a course." There exists a group of individuals with relatively higher probability of developing the condition—namely children of hypertensive parents. Furthermore, since the blood pressure must somehow pass from lower to higher levels as the disease process or processes continue, it is possible that a period of increased vascular response to a variety of external stimuli exists. This is by no means a new idea.

The methods used in this study could only show an association (if a strong enough association existed) between the familial effect and the effect of test response. As such they would at best only provide an indirect answer to the problem. A logically stronger and more direct association would require a lengthy and in this case impractical follow-up.

Scope

The problem of identifying at an early stage those individuals who have a relatively higher risk of developing a disease process is a central one in preventive medicine and public health. In the case of hypertension, such a group was apparently available to the study. They were the children of known hypertensives. Couldn't a group of such children be compared with a group of normal children in the hope of finding a difference simple to describe and having a direct relationship to blood pressure and its fluctuation? The study was limited to children--in particular children between the ages of 8 and 18. Obtaining a probability sample of a large population of children in general or children of hypertensives was out of the question with existing resources of time, personnel, and money. Therefore, available groups were used--specifically, children of bona fide essential hypertensive parents seen at the Hypertension Unit of the University of Michigan Hospital, and as a control group, children attending the University of Michigan grade and high schools--schools in which central activities are experimental teaching, teacher training, and research. Facilities allowed for examining approximately fifty children in each group within a period of six months.

Since significance tests were applied to the data which were collected, it is necessary to specify the population to which these tests and other statistical inferences apply. In situations for which it is impossible to actually sample some physically existing population, an alternative is to carefully specify the characteristics of the groups which are used. In this way hypothetical populations having the

same characteristics can be postulated. Inferences which are made can thus be applied to these populations. The statements made in the preceding paragraph delineate the characteristics of the groups used in the study. They serve to delimit the populations to which inferences apply.

The kinds of tests available for trial necessarily had to be limited. Only tests specifically chosen to change blood pressure, i.e., tests of blood pressure reactivity were considered. Procedures which could be carried out under conditions of limited physical facilities and with personnel of limited training and experience were sought. Each procedure had to be applicable to children. Of course the development of a rigidly standardized test protocol and some estimate of response variability within individuals was necessary. For that reason an extensive program of pilot testing was carried out. Facilities of the University of Michigan Hypertension Unit and Medical School were made available for this purpose.

Procedural Steps

1. A program of initial trials of proposed tests of vascular reactivity was undertaken for the purpose of perfecting techniques.

2. A carefully designed experiment to estimate several sources of variability of the proposed procedure was carried out using a group of medical students as subjects. The design and analysis of this experiment was a key statistical phase of the project.

3. The test procedure as finally standardized was applied to the group of children of hypertensive parents and to the control group, with as many variance stabilization features designed into the study as practical. Linear discriminant analysis was applied to the data in the

hope of finding a clinically and physiologically meaningful set of variables which discriminate between the two groups.

Limitations of the Approach

Several inescapable limitations existed:

1. The impossibility of establishing a direct relationship between test response and eventual development of hypertension.

2. The size and composition of groups imposed by limitations of time, personnel, and money. This in turn limited the populations to which inferences could be applied.

3. The lack of assurance that the differences observed really reflected familial association and were not wholly or in part due to the effects which were confounded with familiality.

4. The limitation of the type of test procedure considered. This was somewhat different from the other limitations in that it was very largely intentional. A widely applicable procedure was sought, and thus only rather simple stimuli were considered. More complicated procedures were outside the scope of this study.

CHAPTER II

REVIEW OF LITERATURE

General

The literature on blood pressure is quite voluminous. A comprehensive bibliography of this literature for the years 1920-1950 compiled by E.K. Koller and Jacob Katz (44) under the sponsorship of the Recess Commission on Hypertension of the Commonwealth of Massachusetts, lists 16,460 references. This bibliography is so arranged as to be of maximum usefulness to the research worker in hypertension. The work is in 3 volumes, of which Volume I is a title and author index arranged alphabetically by author. Volume II is a topical and author index, and volume III gives abstracts of selected papers indexed in volumes I and II.

This bibliography grew out of a symposium on hypertension sponsored by the same commission. Topics presented at the symposium included the epidemiologic approach to the study of hypertension; the problem of defining hypertension; the determination of etiology of hypertension; renal pressor, neurogenic, psychogenic, hereditary and environmental hypotheses concerning etiology; and future possibilities for research. The proceedings of the symposium were published by the Commonwealth of Massachusetts in 1951 (72).

An excellent general reference text on the subject of high blood pressure is Pickering (52). Several topics are discussed which are relevant to the present research. Among these are measurement of arter-

ial pressure in man, the blood pressure in various population groups, and how it is affected by age; pressor tests; and the role of inheritance in essential hypertension.

A number of studies have been made to determine the distribution of blood pressure in a population. In 1939 Robinson and Brucer (59) studied a large group of people accepted for life insurance in the Chicago area in an attempt to fix normal and abnormal values for blood pressure. However, this study contains several rather serious defects of a statistical nature which were nicely summarized by Treloar (65). An example of these defects is the arbitrary truncation of distributions, begging the question of "normal" blood pressure.

Definitions of normal and abnormal blood pressure have never been agreed upon. This is apparently due at least in part to confusion of "normal" in the sense of "usual" or "conforming to the norm," with "healthy." These two concepts are not equivalent. We cannot necessarily assume that the average blood pressure of any particular age and sex subgroup of the American population is a "healthy" or "physiologic" blood pressure. Until these two uses of "normal" are clearly distinguished, we cannot hope for a good definition of the ideal blood pressure for a given person. Certainly the true answer is buried deeply within the person, and has to do with the condition of his circulatory system, his ancestry, possibly his diet and mode of life, and many other factors. What we are searching for today is an indirect estimate of the condition of this inner complex, preferably based on a conventional auscultatory blood pressure determination. We may be asking too much of this measurement.

Master, Dublin, and Marks (47) studied the blood pressure records of 74,000 people applying for work in American factories during World War II. Based on their summary statistics for each age-sex sub-distribution, they made strong recommendations for completely arbitrary definitions of normal, borderline, hypotensive, and hypertensive blood pressure levels. These levels were to be determined by deviations of a certain number of standard deviations from the mean of each distribution. They urged application of these standards to at least the population of the United States, with no apparent concern for the fact that they had not sampled this population and furthermore urged adoption of a statistical standard of normality of the most artificial sort. Other objectionable properties of this study could be mentioned, but these seem to be the most serious.

In another attempt to determine the blood pressure distribution in a large population, Hamilton, Pickering, Roberts and Sowry (32) surveyed the pressures of a group of British clinic patients. These patients were chosen from clinics for conditions not known to be related to blood pressure. The age and sex sub-distributions were again studied. Tests of significance revealed some departure from normality, generally involving positive skewness. The fact that this is again a highly selected group limits the population to which inferences can be applied. These same authors published a paper (33) which gave a method for calculating standard blood pressure scores eliminating the effects of age and sex.

Comstock (14) has recently surveyed the population of a biracial community in Georgia. From a census of the county which was carried out 8 years before his study, he selected a 2% systematic sample. There was

an inherent clustering tendency by family group in the list of serial numbers he sampled, resulting in lowered probability of selecting more than one individual from a family as compared with simple random sampling. However, the most serious defect results from the eight-year gap between the census and the blood pressure survey. Emigration was of such an order that readings were only collected from 60.8% of those who fell into the sample. The effect of this low response rate cannot be estimated.

There have been several attempts in recent years to collect blood pressures from entire communities. An excellent community study was done by Boe, Humerfelt, and Wedervang (9) who collected blood pressures from the adult population of Bergen, Norway. The data obtained were carefully and thoroughly analyzed statistically. Another of these studies is that being carried out by the National Heart Institute in Framingham, Massachusetts. See for example Dawber, Moore, and Mann (16). Determinations of blood pressure are a secondary part of this study, which is scheduled to continue for several years.

Any proposed definition of normal and abnormal blood pressure should meet the test of follow-up study. That is, the proportion of "abnormals" showing no progression or sequelae and the proportion of "normals" showing significant progression or sequelae should be estimated. A good definition should at least minimize these two proportions.

Unfortunately, not many follow-up studies have been carried out in blood pressure research, owing to the normally long course of benign essential hypertension and the correspondingly long follow-up period required. One such study, however, was done by Hines (37) at the Mayo Clinic with interesting results. He rechecked the blood pressures of

1,622 former patients either 10 or 20 years after their first visit. A very sharp spurt in incidence of later disease is noted for both the 10 and 20-year groups at a diastolic pressure on initial visit of 85 mm. Hg. The same criticism regarding sampling (or lack thereof) applies again here, but the results are interesting nonetheless.

In addition to the study of Comstock (14), many other studies have been designed to estimate racial and regional blood pressure differences. Two summaries of the literature on this subject have appeared recently. Bays and Scrimshaw (8) point out the difficulty of comparing different studies, due to the varying degree of control of concomitant variables like weight and technique of measurement. Kean and Hammill (43) review the data on blood pressure of primitive peoples. They present a table giving mean blood pressures at different ages for many different racial and ethnic groups as reported by many different investigators.

There seems to be some tendency today to discount the value of a single blood pressure determination because of the many sources of variability of blood pressure. However, Kurlander, Hill, and Enterline (45) made an interesting study which indicates that blood pressure measurement is a rather good screening device for heart disease and hypertension when compared to the chest X-ray read for heart abnormalities, the medical history, or the electrocardiograph. They used these 4 methods to screen 858 persons who were subsequently given a complete cardiovascular workup as a check. The screening criterion for blood pressure was either a systolic greater than 150 or a diastolic greater than 90. Using this criterion, one blood pressure reading located 86.3% of those with diagnosed heart disease or hypertension, and classified negative

74.0% of those without diagnosed heart disease or hypertension. This was a better performance than that of any of the other screening procedures.

The Measurement of Blood Pressure

Pickering (52) devotes an entire chapter (Chapter Two) to this subject. In addition to a historical summary of various direct (involving puncture of an artery to determine its internal pressure) and indirect methods of measuring blood pressure, the chapter also presents discussions of the comparative accuracy of direct and indirect methods and the effect of arm circumference.

Current recommended American practice for determination of arterial blood pressure by sphygmomanometers was described in 1951 by the Committee of the American Heart Association to Revise Standardization of Blood Pressure Readings (10). Currently, the chief difference between American practice and that of some other countries, including England, is in the determination of diastolic pressure. In England, the beginning of Phase IV of the Korotkoff sounds--the abrupt muffling of sounds prior to their complete disappearance--is the criterion. In America the above committee has recommended the end of Phase IV--complete cessation of sound--as a better criterion. However, the question as to whether one method is superior is not yet settled. There are at least two points which must be considered. (1) Which method, when used clinically, gives smaller measurement error? (2) Which method gives values closer to true intra-arterial diastolic pressure?

This controversy points out one thing which must be kept clearly in mind when comparing different studies. Clear understanding of which

diastolic criterion is used in a particular study is necessary for comparative purposes.

Ragan and Bordley (56) studied 51 adult subjects and accumulated 138 records comparing direct and indirect methods of measurement. They found that the contour of the pulse wave apparently affects the accuracy of indirect systolic determination, as does arm size.

Familial Influence on Blood Pressure

The fact that there is some tendency for high blood pressure to "run in families" is well established. Many studies indicate the existence of this association. However, there is no general agreement as to its nature. This remains one of the currently unsolved problems in blood pressure research. The exact mode of genetic transmission, if any, has not been discovered, and the possibility that part or all of the observed association results from environmental rather than hereditary factors has not been ruled out.

Pickering (52) devotes Chapter 9 to this topic. However, the major portion of the chapter is devoted to a discussion of the research project on this topic undertaken by Hamilton, Pickering, Roberts and Sowry (34).

In this study a comparison is made between blood pressure distributions in the population sample discussed above (32) and those in 376 first-degree relatives (parents, children, or siblings) of known hypertensives and in 373 first-degree relatives of normal controls. The distributions in the control series did not differ markedly from those in the population sample. Relatives of hypertensive subjects had higher pressures in all age groups from the second through the eighth decades.

The resemblance between arterial pressures of relatives is independent of sex. The resemblance to the propositus (person with whom a genetic study begins) is the same for parents, siblings, and children. The authors tend to discount the importance of environmental factors in accounting for the differences observed. As evidence they cite several references indicating a greater resemblance between blood pressures of monozygotic than of dizygotic twins. It is concluded that blood pressure is inherited as a graded characteristic like height and is probably multifactorial in origin. Thus they indicate that the inheritance of arterial blood pressure probably follows a very complex genetic pattern.

Miall and Oldham (48) have recently applied the methods of Hamilton, et al. (34), ostensibly to a better sample. In describing their methods of sampling they say they tried to get a " . . . more representative sample of the general population, and chose our propositi by a random method from the total population over the age of 5 years of a South Wales mining valley, the Rhondda Fach, and thus avoided the artificial division of propositi into those with normal and those with abnormal pressure." Whatever their cryptic "random method" can mean, their sampling fraction was 1 in 90. They managed to measure the casual blood pressure on 95% of their 261 propositi, and also got blood pressures on 98% of the first-degree relatives of these propositi living within 25 miles of the valley, excellent response rates for this type of study. All their readings were taken after at least 5 minutes of rest (seated), and arm girth was measured in each case. The observed relationships between arm girth, weight, and blood pressure led them to wonder if blood pressure inheritance could be entirely explained by weight and arm girth.

To this end an exactly comparable survey was done in the Vale of Glamorgan, a predominantly agricultural area 15 miles from the other. After the 2 groups were found to be very similar, the data were pooled. A combined age and arm girth adjustment was done. They found that below age 37 in females and age 45 in males, no age adjustment was necessary if an arm girth correction was made. Above these ages, however, the blood pressure, after correction for arm girth, increases with age by an almost constant percentage; the percentage increase from year to year has a value of 1.4 for females and 1.2 for males. Their most interesting result, however, is that after the effects of age and arm girth have been removed, the slope of the linear regression of relatives blood pressure on that of propositus has increased, i.e., that there is a more nearly direct relation between the propositus' score and those of his first-degree relatives. This is to date one of the better studies of this question and presents some very interesting results.

In 1936 Ayman (3) studied the blood pressure of 1,524 members of 277 families. That is, he took the blood pressure of every available member of various "unselected" hypertensive and non-hypertensive families. He used the following definitions: above 160/90 was considered essential hypertension and above 140/80 was considered elevated blood pressure in persons 14-39 years of age. He noted that if both parents were normal, 3% of the second generation had elevated blood pressure. If one parent had essential hypertension, this figure rose to 29% of the second generation; while when both parents had essential hypertension, 46% of the next generation had elevated blood pressure. Of 70 siblings of normotensive propositi, 37% had essential hypertension. Of 86 sib-

lings of hypertensive propositi, 65% had essential hypertension.

Hines (38) reported on data from follow-up of 1,374 persons at 10 or 20 years after their first visit to Mayo Clinic. None of these people was hypertensive at the initial visit. A higher incidence of subsequent hypertension was found in those with a positive family history of hypertension. For example, in the 20-year group 44.5% of those with a positive family history developed the disease as compared with 7.5% with a negative family history.

Hines, McIlhaney, and Gage (42) have recently completed a study of monozygotic and dizygotic twins. Seventeen pairs of twins were given detailed clinical study. Eight of these pairs were identical twins with hypertension. The 3 female pairs tended to have similar blood pressure levels and sequelae of hypertension, but the 5 male pairs showed more intra-pair variability of these characteristics. Six pairs of identical twins in the clinical study were normotensive, while the 3 pairs of fraternal twins consisted of one hypertensive and one normotensive individual. Two hundred additional pairs of twins were studied. Of these, 87 were apparently identical, while 113 were fraternal. The identical twins had more similar blood pressure levels than the fraternals and more similar pressure responses to cold (see below). The authors summarize their results by saying, "These findings are evidence that a genetic factor is concerned with the mechanisms that control blood pressure in persons with normal blood pressures as well as in those who have essential hypertension."

Children's Blood Pressures

Various groups of children in many different countries have been

studied in an attempt to establish norms for each age-sex subgroup. In general the comments regarding lack of sampling sophistication which were made earlier apply equally well to these studies. At the present time there seems to have been only the slightest penetration of modern knowledge regarding the design of probability samples into the blood pressure literature. This certainly must change before valid inferences regarding blood pressures of existing populations can be made.

In 1921 Faber and James (24) published the results of 2,710 measurements of the blood pressures of 651 boys and 450 girls. In this series, both systolic and diastolic pressures show an apparent rise with age. Children from ages 3 through 17 were measured. No significant sex difference was found. In this study there is no statement describing the group from which the children were drawn.

Sundal (64) reported on the blood pressures of 1,049 boys and 883 girls in schools of different social levels in Oslo, Norway. In this group, the blood pressure also rises with advancing age--the most rapid increase being between the ages of 9-12 for girls and 10-13 for boys, or roughly the period of puberty. High school students had higher blood pressures than public school students of the same age, an indication of a possible socio-economic effect. In children of the same age, the readings were a little higher for the heavier and taller ones.

Graham, Hines, and Gage (30) published a study " . . . based on 25,000 determinations of blood pressure made by one physician with a constant technique and under identical circumstances on 3,580 school children living in a small city . . . " in Minnesota. These children were followed every year from age 5 through 16. All measurements were taken in the sitting position in the right arm using a cuff of width not

more than two-thirds the length of the upper arm. Three widths were used—12 cm., 9 cm., and the 12 cm. cuff folded in half. Contrary to the studies just reported, a very smooth linear regression on age was found. The regression equations were: systolic blood pressure in mm. Hg. = 85.04 + 2.34 (age in years) and diastolic blood pressure = 51.74 + 0.60 (age in years). Age-sex distributions and summary tables are presented in the paper. An increase in variance of the age specific distributions with increasing age is evident. This change becomes particularly evident at puberty.

Haggerty, Moroney, and Nadas (31) present norms for each age by summarizing 7 "accurate" series in the literature. This summarization fails to show any marked changes at puberty, possibly in part due to the authors' combining of the sex distributions. This table is again presented in Nadas' recent textbook (50).

Downing (20) reports on the blood pressures of girls from 3 to 16 years of age collected at the University of Chicago Laboratory School. The author also presents a chart summarizing data on children's blood pressures from other studies. Girls were followed for as many years as possible, with blood pressures apparently being taken during the course of a routine yearly physical examination. Among the conclusions of the study were: (1) there is a considerable day to day blood pressure variation in the same child; (2) the blood pressure increase from year to year is not necessarily constant in the same child; (3) each child has his own blood pressure pattern.

The Effect of Size of Cuff on Blood Pressure Determinations

Proper measuring technique is essential to the success of any

blood pressure study. In studying children, an important consideration is the selection of a blood pressure cuff of the proper width for each child studied. An extensive literature exists on this subject.

Robinow, Hamilton, Woodbury, and Volpitto (58) examined 62 children, both Negro and white, of ages from 6 weeks to 13 years. Many of these children were healthy, whereas others were convalescing from infections. The authors first did auscultatory determinations with 5 different cuff widths under basal or near basal conditions. The cuff sizes used were 2.5, 4.5, 6.5, 9, and 11.5 cm. Then in 48 children they did an arterial puncture to get simultaneously a direct determination and an indirect reading using a guessed cuff size. Working with the difference between these 2 readings and making the tacit assumption that such a difference is constant within a child at any pressure level, they returned to the curve previously constructed using the 5 different cuff sizes, and so determined the proper cuff width for that child. This method worked well for systolic pressures, but for diastolic even the widest cuff used was often not wide enough. They found that proper cuff width so determined has a correlation coefficient of 0.71 with arm girth, a coefficient of 0.53 with age, and a coefficient of 0.67 with arm length. Each of these coefficients is significantly different from zero.

In 1939, Day (18) published results of observations made on 41 individuals aged from 4 months up. Working entirely with indirect methods of measurement and comparing 2 different cuff widths at a time—one on each arm—he found the following differences in systolic blood pressure:

1. In 190 pairs of observations, the 5 cm. cuff gave readings an average of 19.4 mm. higher than the 13 cm. cuff.

2. In 79 pairs of observations, the 7 cm. cuff gave readings an average of 10.2 mm. higher than the 13 cm. cuff.

3. In 97 pairs of observations, the 9 cm. cuff gave readings an average of 7.7 mm. higher than the 13 cm. cuff.

4. In 30 pairs of observations the 13 cm. cuff gave readings an average of 2.4 mm. higher than the 20 cm. cuff.

The author found no significant association of the errors with arm circumference. He took repeated readings with several different cuff widths on the same individual to get cuff size curves for that individual, thus controlling some of the intra-person variation by averaging readings at the same cuff width in the same person. This removes some of the problems of maintaining basal levels when cuffs are changed and other disturbing factors interfere. He finds that different individuals have different curves of blood pressure on cuff width.

The Committee of the American Heart Association to Revise Standardization of Blood Pressure Readings recommended in 1951 (10) the use of a cuff of width 20% greater than the diameter of the arm or thigh in which the measurement is taken.

Nadas (50) page 14, gives a simple rule of thumb which is easily applied in clinical practice: "The size of the cuff is extremely important in obtaining results comparable to those of arterial blood pressure obtained directly by arterial puncture. As a rough guide, the cuff should cover approximately two-thirds of the upper arm or leg."

Early Stages of Hypertension

The development of tests which can detect susceptibility to hypertension before the blood pressure is permanently elevated is the cen-

tral purpose of the present study. Many writers agree that in the typical course of essential hypertension, an early phase is marked by extreme lability or variability of the blood pressure.

Whitelaw and Smithwick (68) say, "We would feel that the natural history of hypertension of the so-called 'essential' type, which constitutes by far the greatest number of cases, is one of progression from the normo-tensive hyperreactor to sustained hypertension." Ayman and Goldshine (5) put it as follows: "Under various stimuli, such as excitement, pain, cold, heat, and exercise the blood pressure of such patients (early hypertensives) varies markedly." However, the evidence to support this point of view is by no means complete or conclusive. It is hoped that the present study can throw further light on the problem.

Levy, Hillman, Stroud, and White (46) analyzed the medical records of 22,471 army officers. Some definitions they used were as follows:

1. Transient hypertension—over 150 systolic or 90 diastolic, followed at a later examination by a reading below these levels.

2. Sustained hypertension—over 150 systolic or 90 diastolic with no recorded subsequent drop to below these levels.

They found that, at all ages, sustained hypertension developed more frequently in those with previous transient hypertension than in those without. The retirement rates for the transient hypertensives were also higher—significantly for cardiovascular-renal causes of retirement, but not significantly for other diseases. Over age 35, the death rate from cardiovascular-renal diseases is significantly higher in every 5-year age group for the group with transient hypertension. The over-all death rate from other diseases combining all age groups is significantly higher for the transient hypertensives. The death rate from neuro-

psychiatric disorders after age 30 is uniformly significantly higher in the group with transient hypertension. The actual differences in rates are not given. Almost all of these deaths were suicides.

While many flaws can be found in this study (e.g., the observations were made at routine Army or Veterans Administration physical examinations by persons other than the authors, using more or less unstandardized techniques) the results are presented only to suggest the possible importance of transient hypertension. Since transient hypertension does not invariably lead to sustained hypertension or cardiovascular-renal disease, these authors state: "Our next problem is to define, if possible, adequate criteria fro the recognition of those persons in whom transient hypertension is an early sign of future trouble."

Tests of Vascular Reactivity

General

The foregoing discussion leads naturally into the problem of how to test for vascular hyperreactivity. The problem is similar to that in diabetes mellitus except that much more progress has been made toward determining just who is susceptible to development of this disease. The glucose tolerance test or the newer cortisone-glucose tolerance test of Fajans and Conn (25) are examples of what is needed for hypertension.

Smithwick and Robertson (62) state that "More detailed studies of this phenomenon (hyperreactivity) seem indicated . . . " and further that "If a large scale study of the epidemiology of hypertensive cardiovascular disease in man were undertaken, it would seem wise to accumulate data concerning hyperreactivity as part of such a project."

A large number of different kinds of stimulation have been pro-

posed and studied as tests of vascular reactivity.

Cold Pressor

This is the most widely known test of vascular reactivity. There is very extensive literature concerning the test, and the procedure is still used as a routine test of vascular response to aid in the diagnosis of hypertension in many places. The test involves immersing a hand in ice water (temperature less than 4° C) for 60 seconds. Blood pressures are taken after 30 seconds and 60 seconds of immersion. The subject should be resting prior to the test with his blood pressure as close to a basal level as possible.

Hines and Brown (39) originally proposed this procedure in 1932. Another paper describing their early work with the test was published in 1933 (40). They observed 230 subjects. Using an arbitrary definition of hyperreaction to the test, they found that in the immediate ancestry of more than 75% of the hyperreactors there was a history of hypertension or of apoplectic death. At least 98% of the subjects with essential hypertension had hyperreactive responses.

Hines (35) measured the cold pressor responses of 400 school children. He found hyperreaction in children as young as 6 years of age. Eighteen per cent of the entire group were hyperreactive by his standard. The reaction of diastolic blood pressure was much greater in these children than in his series of adults.

Hines and Brown (41) reported on a preliminary study of 190 members of 15 family groups. They concluded that the vasomotor reaction to the cold pressor test follows an inherited pattern and that the excessive or hypertensive type of reaction occurs in families having a history

of hypertension.

Hines (38) reported the reactions of 256 members of 30 families. He summarized his results by pointing out that if one parent had hypertension or had normal blood pressure but was a hyperreactor to the cold pressor test, and the other had normal blood pressure and was a normal reactor, 43.4% of the children were hyperreactors to the cold pressor test. If both parents had hypertension or were hyperreacting normals, 95% of the children were hyperreactors.

Hines, McIlhaney and Gage (42) found more similar cold pressor responses among identical than among fraternal twins.

This series of studies indicates that the cold pressor test rates high priority for consideration in the present study. The reported hereditary influence on response, suitability of the test for application to children and increased response by hypertensives are factors of importance.

Briggs and Oerting (13) on the basis of measurements on 124 individuals concluded that hypertensive males and females both exhibited a characteristic type of cold pressor response. This involved a more marked elevation of systolic blood pressure, with a slower return to basal pressure. Normal individuals, on the other hand, responded with a rapid rise and fall of systolic pressure. The diastolic changes were not uniform or specific in character. In this series the observed differences between normotensives and hypertensives were less than in some of Hines' data.

Ayman and Goldshine (5) give a good review of the literature on the cold pressor test up to the time of their paper (1938). They applied the test to 48 normotensives and 88 hypertensives whose average

age was 50, using techniques very similar to those of Hines. Again the groups were arbitrarily divided into 3 subgroups on the basis of test response:

Group I. Normal hyporeactors. There were 38 subjects in this group with a mean rise in blood pressure of 10.5 mm. systolic and 9.0 mm. diastolic.

Group II. Normal hyperreactors. The 10 subjects in this group showed a mean rise of 33.0 mm. systolic and 17.8 diastolic.

Group III. Hypertensives. In this group many subjects were given the test more than once. The average of the highest responses is 33.5 mm. systolic and 19.0 diastolic. The average of the lowest responses is 23.1 mm. systolic and 16.0 diastolic. The authors noted a slightly slower return to normal in Group III than in the other 2 groups. They found that cold caused some blood pressure rise in 98% of their subjects.

The division of normals into hyperreactors and hyporeactors is not justified by any published data showing a jump in the distribution of response at some point. However, in this study enough data are given to enable calculation of over-all average responses for groups I and II combined. When this is done, the average normal response is an increase of 15.2 mm. systolic and 10.8 mm. diastolic, which is still lower than either pair of averages for group III, but much less so.

The authors reported somewhat more within person response variability than did Hines, noting a variability up to 100% compared to his figure of 10%.

Smithwick and Robertson (62) compared results of a postural change test with those of the cold pressor test in 100 normals, 75 tran-

sient hypertensives, and 176 continued hypertensives. The latter 2 groups subsequently underwent sympathectomy. Responses both before and after the operation were analyzed. The results of the postural test will be described below. Again, the 2 hypertensive groups showed greater cold pressor responses than the normals. These responses were diminished after sympathectomy, although not quite to normal levels. It is impossible to say, however, how much of this reduction was due to factors other than the surgery.

Studies have been done in an attempt to determine the physiologic mechanism of the cold pressor response. Wolff (70) tested the responses of a few subjects suffering anesthesia of a limb. In each case the response to cold in a normal limb exceeded that in the anesthetic limb. This author always tested the anesthetic limb first, thereby confounding the effects of order of testing and anesthetic versus non-anesthetic limb. Sullivan (63) administered the cold pressor test to 4 patients with complete hysterical anesthesia of a hand or foot. The response was approximately the same in both extremities, regardless of whether the anesthetic or normal side was tested first. This author concludes that subjective perception of pain and cold is not necessary for completion of the cold pressor response, whereas Wolff (70) feels that his study shows conclusively that response is dependent upon pain perception. While these two studies contradict one another, the fixed order of administration in Wolff's study and the small sample size in both studies make any conclusions tenuous.

There is much disagreement in the literature regarding the significance of the cold pressor test. For example, Pickering (52) states: "It is extremely doubtful what this test means, and in view of the un-

doubted fact that the large responses are not confined to patients with essential hypertension or small responses to those with 'normal' pressures, it seems profitless to pursue it further." Wolff (70) in a literature review, which is part of the study described above, refers to the many conflicting views and cites references on both sides of several questions.

Pickering and Kissin (53) applied a cold stimulus to 16 control subjects and 12 subjects with essential hypertension. They found no essential difference in response between the 2 groups after the effect of age was taken into account. The responses seemed to be larger among older subjects. However, since the groups were not large and since in this study the stimulus involved immersing a hand in ice water for 3 minutes instead of the 1-minute immersion of Hines and Brown (40), comparisons are difficult.

Armstrong and Rafferty (2) studied a group of 166 Air Force officers. These officers were given the cold pressor test and then followed up continuously for 7 years. The authors found that in predicting blood pressure increase in later life, age and basal blood pressure were relevant, whereas cold pressor response was not. The absence of and need for a mathematical model to distinguish hyperreactors from hyporeactors for predictive purposes is pointed out.

Fishberg (28), pages 764-765, discusses the cold pressor test and concludes that there is no justification for regarding an individual as potentially hypertensive on the basis of cold pressor response alone.

A well-designed statistical study to estimate sources and strengths of variation of response to the cold pressor test has never been carried out. This makes opinions regarding the test, which are

either extremely favorable or extremely unfavorable, premature to say the least.

Breath Holding

Ayman and Goldshine (4) proposed a standard 20-second breath holding test as an index of vascular reactivity. At the end of a normal expiration, the subject stopped breathing. Systolic blood pressure was determined after the breath had been held for 20 seconds. A similar period of breath holding was used to determine diastolic pressure separately. Six hundred and fifty applications of the test were made on 150 ambulatory subjects: 55 normal, 95 hypertensive. Reactions to this test and to the cold pressor test were quite similar. In general, however, the breath holding test gave the greater reaction, e.g., after a good basal level was reached, hypertensives responded with an average rise of 40.7 mm. systolic and 25.4 mm. diastolic. The authors concluded that the test is apparently quite reproducible, the major difficulty being that of reaching a good basal level before starting the test. They felt that the response mechanism was apparently different from that of the cold pressor test, because simultaneous administration of the 2 tests apparently resulted in a summation of effects. This reasoning is of course questionable. They point out that while less equipment is required for this test than for the cold pressor test, more detailed cooperation of the subject is needed.

Feldt and Wonstrand (27) compared responses to the cold pressor and breath holding tests in 185 normal and 15 hypertensive clerical workers. As a definition of hypertension, these authors used blood pressures which remained above 145 mm. systolic and/or 95 mm. diastolic after

20 or more minutes rest in a reclining position. Normal subjects were arbitrarily classified on the basis of their test responses as hypo-reactors or hyperreactors. The breath holding test gave a significantly higher response only among normal hyperreactors. In the combined group the reaction to the cold pressor test was the same as or greater than the reaction to the breath holding test in 73.5% of systolic readings and 78.5% of diastolic readings.

These 2 studies disagree on several points--notably in the results of the comparison between breath holding and cold pressor responses. However, all or some part of these differences might be due to a serious defect in experimental design. Both studies have confounded the effects of order of administration of test and test response. That is, Ayman and Goldshine invariably administered the breath holding test to their subjects first and concluded that it gave a higher reaction. Feldt and Wonstrand made the same mistake 7 years later. However, they gave the cold pressor test first and concluded that it gave the greater response. As a result the question of comparing the two tests remains open. The real point is that it is easy today to design studies which sidestep this difficulty and which permit even more complete and detailed analysis.

Valsalva Procedure

This stimulus consists of increasing intra-pulmonary pressure by a forced and prolonged expiratory effort either against a closed glottis, a column of mercury, or some other restraining force. Dawson (17) gives an excellent historical review of the literature on this stimulus. He refers to many excellent studies in much greater detail than our space

permits.

Rushmer (60) tested 3 modifications of Valsalva's experiment on 16 different subjects. These modifications involved elevating a manometer column with the breath: (a) with the lungs well inflated, (b) with most of the supplemental air exhaled prior to beginning the strain, and (c) inhaling, tensing the voluntary musculature, and then forcing air through a fixed leak in the manometer system. Arterial pressures were recorded directly by arterial puncture, using a Hamilton optical manometer. In each test the pressure rose immediately, then quickly fell (to below the resting level on the first procedure described above) and finally increased to the end of the maneuver, after which it first fell precipitously and then rose rapidly in association with bradycardia. The second procedure described above maintains the pressure at a higher general level than the other 2. The gradual increase in arterial pressure toward the end of the straining period has been attributed to compensation on the part of the peripheral vascular system in the form of vasoconstriction. Some data obtained during circulatory collapse apparently due to brachial artery wall stimulation are presented. The primary purpose of these experiments was to devise some test of the efficiency of the cardiovascular system in compensating for the stress applied by means of modifications of the Valsalva experiment. Some criteria which are intended to describe an ideal test are included and are as follows: "(1) the measurement should be objective, preferably in terms of a numerical scale; (2) the apparatus required to perform the test should be simple and readily available; (3) the test should be easy to perform and not produce pain or discomfort; (4) changes in the measured function should be the direct result of the stress applied, with

as few complicating factors as possible; (5) the response of various subjects should be reproducible on repeated testing of the same subjects under the same conditions; and (6) there must be a close relation between the response of the individual to the test and the state of his vasomotor system."

Wilkins, Culbertson and Halperin (69) found that the typical blood pressure overshoot following the Valsalva strain was depressed after lumbodorsal sympathectomy. In the Valsalva procedure, they found evidence of a marked, though brief, reflex vasopressor response due largely to splanchnic vasoconstriction. This indicates the presence of a neurogenic component to account for at least part of the Valsalva response.

Hyperventilation

The effect of prolonged and rapid deep breathing on the blood pressure has been studied by various authors.

Vincent and Thompson (65) studied the effect of hyperventilation on 41 subjects. They used a continuously recording sphygmomanometer arrangement with pressure set 30 mm. below the initial systolic pressure of the subject. The test was carried out with the subject in the sitting position. Subjects breathed rapidly and deeply through the mouth for 30 seconds, but never long enough to produce apnea. Thirty-seven subjects showed a drop in blood pressure of variable depth. The average was 25 mm., the maximum 53 and the minimum 8. The falls were rapid in onset and reached maximum depth shortly after cessation of forced breathing. They observed that the 4 subjects who showed an increase in blood pressure had slow initial pulse rates—at most 62 beats per minute. In the entire series they felt there was a relationship

between initial pulse rates and the amount of the drop in blood pressure. No correlation analysis was done, however.

Raab (55) studied the lowering of blood pressure in patients with arteriolar hypertension and normals during deep breathing. He found much greater decreases in systolic blood pressure in essential hypertensives than in normal subjects. He concluded that there was a direct and constant relationship between the level of the blood pressure in patients with essential hypertension and the extent to which the CO_2 tension of the arterial blood is lowered.

Proger and Ayman (54) collected detailed observations on 7 hypertensive and 3 normal subjects during deep breathing. Blood pressures, alveolar CO_2 tension, alveolar CO_2 percentage at rest, at peak of hyperventilation and after hyperventilation were determined. There was no uniformity of results. Cardiac output increased during hyperventilation in patients with essential hypertension, but vital capacity and pulse rate were not significantly altered.

CO_2 Inhalation

As part of the study discussed above, Proger and Ayman (54) tested the responses of a few of their subjects to the breathing of a CO_2-rich gas mixture (5% CO_2, 95% O_2). They found large increases of blood pressure both in a subject who showed a large response to hyperventilation and one who showed no response. When a combination of deep breathing and 3% CO_2 inhalation was tested, patients with a large drop in pressure during hyperventilation alone, showed no change. This study strongly suggests the possibility of further investigation of CO_2 inhalation as a pressor test.

Exercise

In 1917, Cotton, Rapport and Lewis (15) reported on the effect on blood pressure of repeatedly lifting and lowering 20-pound dumbbells. They studied 3 controls and 7 soldiers who complained of various symptoms following exercise. They varied the amount of exercise of the subjects "according to capacity." They found that pulse rate is highest at the cessation of exercise and declines rapidly in the next 2 minutes to near the resting level. Curves of systolic blood pressure were low immediately after exercise followed by a steep rise for approximately one and one-half minutes and then a gradual fall. (Blood pressures were determined with a Riva-Rocci sphygmomanometer.) Among both groups a wide day to day variation in response was noted.

More recently Eskildsen, Gotzsche and Hansen (23) conducted over 20 experiments using both hypertensive and normotensive subjects. Cycling exercise was performed using Krogle's ergometer with simultaneous, direct, continuous blood pressure determination from a brachial artery. The general results were:

1. Systolic blood pressure rises rapidly after commencing work. It falls after cessation of work, rapidly at first and then more slowly until after 4 to 5 minutes it is often lower than its value prior to the work. An increase in the amount of work increases the blood pressure.

2. Diastolic blood pressure changes little, but generally follows the systolic pattern on a minor scale.

3. Pressure amplitude rises considerably during work.

The authors say: "In hypertonics (hypertensives) we have observed the mentioned variations of pressure accentuated in proportion to what applies for the normal, namely, greater rise of the systolic pressure at

the same work performed, greater amplitude of the blood pressure, greater fall after the work." Although the authors do not comment on the fact, their curves frequently show a drop in diastolic blood pressure after exercise.

Postural Change

Smithwick and Robertson (62) have devised a hyperreactivity test involving a postural change and the cold pressor test. The procedure consists of taking the subject into a quiet room and letting him lie on a bed to rest for 15 to 30 minutes. The procedure is then explained to him following which blood pressures and pulse rates are measured every minute for the next 5 minutes. He then sits up for 5 more such readings, and he then is given the standard cold pressor stimulus. Five more readings are taken, he stands up, 5 preliminary readings are taken and the cold stimulus is repeated exactly as before. Other features of the study including the cold pressor responses were discussed above in the section on the cold pressor test. Before sympathectomy the average effect of changing posture was about the same in normals, transient hypertensives and continued hypertensives. However, defining a postural hyperreactor as one whose average standing diastolic blood pressure is 25 mm. or more above his average lying diastolic, 8% of the normals were hyperreactors as compared to 16% of the transient hypertensives and 14% of the continued hypertensives. After sympathectomy the average postural response of the hypertensives is reduced to below that of the normals. This agrees with the result reported by Wilkins, Culbertson and Halperin (69) that in their table tilting experiments there is evidence of a vasopressor response due largely to splanchnic vasoconstriction.

Psychopressor Effects

A variety of stimuli will be grouped under this general heading. Such things as the exciting effect of the first blood pressure measurement, the difference between clinical and home determination of blood pressure and stimuli evoking pain, fear, and anger responses.

Schachter (61) studied the responses of 33 subjects to pain, fear and anger. Three stimuli were used—the cold pressor stimulus, presumably to evoke a pain response; the stimulus of a threatened or hinted electrical shock to evoke fear; and the stimulus of being berated and railed at by a technician to evoke anger. Eighteen hypertensives showed significantly greater responses to each stimulus than did 15 normotensives. Variance of blood pressure responses in hypertensives exceeded that in normotensives. Significantly positive correlations were found between resting mean blood pressure and psychological rating of intensity of acute fear and acute anger.

An interesting study of blood pressure variability was done by Diehl and Lees (19). They examined the blood pressures of 100 male students at the University of Minnesota, who were healthy enough to have passed a routine college physical examination. Each student was seated quietly at a table. A blood pressure cuff was placed on the arm at the beginning of the measurement period and left in place until the last observation had been made. Readings were then taken every 5 minutes for an hour. All readings were taken near the same time of day. The first systolic reading was higher than any of the others. The lowest reading was the 8th.

Ayman and Goldshine made 2 studies (6), (7) to compare the effect of clinic vs. home measurements of blood pressure. In the first paper

they studied 34 patients with essential hypertension. In every case the average reading taken at home by the patient or some member of his family was lower than that taken in the clinic by the doctor. Differences between the initial home reading and initial clinic reading were as much as 70 mm. Hg systolic and 36 mm. Hg diastolic. In 30% of the cases the systolic home readings were 40 mm. Hg or more lower than in the clinic and in 24%, the diastolic home readings were 20 mm. Hg or more lower. Those with more stable day to day pressure levels showed less difference between clinic and home measurements. The subjects were followed for an average of 22 months.

The second study was designed to estimate the effectiveness of hypotensive drugs, taking into account the difference between home and clinic blood pressure measurements. The authors conclude that it is apparently not possible for the patient to develop an "immunity" to the pressor effect of the physician's presence.

Comstock's epidemiologic study of a biracial community in Georgia (14) was discussed above. However, as a part of the study he gave a tuberculin test to a subsample of his original group. He measured the blood pressure before and after the skin test and again at the time the test was read. The average of the 3rd readings was appreciably lower than the averages of the first 2. The author felt this was due to the subject's becoming accustomed to the procedure.

Other allusions to the effect of the stimulus of blood pressure measurement are rather frequent. For example, Ayman and Goldshine (5) state: "It was also observed that in a high percentage of patients the ceiling level of response to the cold (pressor) test was close to the blood pressure reading made at the beginning of the rest period before

the test." Hines (37), as discussed above, measured Mayo Clinic patients 10 or 20 years after their first visit. He found that reaction to the psychic stimulation of initial blood pressure measurement is a good indication of future hypertension. Finally, Alam and Smirk (1) in a paper which defined and investigated the concept of basal blood pressure say: "Without habituation of the subject by the continuous presence of the observer and by repeated measurements, the blood pressure falls are less than we report."

Miscellaneous

Many other agents have been suggested as having either a pressor or depressor effect. Pickering (52), pages 145-153, discusses some of these. As an indication of the range of stimuli which have been studied, Bradley, Chasis, Goldring, and Smith (12) who studied the depressor effect of pyrogens and Vincent and Thompson (67) who reported on the effect on the blood pressure of listening to music are cited.

CHAPTER III

EARLY PRETESTING

Purpose

A program of trials of several proposed blood pressure reactivity tests was carried out for the purpose of determining technical feasibility of any given procedure. Four medical students took part as test subjects. Measurements were taken by a nurse and the author. Perfecting of technique was the central purpose of the program. In addition, a selection of tests to be used during the main program of experimentation had to be made. While study of the literature indicated some of the problems which can be encountered in practice, actual trial of the procedures with available personnel and facilities was necessary.

Criteria for Test Selection

The fact that children would eventually be used as subjects suggested several criteria by which the suitability of any proposed procedure could be judged. These criteria were further determined by a desire to find tests which could be performed with a minimum of equipment by personnel of limited training and experience. In other words, a test battery applicable under a wide range of conditions was sought. Thus, important criteria were:

1. A stimulus must not be so painful or uncomfortable that application to children would be a problem.

2. The subject should not feel any embarrassment, such as that caused by disrobing or being asked to perform difficult tasks.

3. No possibility of physical injury or damage should exist in the test.

4. Special equipment not likely to be found routinely in hospitals or clinics should not be required.

5. A minimum of personnel should be required to administer the test.

6. The entire procedure should not require so much time as to be impractical.

7. Performance of the procedure should involve minimal expense for equipment and personnel.

8. The nature of the readings taken and procedures followed must be quite simple, both for observer and subject.

9. Close cooperation, attention, or intelligence of the subject should not be an important factor in performing the test.

10. Only stimuli having some effect on blood pressure, cardiac output, or both, should be considered.

Tests Considered

Preliminary review of the literature, discussions of the problem, and consideration of the criteria listed above suggested several stimuli as candidates. These were:

1. Cold pressor stimulus. Here the stimulus is the immersion of a hand in water of temperature less than 4°C. for a period of 1 minute. The only equipment required is a pan of ice water, a thermometer, a bed (if the test is performed in a recumbent position), a stool to

support the pan, a sphygmomanometer, and a stethoscope.

2. Breath holding. The stimulus in this case is the interruption of the subject's breathing, e.g., for a period of 20 seconds. While some cooperation is required of the subject, the only equipment necessary is a chair or bed and blood pressure equipment.

3. The Valsalva procedure. This stimulus is a forced expiratory effort against pressure and a subsequent release of this pressure. It may be accomplished in several ways, e.g., by using the breath to elevate a column of mercury in a manometer or by a forced expiratory effort against the closed glottis. Again, the extent of subject cooperation required is minimal. The only additional equipment possibly involved is a mercury manometer and mouthpiece for blowing.

4. CO_2 inhalation. Here the subject inhales a mixture of CO_2 and O_2. This directly accomplishes the elevation of CO_2 tension of the blood, with resultant effect on sympathetic discharge and vasomotor tone. However, a tank of the compressed gas mixture and inhalation equipment must be available. In addition, the necessary use of a mask involves a psychogenic stimulus.

5. Exercise. Any rather strenuous exercise may be used to increase cardiac output and pulse pressure. No special equipment is required in this case, and beyond a degree of physical coordination and control, little subject cooperation is involved.

6. Postural change. In compensating for the effect of gravity, the sympathetic nervous system alters vasomotor tone after an abrupt change in posture.

7. Hyperventilation. Rapid breathing with reduction of blood CO_2 tension can cause a reduction of blood pressure. See e.g., Raab (55).

Procedure

The initial testing lasted from July 19 through July 26, 1957. In this early period the general attitude was to perfect technique rather than to collect data for analysis.

Therefore, each day several tests were tried on 1 of the 4 medical students. Choice of tests for a given day was dictated mainly by the need for practice in achieving skill. During the pretesting period, the cold pressor test was administered 6 times and gave no particular difficulty of measurement. The method of Hines and Brown (40) was followed quite closely, except that there was no rest period prior to immersion. This was in line with the attitude stated in the preceding paragraph. The subject was in a recumbent position throughout the test.

The breath holding test was modified slightly from that suggested by Ayman and Goldshine (4). Whereas they used two 20-second periods of breath holding and determined systolic and diastolic pressures separately, a single period of stimulation was used in this study. It was thought that this modification would involve less discomfort, be less time-consuming and be easier from the point of view of subject cooperation. In turn it was recognized that systolic pressure must of necessity be determined somewhat earlier in the stimulus period by this method and that, therefore, the results would not be comparable to those of Ayman. The procedure, then, involves cessation of breathing at the end of a normal expiration for a period of approximately 20 seconds, with a conventional blood pressure being taken just before resumption of breathing. The subject is cautioned not to strain. This avoids the possibility of a Valsalva effect. Sitting position is used for the test.

As an exercise stimulus deep knee bends were used. (The subject stands, hands on hips, and alternately flexes and straightens his knees, keeping his back straight.) The reasons for choosing this exercise include the fact that it can be performed with the blood pressure cuff in place on the arm; it requires little space; no special equipment is required; no great skill or coordination is involved. At first, 10 knee bends were tried as a total stimulus. However, in the medical students this fell far short of being an adequate stimulus. The number was therefore raised to 40, which appeared to give a measurable blood pressure and pulse response without overtiring the subject. (On children, however, this number was subsequently lowered to 30.) In the pretest period the test was tried 5 times with no problems of any kind. The subject was seated both before and after the exercise.

The effect of CO_2 inhalation, using a mixture of 5% CO_2 and 95% O_2, was estimated with various lengths of stimulation. The flow rate was altered according to the apparent demands of the subject for more or less volume. This was because as long as the subject was breathing a fixed mixture, maintenance of a fixed delivery volume was not considered necessary. Furthermore, some subjects required more volume as the test proceeded and to deny this certainly would have compounded the stimulus.

The typical response to the stimulus involved hyperventilation with some increase in blood pressure. This will be discussed more completely later. The equipment required caused added complications with this test. The procedure used was similar to that of Proger and Ayman (54), except that instead of 7 minutes, a 10-minute period of CO_2 inhalation with blood pressures taken every minute was adopted. This gave a better picture of the response curve. A shorter period was used initially,

but it was decided that the longer period would provide considerably more information, with little added discomfort or lost time in the process. Tight placement of the mask was always a problem, and some of the medical students were apprehensive and nervous at first (a factor to be considered when working with children). The procedure was carried out 4 times in this period.

Hyperventilation involving voluntary increase in rate of respiration was tried 6 times. Success with this procedure was not good in any case. Control of breathing rate was one problem. However, this could probably be controlled by using a metronome. To control depth of breathing, a tape measure was placed around the subject's chest. This tape was held at a point corresponding to the subject's maximum (inspired) chest girth. The subject was instructed to inhale with each breath until the tape was tight around his chest, and further instructed to breathe rapidly for a preassigned period, but in any case to stop if he felt faint. Sitting position was used throughout. The difficulty of arriving at a standard stimulus which would avoid dizziness or fainting in all cases and still act as a pressor or depressor stimulus led to our abandoning this test.

Various modifications of the Valsalva stimulus were tried. Success with the procedure was not good. The main difficulty was the determination of a variable which could be readily measured using the standard blood pressure cuff. The impracticality of taking a reading during the strain and the rapid change in blood pressure following release of the strain were the basic problems. For these reasons the procedure was dropped from further consideration.

Conclusions

On the basis of the pretesting program several stimuli were judged technically suitable for further consideration under the criteria listed earlier in this chapter. These were cold pressor, breath holding, CO_2 inhalation, and exercise. The Valsalva procedure and hyperventilation were abandoned as a result of this series of tests.

Early in the testing program several important technical decisions were reached. At first an attempt was made to take diastolic blood pressure both at the abrupt change in sound (Phase IV) as recommended in Britain and at the complete cessation of sound according to current U.S. practice (10). It soon became obvious, however, that nurses and technicians trained in the U.S. cannot be expected routinely to hear and record both sounds, especially when rapid determinations must be made, as in some of these tests. Therefore, all diastolic blood pressures in this study were taken at complete cessation of sound.

Other conventions observed included:

1. All blood pressures were taken in the left arm.

2. Pulse rates were taken at approximately the same time as each blood pressure where possible. (There is no opportunity to take a pulse at the time of the blood pressure taken 30 seconds after immersion in the cold pressor test.)

3. All pulse rates were counted for a 15-second interval and multiplied by 4.

4. Conventional aneroid-type manometers were used throughout the study. These were frequently checked for accuracy against a mercurial manometer.

CHAPTER IV

A MULTIPLE LATIN SQUARE EXPERIMENT TO ESTIMATE THE RESPONSE VARIABILITY OF A STANDARD SERIES OF VASCULAR REACTIVITY TESTS

General Background

The program of early pretesting described in Chapter III suggested that several tests be studied more intensively. These tests were the cold pressor test, breath holding test, CO_2 inhalation test, and exercise test. Other tests which were initially considered were ruled out for reasons discussed in Chapter III. (See also the list of criteria for test inclusion on pages 39-40.)

The literature review (Chapter II) indicated that variability of test response between and within subject had never been adequately studied using statistical methods. In fact the concept that over-all variability of test response can, in a well-designed experiment, be partitioned into contributions from several different sources of variation seems not to have penetrated research in this field. The concept that any well-designed scientific experiment must hold all factors constant but one is still quite prevalent.

The advent of more powerful statistical tools for dealing with multi-factor experiments renders this attitude out of date. Mood (49), page 258, says:

> "Most experimental work today is based on the rule: 'Keep all variables constant but one,' an ancient and erroneous dictum which guarantees a high degree of inefficiency. One well-designed experiment, taking account of all relevant factors, is worth dozens or even hundreds of experiments which study one factor at a time keeping the others constant."

In amplifying this point of view, one recognizes that by and large in medical research, it is impossible to control all factors but 1. Work with human populations requires a realistic awareness of the many sources which contribute to the gross or total variance. Not all the sources can be controlled adequately. On the other hand, not all these sources admit treatment as experimental factors which can be "assigned" to particular pre-chosen individuals.

There is 1 serious limitation of the method which studies a single factor at a time, holding all others constant. That is, in situations where information regarding several factors is needed or desirable, the method provides no estimate of the interaction effects between various factors. Erroneous conclusions may result from neglecting these effects. Results involving only main effects of factors may have very different interpretations for different strengths of interactions between the factors.

For example, one might be studying the effect of antibody titer of several types of vaccine preparation on different strains of mice. Suppose there is no significant difference in the response of the different mouse strains to a particular vaccine (varying only mouse strain, holding type of vaccine constant). Suppose there is a significant difference in response for different types of vaccine preparation on a particular strain of mice (varying only vaccine preparation, holding mouse strain constant). An experiment in which there were no simultaneous variation

of both these factors obviously might miss crucial information. For example, suppose one strain of mice responds strongly to a particular preparation and fails to respond to any other preparation. Suppose a second strain of mice responds only to a different preparation. This would indicate that a realistic estimate of vaccine differences can only be made if strain of mice is taken into account simultaneously. There is an interaction effect here that would have been missed by studying the factors separately. This is a simple illustration of what can become a rather complex situation, especially if more than 2 factors are involved.

In this study of reactivity tests it seemed important to have an experiment which would permit estimation of the contribution to the overall variance of the following sources of variation: between test variance, between subject variance, within subject or day to day variance, order of test administration variance, as well as certain of the interactions of these effects.

The same facilities utilized in the pre-testing program were available and the same 4 medical students were used as subjects. A standard procedure was devised for administering the tests.

Description of the Test Series

Each series of tests was carried out in a quiet examining room. Conversation was kept at a minimum, although a tense atmosphere was avoided. An easy, comfortable relationship was the goal in each case. Two observers collected the data - one taking all the blood pressures while the other took pulses, timed the procedure, and handled the necessary equipment.

A standard rest period preceded the test series. The actual pressor tests were administered in an order which varied, but which was selected in advance according to the design described below. The 5 parts of the series were separated by standard 3-minute rest periods. Each of the rest periods was spent in the posture required for the test which followed, that is, lying for the cold pressor and CO_2 tests and sitting for the breath holding and exercise tests. The dates of this series of tests were July 29 through August 15, 1957. All the tests were performed in the afternoon, starting no earlier than 1:30 P.M. The mean length of the 24 test series administered in this period was 69.96 minutes with a standard deviation of 6.51 minutes and a range of 28 minutes (57 to 85 minutes).

Blood pressures were taken in the left arm and pulse rates were taken in the right arm. A standard aneroid sphygmomanometer was used to take the blood pressures. As pointed out earlier the complete disappearance of sounds was used as the criterion for diastolic blood pressure. Two standard recording forms, one to record pulse rates and times, the other to record blood pressures were used throughout this experiment.

Rest Period

Upon arriving for the test series, the subject entered an examining room where his standing blood pressure and pulse rate were taken immediately. He then lay on the bed and blood pressure and pulse rate were determined. (Unless a special exception is pointed out, the words "measurement" or "reading" or "observation" will henceforth mean systolic and diastolic blood pressures and pulse rate.) Readings were then taken every 5 minutes for 20 minutes, i.e., after 5, 10, 15, and 20 minutes rest.

Between these readings the subject was left alone in the room with the lights on. Turning the lights on and off might have been a pressor stimulus itself in this case since an inside room with only artificial lighting was used. Both observers entered the room to take the resting readings.

Cold Pressor Test

This test was performed with the subject in a recumbent position. A pan containing ice and water at a temperature from 2° to 4° C. was placed on a stool beside the bed. The subject was positioned on the bed in such a way that his shoulder or arm would not be pinched or strained when his hand was immersed. A preliminary measurement was taken just prior to immersion. Since this followed a 3-minute rest period between sections of the test series, no additional attempt to obtain a low reading was made. The right hand was then immersed in the ice water to a point approximately 1 inch above the wrist line. One observer placed the hand in the water while the other took blood pressures after 30 seconds and 60 seconds immersion. The hand was then withdrawn from the water and a pulse rate was taken. Readings were then taken every minute until both the systolic and diastolic blood pressures had returned to less than 2 mm. above their pre-immersion levels. However, in no case were readings taken for less than 3 minutes or more than 6 minutes.

Breath Holding Test

The subject was seated in a comfortable chair for this test. A reading was taken prior to the breath holding. The pulse observer then began watching the subject's breathing cycle. At the end of a normal expiration and without warning, he said, "Hold your breath." The sub-

ject immediately stopped breathing, with no preliminary gasp for air. The procedure was timed so that systolic and diastolic readings were taken after approximately 20 seconds of breath holding. This generally meant that the systolic was recorded just before 20 seconds and the diastolic just after, giving a total holding time of slightly over 20 seconds. As a quality check, total holding time was recorded for 23 out of the 24 administrations of the test. These showed a mean of 23.00 seconds with a standard deviation of 2.02 seconds and a range of 8 seconds (19 to 27 seconds). Pulse rate was estimated just after the subject resumed breathing.

Our procedure differs from that of Ayman and Goldshine (4). They used 2 separate periods of breath holding to determine systolic and diastolic blood pressure. While measurement accuracy is possibly slightly improved by their method, interpretation of results is more difficult due to the double stimulus. Too, application to children seems to call for a somewhat milder challenge.

Again, readings were taken during the recovery period using the same criteria as in the recovery period for the cold pressor test described above.

CO_2 Test

A mixture of 5% CO_2 and 95% O_2 delivered by a standard mask, head strap and tank arrangement was used in this test. The flow rate was initially set at 7 liters per minute with an exhaust pressure of approximately 3 mm. A higher rate of flow was given as the subject required. The main objective was to have the subject breathe this particular atmosphere, thereby controlling quality rather than quantity of the

mixture available. In some cases the face mask had to be plugged around the edges with cleansing tissue to get a good fit. The subject was in a recumbent position for the test.

A reading was taken just prior to placement of the mask. After the mask was in place, observations were made every minute for 10 minutes. The mask was then removed and recovery readings were taken according to the criteria already described. In interpreting results of the CO_2 test, it must be remembered that this is a multiple stimulus involving both the effects of breathing through a mask and of breathing a CO_2-rich mixture.

Exercise Test

This test began with the subject in a sitting position. An initial reading was taken, and then the subject stood and did 40 deep knee bends as described in Chapter III. Following this he sat down immediately for another observation. Readings during the recovery phase were taken as above.

Discussion of the Design and Analysis

A design for the study which would permit simultaneous estimation of the sources of variation described above in the section of this chapter headed General Background was sought.

In situations where several main effects need to be studied without the exhaustive experimentation required by a randomized complete block design, Latin Square or other similar balanced incomplete designs offer a number of advantages. For estimation of main effects, the Latin Square estimates are more efficient than those provided by the complete design. See, for example, Federer, (26) Chapter VI. And of course the

amount of experimentation is highly reduced. For example, a 4 x 4 Latin Square permits estimates of 3 main effects using 16 experimental plots, whereas the corresponding complete design requires 64 plots.

This type of design has some disadvantages. Compared to the complete design, the total number of available degrees of freedom is reduced as is the number of degrees of freedom for estimating the residual variance. More important, however, is the fact that no estimates of interaction effects are provided by the simple Latin Square design. In fact strictly speaking it must be assumed that no interactions exist in order to apply this design. For a discussion of this, see for example, Youden and Hunter (71). In preliminary experimentation like this, main effects are of major importance but of course some of the potential pitfalls of neglecting interactions were discussed above. Then, too as pointed out in this reference, the existence of interactions not incorporated in the design results in confounding of first order interactions with main effects.

Limitations of time and facilities and interest in several main effects dictated the use of some type of incomplete design. A modification and extension of the Latin Square was chosen.

A series of 6 randomly selected 4 x 4 Latin Squares was used. The squares were selected by the method of Fisher and Yates (29), page 15. Figure 1 shows the squares actually selected. Here rows denote subjects, columns denote order of administration of the stimuli, Latin letters denote the particular test. That is, A stands for the cold pressor test, B for breath holding, C for CO_2, and D for exercise. Thus, a particular row of a particular square denotes 1 test series. The 6 squares, with 4 rows each, give a total of 24 administrations of the series of stimuli, in varying orders of course. The 6 different squares indicate different

applications of the same basic design at different times. Thus, selecting the 6 first rows, we have the 6 administrations of the series to subject number 1, again in various orders.

1	2	3
A C B D	D B A C	D A C B
D A C B	C A D B	A C B D
C B D A	A C B D	C B D A
B D A C	B D C A	B D A C

4	5	6
D B C A	B C A D	A D B C
B D A C	C B D A	D A C B
A C B D	D A C B	B C D A
C A D B	A D B C	C B A D

Fig. 1. -- Series of randomly selected Latin Squares used in medical students experiment.

As an illustration of the design configuration, referring to Figure 1, let us look at the second row of the fifth square. From this we see that the fifth time the series was administered to subject number 2, he had CO_2 first, breath holding second, exercise third, and cold pressor fourth.

This design has a number of desirable features. It permits estimations of the following effects: between subjects; between individual tests; order of administration; between administrations of the whole series (day to day variations); and the 3 interactions of this last effect (between squares or day to day) with subjects, tests and order of admin-

istration. Table 1 shows the layout of the analysis with the number of degrees of freedom available for each test. The notation used here is quite similar to that of Federer (26) page 149. His analysis is identical to this except in 2 minor respects. First, he does not partition row and column effects as completely as in Table 1. Second, he uses conventional sums of squares which involve an unnecessary division by the total number of plots for each source in the analysis of variance. Since the F tests provided by the partition involve ratios of 2 mean squares, any convenient constant multiplier can be applied to the mean squares. This method of large mean squares is that of Dwyer (21). See for example, pages 309-314. We have used subtotals wherever possible to simplify notation.

With but minor modifications, standard notation has been employed. Indices are as follows: i indexes squares, h indexes rows, g indexes columns, and j indexes treatments. Dots replace subscripts which have been summed out.

It can be shown that the residual variance is the pooled variance within squares. This pooling operation and tests based on it require the assumption of homoscedasticity (homogeneity of the residual variances for squares). Bartlett's M test (See, for example Pearson and Hartley (51), pages 57-61) was made for each application of the analysis in Table 1. The assumption of normality required in the analysis of variance was not explicitly tested for. The fact that our analysis is based on differences between blood pressures undoubtedly helps to satisfy the assumption. Also Bartlett's test has been found sensitive to departures from normality. See for example Pearson and Hartley (51), page 57. Thus this test frequently indicates violations of both these assumptions. As Box (11)

Table 1. -- Analysis of Variance of Multiple Latin Square Experiment

Source of Variation	Degrees of Freedom	Large Sum of Squares
Squares (Visits)	$s-1$	$s\sum_{i=1}^{s} X_{i\cdots}^2 - X_{\cdots\cdot}^2 = L_S$
Rows (Subjects)	$k-1$	$k\sum_{h=1}^{k} X_{\cdot\cdot h\cdot}^2 - X_{\cdots\cdot}^2 = L_R$
Row-Square Interaction	$(s-1)(k-1)$	$L_{RS} - L_R - L_S = L_{RXS}$
Row-Square Subtotal	$ks-1$	$sk\sum_{i=1}^{s}\sum_{h=1}^{k} X_{i\cdot h\cdot}^2 - X_{\cdots\cdot}^2 = L_{RS}$
Columns (Order)	$k-1$	$k\sum_{g=1}^{k} X_{\cdots g}^2 - X_{\cdots\cdot}^2 = L_C$
Column-Square Interaction	$(s-1)(k-1)$	$L_{CS} - L_C - L_S = L_{CXS}$
Column-Square Subtotal	$ks-1$	$sk\sum_{i=1}^{s}\sum_{g=1}^{k} X_{i\cdot\cdot g}^2 - X_{\cdots\cdot}^2 = L_{CS}$
Treatments (Tests)	$k-1$	$k\sum_{j=1}^{k} X_{\cdot j\cdot\cdot}^2 - X_{\cdots\cdot}^2 = L_T$
Treatment-Square Interaction	$(s-1)(k-1)$	$L_{TS} - L_T - L_S = L_{TXS}$
Treatment-Square Subtotal	$ks-1$	$sk\sum_{i=1}^{s}\sum_{j=1}^{k} X_{ij\cdot\cdot}^2 - X_{\cdots\cdot}^2 = L_{TS}$
Residual	$s(k-1)(k-2)$	$L_{Total} - L_S - L_R - L_{RXS} - L_C - L_{CXS} - L_T - L_{TXS} = L_{Res}$
Total	sk^2-1	$sk^2\sum_{i,j,h,g} X_{ijhg}^2 - X_{\cdots\cdot}^2 = L_{Total}$

points out, however, in general the analysis of variance tests for means are quite "robust" and insensitive to departures from assumptions of normality and homoscedasticity.

Results

Many observers such as Hines and Brown (40) have recommended using the maximum blood pressure response under stimulation as the criterion for response. This approach leads to a difficulty in this test series which is best illustrated by the CO_2 test. Here there are 10 readings under stimulation. Choosing the maximum of these minus the pre-test level might result in a markedly skewed distribution of responses. A uniform criterion of response is easier to interpret, too. That is, to study the distribution of responses to a fixed amount of stimulation seems more rational. Consideration of the test procedures and the mean values of each observation across the 24 tests indicated that the final observation under stimulation generally showed the highest mean level. Thus for each test and variable, response was defined as the last reading under stimulation minus the reading just before stimulation. The variables considered were systolic blood pressure, diastolic blood pressure, pulse pressure (systolic minus diastolic) and pulse rate.

The analysis shown in Table 1 was carried out for each of these variables, after a non-significant Bartlett's M was found. In only 1 case was M significant. That was for pulse pressure response. Here the probability (assuming a X^2 distribution of M) of observing an M larger than ours from homoscedastic data was between .025 and .01. These data were transformed. First the transformation $x \rightarrow 100 \ln (x + 32)$ was

tried. Thirty-two was added to the observations to make them positive and permit taking logarithms. This reduced M, but only to a level which was still significant at the 5% level. Study of the individual distributions of pulse pressure response for each square indicated a positive skewness. Since the natural logarithmic transformation had failed to correct this, a square root transformation of the form $x \rightarrow 10\sqrt{x + 30}$ was tried. This reduced M to between the upper 20% point and upper 10% point of the X^2 distribution and the final analysis is based on this transformation.

Tables 2, 3, 4, and 5 show the analyses of variance. In testing for significance the residual variance was used for comparison exclusively. In these tables each entry in the column headed "Significance" is the probability of observing a larger F if the corresponding hypothesis of no effect is true.

In presenting results, it is first noticed that there is no significant interaction (5% level or less) of a main effect with square (day to day effect). This indicates that the main effects of subjects, order and tests did not change significantly from day to day.

Indeed, the variation from day to day itself was not significant for any of these 4 variables. While one might have expected a "hardening" or "learning" process to take place which would decrease responses as the subjects grew more familiar with the procedure, no such tendency was indicated.

It is further observed that order of administration had no significant effect. This might be due to the rest period between the tests. If so, this is a point in favor of the test protocol. A procedure which had a significant order effect would be difficult to interpret when

Table 2. — Analysis of Variance of Systolic Response

Source	Degrees of Freedom	Large Mean Square	F	Significance
Visits	5	2,118.400	.143	.99 > P > .975
Subjects	3	2,912.000	.196	.90 > P > .75
Subject-Visit Interaction	15	7,500.800	.506	.95 > P > .90
Order	3	12,618.667	.851	.50 > P > .25
Order-Visit Interaction	15	9,770.667	.659	.90 > P > .75
Tests	3	187,690.667	12.654	P < .0005
Test-Visit Interaction	15	4,170.667	.281	.995 > P > .99
Residual	36	14,832.000		
Total	95			
M (Bartlett's Test) = 6.40		(.50 > P > .25)		

Table 3. — Analysis of Variance of Diastolic Response

Source	Degrees of Freedom	Large Mean Square	F	Significance
Visits	5	11,990.400	1.093	.50 > P > .25
Subjects	3	27,024.000	2.463	.10 > P > .05
Subject-Visit Interaction	15	7,126.400	.650	.90 > P > .75
Order	3	6,725.333	.613	.75 > P > .50
Order-Visit Interaction	15	6,973.867	.636	.90 > P > .75
Tests	3	921,200.000	83.969	P < .0005
Test-Visit Interaction	15	17,193.600	1.567	.25 > P > .10
Residual	36	10,970.667		
Total	95			
M (Bartlett's Test) = 5.52		(.50 > P > .25)		

Table 4. — Analysis of Variance of (Transformed) Pulse Pressure Response

Source	Degrees of Freedom	Large Mean Square	F	Significance
Visits	5	13,400.800	1.359	.50 > P > .25
Subjects	3	19,901.333	2.019	.25 > P > .10
Subject-Visit Interaction	15	9,348.533	.948	.75 > P > .50
Order	3	2,882.667	.292	.90 > P > .75
Order-Visit Interaction	15	8,417.867	.854	.75 > P > .50
Tests	3	415,885.333	42.185	P < .0005
Test-Visit Interaction	15	13,222.133	1.341	.25 > P > .10
Residual	36	9,858.667		
Total	95			
M (Bartlett's Test) = 8.61		(.20 > P > .10)		

Table 5. -- Analysis of Variance of Pulse Response

Source	Degrees of Freedom	Large Mean Square	F	Significance
Visits	5	5,680.000	.658	.75 > P > .50
Subjects	3	74,794.667	8.670	P < .0005
Subject-Visit Interaction	15	7,796.267	.904	.75 > P > .50
Order	3	9,152.000	1.061	.50 > P > .25
Order-Visit Interaction	15	7,676.800	.890	.75 > P > .50
Tests	3	1,486,901.333	172.361	P < .0005
Test-Visit Interaction	15	9,739.733	1.129	.50 > P > .25
Residual	36	8,626.667		
Total	95			
M (Bartlett's Test) = 4.86		(.50 > P > .25)		

applied to a single individual, unless, of course, detailed information regarding the effects of any particular order were available.

There was a significant between-subjects effect only for pulse response in which it was very highly significant (.001 level). In the case of diastolic response, this effect reached significance at the 10% level, but not at 5%.

On the other hand, a difference in response to the various stimuli would be expected from their diversity. This analysis certainly bears that out. The between tests effect is significant at the .001 level for each of these variables.

In summary, the fact that day to day variance, its interactions and order variance are not significant is taken as encouraging evidence that this test protocol does not show such extreme variability and sensitivity that it should be dropped from further consideration. The failure of the tests to discriminate better between the subjects is slightly discouraging, but this is perhaps due to the relative homogeneity of our group of subjects. While there was a racial difference (2 subjects being of the yellow and 2 of the white race), age, sex, and certain other variables were quite constant across the group.

F ratios smaller than 1 occur quite frequently in these analyses. This is particularly prominent in the analysis of systolic response. In fact ratios which are significantly small are observed for the visit effect and for the test-visit interaction. The interpretation of these ratios is a little difficult. A possible explanation is that the residual mean square includes variation from several important sources which have not been explained. Certainly it is impossible to adequately control all relevant variables. However, the fact that every mean square

in each analysis is small relative to the corresponding mean square for tests, indicates that the design and experimental procedure is not insensitive to really important sources of variation. That is, compared to the differential effects of the various tests, there is no overlooked factor of similar importance.

Comparison with the analyses for the other responses reveals that a smaller proportion of the total variation for systolic response has been explained by the design. That is, that the residual effects for systolic response form a larger proportion of the total variance than they do for the other variables. This is difficult to explain and somewhat unexpected considering the feeling of most observers that systolic blood pressure is easier and more accurate to determine by indirect methods than is diastolic pressure, and therefore should give less measurement error. This capricious measurement error should of course contribute to the residual variance. On the other hand, it may be that the response of the systolic blood pressure to stimulation is affected by a larger variety of factors than are the responses of the other variables. In this way measurement error might not be of very great relative importance to the variation of responses as compared to the variation of individual blood pressure levels.

Finally it must be remembered that a small F ratio can be due either to a large mean square in the denominator, a small mean square in the numerator, or both. Thus, for example, the effects of visits and subjects on systolic response are probably relatively unimportant.

Table 6 shows the mean response (as defined above) by test for the 24 administrations of each test.

Table 6. — Mean Response by Test and Measurement Variable

	Systolic (mm. Hg)	Diastolic (mm. Hg)	Pulse Pressure (mm. Hg)	Pulse Rate (counts per minute)
Cold Pressor	25.83	33.16	-7.33	-6.17
Breath Holding	5.00	6.67	-1.67	5.33
CO_2	9.17	7.42	1.75	3.75
Exercise	14.67	-15.75	30.42	50.75

Several interesting features of this table° are noticed. In considering the mean responses to cold stimulation, this group of subjects as a whole would be considered hyperreactive by most investigators. See for example reference 40. While there have been various proposed definitions of hyperreactivity, each of the 4 medical students would be hyperreactive to cold by nearly any of the definitions.

While the definition of response to cold used here differs from that used by most authors, this definition should if anything lead to lower mean responses. This is because cold response has previously been defined as the maximum of the 30 and 60-second immersed readings minus the pre-immersion reading, whereas here the 60-second reading was used exclusively. However, this is not an important difference in these data, since the 30-second reading was highest only in 1 systolic and 1 diastolic reading out of the 24 readings of each type.

Hines (35) found rather large responses to cold in young people. In fact 18% of 400 children he studied were hyperreactive by his definition. See Chapter II, page 24. He also reported that the reaction of diastolic blood pressure is much greater in children than in adults.

Thus, it may be that the youthfulness of these subjects is in part responsible for the large responses observed, particularly the large diastolic response. However, responses as large as these are at least unusual, and for this reason the possibility that we are dealing with a group which is exceptional with respect to blood pressure reactivity cannot be overlooked.

On the other hand, the responses of this group to breath holding were rather small. Direct comparisons of these data with the data of Ayman and Goldshine (4) are not valid due to the different test procedures employed.

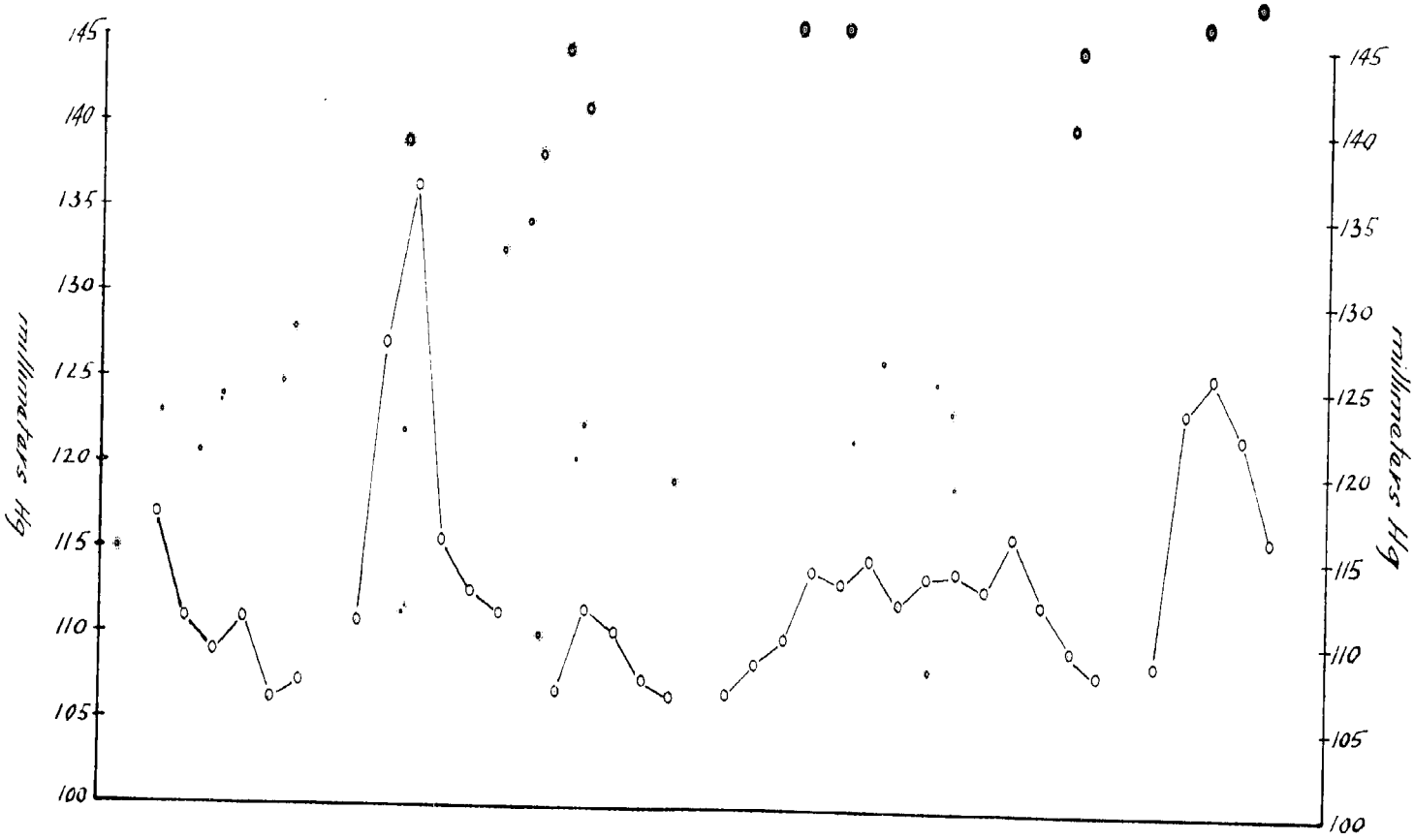
There is only scant literature available with which to compare the response to CO_2 stimulation (54), and again apparently no previous study using this exact stimulus has been reported. However, these data show a much smaller average response to CO_2 breathing than to cold.

No comparable data on exercise stimulation are available, but Table 6 shows a definite systolic increase and diastolic decrease, with a resultant increase in pulse pressure following exercise. Of course pulse rate increases tremendously.

Figures 2, 3, and 4 show the mean across subjects and visits of each of the variables measured in the procedure, i.e., means of 24 observations. The measurement times are indicated on the graph as abscissas. No graph for pulse pressure is presented since the mean pulse pressure for any variable is readily obtained by subtracting mean diastolic blood pressure from mean systolic blood pressure.

During rest there is a fairly sizable drop in blood pressure and pulse rate. This drop is smoothest for pulse rate. Most of the drop takes place when the posture is changed from standing to lying.

FIGURE 2. MEAN SYSTOLIC BLOOD PRESSURES FOR MEDICAL STUDENTS' EXPERIMENTS



Rest period

- 20 min. rest
- 15 min. rest
- 10 min. rest
- 5 min. rest
- lying
- standing

Cold pressor

- 3 min. after
- 2 min. after
- 1 min. after
- 60 sec. immersion
- just prior

Breath holding

- 3 min. after
- 2 min. after
- 1 min. after
- 20 sec. breath holding
- just prior

CO_2

- 3 min.
- 4 min.
- 5 min.
- 6 min.
- 7 min.
- 8 min.
- 9 min.
- 10 min.
- 1 min. after
- 2 min. after
- 3 min. after

Exercise

- 3 min. after
- 2 min. after
- 1 min. after
- immed. after
- just prior

FIGURE 3. MEAN DIASTOLIC BLOOD PRESSURES FOR MEDICAL STUDENTS EXPERIMENTS

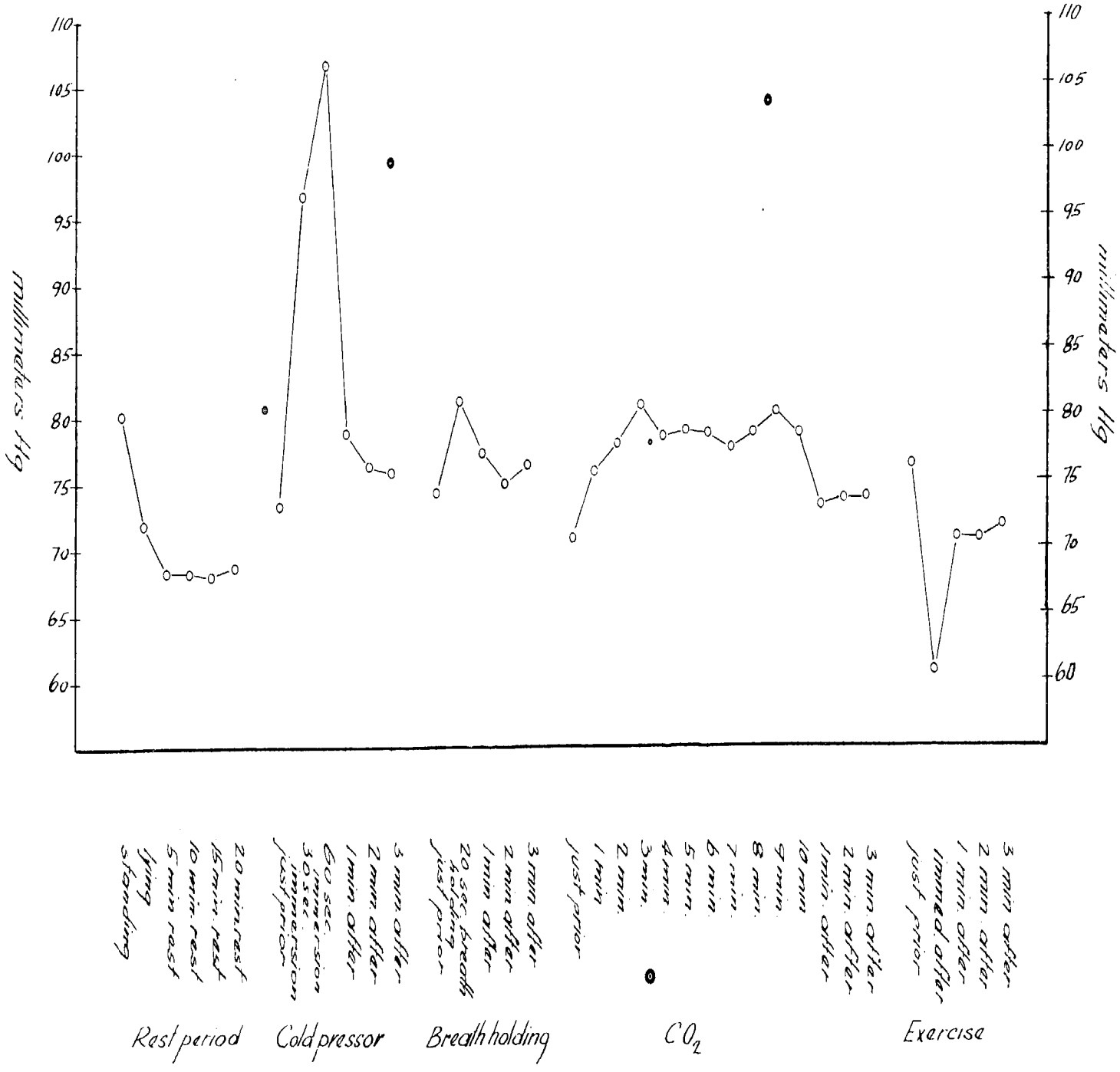
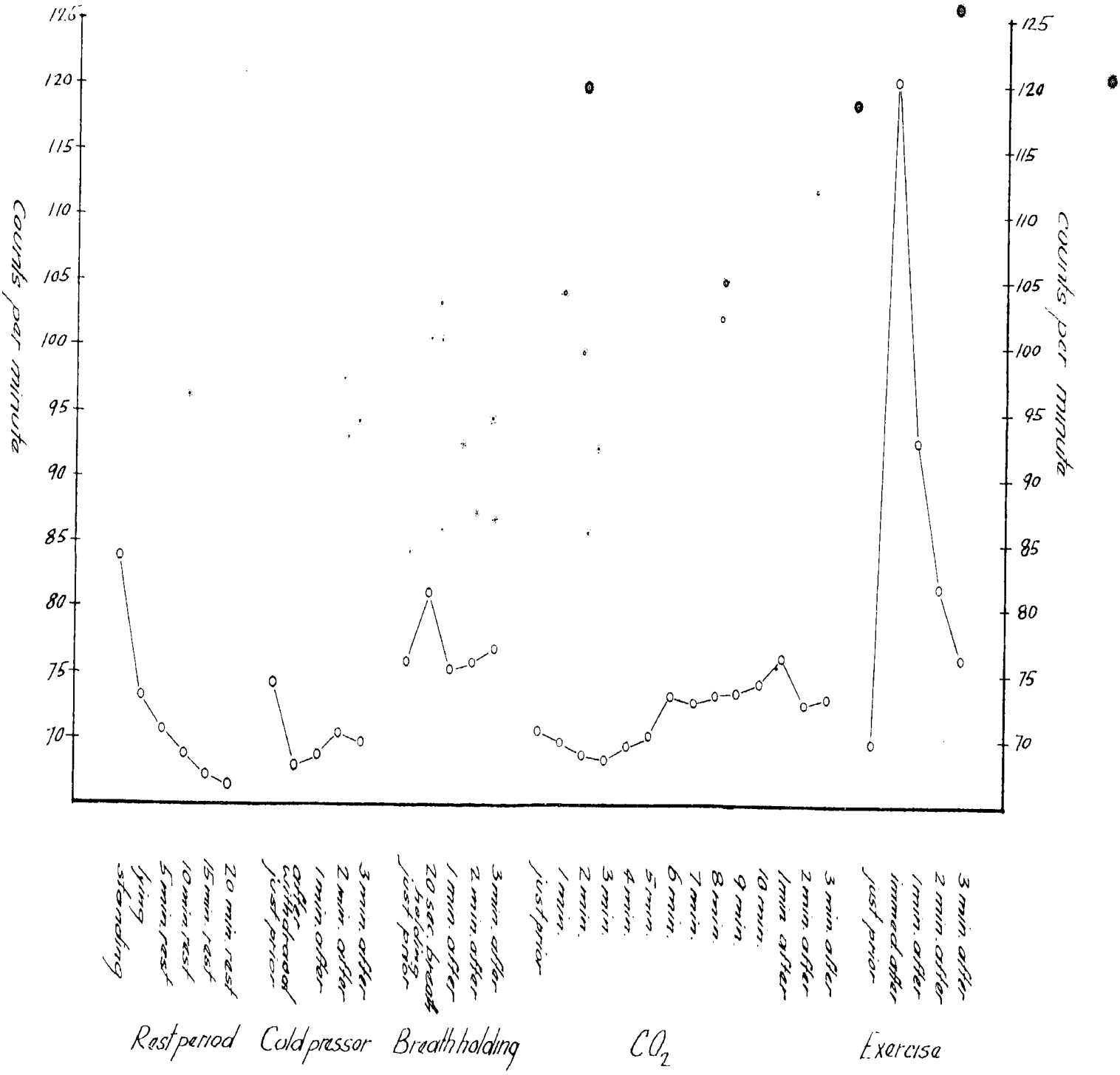


FIGURE 4. MEAN PULSE RATES FOR MEDICAL STUDENTS' EXPERIMENTS



Among the stimuli, we see that the cold pressor stimulus has the largest effect on systolic blood pressure. Exercise has the next highest systolic effect, CO_2 next, and breath holding, the lowest. Quite a bit of variability in means is evident during the rest period and CO_2 test.

Mean diastolic blood pressure sharply increases during cold, sharply decreases after exercise, and moderately increases during breath holding and CO_2 breathing. Diastolic rest period and CO_2 means are less variable than those for systolic blood pressure.

Mean pulse rate increases precipitously after exercise, increases moderately during breath holding and CO_2 breathing, and decreases after cold stimulation.

Computations of Standard Errors

Individual subject means and standard errors were calculated for each of the 143 variables measured, i.e., 36 systolics, 36 diastolics, 36 pulse pressures, and 35 pulse rates. The standard errors of the grand means were calculated by partitioning the over-all variance into variance between and within subjects using the pooled within subject variance. Some assumptions are made in doing this. These include the assumption of homoscedasticity of within subject variances and the assumption that the lack of balance with the effect of order of administration makes no difference. The fact that the order effect was not significant for any of the responses is partial evidence that the second assumption is reasonably well satisfied for these data.

The assumption of homoscedasticity was tested for each of the 143 sets of 4 subject variances. The test used was the $\frac{s^2 max.}{s^2 min.}$ test

described by Pearson and Hartley (51), pages 60-61. Of these, 4 sets were significantly heteroscedastic at the .01 level, while 7 other sets were significant at the .05 level but not at the .01 level. The sets of subject variances which were significantly different were scattered throughout the test procedure as follows: significant (.05 level) systolic sets were obtained for: (1) the reading just prior to immersion in the cold pressor test, and (2) the 4-minute CO_2 value. Significant diastolic sets were: (1) the value taken 2 minutes after the CO_2 stimulus, and (2) 3 minutes after exercise. Highly significant (.01 level) diastolic sets were obtained for: (1) the reading 3 minutes after the cold pressor test, and (2) the reading just prior to exercise. There were no significant sets for pulse pressure. Significant pulse rate readings were: (1) the 7-minute CO_2 value, (2) the value 1 minute after removal of the CO_2 mask, and (3) the value 3 minutes after exercise. Highly significant pulse rate sets were: (1) the 20-minute resting reading, and (2) the 5-minute CO_2 reading.

The 132 other sets were not significantly heteroscedastic between subjects. These results are taken as strong evidence that the data are sufficiently homoscedastic to justify the calculation of standard errors of the over-all means by pooling as described above.

CHAPTER V

COMPARISON OF THE BLOOD PRESSURE RESPONSES OF CHILDREN OF HYPERTENSIVE PATIENTS AND OF NORMAL SCHOOL CHILDREN

Introduction

As mentioned earlier, the central purpose of this study is to compare the blood pressure responses of a group of children of hypertensive parents with those of a presumably normal group. Admitting the existence of a familial factor in the etiology of hypertension as documented in Chapter II, is it possible to characterize and distinguish 2 such groups with respect to blood pressure responses to certain simple stimuli? Criteria for selection of stimuli were discussed at length in Chapter III.

It became evident through several trial applications of the test procedure described in Chapter IV to children that some modifications would be necessary. Particular difficulty was found with the CO_2 test. While this procedure had been applied with little difficulty to the group of medical students, attempts to use it with children were unsuccessful. The major difficulty concerned the use of a mask and semi-closed breathing circuit. This caused a great deal of apprehension in the early trials and several times it was necessary to remove the mask before completion of the test. In each case the child became quite agitated and apparently uncomfortable. In addition, the remote possibility

of unusual sensitivity to CO_2 made the procedure somewhat less safe than the other stimuli. The necessary use of cumbersome equipment in this test was another drawback.

After a preliminary series of applications to 6 children, the decision to drop the CO_2 test from further consideration was made. These trial data were dropped from the experiment and another stimulus was substituted. This was a postural test similar to that of Smithwick and Robertson (62).

Description of the Test Procedure

The tests were again carried out in a quiet examining room. With increasing experience at making the observations, it eventually was possible for 1 person to administer the test series alone. This was particularly fortunate due to the difficulty of getting enough competent and reliable assistants to aid in the data collection. Of a total of 100 administrations of the test series, 1 observer was used to collect both blood pressures and pulse rates on 72 series and 2 observers were used on the remaining 28 series.

The subject first entered the examining room. His arm girth and length were determined for the purpose of selecting a cuff width. Nadas' (50) rule of thumb was used for this purpose. Only the standard adult cuff (five and one-half inches wide) and the standard child's cuff (three and three-quarter inches wide) were used. The cuff of width closest to two-thirds of the arm length from the ante-cubital fold to the axillary fold was used. This determination was made separately for each individual tested. In a large majority of cases the choice was obvious by inspection, but the above method was followed. The cuff was put on the

arm and left in place throughout the entire series of tests.

A standing blood pressure and pulse rate were then taken. (Again the words "measurement," "reading," or "observation" will mean systolic and diastolic blood pressure and pulse rate.) As in the tests on medical students, the subject lay on the bed and a reading was taken immediately. Additional readings were taken every 5 minutes for a 20-minute period. Between these readings the observer or observers left the examining room, leaving the light on to avoid the additional stimulus of a change from darkness to light.

The postural test proceeded directly from the rest period. The verbal comment given by the examiner at this point was, "Now, I'm just going to stay in with you and take your blood pressure every minute for the next few minutes—one right after the other." Three more readings were then taken at 1-minute intervals. The subject was next asked, "Would you stand up beside the bed now so I can take your blood pressure standing up?" A reading was taken immediately after standing and every minute subsequently for 3 minutes. The subject's standing position was gently controlled to avoid his leaning against the bed or wall.

The 3 additional stimuli used were the cold pressor, breath holding, and exercise tests described in detail in Chapter IV. With but minor changes the same procedure was followed. A randomly selected order of administration of these 3 tests was again used.

One change in procedure was necessitated by the lack of familiarity of these subjects with the test protocol. That is, prior to each of the 3 procedures, verbal instructions had to be given the subject. These instructions were given with the subject in the posture required for the test which followed.

While no set of instructions was fixed word-for-word because of the desire to establish and maintain rapport with each subject, the instructions for the individual tests were approximately as follows:

Cold pressor test: "I'm going to take your blood pressure right now and then let you rest for a few minutes. During that time I'll go out and get a pan of ice water, bring it in and set it beside the bed. Then I'll take your blood pressure again and following that, come around and put your hand down into that pan of ice water. Now the water will be very cold and your hand will be uncomfortable and ache a little bit, but it will only be in the water for 1 minute. I have to take your blood pressure after 30 seconds and after 60 seconds and then I'll tell you to take your hand out. Now I want you to be just as relaxed as you can during the test. Don't tense up or hold your breath or anything like that. All right?"

Breath holding test: "I'm going to take your blood pressure right now, let you rest for a few minutes and then take your blood pressure again. Following that second blood pressure at some time you don't expect, I'll say, 'Hold your breath.' As soon as I say that, I want you to stop breathing, take your right hand and cover your nose and mouth tightly—like this (demonstrated). Let's see you do that. (Subject demonstrates.) Good! That's so you won't let any air either in or out through your nose or mouth 'til I tell you to breathe again. It won't be a very long time--just 20 seconds--long enough for me to get your blood pressure. Toward the end of that time, though, you'll feel short of breath and you may have a tendency to tighten up or tense up your chest. I want you to avoid that if you possibly can for 2 reasons. First of all, it makes it harder for me to take your blood pressure and secondly, it

makes it harder for you to hold your breath. The main thing to remember is to stop breathing without gasping or grabbing a breath just as soon as I say 'Hold your breath.'"

Exercise test: "I'm going to take your blood pressure right now, let you rest a few minutes and take your blood pressure again. Following that I want you to stand up and do this exercise (demonstrated). Do you think you can do that all right? I'd like you to do it 30 times. I also want you to time yourself with the metronome like this (metronome demonstrated). I'll count for you and as soon as you've finished, sit down right away and let me take your blood pressure." (Note the reduction in the number of knee bends required of the children as compared to the medical students in Chapter IV.)

Another slight change was introduced as a result of the preliminary experimentation with medical students. Following each stimulus, readings were taken during the recovery period once every minute for 3 minutes. This has the advantage of giving a fixed procedure, the effects of which can then be more objectively studied.

In summary, then, the cold pressor, breath holding, and exercise stimuli were all administered using the same general sequence. That is, instructions, followed by a reading, a 3-minute rest period, another reading, application of the stimulus, reading(s) taken under stimulation, and finally, recovery readings every minute for 3 minutes.

Design of the Study

Two groups of subjects were used. The first group was composed of children of hypertensive patients under treatment at the Hypertension Unit of the University of Michigan Hospital. These patients were selec-

ted as having hypertension which was not secondary to any known condition. Early in the study it became evident that in order to get a reasonable number of subjects, more than one child would have to be taken from some families. Of the 50 children in this group who were tested, 25 different families were represented. The distribution of number of children tested per family is as follows: in 7 families, 1 child was tested; in 14 families, 2 children were tested; in 3 families, 3 children were tested; and in 1 family, 6 children were tested. Appointments were arranged for these children. Because of the work schedule in the Hypertension Unit and because of limitations on the availability of children in the Control group, appointments were set up for the afternoon whenever possible. In 5 cases in this group, only morning appointments could be secured. The remaining 45 children, however, were tested in the afternoon. Children between the ages of 8 and 18 (to nearest completed year) were tested. The age and sex composition of this group with ages given to the nearest whole number of years lived is shown in Table 7.

Table 7. -- Distribution of Ages and Sexes for Children of Hypertensives

Age	8	9	10	11	12	13	14	15	16	17	18	Totals
Number of male children	2	1	1	3	6	7	0	1	2	2	0	25
Number of female children	1	1	4	3	5	1	2	5	2	0	1	25
Totals	3	2	5	6	11	8	2	5	5	2	1	50

The (ungrouped) median age, based on ages to the nearest month at the time of testing was 12 years, four and one-half months.

The fact that the sexes were evenly split is purely coincidental. No attempt was made to control the sex distribution. The age distribution was only controlled to the extent of fixing the age limits in advance. This was done in consultation with 2 pediatricians. The lower limit was more critical and was fixed at the lowest age for which cooperation would be readily obtained.

The control group was composed of children attending the University of Michigan grade and high schools. These are private laboratory schools administered by the University of Michigan. A pairing scheme was followed in the selection of these children. For each of the hypertensives' children, a school child of the same age and sex was chosen. Age was controlled to within a year. These pairs of ages each came out to within a year apart at the time of testing except for 1 of the 50 pairs. In this case the hypertensive's child was 1 year and 2 months older than her paired control at the time of testing. This was due to the unavoidable time lapse between the time of selection of the child and the time of testing. This method of selection meant that the hypertensive's child was always tested first in order that the matching procedure for selecting the paired control could be carried out. After determination of the age and sex of the hypertensive's child, the school grade having children most nearly the same age was selected. From this grade a child of matching sex was selected at random from the attendance roster. This method simplified the use of the roster, which was arranged by grade. The age and sex distribution for the control group, with ages again shown to the nearest whole number of years lived at the time of the test, is shown in Table 8. The median age for this group (calculated as before) was 12 years, 5 months.

Table 8. — Age and Sex Distribution of Control Children

Age	8	9	10	11	12	13	14	15	16	17	18	Totals
Number of male children	1	1	1	3	7	5	2	1	3	1	0	25
Number of female children	1	0	3	5	4	1	7	3	0	0	1	25
Totals	2	1	4	8	11	6	9	4	3	1	1	50

Following the selection of a child from the school roster, a standard letter signed by the principal of the school was sent to the child's parents. If they had questions regarding the procedure, they were asked to refer them to the school pediatrician. The specific stimuli were not mentioned in the letter, and the fact that children were selected at random was stressed. Only 1 parent objected to applying the tests to her daughter. The girl in question was diabetic.

The school's schedule required that all the children in the control group be tested in the afternoon. The children were picked up at school, taken to the Hypertension Unit, tested, and were then either returned to the school or taken home.

Fifty different families were represented in the control group. In 2 cases a brother or sister of a previously tested control child came up in the random selection. These were rejected and new names were selected.

Following completion of the tests, a form was sent to the parents of each control child for the purpose of determining family history of hypertension. Questions were asked regarding the length of time since each parent had previously had a blood pressure taken, and regarding the presence or absence of hypertension. Of 37 responses to this question-

naire, a 74% response rate, 2 children had been adopted and no parental information was available. For the remaining 35 children, 30 mothers and 26 fathers had had their blood pressure taken within the last 3 years, while 3 mothers and 4 fathers had not. No answer was given for 1 mother and 3 fathers, and 1 mother and 2 fathers were deceased longer than 3 years. Hypertension was only known to be present in 2 of the mothers and in these 2 cases, it was transient and associated with pregnancy. Presence or absence of hypertension was not known for 1 mother and 4 fathers and no answer was given for 1 father. In the remaining 32 mothers and 30 fathers, hypertension was specified to be absent.

These results coupled with the method of selection of this group of children is evidence that the group is quite standard with respect to hypertension prevalence.

Several other factors were controlled more or less adequately in an attempt to make the 2 groups as similar as possible. Whenever possible, the same observer took blood pressures on both members of the pair. This was successfully accomplished in all but 4 of the 50 pairs. These 4 deviations from the original plan were due to the irregular availability of the technician who helped with a few tests. Control of the observer effect was thought to be somewhat less important in the case of pulse rate determinations. The pulse rate observers failed to coincide in 11 of the 50 pairs. A cuff of the same size was not necessarily used for both members of a pair. The arm length of each individual determined the size for that individual.

A total of 5 different observers took some part in the data collection. Only 3 of these took blood pressures. The other 2 only assisted by taking pulse rates. As mentioned above, 72 of the 100 series

were administered by a single observer--32 of the 50 tests on hypertensives' children and 40 of the 50 control children. This slight disagreement was again necessitated by personnel difficulties. Table 9 shows the number of tests participated in by each observer, broken down by control versus experimental group and blood pressure versus pulse rate determination. The code for observers is as follows: observer 1 is the author, observer 2 is the technician mentioned above, observer 3 is a registered nurse, and observers 4 and 5 are stenographers trained in the application of this procedure.

Table 9. -- Number of Test Participations by Observer

Observer Number	1	2	3	4	5
Blood Pressures for Hypertensives' Children	33	7	10	0	0
Blood Pressures for Control Children	35	3	12	0	0
Pulse Rates for Hypertensives' Children	23	10	11	5	1
Pulse Rates for Control Children	28	7	13	0	2

It will be noted that 90% of all the blood pressures and 75% of all the pulse rates were taken by the author and the nurse.

Another factor which was controlled for both members of each of the 50 pairs was order of administration of the test stimuli. After a random selection of order had been made for each pair, the recording forms were assembled in the indicated order. Thus the distribution of the various possible orders of administration was identical for the 2 groups.

A factor controlled to a lesser degree was the time of day that the test series was administered. The schedule of school did not permit too rigid control of this factor. An attempt was made to schedule the control child in the early or late afternoon according as his pair mate had been tested in the early or late afternoon. The most serious deviations from this control occurred in the 5 pairs for which the hypertensive's child had to be tested in the morning. An attempt was made not to conduct the tests too soon after lunch. In nearly all cases, at least an hour had elapsed since the subject's last meal.

All the tests were conducted in the Hypertension Unit and whenever possible, the same sphygmomanometer was used for both members of the pair. In any case, however, the aneroid manometers were frequently checked for accuracy with a mercurial manometer.

While all these factors were controlled more or less adequately, a host of others could not be controlled. One of these was the possible socio-economic difference between the groups. Sundal's study (64) in Oslo showed a very slight tendency for private school students of a higher socio-economic level to have higher blood pressures at each age than public school students. However, the differences in age-specific means were generally of the order of 1 mm. If any conclusion from this early foreign study can be applied to the present work, the effect would be to decrease the difference between the average blood pressures of the control and experimental groups, since our control group is probably from a higher socio-economic level.

Another problem in this study was the necessity for the observer to know whether each subject was from the control or experimental group when making the observations. Limitations of personnel and facilities

imposed this restriction. A good deal of advanced preparation including contacting, scheduling and actually getting the subjects and observers together in space and time was involved. Since the same people had to both do the advanced preparation and make the observations, there was no way to make the study "blind" as would have been most desirable. Furthermore, determination of blood pressures and pulse rates are probably objective enough to make subjective factors relatively unimportant, particularly when observations are made by trained, intelligent observers.

Analysis and Results

A number of analytical procedures were carried out to reduce the data and make statistical inferences therefrom. Each test procedure consisted of 32 determinations of systolic and diastolic blood pressures and 31 pulse rates. This gives a total of 9,500 individual observations (3,200 systolics, 3,200 diastolics, and 3,100 pulse rates).

To describe and summarize these data, curves showing the mean values for each observation separately for the 2 groups were constructed. These curves are presented in Figures 5, 6, and 7.

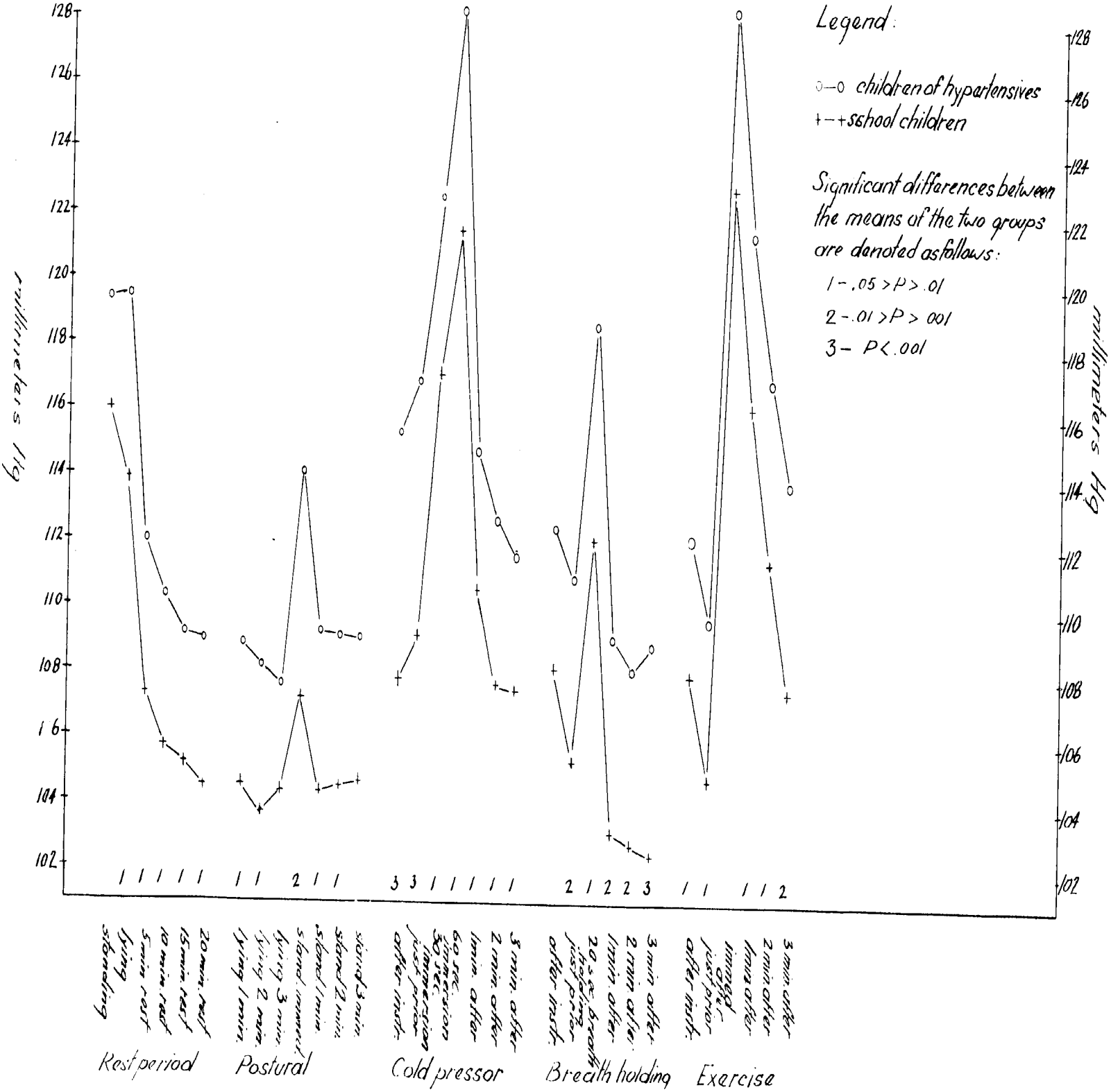
Figure 5 gives the mean systolic blood pressures for each group. The curve with circles indicating particular values gives the mean values for the 50 children of hypertensives. The curve with x's denoting particular values gives the mean values for the 50 control children. These 2 curves are strikingly similar in configuration. In general the pressure drops during rest, rapidly at first and more slowly later. It rises and peaks when the subject stands, but recovers to near its resting level as he remains standing. Keeping in mind the fact that the final 3 tests were not administered in a fixed order, there is a sharp

increase under the stimulus of cold, a moderate increase due to breath holding and another sharp increase after exercise. An interesting thing is noticed in comparing the post-instruction and pre-stimulation levels in the final 3 tests. Anticipation of the cold stimulus apparently causes a slight (1-2mm.) increase in systolic blood pressure, whereas the level drops following instructions in the other 2 tests. Remembering that there is a 3-minute rest period between these 2 readings, a clue to the explanation of this difference is that the pan of ice water was brought into the examining room during the pre-cold rest period.

The above discussion points out the similarities between the 2 groups. Of course, there is a very striking difference which prevails quite generally throughout the tests. That is, the mean systolic blood pressure levels for the experimental group are definitely and uniformly higher than those for the control group. Each of these 32 differences was tested for significance using the Student-Fisher t test and only 3 differences failed to be significant at the 5% level. Levels of significance are indicated below the curves and are explained in the legend. Generally, the higher the number below the curves, the more significant the difference. Assumptions of normality and homoscedasticity are apparently adequately satisfied by these data. While the different significance tests made here are not independent, the uniformity and degree of the significance strongly indicates a real difference between the mean systolic levels of the 2 groups. This difference is in the opposite direction from that expected by socio-economic bias. Sundal (64).

Figure 6 shows the diastolic means for the 2 groups. The configuration of the 2 curves is again similar. There is a drop during the rest period, but it is much less marked than in the case of the systolic

FIGURE 5. MEAN SYSTOLIC BLOOD PRESSURES



means. The postural change produces a marked and sustained elevation of diastolic blood pressure. Cold again produces a sharp increase of pressure, while breath holding produces a lower peak. Exercise causes a sharp drop in diastolic pressure, which recovers quickly, but not quite back to its pre-test level. Prior to the cold stimulus, the diastolic means again increase during the rest period. However, the drop during the rest period prior to breath holding and exercise is less marked for the diastolic than for the systolic means.

The differences between diastolic means are never significant. The means of the control group lie below those of the experimental group throughout the rest period and postural test, but after that the curves are extremely close together and frequently even cross.

In Figure 7 the mean pulse rates are shown. Again the curves are roughly parallel. A drop during rest is apparent. Postural change produces an elevated pulse rate which is sustained during standing. Cold produces a decrease in pulse rate as does breath holding. Exercise, of course, results in a sharp increase. In this case the rest periods prior to the final 3 tests each show an increase in pulse rate.

The pattern here is similar to that for the systolic means except that the control group has uniformly higher mean pulse rates. The differences between the 2 groups are marked and statistically significant at least at the 5% level in all but 8 of the 31 cases. Among these 8 are the values just after stimulation from cold, breath holding, and exercise.

In summarizing the data in Figures 5, 6, and 7, the experimental group has higher mean systolic levels, approximately the same mean diastolic levels, and lower mean pulse rates. This is evidence against a

FIGURE 6. MEAN DIASTOLIC BLOOD PRESSURES

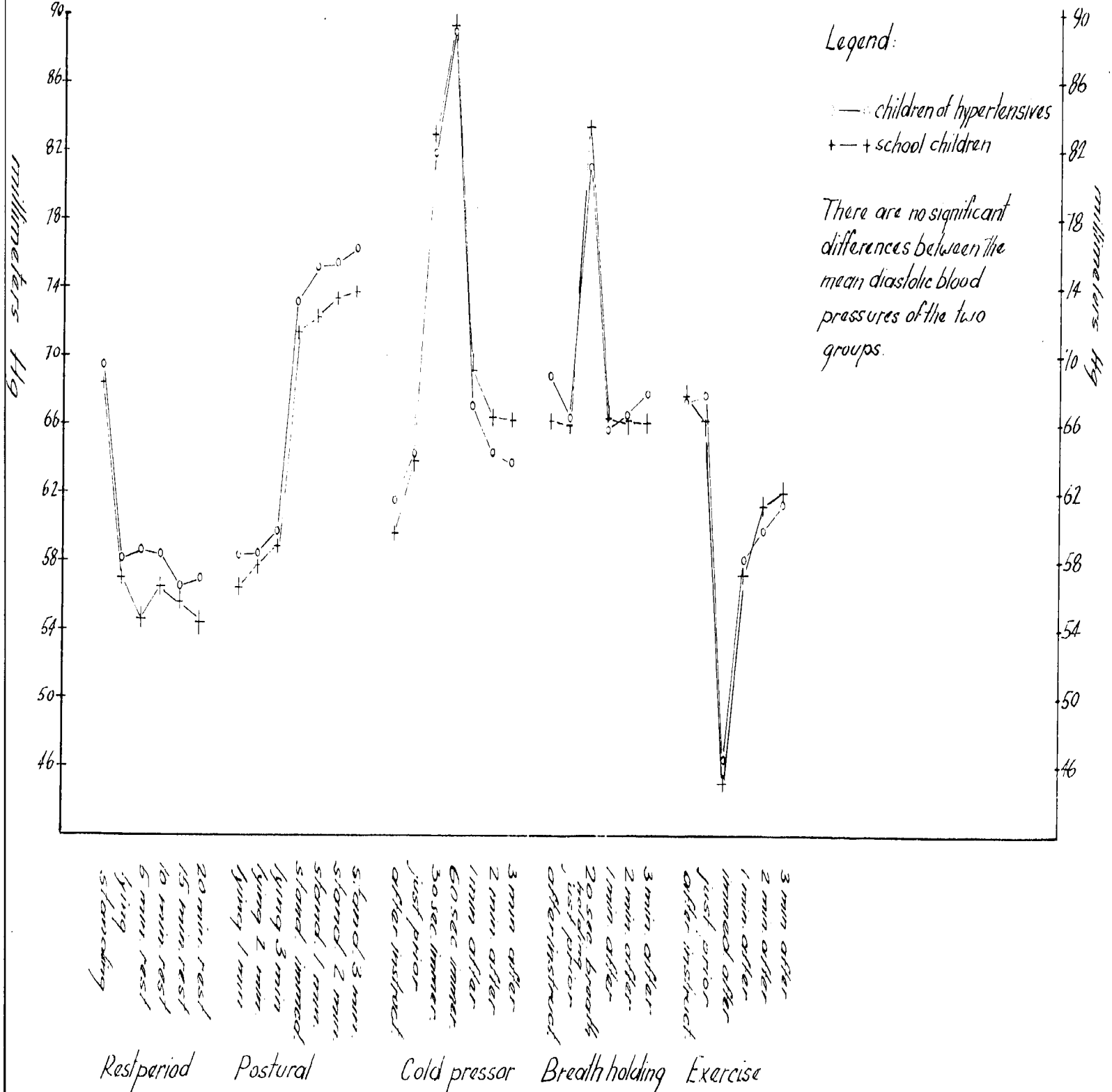
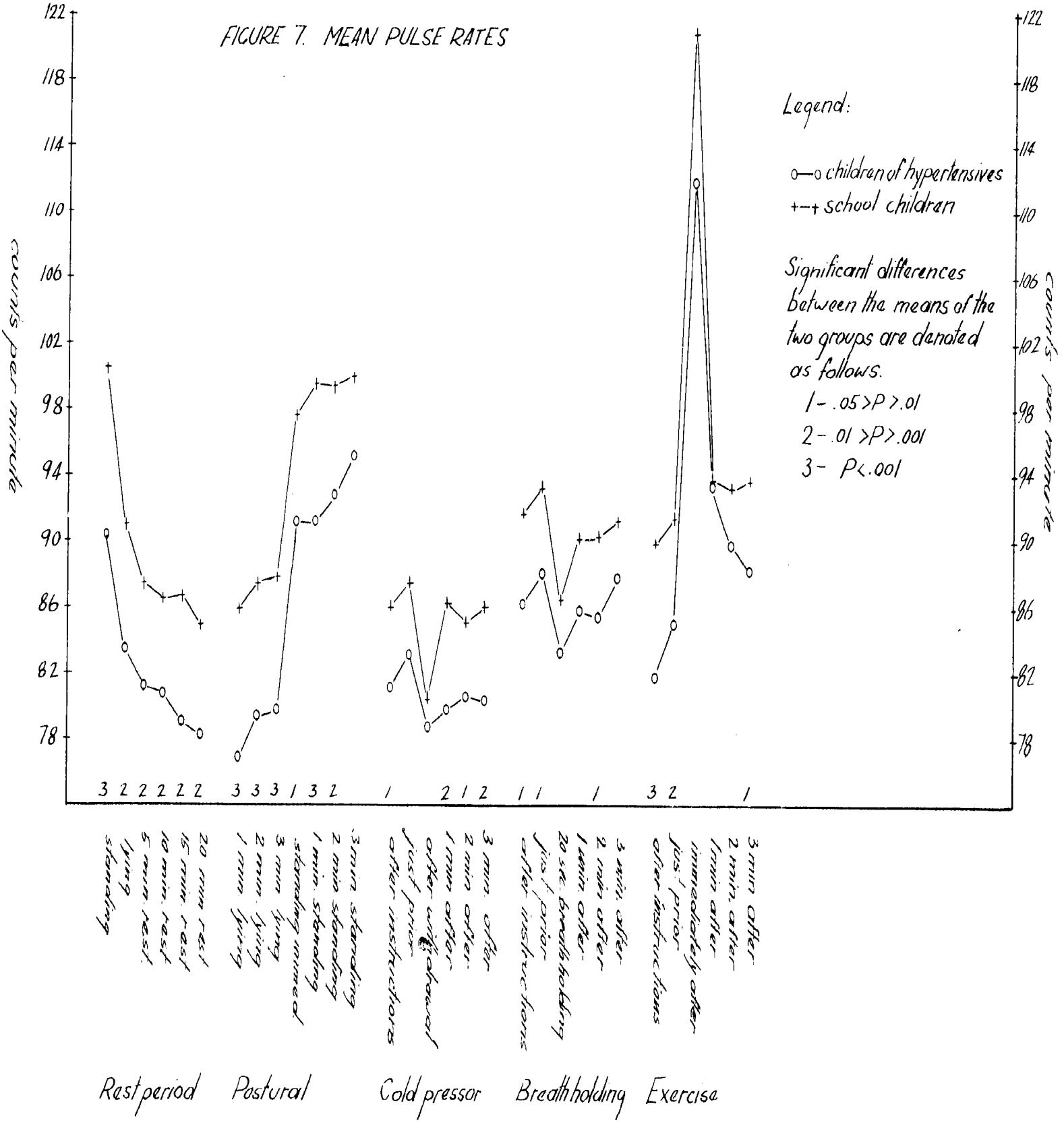


FIGURE 7. MEAN PULSE RATES



consistent observer bias in favor of either group.

The shape and configuration of some of the individual blood pressure and pulse distributions is undoubtedly of some interest. Distributions were calculated for 7 different points in the test series: the first reading, the final lying just prior to standing in the postural test, the reading taken immediately after standing in the postural test, the reading just prior to immersion of the hand in ice water, the reading after 60 seconds immersion (just after withdrawal for pulse rate), the observation made after 20 seconds of breath holding and that taken just after exercise. Separate distributions were calculated for the control and experimental groups, for a total of 42 distributions. These data are presented in Tables 10, 11, 12, 13, 14, and 15. Entries in the individual cells of these tables represent frequency of occurrence.

It will be noticed that the total number of cases in the control group after 60-seconds immersion in the cold pressor test is only 49. One observation was not usable in this group. This was the reading for an 18-year old girl who had a peculiar response to cold. No Korotkoff sounds were present in this girl during cold and hence no blood pressure could be taken. The test was repeated again following completion of all her other tests in normal sequence and the sounds over the brachial artery were again totally absent. This girl professed an extreme dislike for and sensitivity to cold of any sort. While this is apparently an unusual phenomenon, it represents a further limitation on the population to which inferences from the study apply. Only individuals whose responses are measurable are considered.

There is no strong evidence of bimodality in any of these distributions, although the positive skewness sometimes observed could indicate a trend in this direction.

Table 10. — Distributions of Individual Systolic Readings for Experimental Group

Interval (mm. Hg)	First Reading	Final Lying	Immediately after Standing	Just Prior to Cold	After 60 secs. Immersion	After 20 secs. Breath Holding	After Exercise
75,85							
85,95	1	3	2			1	
95,105	7	21	9	6	1	6	2
105,115	12	18	21	18	5	15	6
115,125	17	5	9	18	15	17	16
125,135	9	2	4	4	15	6	13
135,145	1	1	4	3	10	4	7
145,155	1		1	1	3	0	2
155,165	2				0	1	3
165,175					1		0
175,185							1

Table 11. — Distributions of Individual Systolic Readings for Control Group

Interval (mm. Hg)	First Reading	Final Lying	Immediately after Standing	Just Prior to Cold	After 60 secs. Immersion	After 20 secs. Breath Holding	After Exercise
75,85			1				
85,95	1	5	4	2		1	
95,105	11	24	14	18	3	14	6
105,115	10	18	23	19	13	17	11
115,125	17	1	4	9	17	10	9
125,135	9	2	3	2	8	5	12
135,145	2		1		6	2	8
145,155					2	1	3
155,165							1
165,175							
175,185							
185,195							

Table 12. -- Distributions of Individual Diastolic Readings for Experimental Group

Interval (mm. Hg)	First Reading	Final Lying	Immediately after Standing	Just Prior to Cold	After 60 secs. Immersion	After 20 secs. Breath Holding	After Exercise
0							4
5,15							1
15,25				1			2
25,35	2	1		0			6
35,45	2	4		1			6
45,55	5	9	2	6		1	11
55,65	7	20	10	18	3	1	12
65,75	14	14	18	18	5	16	6
75,85	15	1	12	4	16	15	2
85,95	4	1	7	1	9	9	
95,105	1		1	1	10	5	
105,115					4	2	
115,125					3	1	

Table 13. -- Distributions of Individual Diastolic Readings for Control Group

Interval (mm. Hg)	First Reading	Final Lying	Immediately after Standing	Just Prior to Cold	After 60 secs. Immersion	After 20 secs. Breath Holding	After Exercise
0							5
5,15							0
15,25							4
25,35		1					3
35,45		3		1			10
45,55	3	13	2	5			12
55,65	15	22	11	21	1	1	7
65,75	21	9	20	19	4	8	6
75,85	5	2	12	3	13	19	3
85,95	6		4	1	17	15	
95,105			1		9	7	
105,115					5		
115,125							

Table 14. — Distributions of Individual Pulse Rate Readings for Experimental Group

Interval (mm. Hg)	First Reading	Final Lying	Immediately after Standing	Just Prior to Cold	After 60 secs. Immersion	After 20 secs. Breath Holding	After Exercise
35,45					1		
45,55							
55,65	2	4		3	8	3	2
65,75	3	10	3	6	8	11	0
75,85	18	26	16	25	18	18	5
85,95	9	6	13	8	10	7	4
95,105	12	3	10	5	4	8	13
105,115	2	1	8	3	1	3	5
115,125	1						10
125,135	3						1
135,145							3
145,155							3
155,165							2
165,175							2

Table 15. — Distributions of Individual Pulse Rate Readings for Control Group

Interval (mm. Hg)	First Reading	Final Lying	Immediately after Standing	Just Prior to Cold	After 60 secs. Immersion	After 20 secs. Breath Holding	After Exercise
35,45					1		
45,55					0		
55,65				2	5	1	
65,75		6	3	3	7	6	
75,85	5	16	6	18	19	21	6
85,95	16	15	11	11	13	8	4
95,105	13	12	16	14	3	8	7
105,115	6	0	8	2	0	4	2
115,125	8	1	6		1	2	13
125,135	1						3
135,145	0						5
145,155	1						1
155,165							6
165,175							2
175,185							1

In an attempt to study the consistency of the readings of a given individual through the test procedure, an analysis of the rankings of certain special subgroups of individuals was carried out. The question was whether or not, for the experimental group in particular, the individuals with the highest readings tend to remain high throughout the procedure. Insofar as this were true one might believe that the experimental group is composed of a large group of essentially normal individuals, with only a small subgroup showing consistently high readings. In view of the uniformity of the differences between the systolic means for the experimental and control groups and the non-uniformity of the diastolic means, it was decided to limit the analysis to systolic readings.

Several special subgroups were studied in an attempt to assess the consistency of high and low readings. These groups were those individuals with the 5 highest initial readings, the 5 lowest initial readings, the 5 highest final lying readings (just before standing in the postural test), the 5 lowest final lying readings, the 5 highest readings after 60 seconds immersion in the cold pressor test, and the 5 lowest readings after 60 seconds immersion. Only the rank of each reading was considered. In any distribution the lowest reading was assigned rank 1, the next lowest rank 2, etc., with the highest reading being assigned rank 50. The distributions considered were those given in Table 10. Given a rank number, one can refer back to this table to find the corresponding blood pressure to within 10 mm. Hg.

Table 16 gives the results of this analysis. All the entries in a particular row refer to the same individual. To help clarify the contents of this table, consider the entries in the first row. This indi-

Table 16. — Ranks* of Systolic Readings for Various Special Subgroups of Experimental Group

Subgroup	First Reading	Final Lying	Immediately after Standing	Just Prior to Cold	After 60 secs. Immersion	After 20 secs. Breath Holding	After Exercise
Highest	50	48	48	50	49	50	50
First	49	49	45	47	37	47	48
Readings	48	29	40	36	23	42	39
	47	40	31	36	27	24	26
	46	50	50	49	50	47	43
Lowest	5	44	23	39	46	21	24
First	4	7	13	31	13	32	44
Readings	3	1	7	3	1	5	6
	2	2	2	1	16	1	1
	1	13	1	5	4	12	6
Highest	46	50	50	49	50	47	43
Final	49	49	45	47	37	47	48
Lying	50	48	48	50	49	50	50
	40	47	49	41	47	47	41
	40	46	46	46	30	37	48
Lowest	32	5	9	13	42	12	17
Final	15	4	3	5	5	3	21
Lying	18	3	6	22	13	24	8
	2	2	2	1	16	1	1
	3	1	7	3	1	5	6
Highest	46	50	50	49	50	47	43
60 secs.	50	48	48	50	49	50	50
Immersion	43	20	33	30	48	24	16
	40	47	49	41	47	47	41
	5	44	23	39	46	21	24
Lowest	15	4	3	5	5	3	21
60 secs.	1	13	1	5	4	12	6
Immersion	24	30	9	4	3	6	12
	28	7	25	13	2	37	45
	3	1	7	3	1	5	6

*A rank of 1 is assigned to the lowest reading in a distribution. The highest reading is assigned rank 50.

vidual had the highest first reading, the third highest final lying reading, the third highest reading immediately after standing in the postural test, etc. It will be noticed that in some distributions, 2 individuals have been given the same rank. This is due to the occurrence of the same reading in those individuals. In general, these tied values were assigned the average rank number which would have been assigned had they not been tied.

The table shows that there is a very great deal of nonuniformity of the ranks of a given individual. For each of the 3 readings considered (first reading, final lying, 60 secs. immersion), the highest 2 individuals were quite uniform in their ranks. Beyond this, though, there is considerable mixing.

Of the 3 readings considered, the final lying reading seems to best predict where an individual will lie in the distributions for the remainder of the test series. That is, the 5 highest final lying readings are quite consistently high. The 5 lowest final lying readings are somewhat variable, but appear to be slightly more consistent than their counterparts for the first reading and the 60-sec. immersed reading.

The main objective of this study was to compare responses of the blood pressure and pulse rate for the 2 groups to stimuli of various sorts. Again, "response" means the change due to stimulation, i.e., the difference between 2 readings—one under stimulation, the other just prior to stimulation. To this end, 5 responses were studied. These were designated as initial response, postural response, cold response, breath holding response and exercise response. The initial response was the first reading taken minus the lying reading just before standing in the postural test for systolic and diastolic blood pressures and pulse

rate. The postural response was defined to be the reading immediately after standing in the postural test minus the final lying reading, for each of the 3 variables. Cold response was the reading after 60 seconds ice water immersion minus the reading just prior to immersion for systolic and diastolic blood pressure. Pulse rate response was the reading taken just after withdrawal of the hand from the ice water (the pulse was not taken with the hand in the ice water) minus that taken just prior to immersion. Breath holding response was the reading taken after 20 seconds breath holding minus that taken just prior to holding the breath. In this case again, pulse rate was determined just after resumption of breathing and this value minus the reading just prior to cessation of breathing was used. In the exercise test, systolic blood pressure response and pulse rate response were defined to be the reading taken after exercise minus the reading just prior to exercise. However, since the diastolic blood pressure nearly always responded to exercise with a decrease, diastolic response was defined to be the reading just prior to exercise minus the reading just after. This is the negative of the definition used in Chapter IV and was merely adopted here as a computational convenience.

These definitions were chosen because they seem to be most directly related to the stimulus involved in each case. That is, by taking a reading just before a stimulus is applied, applying the stimulus and then looking at the reading during or just after stimulation one is coming closest to measuring the direct, pure effect of the stimulus itself. Choices of definitions of response other than those used would be more difficult to interpret. The choice of a basal or resting level with which to compare the first reading taken provides the only exception to

this in the test procedure. One might at first think that the first reading should be compared with the second reading. However, a basal or near-basal level has certainly not been reached at this point and the confounded effect of the change in posture between the first 2 readings again causes difficulty in interpretation. For this reason the final lying reading taken was chosen in advance as the value which should be used for comparison. At this point the subject's blood pressure had been taken 8 times, he had been resting for approximately 23 minutes, and much of the superimposed apprehension and nervousness of the first reading had been removed. The alternative to this seemed to be a longer rest period and this was not consistent with restrictions of time.

Table 17. — Mean Responses to Various Stimuli for Experimental and Control Groups

	Systolic Blood Pressure		Diastolic Blood Pressure		Pulse Rate	
	Experimental Group	Control Group	Experimental Group	Control Group	Experimental Group	Control Group
Initial	11.68	11.60	9.60	9.76	10.64	12.96
Postural	6.56	2.84	13.40	12.64	11.76	9.92
Cold	11.32	12.49	24.40	25.43	-4.52	-7.10
Breath Holding	7.76	6.72	14.92	17.44	-4.64	-6.72
Exercise	18.72	18.12	21.24*	21.16*	26.68	29.34

*Defined as pre-exercise level minus post-exercise level.

Table 17 shows the mean response for each variable measured for each group and for each type of response, as defined above. The units are millimeters of mercury for blood pressures and counts per minute for pulse

rates.

These results are unusual in several respects. The mean response of the control group frequently exceeds that of the experimental group. This is true throughout the cold pressor test. It is also true for the diastolic and pulse in the initial and breath holding stimuli, and for the pulse response to exercise. Only in the postural test are the responses consistently higher for the experimental group. The differences in this stimulus seem more clear-cut than in the others. This is discussed in more detail below. It must be remembered in reading the table that the mean diastolic response to exercise is a drop in pressure.

The results for the cold pressor test may be compared to those of Hines (35). In 400 school children between the ages of 6 and 18, he found an average increase of 16.2 mm. systolic and 18.3 mm. diastolic. While he probably had achieved a more nearly basal blood pressure before stimulation and used the maximum of the 30-second and 60-second immersed readings to calculate these averages, he found a higher systolic increase and a lower diastolic increase.

The actual distributions of responses to the 5 stimuli are given in Tables 18, 19, 20, 21, 22, and 23.

The technique of linear discriminant function analysis was used in the major analytical portion of the study. The techniques used in the analysis are described by Rao (57), pages 237-257 and Dwyer (22), Chapter 21. The problem is to find the linear combination of several variables measured on each member of 2 groups which best discriminates or separates the groups. "Best" as used here means that function which has a maximum variance between groups relative to its variance within

Table 18. — Distributions of Systolic Blood Pressure Responses for Experimental Group by Stimulus

Interval	Initial	Postural	Cold	Breath Holding	Exercise
-35,-25					
-25,-15	1		1		
-15,-5	2	4	0	3	1
-5,5	12	16	12	16	3
5,15	19	23	19	21	16
15,25	10	6	13	8	18
25,35	5	1	5	2	8
35,45	1				2
45,55					2
55,65					
65,75					
75,85					

Table 19. — Distributions of Systolic Blood Pressure Responses for Control Group by Stimulus

Interval	Initial	Postural	Cold	Breath Holding	Exercise
-35,-25					
-25,-15					
-15,-5	1	8		2	
-5,5	11	24	12	21	3
5,15	19	17	24	23	20
15,25	15	1	8	1	12
25,35	4		2	2	14
35,45			2	1	1
45,55			1		
55,65					
65,75					
75,85					

Table 20. — Distributions of Diastolic Blood Pressure Responses for Experimental Group by Stimulus

Interval	Initial	Postural	Cold	Breath Holding	Exercise
-35,-25	1				
-25,-15	0			2	
-15,-5	8	3		1	1
-5,5	7	8	5	7	8
5,15	18	18	8	13	15
15,25	11	15	14	17	9
25,35	3	4	13	7	7
35,45	2	1	6	2	4
45,55		1	2	1	3
55,65			2		1
65,75					1
75,85					1

Table 21. — Distributions of Diastolic Blood Pressure Responses for Control Group by Stimulus

Interval	Initial	Postural	Cold	Breath Holding	Exercise
-35,-25					1
-25,-15	1				1
-15,-5	4	2		1	2
-5,5	8	10	1	5	7
5,15	25	19	8	15	9
15,25	6	12	13	15	9
25,35	6	6	17	12	10
35,45		1	7	2	5
45,55			3		2
55,65					1
65,75					3
75,85					

Table 22. — Distributions of Pulse Rate Responses for Experimental Group by Stimulus

Interval	Initial	Postural	Cold	Breath Holding	Exercise
-65,-55					
-55,-45			1		
-45,-35			0		
-35,-25			1		
-25,-15	2		9	7	
-15,-5	0	1	11	17	2
-5,5	16	14	18	18	6
5,15	16	17	6	5	9
15,25	11	13	4	3	10
25,35	2	3			6
35,45	3	2			7
45,55					1
55,65					8
65,75					1
75,85					
85,95					
95,105					

Table 23. — Distributions of Pulse Rate Responses for Control Group by Stimulus

Interval	Initial	Postural	Cold	Breath Holding	Exercise
-65,-55			1		
-55,-45			0		
-45,-35			1		
-35,-25			1	2	
-25,-15	1	3	7	9	2
-15,-5	1	3	15	17	1
-5,5	7	10	21	17	8
5,15	15	15	2	2	5
15,25	21	13	1	3	6
25,35	3	5			8
35,45	2	1			9
45,55					1
55,65					5
65,75					3
75,85					1
85,95					0
95,105					1

groups. The additional problem, then, is to test the significance of the discrimination or separation between the groups—that is, to determine whether the variance of the function between groups is significantly larger than its within group variance.

This analysis was carried out separately for each of the 5 stimuli tested to determine which of these best separated the 2 groups. The improved computational techniques presented by Dwyer (22), including the method of matrix square root factorization were used in the analysis.

Systolic response, diastolic response and pulse rate response were the 3 variables used in each discriminant analysis. The square root method readily provides tests of the significance of the discrimination involving subsets of the whole group of variables. For example, in this analysis for each stimulus the significance of the discrimination based on systolic response alone was tested first. Then the significance of the discrimination based on systolic and diastolic responses together was tested and finally the discriminant function based on all 3 variables was tested. These tests involve F ratios with p and $n_1 + n_2 - p - 1$ degrees of freedom, where p is the number of variables in the discriminant function, n_1 is the sample size in the experimental group (50 in this study) and n_2 is the sample size in the control group (also 50, except for the cold stimulus where $n_2 = 49$ as discussed above).

The reasons for testing the discriminant functions in this particular order were as follows. The purpose of the study was to separate the groups, if possible, on the basis of blood pressure response. The determination of pulse rates was definitely of secondary interest. Criteria for the indirect determination of systolic blood pressure are almost universally agreed upon and the systolic pressure is certainly

most easily obtained, particularly in children. For these reasons, discrimination based on systolic response alone was sought first. Next the diastolic was added and finally the pulse rate.

Table 24 gives the successive F ratios for each stimulus based on the 3 subsets of variables.

Table 24. — Values of F for Significance of Discriminant Functions by Stimulus and Set of Variables in the Function

	Systolic Response	Systolic and Diastolic Response	Systolic, Diastolic and Pulse Rate Response
Initial	.002	.004	.329
Postural	5.545	2.831	2.638
Cold	.294	.153	.425
Breath Holding	.382	1.320	1.258
Exercise	.084	.043	.152

With the exception of the cold stimulus, the F ratios in the first column are based on 1 and 98 degrees of freedom, those in the second column on 2 and 97 degrees of freedom, and those in the third column on 3 and 96 degrees of freedom. The cold values are based on 1 and 97, 2 and 96, and 3 and 95 degrees of freedom, respectively. Many of these F ratios are extremely small. Such a ratio is an indication of a very small difference between group means compared to the variability within the means.

Consultation with an F table shows that only the postural stimulus gives a significant discriminant function. Based on systolic response only, the significance level for this value of F is between the

2.5% and 1% levels. Based on systolic and diastolic responses it drops to between the 10% and 5% levels where it remains when all 3 variables are considered. The best linear discriminant function based on all 3 variables is 1.0000S - .1057D + .3577 P, where S, D, and P stand, respectively, for systolic, diastolic, and pulse response.

These data show that by and large this set of stimuli fails to discriminate between the 2 groups in terms of response. The postural test is the only exception, and it probably warrants more detailed study.

In this series of tests, while the order of administration of the cold pressor test, breath holding test, and exercise test was variable and selected at random, the postural test was always given immediately after the rest period. This was done because the best estimate of the subject's lying, resting pressure could probably be obtained at the end of the rest period, after which it was very natural to have him stand immediately. Whether this had any effect on the findings with respect to response is difficult to say and would require further investigation. However, since the aim of this study was to compare several different stimuli in terms of response, the subject's blood pressure could not be maintained at a basal level prior to each of the stimuli, with completion of the procedure in a reasonable length of time. Furthermore, the effect of order of administration was specifically tested for significance in Chapter IV. It was not significant for any of the variables considered (systolic response, diastolic response, pulse pressure response, or pulse response).

Possibly the crucial factor in discriminating between 2 groups such as these on the basis of test response is not so much the nature of the stimulus which is applied, but the extent to which a basal level is

reached prior to stimulation. Hines (36) has stressed the importance of having the blood pressure as close to basal as possible prior to the cold pressor test. This factor has not been specifically investigated simultaneously for a variety of stimuli and certainly should be studied.

It is particularly fortunate that one of the stimuli in this study (postural change) was invariably given with the blood pressure approximately at a basal level. If this had not been so, the possible importance of this factor compared to the actual nature of the stimulus in separating the 2 groups might not have been suggested by the data.

Another postural change took place in the test protocol. This change came between the first 2 readings taken on each individual. The first reading was taken with the subject standing, and the second was taken immediately after the subject lay down at the beginning of the rest period. The correlation coefficient of the 2 systolic responses of the subjects in the experimental group was calculated. More specifically, for each of the 50 experimental subjects, the first systolic reading minus the second systolic reading and the first standing systolic reading in the postural test minus the immediately preceding systolic reading were calculated. These 2 responses had a correlation coefficient of 0.084, which was not significantly different from zero. This indicates that there was no direct linear relationship between the 2 postural systolic responses for the experimental group.

Further analyses were done to determine the association between response level and observer. Each of the 30 response distributions shown in Tables 18 through 23 were broken into 2 sub-distributions--one involving all measurements taken by the author, and the other involving the measurements taken by other observers. The distributions were then

split at a class boundary adjacent to the modal class and 2 x 2 Yates-corrected chi-squares were calculated. This procedure of splitting was done in advance of the analyses as an objective method to obtain sufficiently large expected frequencies to justify the chi-square significance tests. Of the 30 tests made, only 5 yielded significant chi-squares. For the experimental group, these were the breath holding diastolic response ($.05 > P > .025$) and the exercise pulse rate response ($P < .001$). For the control group, significant chi-squares were found for the breath holding systolic response ($.05 > P > .025$), for the cold pulse rate response ($.005 > P > .001$), and for the exercise pulse rate response ($.025 > P > .01$). The association in exercise pulse rate response was expected. This is because in all but 1 case, whenever the author took pulse rates, he also took blood pressures. This caused a slight time lag after the exercise test while the post-exercise blood pressure was determined. During this short time, the subject was seated and his pulse rate had some opportunity to fall below its maximum level. Thus the readings taken by observers other than the author included all but 1 of the cases in which 2 observers administered the tests. These cases permitted a somewhat earlier post-exercise pulse determination. This slight defect which was imposed by personnel limitations is not considered serious. It probably accounts for a portion of the variance in the post-exercise pulse and exercise pulse response distributions.

While finding 5 out of 30 chi-squares significant at the 5% level is probably more than would be expected due to Type I errors, the fact that 2 of these associations were explained and are probably real, reduces the unexplained ones to 3. This does not seem to indicate an important observer effect.

The response data were similarly analyzed to determine the association of age with test response. The experimental and control groups were combined for this analysis. The 15 combined response distributions were then split into the 50 younger children and the 50 older children. Partially by coincidence this age split put the 25 younger experimental children and the 25 younger control children together into the younger combined group, accidentally giving a symmetric configuration to the partition. The distributions were then split adjacent to the modal class and 15 additional Yates-corrected 2 x 2 chi-squares were calculated. The only significant age association was in the exercise responses which each gave significant or nearly significant chi-squares. For systolic response the significance level was between 0.5% and 0.1%, for diastolic response it was between 10% and 5%, and for pulse response it was less than 0.1%. This association is possibly in part due to the variation in physical stamina and coordination associated with age. On the other hand, some of these associations could be artificial and due to the occurrence of Type I errors.

Summary and Conclusions

A standard series of blood pressure reactivity tests was given to 50 children of hypertensives and 50 matched school children between the ages of 8 and 18. The mean systolic blood pressure levels were uniformly and significantly higher for the children of hypertensives. In fact when the mean systolic reading was calculated for each of the 32 different determinations made in the test protocol and for the experimental and control groups, there was a very striking parallelism between the curves for the 2 groups. That is, the means of the experimental

group were always higher than the corresponding means for the control group and by roughly the same amount, 4-6 mm. Since virtually all these differences were significant, consistently in the same direction and approximately the same size, a very firm piece of information was provided. In these groups of children, those with a hypertensive parent had consistently higher mean systolic blood pressures, whether stimulated by any of a variety of stresses or resting.

The situation with respect to diastolic means was much less clear-cut. None of the differences between the means of the 2 groups was significant. While the controls showed some tendency toward lower means, the situation was frequently reversed with the children of hypertensive parents taking the lower value. The differences were generally of the order of 1 mm.

When mean pulse rates were considered, the situation again became quite definite. The curves giving mean values for the 2 groups were once more approximately parallel. In this case, however, the children having a hypertensive parent gave consistently lower mean pulse rates. In some cases, the differences in means were very small, but in the majority of cases they were 4-8 counts per minute. These differences were generally significant and were again remarkably consistent. Among the non-significant differences were the stimulated readings for cold, breath holding, and exercise.

While these 2 groups definitely appeared to be different with respect to mean systolic blood pressures and pulse rates, they were quite similar with respect to the mean change in blood pressure and pulse rate brought about by several stimuli--cold, breath holding, exercise, and the stress of initial measurement (compared with a resting reading).

There appeared to be some difference in the change in blood pressure from resting to standing for the 2 groups. This difference was most pronounced for the change in systolic blood pressure, with the children of hypertensives showing a larger average increase. The possibility that part of the observed difference was due to the fact that a more nearly basal blood pressure level was reached just prior to this stimulus as compared to the other stimuli cannot be overlooked. In general, the groups did not differ significantly in their blood pressure or pulse rate changes due to stimulation, the only possible exception being for the stimulus of postural change.

The results of this study are suggestive for future research. A next step might be the study of a simpler reactivity series on a larger group of individuals--adults and children; hypertensives, normotensives, and hypotensives; and various racial groups. Any future reactivity studies of this sort should include a postural change as one of the procedures.

The effect of seasonal weather variation on responses to these tests could not be estimated in this study. All the work with medical students described in Chapters III and IV was carried out during the summer, whereas the testing of children was done in the winter. Age and other differences made it impossible to separate out a seasonal effect by comparing the data of Chapters III and IV with those of Chapter V. The effect of weather on blood pressure responsiveness needs to be determined by future research.

Further work is needed regarding the effects of psychogenic stimulation. The significance of a labile blood pressure should be carefully investigated by follow-up study.

CHAPTER VI

SUMMARY OF THE STUDY

A series of tests of vascular reactivity was devised for the purpose of determining or measuring increased susceptibility to hypertension. The literature on such tests was reviewed and summarized. A series of preliminary tests of proposed blood pressure stimuli was conducted. An experiment to determine strengths of various sources of variation of response to a standard testing procedure was carried out using a group of medical students as subjects. Analysis of the data showed enough consistency and lack of capricious variation to justify further study of the procedure.

A modified test series was then applied to 2 groups of children between the ages of 8 and 18. One group was composed of children of known hypertensives treated at the University of Michigan Hypertension Unit. The other was a matching control group of school children selected from the University of Michigan grade and high schools. The test was administered to these groups following a procedure designed to control several extraneous sources of variation, and the data were analyzed to determine the character of the test responses for each group.

The group of children having a hypertensive parent had consistently and significantly higher mean systolic blood pressure levels and consistently lower mean pulse rates. The mean diastolic blood pressure levels of the 2 groups were quite similar. The blood pressure and pulse

rate changes due to cold, breath holding, exercise, and the stress of initial measurement were quite similar for the 2 groups. Postural change apparently produced a different response for the 2 groups, particularly with respect to change in systolic blood pressure, but this point requires further study for clarification.

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