THE UNIVERSITY OF OKLAHOMA

GRADUATE COLLEGE

AN APPLICATION OF MULTIVARIATE HOMOGENEITY OF VARIANCE TESTS

TO THE ELECTROCARDIOGRAM IN MYOCARDIAL INFARCTION

A DISSERTATION

SUBMITTED TO THE GRADUATE FACULTY

in partial fulfillment of the requirements for the

degree of

DOCTOR OF PHILOSOPHY

BY

EDWARD NEWMAN BRANDT, JR.

Oklahoma City, Oklahoma

1963

AN APPLICATION OF MULTIVARIATE HOMOGENEITY OF VARIANCE TESTS

TO THE ELECTROCARDIOGRAM IN MYOCARDIAL INFARCTION

APPROVED BY

DISSERTATION COMMITTEE

ACKNOWLEDGEMENTS

TABLE OF CONTENTS

LIST OF TABLES

# AN APPLICATION OF MULTIVARIATE HOMOGENEITY OF VARIANCE TESTS

# TO THE ELECTROCARDIOGRAM IN MYOCARDIAL INFARCTION

## CHAPTER I

## STATEMENT OF THE PROBLEM

Wishart (1928) published the distribution known by his name in 1928, and this publication may be regarded as the beginning of multivariate sampling distribution theory. This was followed by the work of Wilks (1932) who pointed out that the variance-covariance matrix of a multivariate population was the logical multivariate extension of the variance of a univariate population. Because of the univariate theory in which statistical test criteria are based on variance ratios, it seemed only natural to investigate the ratios of variance-covariance matrices.

In the same publication, Wilks (1932) developed the theory necessary for the multivariate extension of various univariate test criteria. However, at the end of that publication, he stated, "The practical application of the criteria developed in this paper must be left for further discussion". Since that time, Pearson and Wilks (1933) have solved the problem for the case of k bivariate populations, and Wilks (1946) has done the same for one p-variate population. Kendall (1961) says, "Methods of a parallel kind could be followed for the testing of k samples of p-variate populations, although I am not aware that the general case has

been worked out explicitly". That is the purpose of this investigation.

In other words, we are interested in the derivation of statistical test criteria for the testing of the three null hypotheses given below in k p-variate normal populations.

$H_1$: The k populations have equal mean vectors and equal variance-covariance matrices.

$H_2$: The k populations have equal variance-covariance matrices irrespective of their mean vectors.

$H_3$: The k populations have equal mean vectors given that the variance-covariance matrices are equal.

In addition to the development of the test criteria, it shall be necessary to investigate their distributions in order that an appropriate test of the three hypotheses can be made. This shall be done in subsequent chapters.

Following the derivation of the test criteria and their distributions, a practical example of the use of these test procedures shall be given. This example was obtained from clinical medicine, and is an attempt to test the three hypotheses given above in 4 populations of patients experiencing an acute myocardial infarction. The variables to be used are measurements obtained from electrocardiograms.

Although much of this theory was first developed by Wilks (1932), it shall be re-developed using matrix notation, and shall be applied so as to arrive at a practical test procedure for the three null hypotheses in k p-variate populations. In so doing, we shall make use of methodology first reported by Tukey and Wilks (1946) and Box (1949).

Of the hypotheses, $H_3$ is the multivariate analog of the

univariate analysis of variance, and as we shall see, its test criterion

has a simpler distribution function than either $H_1$ or $H_2$.

With this background, let us now turn to the development of

the test criteria. This shall be done in CHAPTER II. CHAPTER III will

be devoted to the derivation of the moments of the distributions of the

three test criteria. The nature of the exact distribution of the test

criteria will be investigated in CHAPTER IV, and approximations to these

exact distributions will be obtained in CHAPTER V. Finally, CHAPTER VI

will contain the application of this theory to clinical electrocardio-

graphic parameters.

CHAPTER II

DERIVATION OF THE TEST CRITERIA

In this chapter, we shall be concerned with the derivation of
the test criteria for testing the three hypotheses discussed in CHAPTER
I. These results were first obtained by Wilks (1932) using the method
of maximum likelihood developed by Neyman and Pearson (1928). This deri-
vation will differ from Wilks' in that matrix notation and methods will
be used.

We shall adopt the following notation for our k p-variate nor-
mal populations. Let $\mu^{(t)}$ represent the vector of means for the $t^{\text{th}}$
population, $V^{(t)}$ the matrix of variances and covariances for the $t^{\text{th}}$
population, $R^{(t)}$ the inverse of $V^{(t)}$, $n^{(t)}$ the sample size from the $t^{\text{th}}$
population, $X_i^{(t)}$ the vector of observations obtained from the $t^{\text{th}}$ popu-
lation, and $|V|$ the determinant of the matrix V. The range of t will
be from 1 to k and the range of i will be from 1 to $n^{(t)}$ for the $t^{\text{th}}$
population. We shall use $\hat{V}$ to represent an estimate of V. $n = \sum_{t} n^{(t)}$.

With this notation the distribution for the $t^{\text{th}}$ population will
be:

$$f(X) = \frac{\left| R^{(t)} \right|^{\frac{1}{2}}}{(2\pi)^{\frac{1}{2}p}} \exp \left[ -\frac{1}{2} (X^{(t)} - \mu^{(t)})' R^{(t)} (X^{(t)} - \mu^{(t)}) \right].$$

Now if a sample of size $n^{(t)}$ is drawn from this population, the likelihood

4

function for the sample can be written as:

$$L^{(t)} = \frac{\left| R^{(t)} \right|^{\frac{1}{2}n^{(t)}}}{(2\pi)^{\frac{1}{2}pn^{(t)}}} \exp\left[ -\frac{1}{2} \sum_i (X_i^{(t)} - \mu^{(t)})' R^{(t)} (X_i^{(t)} - \mu^{(t)}) \right].$$

Therefore, the joint likelihood for samples obtained from all of the populations is:

$$L = \prod_{t=1}^{k} \frac{\left| R^{(t)} \right|^{\frac{1}{2}n^{(t)}}}{(2\pi)^{\frac{1}{2}pn^{(t)}}} \exp\left[ -\frac{1}{2} \sum_t \sum_i (X_i^{(t)} - \mu^{(t)})' R^{(t)} (X_i^{(t)} - \mu^{(t)}) \right]$$

Taking the logarithm, we get:

$$\ln L = \frac{1}{2} \sum_t n^{(t)} \ln \left| R^{(t)} \right| - \frac{1}{2}p \sum_t n^{(t)} \ln 2\pi$$

$$-\frac{1}{2} \sum_t \sum_i (X_i^{(t)} - \mu^{(t)})' R^{(t)} (X_i^{(t)} - \mu^{(t)}) .$$

We shall first maximize this likelihood function in the unrestricted parameter space, that is, without restricting the values of the means, variances, or covariances of the k populations. To do so, we need the partial derivatives of ln L with respect to the $\mu^{(t)}$ and $V^{(t)}$.

$$\frac{\partial \ln L}{\partial \mu^{(t)}} = \frac{1}{2} \sum_i 2 R^{(t)} (X_i^{(t)} - \mu^{(t)})$$

Setting this equal to zero and solving, we get:

$$\hat{\mu}^{(t)} = (n^{(t)})^{-1} \sum_t X_i^{(t)} = \bar{X}^{(t)} . \tag{1}$$

Similarly:

$$\frac{\partial \ln L}{\partial R^{(t)}} = \frac{n^{(t)}}{2} \frac{\left|R^{(t)}\right| \left[R^{(t)}\right]^{-1}}{\left|R^{(t)}\right|} -\frac{1}{2} \sum_i 2(X_i^{(t)} - \mu^{(t)})(X_i^{(t)} - \mu^{(t)})'.$$

Again, equating this expression to zero we get:

$$\hat{V}^{(t)} = (\hat{R}^{(t)})^{-1} = (n^{(t)})^{-1} \sum_i (X_i^{(t)} - \bar{X}^{(t)}) (X_i^{(t)} - \bar{X}^{(t)})' . \tag{2}$$

Substituting these expressions into L, the maximum of L can be written as:

$$L(\Omega) = \prod_{t=1}^{k} \left| \hat{V}^{(t)} \right|^{-\frac{1}{2}n^{(t)}} (2\pi)^{-\frac{1}{2}pn^{(t)}} \exp(-\tfrac{1}{2}n) . \tag{3}$$

Let us now consider $H_1$: $\mu^{(1)} = \mu^{(2)} = \ldots = \mu^{(k)} = \mu$, and $V^{(1)} = V^{(2)} = \ldots = V^{(k)} = V$. With these restrictions, ln L becomes:

$$\ln L = -\tfrac{1}{2}np \ln 2\pi + \tfrac{1}{2}n \ln |R| - \tfrac{1}{2} \sum_t \sum_i (X_i^{(t)} - \mu)' R(X_i^{(t)} - \mu) .$$

Maximizing this expression with respect to $\mu$ and R, one obtains:

$$\hat{\mu} = n^{-1} \sum_t n^{(t)} \bar{X}^{(t)} = \bar{X}_o, \tag{4}$$

and:

$$\hat{V} = n^{-1} \sum_t n^{(t)} V^{(t)} + n^{-1} \sum_t n^{(t)} (\bar{X}^{(t)} - \bar{X}_o) (\bar{X}^{(t)} - \bar{X}_o)' \tag{5}$$

$$= \hat{V}_o .$$

Using these estimates, the maximum of L in this restricted parameter space can be written as:

$$\left| \hat{V}_o \right|^{-\frac{1}{2}n} (2\pi)^{-\frac{1}{2}np} \exp(-\tfrac{1}{2}kn).$$

Therefore, the test criterion for hypothesis $H_1$ is:

$$\lambda_1 = \frac{L(w)}{L(\Omega)} = \left| \hat{V}_0 \right|^{-\frac{1}{2}n} \prod_{t=1}^{k} \left| \hat{V}(t) \right|^{\frac{1}{2}n(t)}$$

$$= \prod_{t=1}^{k} \left| \hat{V}_0 \right|^{-\frac{1}{2}n^{(t)}} \left| \hat{V}(t) \right|^{\frac{1}{2}n^{(t)}} \tag{6}$$

Let us now consider $H_2$: $V^{(1)} = V^{(2)} = \ldots = V^{(t)} = V$ irrespective of the value of the means. Under this hypothesis, $L(\Omega)$ remains the same as (3).

In the restricted parameter space:

$$\ln L = \tfrac{1}{2} n \ln |R| - \tfrac{1}{2} np \ln 2\pi - \tfrac{1}{2} \sum_t \sum_i (X_i^{(t)} - \mu^{(t)})' R (X_i^{(t)} - \mu^{(t)}).$$

Differentiating $\ln L$, equating the derivatives to zero, and solving, we obtain:

$$\hat{\mu}^{(t)} = \bar{X}^{(t)} \tag{7}$$

and:

$$\hat{V} = n^{-1} \sum_t n^{(t)} \hat{V}^{(t)} = \hat{V}_a . \tag{8}$$

Using these estimates we find:

$$L(w) = (2\pi)^{-\frac{1}{2}pn} \left| \hat{V}_a \right|^{-\frac{1}{2}n} \exp(-\tfrac{1}{2}kn) \tag{9}$$

and so:

$$\lambda_2 = \frac{L(w)}{L(\Omega)} = \left| \hat{V}_a \right|^{-\frac{1}{2}n} \prod_{t=1}^{k} \left| \hat{V}(t) \right|^{\frac{1}{2}n(t)}$$

$$= \prod_{t=1}^{k} \left| \hat{V}_a \right|^{-\frac{1}{2}n^{(t)}} \left| \hat{V}(t) \right|^{\frac{1}{2}n^{(t)}} . \tag{10}$$

Finally, we shall obtain the test criterion for $H_3$:

$\mu^{(1)} = \mu^{(2)} = \ldots = \mu^{(t)} = \mu$ given that the variance-covariance matrices

are all equal.

Now under the unrestricted hypothesis:

$$\ln L = \tfrac{1}{2}n \ln |R| - \tfrac{1}{2}pn \ln 2\pi - \tfrac{1}{2} \sum_t \sum_i (X_i^{(t)} - \mu^{(t)})' R (X_i^{(t)} - \mu^{(t)}).$$

From this, one can obtain:

$$\hat{\mu}^{(t)} = \bar{X}^{(t)} , \tag{11}$$

and:

$$\hat{V} = n^{-1} \sum_t n^{(t)} \hat{V}^{(t)} = \hat{V}_a , \tag{12}$$

and so:

$$L(\Omega) = (2\pi)^{-\tfrac{1}{2}pn} \left| \hat{V}_a \right|^{-\tfrac{1}{2}n} \exp(-\tfrac{1}{2}kn) \tag{13}$$

With the restriction imposed by the hypothesis of equality of means:

$$\ln L = \tfrac{1}{2}n \ln |R| - \tfrac{1}{2}np \ln 2\pi - \frac{1}{2} \sum_t \sum_i (X_i^{(t)} - \mu)' R (X_i^{(t)} - \mu) .$$

Maximizing this expression, we obtain:

$$\hat{\mu} = \bar{X}_o , \tag{14}$$

and:

$$\hat{V} = \hat{V}_o , \tag{15}$$

and so:

$$L(w) = (2\pi)^{-\tfrac{1}{2}pn} \left| \hat{V}_o \right|^{-\tfrac{1}{2}n} \exp(-\tfrac{1}{2}kn) .$$

Using this, we find:

$$\lambda_3 = \frac{L(w)}{L(\Omega)} = \left| \hat{V}_a \right|^{\tfrac{1}{2}n} \left| \hat{V}_o \right|^{-\tfrac{1}{2}n} . \tag{16}$$

The next chapter will be devoted to investigating the moments of the distributions of these three criteria so that they can be used for the testing of the three null hypotheses.

# CHAPTER III

## MOMENTS OF THE DISTRIBUTIONS OF THE TEST CRITERIA

We are now ready to investigate the distributions of the three test criteria developed in the last section, but first we should review a fundamental multivariate distribution.

Let $\hat{V}$ represent the variance-covariance matrix computed from a sample of n items from a p-variate normal population, that is:

$$n \hat{V} = \sum_i (X_i - \bar{X})(X_i - \bar{X})'$$

where the $X_i$ are independent and normally distributed with mean $\mu$ and variance-covariance matrix V. The distribution of $n\hat{V}$ was first derived by Wishart (1928), and now bears his name. It is given by:

$$\frac{|\hat{V}|^{\frac{1}{2}(n-p-2)} \exp\left[-\frac{1}{2} Tr(V^{-1} \hat{V})\right]}{2^{\frac{1}{2}p(n-1)} \pi^{\frac{1}{4}p(p-1)} |V|^{\frac{1}{2}(n-1)} \prod_{i=1}^{p} \Gamma\left[\frac{1}{2}(n-i)\right]} d\hat{V} \qquad (17)$$

where $Tr(V^{-1} \hat{V})$ represents the trace of the matrix $(V^{-1} \hat{V})$.

From (17), we have:

$$\int |\hat{V}|^{\frac{1}{2}(n-p-2)} \exp\left[-\frac{1}{2} Tr(V^{-1} \hat{V})\right] d\hat{V}$$

$$= |V|^{\frac{1}{2}(n-1)} \quad 2^{\frac{1}{2}(n-1)p} \quad \pi^{\frac{1}{4}p(p-1)} \quad \prod_{i=1}^{p} \Gamma\left[\frac{1}{2}(n-i)\right] \quad (18)$$

$$= W.$$

Then the $k^{\underline{th}}$ moment of this distribution can be obtained as:

$$M_k(\hat{V}) = \frac{1}{W}\int |\hat{V}|^{\frac{1}{2}(n-p-2+2k)} \quad \exp\left[-\frac{1}{2}\operatorname{Tr}(V^{-1}\hat{V})\right] d\hat{V}$$

$$= \frac{1}{W} |V|^{\frac{1}{2}(n+2k-1)} \quad 2^{\frac{1}{2}p(n+2k-1)} \quad \pi^{\frac{1}{4}p(p-1)} \quad \prod_{i=1}^{p} \Gamma\left[\frac{1}{2}(n+2k-i)\right]$$

$$= \frac{|V|^k \quad \prod_{i=1}^{p} \Gamma\left[\frac{n-i}{2}+k\right]}{2^{-kp} \quad \prod_{i=1}^{p} \Gamma\left[\frac{n-i}{2}\right]} \, . \quad (19)$$

With these results, we are now ready to find an expression for the $h^{\underline{th}}$ moment of the first criterion given by (6). Now, $\hat{V}_0$ can be written as $\hat{V}_0' + \hat{V}_0''$ where:

$$\hat{V}_0' = n^{-1} \sum_t n^{(t)} \hat{V}^{(t)}, \text{ and}$$

$$\hat{V}_0'' = n^{-1} \sum_t n^{(t)} (\bar{X}^{(t)} - \bar{X}_0)(\bar{X}^{(t)} - \bar{X}_0)'.$$

Since the $n^{(t)} \hat{V}^{(t)}$ are independently distributed according to the Wishart distribution (17), and since the sum of two Wishart variates is also a Wishart variate, then under $H_1$, the distribution of $\hat{V}_0'$ is given by:

$$\frac{\left|\hat{V}_0{}'\right|^{\frac{1}{2}(n-k-p-1)} \exp\left[-\frac{1}{2}\,\mathrm{Tr}(V^{-1}\,\hat{V}_0{}')\right]}{2^{\frac{1}{2}p(n-k)}\ \pi^{\frac{1}{4}p(p-1)}\ \prod_{i=1}^{p}\Gamma\left[\tfrac{1}{2}(n-k+1-i)\right]}. \tag{20}$$

Also, the means of samples of size $n^{(t)}$ from p-variate normal populations are independently distributed as Gaussian variates. Furthermore, the distribution of these means is independent of that of the variance-covariance matrices. Since $\hat{V}_0{}''$ represents the sample variance-covariance matrix of $\bar{X}^{(t)}$, $\hat{V}_0{}''$ also is distributed as a Wishart variate.

Now, since $\hat{V}_0$ is the sum of two Wishart variates, it also has a Wishart distribution. Consequently from (17) and (19), the $m^{\text{th}}$ moment of $\left|\hat{V}_0\right|^{\frac{1}{2}n^{(t)}}$ can be written as:

$$\left|V\right|^{\frac{1}{2}nm}\ 2^{\frac{1}{2}nmp}\ \prod_{i=1}^{p}\left[\frac{\Gamma\left[\frac{n(1+m)-1}{2}\right]}{\Gamma\left[\frac{n-i}{2}\right]}\right]. \tag{21}$$

But $\hat{V}_0$ is a function of $\hat{V}^{(t)}$ and $\bar{X}^{(t)}$, and so, the $m^{\text{th}}$ moment of $\left|\hat{V}_0\right|^{\frac{1}{2}n^{(t)}}$ can also be written as:

$$\exp\left[-\sum_{t}\mathrm{Tr}\ V(\hat{V}_0{}'+\hat{V}_0{}'')\right]\ \prod_{t=1}^{k}\left|\hat{V}^{(t)}\right|^{\frac{1}{2}(n^{(t)}-p-2)}$$

$$\left|\hat{V}_0\right|^{\frac{1}{2}nm}\ \prod_{t}d\hat{V}^{(t)}\,d\bar{X}^{(t)}. \tag{22}$$

Since (22) represents the product of (k+1) independent integrals of the form of (18), we find, using (19), that the integral given by (22) is

equal to:

$$\left|V\right|^{-\frac{1}{2}nm} \prod_{t=1}^{k} \left|\frac{n}{n^{(t)}} V\right|^{-\frac{1}{2}n^{(t)}} \pi^{\frac{1}{4}kp(p-1)+\frac{1}{2}kp} 2^{\frac{1}{2}k}$$

$$\prod_{i=1}^{p} \left[ \frac{\prod\limits_{t=1}^{k} \Gamma\left[\frac{n^{(t)}-i}{2}\right] \Gamma\left[\frac{n(1+m)-i}{2}\right]}{\Gamma\left[\frac{n-i}{2}\right]} \right] . \qquad (23)$$

Following the argument given by Wilks (1932), in (22) we replace $n^{(t)}$

by $n^{(t)}(1+h)$, $n$ by $n(1+h)$, and $m$ by $-h/(1+h)$, and then multiply by:

$$\prod_{t=1}^{k} \left[ \frac{\left|\frac{n^{(t)}}{n} V\right|^{\frac{1}{2}n^{(t)}} 2^{-\frac{1}{2}k}}{\pi^{\frac{1}{4}p(p-1)+\frac{1}{2}p} \prod\limits_{i=1}^{p} \Gamma\left[\frac{1}{2}(n^{(t)}-i)\right]} \right] .$$

Now the integral given by (22) represents the $h^{\underline{th}}$ moment of $\lambda_1$. There-

fore, performing the same operations on (23) gives the solution to (22),

and so we get for $M_h(\lambda_1)$:

$$\prod_{t=1}^{k} \left[ \left[\frac{n}{n^{(t)}}\right]^{\frac{1}{2}phn^{(t)}} \prod_{i=1}^{p} \left[ \frac{\Gamma\left[\frac{n^{(t)}(1+h)-i}{2}\right]}{\Gamma\left[\frac{n^{(t)}-i}{2}\right]} \right] \prod_{i=1}^{p} \left[ \frac{\Gamma\left[\frac{n-i}{2}\right]}{\Gamma\left[\frac{n(1+h)-i}{2}\right]} \right] \right] \qquad (24)$$

Using this same approach, let us now investigate the moments

of the distribution of $\lambda_2$ given by (10).

Now, $\hat{V}_a = \frac{1}{n} \sum_t n^{(t)} \hat{V}^{(t)}$, and this is the same expression as

that for $\hat{V}_o'$. Therefore, the distribution of $n\hat{V}_a$ is the Wishart

distribution given by (20). With this information, we can use equation

(19) to find the general moment for $\left| \hat{V}_a \right|^{\frac{1}{2}n^{(t)}}$, and then following the

argument outlined in steps (21 through (24), we find that $M_h(\lambda_2)$ can

be written as:

$$\prod_{t=1}^{k} \left[ \frac{n}{n^{(t)}} \right]^{\frac{phn^{(t)}}{2}} \prod_{i=1}^{p} \left[ \frac{\Gamma\left[\frac{n^{(t)}(1+h)-i}{2}\right]}{\Gamma\left[\frac{n^{(t)}-i}{2}\right]} \right] \prod_{i=1}^{p} \left[ \frac{\Gamma\left[\frac{n-k+1-i}{2}\right]}{\Gamma\left[\frac{n(1+h)-k+1-i}{2}\right]} \right] \quad (25)$$

Finally, let us find the moments of the distribution of $\lambda_3$

given by (16). Now, let:

$$L_3 = (\lambda_3)^{2/n} = \left| \hat{V}_a \right| \left| \hat{V}_o \right|^{-1} \quad (26)$$

From the above discussion, we know that $n\hat{V}_a$ and $n\hat{V}_o$ are both

distributed as Wishart variates, and so $L_3$ is distributed as the ratio

of two Wishart variables. Again following the argument outlined in the

derivation of $M_h(\lambda_1)$, we have that:

$$M_h(L_3) = \prod_{i=1}^{p} \left[ \frac{\Gamma\left[\frac{n-i}{2}\right] \Gamma\left[\frac{n+1-k-i}{2}+h\right]}{\Gamma\left[\frac{n-i}{2}+h\right] \Gamma\left[\frac{n+1-k-i}{2}\right]} \right] \quad (27)$$

We now have general expressions for the moments of the distri-

butions of the three test criteria. In the next chapter, we shall

investigate the distributions of these criteria.

# CHAPTER IV

## DISTRIBUTIONS OF THE TEST CRITERIA

To investigate the distributions of the statistical test criteria developed in CHAPTER II, we shall make use of a theorem concerning Beta distributions due to John W. Tukey and S. S. Wilks (1946).

We sahll adopt Tukey's notation. Let:

$$(y)_h = y \, (y+1) \, (y+2) \, \ldots \, (y+h-1), \tag{28}$$

and then:

$$\Gamma(y+h) = (y)_h \, \Gamma(y), \tag{29}$$

and if r is a positive integer:

$$\Gamma(y+rh) = (y)_{rh} \, \Gamma(y) = r^{rh} \, \prod_{i=1}^{r} \left[ \frac{y+i-1}{r} \right]_h \, \Gamma(y) . \tag{30}$$

With this notation, Tukey and Wilks showed that if the moments of the distribution of a statistical test criterion can be written in the form:

$$M_h = \frac{\displaystyle\prod_{i=1}^{r} \left[ 1/a - G_i + 1 \right]_h}{\displaystyle\prod_{i=1}^{r} \left[ 1/a - D_i + 1 \right]_h} \tag{31}$$

where $a = 2/n$ or $2/(n-1)$, and $G_i$ and $D_i$ are real numbers, then the test criterion is distributed as the product of r independent beta variates.

15

We shall now show that the $h^{\underline{th}}$ moment of the distribution of a power of a beta variate can be written in a form which is a special case of (31).

If $y$ is distributed as a beta variate, that is:

$$dF = \frac{\Gamma(r+s)}{\Gamma(r)\,\Gamma(s)} \; y^{r-1} \; (1-y)^{s-1} \, dy \; ,$$

then its $h^{\underline{th}}$ moment can be written in the form:

$$M_h(y) = \frac{(r)_h}{(r+s)_h} \; . \tag{32}$$

If $z = y^v$, that is, if $z$ is a beta variate raised to a power, than its $u^{\underline{th}}$ moment is obtained from (32) by setting $h = v\,u$. Therefore, we can write:

$$M_u(y^v) = \frac{(r)_{uv}}{(r+s)_{uv}} = \frac{\displaystyle\prod_{j=1}^{u}\left[\frac{r+j-1}{v}\right]_u}{\displaystyle\prod_{j=1}^{u}\left[\frac{r+s+j-1}{v}\right]_u} \; . \tag{33}$$

If we let $1/a = (r+s)/v$, $G_i = 1 + (s-i+1)/v$, and $D_i = 1 - (i-1)/v$, then we see that (33) is a special case of (31).

With this background, we are ready to consider the $h^{\underline{th}}$ moment of $\lambda_1$ given by (24). If $\frac{1}{2}\,n^{(t)}$ is an integer for all $t$, we can then use (28), (29), and (30) to obtain:

$$\Gamma\left[\frac{n(1+h)-i}{2}\right] = \left[\frac{n}{2}\right]^{\frac{1}{2}nh} \prod_{j=1}^{\frac{1}{2}n}\left[\frac{n-i+2j-1}{n}\right]_h \Gamma\left[\frac{n-i}{2}\right] \; ,$$

and:

$$\left\lceil \left[ \frac{n^{(t)}(1+h)-i}{2} \right] \right\rceil = \left[ \frac{n^{(t)}}{2} \right]^{\frac{1}{2}n^{(t)}} \prod_{j=1}^{\frac{1}{2}n^{(t)}} \left[ \frac{n^{(t)}-i+2j-1}{n^{(t)}} \right]_h \left\lceil \left[ \frac{n^{(t)}-i}{2} \right] \right\rceil .$$

Using these two expressions, (24) can now be written as:

$$M_h (\lambda_1) = \prod_{t=1}^{k} \left[ \prod_{i=1}^{p} \prod_{j=1}^{\frac{1}{2}n^{(t)}} \left[ \frac{n^{(t)}-i+2j-1}{n^{(t)}} \right]_h \right] \prod_{i=1}^{p} \left[ \frac{1}{\prod_{j=1}^{\frac{1}{2}n} \left[ \frac{n-i+2j-1}{n} \right]_h} \right] \quad (34)$$

For a fixed value of i and t, (34) is in the form of (33) as we wished.

Using the same argument as used with $M_h (\lambda_1)$, we find that $M_h (\lambda_2)$ can be written as:

$$M_h (\lambda_2) = \prod_{t=1}^{k} \left[ \prod_{i=1}^{p} \prod_{j=1}^{\frac{1}{2}n^{(t)}} \left[ \frac{n^{(t)}-i+2j-1}{n^{(t)}} \right]_h \right] \prod_{i=1}^{p} \left[ \frac{1}{\prod_{j=1}^{\frac{1}{2}n} \left[ \frac{n-k-i+2j-1}{n} \right]_h} \right] . \quad (35)$$

Again, this expression is in the same form as (33) as desired.

Finally, we shall consider $M_h (L_3)$. Using (29), we find that:

$$\left\lceil \left[ \frac{n-i}{2} + h \right] \right\rceil = \left[ \frac{n-i}{2} \right]_h \left\lceil \left[ \frac{n-i}{2} \right] \right\rceil ,$$

and:

$$\left\lceil \left[ \frac{n+1-k-i}{2} + h \right] \right\rceil = \left[ \frac{n+1-k-i}{2} \right]_h \left\lceil \left[ \frac{n+1-k-i}{2} \right] \right\rceil .$$

Substituting these expressions into (27), we obtain:

$$M_h(L_3) = \prod_{i=1}^{p} \frac{[n/2 + (1-k-i)/2]_h}{[n/2 - i/2]_h} \tag{36}$$

For a given value of p, this expression is in the same form as (31).

Now, since $M_h(L_3)$ can be written in the form of (31), $L_3$ is distributed as the product of p independent beta variates according to the theorem given at the beginning of this chapter. However, since $M_h(\lambda_1)$ and $M_h(\lambda_2)$ are both expressible in the form of (33) if $n^{(t)}$ is an even integer for all t, then $\lambda_1$ and $\lambda_2$ are each distributed as the product of p independent beta variates each of which is raised to a power. Wilks (1946) and Kendall (1952) both give expressions for the exact distribution of $L_3$ for k = 2 and k = 3. However, the general problem still defies solution, as does the problem of obtaining the exact distributions for $\lambda_1$ and $\lambda_2$. If the expression for the distribution of $L_3$ for k = 3 is any indication, the general solution will not be of practical use since the building of tables from these expressions will be an extremely difficult and time consuming task. This is analogous to certain univariate test criteria such as the one for the testing of the homogeneity of sample variances obtained from univariate normal populations. In that particular case, a Chi Square approximation to the distribution was obtained because of the complexity of the exact distribution.

Therefore, although we know the form of the exact distributions

of our three test criteria, it would seem that their complexity would indicate that for practical use, approximations to these distributions should be sought.  The next chapter is devoted to consideration of procedures for obtaining useful approximations.

CHAPTER V

APPROXIMATE DISTRIBUTIONS OF THE TEST CRITERIA

Box (1949) has said, "Although in many cases, the exact distri-
bution (of a test criterion) cannot be obtained in a form which is of
practical use, it is usually possible to obtain the moments, and these
may be used to obtain approximations". This chapter will be devoted
to the finding of useful approximations using the moments derived in
CHAPTER III.

## Simple Chi Square Approximation

In a paper published in 1938, Wilks proved that if a population
is distributed such that "optimum" estimates of the parameters exist,
then when the null hypothesis is true, and when the sample size is large,
$-2 \ln \lambda$ where $\lambda$ is a maximum likelihood test criterion, is distributed
as a Chi Square variate except for terms of order $n^{-\frac{1}{2}}$ where n is the
size of the sample. The degrees of freedom of this distribution are
the number of parameters of the population less the number of parameters
specified by the hypothesis. Maximum likelihood estimates satisfy the
"optimum" conditions required of the estimates, and so this theorem is
applicable to our three test criteria.

For $\lambda_1$, $-2 \ln \lambda_1$ is approximately distributed as Chi Square.
To determine the degrees of freedom, we must remember that there are

p means for each of the k populations or a total of kp means to be estimated. In addition, there are $\frac{1}{2}p(p+1)$ distinct variances and covariances for each population yielding a total of $kp + \frac{1}{2}kp(p+1)$ or $\frac{1}{2}kp(p+3)$ parameters associated with our likelihood function. Of these, $p + \frac{1}{2}p(p+1)$ or $\frac{1}{2}p(p+3)$ are specified by the hypothesis, and so the desired degrees of freedom for our Chi Square approximation are $\frac{1}{2}kp(p+3)$ $\frac{1}{2}p(p+3)$ or $\frac{1}{2}p(p+3)(k-1)$.

Turning now to $\lambda_2$, $-2 \ln \lambda_2$ is approximately distributed as Chi Square with $\frac{1}{2}kp(p+1) + kp - kp - \frac{1}{2}p(p+1)$ or $\frac{1}{2}p(p+1)(k-1)$ degrees of freedom.

Finally, $-2 \ln \lambda_3 = -2(\frac{1}{2}n) \ln L_3 = -n \ln L_3$ is approximately distributed as Chi Square with $kp + \frac{1}{2}p(p+1) - p - \frac{1}{2}p(p+1)$ or $p(k-1)$ degrees of freedom.

The validity or closeness of this approximation is difficult to judge, however, we do have one guideline. In using this approximation for the distribution of these same test criteria in the case of one p-variate normal distribution, Wilks (1946) found that when k and p are 2 or 3, the Chi Square approximate probability level differed from the exact probability in the third decimal place for n greater than 60. This was also true for p = 4 or 5 in testing the third hypothesis. Since Wilks' distributions are similar to those in this problem, it would seem reasonable to have some confidence in this approximation for n at least 60 if the number of variables and populations is not too large.

## Modified Chi Square Approximation

With a very complex mathematical derivation, Box (1949) demonstrated that modification of the simple Chi Square approximation given in the preceding section produced a closer approximation to the exact distribution of maximum likelihood test criteria. This modification consists of multiplication of the simple approximation $-2 \ln \lambda$, by a factor $C^{-1}$. Because of the length and complexity of Box's derivation, only the method of finding C will be given here.

In order to find C, it is necessary to first introduce the quantity:

$$A_r = \frac{2r \; \alpha_r'}{v^r \; f} \tag{37}$$

where:

r = An integer specifying a particular $A_r$,

$$\alpha_r = \frac{(-1)^r \; k}{r(r+1)(r+2)} \sum_{s=1}^{r+1} \begin{bmatrix} r + 2 \\ s + 1 \end{bmatrix} 2^s \; D_s \; \beta^{r+1-s} \; ,$$

and:  $\beta = v - \rho \, v$,

$\rho$ = An arbitrary constant $\leq 1$,

v = Average degrees of freedom, that is $(n-k)/k$,

$\alpha_r'$ is $\alpha_r$ with $\rho = 1$,

$D_s = \Delta_s \; \gamma_s$,

$$\Delta_s \doteq B_{s+1} \begin{bmatrix} -\tfrac{1}{2}(B+p) \end{bmatrix} - B_{s+1} \begin{bmatrix} -\tfrac{1}{2}B \end{bmatrix} \; ,$$

$B_{s+1}$ is a Bernoulli polynomial and B is a Bernoulli number,

$$\gamma_s = k^{-1} \sum_{t=1}^{k} \left[ \frac{v}{v^{(t)}} \right]^{s-1} - k^{-s}$$

f = degrees of freedom of the simple Chi Square approximation,

n, $n^{(t)}$, and k are as previously defined,

and:

$$v^{(t)} = n^{(t)} - 1.$$

Box further gives the first 3 values of $\Delta_s$ which are:

| s | $\Delta_s$ |
|---|---|
| 0 | $-\frac{1}{2}p,$ |
| 1 | $\frac{1}{4}p(p+1),$ |
| 2 | $-p(2p^2 + 3p - 1)/16,$ |

and the first 2 values of $\alpha_r$ which are:

| r | $\alpha_s$ |
|---|---|
| 1 | $-k(3D_1\beta + 2D_2)/3,$ |
| 2 | $-k(3D_1\beta^2 + 4D_2\beta + 2D_3)/6.$ |

In the computation of $A_r$, we need $\alpha_r'$ which is the corresponding value of $\alpha_r$ with $\rho = 1$ and therefore $\beta = 0$.

In his derivation, Box further showed that if $A_2 = 0$, setting $C = 1 + A_1$ would give the first cumulant of $-(2 \ln \lambda)/C$ to agree with that of the exact distribution to order $v^{-2}$. Further, if $A_2 = A_1^2$, setting $C = (1-A_1)^{-1}$ would give the same order of approximation. As a matter of fact, for large v, if $A_2 - A_1^2 \geq 0$, the first cumulant of the Pearson type VI curve (F distribution) agrees with that of the exact distribution to order $v^{-2}$, if $A_2 - A_1^2 = 0$, the agreement is with the

Pearson type III curve (Chi Square distribution), and finally, if
$A_2 - A_1^2 \leq 0$, the agreement is with the Pearson type I curve. There-
fore, if $A_2 - A_1^2 \geq 0$, then $C = (1-A_1)^{-1}$ would give a chi square approxi-
mation sufficient to produce agreement of their first cumulants to order
of approximately $v^{-2}$.

Let us now derive this scale factor $C$ for each of our test
criteria. We shall first examine $\lambda_2$. The degrees of freedom associ-
ated with $-2 \ln \lambda_2$ are $f = \frac{1}{2}p(p+1)(k-1)$, and so substituting into
equation (37), we get:

$$A_1 = \frac{(2p^2 + 3p - 1)}{6 (p+1)(k-1)} \left[ \sum_{t=1}^{k} \frac{1}{n^{(t)} - 1} - \frac{1}{n-k} \right]$$

and:

$$A_2 = \frac{(p-1)(p+2)}{6 (k-1)} \left[ \sum_{t=1}^{k} \left[ \frac{1}{n^{(t)} - 1} \right]^2 - \left[ \frac{1}{n-k} \right]^2 \right]$$

Therefore, $A_2 - A_1^2$ can be written as:

$$\left[ \frac{k}{k+1} \right]^2 \left[ \frac{\gamma_2^2}{36 (p+1)^2 v^2} \right] \left[ 6 (p-1)(p+1)^2(p+2) \left[ \frac{\gamma_3}{\gamma_2^2} \right] \left[ \frac{k-1}{k} \right] - (2p^2 + 3p-1) \right]$$

where the $\gamma_i$ were defined earlier. As can be seen, $A_2 = 0$ when $p = 1$,
and so will not be zero in multivariate situations. $A_2$ is positive
for $p \geq 1$ except when $p = k = 2$ and the $n^{(t)}$ are equal for all $t$. In
that case, $A_2 - A_1^2$ is almost exactly zero. In all other cases, $A_2 - A_1^2$
is positive, and so by the argument given earlier, we choose $C = (1-A_1)^{-1}$,
that is:

$$C^{-1} = (1 - A_1) = 1 - \frac{(2p^2 + 3p-1)}{6(p+1)(k-1)} \left[ \sum_{t=1}^{k} \frac{1}{n^{(t)}-1} - \frac{1}{n-k} \right] \quad , \quad (38)$$

and so the quantity:

$$\left[ \frac{(2p^2 + 3p-1)}{3(p+1)(k-1)} \left[ \sum_{t} \frac{1}{n^{(t)}-1} - \frac{1}{n-k} \right] - 2 \right] \ln \lambda_2$$

is distributed approximately as chi square with $\frac{1}{2}p(p+1)(k-1)$ degrees of freedom.

For $\lambda_1$, we have $f = \frac{1}{2}p(p+3)(k-1)$, and so:

$$A_1 = \frac{(2p^2 + 3p-1)}{6(p+3)(k-1)} \left[ \sum_{t} \frac{1}{n^{(t)}-1} - \frac{1}{n-k} \right] ,$$

and:

$$A_2 = \frac{(p-1)(p+2)}{6(k-1)} \left[ \sum_{t} \left[ \frac{1}{n^{(t)}-1} \right]^2 - \left[ \frac{1}{n-k} \right]^2 \right]$$

Again, $A_2 = 0$ when $p = 1$ and is otherwise positive. By the same argument as used with $\lambda_2$, $A_2 - A_1^2 \geq 0$, and so we choose $C = (1-A_1)^{-1}$. Therefore, the quantity:

$$\left[ \frac{(2p^2 + 3p-1)}{3(p+3)(k-1)} \left[ \sum_{t} \frac{1}{n^{(t)}-1} - \frac{1}{n-k} \right] -2 \right] \ln \lambda_1 \quad (39)$$

is distributed approximately as chi square with $\frac{1}{2}p(p+3)(k-1)$ degrees of freedom.

Finally, considering $\lambda_3$, we find that:

$$A_1 = \frac{(2p^2 + 3p-1)}{6k(p-1)} \left[ \sum_{t} \frac{1}{n^{(t)}-1} - \frac{1}{n-k} \right]$$

and:

$$A_2 = \frac{p(p+1)(p+2)}{6k} \left[ \sum_t \left[ \frac{1}{n^{(t)}-1} \right]^2 - \left[ \frac{1}{n-k} \right]^2 \right].$$

By the same argument utilized earlier, we choose $C = (1 - A_1)^{-1}$ and so the quantity:

$$\left[ \frac{n(2p^2 + 3p-1)}{6k(p-1)} \left[ \sum_t \frac{1}{n^{(t)}-1} - \frac{1}{n-k} \right] - n \right] \ln L_3 \qquad (40)$$

is distributed approximately as chi square with $p(k-1)$ degrees of freedom.

## F Approximation

In the same paper referred to earlier, Box (1949) also showed that if $A_2 - A_1^2$ is positive, and if:

$$f_1 = \frac{f + 2}{A_2 - A_1^2}, \qquad (41)$$

and if:

$$b = \frac{f}{1 - A_1 - f/f_1} \qquad (42)$$

then $-(2 \ln \lambda)/b$ is distributed approximately as F with $f$ and $f_1$ degrees of freedom. Because of the complexity of the expressions for $-(2 \ln \lambda)/b$ for our three test criteria, we shall not write them out in their general form, but shall illustrate their use with an example later in this paper.

## Summary

In this chapter we have demonstrated methods for obtaining chi

square and F approximations to the distributions of our three test criteria using methods originally developed by Wilks (1946) and Box (1949). Although the computations necessary to use these approximations are tedious, they do allow us to make use of these test criteria to test a general range of hypotheses. Unfortunately we do not know how close these approximations are to the exact distribution. From results given by Wilks (1946) and Box (1949) with test criteria having similar distributions, we can gain some confidence in these approximations for $n^{(t)}$ large enough, say greater than 60 and for p and k not large. The real determination as to the validity of these approximations must await solution to the problem of finding a workable expression for their exact distribution. However, an approach possible today would be to perform an empirical study and compute the probability levels given by each of these approximations. This would necessitate sampling from known multivariate normal populations letting the sizes of the sample, the number of variates in each distribution, the distribution parameters, and the number of distributions vary. It should then be possible to evaluate those values of the three quantities (sample size, number of variates, and number of distributions) for which the three approximate distributions yield probability levels which agree and those for which the probability values disagree. One could then try to solve the exact distribution for those quantities producing disagreement among the probability levels yielded by the three approximations, and thereby determine which of these three approximations is closest to the exact distributions. Such a study should follow this one.

We have now developed the theory necessary for the testing of

the three null hypotheses outlined in CHAPTER I. The remainder of this study shall be devoted to an example utilizing the theory outlined in these first 5 chapters.

CHAPTER VI

A STUDY OF ELECTROCARDIOGRAPHIC MEASUREMENTS

IN ACUTE MYOCARDIAL INFARCTION

This chapter will be devoted to an illustration of the application of the previously developed test criteria and their approximate distributions. The particular problem to be discussed is one from clinical medicine, and is concerned with electrocardiographic parameters in patients experiencing an acute myocardial infarction. With the advent of high speed computing techniques, several workers have studied the electrocardiogram in various illnesses. For example, Rikli, et al. (1961) and Evans (1962) reported differences in electrocardiographic measurements existing between normal and hypertensive persons; Cady, et al. (1961) reported results of an investigation of left ventricular hypertrophy; Caceres, et al. (1962) and Pipberger (1962) discussed the general problem of estimating electrocardiographic parameters using electronic computers; and Cady, et al. (1962) presented methods for the mass screening of electrocardiograms.

In recent years, there has been much interest in the determination of those factors related to prognosis in patients experiencing an acute myocardial infarction. Several large series of patients have been studied in an attempt to solve this problem, but thus far these studies have limited themselves to clinical parameters and electrocardiographic

diagnoses. It is the purpose of this study to investigate the standard clinical electrocardiographic measurements to determine whether one or more of these might be an important prognostic factor. The results of these other studies are summarized in a recent article by Hughes, et al. (1963).

The data for this study were obtained by reviewing records of all patients with a diagnosis of acute myocardial infarction admitted to the University of Oklahoma Medical Center (including the University, Veterans Administration, and Wesley Hospitals) between January, 1953 and January, 1963. The criteria necessary for inclusion of a patient in this study were characteristic QRST electrocardiographic changes, or autopsy demonstration of an acute infarction. It was also necessary that they have a readable electrocardiogram available. Using these criteria, it was possible to obtain 370 patients for the study.

The electrocardiograms used herein were taken by heart station personnel of the hospitals in the routine manner, and the measurements of interest were obtained from the paper reproductions of these electro-cardiograms by manual measurement techniques. In every case, the electro-cardiogram obtained at the time of admission was used.

In addition to the electrocardiogram, other information was obtained from each patient's record. These are listed in Table 1. Table 2 contains the particular electrocardiographic measurements obtained.

A complete report of a linear discriminant analysis performed on the "clinical measurements" is given by Hughes, et al. (1963). In this report, it was determined that age was one of the most important determinants of mortality following an acute myocardial infarction since

TABLE 1

CLINICAL MEASUREMENTS

Age

Sex

History of Previous Myocardial Infarction

History of Angina Pectoris

History of Diabetes Mellitus

History of Hypertensive Cardiovascular Disease

Systolic and Diastolic Blood Pressure

Pulse

Temperature

Presence of Pulmonary Infarction

Presence of Congestive Heart Failure

Presence of Shock

White Blood Cell Count

Erythrocyte Sedimentation Rate

Serum Glutamic Oxalacetic Transaminase

TABLE 2

ELECTROCARDIOGRAPHIC VARIABLES

$X_1$ : Longest PR Interval of Leads I, AVF, V4R, or VI

$X_2$ : Longest QRS Interval of Leads I, AVF, V4R, or VI

$X_3$ : Longest QT Interval of Leads I, AVF, V4R, or VI

$X_4$ : Ventricular Rate

$X_5$ : Maximum P Duration of Leads I, AVF, V4R, or VI

$X_6$ : Maximum P Height of Leads I, AVF, V4R, or VI

$X_7$ : Mean QRS Axis

$X_8$ : Duration of Q or QS Deflection In Region of Infarction

$X_9$ : Depth of Q or QS Deflection In Region of Infarction

$X_{10}$: Maximum Amplitude of R in V4, V5, or V6

$X_{11}$: Intrinsicoid Deflection in V4 or V5

$X_{12}$: Maximum ST Segment Displacement In Region of Infarction

the mortality rate increased with increasing age especially over 65 years. Therefore, in this study, all patients were placed into one of the following 4 groups, namely (1) patients under 65 who survived their acute infarction (i.e. lived for six weeks after the onset of their symptoms), (2) patients over 65 who survived, (3) patients under 65 who did not survive, and (4) patients over 65 who did not survive. By use of this classification, it should be possible to determine those electrocardiographic measurements which will differ between surviving and dying patients and at the same time account for differences between those over and under 65 years of age. Therefore, this study is concerned with 4 populations each consisting of the 12 variables listed in Table 2.

### Preliminary Sample Information

The sample sizes obtained are given by the following: (a) for population 1 (surviving patients under 65), 176; (b) for population 2 (surviving patients over 65), 84; (c) for population 3 (dying patients under 65), 46; and (d) for population 4 (dying patients over 65), 64.

Table 3 contains the means for each of the 12 variables in the 4 samples. It was assumed that the distributions of these variables could be described by multivariate normal distributions.

Tables 4, 5, 6 and 7 give the variance-covariance matrices for each of the 4 samples. In our previous notation, these matrices are $\hat{V}^{(1)}$, $\hat{V}^{(2)}$, $\hat{V}^{(3)}$, and $\hat{V}^{(4)}$ respectively. $\hat{V}_o$ and $\hat{V}_a$ are shown in Tables 8 and 9, respectively.

All of the tables give the values expressed in the original measurement units which are listed in Table 3.

TABLE 3

AVERAGE VALUES FOR ALL SAMPLES

| Variable | Sample | | | | |
|---|---|---|---|---|---|
| | Living Under 65 | Living Over 65 | Dead Under 65 | Dead Over 65 | All Groups Combined |
| $X_1$ : Longest PR Interval (sec.) | .15 | .15 | .13 | .13 | .147 |
| $X_2$ : Longest QRS Interval (sec.) | .09 | .09 | .10 | .10 | .095 |
| $X_3$ : Longest QT Interval (sec.) | .37 | .37 | .34 | .35 | .360 |
| $X_4$ : Ventricular Rate (beats) | 80.00 | 79.60 | 97.50 | 90.10 | 83.880 |
| $X_5$ : Maximum P Duration (sec.) | .07 | .06 | .06 | .05 | .060 |
| $X_6$ : Maximum P Height (mm.) | .89 | .97 | 1.01 | .81 | .910 |
| $X_7$ : Mean QRS Axis (degrees) | 22.20 | 1.80 | 20.40 | 11.90 | 15.600 |
| $X_8$ : Maximum Q Duration (sec.) | .06 | .07 | .08 | .06 | .060 |
| $X_9$ : Maximum Q Depth (mm.) | 6.90 | 7.30 | 9.60 | 7.50 | 7.430 |
| $X_{10}$: Maximum R Amplitude (mm.) | 10.90 | 11.40 | 8.50 | 8.40 | 10.280 |
| $X_{11}$: Intrinsicoid Deflection (sec.) | .04 | .04 | .05 | .04 | .042 |
| $X_{12}$: ST Segment Displacement (mm.) | 1.23 | 1.44 | 2.16 | 2.08 | 1.543 |

## Statistical Analysis

The purpose of this study is to determine whether any differences exist among the four populations with respect to the twelve electrocardiographic measurements under consideration. Therefore, we shall first test $H_1$: the four populations have equal mean vectors and equal variance-covariance matrices. The formula for the test criterion, $\lambda_1$, for this hypothesis is given by equation (6). To calculate it, we need the following values:

$$\left| \hat{v}^{(1)} \right| = 3.0810903 \ (10^{-11}),$$

$$\left| \hat{v}^{(2)} \right| = 5.4584317 \ (10^{-10}),$$

$$\left| \hat{v}^{(3)} \right| = 1.0459134 \ (10^{-7}),$$

$$\left| \hat{v}^{(4)} \right| = 1.8851860 \ (10^{-8}),$$

$$\left| \hat{v}_a \right| = 1.0802156 \ (10^{-8}),$$

and:

$$\left| \hat{v}_o \right| = 1.3017426 \ (10^{-8}).$$

Using logarithms, we find that:

$$\Sigma \ \tfrac{1}{2} \ n^{(t)} \ \ln \left| \hat{v}^{(t)} \right| = - \ 3761.93945, \qquad (42)$$

$$\tfrac{1}{2} \ n \ \ln \left| \hat{v}_a \right| = - \ 3393.57764, \qquad (43)$$

and:

$$\tfrac{1}{2} \ n \ \ln \left| \hat{v}_o \right| = - \ 3359.06892. \qquad (44)$$

Therefore, from (42) and (44):

$$\ln \lambda_1 = -3761.93945 + 3359.06892$$

$$= - \ 402.87053.$$

With the value of $\ln \lambda_1$, we are now ready to make use of the approximate distribution theory developed in CHAPTER V for this test criterion.

To use the simple chi square approximation we need:

$$- 2 \ln \lambda_1 = 805.74106.$$

The degrees of freedom associated with this value are $\frac{1}{2} p(p+3)(k-1) = \frac{1}{2}(6)(15)(3) = 270$. Making use of the equation:

$$\text{Chi Square} = \frac{1}{2}(X + \sqrt{2d-1})^2 \tag{45}$$

where X is the standard normal deviate for the appropriate probability level and d is the degrees of freedom, we find that the tabulated value of the chi square variate for 270 degrees of freedom at the .05 probability level is 309.13163, and at the .01 probability level, it is 326.30672. Since the computed value exceeds this, we reject the hypothesis of no difference among the four populations of the mean vectors and variance-covariance matrices.

Now, to obtain the modified chi square approximation, we make use of equation (39). Substituting into the equation, we get as our statistic:

$$\left[ (323/135)(.05311) - 2 \right] \ln \lambda_1 = (-1.87824) \ln \lambda_1$$
$$= 756.68754.$$

Again, this value exceeds the tabulated chi square value for 270 degrees of freedom at the .01 probability level, and so, our conclusion to reject the null hypothesis remains unaltered.

To obtain the statistic approximately distributed as an "F" variable, we must first compute $f_1$ and b given by equations (40) and (41). Substituting, we find that:

$$f_1 = 272/.00383 = 71018.277,$$

and:

$$b = \frac{270}{.93647 - (270/71018.277)} = 289.4915.$$

Therefore, the test statistic $-(2 \ln \lambda_1)/b$ is equal to 2.78329. The tabulated "F" values for 270 and $\infty$ degrees of freedom are 1.17 and 1.25 for the .05 and .01 probability levels respectively. Since 2.78 is greater than 1.25, we again conclude that the null hypothesis is to be rejected, so all three of the approximations, simple chi square, modified chi square and F, yield the same conclusion.

Rejection of $H_1$ does not yield information as to whether the existing difference is among the mean vectors, the variance-covariance matrices, or both. It is, therefore, imperative to attempt to obtain such information if possible. The next logical step would be to test $H_2$: the four populations have equal variance-covariance matrices irrespective of the means. If this hypothesis is not rejected, we then know that any differences must involve only the means; however, if it is rejected, then we will know only that the variance-covariance matrices are not equal but we will have no information about the means. To my knowledge, there is no good solution to the multivariate problem of testing for differences among mean vectors given that the variance-covariance matrices are unequal.

Therefore, let us use the approximations derived in CHAPTER 5 to test $H_2$. The test criterion, $\lambda_2$, is given by equation (10), and using the calculations given in (42) and (43), we obtain:

$$\ln \lambda_2 = -3761.93945 + 3393.57764$$
$$= -368.36181.$$

Turning now to the approximate distributions, $-2 \ln \lambda_2 = 736.72362$ is

distributed approximately as chi square with $\frac{1}{2}p$ (p+1)(k-1) = 234 degrees

of freedom under $H_2$. Again making use of equation (45), we find the

tabulated chi square values for 234 degrees of freedom and probability

levels of .05 and .01 to be 270.99680 and 286.47802 respectively.

To obtain the modified chi square statistic, it is necessary

to use equation (38) to obtain:

$$\left[(323/117)(.05311) - 2\right] \ln \lambda_2 = -1.85338 \ln \lambda_2$$

$$= 682.71441.$$

Finally for the "F" approximation, we need:

$$f_1 = 236/.06544 = 3606.357,$$

and:

$$b = \frac{234}{.92667 - (234/3606.357)} = 271.52156.$$

Therefore:

$$(-2 \ln \lambda_2)/b = 2.71331.$$

The tabulated "F" values for 234 and $\infty$ degrees of freedom at the .05 and

.01 probability levels are 1.17 and 1.25 respectively.

As with $H_1$, the conclusions yielded by use of the three approxi-

mations are the same, namely, to reject the hypothesis of equality of the

four population variance-covariance matrices.

As was pointed out earlier, it is not possible to adequately

test for equality of the four mean vectors; however, if we visually

compare the sample values given in Table 3, we see that the only size-

able differences occur in the variables $X_4$ (ventricular rate), $X_7$ (mean

QRS axis), $X_9$ (maximum depth of Q), $X_{10}$ (maximum amplitude of R), and

$X_{12}$ (maximum ST segment displacement). Considering $X_4$, it seems that

the two samples from dying patients had faster ventricular rates than the two living groups. There does not seem to be a relationship with age. This difference is probably a reflection of shock since no patients in our group who developed shock survived. All of these people had rapid pulses (i.e. over 100), and so would tend to increase the average. The difference in mean QRS axis seems to represent an age related rather than a mortality related phenomenon. This tendency towards a leftward shift of the QRS axis with increasing age has been reported by Hiss (1960), and is probably of no significance in mortality prediction. The depth of the Q wave is a very gross measure of the size of the infarcted area of the myocardium. In this study, there is an apparent tendency for the dying patients to have a deeper Q wave than those who survived. Whether differences of this magnitude are of clinical importance is debatable since the depth of the Q wave is influenced by many factors including electrode placement, and spatial orientation of the heart in the chest. These same comments are also applicable to the ST segment displacement since it is also a gross measure of the size of the infarcted area. It appears that there is a smaller R amplitude in the dying group as compared to the survivors. This also may be due to the influence of the patients in shock.

Let us now consider the variances of the twelve variables in the four samples. Here, we see large differences occurring between the dying and living groups in all variables except possibly the QT interval. This is also apparently true of the covariances as well. In every case except for the R wave amplitude, the dying groups are more variable than the living. This finding is compatible with an increased incidence of

other cardiac defects (as for example, conduction and rhythm abnormalities)
in the dying group. One would of course, anticipate that the incidence
of death would increase with the presence of other cardiac abnormalities.
However, this finding is also compatible with the possibility that many
of the patients who died had measurements near the extremes of the
"normal ranges" and that a combination of several "borderline" measure-
ments might indicate a poor prognosis. Also, these findings could merely
represent sampling errors in that the dying samples might not truly re-
present the populations from which they were obtained and therefore,
these variance estimates are too high. Finally, it may be that patients
who do not survive may be more electrocardiographically variable than
those who do survive, and therefore, this higher inter-patient variation
may be a reflection of a higher intra-patient variability. A second
larger study aimed specifically at answering these questions should be
performed before a final decision is made.

In summary, application of the statistical theory for the test-
ing of three null hypotheses concerning the mean vectors and variance-
covariance matrices of four multivariate populations of electrocardio-
graphic measurements resulted in rejection of the hypotheses of equality
of both the mean vectors and variance-covariance matrices and of equality
of the variance-covariance matrices irrespective of the means. Examina-
tion of these matrices revealed that, in general, the dying groups were
more variable in all of the measurements except the QT interval.
Possible explanations for this were discussed, but the most likely ex-
planation is that these differences reflect an increased incidence of
cardiac complications such as arrythmias and conduction abnormalities

in the dying patients.  However, further studies involving more patients

will be necessary before a definite answer can be given.

## TABLE 4

### VARIANCE-COVARIANCE MATRIX

| | $X_1$ | $X_2$ | $X_3$ | $X_4$ | $X_5$ | $X_6$ |
|---|---|---|---|---|---|---|
| | | | Sample 1: Living, Under 65 | | | |
| $X_1$ | .000961 | .000045 | .000044 | -.107475 | .000155 | .001392 |
| $X_2$ | | .000257 | .000027 | .030610 | .000035 | .000283 |
| $X_3$ | | | .003040 | -.382277 | .000040 | -.000413 |
| $X_4$ | | | | 300.9182 | -.033675 | .938600 |
| $X_5$ | | | | | .000296 | .000192 |
| $X_6$ | | | | | | .248200 |
| $X_7$ | | | | | | |
| $X_8$ | | | | | | |
| $X_9$ | | | | | | |
| $X_{10}$ | | | | | | |
| $X_{11}$ | | | | | | |
| $X_{12}$ | | | | | | |

TABLE 4 - Continued

| | $X_7$ | $X_8$ | $X_9$ | $X_{10}$ | $X_{11}$ | $X_{12}$ |
|---|---|---|---|---|---|---|
| | Sample 1: Living, Under 65 | | | | | |
| $X_1$ | -.091680 | .000129 | -.000272 | -.007733 | .000005 | .000987 |
| $X_2$ | -.028150 | -.000092 | -.013890 | .007464 | .000045 | .003779 |
| $X_3$ | .383380 | -.000125 | -.039141 | .036841 | .000001 | -.000376 |
| $X_4$ | 25.1290 | .040866 | 20.7817 | -20.0596 | -.024205 | 2.1992 |
| $X_5$ | .082490 | .000189 | .003498 | .009294 | -.000001 | .002873 |
| $X_6$ | 2.2822 | -.000761 | .193900 | -.136000 | -.000498 | .002100 |
| $X_7$ | 2738.5408 | .345475 | 83.9833 | -27.7436 | -.059946 | 8.3549 |
| $X_8$ | | .002621 | .288145 | -.060189 | .000004 | .017224 |
| $X_9$ | | | 101.3470 | -18.1576 | -.001102 | 6.5151 |
| $X_{10}$ | | | | 48.8965 | .030839 | -1.0585 |
| $X_{11}$ | | | | | .000163 | .000071 |
| $X_{12}$ | | | | | | 1.7654 |

TABLE 5

VARIANCE-COVARIANCE MATRIX

| | | | Sample 2: Living, Over 65 | | | |
|---|---|---|---|---|---|---|
| | $X_1$ | $X_2$ | $X_3$ | $X_4$ | $X_5$ | $X_6$ |
| $X_1$ | .003306 | .000072 | -.000044 | -.307585 | .000809 | .014882 |
| $X_2$ | | .000233 | .000068 | -.031621 | -.000025 | -.000157 |
| $X_3$ | | | .003937 | -.692452 | .000110 | -.005589 |
| $X_4$ | | | | 467.7136 | -.107015 | .104200 |
| $X_5$ | | | | | .000596 | .006187 |
| $X_6$ | | | | | | .389800 |
| $X_7$ | | | | | | |
| $X_8$ | | | | | | |
| $X_9$ | | | | | | |
| $X_{10}$ | | | | | | |
| $X_{11}$ | | | | | | |
| $X_{12}$ | | | | | | |

TABLE 5 - <u>Continued</u>

| | $X_7$ | $X_8$ | $X_9$ | $X_{10}$ | $X_{11}$ | $X_{12}$ |
|---|---|---|---|---|---|---|
| | | | Sample 2: Living, Over 65 | | | |
| $X_1$ | -.467537 | .000248 | .018341 | -.076727 | .000026 | -.015148 |
| $X_2$ | -.046335 | .000049 | -.021176 | .001885 | .000041 | .000786 |
| $X_3$ | -.407826 | -.000145 | -.008299 | -.015270 | -.000005 | -.009014 |
| $X_4$ | 174.0580 | .090983 | 33.4909 | -13.5888 | -.014082 | 3.9545 |
| $X_5$ | -.036560 | -.000235 | -.059544 | -.020555 | -.000021 | -.002177 |
| $X_6$ | -.102100 | .002111 | -.024600 | -1.0376 | .000793 | -.094100 |
| $X_7$ | 2798.4590 | .247023 | -27.6965 | 55.5556 | .074211 | -1.4005 |
| $X_8$ | | .003323 | .299576 | -.072913 | .001614 | .017525 |
| $X_9$ | | | 111.8856 | -18.6237 | .005306 | 4.1510 |
| $X_{10}$ | | | | 61.2180 | .034249 | -.890300 |
| $X_{11}$ | | | | | .000130 | .000711 |
| $X_{12}$ | | | | | | 2.2890 |

TABLE 6

VARIANCE-COVARIANCE MATRIX

| | Sample 3: Dying, Under 65 | | | | | |
|---|---|---|---|---|---|---|
| | $X_1$ | $X_2$ | $X_3$ | $X_4$ | $X_5$ | $X_6$ |
| $X_1$ | .004020 | -.000341 | -.000334 | .184816 | .000512 | .011722 |
| $X_2$ | | .000645 | -.000060 | -.046376 | -.000036 | -.003935 |
| $X_3$ | | | .003026 | -1.0468 | .000126 | -.000017 |
| $X_4$ | | | | 725.8982 | -.123531 | .383800 |
| $X_5$ | | | | | .000478 | .005373 |
| $X_6$ | | | | | | .367800 |
| $X_7$ | | | | | | |
| $X_8$ | | | | | | |
| $X_9$ | | | | | | |
| $X_{10}$ | | | | | | |
| $X_{11}$ | | | | | | |
| $X_{12}$ | | | | | | |

TABLE 6 - <u>Continued</u>

| | $X_7$ | $X_8$ | $X_9$ | $X_{10}$ | $X_{11}$ | $X_{12}$ |
|---|---|---|---|---|---|---|
| | | | Sample 3: Dying, Under 65 | | | |
| $X_1$ | 1.5315 | -.000450 | .132541 | -.065130 | -.000035 | .031520 |
| $X_2$ | -.307101 | .000242 | .008724 | -.026367 | .000189 | .001472 |
| $X_3$ | -.271110 | -.000088 | -.086000 | .026666 | -.000589 | -.022177 |
| $X_4$ | -270.2414 | .193444 | 69.3950 | -2.1990 | .461196 | 4.4928 |
| $X_5$ | .555797 | -.000179 | .030338 | -.030956 | -.000013 | .014856 |
| $X_6$ | 20.9830 | -.002933 | 1.0985 | -.670800 | .009587 | .303400 |
| $X_7$ | 4904.2513 | -.856666 | 64.8406 | -92.7681 | .156961 | 52.9396 |
| $X_8$ | | .004150 | .525777 | -.165777 | -.001566 | .004222 |
| $X_9$ | | | 135.5768 | -29.5198 | -.190409 | 2.4754 |
| $X_{10}$ | | | | 40.1217 | .048268 | -2.7430 |
| $X_{11}$ | | | | | .007366 | .015396 |
| $X_{12}$ | | | | | | 4.9437 |

TABLE 7

VARIANCE-COVARIANCE MATRIX

| | $X_1$ | $X_2$ | $X_3$ | $X_4$ | $X_5$ | $X_6$ |
|---|---|---|---|---|---|---|
| | | Sample 4: Dying, Over 65 | | | | |
| $X_1$ | .004851 | .000026 | .000243 | -.000679 | .001178 | .020338 |
| $X_2$ | | .000631 | -.000098 | -.012532 | .000056 | -.000706 |
| $X_3$ | | | .003865 | -.556054 | .000420 | .003019 |
| $X_4$ | | | | 597.3712 | -.008757 | 1.0824 |
| $X_5$ | | | | | .001045 | .009874 |
| $X_6$ | | | | | | .430800 |
| $X_7$ | | | | | | |
| $X_8$ | | | | | | |
| $X_9$ | | | | | | |
| $X_{10}$ | | | | | | |
| $X_{11}$ | | | | | | |
| $X_{12}$ | | | | | | |

TABLE 7 - Continued

| | $X_7$ | $X_8$ | $X_9$ | $X_{10}$ | $X_{11}$ | $X_{12}$ |
|---|---|---|---|---|---|---|
| | | | Sample 4: Dying, Over 65 | | | |
| $X_1$ | -.511357 | -.000034 | -.073101 | -.027543 | .000065 | -.002001 |
| $X_2$ | -.129026 | -.000088 | -.042439 | -.018891 | -.000010 | .001213 |
| $X_3$ | -.606670 | .000002 | -.003461 | .013800 | -.000088 | .019717 |
| $X_4$ | -1.4355 | .000987 | .419399 | -.070519 | -.000600 | -.040264 |
| $X_5$ | -.103485 | .000309 | .063149 | -.006112 | .000068 | .003876 |
| $X_6$ | -7.1832 | -.001328 | .553300 | -.430100 | .001113 | .076200 |
| $X_7$ | 3495.8534 | -.331610 | -95.3485 | 62.0913 | .317337 | -11.3221 |
| $X_8$ | | .002320 | .258305 | -.047362 | -.000093 | .006454 |
| $X_9$ | | | 73.0024 | -7.5769 | -.027379 | .770400 |
| $X_{10}$ | | | | 41.3615 | .039981 | -5.2319 |
| $X_{11}$ | | | | | .000041 | -.009993 |
| $X_{12}$ | | | | | | 5.4393 |

TABLE 8

VARIANCE-COVARIANCE MATRIX

| | $X_1$ | $X_2$ | $X_3$ | $X_4$ | $X_5$ | $X_6$ |
|---|---|---|---|---|---|---|
| All Samples Pooled And Adjusted For Grand Mean $(\hat{V}_o)$ | | | | | | |
| $X_1$ | .002675 | -.000090 | .000167 | -.201762 | .000595 | .009100 |
| $X_2$ | | .000421 | -.000083 | .062103 | -.000031 | -.000467 |
| $X_3$ | | | .003523 | -.673325 | .000195 | -.000979 |
| $X_4$ | | | | 521.4965 | -.096556 | .798000 |
| $X_5$ | | | | | .000566 | .004035 |
| $X_6$ | | | | | | .331400 |
| $X_7$ | | | | | | |
| $X_8$ | | | | | | |
| $X_9$ | | | | | | |
| $X_{10}$ | | | | | | |
| $X_{11}$ | | | | | | |
| $X_{12}$ | | | | | | |

TABLE 8 - <u>Continued</u>

| | | All Samples Pooled And Adjusted For Grand Mean $(\hat{V}_o)$ | | | | |
|---|---|---|---|---|---|---|
| | $X_7$ | $X_8$ | $X_9$ | $X_{10}$ | $X_{11}$ | $X_{12}$ |
| $X_1$ | .039097 | .000003 | .022135 | -.012272 | .000009 | -.058530 |
| $X_2$ | -.983600 | .000021 | -.010332 | -.014261 | .000061 | .006419 |
| $X_3$ | -.072389 | -.000156 | -.043544 | .042088 | -.000102 | -.007964 |
| $X_4$ | 3.6862 | .129085 | 42.9710 | -28.8832 | .051436 | 6.3838 |
| $X_5$ | .125432 | .000049 | -.000194 | .004396 | .000016 | .000065 |
| $X_6$ | 2.1600 | -.000069 | .374000 | -.415700 | .001704 | .030800 |
| $X_7$ | 3262.3470 | .035169 | 25.0516 | -3.9598 | .070287 | 6.8841 |
| $X_8$ | | .002937 | .320178 | -.079566 | -.000174 | .016457 |
| $X_9$ | | | 103.6011 | -19.1231 | -.022540 | 4.9710 |
| $X_{10}$ | | | | 51.9087 | .034225 | -2.8191 |
| $X_{11}$ | | | | | .001101 | .000957 |
| $X_{12}$ | | | | | | 3.1839 |

TABLE 9

VARIANCE-COVARIANCE MATRIX

| | All Samples Pooled ($\hat{V}_a$) | | | | | |
|---|---|---|---|---|---|---|
| | $X_1$ | $X_2$ | $X_3$ | $X_4$ | $X_5$ | $X_6$ |
| $X_1$ | .002599 | -.000047 | .000090 | .149405 | .000558 | .009012 |
| $X_2$ | | .000391 | -.000043 | .032704 | -.000007 | -.000508 |
| $X_3$ | | | .003439 | -.616379 | .000164 | -.001048 |
| $X_4$ | | | | 480.1972 | -.076472 | .750500 |
| $X_5$ | | | | | .000539 | .003935 |
| $X_6$ | | | | | | .327700 |
| $X_7$ | | | | | | |
| $X_8$ | | | | | | |
| $X_9$ | | | | | | |
| $X_{10}$ | | | | | | |
| $X_{11}$ | | | | | | |
| $X_{12}$ | | | | | | |

TABLE 9 - <u>Continued</u>

| | $X_7$ | $X_8$ | $X_9$ | $X_{10}$ | $X_{11}$ | $X_{12}$ |
|---|---|---|---|---|---|---|
| | | All Samples Pooled ($\hat{V}_a$) | | | | |
| $X_1$ | -.044194 | .000029 | .027404 | .022845 | .000012 | -.002681 |
| $X_2$ | -.090986 | .000001 | -.013895 | -.008868 | .000056 | .004433 |
| $X_3$ | -.059762 | .000129 | -.037528 | .030914 | -.000095 | -.004720 |
| $X_4$ | -1.7757 | .104734 | 38.0102 | -21.4602 | .041351 | 4.0807 |
| $X_5$ | .103160 | .000059 | .001441 | -.000292 | .000011 | .001712 |
| $X_6$ | 2.2662 | -.000274 | .345300 | -.433600 | .001503 | .030500 |
| $X_7$ | 3193.7945 | .046063 | 25.0485 | -2.6477 | .066270 | 7.5130 |
| $X_8$ | | .002914 | .316168 | -.073679 | -.000188 | .015079 |
| $X_9$ | | | 102.8632 | -18.3944 | -.024923 | 4.7097 |
| $X_{10}$ | | | | 50.3845 | .034640 | -2.3809 |
| $X_{11}$ | | | | | .108781 | .000647 |
| $X_{12}$ | | | | | | 3.0382 |

BIBLIOGRAPHY

Anderson, T. W.  An Introduction to Multivariate Statistical Analysis.
        New York:  John Wiley and Sons, Inc., 1960.

Box, G. E. P.  "A General Distribution Theory For a Class of Likelihood
        Criteria," Biometrika, XXXVI (1949), pp. 317-346.

Caceres, Cesar A., C. A. Steinberg, S. Abraham, W. J. Carbery, J. M.
        McBride, W. E. Tolks, and A. E. Rikli.  "Computer Extraction
        of Electrocardiographic Parameters," Circulation, XXV (1962),
        pp. 356-362.

Cady, L. D., M. A. Woodbury, L. J. Tick, and M. M. Gerther.  "A Method
        for Electrocardiogram Wave-Pattern Estimation. Example: Left
        Ventricular Hypertrophy," Circulation Research, IX (1961),
        pp. 1078-1082.

Cady, L. D., M. A. Woodbury, M. M. Gerther, and L. J. Tick.  "Mass
        Screening of Cardiograms," American Journal of Public Health,
        LII (1962), pp. 1872-1876.

Hiss, R. G., L. E. Lamb, and M. F. Allen.  "Electrocardiographic Find-
        ings in 67,375 Asymptomatic Subjects. X. Normal Values,"
        American Journal of Cardiology, VI (1960), pp. 200-231.

Hughes, W. L., J. M. Kalbfleisch, E. N. Brandt, Jr., and J. P. Costiloe.
        "Myocardial Infarction Prognosis by Discriminant Analysis,"
        Archives of Internal Medicine, CXI (1963), pp. 338-345.

Kendall, M. G.  A Course in Multivariate Analysis. New York:  Hafner
        Publishing Co., 1961.

Kendall, M. G.  The Advanced Theory of Statistics. Volume 2. New York:
        Hafner Publishing Co., 1952.

Lawley, D. N.  "A General Method for Approximating to the Distribution
        of Likelihood Ratio Criteria," Biometrika, XXXXIII (1956),
        pp. 295-303.

Neyman, J. and E. S. Pearson.  "On the Use and Interpretation of Certain
        Test Criteria For Purposes of Statistical Inference," Biome-
        trika, XXA (1928), pp. 175-263.

Pearson, E. S. and S. S. Wilks. "Methods of Statistical Analysis Appropriate for k Samples of Two Variables," Biometrika, XXV (1933), pp. 353-378.

Pipberger, H. V. "Use of Computers in Interpretation of Electrocardiograms, " Circulation Research, IX (1962), pp. 555-562.

Prinzmetal, M., H. Toyoshima, A. Ekmekci and T. Nagaya. "Angina Pectoris VI. The Nature of ST Segment Elevation and Other ECG Changes in Acute Severe Myocardial Ischemia," Clinical Science, XXIII (1962), pp. 489-514.

Rao, C. R. Advanced Statistical Methods in Biometric Research. New York: John Wiley and Sons, Inc., 1952.

Rikli, A. E., W. E. Tolles, C. A. Steinberg, W. J. Carbery, A. H. Freiman, S. Abraham and C. A. Caceres. "Computer Analysis of Electrocardiographic Measurements," Circulation, XXIV (1961), pp. 643-649.

Tukey, J. W. and S. S. Wilks. "Approximation of The Distribution of The Product of Beta Variables By A Single Beta Variable," Annals of Mathematical Statistics, XVII (1946), pp. 318-324.

Wilks, S. S. "Certain Generalizations In The Analysis of Variance," Biometrika, XXIV (1932), pp. 471-494.

Wilks, S. S. "The Large Sample Distribution of The Likelihood Ratio For Testing Composite Hypotheses," Annals of Mathematical Statistics, IX (1938), pp. 60-62.

Wilks, S. S. "Sample Criteria For Testing Equality of Means, Equality of Variances, and Equality of Covariances in a Normal Multivariate Distribution," Annals of Mathematical Statistics, XVII (1946), pp. 257-281.

Wilks, S. S. Mathematical Statistics. New York: John Wiley and Sons, Inc., 1962.

Wishart, J. "The Generalized Product Moment Distribution in Samples From a Normal Multivariate Population," Biometrika, XXA (1928), pp. 32-52.