IMPLEMENTATION OF BAYESIAN METHODS IN THE PHARMACEUTICAL INDUSTRY

by

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TABLE OF CONTENTS.

ACKNOWLEDGEMENTS. iv
ABSTRACT. v

1 INTRODUCTION. 1-1

2 TWO TREATMENT CROSSOVER DESIGNS - A REVIEW. 2-1
2.1 Introduction. 2-1
2.2 Grizzle's Models for the Two-Period Two-Treatment Crossover. 2-2
2.3 Analysis of Variance (ANOVA) for Model II. 2-2
2.4 Analysis of Model I. 2-3
2.5 Hills-Armitage Approach. 2-5
2.6 Other Assumptions and Approaches. 2-6
2.7 An Example of the Basic Two-Period Two-Treatment Crossover. 2-6
2.8 Baselines in the Two-Period Crossover. 2-11
2.9 An Example of the Two-Period Crossover with Baselines. 2-14
2.10 Extra-Period Crossover Designs. 2-14
2.10.1 Three-Period Designs with Two Sequences. 2-15
2.10.2 Three-Period Designs with Four Sequences. 2-16
2.11 An Example of an Extra-Period Crossover Design. 2-16

3 BAYESIAN ANALYSES OF MULTIVARIATE NORMAL SAMPLES WITH A COMMON UNIFORM COVARIANCE MATRIX. 3-1

4 THE TWO-PERIOD TWO-TREATMENT CROSSOVER. 4-1
4.1 Basic Distributions. 4-1
4.2 The Variance Component Constraint. 4-3
4.3 Approximation to the Marginal Posterior Distribution of τ. 4-4
4.4 Approximating (4.14). 4-4
4.5 A Preliminary Bayesian Analysis of Wheatley's(1987) Anginal Attack Data. 4-8
4.6 Using a Bayes Factor to Decide Between Models I and II. 4-8
4.7 Bayesian Analyses Using Informative Priors. 4-12
4.8 Spiegelhalter's View. 4-15

5 THE TWO-PERIOD CROSSOVER WITH A SINGLE BASELINE. 5-1
5.1 Cell Means Model. 5-1
5.2 Basic Distributions. 5-2
5.3 An Example of the Two-Period Crossover with a Single Baseline. 5-4
5.4 Preliminary Bayesian Analysis of Barnes *et al*'s Data. 5-4
5.5 Bayes Factor - General Issues. 5-6
5.6 Bayes Factor - General Result. 5-9
5.7 Using a Bayes Factor in the Two-Period Crossover with a Single Baseline. 5-10

6 THE TWO-PERIOD CROSSOVER WITH TWO BASELINES. 6-1
6.1 Cell Means Model. 6-1
6.2 Basic Distributions. 6-1
6.3 Preliminary Bayesian Analysis of GTN Consumption Data Taken from Nicholls *et al*'s(1986). 6-4
6.4 Using Bayes Factors. 6-7
6.5 Graphical Representation of the Dependence of Posterior Inference on Prior Beliefs. 6-10
6.6 Analysis of Weekly Attack Data from Nicholls *et al*(1986). 6-14

7 EXTRA PERIOD CROSSOVER DESIGNS. 7-1
7.1 Introduction. 7-1
7.2 Three-Period Design with Two Sequences. 7-1
7.2.1 Cell Means Model. 7-1
7.2.2 Basic Distributions. 7-1
7.2.3 An Example of the Three-Period, Two-Treatment Crossover with Two Sequence Groups. 7-3
7.3 Three-Period Designs with Two Sequences. 7-5
7.3.1 Cell Means Model. 7-5
7.3.2 Basic Distributions. 7-5
7.3.3 Preliminary Analysis of the Data Displayed in Table 2.11. 7-13

7.3.4 Bayes Factors in the Three-Period Two-Treatment Crossover with Four Sequence Groups. 7-15

8 ANALYSES OF TWO-TREATMENT CROSSOVERS UNDER NON-UNIFORMITY. 8-1
8.1 A Bayesian Analysis of Multivariate Normal Samples Under Non-Uniformity. 8-1
8.2 The Two-Period, Two-Treatment Crossover. 8-4
8.3 Discussion. 8-5

9 TREATMENT OF MISSING VALUES IN CROSSOVER DESIGNS. 9-1
9.1 Introduction. 9-1
9.2 Missing Values in the Two-Period Crossover. 9-2
9.3 An Example of a Two-Period Two-Treatment Crossover with Missing Data. 9-5
9.4 Relative Efficiencies and Bayes Factors. 9-7

10 ACUTE TOXICITY TESTING AND LD50 ESTIMATION - A REVIEW. 10-1
10.1 Introduction. 10-1
10.2 Tolerance Distributions. 10-2
10.3 Maximum Likelihood Estimation. 10-2
10.4 Fieller's Theorem. 10-4
10.5 The Modern Controversy. 10-4

11 A BAYESIAN APPROACH TO LD50 EXPERIMENTS. 11-1
11.1 Introduction. 11-1
11.2 A Bayesian Analysis Using an Improper Prior. 11-3
11.3 Exact Analysis for a Logit Model and Two Dose Groups. 11-9
11.4 A Bayesian Analysis Using an Informative Prior for α and β. 11-12
11.5 Determining a Prior Distribution for α and β. 11-12
11.5.1 A Semi-Uninformative Prior Distribution for α and β Determined using Probabilities of Response. 11-13
11.5.2 An Alternative Determination of $p(\alpha, \beta)$ Using Probabilities of Response. 11-13
11.5.3 Determining $p(\alpha, \beta)$ using Prior Probabilities of the Toxicity Classes. 11-14
11.5.4 Numerical Examples of the Determination of $p(\alpha, \beta)$. 11-15
11.6 H.P.D. Intervals for the LD50 - Choosing the Scale for Making Inferences. 11-17
11.7 Profile Likelihood Approach. 11-22

12 PREDICTION IN LD50 EXPERIMENTS. 12-1
12.1 Introduction. 12-1
12.2 Background to the Applications. 12-1
12.3 Predicting the results of a Future LD50 Experiment. 12-4
12.4 Approximating the Predictive Distribution. 12-6
12.5 Results. 12-7
12.5.1 Toxicity of Basudin. 12-7
12.5.2 Toxicity of Miral. 12-8
12.6 Discussion. 12-8

13 DISCUSSION. 13-1

14 REFERENCES. 14-1

A APPENDICES. A-1
A1 BEHRENS-FISHER DENSITIES AND ORTHOGONAL POLYNOMIALS. A-1
A1.1 Background. A-1
A1.2 Quadrature Using Harper Polynomials. A-2
A1.3 Quadrature Using Hermite Polynomials. A-3
A1.4 Quadrature Using Jacobi Polynomials. A-4
A1.5 Expansion in Terms of Harper Polynomials. A-6
A1.6 Application of the Approximations. A-9
A2 ORTHOGONAL POLYNOMIALS. A-14
A2.1 Harper Polynomials. A-14
A2.1.1 Zeros and Weights of Harper Polynomials. A-15
A2.1.2 Additional Applications of Harper Polynomials - Predictive Probability in Clinical Trials. A-25
A2.1.3 Applications of Harper Polynomials - Missing Data in Bivariate Normal Samples. A-31

A2.2 Polynomials for Normal Kernels Over a Truncated Range. A-33
A3 MOMENTS OF t-DISTRIBUTIONS. A-36
A3.1 Standard t-distributions - $t(\nu)$. A-36
A3.2 Shifted and Scaled t-distributions - $t(\theta, \alpha, \nu)$. A-36
A4 DENSITY AND DISTRIBUTION FUNCTIONS OF THE RATIO OF NORMAL VARIABLES A-37
A5 FORTRAN PROGRAM FOR LD50 ESTIMATION. A-39
A5.1 Introduction. A-39
A5.2 Program Descriptions. A-39
A5.3 Program Listings. A-46
A5.4 Input. A-63
A5.5 Examples. A-64
A5.5.1 Input for Examples. A-64
A5.5.2 Example 1. ..... A-65
A5.5.3 Example 2. ..... A-69
A5.5.4 Example 3. ..... A-76
A6 SAS PROGRAMS FOR BAYESIAN ANALYSES ASSOCIATED WITH THE TWO-PERIOD TWO-TREATMENT CROSSOVER. A-80
A6.1 Bayesian Analysis of §4. ..... A-80
A6.1.1 Introduction. A-80
A6.1.2 Program Description. A-80
A6.1.3 Program Listing. A-81
A6.2 Bayesian Analysis of §9.2. ..... A-85
A6.2.1 Introduction. A-85
A6.2.2 Program Description. A-85
A6.2.3 Program Listing. A-86
A6.3 A SAS Program for Determining the Bayes Factor in a Two Period Crossover with Missing Data. A-88
A6.3.1 Introduction. A-88
A6.3.2 Program Description. A-88
A6.3.3 Program Listing. A-88
A7 SAS MACROS FOR CALCULATING THE ZEROS AND WEIGHTS OF ORTHOGONAL POLYNOMIALS. A-91
A7.1 Introduction. A-91
A7.2 Harper Polynomials. A-91
A7.3 Polynomials for a Normal Kernel Over a Truncated Range. A-92
A7.4 Jacobi Polynomials. A-94

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ANDREW P. GRIEVE

ABSTRACT.

This thesis is concerned primarily with the practical implementation of Bayesian methodology within the context of the pharmaceutical industry. The implementation includes the development, where appropriate, of analytic approximations to the posterior distributions of interest and graphical methods for mapping prior assumptions to posterior inference. Two critical areas within pharmaceutical research, critical in the sense of the controversy which they have aroused, have been investigated.

First, Bayesian methods for the analysis of two-treatment crossover designs which fell in to disfavour in the late 1970's and early 1980's because of the US Food and Drug Administration's published view that the two-treatment two-period design was not the design of first choice if unequivocal evidence of a treatment effect was required were developed. Each type of design considered and for which methods are developed are illustrated with examples from clinical trials which have already been reported in the medical literature.

Second, a Bayesian method is developed whose purpose is to classify test compounds into one of several toxicity classes on the basis of an LD_{50} estimate. The method is generalised to deal with a non-standard LD_{50} problem related to the prediction of results from a future LD_{50} experiment. Both of these applications arose out of a practical consultancy session within the context of a statistics group in the chemical/pharmaceutical industry.

As part of the methods required for carrying out these analyses the zeros and weights associated with some non-standard orthogonal polynomial are developed as a result of which a new asymptotic expansion of the Behrens-Fisher density is developed. Further applications of the polynomials orthogonal to t-kernels are developed including problems associated with prediction in clinical trials.

A FORTRAN program which has been implemented at a laboratory level within the pharmaceutical toxicology department at CIBA-GEIGY in Switzerland is provided. SAS programs for a variety of the analyses developed for the two-treatment crossover designs are provided as are SAS programs for determining the zeros and weights of a number of different classes of orthogonal polynomials.

1 INTRODUCTION.

There have been at least two major hindrances to the use of Bayesian methods in practice. Firstly, there have been the philosophical objections to the use of prior distributions and secondly there have been the purely numerical and practical problems associated with multidimensional integration. As Racine *et al*(1986) point out, much of the philosophical debate has been conducted in an arid, theoretical atmosphere in which the practical benefits of Bayesian methods have been largely ignored. The last ten years have seen a number of attempts to bring to the attention of applied statisticians and scientists Bayesian ideas and their implementation in practical contexts. This has been particularly true in the medical and biological sciences, the reason perhaps being that,

> "Since the biostatisticians evidently refuse to go to Bayes, the Bayesians will have to come to biostatistics if they wish to demonstrate the value of their viewpoint for statistical applications in biology and medicine" (Breslow,1989).

It is precisely in this spirit that Spiegelhalter and Freedman(1988) proposed a staged introduction of Bayesian ideas into clinical trials, Racine *et al*(1986) compiled four applications of Bayesian methods in the pharmaceutical industry and Grieve(1988) showed how some predictive problems in pharmaceutical research could be relatively easily tackled in a Bayesian framework. America has also not been without its innovators and as Breslow(1989) points out important applications of Bayesian ideas to biomedical problems have been reported by Dempster, Rubin, their students and pharmaceutical industry collaborators.

It is not unduly surprising that so many recent applications of Bayesian methods to biomedical problems have been developed either wholly, or partially, within the pharmaceutical industry. New drugs are not developed by serendipity, but arise out of a long, complex, development process at each stage of which information is gleaned about a new chemical entity and used either to plan the next stage of experimentation or to cease investigation of this particular chemical entity and to perhaps begin investigation of a different one, discovered in an earlier screening phase. Such a development process mirrors closely the cyclic portrait of the scientific method given by Box(1976,1980,1983) in which knowledge at a particular stage of the cyclic process drives the experimental design of the next stage leading to increased knowledge which in turn drives subsequent cycles. Box argues that this view of the scientific method fits precisely into the framework of Bayesian statistics since today's posterior is tomorrow's prior.

In many biomedical applications, and in particular pharmaceutical industry clinical trials, there is considerable prior knowledge concerning the chemical entity under test to ignore which is undesirable, as Newman(1983) forcibly argues:

> "Each clinical trial should start with fairly strong prior information about efficacy and safety yet this is ignored as the data are subjected to techniques related to non-informative priors. The process of approval must in some way balance the benefits against the risk of serious and rare side-effects. Without consideration of the prior probabilities and the losses involved the statistics end up as numbers floating in a whirlwind of prejudice and intuition".

Such a view is supported by Healy(1983),

> ".... is it fair to regard the results of a phase III trial in total isolation? The cost of such a trial will not be small, but it can only be one stage in a long period of development whose overall cost will usually be very large indeed. Certainly the company's prior belief in the efficacy of the new product will be fairly high, and it will back this up with animal results and those from phases I and II".

These views have not received unanimous support. To illustrate, Spiegelhalter and Freedman (1988) provide the following quote from Feinstein(1977),

> " A statistical consultant who proposes a Bayesian analysis should therefore be expected to obtain a suitably informed consent from the clinical client whose data are to be subjected to the experiment."

and even more extreme reactions can be found,

> "... I have yet to find a scientist who would be convinced by a posterior distribution on the methotrexate and colon cancer question if the prior has been supplied by a pharmaceutical company." (Le Cam,1985)

Spiegelhalter and Freeedman(1988) identify three groups of individuals, who each have their own motivations, and who interact with each other during the lengthy, complex developmental process which culminates in the implementation of a new medical treatment, be it chemical or surgical. These groups they term the experimenters, the reviewers and the consumers. The aim of the experimenters, amongst whom are individual pharmaceutical companies, research organisations and clinicians, is to influence the consumers, who are the clinicians who treat patients. They do this by providing them with information which has, in a sense, been "sanitised" to ensure objectivity by the reviewers, who are the editors of journals and regulatory authorities whom Sir David Cox has called the "last holders of absolute power." A statistician's job is not completed when the last analysis, Bayesian or not, is performed since thought needs to be given to the transmission of information to these diverse groups of remote clients.

The problem is to determine what is the appropriate approach to transmission of information to these remote clients. This issue is by no means new, in fact the term "remote clients" has been taken from Hildreth(1963) in which he examines the difficulty of transmitting information to vaguely known clients, whose use of the information may extend long after the statistician's contribution has been completed. Hildreth considers what parcels of information can be efficiently transmitted to remote clients and lists a number, among which are the data, the likelihood and the posterior distributions derived from a series of representative prior distributions. Spiegelhalter and Freedman(1988) regard this latter parcel as being the ideal solution but it may be necessary to provide more than one parcel of information. There has been a growing degree of unanimity

between Bayesian and frequentist statisticians that in journal articles which report the results of clinical trials the *Results* section should contain the data, or the likelihood, and that the *Discussion* is the proper place for Bayesian approaches , including posterior distributions.

In this thesis we investigate two particular areas of pharmaceutical research which have during the last 10-15 years generated considerable controversy, and research interest. First we consider two treatment crossover studies and second LD_{50} studies. Since 1977 when the FDA expressed concern about certain aspects of the analysis of the two-period two-treatment crossover design there has been continuing debate about the appropriateness of the design in general, and the traditional analysis proposed by Grizzle(1965). The recent past has also seen considerable controversy concerning the ethics of conducting LD_{50} studies. In particular Zbinden and Fluri-Roversi(1981) have expressed doubts as to the value of the information to be extracted from such studies. Our aim is to investigate the applicability of Bayesian methodology in these two areas, in particular to derive methods for the transmission of information to remote clients which will allow them to input their own beliefs and subsequently derive their own posterior distributions. We do not restrict attention to the simplest type of each of these studies but generalise to more complex two-treatment crossover designs and also look at prediction in LD_{50} studies.

2 TWO TREATMENT CROSSOVER DESIGNS - A REVIEW.

2.1 Introduction.

The central feature of a crossover clinical trial is that each patient receives more than one of the treatments in the study. In the simplest two treatment, two period design with treatments A and B, patients are randomly allocated to one of the treatment sequences A→B or B→A. Patients allocated to sequence A→B receive treatment A during the first treatment period and treatment B during the second, while patients allocated to sequence B→A receive treatment B followed by treatment A. Such designs, or similar, more complicated designs with more than two treatments and/or periods, are attractive to clinical investigators due mainly to an intuitive belief that the comparison of different treatments on the same patients is likely to be more efficient than comparing treatments on different patients. Such intuition has two elements. First, each patient is his, or her, own control; this increases the precision of treatment comparisons because they are made within patients rather between patients. Second, patients can express preferences for one or more of the trial treatments. The former element is perhaps the more important since it has important ethical and economic consequences. Ethical, in that the investigator will wish to minimise the number of patients receiving less efficacious treatments; economic, in that the use of fewer patients will reduce the cost of experimentation. The basic argument in favour of crossover designs is that to obtain a given treatment-comparison precision, a within-patient comparison requires fewer patients than does a between-patient comparison; crossover designs are therefore more ethical and less costly. The second element is potentially important for diseases in which objective measurement of the disease is difficult or impossible.

These, or similar arguments, in favour of crossover designs would make them the designs of choice in a large number of clinical trials were it not for three disadvantages. First, crossover designs are clearly not applicable in diseases in which either the treatments are expected to effect a cure, or in which the natural history of the disease, or condition, is such that it would vanish within a short period, for example the common cold. Second, crossover designs with a large number of treatments and/or periods are potentially disadvantageous because the number of patients dropping out may become large. Finally, if the effect of a treatment is not confined to the period in which it is applied, or if the effect of a treatment differs from period to period, then estimates of treatment differences may be biased.

It was this last possibility which lead the Biometric and Epidemiology Methodology Advisory Committee (BEMAC) of the American Food and Drug Administration (FDA) to conclude with respect to the two-period crossover design that it "is not the design of choice in clinical trials when unequivocal evidence of treatment effect is required". Instead they recommended "in most cases, the completely randomized (or randomized block) design with baseline measurements will be the design of choice because it furnishes unbiased estimates of treatment effects without appeal to any modelling assumptions save those associated with the randomization procedure itself." (FDA,1977; see also O'Neill,1978).

Fuelled by the FDA's publicised concern over the use of the two-period crossover design, the late 1970's and early 1980's witnessed the re-emergence of research interest in crossovers (historically, research interest began in agriculture; see, for instance, Cochran *et al*, 1941). This increase in research effort, together with the FDA view that "estimation of treatment effects from the crossover depends on an assumption that will require convincing support, from prior information or from the experimental data themselves..." (FDA,1977) motivated my examination of the use of Bayesian methods in the analysis of crossover designs. In this section the standard analyses of two treatment crossover designs are reviewed. Included are the standard two period design (Grizzle,1965), two period designs with baseline measurements, and the extra-period designs (Ebbutt,1984).

2.2 Grizzle's Models for the Two-Period Two-Treatment Crossover.

The standard, classical approach, to the analysis of the two-period crossover design for clinical trials was proposed by Grizzle(1965) - see also Grizzle(1974) and Grieve(1982). Suppose patients have been randomised to one of the treatment sequences A→B or B→A, where A and B are the treatments, and that a single observation is made on each patient during each of the two treatment periods, which are separated by a washout period. Assume that the trial produces n_1 patients in the first sequence group and n_2 patients in the second and let y_{ijk} denote the response of the jth patient in the ith sequence in the kth period. Under these assumptions Grizzle(1965) considers the following two statistical models :

$$I: y_{ijk} = \mu + \pi_k + \tau_l + \lambda_{l'} + \xi_{ij} + \epsilon_{ijk} \qquad (i = 1,2; j = 1,..,n_i; k = 1,2; l = 1,2; l' \neq l)$$

$$II: y_{ijk} = \mu + \pi_k + \tau_l + \xi_{ij} + \epsilon_{ijk} \qquad (i = 1,2; j = 1,..,n_i; k = 1,2; l = 1,2)$$

where $\mu, \pi_k, \tau_l, \lambda_{l'}$ are the overall mean, period, direct treatment and carryover effects (also termed residual effect or period by treatment interaction) respectively, and ξ_{ij} and ϵ_{ijk} are the random patient and error effects, which are assumed to be independently, normally distributed with zero means and variances σ_ξ^2 and σ_ϵ^2 respectively. For convenience of exposition we reparametrise models I and II by defining,

$$\pi_1 = -\pi_2 = \pi; \tau_1 = -\tau_2 = \tau; \lambda_1 = -\lambda_2 = \lambda,$$

that is we consider a cell mean model with means defined as in Table 2.1.

TABLE 2.1 Cell Means for Model I.

Sequence Group	Periods	
	1	2
A→B	$\mu + \pi + \tau$	$\mu - \pi - \tau + \lambda$
B→A	$\mu + \pi - \tau$	$\mu - \pi + \tau - \lambda$

We also define $N = n_1 + n_2$, $q = N/(n_1 n_2)$, $\sigma^2 = \sigma_\epsilon^2 + \sigma_\xi^2$, and $\sigma_\lambda^2 = \sigma_\epsilon^2 + 2\sigma_\xi^2$. Model II may be derived from Model I by setting $\lambda = 0$. (It should be noted that treatment effect refers to the difference between the effects of treatments A and B, and that a test for treatment effect is a test of the null hypothesis $H_0: \tau = 0$. These remarks apply equally to period and carryover effects.) These parametrisations follow Selwyn *et al*(1981), Grieve(1985) and Racine *et al*(1986). The cell means model described above is convenient for exposition; however in Model I there are problems of estimability - see Grizzle(1965) for details.

2.3 Analysis of Variance (ANOVA) for Model II.

Under Model II the standard ANOVA is as shown in Table 2.2 (see Grizzle,1965; Grizzle,1974; Grieve,1982). Corresponding to the sums of squares for periods and treatments the least-squares estimates of the parameters are,

$$\hat{\pi} = (\bar{y}_{1.1} - \bar{y}_{1.2} + \bar{y}_{2.1} - \bar{y}_{2.2})/4$$

and

$$\hat{\tau} = (\bar{y}_{1.1} - \bar{y}_{1.2} - \bar{y}_{2.1} + \bar{y}_{2.2})/4 \qquad (2.1)$$

It is clear from Table 2.2 that a valid test for treatment effect under Model II may be made by forming the ratio of the treatment and error mean squares, which we will denote by F_τ, and that this will have an F-distribution with 1 and N-2 degrees of freedom (df) under the null hypothesis of no treatment effect.

TABLE 2.2 ANOVA for Model II.

Source	df	Sums of Squares	Expected Mean Squares
Patients	$N-1$	$2\sum_i \sum_j \bar{y}^2_{ij.} - 2N\bar{y}^2_{...}$	σ^2_A
Periods	1	$(\bar{y}_{1.1} - \bar{y}_{1.2} + \bar{y}_{2.1} - \bar{y}_{2.2})^2/2q$	$\sigma^2_\epsilon + 8\pi^2/q$
Treatments	1	$(\bar{y}_{1.1} - \bar{y}_{1.2} - \bar{y}_{2.1} + \bar{y}_{2.2})^2/2q$	$\sigma^2_\epsilon + 8\tau^2/q$
Error	$N-2$	$SSE = \sum_i \sum_j \sum_k y^2_{ijk} - 2\sum_i \sum_j \bar{y}^2_{ij.} - \sum_i n_i \sum_k \bar{y}^2_{i.k} + 2\sum_i n_i \bar{y}^2_{i..}$	σ^2_ϵ

2.4 Analysis of Model I.

The incorporation of λ in Model I results in a less simple analysis than under Model II. Under Model I the expected value of $\hat{\tau}$ given above is $\tau - \lambda/2$ and it is therefore no longer an unbiased estimate of the direct treatment effect. On the other hand, an unbiased estimate of λ does exist, being given by,

$$\hat{\lambda} = (\bar{y}_{1.1} + \bar{y}_{1.2} - \bar{y}_{2.1} - \bar{y}_{2.2})/2 \qquad (2.2)$$

and therefore under this model an unbiased estimate of τ is,

$$\tilde{\tau} = \hat{\tau} + \hat{\lambda}/2 = (\bar{y}_{1.1} - \bar{y}_{2.1})/2. \qquad (2.3)$$

The significance of the carryover effect may be tested by noting that,

$$\mathrm{var}(\hat{\lambda}) = q\sigma^2_A/2$$

and that the expected value of the sum of squares,

$$SSP = 2\left(\sum_i \sum_j \bar{y}^2_{ij.} - \sum_i n_i \bar{y}^2_{i..}\right)$$

is $(N-2)\sigma^2_A$, so that since $\hat{\lambda}$ and SSP are independent,

$$F_\lambda = \frac{2(N-2)\hat{\lambda}^2}{qSSP}$$

follows an F-distribution with 1 and (N-2) df. It may also be shown that,

$$var(\tilde{\tau}) = q\sigma^2/4$$

and although $E(SSE + SSP) = 2(N-2)\sigma^2$, it does not have a χ^2distribution (see Grizzle,1965). Because of this Grizzle suggests that the sum of squares,

$$SS_1 = \sum_i \sum_j (y_{ij1} - \bar{y}_{i.1})^2$$

be used for testing the significance of τ under Model I since its expected value is $(N-2)\sigma^2$ and it is χ^2-distributed, independently of $\tilde{\tau}$ so that,

$$F_1 = \frac{4(N-2)\tilde{\tau}^2}{qSS_1}$$

follows an F-distribution with 1 and (N-2) df.

Grieve(1987b) also considers the problem of making inferences about τ under Model I. He shows that under this model,

$$var(\tilde{\tau}) = q\sigma_\epsilon^2/8 \quad , \quad E(\tilde{\tau}\tilde{\lambda}) = 0.$$

Further since $SSE/\sigma_\epsilon^2 \sim \chi^2_{N-2}$ and $SSP/\sigma_\lambda^2 \sim \chi^2_{N-2}$ it follows that,

$$\frac{[8(N-2)]^{1/2}[\hat{\tau} - (\tau - \lambda/2)]}{(qSSE)^{1/2}} \sim t_{N-2}$$

and

$$\frac{[8(N-2)]^{1/2}[\hat{\lambda}/2 - \lambda/2]}{(qSSP)^{1/2}} \sim t_{N-2}$$

Thus the problem of testing the significance of treatment effects under Model I is equivalent to a Behrens-Fisher problem since $\tilde{\tau}$ may be written as a weighted sum of independent t-statistics with different variances. From a Bayesian perspective this result was first pointed out by Grieve(1985). Since no universally acceptable solution to the Behrens-Fisher problem exists, the choice of procedure to be used will depend on one's belief in the "correctness" of the competing schools of statistical inference - frequency, fiducial or Bayesian. Grieve(1987b) compares various approximate solutions to the Behrens-Fisher problem as it relates to the two-period crossover. For the moment we will consider only Grizzle's original analysis based on first period data alone, but will return to Behrens-Fisher aspects later when dealing with a Bayesian approach.

Based on work by Larson and Bancroft(1963), Grizzle(1965) proposes that because the test for carryover is a preliminary test, in that the main interest focuses on the treatment effect, it should be carried out at a higher level of significance than usual, namely 10%. If the hypothesis of no carryover is rejected, Model I should be used to test for a treatment effect, using F_1; if accepted Model II should be used and F_τ is used to test for treatment effect. Figure 2.1 summarises Grizzle's approach to the analysis of the two-period crossover design.

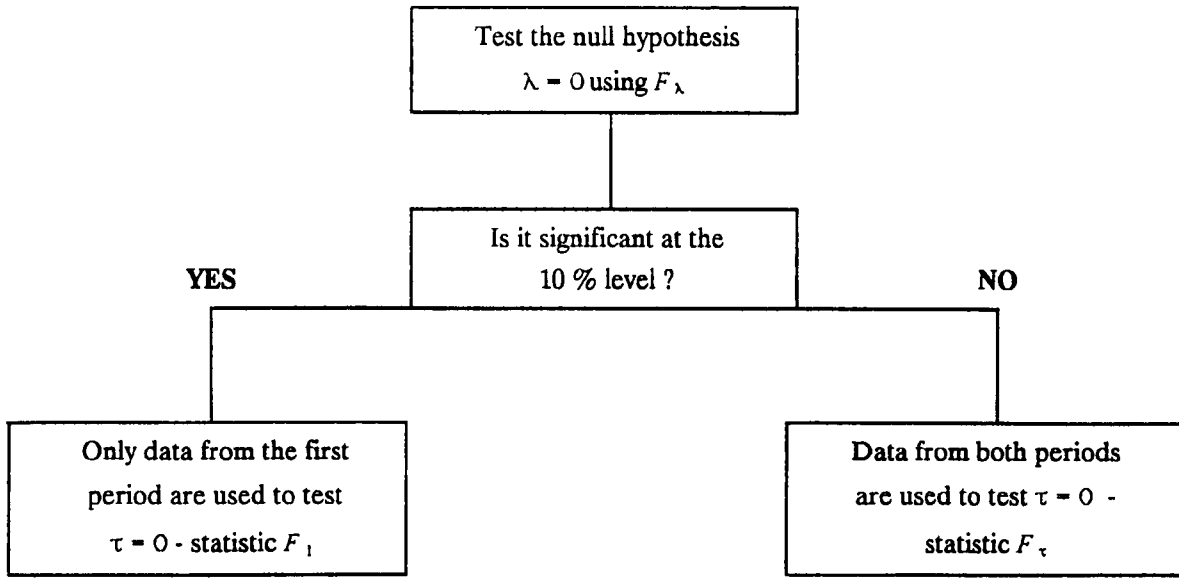


FIGURE 2.1 Grizzle's approach to the analysis of the two-period crossover.

2.5 Hills-Armitage Approach.

Grizzle's approach above is based on standard linear model theory with slight modifications for Model I. Hills and Armitage(1979) provide a slightly different view leading to the same results.

Under Model II consider the differences,

$$d_{1j} = y_{1j1} - y_{1j2} \quad , \quad d_{2j} = y_{2j1} - y_{2j2}$$

which have expectations,

$$2\pi + 2\tau \quad \text{and} \quad -2\pi + 2\tau$$

respectively, and common variance σ_ϵ^2. Then clearly since d_{1j} and d_{2j} are independent, $\bar{d}_{1.} + \bar{d}_{2.}$ and $\bar{d}_{1.} - \bar{d}_{2.}$ have expectations 4τ and -4π with common variance $2q\sigma_\epsilon^2$. It is therefore possible under Model II to test for both period and treatment effects using t-statistics which are the square-roots of the corresponding F-statistics derivable from Table 2.2.

Under Model I consider the sums,

$$s_{1j} = y_{1j1} + y_{1j2} \quad , \quad s_{2j} = y_{2j1} + y_{2j2}$$

with expectations

$$2\pi + 2\tau + \lambda \quad \text{and} \quad 2\pi + 2\tau - \lambda$$

respectively. Therefore $\bar{s}_{1.} - \bar{s}_{2.}$ has expectation 2λ and variance $2q\sigma_A^2$, so that again a standard t-statistic, the square root of F_τ, may be used to test for a carryover effect.

2.6 Other Assumptions and Approaches.

Grizzle's and Hills and Armitage's approaches to the analysis of the two-period crossover are based on the assumption that the data follow a normal-theory linear model. Clearly this is a strong assumption and needs to be investigated for each individual case. One possibility would be to consider the use of transformations - see the discussion and reply in Racine *et al*(1986). Alternative assumptions have been considered by many authors.

Many authors consider two-period crossover designs in which the response variable is binary - Gart(1969), Zimmermann and Rahlfs(1978), Hills and Armitage(1979), Prescott(1981), Armitage and Hills(1982), Fidler(1984), Farewell(1985), Nagelkerke *et al*(1986), Kenward and Jones(1987a) and Jones and Kenward(1987). Layard and Arvesen(1978) consider the analysis of Poisson-distributed data basing their test procedures on a conditional analysis following work by Gart(1975) and Hamilton and Bissonette(1975). Koch(1972) proposes a non-parametric alternative to Grizzle's analysis. In essence Koch's approach is equivalent to replacing the t-statistics outlined in section §2.5 by Wilcoxon statistics (see also Taulbee,1982 and Brunner and Neumann,1987). Gomez-Marin and McHugh(1984) derive randomisation analogues of Grizzle's tests based on a finite permutation model (see also McHugh and Gomez-Marin,1987). Zimmermann and Rahlfs(1980) consider a multivariate normal analysis of the two-period crossover.

One final approach, more an aid to interpretation than an inferential procedure, is a graphical method proposed by Huitson(1980) and Hews(1980) - see also Barker *et al*(1982). The graphical method is as follows:

1) plot the period 2 observation y_2 for each patient against the period 1 observation y_1, with the sequence groups being separately identified.

2) add the lines $y_2 = y_1$ and $y_2 + y_1 = c$ where c is a constant equal to the mean total of period 1 and 2.

3) period, treatment and carryover effects will be noticeable by separation of the centroids of the two groups in different directions.

The types of separation which can occur are shown in Figure 2.2. For example, separation about the line $y_2 = y_1$ indicates a treatment effect, while separation about $y_2 + y_1 = c$ indicates a carryover effect. Clearly with real data the separation of the centroids will not be perfect and the convex hulls of each sequence group may be used as an aid to identifying the group centroids.

2.7 An Example of the Basic Two-Period Two-Treatment Crossover.

The data displayed in Table 2.3 are taken from a study carried out by CIBA-GEIGY to assess the effectiveness of transdermal nitroglycerin in controlling the symptoms of angina pectoris in patients seen in general practice. Results from this study are reported by Wheatley(1987).

Angina pectoris is a symptom and not a disease. The most common cause of the symptom is coronary artery atheroma, which is a thickening of the inner lining of the arteries. The symptom is predominantly a discomfort located in the chest or adjacent areas, brought on by an inadequate supply of blood to the heart. The use of nitrates in the treatment of angina is well established, and although the precise mode of action is not known it is believed that their basic pharmacological action is to relax smooth muscle. Sublingual nitroglycerin has

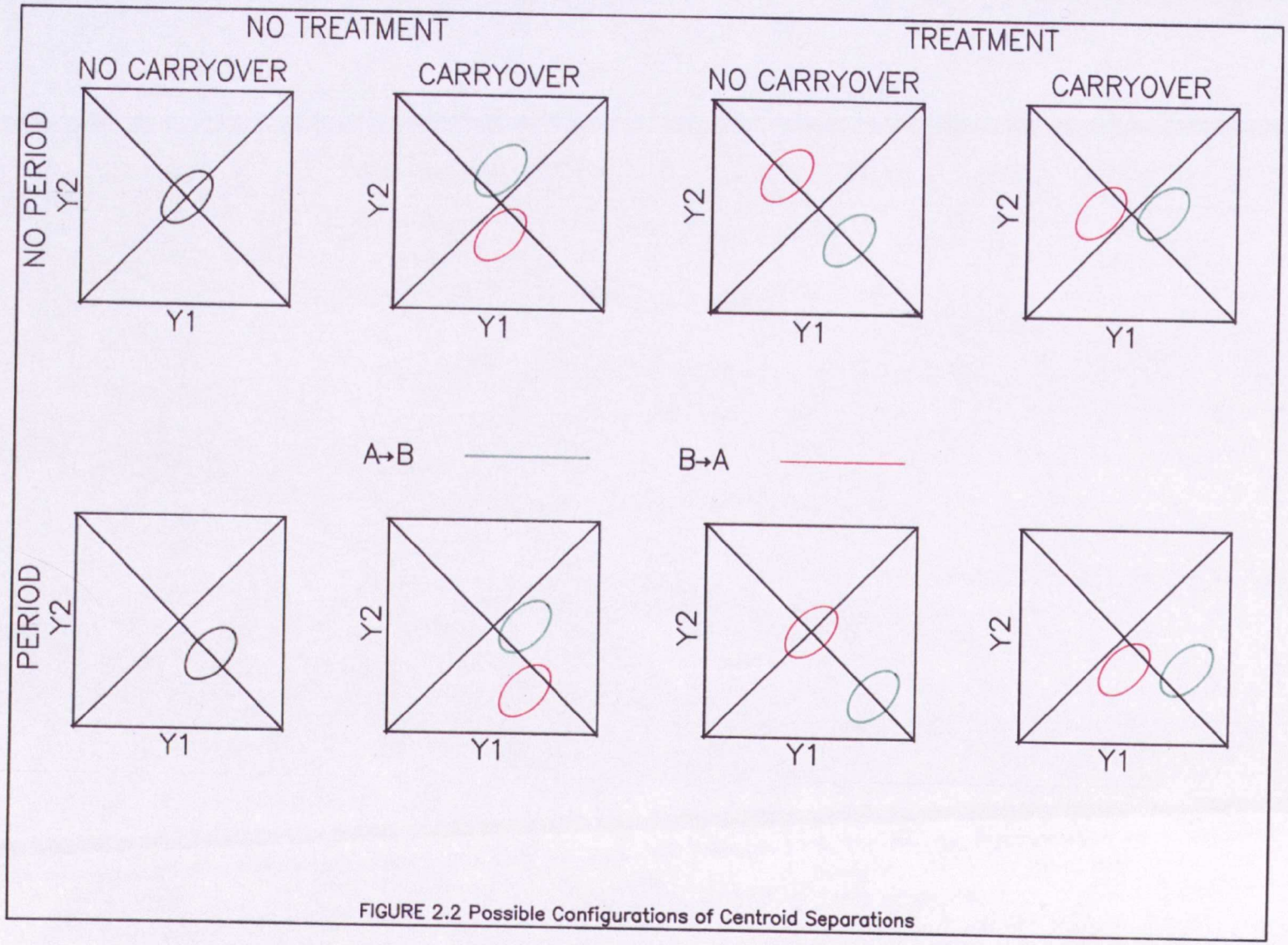


FIGURE 2.2 Possible Configurations of Centroid Separations

TABLE 2.3 Weekly Anginal Attack Rates During 3rd week of Treatment.

Sequence	Patient	Period 1	Period 2	Sequence	Patient	Period 1	Period 2
PL→TN	19	3	10	TN→PL	20	12	16
	22	8	6		21	4	11
	24	6	4		23	6	5
	35	1	0		36	7	14
	38	12	6		37	13	25
	39	4	2		40	9	11
	42	6	3		41	1	1
	59	11	3		43	4	0
	64	3	4		56	4	10
	73	11	3		57	2	5
	76	8	8		60	0	8
	78	8	9		61	17	13
	80	18	4		65	1	1
	81	12	5		67	6	8
	84	12	2		75	8	8
	85	3	1		77	7	4
	115	1	3		79	3	19
	122	12	4		82	4	19
	124	8	6		83	3	12
	126	7	12		86	2	4
	128	1	1		87	2	1
	140	2	0		121	4	7
	142	3	0		123	3	1
	146	21	10		125	3	3
	147	17	7		127	1	0
	150	12	5		130	41	36
	201	4	5		145	10	24
	209	0	1		148	9	18
	211	7	0		149	4	13
	233	11	0		210	8	1
	236	18	7		234	5	7
					235	0	9

been used for a long time to good effect, typically producing relief within 1 to 3 minutes, although it has the disadvantage that its effect lasts for only 10 to 20 minutes. Other methods of drug delivery have been considered and in particular nitroglycerin ointment has been available for a number of years. Such ointments, whilst effective, have the disadvantage that they need to be covered by a dressing and that application of accurate dosages is difficult. New delivery systems have recently been developed, in particular self-adhesive patches which contain a reservoir of nitroglycerin which diffuses through a semipermeable membrane into the skin so as to give a sustained, and constant, release of nitroglycerin over 24 hours.

The aim of this study was to investigate the use of Transiderm-Nitro (TN) patches in the prophylaxis of angina in general practice. Patients were randomly allocated to three weeks treatment with placebo (PL) followed by TN or vice versa. At the end of the first week of treatment, if the angina attack rate had not fallen by more than 20% compared to a one-week PL run-in period, the dose was increased from the original two patches to three. After three weeks treatment, the patients crossed to the alternative treatment starting again on two patches.

The data shown in Table 2.3 are the weekly attack rates during the third week of each treatment period. The data are presented in graphical form in Figure 2.3 using the method described in §2.6. This figure brings out two features of the data. First, there is one extreme patient in the TN→PL group (patient 130) who suffered considerably more attacks in both treatment periods than other patients. Second, the centroids of the two groups, as represented by the innermost convex hulls, are clearly separated about the line $y_2 = y_1$ suggesting a difference between treatments. For the moment we will ignore the extremeness of patient 130 and analyse the data as it stands, returning to the problem of outliers in §9.

TABLE 2.4 Model II ANOVA for Data in Table 2.3.

Source	df	Sums of Squares	Mean Squares	F-Ratios	P-Values
Patients	62	4356.968	70.274		
Periods	1	1.078	1.078	0.068	0.795
Treatments	1	420.411	420.411	$F_\tau = 26.545$	$< 10^{-5}$
Error	61	966.081	15.837		
Cell means :		$\bar{y}_{1.1} = 8.065$		$\bar{y}_{1.2} = 4.226$	
		$\bar{y}_{2.1} = 6.344$		$\bar{y}_{2.2} = 9.813$	

Table 2.4 displays the Model II ANOVA for this data together with the cell means. These cell means imply the following estimated period and treatment effects :

$$\hat{\pi} = (8.065 - 4.226 + 6.344 - 9.813)/4 = 0.093$$

$$\hat{\tau} = (8.065 - 4.226 - 6.344 + 9.813)/4 = 1.827$$

both of which have standard error 0.355. There is therefore strong evidence of a large difference between treatments, the estimate $\hat{\tau}$ suggesting that TN causes a reduction of on average approximately 3-4 attacks per week compared with PL.

Under Model I the unbiased estimate of the carryover is,

$$\hat{\lambda} = (8.065 + 4.226 - 6.344 - 9.813)/2 = -1.933$$

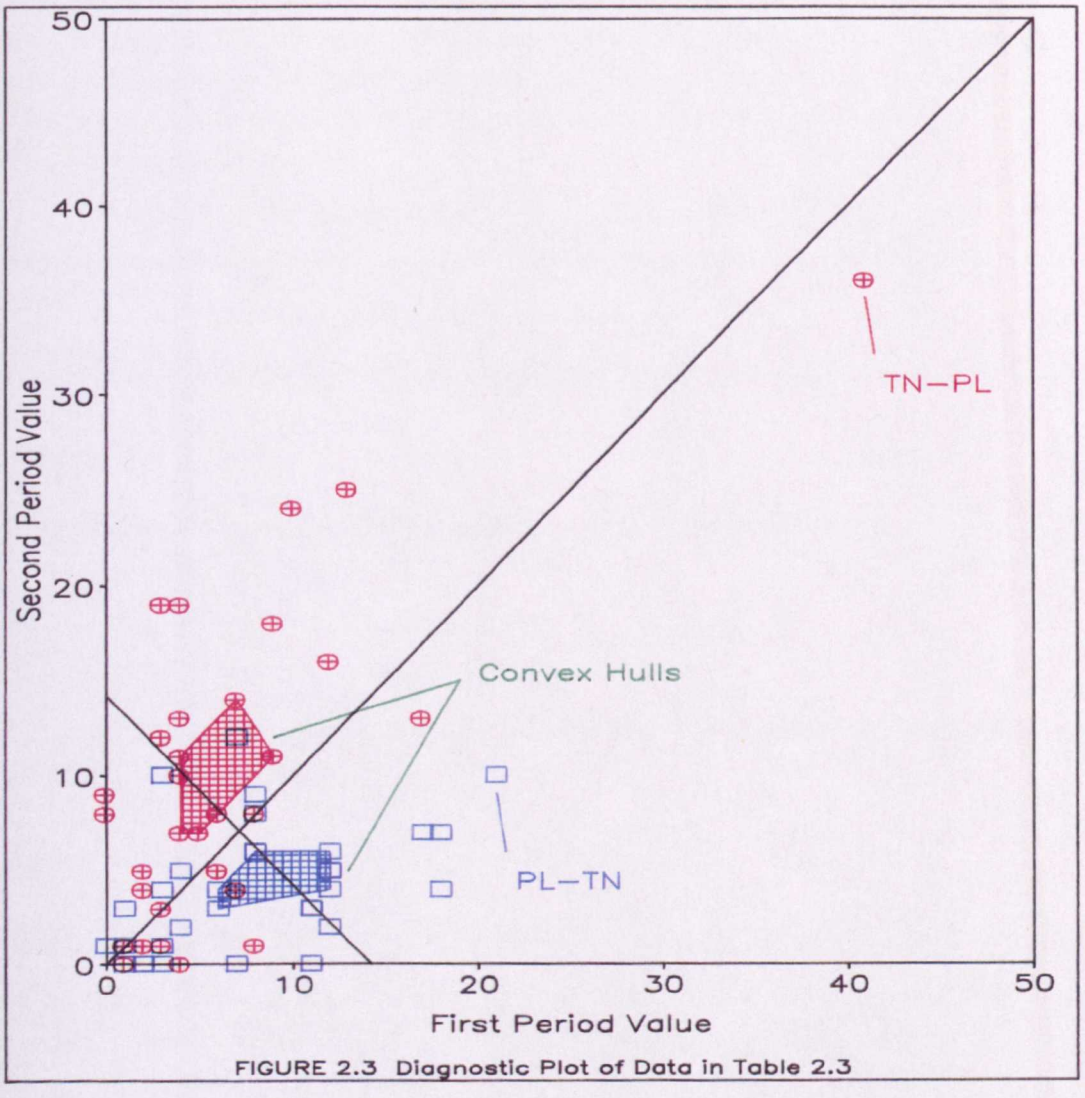


FIGURE 2.3 Diagnostic Plot of Data in Table 2.3

which has standard error 1.486. There is therefore little evidence to suggest the existence of a carryover effect, since the estimate of λ is only 30% larger in absolute value than its standard error (the classical p-value is 0.198).

2.8 Baselines in the Two-Period Crossover.

Various models have been suggested for the incorporation of baseline measurements in the two-period crossover. In this section suggestions by Willan and Pater(1986a), Varma and Chilton(1974), Kenward and Jones(1987b) and Patel(1983) are reviewed.

Suppose that , as in §2.2, the post-treatment response of the jth patient in the ith sequence in the kth period is denoted by y_{ijk}, and that correspondingly x_{ijk} is the pre-treatment response. Suppose further that y_{ijk} follows Model I and that x_{ijk} follows Model I excluding the treatment effect, so that the expected cell means for the x_{ijk}'s are as shown in Table 2.5. Willan and Pater(1986a) propose such a model except that they introduce an additional random effect, which they characterise as a patient by period interaction, whose purpose is to model larger correlations between observations within the same period than between observations from different periods.

TABLE 2.5 Pre-Treatment Cell Means for Willan and Pater's(1986a) Model.

Sequence Group	Periods	
	1	2
A→B	$\mu + \pi$	$\mu - \pi + \lambda$
B→A	$\mu + \pi$	$\mu - \pi - \lambda$

Define,

$$\hat{\tau}_B = (\bar{d}_{1.1} - \bar{d}_{1.2} - \bar{d}_{2.1} + \bar{d}_{2.2})/4.$$

where $d_{ijk} = y_{ijk} - x_{ijk}$, having expectation τ and variance $q\sigma_\epsilon^2/4$. The null hypothesis of no treatment effect can be tested by using the statistic,

$$F_{\tau B} = \frac{4(N-2)\hat{\tau}_B^2}{qSSB}$$

where $SSB/(N-2)$ is an estimate of σ_ϵ^2. Under $H_0: \tau = 0$, $F_{\tau B}$ has an F-distribution with 1 and N-2 df.

Varma and Chilton(1974) consider an extended form of Willan and Pater's model including in addition to a carryover effect, an effect which they term the residual effect. This residual effect appears in cell means for both pre- and post-treatment measurements in the second period, while the carryover effect appears only in the cell means of the post-treatment measurements. Under this model, inferences about treatment effect can only be made using data from both periods if the carryover effect is non-significant - in the same way as for Model I - and is essentially identical to the Willan and Pater analysis above. If the carryover is significant, an analysis identical to Chassan's(1970) analysis of a parallel design with baseline measurements is used. Define $d_{ij} = y_{ij1} - x_{ij1}$ which have means τ and $-\tau$ in groups 1 and 2 respectively and common variance $2\sigma_\epsilon^2$ From the independence of $\bar{d}_{1.}$ and $\bar{d}_{2.}$ it follows that,

$$(\bar{d}_{1.} - \bar{d}_{2.})/2 \sim N(\tau, q\sigma_\varepsilon^2)$$

so that,

$$\frac{(N-2)(\bar{d}_{1.} - \bar{d}_{2.})^2}{2q\sum_i \sum_j (d_{ij} - \bar{d}_{i.})^2}$$

has an F-distribution with 1 and N-2 df under the null hypothesis of no treatment effect.

Both the approach of Willan and Pater(1986a) and that of Varma and Chilton(1974) use a "gains-score" (GS) method, that is they analyse differences between post- and pre-treatment measurements. In the area of parallel group designs with baselines much recent research considers whether a GS analysis is preferable to one in which the pre-treatment measurement is used as a covariate to adjust post-treatment values (see for instance Brogan and Kutner,1980; Lee,1980; Schafer,1981; Laird,1983). Many of the arguments for preferring the analysis of covariance (ANCOVA) to a GS analysis are irrelevant to clinical studies, since they have to do with non-random allocation of subjects to groups - examples are given in Lord(1967) and Lee(1980). Bock(1975) investigates the use of both analyses from a "randomised perspective" and concludes, based on the grounds of efficiency, that ANCOVA is the preferred approach. To illustrate the argument consider again Chassan's(1970) analysis. The structure of the model is such that y_{ij1} and x_{ij1} are bivariately, normally distributed with covariance matrix,

$$\begin{pmatrix} \sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \sigma^2 \end{pmatrix}$$

where $\sigma^2 = \sigma_\xi^2 + \sigma_\varepsilon^2$ and $\rho = \sigma_\xi^2/(\sigma_\xi^2 + \sigma_\varepsilon^2)$. From standard properties of bivariate normal distributions the expected values of y_{1j1} and y_{2j1}, given that x_{ij1} takes the value x, are $\mu + \pi + \tau + \rho(x - \mu - \pi)$ and $\mu + \pi - \tau + \rho(x - \mu - \pi)$ respectively, with common variance $\sigma^2(1 - \rho^2)$ from which it follows that,

$$E[(\bar{y}_{1.1} - \bar{y}_{2.1})/2 \mid x] = \tau$$

and

$$var[(\bar{y}_{1.1} - \bar{y}_{2.1})/2 \mid x] = q\sigma^2(1 - \rho^2)/4$$

If the relative efficiency (RE) of ANCOVA to that of the GS analysis is measured by the ratio of the respective variances then,

$$RE = \frac{q\sigma^2(1-\rho)/2}{q\sigma^2(1-\rho^2)/4} = \frac{2}{1+\rho}$$

Only when $\rho = 1$ are the analyses equally efficient, and are in this case identical.

Patel(1983) considers the ANCOVA approach to the analysis of Varma and Chilton's model, generalising it by assuming arbitrary covariance matrices in the two sequence groups. He considers a number of different hypotheses of interest which may be tested using his model, for instance both carryover effect and period by treatment interaction are testable.

Both types of analysis are considered by Kenward and Jones(1987b). The cell mean model which they consider is shown in Table 2.6 where γ, θ and λ are the sequence group, first and second order carryover effects respectively. As Kenward and Jones point out, the inclusion of γ is somewhat artificial since randomisation should ensure that there is no group effect. Its inclusion is merely to ensure that all other estimators are based on within-patient contrasts. The analyses which Kenward and Jones(1987b) consider are too numerous to detail here, but they will be referred to in subsequent sections.

TABLE 2.6 Cell Means for Kenward and Jones'(1987b) Model.

Sequence Group	Measurement	Periods 1	Periods 2
A→B	Pre-Treatment	$\mu + \gamma + \pi_1$	$\mu + \gamma + \pi_3 + \theta$
	Post-Treatment	$\mu + \gamma + \pi_2 + \tau$	$\mu + \gamma - \pi_1 - \pi_2 - \pi_3 - \tau + \lambda$
B→A	Pre-Treatment	$\mu - \gamma + \pi_1$	$\mu - \gamma + \pi_3 - \theta$
	Post-Treatment	$\mu - \gamma + \pi_2 - \tau$	$\mu - \gamma - \pi_1 - \pi_2 - \pi_3 + \tau - \lambda$

That the use of baselines in crossover designs is not without danger is highlighted by Fleiss *et al*(1985). These authors suppose that given that the length of a treatment period is one time unit and that the length of the washout period between treatment periods is ω units, then the total length of time between the ends of the first and second treatment periods, $1 + \omega$, is sufficiently long to ensure that there is no carryover effect, but that w itself is insufficiently long to eliminate the effect of the first period treatment on the second period's baseline measurements. Explicitly they assume that the y_{ijk}'s have Model II cell means, while the x_{ijk} have the cell means shown in Table 2.7, where α is a not necessarily linear function of ω.

TABLE 2.7 Pre-Treatment Cell Means for Fleiss *et al*'s(1985) Model

Sequence Group	Periods 1	Periods 2
A→B	μ_0	$\mu_1 + \alpha\tau$
B→A	μ_0	$\mu_1 - \alpha\tau$

Under this set-up consider a GS analysis using $d_{ijk} = y_{ijk} - x_{ijk}$. Clearly the d's have expected values,

$$\mu - \mu_0 + \pi + \tau \quad , \quad \mu - \mu_1 - \pi - \tau - \alpha\tau$$

in sequence 1 and,

$$\mu - \mu_0 + \pi - \tau \quad , \quad \mu - \mu_1 - \pi + \tau + \alpha\tau$$

in sequence 2, so that the estimated "carryover effect" has expectation $-\alpha\tau$, which is opposite in sign to the treatment effect τ. Fleiss *et al* conclude from the above analysis that there are potentially two serious problems. First, the use of baseline measurements may artificially induce an apparent carryover effect, which will cause

the analysis of treatment effect to be carried out using period 1 data only, with a consequent loss in efficiency. Second, it may have consequences for the conduct of future trials in that clinicians may be wrongly dissuaded from using a crossover design in testing similar drugs in the same condition. They note that ANCOVA does not obviate the bias induced by using baseline measurements with an insufficiently long washout period.

2.9 An Example of the Two-Period Crossover with Baselines.

The data displayed in Table 2.8 are taken from a study carried out by CIBA-GEIGY to investigate claims that TN was not effective in the treatment of angina. Results from the study are reported by Nicholls *et al* (1986). Patients were randomly allocated to four weeks treatment with TN followed by four weeks treatment with oral isosorbide dinitrate (ISDN) or vice versa. In the two weeks prior to each treatment period, placebo patches and tablets were given to obtain baseline measurements. The data shown in Table 2.8 are the weekly rates of sublingual glyceryl trinitrate (GTN) consumption, the allowed rescue therapy. Other data from this study will be introduced in a later section.

TABLE 2.8 Weekly GTN Consumption.

		1st Period		2nd Period	
Sequence	Patient	Baseline	Treated	Baseline	Treated
TN→ISDN	1	1.00	2.00	2.00	0.25
	4	24.50	29.00	31.50	27.00
	10	22.00	25.25	30.00	36.50
	12	0.00	0.00	0.00	0.00
	14	14.50	19.75	13.00	9.25
	15	2.00	4.25	6.00	2.75
	17	10.00	10.75	14.50	10.75
	20	10.50	8.50	6.00	4.25
	22	19.50	15.00	14.50	8.00
	24	7.50	4.25	0.00	3.50
ISDN→TN	3	21.00	21.50	22.00	38.00
	5	10.50	5.25	3.50	2.50
	7	3.50	2.00	1.50	4.50
	9	10.00	16.75	9.50	18.25
	13	1.50	1.50	0.50	0.75
	16	6.00	3.25	2.00	2.50
	18	1.50	0.00	0.00	0.00
	21	3.50	1.00	3.50	8.00
	23	9.50	1.00	0.50	1.50
	25	11.00	14.50	11.00	17.25

2.10 Extra-Period Crossover Designs.

The basic disadvantage of the simple two-treatment two-period crossover design is that the estimate of the carryover effect, or the test of the null hypothesis of no carryover effect, are based on between-subject variability so that the estimate of carryover effect is associated with a wide confidence interval, while the test for zero

carryover lacks power. If extra period designs are used, the carryover effect can be estimated within patients, increasing sensitivity and power. Additionally it is possible using extra-period designs to contemplate estimating other effects apart from simply treatment and carryover.

This latter advantage is potentially important. In §2.1 we noted that in certain circumstances the two-treatment two-period crossover is inappropriate, and in §2.2 that the carryover effect is sometimes termed the residual effect, or period by treatment interaction. These are different sides of the same coin, meaning that what has been called, in this chapter, carryover effect can have more than a single cause. Hills and Armitage(1979) suggest three possible causes of what we have termed carryover effect. First, the washout period may be inadequate, allowing the treatment in the first period to persist into the second period. Second the treatment received in the first period may induce changes in the patients' psychological and/or physiological states. Finally, the treatment effect may be proportional to the patients' overall disease states. Additionally there may be a difference between the sequence groups with respect to their average levels, which, because of randomisation, is essentially a type I error. Hecker(1986) investigates "carryover" and has shown that there are no two-treatment two-period designs which can fully utilise data from both periods without assuming that one, or more, of the above causes are nonexistent. Some extra-period designs allow more than one of these possible causes to be estimated - with the additional advantage that they are estimated within-patient.

Whilst a number of authors have investigated properties of general, multi-period, two treatment designs, practical and economic constraints would suggest that it is not realistic to consider designs of more than three periods and we therefore restrict ourselves to three-period designs. General optimality criteria for crossover designs, considered for example by Hedayat and Afsinejad(1975,1978), all reduce in the case of two treatment designs to the search for designs which give minimum variance treatment estimators. In the case of two treatment designs a number of authors (Kershner and Federer,1981; Laska *et al*,1983; Laska and Meisner,1985; Ebbutt,1984 and Matthews, 1987) have shown that the design **ABB,BAA** is universally optimal. In the following subsection we consider this optimal design. We subsequently consider the 4-sequence design **ABB,BAA,ABA,BAB** which whilst sub-optimal has certain advantageous features.

2.10.1 Three-Period Designs with Two Sequences.

Suppose that $y_{ijk}(i = 1, 2; j = 1, 2, 3)$ is the response of the j^{th} patient in the i^{th} sequence in the k^{th} period. Jones and Kenward(1989) suppose the cell means model shown in Table 2.10 is appropriate in which γ_1 and γ_2 define sequence effects, π_1 and π_2 periods effects and τ and λ are the treatments and carryover effects respectively.

TABLE 2.10 Jones and Kenwards's(1989) Cell Means Model for a Three-Period Two Sequence Design .

Sequence Group	Periods		
	1	2	3
ABB	$\gamma_1 + \pi_1 + \tau$	$\gamma_1 + \pi_2 - \tau + \lambda$	$\gamma_1 - \pi_1 - \pi_2 - \tau - \lambda$
BAA	$\gamma_2 + \pi_1 - \tau$	$\gamma_2 + \pi_2 + \tau - \lambda$	$\gamma_2 - \pi_1 - \pi_2 + \tau + \lambda$

Define,

$$\hat{\lambda} = (-\bar{y}_{1.2} + \bar{y}_{1.3} + \bar{y}_{2.2} - \bar{y}_{2.3})/4$$

and

$$\hat{\tau} = (-2\bar{y}_{1.1} + \bar{y}_{1.2}\bar{y}_{1.3} + 2\bar{y}_{2.1} - \bar{y}_{2.2} - \bar{y}_{2.3})/8$$

which have expectations λ and τ and variances $q\sigma^2/8$ and $3q\sigma^2/32$ respectively. In contrast, therefore, to the standard two-period crossover the estimator $\hat{\tau}$ is unbiased even if $\lambda \neq 0$. In fact the estimator of τ given $\lambda = 0$ remains $\hat{\tau}$.

2.10.2 Three-Period Designs with Four Sequences.

We noted previously that the design considered in §2.10.1 was universally optimal amongst all three-period two treatment designs. There are however some disadvantages to its use. First the carryover effect and the treatment by period interaction are aliased, and secondly the design may lead to unintentional bias since the clinician will know that the treatments in the final two periods are always the same.

We postpone consideration of this design to §7 when a Bayesian analysis is dealt with.

2.11 An Example of an Extra-Period Crossover Design.

The data shown in Table 2.11 are taken from a study undertaken by CIBA-GEIGY to compare the anti-hypertensive effects of Lopressor (L), and Lopresoretic (LC) which is a combination of Lopressor and the diuretic Chlorthalidone. A subsidiary aim of the study was to investigate carryover effects in a within-patient design. Patients were randomly allocated to one of the four treatment sequences L-LC-LC, LC-L-L, L-LC-L or LC-L-LC. Each treatment period lasted six weeks treatment.

The data in Table 2.11 are the diastolic blood pressures (mm Hg) recorded at the end of each six week treatment period. A preliminary report of this study was given by Ebbutt(1984), while Jones and Kenward use the corresponding systolic blood pressure data to illustrate various analyses of extra period designs. As mentioned above analysis of this data is postponed until §7 when considering Bayesian analyses of extra-period designs.

TABLE 2.11 Diastolic Blood Pressure (mm Hg)

Sequence	Patient	Period 1	Period 2	Period 3
L-LC-LC	2	103	96	84
	5	95	90	96
	17	100	96	86
	29	100	100	94
	33	100	95	100
	60	110	98	80
	71	100	90	85
	83	100	78	90
	94	100	106	100
	97	100	90	110
	102	75	75	80
	125	100	102	100
	153	100	100	95
	167	85	90	85
	177	95	80	75
	182	90	98	95
	204	100	90	82
	205	90	86	98
	210	90	90	100
	216	95	85	90
	217	112	104	107
	224	90	90	90
L-LC-L	1	100	96	96
	19	100	90	84
	25	100	110	95
	31	70	68	80
	35	90	90	95
	56	90	98	90
	70	90	80	95
	82	100	94	102
	95	100	84	118
	100	100	90	90
	103	80	80	85
	110	110	100	100
	113	76	72	80
	120	90	85	90
	127	98	106	102
	155	100	100	100
	166	90	90	80
	185	110	100	109
	190	94	84	92
	201	92	75	80
	214	80	80	85
	219	106	112	90
	222	80	80	80

Sequence	Patient	Period 1	Period 2	Period 3
LC-L-L	3	100	105	106
	16	100	100	95
	18	82	80	90
	28	95	90	90
	30	102	100	110
	34	110	110	110
	46	90	100	90
	54	80	98	90
	59	76	80	98
	72	70	80	80
	93	8	84	74
	99	90	100	80
	104	90	95	80
	111	105	100	100
	119	90	80	90
	128	94	102	96
	136	100	105	110
	149	80	85	80
	156	80	75	80
	168	90	90	80
	179	105	102	100
	183	95	80	105
	189	80	88	80
	197	90	80	75
	202	75	90	90
	209	90	90	80
	218	94	90	88
LC-L-LC	4	99	92	81
	7	118	89	92
	13	90	90	90
	55	90	80	84
	57	90	82	90
	69	85	75	85
	96	88	98	94
	98	95	100	90
	101	85	80	85
	109	60	75	60
	126	102	102	92
	178	102	100	102
	181	90	90	85
	203	90	90	80
	207	92	100	96
	211	80	80	80
	221	90	80	80

3 BAYESIAN ANALYSIS OF MULTIVARIATE NORMAL SAMPLES WITH A COMMON UNIFORM COVARIANCE MATRIX.

Suppose in a clinical trial that patients are randomised to g independent groups, and that measurements are taken on k occasions. Suppose further that the data are multivariate normal with expected values $\mu_i (i = 1, \ldots, g)$ and common covariance matrix Λ where

$$\Lambda = \sigma^2 \begin{pmatrix} 1 & \rho & \rho & \ldots & \rho \\ \rho & 1 & \rho & \ldots & \rho \\ \rho & \rho & 1 & \ldots & \rho \\ \cdot & \cdot & \cdot & & \cdot \\ \cdot & \cdot & \cdot & & \cdot \\ \cdot & \cdot & \cdot & & \cdot \\ \rho & \rho & \rho & \ldots & 1 \end{pmatrix}$$

In this chapter a Bayesian analysis of this set-up is considered.

Suppose at the end of the study that n_i patients in group i complete the study and let $\bar{y}_i$ and B_i be the mean vectors and matrices of sums of squares and cross products respectively. With these definitions the likelihood has the form,

$$\prod_{i=1}^{g} |\Lambda|^{-\frac{1}{2}} \exp\left(-\frac{n_i}{2}(\bar{y}_i - \mu_i)' \Lambda^{-1} (\bar{y}_i - \mu_i)\right) \times |\Lambda|^{-(n_i - 1)/2} \exp\left(-\frac{1}{2} tr(\Lambda^{-1} B_i)\right) \qquad (3.1)$$

Clearly $|\Lambda| = \sigma^{2k}[1 + (k-1)\rho](1-\rho)^{k-1}$ and

$$\Lambda^{-1} = \frac{1}{\sigma^2(1-\rho)[1 + (k-1)\rho]} \begin{pmatrix} 1 + (k-2)\rho & -\rho & \ldots & -\rho \\ -\rho & 1 + (k-2)\rho & \ldots & -\rho \\ \cdot & \cdot & & \cdot \\ \cdot & \cdot & & \cdot \\ -\rho & -\rho & \ldots & 1 + (k-2)\rho \end{pmatrix}$$

so that (3.1) may be written as,

$$\sigma^{-Nk}[1 + (k-1)\rho]^{-N/2}(1-\rho)^{-N(k-1)/2} \times \exp\left(-\frac{1}{2}\sum_i [n_i(\bar{y}_i - \mu_i)' \Lambda^{-1} (\bar{y}_i - \mu_i) - tr(\Lambda^{-1} B_i)]\right) \qquad (3.2)$$

where $N = \sum_i n_i$.

Following Geisser(1964) suppose that a realistic "ignorance" prior for the parameters $\mu_1, \mu_2, \ldots, \mu_g, \sigma^2$ and ρ has the form,

$$p(\mu_1, \mu_2, \ldots, \mu_g, \sigma^2, \rho) \propto \frac{1}{\sigma^2(1-\rho)[1 + (k-1)\rho]} \qquad (3.3)$$

where $\rho > 0$. We will return to consider the reasonableness or otherwise of this prior specification at a later stage. Combining (3.2) and (3.3) gives the posterior distribution of the parameters in the form,

$$p(\mu_1,\mu_2,\ldots,\mu_g,\sigma^2,\rho\mid X) \propto \sigma^{-Nk-2}[1+(k-1)\rho]^{-N/2-1}(1-\rho)^{-N(k-1)/2-1}$$
$$\times \exp\left(-\frac{1}{2}\sum_i [n_i(\bar{y}_i-\mu_i)'\Lambda^{-1}(\bar{y}_i-\mu_i)-tr(\Lambda^{-1}B_i)]\right) \tag{3.4}$$

where X denotes the data. The marginal distribution of the second-order parameters σ^2 and ρ may be obtained by integrating $\mu_1,\mu_2,\ldots,\mu_g$ out of (3.4) to give,

$$p(\sigma^2,\rho\mid X) \propto (\sigma^2)^{-(N-g)k/2-1}[1+(k-1)\rho]^{-(N-g)/2-1}(1-\rho)^{-(N-g)(k-1)/2-1}$$
$$\times \exp\left(-\frac{1}{2}\sum_i tr(\Lambda^{-1}B_i)\right). \tag{3.5}$$

Combining (3.4) and (3.5) gives,

$$p(\mu_1,\mu_2,\ldots,\mu_g\mid\sigma^2,\rho,X) \propto \exp\left(-\frac{1}{2}\sum_i n_i(\bar{y}_i-\mu_i)'\Lambda^{-1}(\bar{y}_i-\mu_i)\right)$$

implying that,

$$p(\mu_1,\mu_2,\ldots,\mu_g\mid\sigma^2,\rho,X) = N_{gk}[(\bar{y}_1\bar{y}_2\ldots\bar{y}_g)',\Sigma] \tag{3.6}$$

where,

$$\Sigma = \begin{pmatrix} \frac{1}{n_1} & & & \\ & \frac{1}{n_2} & & \\ & & \ddots & \\ & & & \frac{1}{n_g} \end{pmatrix} \otimes \Lambda$$

and $\otimes$ denotes the right Kronecker product. The exponent in (3.5) may be expanded to give,

$$p(\sigma^2,\rho\mid X) \propto \sigma^{-(N-g)k-2}[1+(k-1)\rho]^{-(N-g)/2-1}(1-\rho)^{-(N-g)(k-1)/2-1}$$
$$\times \exp\left(-\frac{\sum_i S_i[1+(k-2)\rho]-\rho R_i}{2\sigma^2(1-\rho)[1+(k-1)\rho]}\right) \tag{3.7}$$

where,

$$S_i = \sum_{i=1}^{k}\{B_i\}_{jj} \quad \text{and} \quad R_i = \sum_{j\neq i}\{B_i\}_{jj}.$$

Make the transformation,

$$\sigma_1^2 = \sigma^2[1+(k-1)\rho] \quad , \quad \sigma_2^2 = \sigma^2(1-\rho) \tag{3.8}$$

with Jacobian $[\sigma_1^2 + (k-1)\sigma_2^2]^{-1}$ to give,

$$p(\sigma_1^2, \sigma_2^2 \mid X) \propto \sigma_1^{-(N-g)-2} \exp\left(-\frac{\sum_{i=1}^{g} S_i + R_i}{2k\sigma_1^2} \right)$$

$$\times \sigma_2^{-(N-g)(k-1)-2} \exp\left(-\frac{\sum_{i=1}^{g} (k-1)S_i - R_i}{2k\sigma_2^2} \right)$$

$$= \sigma_1^{-(N-g)-2} \exp\left(-\frac{SS_1}{2\sigma_1^2} \right) \sigma_2^{-(N-g)(k-1)-2} \exp\left(-\frac{SS_2}{2\sigma_2^2} \right) \qquad (3.9)$$

where $SS_1 = \sum_i (S_i + R_i)/k$ and $SS_2 = \sum_i [(k-1)S_i - R_i]/k$. . The constraint $\rho > 0$ given in the prior specification is equivalent to $\sigma_1^2 > \sigma_2^2$ so that use of standard results - see for instance Box and Tiao(1973) §1.5 - shows that,

$$p(\sigma_1^2, \sigma_2^2 \mid X, \sigma_1^2 > \sigma_2^2) = \frac{p(\sigma_1^2, \sigma_2^2 \mid X)}{P(\sigma_1^2 > \sigma_2^2 \mid X)} , \quad \sigma_1^2 > \sigma_2^2 \qquad (3.10)$$

$$= 0 , \quad \text{otherwise.}$$

The transformation,

$$\phi = \frac{\sigma_1^2}{\sigma_2^2} \frac{N-g}{SS_1} \frac{SS_2}{(N-g)(k-1)} \quad \text{and} \quad \psi = \sigma_2^2$$

with Jacobian

$$\psi \frac{SS_1}{N-g} \frac{(N-g)(k-1)}{SS_2}$$

applied to (3.9) gives,

$$p(\psi, \phi \mid X) \propto \psi^{-(N-g)k/2-1} \phi^{-(N-g)/2-1} \exp\left(-\frac{SS_1}{2\psi} \left[1 + \frac{N-g}{\phi(N-g)(k-1)} \right] \right).$$

Integrate out ψ to give,

$$p(\phi \mid X) \propto \phi^{-(N-g)/2-1} \left[1 + \frac{N-g}{\phi(N-g)(k-1)} \right]^{-(N-g)k/2} ,$$

so that ϕ has an F-distribution with N-g and (N-g)(k-1) df, from which we may derive,

$$P(\sigma_1^2 > \sigma_2^2 \mid X) = P\left(F_{N-g,(N-g)(k-1)} < \frac{SS_1}{N-g} \frac{(N-g)(k-1)}{SS_2} \right). \qquad (3.11)$$

This probability may be used together with (3.10) to give the posterior distribution of the variance components σ_1^2 and σ_2^2. In later sections we will see that in the cases in which we are interested the constraint is of little importance if the correct models are used.

4 THE TWO-PERIOD TWO-TREATMENT CROSSOVER.

4.1 Basic Distributions.

The results in §3 may be used to derive a Bayesian analysis of the two-period crossover under a standard mixed-model with an "uninformative" prior. These results have been reported in Grieve(1985) - see also Grieve(1986) and Racine *et al*(1986). The development in those papers was more direct than here, in that the standard ANOVA decomposition was used. The approach taken here is preferable as it is easier to generalise to more complex crossover designs, as will be seen in subsequent sections.

The cell means model shown in Table 2.1 may be put into the general structure of the previous section by setting $k = g = 2$ and by noting that,

$$\begin{pmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{21} \\ \mu_{22} \end{pmatrix} = \begin{pmatrix} 1 & 1 & 1 & 0 \\ 1 & -1 & -1 & 1 \\ 1 & 1 & -1 & 0 \\ 1 & -1 & 1 & -1 \end{pmatrix} \begin{pmatrix} \mu \\ \pi \\ \tau \\ \lambda \end{pmatrix}$$

The inverse transformation has the form,

$$\begin{pmatrix} \mu \\ \pi \\ \tau \\ \lambda \end{pmatrix} = \begin{pmatrix} 1/4 & 1/4 & 1/4 & 1/4 \\ 1/4 & -1/4 & 1/4 & -1/4 \\ 1/2 & 0 & -1/2 & 0 \\ 1/2 & 1/2 & -1/2 & -1/2 \end{pmatrix} \begin{pmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{21} \\ \mu_{22} \end{pmatrix} \tag{4.1}$$

Consider the transformation (4.1) applied to (3.6) with $k = g = 2$. From standard properties of the normal distribution the conditional posterior distribution of the location parameters μ, π, τ and λ given the second order parameters σ^2 and ρ has the form,

$$p(\mu, \pi, \tau, \lambda \mid \sigma^2, \rho, X) = N\left[\begin{pmatrix} (\bar{y}_{1.1} + \bar{y}_{1.2} + \bar{y}_{2.1} + \bar{y}_{2.2})/4 \\ (\bar{y}_{1.1} - \bar{y}_{1.2} + \bar{y}_{2.1} - \bar{y}_{2.2})/4 \\ (\bar{y}_{1.1} - \bar{y}_{2.1})/2 \\ (\bar{y}_{1.1} + \bar{y}_{1.2} - \bar{y}_{2.1} - \bar{y}_{2.2})/2 \end{pmatrix}, \Sigma_1 \right] \tag{4.2}$$

where,

$$\Sigma_1 = \frac{\sigma^2}{8} \begin{pmatrix} q(1+\rho) & 0 & r(1+\rho) & 2r(1+\rho) \\ 0 & q(1-\rho) & r(1-\rho) & 0 \\ r(1+\rho) & r(1-\rho) & 2q & 2q(1+\rho) \\ 2r(1+\rho) & 0 & 2q(1+\rho) & 4q(1+\rho) \end{pmatrix}$$

and $r = 1/n_1 - 1/n_2$.

From (4.2) the following are derived,

$$p(\tau, \lambda \mid \sigma_1^2, \sigma_2^2, X) = N\left[\begin{pmatrix} \tilde{\tau} \\ \hat{\lambda} \end{pmatrix}, \begin{pmatrix} q(\sigma_1^2 + \sigma_2^2)/8 & q\sigma_1^2/4 \\ q\sigma_1^2/4 & q\sigma_1^2/2 \end{pmatrix} \right] \tag{4.3}$$

$$p(\lambda \mid \sigma_1^2, \sigma_2^2, X) = N[\hat{\lambda}, q\sigma_1^2/2] \tag{4.4}$$

$$p(\tau \mid \sigma_1^2, \sigma_2^2, X) = N[\tilde{\tau}, q(\sigma_1^2+\sigma_2^2)/8] \quad (4.5)$$

$$p(\tau \mid \lambda, \sigma_1^2, \sigma_2^2, X) = N[\hat{\tau}+\lambda/2, q\sigma_1^2/8] \quad (4.6)$$

where $\hat{\lambda}$, $\hat{\tau}$ and $\tilde{\tau}$ are defined in (2.1), (2.2) and (2.3) respectively, and where from (3.8) $\sigma_1^2 = \sigma^2(1+\rho)$ and $\sigma_2^2 = \sigma^2(1-\rho)$, which in the notation of §2.2 equal σ_A^2 and σ_ϵ^2 respectively. Setting $k = g = 2$ in (3.9) gives,

$$p(\sigma_A^2, \sigma_\epsilon^2 \mid X) \propto (\sigma_A^2\sigma_\epsilon^2)^{-N/2}\exp\left(-\frac{1}{2}\left[\frac{SSP}{\sigma_A^2}+\frac{SSE}{\sigma_\epsilon^2}\right]\right) \quad (4.7)$$

where $SSP = SS_1$ and $SSE = SS_2$. The joint posterior distribution of τ and λ may be derived as follows,

$$p(\tau, \lambda \mid X) \propto \int_{\sigma_A^2}\int_{\sigma_\epsilon^2} p(\tau, \lambda \mid \sigma_A^2, \sigma_\epsilon^2, X)p(\sigma_A^2, \sigma_\epsilon^2 \mid X)d\sigma_A^2 d\sigma_\epsilon^2$$

$$\propto \left[SSP+\frac{2}{q}(\lambda-\hat{\lambda})^2\right]^{-(N-1)/2}\left[SSE+\frac{8}{q}(\tau-\lambda/2-\hat{\tau})^2\right]^{-(N-1)/2} \quad (4.8)$$

In §3 the posterior distribution of σ_A^2 and σ_ϵ^2 given the constraint $\sigma_A^2 > \sigma_\epsilon^2$ was derived using results from Box and Tiao (1973) §1.5. Box and Tiao's general result has the form,

$$p(\theta \mid C, X) = \frac{p(\theta \mid X)P(C \mid \theta, X)}{P(C \mid X)} \quad (4.9)$$

where Θ is a vector of parameters of interest and C is the constraint.

From (4.2) and (4.7) the conditional distribution of σ_A^2 and σ_ϵ^2 given τ and λ has the form ,

$$p(\sigma_A^2, \sigma_\epsilon^2 \mid \tau, \lambda, X) \propto (\sigma_A^2\sigma_\epsilon^2)^{-(N+2)/2}\exp\left[-\frac{Q_1}{2\sigma_A^2}-\frac{Q_2}{2\sigma_\epsilon^2}\right]$$

where $Q_1 = SSP+\frac{2}{q}(\lambda-\hat{\lambda})^2$ and $Q_2 = SSE+\frac{8}{q}(\tau-\lambda/2-\hat{\tau})^2$

which has the same form as (3.9), so that the derivation of (3.11) may be followed to give,

$$P(\sigma_A^2 > \sigma_\epsilon^2 \mid \tau, \lambda, X) = P\left(F_{N-1,N-1} < \frac{Q_1}{Q_2}\right). \quad (4.10)$$

Combining (4.8), (4.10) and (3.11) gives the posterior distribution of τ and λ in the form,

$$p(\tau, \lambda \mid \sigma_A^2 > \sigma_\epsilon^2, X) \propto \frac{(Q_1Q_2)^{-(N-1)/2}P\left(F_{N-1,N-1} < \frac{Q_1}{Q_2}\right)}{P\left(F_{N-2,N-2} < \frac{SSP}{SSE}\right)} \quad (4.11)$$

Similar calculations lead to the following posteriors :

$$p(\lambda \mid \sigma_A^2 > \sigma_\epsilon^2, X) \propto \frac{Q_1^{-(N-1)/2} P\left(F_{N-1,N-2} < \frac{(N-2)Q_1}{(N-1)SSE}\right)}{P\left(F_{N-2,N-2} < \frac{SSP}{SSE}\right)} \tag{4.12}$$

$$p(\tau \mid \lambda, \sigma_A^2 > \sigma_\epsilon^2, X) \propto \frac{Q_2^{-(N-1)/2} P\left(F_{N-1,N-1} < \frac{Q_1}{Q_2}\right)}{P\left(F_{N-1,N-2} < \frac{(N-2)Q_1}{(N-1)SSE}\right)} \tag{4.13}$$

$$p(\tau \mid \sigma_A^2 > \sigma_\epsilon^2, X) = \int_\lambda p(\tau, \lambda \mid \sigma_A^2 > \sigma_\epsilon^2, X) d\lambda \tag{4.14}$$

The marginal distribution of τ is not available analytically, apart from unrealistic special cases, so that it may only be obtained by numerically integrating λ out of (4.11) using for instance the method described by Naylor and Smith(1982).

4.2 The Variance Component Constraint.

It is possible, using the methods given by Box and Tiao(1973) §6.3.1, to develop approximations to the distributions (4.11),(4.12) and (4.13) however this presupposes that it is important to take into account the constraint on the variance components inherent in the model. Jones(1986) reports results obtained by Denham in an unpublished University of Kent M.Sc. dissertation in which the posterior distributions with and without the constraint were compared using two measures based on the absolute difference between the distributions. For example Denham computed the maximum absolute difference, $D = \max \mid p(\pi \mid X) - p(\pi \mid \sigma_A^2 > \sigma_\epsilon^2, X) \mid$, where $\pi = \tau, \lambda, \tau \mid \lambda = 0$, for the data in Grizzle(1965), Hills and Armitage(1979) and Brown(1980). The results of Denham's calculations are shown in Table 4.1 together with the probability of the constraint defined by (3.11).

TABLE 4.1 Comparison of Constrained and Unconstrained Posterior Distributions.

	Posterior Distribution		
Data	τ	λ	$\tau \mid \lambda = 0$
Grizzle	0.001	0.212	0.158
Hills & Armitage	0.000	0.000	0.000
Brown	0.002	0.875	0.659

These results raise two issues. Firstly, as Grieve(1985) and Jones(1986) note, the differences between the constrained and unconstrained posterior distributions evidenced in the case of Grizzle's and Brown's data are a direct consequence of analysing differences from baseline which automatically induces zero correlation between the derived observations in each period. (This issue will be further considered when the two-period crossover with baselines is treated). It is not necessary to calculate the measures considered by Denham, as it is sufficient to calculate $P(\sigma_1^2 > \sigma_2^2 \mid X)$. For the above examples these probabilities are 0.355 (Grizzle), 0.9996 (Hills and Armitage) and 0.024 (Brown) respectively. Alternatively the posterior distribution of σ_1^2 and

σ_2^2 may be inspected. To illustrate, Figure 4.1 displays (4.7) for the data shown in Table 2.3. and it is clear that in this case the constraint is irrelevant as the bivariate posterior for the variance components lies almost wholly in the region defining the constraint. On the other hand for the data given in Brown(1980) involving, as we have already seen, differences from baseline the constraint is important as is shown by the posterior distribution of the variance components displayed in Figure 4.2. and by the posterior distributions of λ and $\tau \mid \lambda = 0$ shown in Figure 4.3.

Secondly, the effect of the constraint is least in the case of the treatment effect, τ. This observation is intuitively reasonable since the unconstrained posterior distribution of τ given the variance components depends on $\sigma_1^2 + \sigma_2^2$ so that it is irrelevant whether σ_1^2 is greater than σ_2^2. Such a view was expressed by Cochran(1963) who suggested that the small discrepancies in such cases might be due to rounding errors in the numerical integration , although he was unable to prove this analytically. In fact it is not the case that the constrained and unconstrained distributions of τ are identical although the differences are small.

4.3 Approximation to the Marginal Posterior Distribution of τ.

Even when the variance component constraint is ignored the integral in (4.14) is not analytically solvable and one possibility is again to use numerical methods. Alternatively, an analytical approximation may be derived. In (4.8) make the transformation $\psi_1 = \lambda/2$, $\psi_2 = \tau - \lambda/2$ giving,

$$p(\psi_1, \psi_2 \mid X) \propto \left(\left[SSP + \frac{8}{q}(\psi_1 - \hat{\lambda}/2)^2 \right] \left[SSE + \frac{8}{q}(\psi_2 - \hat{\tau})^2 \right] \right)^{-(N-1)/2}$$

Clearly ψ_1 and ψ_2 have independent shifted and scaled t-distributions with unequal variances and since $\tau = \psi_1 + \psi_2$ it has a Behrens-Fisher distribution. Therefore, using the results of Patil(1965), the marginal posterior distribution of τ may be approximated by

$$p(\tau \mid X) \propto \left[\nu^* s^{*2} + \frac{8}{q}(\tau - \hat{\tau} - \hat{\lambda}/2)^2 \right]^{-(\nu^*+1)/2} \qquad (4.15)$$

where,

$$\nu^* = \frac{(SSE + SSP)^2 (N-6)}{SSE^2 + SSP^2} + 4 \ , \ s^{*2} = \frac{(\nu^* - 2)(SSE + SSP)}{\nu^* (N-4)}$$

(see A1.5). (Appendix A1 gives consideration to various approximations to Behrens-Fisher densities and distribution functions).

4.4 Approximating (4.14).

We noted, following (4.14), that the marginal distribution of τ is not available analytically; however an approximation based on a t-distribution may be developed. The posterior distribution of τ may be written in the form,

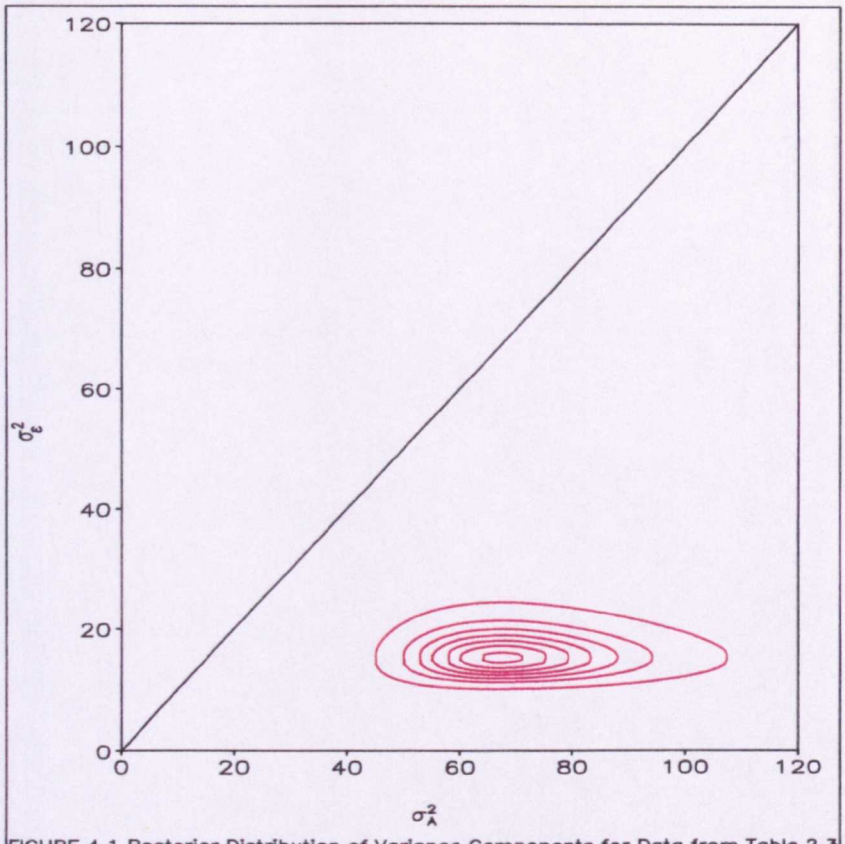


FIGURE 4.1 Posterior Distribution of Variance Components for Data from Table 2.3

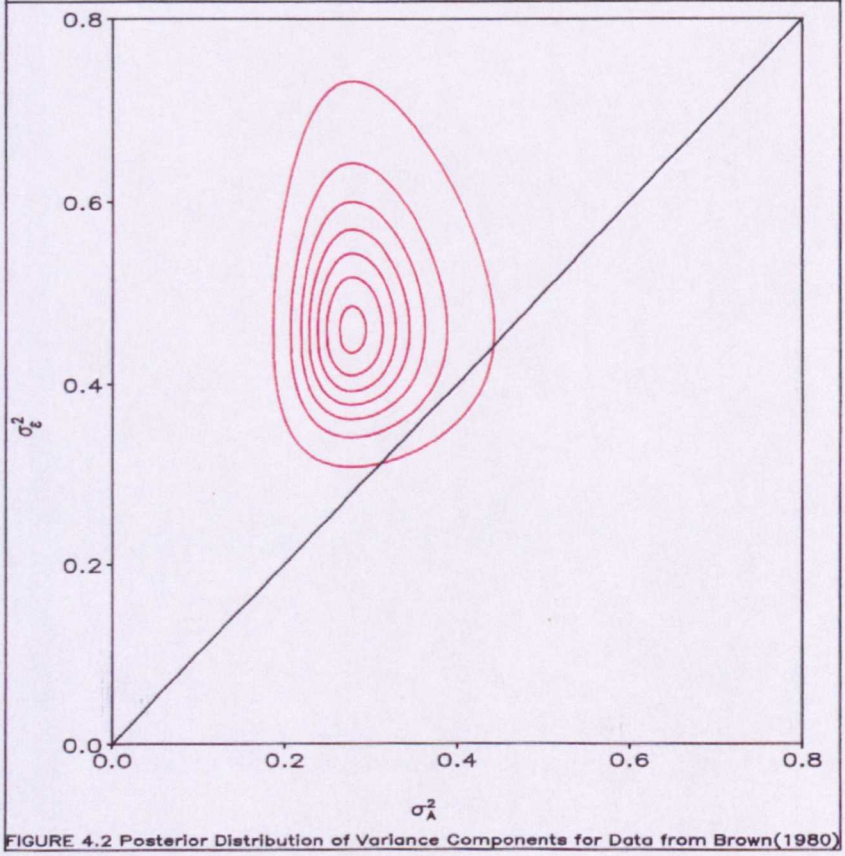


FIGURE 4.2 Posterior Distribution of Variance Components for Data from Brown(1980)

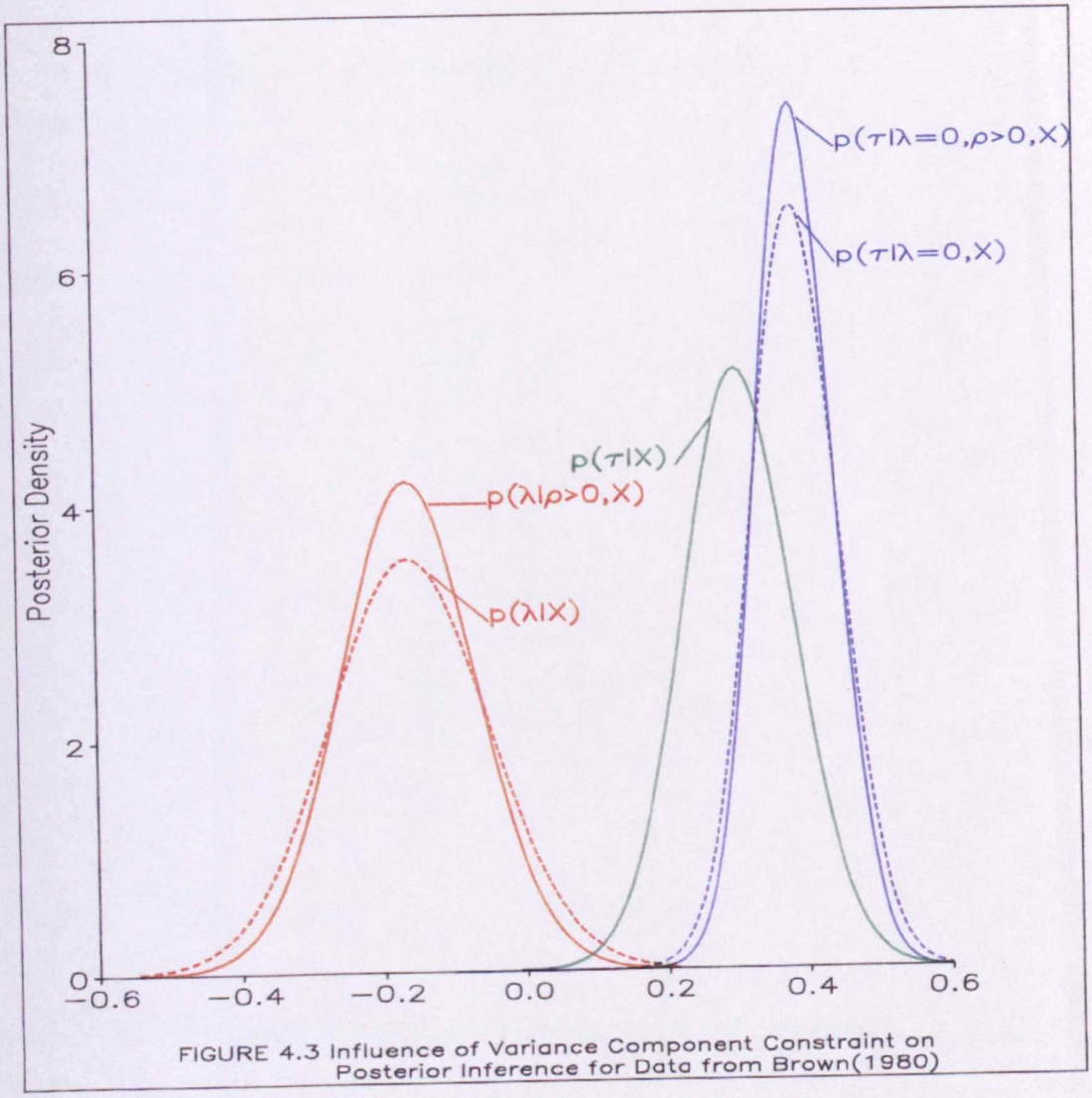


FIGURE 4.3 Influence of Variance Component Constraint on Posterior Inference for Data from Brown(1980)

$$p(\tau \mid X) = \int_{\sigma_A^2} \int_{\sigma_\epsilon^2} p(\tau \mid \sigma_A^2, \sigma_\epsilon^2, X) p(\sigma_A^2, \sigma_\epsilon^2 \mid X) d\sigma_A^2 d\sigma_\epsilon^2$$

From (4.5) the unconstrained conditional distribution of τ, given σ_A^2 and σ_ϵ^2, is $N(\tilde{\tau}, q(\sigma_A^2 + \sigma_\epsilon^2)/8)$. Since once the pair of variance components is given the constraint $\sigma_A^2 > \sigma_\epsilon^2$ has no effect on the distribution of τ then the first term in the integral is precisely $N(\tilde{\tau}, q(\sigma_A^2 + \sigma_\epsilon^2)/8)$. From (3.10) and (3.11) the posterior distribution of σ_A^2 and σ_ϵ^2 is,

$$p(\sigma_A^2, \sigma_\epsilon^2 \mid X) \propto \frac{(\sigma_A^2 \sigma_\epsilon^2)^{-N/2} \exp\left(-\frac{1}{2}\left[\frac{SSP}{\sigma_A^2} + \frac{SSE}{\sigma_\epsilon^2}\right]\right)}{P\left(F_{N-2,N-2} < \frac{SSP}{SSE}\right)} \qquad \sigma_A^2 > \sigma_\epsilon^2$$

From the results in §5.2.6 and §5.2.12 of Box and Tiao(1973) the posterior distributions of σ_A^2 and σ_ϵ^2 may be approximated by,

$$\sigma_\epsilon^2 \sim \frac{SSP}{a_1} \chi_{b_1}^{-2} \quad , \quad \sigma_A^2 \sim \frac{SSP}{a_2} \chi_{b_2}^{-2}$$

where,

$$a_1 = \frac{N I_x\left(\frac{N-2}{2}, \frac{N+2}{2}\right)}{2 I_x\left(\frac{N-2}{2}, \frac{N}{2}\right)} - \frac{(N-2) I_x\left(\frac{N-2}{2}, \frac{N}{2}\right)}{2 I_x\left(\frac{N-2}{2}, \frac{N-2}{2}\right)}$$

$$a_2 = \frac{N I_x\left(\frac{N+2}{2}, \frac{N-2}{2}\right)}{2 I_x\left(\frac{N}{2}, \frac{N-2}{2}\right)} - \frac{(N-2) I_x\left(\frac{N}{2}, \frac{N-2}{2}\right)}{2 I_x\left(\frac{N-2}{2}, \frac{N-2}{2}\right)}$$

$$b_1 = \frac{(N-2) I_x\left(\frac{N-2}{2}, \frac{N}{2}\right)}{a_1 I_x\left(\frac{N-2}{2}, \frac{N-2}{2}\right)}$$

$$b_2 = \frac{(N-2) I_x\left(\frac{N}{2}, \frac{N-2}{2}\right)}{a_2 I_x\left(\frac{N-2}{2}, \frac{N-2}{2}\right)}$$

and

$$x = \frac{SSP}{SSP + SSE}.$$

The construction above shows that σ_A^2 and σ_ϵ^2 are independently, approximately χ^{-2} distributed so that,

$$E(\sigma_A^2 + \sigma_\epsilon^2) \approx \frac{SSE}{a_1(b_1 - 2)} + \frac{SSP}{a_2(b_2 - 2)} = E$$

$$Var(\sigma_A^2 + \sigma_\epsilon^2) \approx \frac{2SSE^2}{a_1^2(b_1 - 2)^2(b_1 - 4)} + \frac{2SSP^2}{a_2^2(b_2 - 2)^2(b_2 - 4)} = V$$

Suppose $\sigma_A^2 + \sigma_\epsilon^2$ is approximately distributed as $b_{00}\chi_{b_{11}}^{-2}$ implying that $E(\sigma_A^2 + \sigma_\epsilon^2) \approx b_{00}/(b_{11}-2)$ and $Var(\sigma_A^2 + \sigma_\epsilon^2) \approx 2b_{00}^2/[(b_{11}-2)^2(b_{11}-4)]$. Equating these to E and V above gives,

$$b_{11} = \frac{2E^2}{V} + 4 \quad , \quad b_{00} = (b_{11}-2)E$$

Combining this approximate distribution with (4.14) and integrating out $\sigma_A^2 + \sigma_\epsilon^2$ gives

$$p(\tau \mid \sigma_A^2 > \sigma_\epsilon^2, X) \approx t\left(\tilde{\tau}, \frac{mb_{00}}{8b_{11}}, b_{11}\right)$$

4.5 A Preliminary Bayesian Analysis of Wheatley's(1987) Anginal Attack Rate Data.

The use of the posterior distributions derived above is illustrated using the data from Wheatley(1987) given in Table 2.3. Figure 4.4 displays (4.11), (4.12), (4.13) with $\lambda = 0$ and (4.14). Comparison of the classical ANOVA with the posterior summaries is enlightening. As has been seen in other cases (Grieve,1985; Racine *et al*,1986) the distributions $p(\tau \mid \lambda = 0, X)$ and $p(\tau \mid X)$ differ radically and the use of one in preference to the other would lead to very different conclusions vis-a-vis the treatment effect. For example $P(\tau > 0 \mid \lambda = 0, X) > 0.999$ whilst $P(\tau > 0 \mid X) = 0.85$. These results show that it is crucial when comparing treatments to be sure that the correct model is being used. The classical approach to differentiating between Models I and II is to use F_λ (see §2.4) . In the present case, as noted in §2.7, the p-value associated with F_λ is 0.198 which, according to Grizzle's procedure, would allow one to accept the veracity of Model II. However the posterior density $p(\lambda \mid X)$ suggests the presence of a carryover effect, giving credence to the view that the implicit either/or decision associated with the test for carryover effect does not provide an adequate representation of the uncertainties involved.

4.6 Using a Bayes Factor to Decide Between Models I and II.

The Bayesian approach to the problem of differentiating between Models I and II is to seek a form of prior specification which allows the direct incorporation of an assessment of the likelihood of each model. One method of doing this is to model the set up as a mixture of the two individual models corresponding to the "absence of carryover" (Model II) and "carryover" (Model I). If we denote these two models by M_0 and M_1 respectively, let the prior have the form,

$$p(\mu, \pi, \tau, \lambda, \sigma_\epsilon^2, \sigma_A^2 \mid M_i) \propto \sigma_\epsilon^{-2}\sigma_A^{-2} \qquad (i = 0, 1) \tag{4.16}$$

and define prior odds , $\kappa = P(M_0)/P(M_1)$, on the "absence of carryover" then the posterior probabilities of the two models are,

$$P(M_0 \mid X) = \frac{\kappa B_{01}}{1 + \kappa B_{01}} \quad , \quad P(M_1 \mid X) = \frac{1}{1 + \kappa B_{01}}$$

where B_{01} is the Bayes factor given by,

$$B_{01} = \frac{P(M_0 \mid X)}{P(M_0)} \frac{P(M_1)}{P(M_1 \mid X)} = \frac{P(X \mid M_0)}{P(X \mid M_1)}.$$

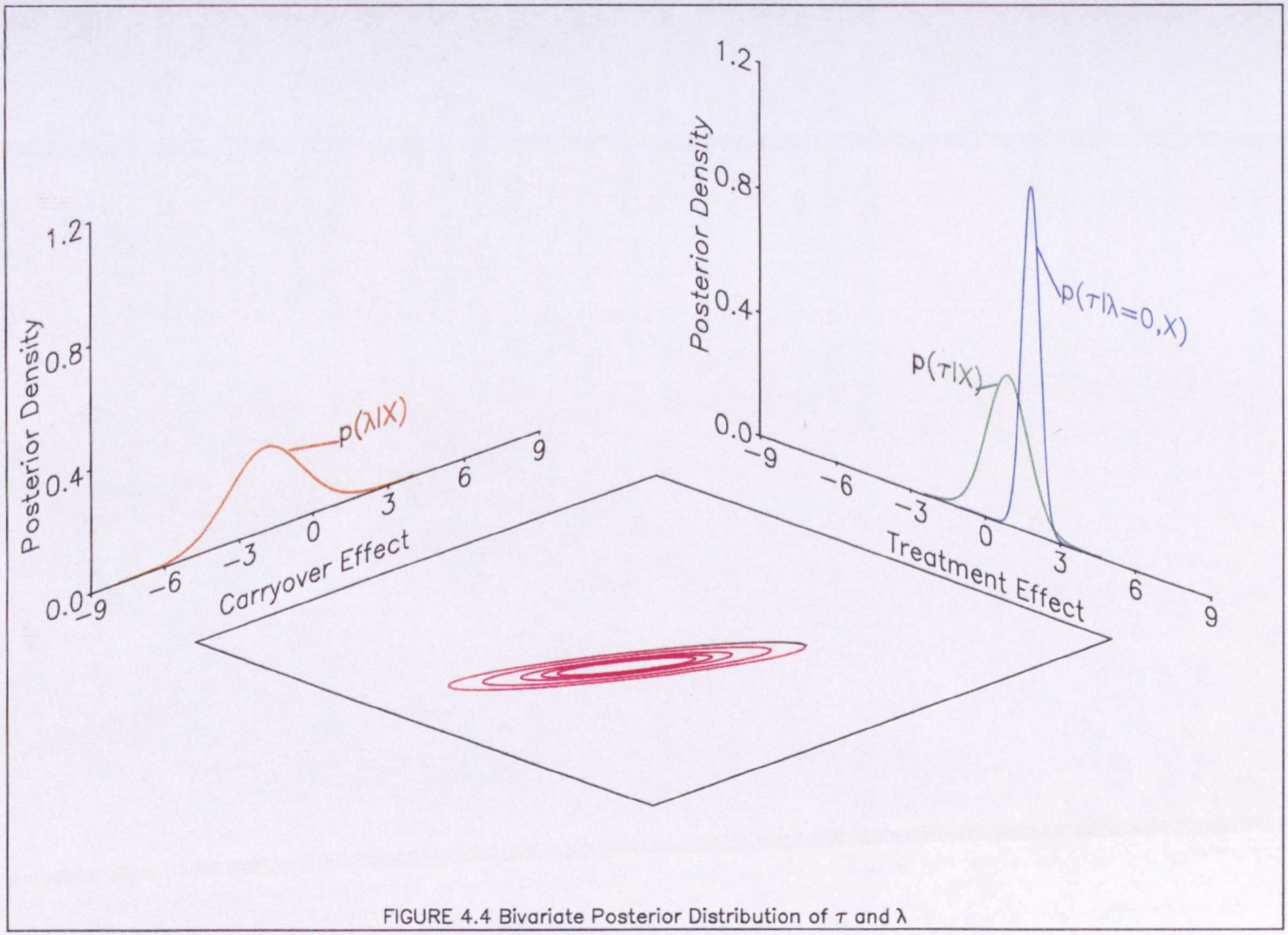


FIGURE 4.4 Bivariate Posterior Distribution of τ and λ

The Bayes factor is the ratio of posterior to prior odds on M_0, i.e. against a carryover effect. Inference concerning the treatment effect τ can then be made using the mixture posterior distribution,

$$p(\tau \mid X) = \frac{\kappa B_{01}}{1+\kappa B_{01}} p(\tau \mid M_0, X) + \frac{1}{1+\kappa B_{01}} p(\tau \mid M_1, X) \qquad (4.17)$$

where $p(\tau \mid M_0, X)$ is given by (4.13) with $\lambda = 0$, and $p(\tau \mid M_1, X)$ is given by (4.14).

The Bayes factor, B_{01}, may be expressed as a ratio of integrated likelihoods and therefore involves the ratio of unspecified proportionality constants implicit in the priors defined by (4.16). Spiegelhalter and Smith (1982) show how to obtain a definitive form for B_{01} in such models by using the so-called "device of imaginary observations". Grieve(1985) points out that since F_λ is merely the square of an unpaired t-test, equation (12) of Spiegelhalter and Smith(1982) gives the Bayes factor against a carryover effect as,

$$B_{01} = \left(\frac{3}{2q}\right)^{1/2}\left(1+\frac{F_\lambda}{N-2}\right)^{-N/2} \qquad (4.18)$$

To choose a value of κ is to specify one's personal belief in the likelihood or otherwise of a carryover effect, thus providing a means of introducing a sliding-scale of plausibility between the extremes of assuming either the absence of a carryover effect or of assuming that a carryover effect is absolutely certain. Such a choice is forced upon one if the classical significance testing procedure is used. Clearly posterior beliefs depend on prior beliefs so that a "fair" representation of conclusions should show this dependence. Figure 4.5 provides summaries of $p(\tau \mid X)$ as a function of $P(M_1) = (1+\kappa)^{-1}$. In this figure the posterior expected treatment effect and its associated 95% highest posterior density (H.P.D.) interval are plotted on the left-hand vertical axis and the posterior probability of a positive effect on the right-hand vertical axis.

To appreciate how Figure 4.5 may be used, suppose that interest centres in a positive treatment effect, which in the context of our example implies that we are interested in lower incidence of attacks when TN is used compared to Placebo. If *a priori* we are indifferent to the choice of model, that is, $\kappa = 1$, then the posterior probability of a positive treatment effect is 0.95, the corresponding posterior probabilities for $\kappa = \frac{1}{3}, \frac{1}{2}, 2,$ and 3 are 0.91, 0.93, 0.97 and 0.98 respectively. Thus, for this experiment, we need only be 50% sure *a priori* that there is no carryover effect in order to achieve a posterior probability greater than 95% that the treatment effect is positive.

Figure 4.5 shows that inferences concerning the effect of TN are highly dependent on our prior belief in the likelihood of a carryover effect. As Grieve(1985) points out this dependence may be due to the relatively small value of B_{01} which is indeed the case for Wheatley's data ($B_{01} = 2.052$) . From (4.18) it is clear that B_{01} depends both on F_λ and on the numbers of patients in each sequence group n_1 and n_2 in such a way that i) it has no minimum value, ii) the maximum value, given by $F_\lambda = 0$, is a simple function of n_1 and n_2. Analogous to the results given in Grieve(1985), Table 4.2 presents $P(M_0 \mid X)$ for selected values of $P(M_0)$ for both the observed B_{01} and for its theoretical maximum value. Table 4.2 demonstrates a characteristic of "small" experiments in that even when, in the classical sense, there is little, or no evidence to suggest a carryover effect,

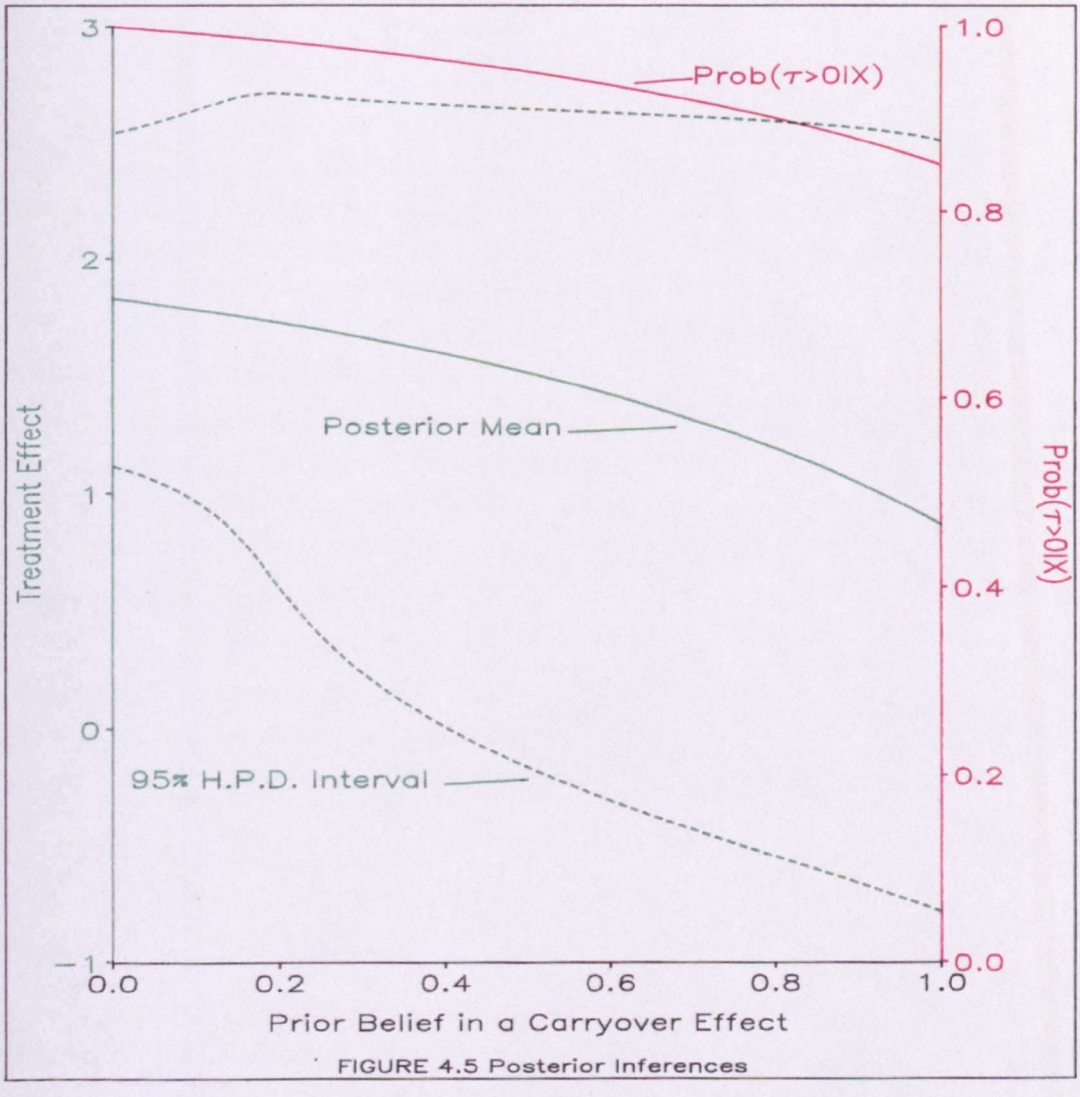


FIGURE 4.5 Posterior Inferences

the inferences which we are able to make depend fundamentally on $P(M_1)$. This is related to Jeffrey's(1983,p.434) observation that small experiments cannot provide strong evidence in support of a null hypothesis, although they can provide strong evidence against it.

TABLE 4.2 Posterior Beliefs in "Absence of Carryover" for Various Prior Beliefs.

		$P(M_0 \mid X)$	
κ	$P(M_0)$	$B_{01} = 2.052$	$B_{01} = 4.860$
1/9	0.1	0.186	0.351
1/4	0.2	0.339	0.526
1	0.5	0.672	0.829
4	0.8	0.891	0.951
9	0.9	0.949	0.978

A second point concerning Figure 4.5 relates to the apparently idiosyncratic relationship between the 95% HPD interval and $P(M_1)$. In fact this shape is characteristic of crossover trials (cf. Grieve,1985; Racine *et al*,1986; Grieve,1989) arising from the mixture of distributions in (4.17). To illustrate, Figure 4.6 presents $p(\tau \mid X)$ for different values of $P(M_1)$. Although in this instance $p(\tau \mid X)$ is not bimodal such forms can arise if $\hat{\tau}$ and $\hat{\tau} + \hat{\lambda}/2$ are widely separated.

Spiegelhalter(1986a) questions whether the use of the Bayes factor is only marginally better than the classical "either-or" mentality because it effectively models prior beliefs as a mixture of a sharp peak at the null hypothesis, the remainder being distributed over the real line as a representation of ignorance. Before examining this view we consider in the next section the use of informative prior distributions.

4.7 Bayesian Analyses with Informative Priors.

Selwyn *et al* (1981) develop a Bayesian analysis for a balanced two-period crossover design, $n_1 = n_2$, for a problem in bioequivalence testing. In their work they consider a number of different models one of which corresponds to Model I. They take as the joint prior density of the parameters,

$$p(\mu, \pi, \tau, \lambda, \sigma_\epsilon^2, \sigma_\lambda^2) \propto \sigma_\epsilon^{-2}\sigma_\lambda^{-2}\exp\left(-\frac{\lambda^2}{2\sigma_\lambda^2}\right) \qquad (4.19)$$

so that *a priori* λ is normally distributed with mean 0 and variance σ_λ^2. By considering a range of values for σ_λ^2 a variety of prior beliefs concerning the likelihood or otherwise of a carryover effect may be obtained. For example, $\sigma_\lambda^2 = 0$ corresponds to absolute certainty that there is no carryover effect, while $\sigma_\lambda^2 = \infty$ is equivalent to the conventional uninformative prior which we have already considered. Now suppose that our prior belief concerning λ, generalizing (4.19), may be represented by a normal distribution with mean λ_0 and variance σ_λ^2 so that our prior for the parameters of the model has the form,

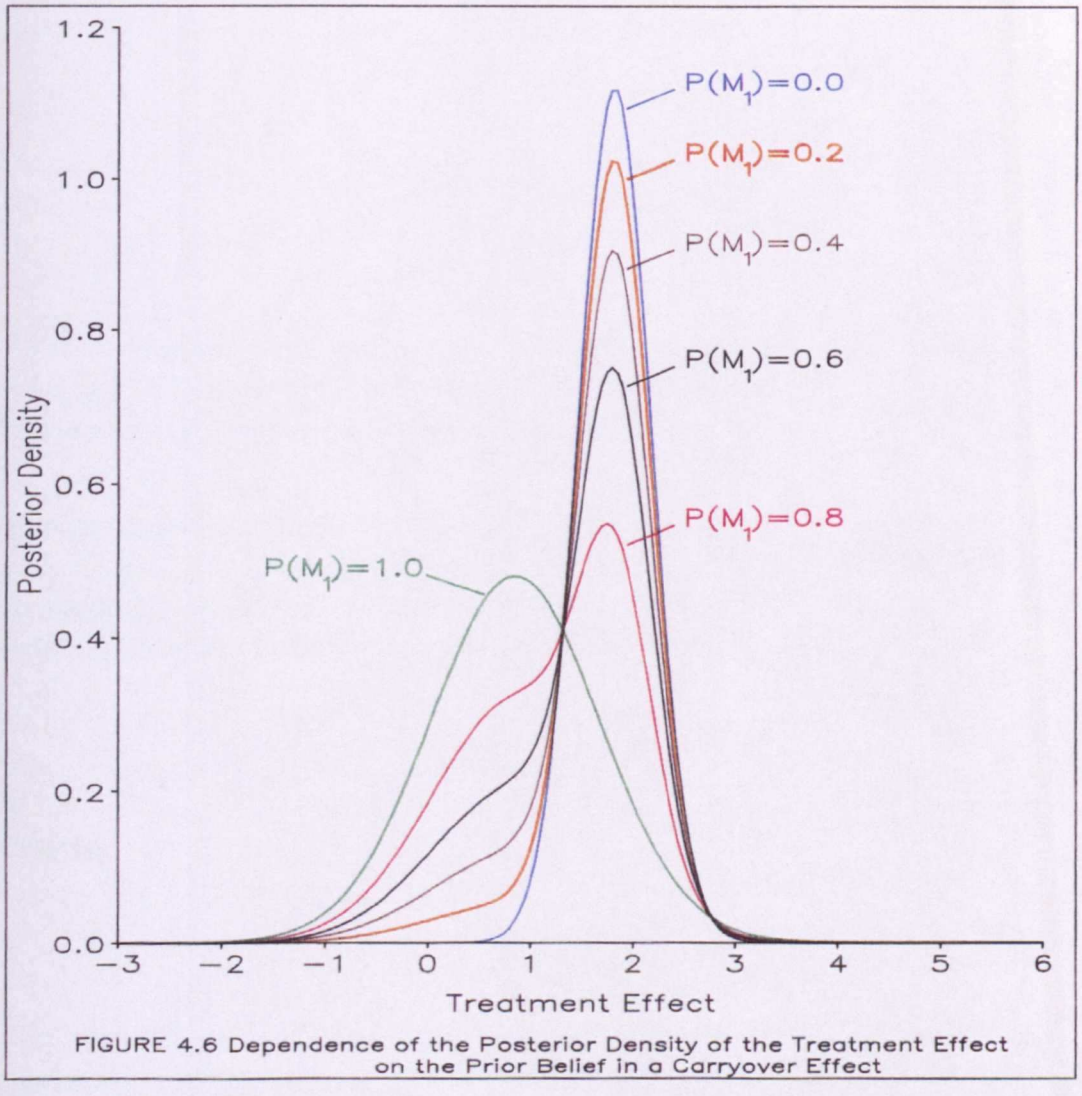


FIGURE 4.6 Dependence of the Posterior Density of the Treatment Effect on the Prior Belief in a Carryover Effect

$$p(\mu,\pi,\tau,\lambda,\sigma_\epsilon^2,\sigma_\lambda^2) \propto \sigma_\epsilon^{-2}\sigma_\lambda^{-2}\exp\left(-\frac{(\lambda-\lambda_0)^2}{2\sigma_\lambda^2}\right) \tag{4.20}$$

Using this prior standard Bayesian manipulations with normal kernels shows that the posterior distribution of τ given the variance components σ_ϵ^2 and σ_λ^2 is,

$$p(\tau \mid \sigma_\epsilon^2,\sigma_\lambda^2,X) = N(u,v) \tag{4.21}$$

where,

$$u = \hat{\tau} + \frac{\frac{1}{2}\sigma_\lambda^2\hat{\lambda} + \frac{1}{2}q\sigma_\lambda^2\lambda_0/2}{\sigma_\lambda^2 + \frac{1}{2}q\sigma_\lambda^2}$$

and

$$v = \frac{\frac{1}{2}q\sigma_\lambda^2\sigma_\lambda^2 + \left(\frac{1}{2}q\sigma_\epsilon^2\right)\left(\frac{1}{2}q\sigma_\lambda^2\right) + \frac{1}{2}q\sigma_\epsilon^2\sigma_\lambda^2}{4\left(\sigma_\lambda^2 + \frac{1}{2}q\sigma_\lambda^2\right)}$$

As $\sigma_\lambda^2 \to \infty$ this reduces to (4.6), while as $\sigma_\lambda^2 \to 0$, $u \to \hat{\tau} + \lambda_0/2$ and $v \to q\sigma_\epsilon^2/8$. This latter result implies that if we have, *a priori*, a strong belief that the carryover effect is in a small region centred on λ_0 we may remove the carryover effect from the biased estimate of τ, that is from $\hat{\tau}$.

Suppose that our *a priori* information is obtained from the results of a pilot study whose results are denoted by $\hat{\mu}_0, \hat{\pi}_0, \hat{\tau}_0, \hat{\lambda}_0, SSP_0, SSE_0, N_0$ and q_0. Now since the joint posterior distribution of $\mu, \pi, \tau, \lambda, \sigma_\epsilon^2$ and σ_λ^2 is conjugate to the likelihood, standard manipulations may be used to show that the marginal posterior distribution of τ given the variance components has a normal distribution having mean,

$$\frac{q(\hat{\tau}_0 + \hat{\lambda}_0/2) + q_0(\hat{\tau} + \hat{\lambda}/2)}{q_0 + q}$$

and variance,

$$\frac{q_0 q(\sigma_\epsilon^2 + \sigma^2)}{8(q_0 + q)}$$

Since there will generally be far fewer patients in the pilot study than in the main study, $q_0 \gg q$, and therefore the pilot study will not provide sufficient information to remove the bias from $\hat{\tau}$.

If we use Selwyn *et al*'s(1981) prior (4.19) then the mode of the posterior distribution of τ given σ_λ^2 and σ_ϵ^2 has the form $\hat{\tau} + (\sigma_\lambda^2\hat{\lambda}/2)/(\sigma_\lambda^2 + q\sigma_\lambda^2/2)$ which tends to $\hat{\tau}$ as $\sigma_\lambda^2 \to 0$. In other words if we are fairly sure that the

carryover effect lies in a narrow interval around zero, the posterior distribution of τ will be similar to the distribution we would have obtained had we assumed that the carryover effect was zero. On the other hand as $\sigma^2_\lambda \to \infty$ the analysis reduces to that given in §4.1.

4.8 Spiegelhalter's View.

From (4.17) it may be seen that the posterior mean for τ has the form,

$$\frac{\kappa B_{01}}{1+\kappa B_{01}}\hat{\tau} + \frac{1}{1+\kappa B_{01}}(\hat{\tau}+\hat{\lambda}/2)$$

while, for given σ^2_λ, the corresponding posterior mean using Selwyn *et al*'s(1981) prior has the form,

$$\frac{2\sigma^2_\lambda/q\sigma^2_\lambda}{1+2\sigma^2_\lambda/q\sigma^2_\lambda}\hat{\tau} + \frac{1}{1+2\sigma^2_\lambda/q\sigma^2_\lambda}(\hat{\tau}+\hat{\lambda}/2)$$

This pair of means are very similar and it is therefore not surprising that Spiegelhalter(1986a) was able to provide an analysis using an informative prior for λ which almost exactly mirrored the analysis based on the Bayes factor.

The decision then has to be taken as to whether prior beliefs concerning potential carryover effects are more easily determined, and incorporated, via the Bayes factor or proper prior approaches. It was argued in Grieve(1985) that the Bayes factor approach is preferable since for example indifference to model M_0 or M_1 is simply defined by $\kappa = 1$, while if σ^2_λ is used it is not at all clear how indifference should be defined. Further support for the Bayes factor approach will be given in later sections.

4.9 Discussion.

A number of analyses have been considered in this chapter and before discussing other approaches in the light of our preferred Bayesian approach it is helpful to summarise our approach by distinguishing three particular cases. In the notation of §4.6 there are in terms of $P(M_1)$, which is our prior belief in the presence of a carryover effect, the following three distinct scenarios to be looked at :

$$(i)\quad P(M_1) = 0$$

$$(ii)\quad P(M_1) = 1$$

$$(iii)\quad 0 < P(M_1) < 1$$

A strategy needs to be decided upon for each scenario, and the question is What strategy ?

In the case of (i) we are *a priori* absolutely certain that there is no carryover effect. The two-treatment two-period crossover then presents no difficulties and we may use the conditional distribution of τ given $\lambda = 0$, either by setting $\lambda = 0$ in (4.13) if we wish to take account of the variance component constraint or by setting $\lambda = 0$ in the second component of (4.8) if we are prepared to ignore it. This is essentially the approach taken by the majority of statisticians when analysing bioequivalence studies in which it is believed to be unnecessary to consider the incorporation of a drug carryover effect since blood samples drawn immediately prior to

application of the drug in the second period will reveal whether during the washout period elimination of the drug has occurred. This assumes that the particular drug does not have an effect directly and/or indirectly on the absorption and elimination mechanisms of the body.

In case (ii) there are two distinct subcases to be considered. In the first subcase we suppose that we have no *a priori* information concerning the likely magnitude of a carryover effect other than that it exists. If this is the case then whilst perfectly valid inferences concerning the treatment effect τ can be made - using, for example, the results in §4.3 and §4.4 - the standard arguments concerning the sensitivity of the crossover design compared to the parallel group design (see for example Brown,1980) would predicate against the use of the former design as opposed to the latter. It is , however, contradictory to suppose that $P(M_1) = 1$ and at the same time to say we know nothing of its magnitude. In the second subcase we suppose that there is considerable information concerning the likely magnitude of a carryover effect and that it is possible to specify it through a Normal density with mean λ_0 and variance σ_λ^2. Such information, if available, can be incorporated in the analysis and the results in §4.7 show that if σ_λ^2 is small, corresponding to large amounts of information, then to a good approximation the posterior distribution of τ will be given by the conditional posterior distribution of τ given the prior expectation of the carryover effect, i.e. $\lambda = \lambda_0$ in place of $\lambda = 0$ above.

In case (iii) inferences about τ may be made either using the approach of Selwyn et al(1981), as championed by Spiegelhalter(1986a) - see §4.8 - or by using the Bayes factor approach given in §4.6. In the light of Spiegelhalter's demonstration of the near equivalence of the two approaches the difference between them is perhaps more apparent than real. Nonetheless the consideration of how to specify indifference between the models M_0 and M_1 leads to the Bayes factor approach in preference to Spiegelhalter's.

In 1979 the British pharmaceutical industry body "Statisticians in the Pharmaceutical Industry" (PSI) constituted a working-party with the remit to investigate, in the light of the FDA position, the two-treatment two-period crossover (Poloniecki and Daniel,1981; Huitson *et al*,1982; Barker *et al*,1982; Poloniecki and Pearce,1983). One proposal which they made was to investigate the relative magnitude of the treatment and carryover effects. In the notation of Poloniecki and Daniel(1983) their suggestion was to determine the posterior probability that $|\tau| > |\gamma|$ where τ and γ denote the treatment and carryover effects respectively. The major deficiency of this idea is that the Poloniecki and Daniel definition of τ would, in our notation, correspond to $\tau - \lambda/2$. Translating their suggestion into our notation implies that one should calculate either $P(\tau - \lambda > 0 \wedge \tau > 0 \mid X)$ or $P(\tau - \lambda < 0 \wedge \tau < 0 \mid X)$ depending on whether τ is "significantly" positive or negative. Effectively, their proposal for $\tau > 0$ is to calculate the posterior probability that τ and λ lie to the right of the line $\tau = 0$ and below the line $\tau = \lambda$. In Figure 4.7 the red contour lines are taken from Figure 4.4 - corresponding to the posterior density of τ and λ for Wheatley's(1987) data; the green contour lines have been obtained by shifting the red contours. From this figure it is clear that in the case of the green contours $P(\tau > 0 \mid X) \approx 1$ whilst $P(\tau - \lambda > 0 \wedge \tau > 0 \mid X) \approx 0$. It seems difficult, therefore, to justify such the region suggested by Poloniecki and Pearce since the result $P(\tau > 0 \mid X) \approx 1$ implies that conditional on any reasonable value of λ suggested by the data, the posterior probability that τ is positive is high.

Willan and Pater(1986) and Willan(1988) have also suggested that in certain circumstances the fact that there is a significant carryover does not preclude an analysis based on data from both periods. They argue that if,

$$\frac{\lambda}{\tau} < 2 - \sqrt{2(1-\rho)} \qquad (4.22)$$

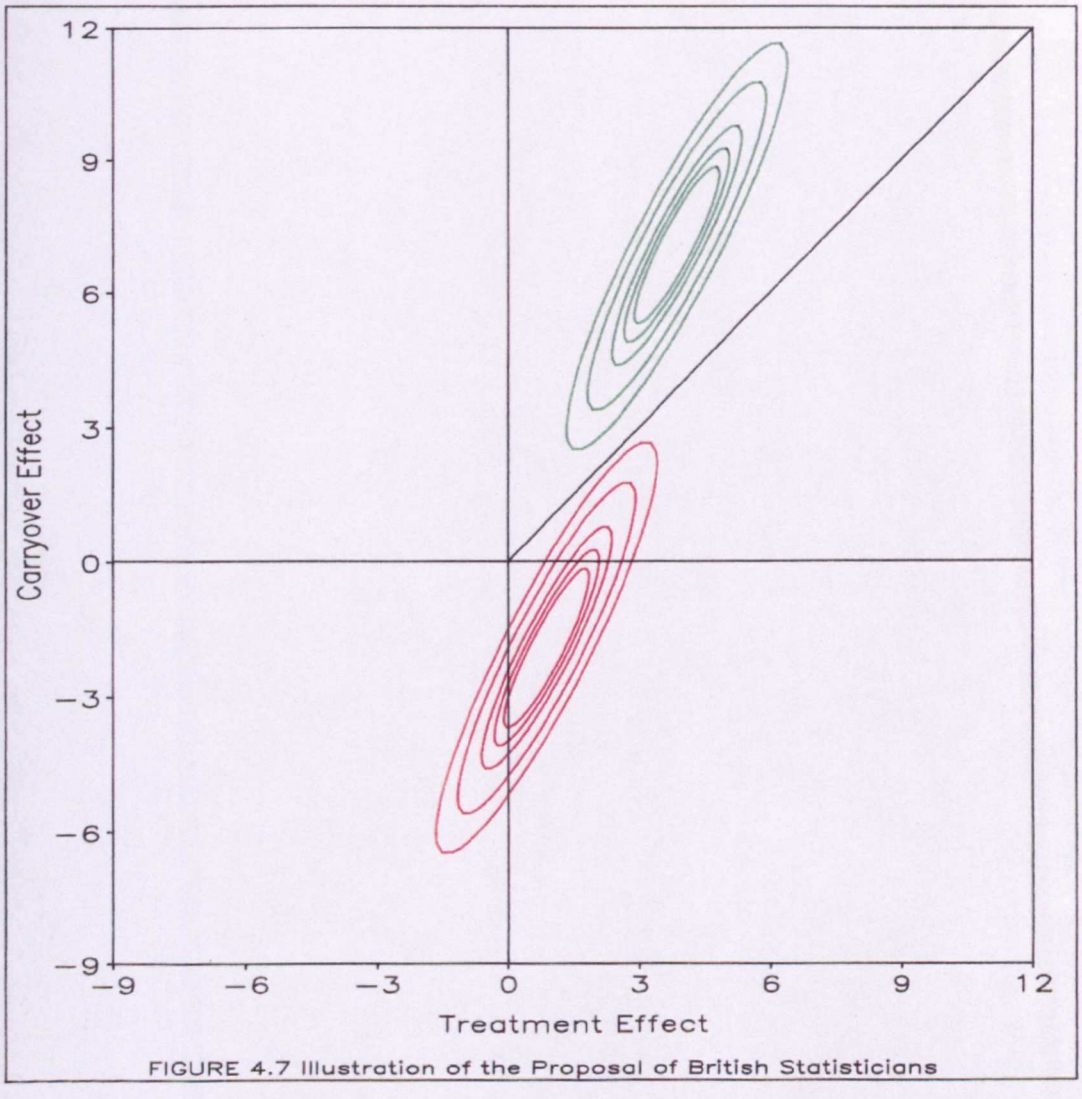


FIGURE 4.7 Illustration of the Proposal of British Statisticians

then an analysis based on data from both periods is preferable since even when there is considerable carryover such an analysis provides a more powerful test of treatment effect than one based on the first period data alone.

Whilst it is laudable to search for circumstances under which conditions such as (4.22) are satisfied it raises a number of issues. First, whilst it is a more complex region than the one considered by Poloniecki and Pearce(1983), involving as it does the correlation ρ , (4.22) is nonetheless a region based on population values and it is therefore not possible to use it pre-study to determine which analysis is to be performed. Second, it is possible, as we did above, to provide examples in which, although the condition (4.22) does not hold, nonetheless there is a very high probability that a highly "significant" carryover effect exists.

5 THE TWO-PERIOD CROSSOVER WITH A SINGLE BASELINE.

The standard two-period design, whose Bayesian analysis was outlined in §4, has no baseline data. As Freeman(1986) comments the majority of crossover studies feature baseline data which are often ignored. In this section the incorporation of a single baseline measurement is considered.

5.1 Cell Means Model.

In Section §2.8 we saw that for a two-treatment crossover with baselines prior to each treatment period there were a number of potential models. The same is true in the case of a single baseline measurement. In essence the observations on patients, pre-treatment, provide the possibility of estimating two additional parameters corresponding to the pre-treatment cell means in each sequence group. There are a number of pairs of model parameters which could be considered. For example one might wish to include both carryover and period-treatment interaction, so that one of the additional parameters would correspond to the latter. Such a parametrization is not appropriate because the period-treatment parameter is a linear combination of the treatment and carryover effects.

In the two-treatment, two-period crossover, the carryover effect is completely confounded with both the period-treatment interaction and with the sequence effect. In the present design the sequence effect is no longer confounded with the carryover effect so that in analogy to the model considered by Kenward and Jones(1987b) additional parameters for the sequence effect (γ) and for the pre-treatment period are incorporated. The cell means model which we consider is shown in Table 5.1 where π_1 and π_2 denote independent period effects.

TABLE 5.1 Cell Means for a Two-Period Crossover with a Single Baseline.

Sequence Group	Pre-Treatment	Periods	
		1	2
A→B	$\mu+\gamma+\pi_1$	$\mu+\gamma+\pi_2+\tau$	$\mu+\gamma-\pi_1-\pi_2-\tau+\lambda$
B→A	$\mu-\gamma+\pi_1$	$\mu-\gamma+\pi_2-\tau$	$\mu-\gamma-\pi_1-\pi_2+\tau-\lambda$

We will in the main when considering more complicated designs than the straightforward two-period two-treatment crossover adopt the Kenward and Jones(1987b) approach of incorporating a parameter γ for a sequence effect. These authors argue for such an approach on the grounds that then all parameters of interest can be estimated within patients. It can of course be argued that it is not appropriate to introduce a sequence effect parameter since if patients are randomised to the sequence groups no such effect should exist - classically it would be argued that a significant test for a sequence effect would be a type I error. From another standpoint Gough(1989) has argued that by dropping the sequence effect from the model between patient information about treatment and carryover effects can be obtained with a consequent increase in precision. We will return to consider this point later.

5.2 Basic Distributions.

The cell means model shown in Table 5.1 may be fitted into the general structure of §3 by setting $g = 2$ and $k = 3$ and by noting that,

$$\begin{pmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{13} \\ \mu_{21} \\ \mu_{22} \\ \mu_{23} \end{pmatrix} = \begin{pmatrix} 1 & 1 & 1 & 0 & 0 & 0 \\ 1 & 1 & 0 & 1 & 1 & 0 \\ 1 & 1 & -1 & -1 & -1 & 1 \\ 1 & -1 & 1 & 0 & 0 & 0 \\ 1 & -1 & 0 & 1 & -1 & 0 \\ 1 & -1 & -1 & -1 & 1 & -1 \end{pmatrix} \begin{pmatrix} \mu \\ \gamma \\ \pi_1 \\ \pi_2 \\ \tau \\ \lambda \end{pmatrix}$$

The inverse transformation has the form,

$$\begin{pmatrix} \mu \\ \gamma \\ \pi_1 \\ \pi_2 \\ \tau \\ \lambda \end{pmatrix} = \begin{pmatrix} 1/6 & 1/6 & 1/6 & 1/6 & 1/6 & 1/6 \\ 1/2 & 0 & 0 & -1/2 & 0 & 0 \\ 1/3 & -1/6 & -1/6 & 1/3 & -1/6 & -1/6 \\ -1/6 & 1/3 & -1/6 & -1/6 & 1/3 & -1/6 \\ -1/2 & 1/2 & 0 & 1/2 & -1/2 & 0 \\ -1 & 1/2 & 1/2 & 1 & -1/2 & -1/2 \end{pmatrix} \begin{pmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{13} \\ \mu_{21} \\ \mu_{22} \\ \mu_{23} \end{pmatrix} \qquad (5.1)$$

Consider the transformation (5.1) applied to (3.6) with $g = 2$ and $k = 3$. From standard properties of the normal distribution the conditional posterior distribution of the location parameters $\mu, \gamma, \pi_1, \pi_2, \tau$ and λ given σ^2 and ρ has the form,

$$p(\mu, \gamma, \pi_1, \pi_2, \tau, \lambda \mid \sigma^2, \rho, X) = N\left[\begin{pmatrix} (\bar{y}_{1.1} + \bar{y}_{1.2} + \bar{y}_{1.3} + \bar{y}_{2.1} + \bar{y}_{2.2} + \bar{y}_{2.3})/6 \\ (\bar{y}_{1.1} - \bar{y}_{2.1})/2 \\ (2\bar{y}_{1.1} - \bar{y}_{1.2} - \bar{y}_{1.3} + 2\bar{y}_{2.1} - \bar{y}_{2.2} - \bar{y}_{2.3})/6 \\ (-\bar{y}_{1.1} + 2\bar{y}_{1.2} - \bar{y}_{1.3} - \bar{y}_{2.1} + 2\bar{y}_{2.2} - \bar{y}_{2.3})/6 \\ (-\bar{y}_{1.1} + \bar{y}_{1.2} + \bar{y}_{2.1} - \bar{y}_{2.2})/2 \\ (-2\bar{y}_{1.1} + \bar{y}_{1.2} + \bar{y}_{1.3} + 2\bar{y}_{2.1} - \bar{y}_{2.2} - \bar{y}_{2.3})/2 \end{pmatrix}, \Sigma_2 \right] \qquad (5.2)$$

where,

$$\Sigma_2 = \frac{\sigma^2}{12} \begin{pmatrix} q(1+2\rho) & r(1+2\rho) & 0 & 0 & 0 & 0 \\ r(1+2\rho) & 3q & 2r(1-\rho) & -r(1-\rho) & -3q(1-\rho) & -6q(1-\rho) \\ 0 & 2r(1-\rho) & 2q(1-\rho) & -q(1-\rho) & -3r(1-\rho) & -6r(1-\rho) \\ 0 & -r(1-\rho) & -q(1-\rho) & 2q(1-\rho) & 3r(1-\rho) & 3r(1-\rho) \\ 0 & -3q(1-\rho) & -3r(1-\rho) & 3r(1-\rho) & 6q(1-\rho) & 9q(1-\rho) \\ 0 & -6q(1-\rho) & -6r(1-\rho) & 3r(1-\rho) & 9q(1-\rho) & 18q(1-\rho) \end{pmatrix}$$

Using properties of multivariate normal distributions the following posterior distributions may be derived from (5.2),

$$p(\gamma,\tau,\lambda\mid\sigma_1^2,\sigma_2^2,X) = N\left[\begin{pmatrix}\hat{\gamma}\\ \hat{\tau}\\ \hat{\lambda}\end{pmatrix},\frac{q}{4}\begin{pmatrix}(\sigma_1^2+2\sigma_2^2)/3 & -\sigma_2^2 & -2\sigma_2^2\\ -\sigma_2^2 & 2\sigma_2^2 & 3\sigma_2^2\\ -2\sigma_2^2 & 3\sigma_2^2 & 6\sigma_2^2\end{pmatrix}\right] \tag{5.3}$$

$$p(\gamma\mid\sigma_1^2,\sigma_2^2,X) \sim N(\hat{\gamma},q(\sigma_1^2+2\sigma_2^2)/12) \tag{5.4}$$

$$p(\tau\mid\sigma_1^2,\sigma_2^2,X) \sim N(\hat{\tau},q\sigma_2^2/2) \tag{5.5}$$

$$p(\lambda\mid\sigma_1^2,\sigma_2^2,X) \sim N(\hat{\lambda},3q\sigma_2^2/2) \tag{5.6}$$

$$p(\tau\mid\lambda,\sigma_1^2,\sigma_2^2,X) \sim N\left(\hat{\tau}-\frac{\hat{\lambda}}{2}+\frac{\lambda}{2},q\sigma_2^2/8\right) \tag{5.7}$$

where,

$$\hat{\gamma} = (\bar{y}_{1.1}-\bar{y}_{2.1})/2$$

$$\hat{\tau} = (-\bar{y}_{1.1}+\bar{y}_{1.2}+\bar{y}_{2.1}-\bar{y}_{2.2})/2$$

$$\hat{\lambda} = (-2\bar{y}_{1.1}+\bar{y}_{1.2}+\bar{y}_{1.3}+2\bar{y}_{2.1}-\bar{y}_{2.2}-\bar{y}_{2.3})/2$$

and where $\sigma_1^2 = \sigma^2(1+2\rho)$ and σ_2^2, q and r are as previously defined.

Setting $g = 2$ and $k = 3$ in (3.9) gives,

$$p(\sigma_1^2,\sigma_2^2\mid X) \propto (\sigma_1^2)^{-N/2}\exp\left(-\frac{SS_1}{2\sigma_1^2}\right)(\sigma_2^2)^{-N+1}\exp\left(-\frac{SS_2}{2\sigma_2^2}\right) \tag{5.8}$$

Combining (5.8) with in turn (5.5) and (5.6) and integrating out σ_2^2 gives,

$$p(\tau\mid X) \propto \left[SS_2+\frac{2}{q}(\tau-\hat{\tau})^2\right]^{-(2N-3)/2} \tag{5.9}$$

$$p(\lambda\mid X) \propto \left[SS_2+\frac{2}{3q}(\lambda-\hat{\lambda})^2\right]^{-(2N-3)/2} \tag{5.10}$$

In analogy to the two-period crossover without baseline measurements analysed in §4 we denote the model containing a carryover effect by M_1 and that in which it is assumed that there is no carryover by M_0. This latter model may be obtained from model M_1 by setting $\lambda = 0$, in which case,

$$p(\tau\mid\lambda=0,\sigma_1^2,\sigma_2^2,X) \sim N(\hat{\tau}-\hat{\lambda}/2,q\sigma_2^2/8) \tag{5.11}$$

and

$$p(\sigma_2^2 \mid \lambda = 0, X) \propto (\sigma_2^2)^{-N+1/2} \exp\left(-\frac{SS_2 + 2\hat{\lambda}^2/(3q)}{2\sigma_2^2}\right) \qquad (5.12)$$

The second term in the exponential function in (5.12) arises from setting $\lambda = 0$ in (5.6). Combining (5.11) and (5.12) and integrating σ_2^2 gives,

$$p(\tau \mid \lambda = 0, X) \propto \left[SS_2 + \frac{2\hat{\lambda}^2}{3q} + \frac{8}{q}\left(\tau - \hat{\tau} + \frac{\hat{\lambda}}{2}\right)^2\right]^{-(2N-2)/2} \qquad (5.13)$$

When we considered the posterior distribution of the treatment effect under M_0 in §4.1 an additional term equivalent to $2\hat{\lambda}^2/(3q)$ did not arise. This is because in the present case both τ and λ are estimated within patients so that knowing that $\lambda = 0$ implies increased knowledge about within patient variability whilst in the former case λ is estimated between patients so that knowing it is zero increases knowledge about between patient variability which cannot be used for making inferences about τ which under these conditions is based on within patient variability.

We saw in the previous section that whilst it is possible to allow for the constraint $\sigma_1^2 > \sigma_2^2$ it is not necessary if the correct model is used, the same is true in this case. Analogously to the two-period two-treatment case the probability $P(\sigma_1^2 > \sigma_2^2 \mid X)$ which, from (3.11), is given by,

$$P(\sigma_1^2 > \sigma_2^2 \mid X) = P\left(F_{N-2,2(N-2)} < \frac{SS_1}{N-2}\frac{2(N-2)}{SS_2}\right)$$

may be used to confirm the appropriateness or otherwise of ignoring the constraint.

5.3 An Example of the Two-Period Crossover with a Single Baseline.

The data displayed in Table 5.2 are taken from a study carried out by CIBA-GEIGY to compare the efficacy and tolerability of Voltarol (V) and Indomethacin (I) in patients with rheumatoid arthritis and osteoarthritis. Results from the study are reported by Barnes *et al*(1978).

Patients were randomly assigned to receive two weeks treatment with 25 mg of Voltarol four times daily (*qds*) followed by two weeks treatment with 25 mg of Indomethacin *qds* or vice versa. Patients were seen on entry to the study, and at the end of each two-week treatment period at which times a number of efficacy parameters were assessed. In particular the data shown in Table 5.2 are the recorded values of the Ritchie index, which is an assessment of joint tenderness in patients with rheumatoid arthritis (see Ritchie *et al*,1968).

5.4 Preliminary Bayesian Analysis of Barnes *et al*'s Data

For the Ritchie-Index data from Barnes *et al*(1978) the sample mean vectors and associated matrices of sums of squares and cross-products given in Table 5.2 may be used to derive the following statistics:

TABLE 5.2 Value of the Ritchie Index at Baseline and After Each Two-Week Treatment Period.

Sequence	Patient	Baseline	Period 1	Period 2
V→I	106	14	25	25
	111	9	9	4
	206	8	4	8
	207	9	8	7
	210	1	1	7
	211	20	25	16
	301	3	7	8
	304	3	4	5
	306	2	1	2
	308	4	4	2
	309	2	0	4
	311	3	0	0
	331	6	6	6
	334	1	1	1
	335	2	0	0
	401	11	5	3
	408	16	0	0
	410	24	16	10
	411	16	3	12
	414	21	18	18
	415	19	6	11
	432	22	10	7
	434	33	22	19
	501	12	15	11

Sequence	Patient	Baseline	Period 1	Period 2
I→V	102	12	9	10
	104	12	8	10
	105	19	21	16
	107	10	11	12
	112	33	34	36
	202	2	3	0
	203	19	8	11
	205	40	39	39
	208	1	0	0
	209	20	21	35
	212	1	0	1
	302	2	6	6
	307	4	2	3
	312	7	4	1
	315	9	0	0
	332	4	2	4
	333	9	6	6
	402	6	5	5
	406	14	17	16
	407	8	3	0
	409	27	23	25
	412	10	6	7
	413	27	8	8
	433	7	2	0
	435	24	8	27
	502	21	18	15

$$\bar{y}_{1.1} = 10.875$$
$$\bar{y}_{1.2} = 7.917$$
$$\bar{y}_{1.3} = 7.750$$

$$B_1 = \begin{pmatrix} 1804.625 & 1162.750 & 878.250 \\ 1162.750 & 1485.833 & 1060.500 \\ 878.250 & 1060.500 & 996.500 \end{pmatrix}$$

$$\bar{y}_{2.1} = 13.385$$
$$\bar{y}_{2.2} = 10.538$$
$$\bar{y}_{2.3} = 11.269$$

$$B_2 = \begin{pmatrix} 2714.154 & 2378.615 & 2679.308 \\ 2378.615 & 2710.462 & 2782.231 \\ 2679.308 & 2782.231 & 3533.115 \end{pmatrix}$$

$$\hat{\gamma} = -1.255$$

$$\hat{\tau} = -0.056$$

$$\hat{\lambda} = -0.561$$

$$SS_1 = 11709.332$$

$$SS_2 = 1535.357$$

Using these statistics the posterior distributions derived above are as shown in Figure 5.1. In this figure (5.9),(5.10) and (5.13) are displayed.

In contrast to the analysis of Wheatley's(1987) data in §4.4 there is not a great difference between the inferences we may make about the treatment effect under the two models M_0 and M_1 ; indeed in this case $P(\tau > 0 \mid X) = 0.472$ whilst $P(\tau > 0 \mid \lambda = 0, X) = 0.713$. That this should be so is not so surprising since $P(\lambda > 0 \mid X) = 0.343$. For this particular data then it makes little difference whether one makes inferences about the treament effect, τ , under model M_0 or M_1 .

5.5 Bayes Factors - General Issues.

Whilst in this case we could again argue that because the posterior distribution of λ is a shifted and scaled t-distribution the Bayes factor against carryover will have the same form as that given by Spiegelhalter and Smith(1982) it is instructive to derive the Bayes factor directly, firstly because in subsequent sections this simple analogy will not always be available, and secondly because an issue concerning improper prior distributions has been obscured in the treatment of Bayes factors in §4.6.

We noted in §4.6 that Spiegelhalter and Smith(1982) had circumvented some problems in the use of Bayes factors in situations in which improper prior densities were used by appealing to invariance arguments. In essence they argued as follows.

Suppose that interest centres on the comparison of two nested linear models with Gaussian error structure, $M_0 \subset M_1$, and that the models are defined by,

$$y \sim N(A_i\theta_i, \sigma^2 I_n) \quad i = 0, 1,$$

where y is an n-vector of observations, A_i is a known matrix of rank p_i, θ_i is a p_i-vector of unknown parameters and σ^2 is unknown. Then if $p(\theta_i, \sigma^2 \mid A_i)$ are the prior distributions for the unknown parameters under the two models, the Bayes factor for M_0 against M_1 is,

$$B_{01} = \frac{\int\int p(y \mid A_0, \theta_0, \sigma^2 I_n) p(\theta_0, \sigma^2 \mid A_0) d\theta_0 d\sigma^2}{\int\int p(y \mid A_1, \theta_1, \sigma^2 I_n) p(\theta_1, \sigma^2 \mid A_1) d\theta_1 d\sigma^2}$$

Under the assumption that the prior distributions, $P(\theta_i, \sigma^2 \mid A_i)$, have the improper limiting version of the normal-inverse-χ^2 conjugate density written in the form,

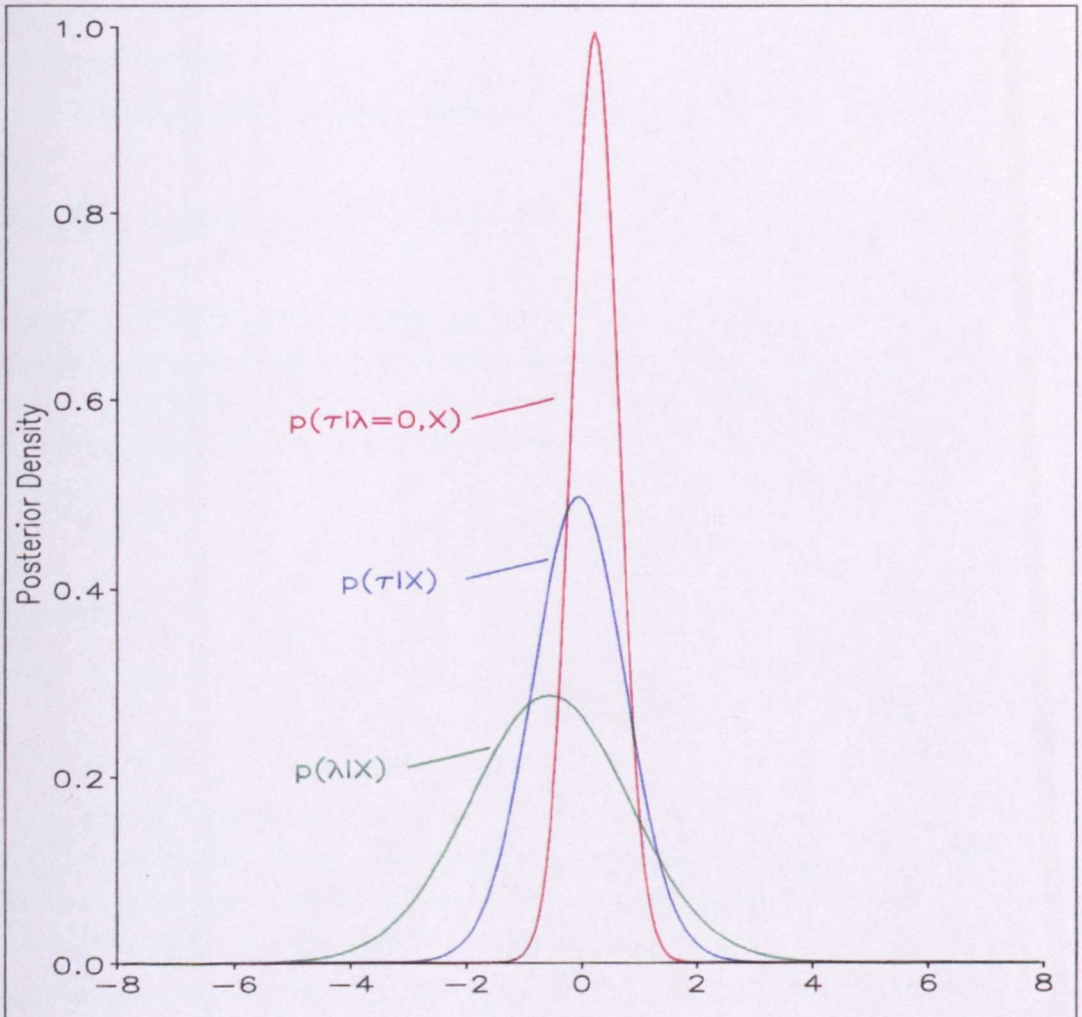


FIGURE 5.1 Posterior Distributions for the Ritchie–Index Data

$$p(\theta_i, \sigma^2 \mid M_i) = c_i(2\pi)^{-p_i/2}(\sigma^2)^{-(p_i/2+1)} \qquad (5.14)$$

where $c_i (i = 0, 1)$ are undefined constants, the Bayes factor may be written as,

$$B_{01} = \frac{c_0}{c_1}\left(\frac{|A_1'A_1|}{|A_0'A_0|}\right)^{1/2}\left[1 + \frac{(p_1 - p_0)F}{n - p_1}\right]^{-n/2} \qquad (5.15)$$

where F is the usual F-statistic for comparing M_0 and M_1. The form for the Bayes factor in (5.15) is indeterminate because of the ratio of undefined constants c_0/c_1. Spiegelhalter and Smith(1982) circumvent the problem of unknown constants by utilising Good's(1947) *imaginary training sample*.

Imagine a data set which

(i) has the minimum possible sample size allowing estimation of the parameters and thus comparison of M_0 and M_1.

(ii) provides the maximum amount of support for M_0.

The implication of (ii) is that $B_{01} > 1$, since the data indicate that M_0 is more likely than M_1. This needs to be tempered by (i) since any evidence provided by the data must needs be weak because of the small sample size, so that approximately $B_{01} \approx 1 + \epsilon$ where ϵ is small. Maximum support for M_0 leads to an F-statistic of 0 and therefore if E_0 and E_1 correspond to the design matrices in our "imaginary experiment", (5.15) gives,

$$1 + \epsilon = \frac{c_0}{c_1}\left(\frac{|E_1'E_1|}{|E_0'E_0|}\right)^{1/2}$$

implying that

$$\frac{c_0}{c_1} \approx \left(\frac{|E_1'E_1|}{|E_0'E_0|}\right)^{-1/2} \qquad (5.16)$$

Clearly the form of (5.15) is dependent upon the appropriateness or otherwise of (5.14). Spiegelhalter and Smith(1982) argue for (5.15) in preference to other forms which have been proposed because (5.15) is invariant to both linear transformations of the design matrices as well as to scale changes in the dependent variable, whereas its competitors are only invariant in the former case.

Two general issues are raised by this analysis. Firstly our model for crossover designs involves two sources of random variation, between patient and within patient, and both of these need to be taken into account when using Spiegelhalter and Smith's results. This raises no particular problems, the solution which drops out of a general analysis being a sensible partition of the total degrees of freedom into a within and a between patient component. The second issue concerns the improper prior distributions. The analysis in §4, and in this chapter too, is based on standard improper priors for the two variance components. This may be seen from (3.3) from which the prior densities for $\sigma_1^2 = \sigma^2[1 + (k-1)\rho]$ - between patients - and $\sigma_2^2 = \sigma^2(1-\rho)$ - within patients - can be derived in the form, $p(\sigma_1^2, \sigma_2^2) \propto (\sigma_1^2\sigma_2^2)^{-1}$. The essential problem, therefore, is that the Bayes factor

approach requires a different *a priori* specification than would standardly be used. Whilst this difference is of theoretical interest/importance, in practice it is likely to be of only minor significance since it will effectively only change the degrees of freedom in the posterior t-densities of the parameters of interest marginally - an additional few degrees of freedom. For this reason we have taken a pragmatic approach and have not used the Bayes factor prior densities for determining the component posterior distributions of the parameters of interest, but have used the standard one above.

5.6 Bayes Factors - General Result.

In each particular case which we consider it would be possible to calculate the Bayes factor from scratch. However, the following general result is simply derivable:

For the likelihood given in (3.1) defining the saturated model M_s and for the prior given by,

$$p(\mu_1,\mu_2,\ldots,\mu_g,\sigma^2,\rho) \propto b_s w_s (2\pi)^{-\frac{gk}{2}} (\sigma^2)^{-\left(\frac{gk}{2}+1\right)} [1+(k-1)\rho]^{-\left(\frac{g}{2}+1\right)} (1-\rho)^{-\left(\frac{g(k-1)}{2}+1\right)}$$

then

$$p(X \mid M_s) = b_s w_s \Gamma\left(\frac{N}{2}\right)\left(\frac{SS_1}{2}\right)^{-\frac{N}{2}} \Gamma\left(\frac{N(k-1)}{2}\right)\left(\frac{SS_2}{2}\right)^{-\frac{N(k-1)}{2}} \qquad (5.17)$$

For the reduced model M_r defined by,

$$C_{(t\times kg)}\begin{pmatrix}\mu_1\\ \mu_2\\ \cdot\\ \cdot\\ \cdot\\ \mu_g\end{pmatrix} = 0_{(t\times 1)}$$

and prior given by,

$$p(\mu_1,\mu_2,\ldots,\mu_g,\sigma^2,\rho) \propto b_r w_r (2\pi)^{-\frac{(gk-t)}{2}} (\sigma^2)^{-\left(\frac{gk}{2}+1\right)} [1+(k-1)\rho]^{-\left(\frac{g}{2}-t+1\right)} (1-\rho)^{-\left(\frac{g(k-1)}{2}-t+1\right)}$$

then

$$p(X \mid M_r) = b_r w_r \Gamma\left(\frac{N}{2}\right)\left(\frac{SS_1}{2}\right)^{-\frac{N}{2}} \Gamma\left(\frac{N(k-1)}{2}\right) |CDC'|^{-1/2}$$

$$\times \left(\frac{SS_2+(\bar{y}_1\bar{y}_2\ldots\bar{y}_g)C'(CDC')^{-1}C(\bar{y}_1\bar{y}_2\ldots\bar{y}_g)'}{2}\right)^{-\frac{N(k-1)}{2}} \qquad (5.18)$$

where,

$$D = \begin{pmatrix} \frac{1}{n_1} & & & \\ & \frac{1}{n_2} & & \\ & & \ddots & \\ & & & \frac{1}{n_g} \end{pmatrix} \otimes I_{k\times k}$$

5.7 Using a Bayes Factor in the Two-Period Crossover with a Single Baseline.

In the present case we may set $g = 2$ and $k = 3$ in (5.17) to give, for the saturated model, M_1 ,

$$P(X \mid M_1) = b_1 w_1 \Gamma\left(\frac{N}{2}\right)\left(\frac{SS_1}{2}\right)^{-N/2} \Gamma(N)\left(\frac{SS_2}{2}\right)^{-N} \qquad (5.19)$$

The model M_0 is defined by the contrast,

$$(-1 \quad 1/2 \quad 1/2 \quad 1 \quad -1/2 \quad -1/2)\begin{pmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{13} \\ \mu_{21} \\ \mu_{22} \\ \mu_{23} \end{pmatrix} = 0$$

so that since

$$D = \begin{pmatrix} \frac{1}{n_1} & 0 \\ 0 & \frac{1}{n_2} \end{pmatrix} \otimes \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

(5.18) gives,

$$P(X \mid M_0) = b_1 w_0 \Gamma\left(\frac{N}{2}\right)\left(\frac{SS_1}{2}\right)^{-N/2} \Gamma(N)\left(\frac{2}{3q}\right)^{1/2}\left(\frac{SS_2 + \frac{2\lambda^2}{3q}}{2}\right)^{-N} \qquad (5.20)$$

From (5.19) and (5.20) we have,

$$B_{01} = \frac{w_0}{w_1}\left(\frac{2}{3q}\right)^{1/2}\left(1 + \frac{2\lambda^2}{3qSS_2}\right)^{-N}$$

The minimum sample sizes allowing comparison of M_0 and M_1 are $n_1 = 2$, $n_2 = 1$, or vice versa, and therefore Spiegelhalter and Smith's(1982) proposal leads to,

$$1 = \frac{w_0}{w_1}\left(\frac{4}{9}\right)^{1/2}$$

which implies that

$$\frac{w_0}{w_1} = \frac{3}{2}$$

and

$$B_{01} = \left(\frac{3}{2q}\right)^{1/2}\left(1+\frac{2\hat{\lambda}^2}{3qSS_2}\right)^{-N}$$

For the data in Table 5.2,

$$q = 0.08013 \;,\; N = 50 \;,\; SS_2 = 1535.357 \;,\; \hat{\lambda} = -0.561$$

so that $B_{01} = 3.975$. As we previously noted there is little evidence to suggest that carryover has a significant influence in this data set - $P(\lambda > 0 \mid X) = 0.343$ - and this is confirmed by the Bayes factor analysis which implies that, *a priori*, one would need to believe it more than four times likelier that there was a carryover than that there was not in order that the data and prior beliefs combined indicate that it is more likely than not that there is a carryover. In other words if κ is the prior odds against a carryover effect then,

$$\kappa < 1/4 \Rightarrow P(M_1 \mid X) > \frac{1}{2}$$

Table 5.3 presents transformations of prior to posterior beliefs about the likelihood of a carryover effect in the light of the data in Table 5.2. These results confirm that the data give little evidence in favour of a carryover effect.

TABLE 5.3 Posterior Beliefs in "Carryover" for Various Prior Beliefs.

$P(M_1)$	κ	$P(M_1 \mid X)$
0.1	9	0.027
0.2	4	0.059
0.5	1	0.201
0.8	1/4	0.502
0.9	1/9	0.694

Following the analysis in §4.6 we may present inferences about the treatment effect, consequent upon assumptions concerning carryover, graphically. Figure 5.2 presents the posterior expectation of treatment effect (solid green line) and the associated 95% H.P.D. interval (dashed green line), together with the posterior probability that there is a positive treatment effect (red line) as a function of our prior belief in a carryover effect. It is clear from this figure that there is little evidence to suggest a real treatment effect irrespective of our prior beliefs in the model.

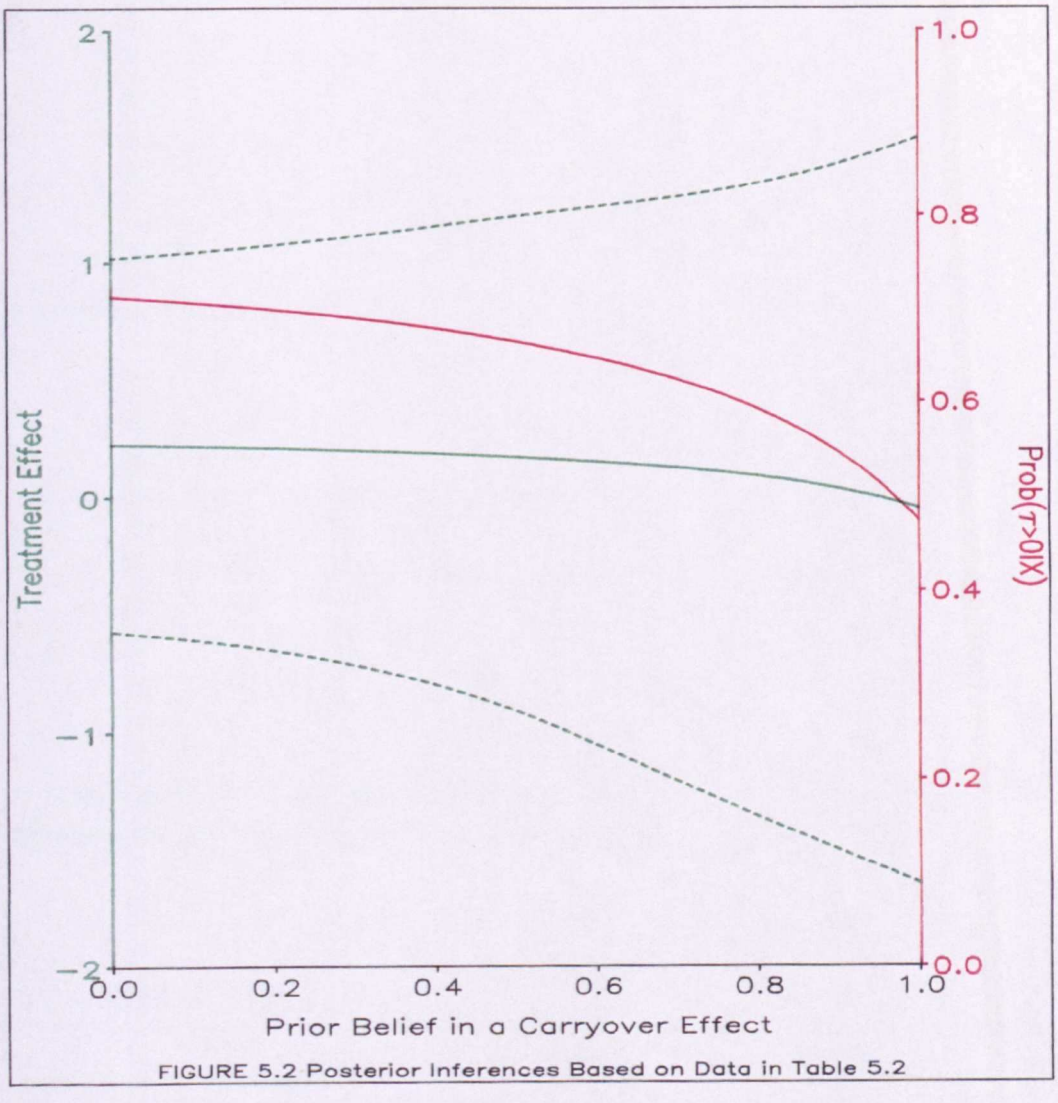


FIGURE 5.2 Posterior Inferences Based on Data in Table 5.2

6 THE TWO-PERIOD CROSSOVER WITH TWO BASELINES.

6.1 Cell Means Model.

In Section §2.8 the cell means model proposed by Kenward and Jones(1987b) was introduced - see Table 2.6. This model is a natural generalization of the model displayed in Table 5.1 for a crossover design with a single baseline.The Kenward and Jones model will be used in this section.

6.2 Basic Distributions.

The cell means model put forward by Kenward and Jones(1987b) may be put into the general framework of §3 by setting $g = 2$ and $k = 4$ and by noting that,

$$\begin{pmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{13} \\ \mu_{14} \\ \mu_{21} \\ \mu_{22} \\ \mu_{23} \\ \mu_{24} \end{pmatrix} = \begin{pmatrix} 1 & 1 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 1 & 0 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 & 0 & 1 & 0 \\ 1 & 1 & -1 & -1 & -1 & -1 & 0 & 1 \\ 1 & -1 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & 1 & 0 & -1 & 0 & 0 \\ 1 & -1 & 0 & 0 & 1 & 0 & -1 & 0 \\ 1 & -1 & -1 & -1 & -1 & 1 & 0 & -1 \end{pmatrix} \begin{pmatrix} \mu \\ \gamma \\ \pi_1 \\ \pi_2 \\ \pi_3 \\ \tau \\ \theta \\ \lambda \end{pmatrix}$$

The inverse transformation has the form,

$$\begin{pmatrix} \mu \\ \gamma \\ \pi_1 \\ \pi_2 \\ \pi_3 \\ \tau \\ \theta \\ \lambda \end{pmatrix} = \begin{pmatrix} 1/8 & 1/8 & 1/8 & 1/8 & 1/8 & 1/8 & 1/8 & 1/8 \\ 1/2 & 0 & 0 & 0 & -1/2 & 0 & 0 & 0 \\ 3/8 & -1/8 & -1/8 & -1/8 & 3/8 & -1/8 & -1/8 & -1/8 \\ -1/8 & 3/8 & -1/8 & -1/8 & -1/8 & 3/8 & -1/8 & -1/8 \\ -1/8 & -1/8 & 3/8 & -1/8 & -1/8 & -1/8 & 3/8 & -1/8 \\ -1/2 & 1/2 & 0 & 0 & 1/2 & -1/2 & 0 & 0 \\ -1/2 & 0 & 1/2 & 0 & 1/2 & 0 & -1/2 & 0 \\ -1 & 1/2 & 0 & 1/2 & 1 & -1/2 & 0 & -1/2 \end{pmatrix} \begin{pmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{13} \\ \mu_{14} \\ \mu_{21} \\ \mu_{22} \\ \mu_{23} \\ \mu_{24} \end{pmatrix} \qquad (6.1)$$

Consider the transformation (6.1) applied to (3.6) with $g = 2$ and $k = 4$. Standard properties of multivariate normal distributions allow the following conditional posterior distributions to be derived,

$$p(\gamma, \tau, \theta, \lambda \mid \sigma_1^2, \sigma_2^2, X) = N\left[\begin{pmatrix} \hat{\gamma} \\ \hat{\tau} \\ \hat{\theta} \\ \hat{\lambda} \end{pmatrix}, \frac{q}{4} \begin{pmatrix} (\sigma_1^2 + 3\sigma_2^2)/4 & -\sigma_2^2 & -\sigma_2^2 & -2\sigma_2^2 \\ -\sigma_2^2 & 2\sigma_2^2 & \sigma_2^2 & 3\sigma^2 \\ -\sigma_2^2 & \sigma_2^2 & 2\sigma_2^2 & 2\sigma^2 \\ -2\sigma_2^2 & 3\sigma_2^2 & 2\sigma_2^2 & 6\sigma_2^2 \end{pmatrix} \right] \qquad (6.2)$$

$$p(\gamma \mid \sigma_1^2, \sigma_2^2, X) \sim N(\hat{\gamma}, q(\sigma_1^2 + 3\sigma_2^2)/16) \quad (6.3)$$

$$p(\tau \mid \sigma_1^2, \sigma_2^2, X) \sim N(\hat{\tau}, q\sigma_2^2/2) \quad (6.4)$$

$$p(\theta \mid \sigma_1^2, \sigma_2^2, X) \sim N(\hat{\theta}, q\sigma_2^2/2) \quad (6.5)$$

$$p(\lambda \mid \sigma_1^2, \sigma_2^2, X) \sim N(\hat{\lambda}, 3q\sigma_2^2/2) \quad (6.6)$$

where,

$$\hat{\gamma} = (\bar{y}_{1.1} - \bar{y}_{2.1})/2$$

$$\hat{\tau} = (-\bar{y}_{1.1} + \bar{y}_{1.2} + \bar{y}_{2.1} - \bar{y}_{2.2})/2$$

$$\hat{\theta} = (-\bar{y}_{1.1} + \bar{y}_{1.3} + \bar{y}_{2.1} - \bar{y}_{2.3})/2$$

$$\hat{\lambda} = (-2\bar{y}_{1.1} + \bar{y}_{1.2} + \bar{y}_{1.4} + 2\bar{y}_{2.1} - \bar{y}_{2.2} - \bar{y}_{2.4})/2$$

and where $\sigma_1^2 = \sigma^2(1 + 3\rho)$ and, as before, $\sigma_2^2 = \sigma^2(1 - \rho)$.

Putting $g = 2$ and $k = 4$ in (3.9) gives,

$$p(\sigma_1^2, \sigma_2^2 \mid X) \propto (\sigma_1^2)^{-N/2} \exp\left(-\frac{SS_1}{2\sigma_1^2}\right)(\sigma_2^2)^{-3N/2+2} \exp\left(-\frac{SS_2}{2\sigma_2^2}\right) \quad (6.7)$$

Combining the marginal posterior distribution of σ_2^2 from (6.7) with in turn (6.4),(6.5) and (6.6) and integrating out σ_2^2 gives,

$$p(\tau \mid X) \propto \left[SS_2 + \frac{2}{q}(\tau - \hat{\tau})^2\right]^{-(3N-3)/2} \quad (6.8)$$

$$p(\theta \mid X) \propto \left[SS_2 + \frac{2}{q}(\theta - \hat{\theta})^2\right]^{-(3N-3)/2} \quad (6.9)$$

$$p(\lambda \mid X) \propto \left[SS_2 + \frac{2}{3q}(\lambda - \hat{\lambda})^2\right]^{-(3N-3)/2} \quad (6.10)$$

For this crossover design the probability of the variance component constraint is given by,

$$P(\sigma_1^2 > \sigma_2^2 \mid X) = P\left(F_{N-2,3(N-2)} < \frac{SS_1}{N-2}\frac{3(N-2)}{SS_2}\right)$$

In the previous chapters there were two models M_0 and M_1 within which it was possible to estimate the treatment effect, τ. In the current context there are four potential models within which we can estimate the treatment effect. The four models, which we denote by M_2, M_{11}, M_{12} and M_0, are defined as follows :

M_2 : saturated model

M_{11} : $\theta = 0$

M_{12} : $\lambda = 0$

M_0 : $\theta = 0$, $\lambda = 0$

From (6.2) conditional properties of multivariate normal distributions lead to,

$$p(\tau, \lambda \mid \theta, \sigma_1^2, \sigma_2^2, X) \sim N\left[\begin{pmatrix} \hat{\tau} + (\theta - \hat{\theta})/2 \\ \hat{\lambda} + (\theta - \hat{\theta}) \end{pmatrix}, \frac{q\sigma_2^2}{8}\begin{pmatrix} 3 & 4 \\ 4 & 8 \end{pmatrix}\right] \tag{6.11}$$

$$p(\tau, \theta \mid \lambda, \sigma_1^2, \sigma_2^2, X) \sim N\left[\begin{pmatrix} \hat{\tau} + (\lambda - \hat{\lambda})/2 \\ \hat{\theta} + (\lambda - \hat{\lambda})/3 \end{pmatrix}, \frac{q\sigma_2^2}{24}\begin{pmatrix} 3 & 0 \\ 0 & 8 \end{pmatrix}\right] \tag{6.12}$$

$$p(\tau \mid \lambda, \theta, \sigma_1^2, \sigma_2^2, X) \sim N(\hat{\tau} + (\lambda - \hat{\lambda})/2, q\sigma_2^2/8) \tag{6.13}$$

From (6.11),(6.12) and (6.13) the posterior densities of the treatment effect, conditional on the variance components, are

$$p(\tau \mid \theta = 0, \sigma_1^2, \sigma_2^2, X) \sim N\left(\hat{\tau} - \frac{\hat{\theta}}{2}, \frac{3q\sigma_2^2}{8}\right) \tag{6.14}$$

$$p(\tau \mid \lambda = 0, \sigma_1^2, \sigma_2^2, X) \sim N\left(\hat{\tau} - \frac{\hat{\lambda}}{2}, \frac{q\sigma_2^2}{8}\right) \tag{6.15}$$

$$p(\tau \mid \theta = 0, \lambda = 0, \sigma_1^2, \sigma_2^2, X) \sim N\left(\hat{\tau} - \frac{\hat{\lambda}}{2}, \frac{q\sigma_2^2}{8}\right) \tag{6.16}$$

under models M_{11}, M_{12} and M_0 respectively.

In Table 6.1 we summarise the conditional posterior distributions of the parameters of interest in the four models M_2, M_{11}, M_{12} and M_0. In order to derive the marginal distributions of the parameters in the various models, we need the marginal distribution of σ_2^2 under these models. Simple manipulation of (6.7),(6.11),(6.12) and (6.13) gives,

$$p(\sigma_2^2 \mid X, M_{11}) \propto (\sigma_2^2)^{-3N/2+3/2} \exp\left(-\frac{SS_2 + 2\hat{\theta}^2/q}{2\sigma_2^2}\right)$$

$$p(\sigma_2^2 \mid X, M_{12}) \propto (\sigma_2^2)^{-3N/2+3/2} \exp\left(-\frac{SS_2 + 2\hat{\lambda}^2/(3q)}{2\sigma_2^2}\right)$$

$$p(\sigma_2^2 \mid X, M_0) \propto (\sigma_2^2)^{-3N/2+2/2} \exp\left(-\frac{SS_2 + 3\hat{\theta}^2/q - 2\hat{\theta}\hat{\lambda}/q + \hat{\lambda}^2/q}{2\sigma_2^2}\right)$$

combining these posteriors with (6.14),(6.15) and (6.16) respectively, and in each case integrating out σ_2^2 gives,

TABLE 6.1 Conditional Posterior Distributions in Nested Models : $N(\alpha, \beta m \sigma_2^2)$

$M_2 : \tau, \theta, \lambda$		
τ	$\sim \hat{\tau}$,	$1/2$
θ	$\sim \hat{\theta}$,	$1/2$
λ	$\sim \hat{\lambda}$,	$3/2$

$M_{11} : \tau, \lambda(\theta = 0)$			$M_{12} : \tau, \theta(\lambda = 0)$		
τ	$\sim \hat{\tau} - \hat{\theta}/2$,	$3/8$	τ	$\sim \hat{\tau} - \hat{\lambda}/2$,	$1/8$
λ	$\sim \hat{\lambda} - \hat{\theta}$,	1	θ	$\sim \hat{\theta} - \hat{\lambda}/3$,	$1/3$

$M_0 : \tau(\theta = 0, \lambda = 0)$		
τ	$\sim \hat{\tau} - \hat{\lambda}/2$,	$1/8$

$$p(\tau \mid X, M_{11}) \propto \left[SS_2 + \frac{2\hat{\theta}^2}{q} + \frac{8}{3q}\left(\tau - \hat{\tau} + \frac{\hat{\theta}}{2}\right)^2 \right]^{-(3N-4)/2} \tag{6.17}$$

$$p(\tau \mid X, M_{12}) \propto \left[SS_2 + \frac{2\hat{\lambda}^2}{3q} + \frac{8}{q}\left(\tau - \hat{\tau} + \frac{\hat{\lambda}}{2}\right)^2 \right]^{-(3N-4)/2} \tag{6.18}$$

$$p(\tau \mid X, M_0) \propto \left[SS_2 + \frac{3\hat{\theta}^2}{q} - \frac{2\hat{\theta}\hat{\lambda}}{q} + \frac{\hat{\lambda}^2}{q} + \frac{8}{q}\left(\tau - \hat{\tau} + \frac{\hat{\theta}}{2}\right)^2 \right]^{-(3N-3)/2} \tag{6.19}$$

We may similarly derive,

$$p(\lambda \mid X, M_{11}) \propto \left[SS_2 + \frac{2\hat{\theta}^2}{q} + \frac{1}{q}(\lambda - \hat{\lambda} + \hat{\theta})^2 \right]^{-(3N-4)/2} \tag{6.20}$$

$$p(\theta \mid X, M_{12}) \propto \left[SS_2 + \frac{2\hat{\lambda}^2}{3q} + \frac{3}{q}\left(\theta - \hat{\theta} + \frac{\hat{\lambda}}{3}\right)^2 \right]^{-(3N-4)/2} \tag{6.21}$$

The distributions above allow inferences about any, or all, of the parameters of a particular model to be made, conditional of course on the assumption that the particular model is the correct one.

6.3 Preliminary Analysis of GTN Consumption DATA Taken from Nicholls *et al*(1986).

The GTN consumption data taken from Nicholls *et al*(1986) and displayed in Table 2.8 give the following summary statistics :

$$\bar{y}_{1.1} = 11.150$$
$$\bar{y}_{1.2} = 11.875$$
$$\bar{y}_{1.3} = 11.750$$
$$\bar{y}_{1.4} = 10.225$$

$$B_1 = \begin{pmatrix} 703.025 & 759.938 & 814.875 & 798.663 \\ 759.938 & 911.406 & 986.313 & 971.844 \\ 814.875 & 986.313 & 1177.125 & 1178.688 \\ 798.663 & 971.844 & 1178.688 & 1318.806 \end{pmatrix}$$

$$\bar{y}_{2.1} = 7.800$$
$$\bar{y}_{2.2} = 6.675$$
$$\bar{y}_{2.3} = 5.400$$
$$\bar{y}_{2.4} = 9.325$$

$$B_2 = \begin{pmatrix} 319.100 & 354.725 & 328.550 & 543.275 \\ 354.725 & 553.881 & 463.800 & 791.244 \\ 328.550 & 463.800 & 434.900 & 745.200 \\ 543.275 & 791.244 & 745.200 & 1304.631 \end{pmatrix}$$

from which the following may be derived:

$$\hat{\gamma} = 1.675$$
$$\hat{\tau} = 0.925$$
$$\hat{\theta} = 1.500$$
$$\hat{\lambda} = -0.300$$
$$SS_1 = 6049.275$$
$$SS_2 = 673.600$$

Using these statistics the posterior distributions derived above, namely (6.8), (6.9), (6.10), (6.17), (6.18), (6.19), (6.20) and (6.21) are as displayed in Figure 6.1.

In this instance we again face the problems associated with choosing the "correct" model for making inferences. To illustrate under models M_2, M_{11}, M_{12} and M_0 the posterior probabilities of a positive treatment effect are :

$$P(\tau > 0 \mid M_2) = 0.794$$
$$P(\tau > 0 \mid M_{11}) = 0.571$$
$$P(\tau > 0 \mid M_{12}) = 0.971$$
$$P(\tau > 0 \mid M_0) = 0.969$$

respectively. Thus the inferences which we are able to make about the treatment effect are highly dependent on the choice of the model to be used to make the inferences. Kenward and Jones(1987b) propose the following scheme :

i) Test the significance of θ - compare models M_2 and M_{11}.

ii) If θ is not significant, then test the significance of λ - i.e. compare models M_{11} and M_0. If θ is significant, inferences concerning the treatment effect, τ , may be made using model M_2.

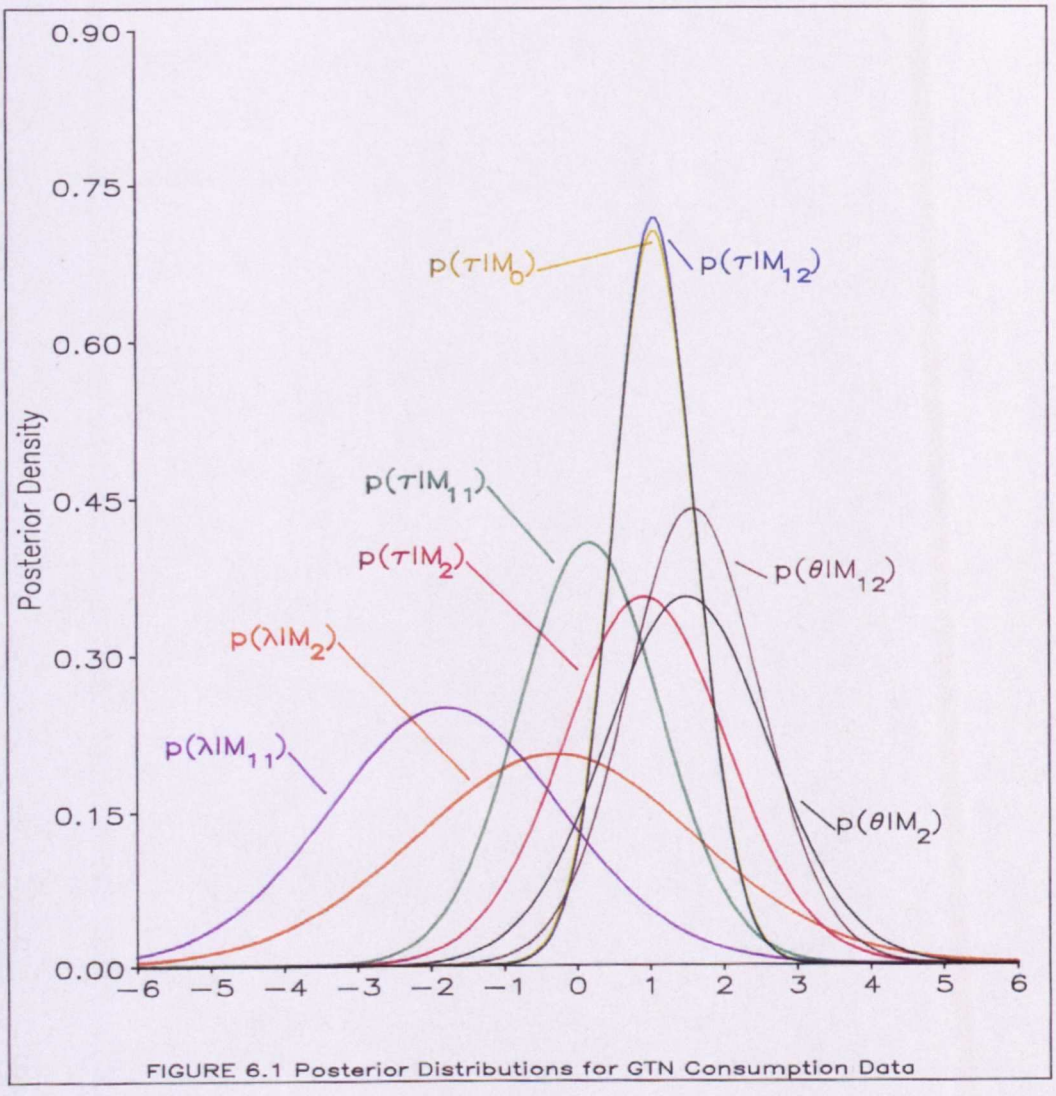


FIGURE 6.1 Posterior Distributions for GTN Consumption Data

iii) If λ is not significant, inferences concerning the treatment effect, τ , may be made using model M_0 , otherwise M_{11} should be used.

Applying this scheme to the Nicholls *et al* data would lead to the use of model M_0 for making inferences about the treatment effect. The ultimate classical inference, therefore, would estimate the treatment effect as 1.075 with associated 95% confidence interval (-0.055 , 2.205) and perhaps one would conclude that there is marginal evidence supporting a significant difference between treatments.

6.4 Using Bayes Factors in the Two-Period Crossover with a Two Baselines.

If we set $g = 2$ and $k = 4$ in (5.17) then for the saturated model M_2 we have,

$$P(X \mid M_2) = b_2 w_2 \Gamma\left(\frac{N}{2}\right)\left(\frac{SS_1}{2}\right)^{-N/2} \Gamma\left(\frac{3N}{2}\right)\left(\frac{SS_2}{2}\right)^{-3N/2} \qquad (6.22)$$

The model M_{11} is defined by the contrast,

$$(-1/2 \;\; 0 \;\; 1/2 \;\; 0 \;\; 1/2 \;\; 0 \;\; -1/2 \;\; 0)\begin{pmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{13} \\ \mu_{14} \\ \mu_{21} \\ \mu_{22} \\ \mu_{23} \\ \mu_{24} \end{pmatrix} = 0$$

so that since

$$D = \begin{pmatrix} \frac{1}{n_1} & 0 \\ 0 & \frac{1}{n_2} \end{pmatrix} \otimes \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

(5.18) gives,

$$P(X \mid M_{11}) = b_2 w_{11} \Gamma\left(\frac{N}{2}\right)\left(\frac{SS_1}{2}\right)^{-N/2} \Gamma(3N/2)\left(\frac{2}{q}\right)^{1/2}\left(\frac{SS_2 + \frac{2\hat{\theta}^2}{q}}{2}\right)^{-3N/2} \qquad (6.23)$$

From (6.22) and (6.23) we have,

$$B_{11,2} = \frac{w_{11}}{w_2}\left(\frac{2}{q}\right)^{1/2}\left(1 + \frac{2\hat{\theta}^2}{qSS_2}\right)^{-3N/2}$$

The minimum sample sizes allowing comparison of M_{11} and M_2 are $n_1 = 2$, $n_2 = 1$, or vice versa, so that Spiegelhalter and Smith's(1982) proposal leads to,

$$1 = \frac{w_{11}}{w_2}\left(\frac{4}{3}\right)^{1/2}$$

implying that

$$B_{11.2} = \left(\frac{3}{2q}\right)^{1/2}\left(1+\frac{2\hat{\theta}^2}{qSS_2}\right)^{-3N/2} \tag{6.24}$$

Similarly for the model M_{12} defined by the contrast,

$$(-1 \quad 1/2 \quad 0 \quad 1/2 \quad 1 \quad -1/2 \quad 0 \quad -1/2)\begin{pmatrix}\mu_{11}\\ \mu_{12}\\ \mu_{13}\\ \mu_{14}\\ \mu_{21}\\ \mu_{22}\\ \mu_{23}\\ \mu_{24}\end{pmatrix} = 0$$

we have,

$$B_{12.2} = \left(\frac{3}{2q}\right)^{1/2}\left(1+\frac{2\hat{\lambda}^2}{3qSS_2}\right)^{-3N/2} \tag{6.25}$$

and for the model M_0 defined by the contrast,

$$\begin{pmatrix}-1/2 & 0 & 1/2 & 0 & 1/2 & 0 & -1/2 & 0\\ -1 & 1/2 & 0 & 1/2 & 1 & -1/2 & 0 & -1/2\end{pmatrix}\begin{pmatrix}\mu_{11}\\ \mu_{12}\\ \mu_{13}\\ \mu_{14}\\ \mu_{21}\\ \mu_{22}\\ \mu_{23}\\ \mu_{24}\end{pmatrix} = \begin{pmatrix}0\\0\end{pmatrix}$$

we have,

$$B_{02} = \frac{3}{2q}\left(1+\frac{3\hat{\theta}^2-2\hat{\theta}\hat{\lambda}+\hat{\lambda}^2}{qSS_2}\right)^{-3N/2} \tag{6.26}$$

Suppose there are three models M_i, M_j and M_k in which we have interest then from the definition of Bayes factors,

$$B_{ij} = \frac{P(M_i|X)}{P(M_i)}\frac{P(M_j)}{P(M_j|X)} \quad , \quad B_{jk} = \frac{P(M_j|X)}{P(M_j)}\frac{P(M_k)}{P(M_k|X)}$$

so that clearly,

$$B_{ij}B_{jk} = \frac{P(M_i|X)}{P(M_i)}\frac{P(M_j)}{P(M_j|X)}\frac{P(M_j|X)}{P(M_j)}\frac{P(M_k)}{P(M_k|X)} = \frac{P(M_i|X)}{P(M_i)}\frac{P(M_k)}{P(M_k|X)} = B_{ik}$$

In other words Bayes factors are transitive. Using this result, and the clear fact that $B_{ij} = 1/B_{ji}$,we may derive using (6.24),(6.25) and (6.26) the following Bayes factors :

$$B_{12,11} = \left(\frac{SS_2 + 2\hat{\lambda}^2/(3q)}{SS_2 + 2\hat{\theta}^2/q}\right)^{-3N/2}$$

$$B_{0,11} = \left(\frac{3}{2q}\right)^{1/2}\left(\frac{SS_2 + 3\hat{\theta}^2/q - 2\hat{\theta}\hat{\lambda}/q + \hat{\lambda}^2/q}{SS_2 + 2\hat{\theta}^2/q}\right)^{-3N/2}$$

$$B_{0,12} = \left(\frac{3}{2q}\right)^{1/2}\left(\frac{SS_2 + 3\hat{\theta}^2/q - 2\hat{\theta}\hat{\lambda}/q + \hat{\lambda}^2/q}{SS_2 + 2\hat{\lambda}^2/(3q)}\right)^{-3N/2}$$

By definition,

$$B_{02}\kappa_{02} = \frac{P(M_0|X)}{P(M_2|X)} \quad , \quad B_{11,2}\kappa_{11,2} = \frac{P(M_{11}|X)}{P(M_2|X)} \quad , \quad B_{12,2}\kappa_{12,2} = \frac{P(M_{12}|X)}{P(M_2|X)}$$

where $\kappa_{ij} = P(M_i)/P(M_j)$ so that,

$$P(M_2|X) = \frac{1}{1 + B_{02}\kappa_{02} + B_{11,2}\kappa_{11,2} + B_{12,2}\kappa_{12,2}}$$

$$P(M_{11}|X) = \frac{B_{11,2}\kappa_{11,2}}{1 + B_{02}\kappa_{02} + B_{11,2}\kappa_{11,2} + B_{12,2}\kappa_{12,2}}$$

$$P(M_{12}|X) = \frac{B_{12,2}\kappa_{12,2}}{1 + B_{02}\kappa_{02} + B_{11,2}\kappa_{11,2} + B_{12,2}\kappa_{12,2}}$$

$$P(M_0|X) = \frac{B_{02}\kappa_{02}}{1 + B_{02}\kappa_{02} + B_{11,2}\kappa_{11,2} + B_{12,2}\kappa_{12,2}}$$

The application of the above results requires specification of either the prior odds ratios, κ_{ij} , or alternatively the prior probabilities of the individual models M_i . In §4.6 we suggested that indifference to the choice of model could be represented by $\kappa = 1$. In the present context indifference translates to $\kappa_{11,2} = \kappa_{12,2} = \kappa_{0,2} = 1$ or alternatively $P(M_2) = P(M_{11}) = P(M_{12}) = P(M_0) = 0.25$ and application of this idea to the present data gives the following :

$$B_{11,2} = 1.022$$

$$B_{12,2} = 2.702$$

$$B_{02} = 1.404$$

$$B_{12,11} = 2.644$$

$$B_{0.11} = 1.373$$

$$B_{0.12} = 0.519$$

suggesting that there is no strong evidence in favour of one particular model and this is confirmed by the posterior probabilities of the individual models :

$$P(M_2) = 0.163$$

$$P(M_{11}) = 0.167$$

$$P(M_{12}) = 0.441$$

$$P(M_0) = 0.229$$

What is interesting is that if *a priori* we are indifferent to the choice of model, the data suggest that M_{12} is the most likely. This clearly conflicts with the Kenward and Jones(1987b) approach which effectively assumes that M_0 is the "correct" model with probability 1. We can progress the analysis by calculating the unconditional posterior probability of a positive treatment effect from :

$$\begin{aligned} P(\tau > 0 \mid X) = {} & P(\tau > 0 \mid X, M_2)P(M_2 \mid X) + P(\tau > 0 \mid X, M_{11})P(M_{11} \mid X) \\ + {} & P(\tau > 0 \mid X, M_{12})P(M_{12} \mid X) + P(\tau > 0 \mid X, M_0)P(M_0 \mid X) \end{aligned} \qquad (6.27)$$

which for the present data gives $P(\tau > 0 \mid X) = 0.875$, suggesting no strong evidence that there is a difference between treatments.

It is tempting to suppose that with the calculation of the above unconditional posterior probability the analysis is complete with the exception of providing the unconditional posterior density of the treatment effect, $p(\tau \mid X)$, which is shown in Figure 6.2 together with the conditional posterior treatment densities. However, as we pointed out in §4.6, posterior beliefs about treatment effects depend on prior beliefs about the "correct" model and in order to present conclusions in a way that allows different individuals to input their own subjective beliefs we need a way of representing this dependence. In the next section we present one method of graphical representation.

6.5 Graphical Representation of the Dependence of Posterior Inference on Prior Beliefs.

Suppose that interest centres on the calculation of $P(\tau > 0 \mid X)$ and that we wish , in analogy to the analysis in §4.6, to provide a graphical display of the dependence of $P(\tau > 0 \mid X)$ on $P(M_2)$, $P(M_{11})$, $P(M_{12})$ and $P(M_0)$. In order to simplify the notation somewhat let $P_{U|X}$ denote the unconditional posterior probability $P(\tau > 0 \mid X)$; $P_{2|X}$, $P_{11|X}$, $P_{12|X}$ and $P_{0|X}$ the conditional probabilities $P(\tau > 0 \mid X, M_2)$, $P(\tau > 0 \mid X, M_{11})$, $P(\tau > 0 \mid X, M_{12})$ and $P(\tau > 0 \mid X, M_0)$ and P_2 , P_{11} , P_{12} and P_0 the prior probabilities $P(M_2)$, $P(M_0)$, $P(M_0)$ and $P(M_0)$. We may manipulate (6.27) to write it in the form,

$$P_{U|X} = \frac{P_2 P_{2|X} + B_{11.2} P_{11} P_{11|X} + B_{12.2} P_{12} P_{12|X} + B_{02} P_0 P_{0|X}}{P_2 + B_{11.2} P_{11} + B_{12.2} P_{12} + B_{02} P_0} \qquad (6.28)$$

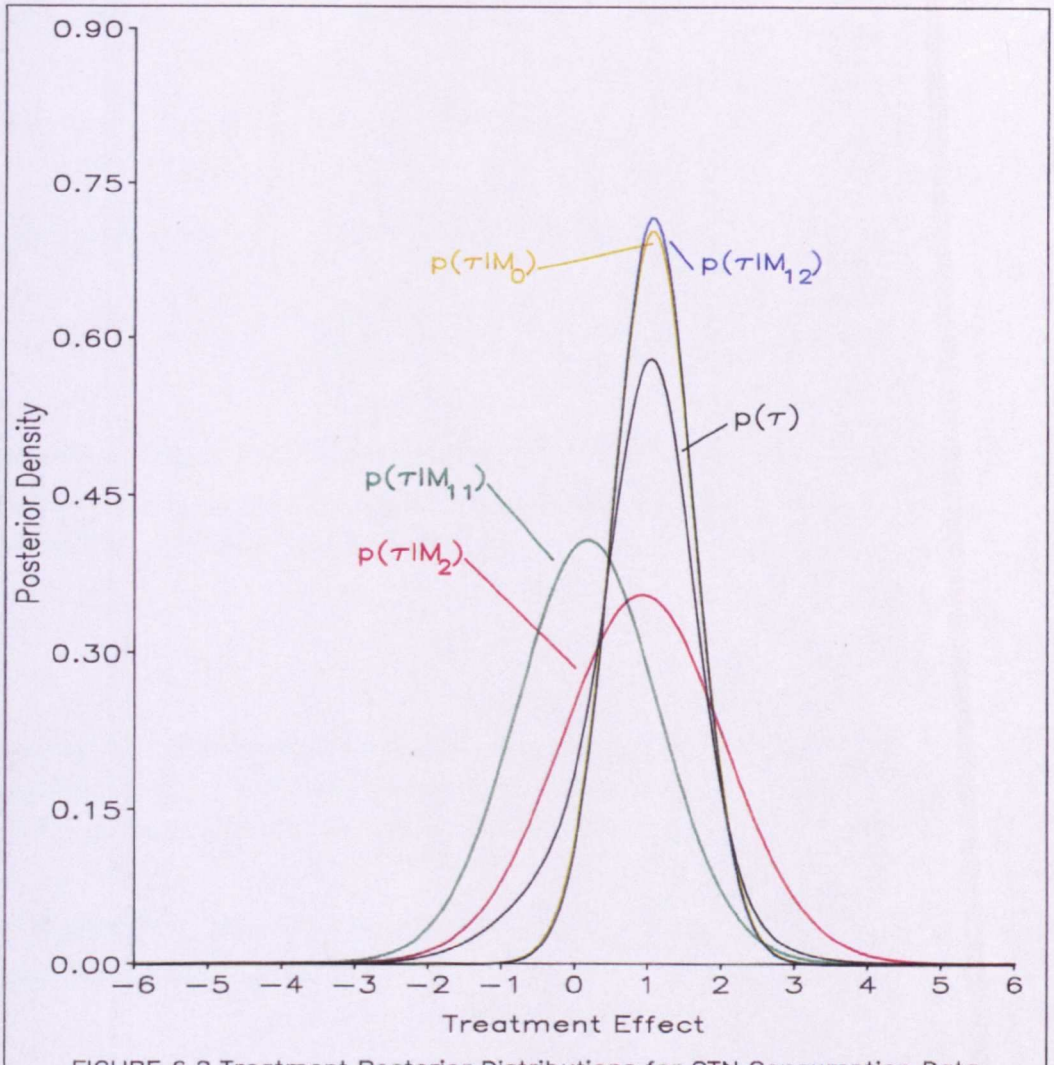


FIGURE 6.2 Treatment Posterior Distributions for GTN Consumption Data

Suppose we fix P_2, the (6.28) can be thought of as providing a means of displaying straight line contours of $P_{U|X}$ over the simplex $P_{11} + P_{12} + P_0 = 1 - P_2$. The intersection of the contours with the edges of the simplex may be derived as follows :

i) set $P_0 = 0$, $P_{12} = 1 - P_2 - P_{11}$ and solve (6.28) for P_{11} to give,

$$P_{11} = \frac{P_2(P_{2|X} - P_{U|X}) + (1 - P_2)B_{12.2}(P_{12|X} - P_{U|X})}{B_{12.2}(P_{12|X} - P_{U|X}) - B_{11.2}(P_{11|X} - P_{U|X})}$$

ii) set $P_{11} = 0$, $P_0 = 1 - P_2 - P_{12}$ and solve (6.28) for P_{12} to give,

$$P_{12} = \frac{P_2(P_{2|X} - P_{U|X}) + (1 - P_2)B_{02}(P_{0|X} - P_{U|X})}{B_{02}(P_{0|X} - P_{U|X}) - B_{12.2}(P_{12|X} - P_{U|X})}$$

iii) set $P_{12} = 0$, $P_{11} = 1 - P_2 - P_0$ and solve (6.28) for P_0 to give,

$$P_0 = \frac{P_2(P_{2|X} - P_{U|X}) + (1 - P_2)B_{11.2}(P_{11|X} - P_{U|X})}{B_{11.2}(P_{11|X} - P_{U|X}) - B_{02}(P_{0|X} - P_{U|X})}$$

If, for a given value of $P_{U|X}$, there exist values of P_2 , P_{11} , P_{12} and P_0 giving rise to this value then only two of the three above cases give the endpoints of the particular contour. Which two of the three are the correct ones may be easily found from the condition,

$$0 < P_{11}, P_{12}, P_0 < 1 - P_2$$

A graphical display of the dependence of posterior inference on prior beliefs may therefore be created by displaying contours of $P(\tau > 0 \mid X)$ on a triangular plot of the simplex $P_{11} + P_{12} + P_0 = 1 - P_2$ for a number of values of P_2. To illustrate we have used the method for the GTN consumption data taken from Nicholls *et al* (1986).

The choice of values for P_2 is essentially arbitrary although some values are clearly of interest. We have chosen for this application the following values :

$$P_2 = 0.0 \ , \ 0.25 \ , \ 0.50 \ , \ 0.75$$

Use of $P_2 = 0$ allows us to look at the case when we assume *a priori* that the saturated model is impossible whilst $P_2 = 0.25$ allows us to consider the case of indifference $P_2 = P_{11} = P_{12} = P_0$. We have purposely ignored the value $P_2 = 1$ since in this case the posterior inference which we make is simply based on $P_{2|X}$;

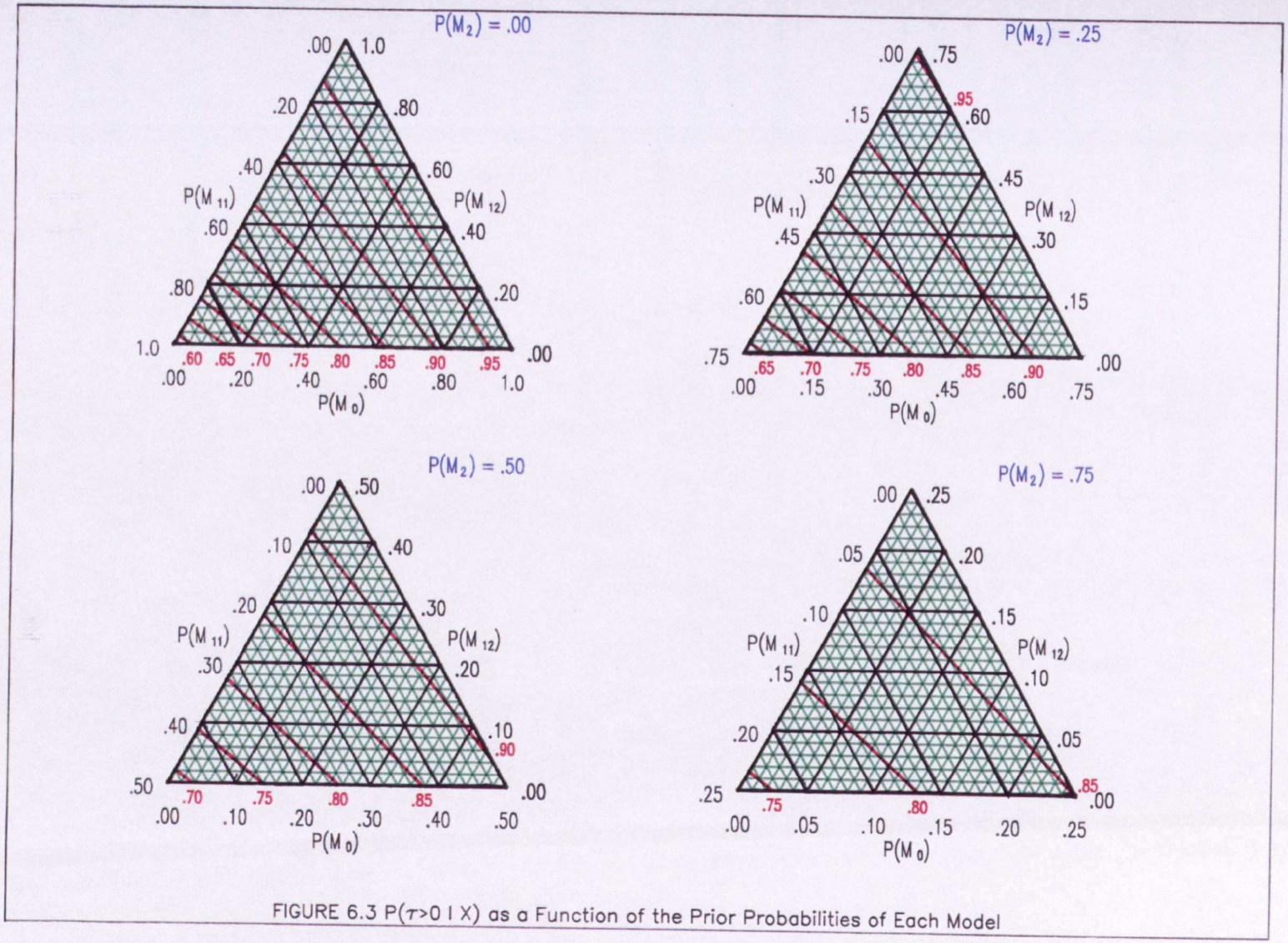


FIGURE 6.3 $P(\tau>0 \mid X)$ as a Function of the Prior Probabilities of Each Model

effectively this corresponds to the assumption that M_2 is the correct model with probability 1. As we said before, the choice of values is essentially arbitrary and the values 1/2 and 3/4 were merely chosen to span the range between indifference and certainty. Applying these ideas to the Nicholls *et al* data gives rise to the graphical display shown in Figure 6.3.

There are a couple of features of Figure 6.3 which are worthy of comment :

i) Whilst the contours are linear functions of the individual model probabilities, the separation of the contours is non-linear. This feature corresponds to the non-linear relationship between $P(\tau > 0 \mid X)$ and $P(M_1)$ shown in both Figures 4.5 and 5.1.

ii) If we are interested in posterior probabilities of a positive treatment effect greater than 0.95, then our initial prior belief in the likelihood of the saturated model M_2 must be less than 0.25, at the same time our initial prior belief in model M_{11} must be less than approximately 0.10. This requirement effectively says that we would need to be *a priori* fairly certain that there is unlikely to be a second-order carryover effect (treatment × period interaction) in order that posterior probability of positive treatment effect is high.

6.6 Analysis of Weekly Anginal Attack Data from Nicholls *et al*(1986).

Table 6.2 displays a second set of data from the study reported by Nicholls *et al*(1986). In this instance the data relate to weekly angina attack rates. The table also contains the mean vectors and matrices of corrected sums of squares and cross-products derived from the data.

From the summary statistics the following may be derived :

$$\hat{\gamma} = 2.800$$
$$\hat{\tau} = -0.650$$
$$\hat{\theta} = -0.475$$
$$\hat{\lambda} = -3.125$$
$$SS_1 = 4927.372$$
$$SS_2 = 392.216$$

The scheme proposed by Kenward and Jones(1987b) allows the following conclusions to may be made :

i) $\hat{\theta} = -0.475$, $s.e.(\hat{\theta}) = 0.852$, with associated two-sided p-value 0.5796, from which we conclude that we may reject the saturated model M_2.

TABLE 6.2 Weekly Angina Attack Rate.

Sequence	Patient	1st Period		2nd Period	
		Baseline	Treated	Baseline	Treated
TN→ISDN	1	1.00	2.00	2.00	1.25
	4	41.50	30.00	31.50	27.00
	10	20.50	20.50	21.00	25.50
	12	15.50	14.50	14.50	13.25
	14	16.00	18.00	12.50	9.00
	15	2.00	3.50	3.00	2.25
	17	10.00	9.00	7.50	5.50
	20	10.00	8.50	6.00	4.25
	22	14.00	2.00	2.00	1.25
	24	5.50	2.50	1.50	2.50
ISDN→TN	3	17.50	19.25	19.00	21.25
	5	11.00	6.50	7.50	6.50
	7	4.00	2.00	1.50	3.00
	9	11.00	16.50	10.00	18.25
	13	6.50	4.25	0.50	1.25
	16	6.00	3.25	2.00	4.00
	18	1.00	0.00	0.00	0.00
	21	3.00	0.75	3.00	5.25
	23	9.50	1.00	0.50	8.50
	25	10.50	14.00	11.00	17.25

$\bar{y}_{1.1} = 13.600$
$\bar{y}_{1.2} = 11.050$
$\bar{y}_{1.3} = 10.150$
$\bar{y}_{1.4} = 9.175$

$$B_1 = \begin{pmatrix} 1220.400 & 900.950 & 961.350 & 879.325 \\ 900.950 & 813.225 & 829.925 & 777.788 \\ 961.350 & 829.925 & 881.025 & 841.613 \\ 879.325 & 777.788 & 841.613 & 856.756 \end{pmatrix}$$

$\bar{y}_{2.1} = 8.000$
$\bar{y}_{2.2} = 6.750$
$\bar{y}_{2.3} = 5.500$
$\bar{y}_{2.4} = 8.525$

$$B_2 = \begin{pmatrix} 213.000 & 263.750 & 235.500 & 283.875 \\ 263.750 & 459.625 & 376.625 & 455.250 \\ 235.500 & 376.625 & 351.500 & 389.000 \\ 283.875 & 455.250 & 389.000 & 524.056 \end{pmatrix}$$

ii) In model M_{11} , $\hat{\lambda} = -2.650$, $s.e.(\hat{\lambda}) = 1.198$, with associated two-sided p-value 0.0311, so that we cannot reject model M_{11}.

iii) In model M_{11} , $\hat{\tau} = -0.413$, $s.e.(\hat{\tau}) = 0.733$, with associated two-sided p-value 0.5761, so that the ultimate classical conclusion is that there is no evidence of a significant treatment effect.

The Bayesian analysis is based on the posterior distributions (6.8)-(6.9) and (6.17)-(6.21) which are displayed in Figure 6.4. Inspection of this figure shows, firstly, that in both models M_2 and M_{11} there is evidence to suggest that the second order carryover, λ , is important - under M_2 the 95% H.P.D. interval for λ is (-6.085,-0.165) whilst the corresponding interval under M_{11} is (-5.050,-0.250). Secondly, treatment inferences are again highly dependent upon the model. As illustration the following posterior probabilities may be calculated :

$$P(\tau > 0 \mid M_2) = 0.225$$

$$P(\tau > 0 \mid M_{11}) = 0.288$$

$$P(\tau > 0 \mid M_{12}) = 0.979$$

$$P(\tau > 0 \mid M_0) = 0.979$$

and by implication the second order carryover, λ , determines whether one is able to conclude that there is a real treatment effect, or not.

The data give rise to the following Bayes factors:

$$B_{11.2} = 2.306$$

$$B_{12.2} = 0.250$$

$$B_{02} = 0.489$$

which, if we are indifferent to the choice of model, give

$$P(M_2) = 0.247$$

$$P(M_{11}) = 0.570$$

$$P(M_{12}) = 0.062$$

$$P(M_0) = 0.121$$

Thus under an indifference model there is much more evidence to support models including λ rather than excluding it and therefore we are led to conclude that there is no great evidence for a treatment effect, indeed the marginal probability of a positive treatment effect is 0.399.

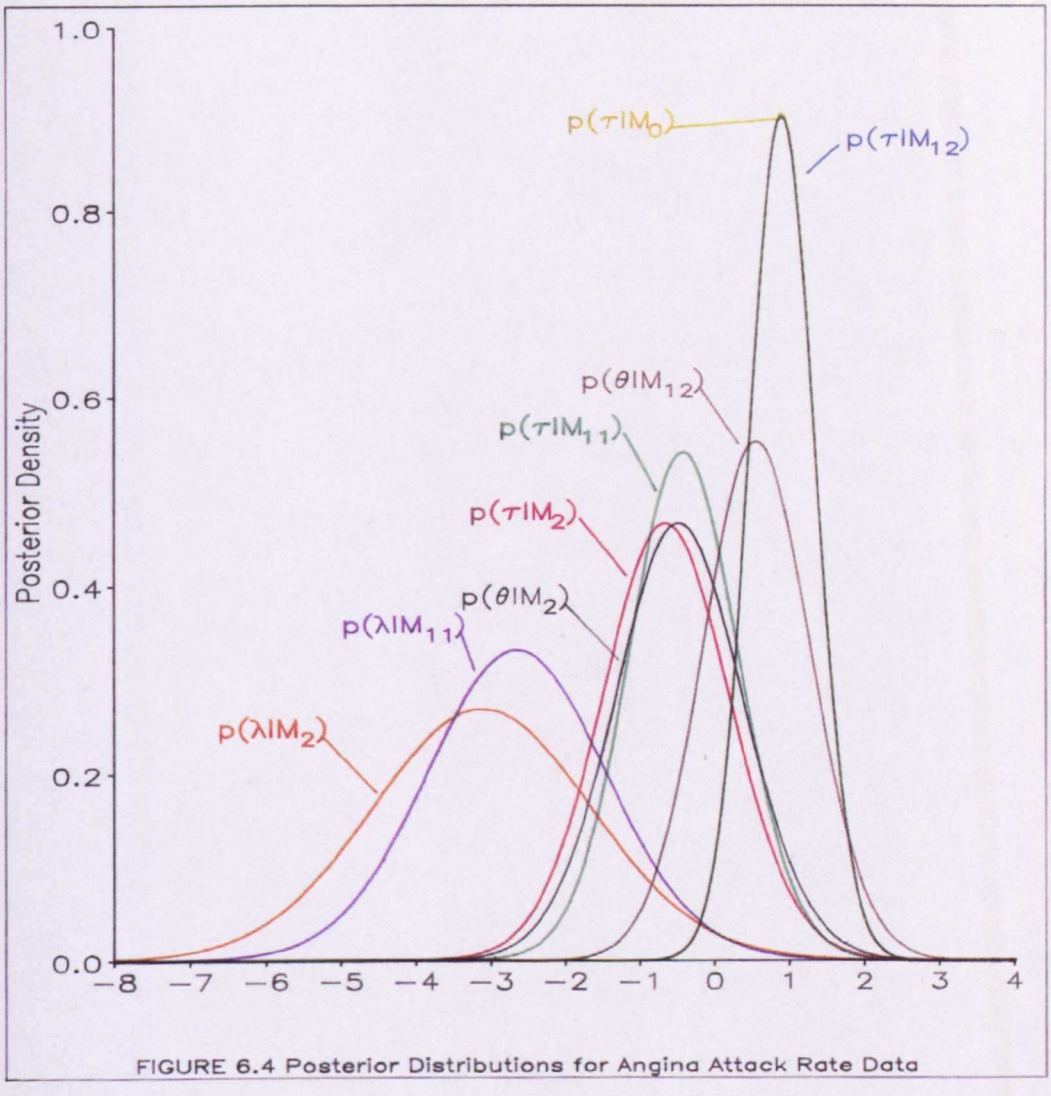


FIGURE 6.4 Posterior Distributions for Angina Attack Rate Data

Figure 6.5 provides a graphical display of the posterior distributions of the treatment effect under the models M_2, M_{11}, M_{12}, M_0 together with the marginal posterior distribution of the treatment effect under the indifference model. This latter distribution is of particular interest evidencing, as it does, the sort of shoulder described in §4.6 even though the more peaked densities are less than 1/5 as likely than the less peaked densities.

We can again provide a graphical display of the relationship between the prior model beliefs and posterior inference. This we give in Figure 6.6. It is clear from the top left-hand triangle, that is when $P(M_2) = 0$, that only when we are practically sure that λ is not in the model can we conclude that there is a real treatment effect.

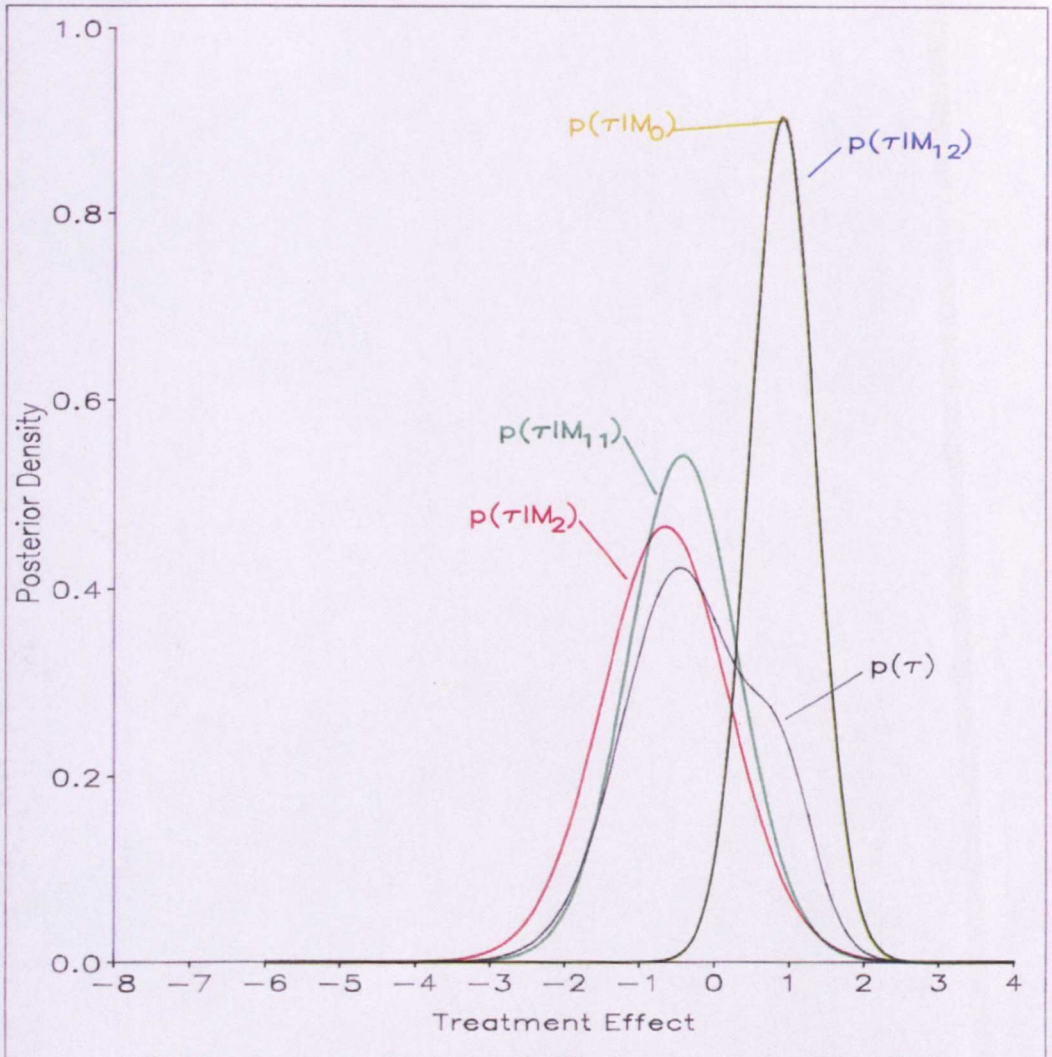


FIGURE 6.5 Treatment Posterior Distributions for Angina Attack Data

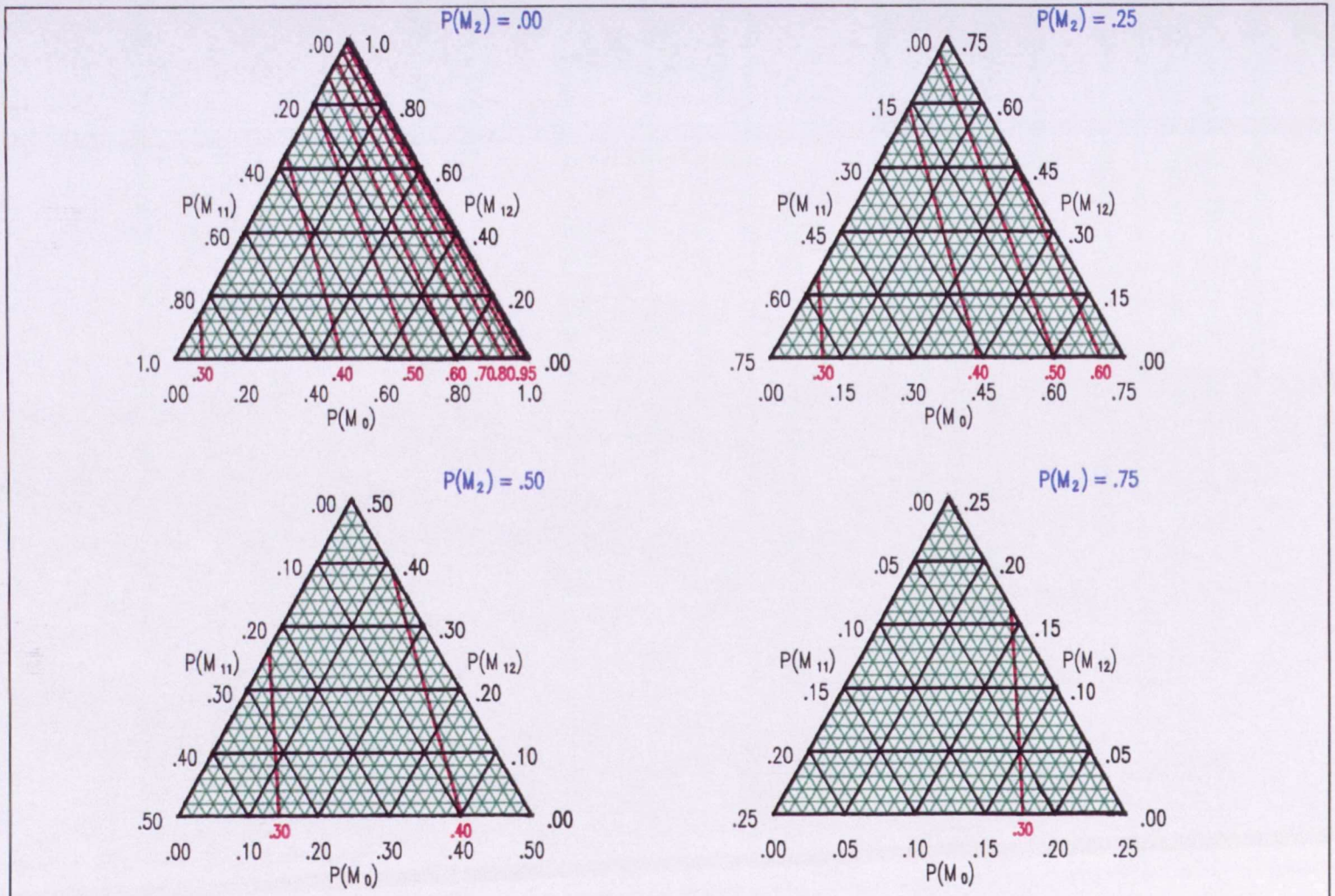


FIGURE 6.6 $P(\tau>0 \mid X)$ as a Function of the Prior Probabilities of Each Model

7 EXTRA PERIOD CROSSOVER DESIGNS.

7.1 Introduction.

In this chapter we investigate Bayesian analyses of extra-period crossover designs. These designs have been recommended by numerous authors as preferable to the simple two-period two-treatment crossover design mainly because the contaminating factor - carryover or period × treatment interaction - can be estimated within patients.

7.2 Three Period Design with Two Sequences.

We noted previously that the three-period two-treatment crossover design **ABB,BAA** is universally optimal amongst all three-period two-treatment designs and we will therefore restrict our attention to this design. In the discussion, however, we will return to other designs in the class of three-period two-treatment designs to see how, for a Bayesian, they are inferior to the above design.

7.2.1 Cell Means Model.

In §2.10.1 the cell means model considered by Kenward and Jones(1989) was introduced - see Table 2.10. In line with our parametrizations of previous models we use the cell means model shown in Table 7.1 where, as previously, γ represents the sequence effect, π_1 and π_2 independent period effects, μ the overall mean, τ the treatment effect and λ the carryover effect.

TABLE 7.1 Cell Means Model for the Design **ABB,BAA.**

Sequence Group	Periods		
	1	2	3
ABB	$\mu+\gamma+\pi_1+\tau$	$\mu+\gamma+\pi_2-\tau+\lambda$	$\mu+\gamma-\pi_1-\pi_2-\tau-\lambda$
BAA	$\mu-\gamma+\pi_1-\tau$	$\mu-\gamma+\pi_2+\tau-\lambda$	$\mu-\gamma-\pi_1-\pi_2+\tau+\lambda$

7.2.2 Basic Distributions.

By setting $g = 2$ and $k = 3$ and by noting that,

$$\begin{pmatrix}\mu_{11}\\ \mu_{12}\\ \mu_{13}\\ \mu_{21}\\ \mu_{22}\\ \mu_{23}\end{pmatrix} = \begin{pmatrix}1 & 1 & 1 & 0 & 1 & 0\\ 1 & 1 & 0 & 1 & -1 & 1\\ 1 & 1 & -1 & -1 & -1 & -1\\ 1 & -1 & 1 & 0 & -1 & 0\\ 1 & -1 & 0 & 1 & 1 & -1\\ 1 & -1 & -1 & -1 & 1 & 1\end{pmatrix}\begin{pmatrix}\mu\\ \gamma\\ \pi_1\\ \pi_2\\ \tau\\ \lambda\end{pmatrix}$$

the cell means above may be put into the general framework of §3. The inverse transformation takes the form,

$$\begin{pmatrix}\mu\\ \gamma\\ \pi_1\\ \pi_2\\ \tau\\ \lambda\end{pmatrix} = \begin{pmatrix} 1/6 & 1/6 & 1/6 & 1/6 & 1/6 & 1/6\\ 1/4 & 1/8 & 1/8 & -1/4 & -1/8 & -1/8\\ 1/3 & -1/6 & -1/6 & 1/3 & -1/6 & -1/6\\ -1/6 & 1/3 & -1/6 & -1/6 & 1/3 & -1/6\\ 1/4 & -1/8 & -1/8 & -1/4 & 1/8 & 1/8\\ 0 & 1/4 & -1/4 & 0 & -1/4 & 1/4\end{pmatrix}\begin{pmatrix}\mu_{11}\\ \mu_{12}\\ \mu_{13}\\ \mu_{21}\\ \mu_{22}\\ \mu_{23}\end{pmatrix} \qquad (7.1)$$

By applying the transformation (7.1) to (3.6) with $g = 2$ and $k = 3$. From standard properties of the normal distribution the conditional posterior distribution of the location parameters $\mu, \gamma, \pi_1, \pi_2, \tau$ and λ given σ^2 and ρ takes the form,

$$p(\mu,\gamma,\pi_1,\pi_2,\tau,\lambda \mid \sigma^2,\rho,X) = N\left[\begin{pmatrix}(\bar{y}_{1.1}+\bar{y}_{1.2}+\bar{y}_{1.3}+\bar{y}_{2.1}+\bar{y}_{2.2}+\bar{y}_{2.3})/6\\ (2\bar{y}_{1.1}+\bar{y}_{1.2}+\bar{y}_{1.3}-2\bar{y}_{2.1}-\bar{y}_{2.2}-\bar{y}_{2.3})/8\\ (2\bar{y}_{1.1}-\bar{y}_{1.2}-\bar{y}_{1.3}+2\bar{y}_{2.1}-\bar{y}_{2.2}-\bar{y}_{2.3})/6\\ (-\bar{y}_{1.1}+2\bar{y}_{1.2}-\bar{y}_{1.3}-\bar{y}_{2.1}+2\bar{y}_{2.2}-\bar{y}_{2.3})/6\\ (2\bar{y}_{1.1}-\bar{y}_{1.2}-\bar{y}_{1.3}-2\bar{y}_{2.1}+\bar{y}_{2.2}+\bar{y}_{2.3})/8\\ (\bar{y}_{1.2}-\bar{y}_{1.3}+-\bar{y}_{2.2}+\bar{y}_{2.3})/4\end{pmatrix}, \Sigma_3\right] \qquad (7.2)$$

where,

$$\Sigma_3 = \frac{\sigma^2}{96}\begin{pmatrix} 8q(1+2\rho) & 8r(1+2\rho) & 0 & 0 & 0 & 0\\ 8r(1+2\rho) & 3q(3+5\rho) & 4r(1-\rho) & -2r(1-\rho) & 3q(1-\rho) & 0\\ 0 & 4r(1-\rho) & 16q(1-\rho) & -8q(1-\rho) & 12r(1-\rho) & 0\\ 0 & -2r(1-\rho) & -8q(1-\rho) & 16(1-\rho) & -6r(1-\rho) & 12r(1-\rho)\\ 0 & 3q(1-\rho) & 12r(1-\rho) & -6r(1-\rho) & 9q(1-\rho) & 0\\ 0 & 0 & 0 & 12r(1-\rho) & 0 & 12q(1-\rho)\end{pmatrix}$$

From standard properties of multivariate normal distributions the following posterior distributions may be derived from (7.2),

$$p(\tau,\lambda \mid \sigma_1^2,\sigma_2^2,X) = N\left[\begin{pmatrix}\hat{\tau}\\ \hat{\lambda}\end{pmatrix}, \frac{q}{32}\begin{pmatrix}3\sigma_2^2 & 0\\ 0 & 4\sigma_2^2\end{pmatrix}\right] \qquad (7.3)$$

$$p(\tau \mid \sigma_1^2,\sigma_2^2,X) = N(\hat{\tau}, 3q\sigma_2^2/32) \qquad (7.4)$$

$$p(\lambda \mid \sigma_1^2,\sigma_2^2,X) = N(\hat{\lambda}, 4q\sigma_2^2/32) \qquad (7.5)$$

where

$$\hat{\tau} = (2\bar{y}_{1.1}-\bar{y}_{1.2}-\bar{y}_{1.3}-2\bar{y}_{2.1}+\bar{y}_{2.2}+\bar{y}_{2.3})/8$$

$$\hat{\lambda} = (\bar{y}_{1.2}-\bar{y}_{1.3}-\bar{y}_{2.2}+\bar{y}_{2.3})/4$$

and σ^2, q and r are as previously defined.

Setting $g = 2$ and $k = 3$ in (3.9) gives,

$$p(\sigma_1^2, \sigma_2^2 \mid X) \propto (\sigma_1^2)^{-N/2} \exp\left(-\frac{SS_1}{2\sigma_1^2}\right)(\sigma_2^2)^{-N+1} \exp\left(-\frac{SS_2}{2\sigma_2^2}\right) \tag{7.6}$$

Combining (7.6) with in turn (7.4) and (7.5) and integrating out σ_2^2 gives,

$$p(\tau \mid X) \propto \left[SS_2 + \frac{32}{3q}(\tau - \hat{\tau})^2\right]^{-(2N-3)/2} \tag{7.7}$$

$$p(\lambda \mid X) \propto \left[SS_2 + \frac{32}{4q}(\lambda - \hat{\lambda})^2\right]^{-(2N-3)/2} \tag{7.8}$$

We could at this stage proceed precisely as we did in §4 and §5 defining M_1 to be the model containing carryover and M_0 the model without carryover. However examination of (7.3) shows that τ and λ are independent, and therefore the only thing to be gained from such an analysis is an extra single degree of freedom in the posterior distribution of σ_2^2.

7.2.3 An Example of the Three-Period, Two-Treatment Crossover with Two Sequence Groups.

In Table 2.11 we presented data from a study involving anti-hypertensive treatment. The first two sequences of that design, namely L-LC-LC and LC-L-L, form precisely the design considered above and we may therefore analyse those sequences alone following the method given in §7.2.2. These data give rise to the following summary statistics,

$$\begin{aligned} \bar{y}_{1.1} &= 96.818 \\ \bar{y}_{1.2} &= 92.227 \\ \bar{y}_{1.3} &= 91.909 \end{aligned} \qquad B_1 = \begin{pmatrix} 1355.273 & 831.909 & 359.636 \\ 831.909 & 1421.864 & 732.455 \\ 359.636 & 732.455 & 1765.818 \end{pmatrix}$$

$$\begin{aligned} \bar{y}_{2.1} &= 90.333 \\ \bar{y}_{2.2} &= 91.815 \\ \bar{y}_{2.3} &= 90.630 \end{aligned} \qquad B_2 = \begin{pmatrix} 2674.000 & 1815.667 & 1887.333 \\ 1815.667 & 2528.074 & 1637.148 \\ 1887.333 & 1637.148 & 3280.296 \end{pmatrix}$$

from which the following statistics may be calculated,

$$\begin{aligned} \hat{\tau} &= 1.410 \\ \hat{\lambda} &= -0.217 \\ SS_1 &= 9184.540 \\ SS_2 &= 3840.785 \end{aligned}$$

Using these statistics the posterior distributions derived above namely (7.4) and (7.5) are as shown in Figure 7.1. The posterior distribution of the treatment effect, τ, shows that there is evidence to suggest that there is a difference between Lopressor(L) and Lopresoretic(LC) with respect to their effect on diastolic blood pressure. The posterior probability that τ is positive is 0.9931 and the posterior expected value is 1.410

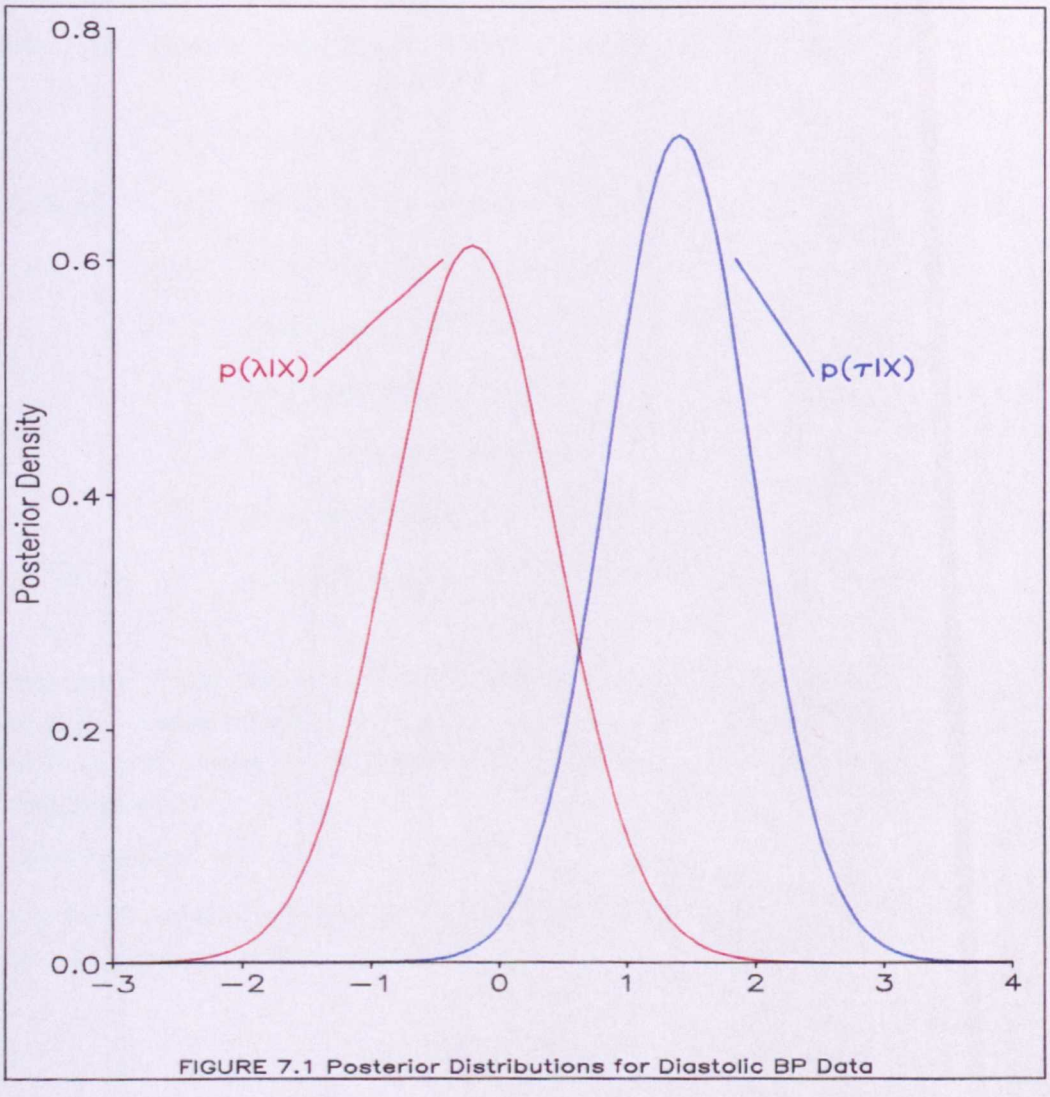


FIGURE 7.1 Posterior Distributions for Diastolic BP Data

corresponding, to Lopresoretic reducing diastolic blood pressure by approximately 3 mm Hg more than Lopressor. In contrast, the posterior distribution of the carryover effect, λ , shows little evidence of a carryover effect, although the 95% H.P.D. interval for λ is (-1.506,1.072).

7.3 Three Period Design with Four Sequences.

Ebbutt(1984) whilst acknowledging the optimality of the two-sequence three-period design considered in §7.2 argues that the four-sequence three-period design in this section is preferable a) because the latter design allows more complex models to be considered, b) the former design does not have the same treatment in consecutive periods which should highlight carryover effects most clearly and c) the former design may cause bias since investigators will know that the treatments in the last two periods are always identical.

7.3.1 Cell Means Model.

The cell means model which we consider in this chapter is shown in Table 7.2 where,

μ	-	overall mean,
γ_i $(i=1,..,3)$	-	independent sequence group effects,
π_i $(i=1,2)$	-	independent period effects,
τ	-	direct treatment effect,
λ	-	first-order carryover effect,
θ	-	second-order carryover effect,
$(\lambda\tau)$	-	interaction of direct and first-order carryover effect,
$(\gamma\pi)_i$ $(i=1,2)$	-	independent group × period interaction effects.

These last two effects are included to complete the partition of the total 12 degrees of freedom available in a three-period design with four sequences. We will, when considering basic distributions for analysing this design, condition on these effects being zero and they will thus contribute to our knowledge on the within patient variance component alone.

7.3.2 Basic Distributions.

We may place the above cell means model into the general framework developed in §3.1 by setting $g = 4$ and $k = 3$ and by noting that,

TABLE 7.2 Cell Means Model for the Design **ABB,BAA,ABA,BAB.**

Sequence Group	Periods		
	1	2	3
ABB	$\mu+\gamma_1+\pi_1+\tau-(\gamma\pi)_1$	$\mu+\gamma_1+\pi_2-\tau+\lambda-(\tau\lambda)+(\gamma\pi)_1$	$\mu+\gamma_1-\pi_1-\pi_2-\tau-\lambda+\theta+(\tau\lambda)$
BAA	$\mu+\gamma_2+\pi_1-\tau-(\gamma\pi)_2$	$\mu+\gamma_2+\pi_2+\tau-\lambda-(\tau\lambda)+(\gamma\pi)_2$	$\mu+\gamma_2-\pi_1-\pi_2+\tau+\lambda-\theta+(\tau\lambda)$
ABA	$\mu+\gamma_3+\pi_1+\tau+(\gamma\pi)_1$	$\mu+\gamma_3+\pi_2-\tau+\lambda-(\tau\lambda)-(\gamma\pi)_1$	$\mu+\gamma_3-\pi_1-\pi_2+\tau-\lambda+\theta-(\tau\lambda)$
BAB	$\mu-\gamma_1-\gamma_2-\gamma_3+\pi_1-\tau+(\gamma\pi)_2$	$\mu-\gamma_1-\gamma_2-\gamma_3+\pi_2+\tau-\lambda-(\tau\lambda)-(\gamma\pi)_2$	$\mu-\gamma_1-\gamma_2-\gamma_3-\pi_1-\pi_2-\tau+\lambda-\theta-(\tau\lambda)$

$$\begin{pmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{13} \\ \mu_{21} \\ \mu_{22} \\ \mu_{23} \\ \mu_{31} \\ \mu_{32} \\ \mu_{33} \\ \mu_{41} \\ \mu_{42} \\ \mu_{43} \end{pmatrix} = \begin{pmatrix} 1 & 1 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & -1 & 0 \\ 1 & 1 & 0 & 0 & 0 & 1 & -1 & 1 & 0 & -1 & 1 & 0 \\ 1 & 1 & 0 & 0 & -1 & -1 & -1 & -1 & 1 & 1 & 0 & 0 \\ 1 & 0 & 1 & 0 & 1 & 0 & -1 & 0 & 0 & 0 & 0 & -1 \\ 1 & 0 & 1 & 0 & 0 & 1 & 1 & -1 & 0 & -1 & 0 & 1 \\ 1 & 0 & 1 & 0 & -1 & -1 & 1 & 1 & -1 & 1 & 0 & 0 \\ 1 & 0 & 0 & 1 & 1 & 0 & 1 & 0 & 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 1 & 0 & 1 & -1 & 1 & 0 & -1 & -1 & 0 \\ 1 & 0 & 0 & 1 & -1 & -1 & 1 & -1 & 1 & -1 & 0 & 0 \\ 1 & -1 & -1 & -1 & 1 & 0 & -1 & 0 & 0 & 0 & 0 & 1 \\ 1 & -1 & -1 & -1 & 0 & 1 & 1 & -1 & 0 & -1 & 0 & -1 \\ 1 & -1 & -1 & -1 & -1 & -1 & -1 & 1 & -1 & -1 & 0 & 0 \end{pmatrix} \begin{pmatrix} \mu \\ \gamma_1 \\ \gamma_2 \\ \gamma_3 \\ \pi_1 \\ \pi_2 \\ \tau \\ \lambda \\ \theta \\ (\tau\lambda) \\ (\gamma\pi)_1 \\ (\gamma\pi)_2 \end{pmatrix}$$

whose inverse transformation has the form,

$$\begin{pmatrix} \mu \\ \gamma_1 \\ \gamma_2 \\ \gamma_3 \\ \pi_1 \\ \pi_2 \\ \tau \\ \lambda \\ \theta \\ (\tau\lambda) \\ (\gamma\pi)_1 \\ (\gamma\pi)_2 \end{pmatrix} = \frac{1}{24} \begin{pmatrix} 1 & 1 & 4 & 1 & 1 & 4 & 3 & 3 & 0 & 3 & 3 & 0 \\ 5 & -1 & -4 & 5 & -1 & -4 & 3 & -3 & 0 & 3 & -3 & 0 \\ -4 & 2 & 2 & -4 & 2 & 2 & 0 & 6 & -6 & 0 & 6 & -6 \\ 9 & 3 & 6 & -3 & 3 & -6 & 3 & -3 & -6 & -9 & -3 & 6 \\ -3 & 3 & -6 & 9 & 3 & 6 & -9 & -3 & 6 & 3 & -3 & -6 \\ -3 & -9 & 6 & -3 & 3 & -6 & 15 & 9 & -6 & -9 & -3 & 6 \\ 3 & 3 & -6 & -3 & -3 & 6 & -3 & -3 & 6 & 3 & 3 & -6 \\ 0 & 12 & -12 & 0 & -12 & 12 & -12 & 0 & 12 & 12 & 0 & -12 \\ -3 & 15 & -12 & 3 & -15 & 12 & -21 & -3 & 24 & 21 & 3 & 24 \\ -3 & -3 & 6 & -3 & -3 & 6 & 3 & 3 & -6 & 3 & 3 & -6 \\ -6 & 6 & 0 & 0 & 0 & 0 & 6 & -6 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -6 & 6 & 0 & 0 & 0 & 0 & 6 & -6 & 0 \end{pmatrix} \begin{pmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{13} \\ \mu_{21} \\ \mu_{22} \\ \mu_{23} \\ \mu_{31} \\ \mu_{32} \\ \mu_{33} \\ \mu_{41} \\ \mu_{42} \\ \mu_{43} \end{pmatrix} \tag{7.9}$$

Consider the transformation (7.9) applied to (3.6) with $g = 4$ and $k = 3$. Once again standard properties of multivariate normal distributions allow the following conditional posterior distribution to be derived,

$$p(\tau, \lambda, \theta, (\tau\lambda)(\gamma\pi)_1, (\gamma\pi)_2 \mid \sigma^2, \rho, X) = N\left[\begin{pmatrix} \hat{\tau} \\ \hat{\lambda} \\ \hat{\theta} \\ (\hat{\tau\lambda}) \\ (\hat{\gamma\pi})_1 \\ (\hat{\gamma\pi})_2 \end{pmatrix}, \Sigma_4 \right] \tag{7.10}$$

where,

$$\hat{\tau} = (\bar{y}_{1.1} + \bar{y}_{1.2} - 2\bar{y}_{1.3} - \bar{y}_{2.1} - \bar{y}_{2.2} + 2\bar{y}_{2.3} - \bar{y}_{3.1} - \bar{y}_{3.2} + 2\bar{y}_{3.3} + \bar{y}_{4.1} + \bar{y}_{4.2} - 2\bar{y}_{4.3})/8$$

$$\hat{\lambda} = (\bar{y}_{1.2} - \bar{y}_{1.3} - \bar{y}_{2.2} + \bar{y}_{2.3} - \bar{y}_{3.1} + \bar{y}_{3.3} + \bar{y}_{4.1} - \bar{y}_{4.3})/2$$

$$\hat{\theta} = (-\bar{y}_{1.1} + 5\bar{y}_{1.2} - 4\bar{y}_{1.3} + \bar{y}_{2.1} - 5\bar{y}_{2.2} + 4\bar{y}_{2.3} - 7\bar{y}_{3.1} - \bar{y}_{3.2} + 8\bar{y}_{3.3} + 7\bar{y}_{4.1} + \bar{y}_{4.2} - 8\bar{y}_{4.3})/8$$

$$(\tau\lambda) = (-\bar{y}_{1.1} - \bar{y}_{1.2} + 2\bar{y}_{1.3} - \bar{y}_{2.1} - \bar{y}_{2.2} + 2\bar{y}_{2.3} + \bar{y}_{3.1} + \bar{y}_{3.2} - 2\bar{y}_{3.3} + \bar{y}_{4.1} + \bar{y}_{4.2} - 2\bar{y}_{4.3})/8$$

$$(\gamma\hat{\pi})_1 = (-\bar{y}_{1.1} + \bar{y}_{1.2} + \bar{y}_{3.1} - \bar{y}_{3.2})/4$$

$$(\gamma\hat{\pi})_2 = (-\bar{y}_{2.1} + \bar{y}_{2.2} + \bar{y}_{4.1} - \bar{y}_{4.2})/4$$

$$\Sigma_4 = \frac{\sigma^2(1-\rho)}{32}\begin{pmatrix} 3m_1 & 6m_1 & 6m_2 & 3m_3 & 0 & 0 \\ 6m_1 & 16m_1 & 6m_4 & 6m_3 & 4m_5 & 4m_6 \\ 6m_2 & 6m_4 & 3m_7 & 6m_8 & 6m_5 & 6m_6 \\ 3m_3 & 6m_3 & 6m_8 & 3m_1 & 0 & 0 \\ 0 & 4m_5 & 6m_5 & 0 & 4m_9 & 0 \\ 0 & 4m_6 & 6m_6 & 0 & 0 & 4m_{10} \end{pmatrix}$$

$$m_1 = \frac{1}{n_1} + \frac{1}{n_2} + \frac{1}{n_3} + \frac{1}{n_4} \quad , \quad m_2 = \frac{1}{n_1} + \frac{1}{n_2} + \frac{2}{n_3} + \frac{2}{n_4}$$

$$m_3 = -\frac{1}{n_1} + \frac{1}{n_2} - \frac{1}{n_3} + \frac{1}{n_4} \quad , \quad m_4 = \frac{3}{n_1} + \frac{3}{n_2} + \frac{5}{n_3} + \frac{5}{n_4}$$

$$m_5 = \frac{1}{n_1} - \frac{1}{n_3} \quad , \quad m_6 = -\frac{1}{n_2} + \frac{1}{n_4}$$

$$m_7 = \frac{7}{n_1} + \frac{7}{n_2} + \frac{19}{n_3} + \frac{19}{n_4} \quad , \quad m_8 = -\frac{1}{n_1} + \frac{1}{n_2} - \frac{2}{n_3} + \frac{2}{n_4}$$

$$m_9 = \frac{1}{n_1} + \frac{1}{n_3} \quad , \quad m_{10} = \frac{1}{n_2} + \frac{1}{n_4}$$

Setting $g = 4$ and $k = 3$ in (3.9) gives

$$p(\sigma_1^2, \sigma_2^2 \mid X) \propto (\sigma_1^2)^{-N/2+1} \exp\left(-\frac{SS_1}{2\sigma_1^2}\right)(\sigma_2^2)^{-N+3} \exp\left(-\frac{SS_2}{2\sigma_2^2}\right) \qquad (7.11)$$

We noted previously that the effects $(\gamma\pi)_1$ and $(\gamma\pi)_2$ were of no particular importance and that we would condition on their being zero. From conditional properties of normal distributions the following distributions may be derived where we have notationally ignored that the distributions are conditional on the above two parameters being zero,

$$p(\tau,\lambda,\theta,(\tau\lambda)\,|\,\sigma_1^2,\sigma_2^2,X) = N\left[\begin{pmatrix}\hat{\tau}\\ \hat{\lambda}^*\\ \hat{\theta}^*\\ (\hat{\tau\lambda})\end{pmatrix},\frac{\sigma_2^2}{32}\begin{pmatrix}3m_1 & 6m_1 & 6m_2 & 3m_3\\ 6m_1 & 4m_{11} & 6m_{12} & 6m_3\\ 6m_2 & 6m_{12} & 3m_{13} & 6m_8\\ 3m_3 & 6m_3 & 6m_8 & 3m_1\end{pmatrix}\right] \quad (7.12)$$

$$p(\tau\,|\,\sigma_1^2,\sigma_2^2,X) = N\left(\hat{\tau},\frac{3m_1\sigma_2^2}{32}\right) \quad (7.13)$$

$$p(\lambda\,|\,\sigma_1^2,\sigma_2^2,X) = N\left(\hat{\lambda}^*,\frac{m_{11}\sigma_2^2}{8}\right) \quad (7.14)$$

$$p(\theta\,|\,\sigma_1^2,\sigma_2^2,X) = N\left(\hat{\theta}^*,\frac{3m_{13}\sigma_2^2}{32}\right) \quad (7.15)$$

$$p((\tau\lambda)\,|\,\sigma_1^2,\sigma_2^2,X) = N\left((\hat{\tau\lambda}),\frac{3m_1\sigma_2^2}{32}\right) \quad (7.16)$$

where

$$\hat{\lambda}^* = \hat{\lambda}-\frac{(n_3-n_1)(\hat{\gamma\pi})_1}{n_1+n_3}-\frac{(n_2-n_4)(\hat{\gamma\pi})_2}{n_2+n_4}$$

$$\hat{\theta}^* = \hat{\theta}-\frac{3(n_3-n_1)(\hat{\gamma\pi})_1}{2(n_1+n_3)}-\frac{3(n_2-n_4)(\hat{\gamma\pi})_2}{2(n_2+n_4)}$$

$$m_{11} = 4m_1-\frac{m_5^2}{m_9}-\frac{m_6^2}{m_{10}}$$

$$m_{12} = m_4-\frac{m_5^2}{m_9}-\frac{m_6^2}{m_{10}}$$

$$m_{13} = m_7-\frac{3m_5^2}{m_9}-\frac{3m_6^2}{m_{10}}$$

Since we have set $(\gamma\pi)_1$ and $(\gamma\pi)_2$ to zero (7.11) no longer provides the posterior distribution of σ^2 which now becomes,

$$p(\sigma_2^2\,|\,X) \propto (\sigma_2^2)^{-N+2}\exp\left(-\frac{SS_2+8(\hat{\gamma\pi})_1{}^2/m_9+8(\hat{\gamma\pi})_2{}^2/m_{10}}{2\sigma_2^2}\right) \quad (7.17)$$

Combining the marginal distribution of σ_2^2 from (7.17) with in turn (7.13),(7.14),(7.15) and (7.16) and integrating out σ_2^2 gives,

$$p(\tau\,|\,X) \propto \left[SS_2+\frac{8(\hat{\gamma\pi})_1{}^2}{m_9}+\frac{8(\hat{\gamma\pi})_2{}^2}{m_{10}}+\frac{32}{3m_1}(\tau-\hat{\tau})^2\right]^{-(2N-5)/2} \quad (7.18)$$

$$p(\lambda\,|\,X) \propto \left[SS_2+\frac{8(\hat{\gamma\pi})_1{}^2}{m_9}+\frac{8(\hat{\gamma\pi})_2{}^2}{m_{10}}+\frac{8}{m_{11}}(\lambda-\hat{\lambda}^*)^2\right]^{-(2N-5)/2} \quad (7.19)$$

$$p(\theta \mid X) \propto \left[SS_2 + \frac{8(\gamma\hat{\pi})_1^2}{m_9} + \frac{8(\gamma\hat{\pi})_2^2}{m_{10}} + \frac{32}{3m_{13}}(\theta - \hat{\theta}^*)^2 \right]^{-(2N-5)/2} \tag{7.20}$$

$$p((\tau\lambda) \mid X) \propto \left[SS_2 + \frac{8(\gamma\hat{\pi})_1^2}{m_9} + \frac{8(\gamma\hat{\pi})_2^2}{m_{10}} + \frac{32}{3m_1}((\tau\lambda) - (\tau\hat{\lambda}))^2 \right]^{-(2N-5)/2} \tag{7.21}$$

In the previous chapter there were four potential models within which the treatment effect could be estimated. In the present case we consider the following models :

M_3 : full model

M_2 : $(\tau\lambda) = 0$

M_{11} : $(\tau\lambda) = 0$, $\theta = 0$

M_{12} : $(\tau\lambda) = 0$, $\lambda = 0$

M_0 : $(\tau\lambda) = 0$, $\theta = 0$, $\lambda = 0$

Clearly there are other models which could be investigated, however considerations of marginality suggest that the above models are the only ones which need to be considered.

From (7.12) conditional properties of multivariate normal distributions lead to,

Model M_2

$$p(\tau \mid (\tau\lambda) = 0, \sigma_1^2, \sigma_2^2, X) \sim N\left(\hat{\tau}^{**}, \frac{3\sigma_2^2 m_{14}}{32 m_1}\right) \tag{7.22}$$

$$p(\lambda \mid (\tau\lambda) = 0, \sigma_1^2, \sigma_2^2, X) \sim N\left(\hat{\lambda}^{**}, \frac{4\sigma_2^2 m_{15}}{32 m_1}\right) \tag{7.23}$$

$$p(\theta \mid (\tau\lambda) = 0, \sigma_1^2, \sigma_2^2, X) \sim N\left(\hat{\theta}^{**}, \frac{3\sigma_2^2 m_{16}}{32 m_1}\right) \tag{7.24}$$

where

$$\hat{\tau}^{**} = \hat{\tau} - \frac{m_3}{m_1}(\tau\hat{\lambda})$$

$$\hat{\lambda}^{**} = \hat{\lambda}^* - \frac{2m_3}{m_1}(\tau\hat{\lambda})$$

$$\hat{\theta}^{**} = \hat{\theta}^* - \frac{2m_8}{m_1}(\tau\hat{\lambda})$$

$$m_{14} = m_1^2 - m_3^2$$

$$m_{15} = m_1 m_{11} - 3m_3^2$$

$$m_{16} = m_1 m_{13} - 4m_8^2$$

Model M_{11}

$$p(\tau \mid (\tau\lambda)=0, \theta=0, \sigma_1^2, \sigma_2^2, X) \sim N\left(\hat{\tau}^{***}, \frac{3\sigma_2^2 m_{17}}{32 m_1}\right) \quad (7.25)$$

$$p(\lambda \mid (\tau\lambda)=0, \theta=0, \sigma_1^2, \sigma_2^2, X) \sim N\left(\hat{\lambda}^{***}, \frac{\sigma_2^2 m_{18}}{8 m_1}\right) \quad (7.26)$$

where

$$\tau^{***} = \tau^{**} - 2\frac{m_1 m_2 - m_3 m_8}{m_1 m_{13} - 4m_8^2}\theta^{**}$$

$$\lambda^{***} = \lambda^{**} - 2\frac{m_1 m_{12} - 2m_3 m_8}{m_1 m_{13} - 4m_8^2}\theta^{**}$$

$$m_{17} = m_1^2 - m_3^2 - \frac{4(m_1 m_2 - m_3 m_8)^2}{m_1 m_{13} - 4m_8^2}$$

$$m_{18} = m_1 m_{11} - 3m_3^2 - \frac{3(m_1 m_{12} - 2m_3 m_8)^2}{m_1 m_{13} - 4m_8^2}$$

Model M_{12}

$$p(\tau \mid (\tau\lambda)=0, \lambda=0, \sigma_1^2, \sigma_2^2, X) \sim N\left(\hat{\tau}^{****}, \frac{3\sigma_2^2 m_{19}}{32 m_1}\right) \quad (7.27)$$

$$p(\theta \mid (\tau\lambda)=0, \lambda=0, \sigma_1^2, \sigma_2^2, X) \sim N\left(\hat{\theta}^{***}, \frac{3\sigma_2^2 m_{20}}{32 m_1}\right) \quad (7.28)$$

where

$$\tau^{****} = \tau^{**} - \frac{3}{2}\frac{m_1^2 - m_3^2}{m_1 m_{11} - 3m_3^2}\lambda^{**}$$

$$\theta^{***} = \theta^{**} - \frac{3}{2}\frac{m_1 m_{12} - 2m_3 m_8}{m_1 m_{11} - 3m_3^2}\lambda^{**}$$

$$m_{19} = m_1^2 - m_3^2 - \frac{3(m_1^2 - m_3^2)^2}{m_1 m_{11} - 3m_3^2}$$

$$m_{20} = m_1 m_{13} - 4m_8^2 - \frac{3(m_1 m_{12} - 2m_3 m_8)^2}{m_1 m_{11} - 3m_3^2}$$

Model M_0

$$p(\tau \mid (\tau\lambda)=0, \lambda=0, \theta=0, \sigma_1^2, \sigma_2^2, X) \sim N\left(\hat{\tau}^{*****}, \frac{3m_{21}\sigma_2^2}{32 m_1 (m_1 m_{11} - 3m_3^2)}\right) \quad (7.29)$$

where

$$\tau^{\cdots\cdots} = \tau^{\cdots\cdot} - \frac{2(m_1m_2 - m_3m_8)(m_1m_{11} - 3m_3^2) - 3(m_1^2 - m_3^2)(m_1m_{12} - 2m_3m_8)}{(m_1m_{13} - 4m_8^2)(m_1m_{11} - 3m_3^2) - 3(m_1m_{12} - 2m_3m_8)^2}\theta^{\cdots\cdot}$$

$$m_{21} = (m_1^2 - m_3^2)(m_1m_{11} - 3m_3^2) - 3(m_1^2 - m_3^2)^2 - \frac{3(2(m_1m_2 - m_3m_8)(m_1m_{11} - 3m_3^2) - 3(m_1^2 - m_3^2)(m_1m_{12} - 2m_3m_8))^2}{((m_1m_{13} - 4m_8^2)(m_1m_{11} - 3m_3^2) - 3(m_1m_{12} - 2m_3m_8)^2)(m_1m_{11} - 3m_3^2)}$$

The posterior distribution of σ_2^2 depends upon the particular model considered. Under M_3 the posterior distribution of σ_2^2 is given by (7.17) while the remaining cases are as follows :

$$M_2: p(\sigma_2^2 \mid X) \propto (\sigma_2^2)^{-N+3/2} \exp\left\{-\frac{1}{2\sigma_2^2}\left[SS_2 + \frac{8(\gamma\hat{\pi})_1^2}{m_9} + \frac{8(\gamma\hat{\pi})_2^2}{m_{10}} + \frac{32(\tau\hat{\lambda})^2}{3m_1}\right]\right\} \tag{7.30}$$

$$M_{11}: p(\sigma_2^2 \mid X) \propto (\sigma_2^2)^{-N+1} \exp\left\{-\frac{1}{2\sigma_2^2}\left[SS_2 + \frac{8(\gamma\hat{\pi})_1^2}{m_9} + \frac{8(\gamma\hat{\pi})_2^2}{m_{10}} + \frac{32(\tau\hat{\lambda})^2}{3m_1} + \frac{32m_1(\theta^{\cdot\cdot})^2}{3(m_1m_{13} - 4m_8^2)}\right]\right\} \tag{7.31}$$

$$M_{12}: p(\sigma_2^2 \mid X) \propto (\sigma_2^2)^{-N+1} \exp\left\{-\frac{1}{2\sigma_2^2}\left[SS_2 + \frac{8(\gamma\hat{\pi})_1^2}{m_9} + \frac{8(\gamma\hat{\pi})_2^2}{m_{10}} + \frac{32(\tau\hat{\lambda})^2}{3m_1} + \frac{32m_1(\lambda^{\cdot\cdot})^2}{4(m_1m_{11} - 3m_3^2)}\right]\right\} \tag{7.32}$$

$$M_0: p(\sigma_2^2 \mid X) \propto (\sigma_2^2)^{-N+1/2} \exp\left\{-\frac{1}{2\sigma_2^2}\left[SS_2 + \frac{8(\gamma\hat{\pi})_1^2}{m_9} + \frac{8(\gamma\hat{\pi})_2^2}{m_{10}} + \frac{32(\tau\hat{\lambda})^2}{3m_1} + \frac{32m_1(\theta^{\cdot\cdot})^2}{3(m_1m_{13} - 4m_8^2)}\right]\right\}$$
$$\left\{\left[+\frac{32m_1(\lambda^{\cdot\cdot\cdot})^2}{4(m_1m_{11} - 3m_3^2) - 12(m_1m_{12} - 2m_3m_8)^2/(m_1m_{13} - 4m_8^2)}\right]\right\} \tag{7.33}$$

Under M_2 the posterior distributions of τ, λ and θ may be obtained by combining respectively (7.22), (7.23) and (7.24) with (7.30) and integrating out σ_2^2 each giving a t-kernel. Likewise, under M_{11} (7.25) and (7.26) are combined with (7.31) to give the posterior distributions of τ and λ respectively; under M_{12} (7.27) and (7.28) are combined with (7.32) to give the posterior distributions of τ and θ respectively; under M_0 (7.29) is combined with (7.33) to give the posterior distribution of τ.

Before applying these results to the complete data in Table 2.11 it is instructive to consider the case of equal n_i. Suppose, therefore, that $n_1 = n_2 = n_3 = n_4 = n$, then conditional on knowing the variance components the marginal posterior distributions of the effects in each of the models M_3, M_2, M_{11}, M_{12} and M_0 are, in a similar notation to that of Table 6.11, as given in Table 7.3.

The fact that the posterior distributions of τ, λ and θ under models M_3 and M_2 are identical reflects the fact that the effects $(\gamma\pi)_1$ and $(\gamma\pi)_2$ are orthogonal to the other effects in the full model as pointed out by Jones and Kenward(1989,§4.8). The remaining results in Table 7.3 are also to be found in §4.8 of Jones and Kenward(1989).

TABLE 7.3 Conditional Posterior Distributions in Nested Models : $N(\alpha, \beta\sigma_2^2/n)$

Model	Effect	α	β
M_3	τ	$\hat{\tau}$	3/8
	λ	$\hat{\lambda}$	2
	θ	$\hat{\theta}$	39/8
	$(\tau\lambda)$	$(\tau\lambda)$	3/8
M_2	τ	$\hat{\tau}$	3/8
	λ	$\hat{\lambda}$	2
	θ	$\hat{\theta}$	39/8
M_{11}	τ	$\hat{\tau}-3\hat{\theta}/13$	3/26
	λ	$\hat{\lambda}-8\hat{\theta}/13$	2/13
M_{12}	τ	$\hat{\tau}-3\hat{\lambda}/8$	3/32
	θ	$\hat{\theta}-3\hat{\lambda}/2$	3/8
M_0	τ	$\hat{\tau}-3\hat{\lambda}/8$	3/32

7.3.3 Preliminary Analysis of the Data Displayed in Table 2.11.

The diastolic blood pressure data given in Table 2.11 give rise to the following summary statistics :

$$\bar{y}_{1.1} = 96.818$$
$$\bar{y}_{1.2} = 92.227$$
$$\bar{y}_{1.3} = 91.909$$
$$\bar{y}_{3.1} = 90.333$$
$$\bar{y}_{3.2} = 91.815$$
$$\bar{y}_{3.3} = 90.630$$
$$\bar{y}_{3.1} = 93.304$$
$$\bar{y}_{3.2} = 89.739$$
$$\bar{y}_{3.3} = 92.087$$
$$\bar{y}_{4.1} = 90.941$$
$$\bar{y}_{4.2} = 88.412$$
$$\bar{y}_{4.3} = 86.235$$

$$B_1 = \begin{pmatrix} 1355.273 & 831.909 & 359.636 \\ 831.909 & 1421.864 & 732.455 \\ 359.636 & 732.455 & 1765.818 \end{pmatrix}$$

$$B_2 = \begin{pmatrix} 2674.000 & 1815.667 & 1887.333 \\ 1815.667 & 2528.074 & 1637.148 \\ 1887.333 & 1637.148 & 3280.296 \end{pmatrix}$$

$$B_3 = \begin{pmatrix} 2484.870 & 2177.826 & 1595.391 \\ 2177.826 & 3084.435 & 1298.522 \\ 1595.391 & 1298.522 & 2233.826 \end{pmatrix}$$

$$B_4 = \begin{pmatrix} 2220.941 & 1008.412 & 1257.235 \\ 1008.412 & 1384.118 & 949.353 \\ 1257.235 & 949.353 & 1335.059 \end{pmatrix}$$

from which the following may be derived :

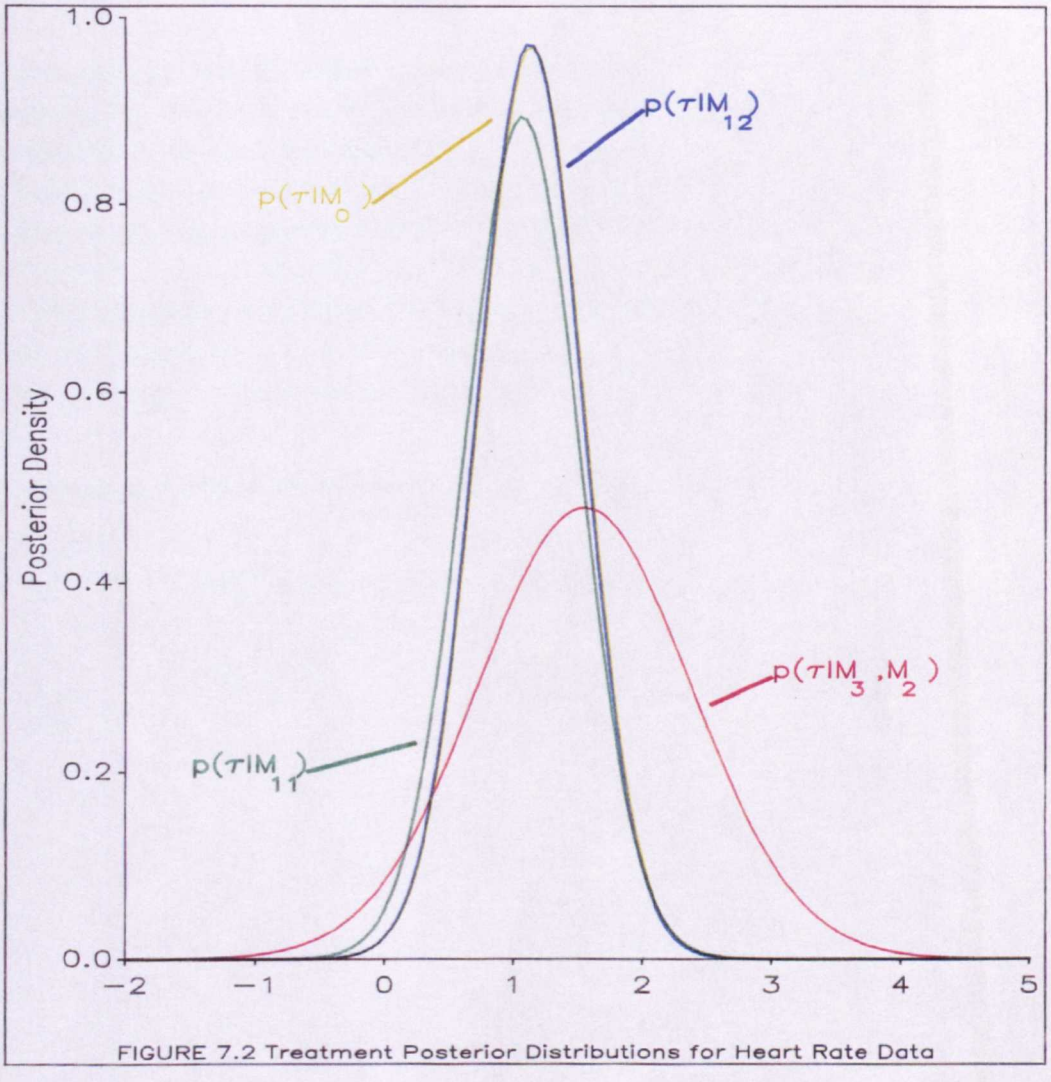


FIGURE 7.2 Treatment Posterior Distributions for Heart Rate Data

$$
\begin{aligned}
\hat{\tau} &= 1.544 \\
\hat{\lambda} &= 1.311 \\
\hat{\theta} &= 2.425 \\
(\tau\hat{\lambda}) &= -0.046 \\
(\gamma\hat{\pi})_1 &= -0.256 \\
(\gamma\hat{\pi})_2 &= 1.003 \\
SS_1 &= 18963.449 \\
SS_2 &= 6825.124
\end{aligned}
$$

At this juncture we could, as in §6.3 and §6.6, display posterior distributions for all of the parameters in each of the models M_3, M_2, M_{11}, M_{12} and M_0, and that is clearly appropriate for the purpose of assessing the likely importance of the nuisance parameters λ, θ and $(\tau\lambda)$. Accepting the importance of such a display, here we will only display the posterior distributions of the treatment effect, τ, under each model as the treatment effect is generally of primary interest. The posterior distribution (7.18), and those derived from (7.22) and (7.30), (7.25) and (7.31), (7.27) and (7.32) and (7.29) and (7.33) are shown in Figure 7.2. The posterior distributions displayed in Figure 7.2 clearly demonstrate that inferences concerning τ are dependent upon whether $(\tau\lambda)$ and either λ or θ may be assumed to be negligible or not, although it should be noted that under any of the models there is evidence of a positive treatment effect. In general this will not always be the case.

7.3.4 Bayes Factors in the Three-Period Two-Treatment Crossover with Four Sequence Groups.

If we set $g = 4$ and $k = 3$ in (5.7) then since the model M_3 is determined by the contrast,

$$
C = \frac{1}{4}\begin{pmatrix} -1 & 1 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & 1 & 0 & 0 & 0 & 0 & 1 & -1 & 0 \end{pmatrix}
$$

and since

$$
D = \begin{pmatrix} \frac{1}{n_1} & 0 & 0 & 0 \\ 0 & \frac{1}{n_2} & 0 & 0 \\ 0 & 0 & \frac{1}{n_3} & 0 \\ 0 & 0 & 0 & \frac{1}{n_4} \end{pmatrix} \otimes \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}
$$

(5.18) gives

$$P(X \mid M_3) = b_3 w_3 \Gamma\left(\frac{N}{2}\right)\left(\frac{SS_1}{2}\right)^{-N/2}\Gamma\left(\frac{3N}{2}\right)$$

$$\times (m_9 m_{10}/64)^{-1/2}\left(\frac{1}{2}\left[SS_2 + \frac{8(\gamma\hat{\pi})_1^2}{m_9} + \frac{8(\gamma\hat{\pi})_2^2}{m_{10}}\right]\right)^{-3N/2} \qquad (7.34)$$

Similarly M_2 is defined by

$$C = \frac{1}{8}\begin{pmatrix} -1 & -1 & 2 & -1 & -1 & 2 & 1 & 1 & -2 & 1 & 1 & -2 \\ -2 & 2 & 0 & 0 & 0 & 0 & 2 & -2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -2 & 2 & 0 & 0 & 0 & 0 & 2 & -2 & 0 \end{pmatrix}$$

so that from (5.18)

$$P(X \mid M_2) = b_3 w_2 \Gamma\left(\frac{N}{2}\right)\left(\frac{SS_1}{2}\right)^{-N/2}\Gamma\left(\frac{3N}{2}\right)$$

$$\times (48 m_1 m_9 m_{10}/32^3)^{-1/2}\left(\frac{1}{2}\left[SS_2 + \frac{8(\gamma\hat{\pi})_1^2}{m_9} + \frac{8(\gamma\hat{\pi})_2^2}{m_{10}} + \frac{32(\tau\hat{\lambda})^2}{3m_1}\right]\right)^{-3N/2} \qquad (7.35)$$

M_{11} is defined by

$$C = \frac{1}{8}\begin{pmatrix} -1 & 5 & -4 & 1 & -5 & 4 & -7 & -1 & 8 & 7 & 1 & -8 \\ -1 & -1 & 2 & -1 & -1 & 2 & 1 & 1 & -2 & 1 & 1 & -2 \\ -2 & 2 & 0 & 0 & 0 & 0 & 2 & -2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -2 & 2 & 0 & 0 & 0 & 0 & 2 & -2 & 0 \end{pmatrix}$$

so that from (5.18)

$$P(X \mid M_{11}) = b_3 w_{11} \Gamma\left(\frac{N}{2}\right)\left(\frac{SS_1}{2}\right)^{-N/2}\Gamma\left(\frac{3N}{2}\right)$$

$$\times (48 m_1 m_9 m_{10}/32^3)^{-1/2}\left[\frac{3m_7}{32} - \frac{1}{32}\left(\frac{12m_8^2}{m_1} + \frac{9m_5^2}{m_9} + \frac{9m_6^2}{m_{10}}\right)\right]^{-1/2}$$

$$\times\left(\frac{1}{2}\left[SS_2 + \frac{8(\gamma\hat{\pi})_1^2}{m_9} + \frac{8(\gamma\hat{\pi})_2^2}{m_{10}} + \frac{32(\tau\hat{\lambda})^2}{3m_1} + \frac{32m_1(\theta^{**})^2}{3(m_1 m_{13} - 4m_8^2)}\right]\right)^{-3N/2} \qquad (7.36)$$

M_{12} is defined by

$$C = \frac{1}{24}\begin{pmatrix} 0 & 4 & -4 & 0 & -4 & 4 & -4 & 0 & 4 & 4 & 0 & -4 \\ -3 & -3 & 6 & -3 & -3 & 6 & 3 & 3 & -6 & 3 & 3 & -6 \\ -6 & 6 & 0 & 0 & 0 & 0 & 6 & -6 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -6 & 6 & 0 & 0 & 0 & 0 & 6 & -6 & 0 \end{pmatrix}$$

so that from (5.18)

$$P(X \mid M_{12}) = b_3 w_{12} \Gamma\left(\frac{N}{2}\right)\left(\frac{SS_1}{2}\right)^{-N/2} \Gamma\left(\frac{3N}{2}\right)$$

$$\times (48 m_1 m_9 m_{10}/32^3)^{-1/2}\left[\frac{16m_1}{32} - \frac{1}{32}\left(\frac{12m_3^2}{m_1} + \frac{4m_5^2}{m_9} + \frac{4m_6^2}{m_{10}}\right)\right]^{-1/2}$$

$$\times\left(\frac{1}{2}\left[SS_2 + \frac{8(\gamma\hat{\pi})_1^2}{m_9} + \frac{8(\gamma\hat{\pi})_2^2}{m_{10}} + \frac{32(\tau\hat{\lambda})^2}{3m_1} + \frac{32m_1(\lambda^{**})^2}{4(m_1 m_{11} - 3m_3^2)}\right]\right)^{-3N/2} \tag{7.37}$$

M_0 is defined by

$$C = \frac{1}{24}\begin{pmatrix} 0 & 4 & -4 & 0 & -4 & 4 & -4 & 0 & 4 & 4 & 0 & -4 \\ -3 & 15 & -12 & 3 & -15 & 12 & -21 & -3 & 24 & 21 & 3 & -24 \\ -3 & -3 & 6 & -3 & -3 & 6 & 3 & 3 & -6 & 3 & 3 & -6 \\ -6 & 6 & 0 & 0 & 0 & 0 & 6 & -6 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -6 & 6 & 0 & 0 & 0 & 0 & 6 & -6 & 0 \end{pmatrix}$$

so that from (5.18)

$$P(X \mid M_0) = b_3 w_0 \Gamma\left(\frac{N}{2}\right)\left(\frac{SS_1}{2}\right)^{-N/2} \Gamma\left(\frac{3N}{2}\right)$$

$$\times (48 m_1 m_9 m_{10}/32^3)^{-1/2}\left|\frac{1}{32}\begin{pmatrix} 16m_1 - \frac{12m_3^2}{m_1} - \frac{4m_5^2}{m_9} - \frac{4m_6^2}{m_{10}} & 6m_4 - \frac{12m_3 m_8}{m_1} - \frac{6m_5^2}{m_9} - \frac{6m_6^2}{m_{10}} \\ 6m_4 - \frac{12m_3 m_8}{m_1} - \frac{6m_5^2}{m_9} - \frac{6m_6^2}{m_{10}} & 3m_7 - \frac{12m_8^2}{m_1} - \frac{4m_5^2}{m_9} - \frac{4m_6^2}{m_{10}} \end{pmatrix}\right|^{-1/2}$$

$$\times\left(\frac{1}{2}\left[SS_2 + \frac{8(\gamma\hat{\pi})_1^2}{m_9} + \frac{8(\gamma\hat{\pi})_2^2}{m_{10}} + \frac{32(\tau\hat{\lambda})^2}{3m_1} + \frac{32m_1(\theta^{**})^2}{3(m_1 m_{13} - 4m_8^2)}\right.\right.$$

$$\left.\left. + \frac{32m_1(\lambda^{***})^2}{4(m_1 m_{11} - 3m_3^2) - 12(m_1 m_{12} - 2m_3 m_8)^2/(m_1 m_{13} - 4m_8^2)}\right]\right)^{-3N/2} \tag{7.38}$$

From (7.34) and (7.35) we have

$$B_{23} = \frac{w_2}{w_3}\left(\frac{32}{3m_1}\right)^{1/2}\left[1 + \frac{32(\tau\hat{\lambda})^2}{3m_1\left\{SS_2 + \frac{8(\gamma\hat{\pi})_1^2}{m_9} + \frac{8(\gamma\hat{\pi})_2^2}{m_{10}}\right\}}\right]^{-3N/2} \tag{7.39}$$

Similarly, (7.35) and (7.36) give,

$$B_{11.2} = \frac{w_{11}}{w_2}\left[\frac{3m_7}{32} + \frac{1}{32}\left(\frac{12m_8^2}{m_1} + \frac{9m_5^2}{m_9} + \frac{9m_6^2}{m_{10}}\right)\right]^{-1/2}$$

$$\times\left[1 + \frac{32m_1(\theta^{**})^2}{3(m_1 m_{13} - 4m_8^2)\left\{SS_2 + \frac{8(\gamma\hat{\pi})_1^2}{m_9} + \frac{8(\gamma\hat{\pi})_2^2}{m_{10}} + \frac{32(\tau\hat{\lambda})^2}{3m_1}\right\}}\right]^{-3N/2} \tag{7.40}$$

(7.35) and (7.37) give,

$$B_{12.2} = \frac{w_{12}}{w_2}\left[\frac{16m_1}{32} + \frac{1}{32}\left(\frac{12m_3^2}{m_1} + \frac{4m_5^2}{m_9} + \frac{4m_6^2}{m_{10}}\right)\right]^{-1/2}$$

$$\times\left[1 + \frac{32m_1(\lambda^{**})^2}{4(m_1m_{11} - 3m_3^2)\left\{SS_2 + \frac{8(\gamma\hat{\pi})_1^2}{m_9} + \frac{8(\gamma\hat{\pi})_2^2}{m_{10}} + \frac{32(\tau\hat{\lambda})^2}{3m_1}\right\}}\right]^{-3N/2} \qquad (7.41)$$

and finally (7.35) and (7.38) give

$$B_{02} = \frac{w_0}{w_2}\left|\frac{1}{32}\begin{pmatrix} 16m_1 - \frac{12m_3^2}{m_1} - \frac{4m_5^2}{m_9} - \frac{4m_6^2}{m_{10}} & 6m_4 - \frac{12m_3m_8}{m_1} - \frac{6m_5^2}{m_9} - \frac{6m_6^2}{m_{10}} \\ 6m_4 - \frac{12m_3m_8}{m_1} - \frac{6m_5^2}{m_9} - \frac{6m_6^2}{m_{10}} & 3m_7 - \frac{12m_3^2}{m_1} - \frac{4m_5^2}{m_9} - \frac{4m_6^2}{m_{10}} \end{pmatrix}\right|^{-1/2}$$

$$\times\left[1 + \left(\frac{32m_1(\theta^{**})^2}{3(m_1m_{13} - 4m_8^2)} + \frac{32m_1(\lambda^{***})^2}{4(m_1m_{11} - 3m_3^2) - 12(m_1m_{12} - 2m_3m_8)^2/(m_1m_{13} - 4m_8^2)}\right)\right.$$

$$\left./\quad\left(SS_2 + \frac{8(\gamma\hat{\pi})_1^2}{m_9} + \frac{8(\gamma\hat{\pi})_2^2}{m_{10}} + \frac{32(\tau\hat{\lambda})^2}{3m_1}\right)\right]^{-3N/2} \qquad (7.42)$$

Our standard approach would now be to use Good's method of imaginary observations and to set $n_1 = 2, n_2 = n_3 = n_4 = 1$ or any other permutation of the indices. However, whilst this approach is applicable to (7.39), there is a problem when applying it to (7.40), (7.41) or (7.42). The essential problem is evident in the definition of the m_i's on pages 7-8 and 7-9, namely that the coefficients of the terms are not symmetric in the n_i's. Thus, for example, m_4 has a different coefficient for $\frac{1}{n_1}$ than it does for $\frac{1}{n_3}$; this is also the case for m_7 and m_8. In fact the condition $n_1 = 2, n_2 = n_3 = n_4 = 1$ is not necessary in this design since all effects, other than the group effects are estimated within patients, and since we have conditioned $(\gamma\pi)_1$ and $(\gamma\pi)_2$ to be zero there are 2 degrees of freedom available for estimating σ_2^2. Thus we propose setting $n_1 = n_2 = n_3 = n_4 = 1$ for determining the ratios of the constants $w_2/w_3, w_{11}/w_2, w_{12}/w_2$ and w_0/w_2 giving the following:

$$1 = \frac{w_2}{w_3}\left(\frac{32}{3\cdot 4}\right)^{1/2} \quad \Rightarrow \quad \frac{w_2}{w_3} = \left(\frac{8}{3}\right)^{-1/2}$$

$$1 = \frac{w_{11}}{w_2}\left(\frac{3\cdot 52}{32}\right)^{-1/2} \quad \Rightarrow \quad \frac{w_{11}}{w_2} = \left(\frac{39}{8}\right)^{1/2}$$

$$1 = \frac{w_{12}}{w_2}\left(\frac{16\cdot 4}{32}\right)^{-1/2} \quad \Rightarrow \quad \frac{w_{12}}{w_2} = 2^{1/2}$$

$$1 = \frac{w_0}{w_2}\left(\frac{3}{4}\right)^{-1/2} \quad \Rightarrow \quad \frac{w_0}{w_2} = \left(\frac{4}{3}\right)^{1/2}$$

These ratios may be substituted into (7.39), (7.40), (7.41) and (7.42) to give $B_{23}, B_{11.2}, B_{12.2}$ and B_{02} respectively from which the following may be derived using the transitivity property of Bayes factors developed in §6.4 :

$$B_{11.3} = B_{11.2}B_{23} \quad , \quad B_{12.3} = B_{12.2}B_{23} \quad , \quad B_{03} = B_{02}B_{23}$$

Generalising the approach taken in §6.4, then given that $\kappa_{ij} = P(M_i)/P(M_j)$ and since by definition

$$B_{03}\kappa_{03} = \frac{P(M_0 \mid X)}{P(M_3 \mid X)} \quad , \quad B_{02}\kappa_{02} = \frac{P(M_0 \mid X)}{P(M_2 \mid X)} \quad , \quad B_{11.2}\kappa_{11.2} = \frac{P(M_{11} \mid X)}{P(M_2 \mid X)} \quad , \quad B_{12.2}\kappa_{12.2} = \frac{P(M_{12} \mid X)}{P(M_2 \mid X)}$$

then,

$$P(M_3 \mid X) = \frac{1}{1 + B_{23}\kappa_{23} + B_{11.3}\kappa_{11.3} + B_{12.3}\kappa_{12.3} + B_{03}\kappa_{03}}$$

$$P(M_2 \mid X) = \frac{B_{23}\kappa_{23}}{1 + B_{23}\kappa_{23} + B_{11.3}\kappa_{11.3} + B_{12.3}\kappa_{12.3} + B_{03}\kappa_{03}}$$

$$P(M_{11} \mid X) = \frac{B_{11.3}\kappa_{11.3}}{1 + B_{23}\kappa_{23} + B_{11.3}\kappa_{11.3} + B_{12.3}\kappa_{12.3} + B_{03}\kappa_{03}}$$

$$P(M_{12} \mid X) = \frac{B_{12.3}\kappa_{12.3}}{1 + B_{23}\kappa_{23} + B_{11.3}\kappa_{11.3} + B_{12.3}\kappa_{12.3} + B_{03}\kappa_{03}}$$

$$P(M_0 \mid X) = \frac{B_{03}\kappa_{03}}{1 + B_{23}\kappa_{23} + B_{11.3}\kappa_{11.3} + B_{12.3}\kappa_{12.3} + B_{03}\kappa_{03}}$$

As before an assumption of model indifference translates to $\kappa_{23} = \kappa_{11.3} = \kappa_{12.3} = \kappa_{03} = 1$ or alternatively $P(M_3) = P(M_2) = P(M_{11}) = P(M_{12}) = P(M_0) = \frac{1}{5}$. Applying these results to the data in §7.3.3 gives rise directly to the following :

$$B_{23} = 4.642$$

$$B_{11.2} = 3.171$$

$$B_{12.2} = 3.634$$

$$B_{02} = 18.619$$

and from the above relationships ,

$$B_{11.3} = 14.717$$

$$B_{12.3} = 16.870$$

$$B_{03} = 86.424$$

giving,

$$P(M_3 \mid X) = 0.008$$

$$P(M_2 \mid X) = 0.038$$

$$P(M_{11} \mid X) = 0.119$$

$$P(M_{12} \mid X) = 0.136$$

$$P(M_0 \mid X) = 0.699$$

These results indicate that it is unlikely, even under an indifference model, that any of the carryover-type nuisance parameters, namely $(\tau\lambda)$, θ and λ, are in any sense significant.

Continuing the generalisation we may calculate the unconditional posterior probability of a positive treatment effect using :

$$\begin{aligned} P(\tau > 0 \mid x) = {} & P(\tau > 0 \mid X, M_3)P(M_3 \mid X) + P(\tau > 0 \mid M_2)P(M_2 \mid X) \\ & + P(\tau > 0 \mid X, M_{11})P(M_{11} \mid X) + P(\tau > 0 \mid M_{12})P(M_{12} \mid X) \\ & + P(\tau > 0 \mid X, M_0)P(M_0 \mid X) \end{aligned} \tag{7.43}$$

The data under consideration gave the following :

$$P(\tau > 0 \mid X, M_3) = 0.9670$$

$$P(\tau > 0 \mid X, M_2) = 0.9676$$

$$P(\tau > 0 \mid X, M_{11}) = 0.9909$$

$$P(\tau > 0 \mid X, M_{12}) = 0.9968$$

$$P(\tau > 0 \mid X, M_0) = 0.9966$$

so that from (7.43) we may determine $P(\tau > 0 \mid X) = 0.9946$ indicating that there is considerable evidence in favour of a positive treatment effect. Interestingly the analysis of the data from the sequences **ABB** and **BAA** gave a posterior probability of a positive treatment effect 0.9931 with a posterior expectation of 1.410 mm Hg, in contrast to a posterior expectation of 1.136 mm Hg in this section.

One further generalisation which we do not pursue in detail is to extend the graphical analysis developed in §6.5. Using the same notation as in that section we may manipulate (7.43) to write it in the form,

$$P_{U|X} = \frac{P_3 P_{3|X} + B_{23} P_2 P_{2|X} + B_{11,3} P_{11} P_{11|X} + B_{12,3} P_{12} P_{12|X} + B_{03} P_0 P_{0|X}}{P_3 + B_{23} P_2 + B_{11,3} P_{11} + B_{12,3} P_{12} + B_{03} P_0} \tag{7.44}$$

Suppose now we fix both P_3 and P_2 then again (7.44) can be used for displaying straight line contours of $P_{U|X}$ over the simplex $P_{11} + P_{12} + P_0 = 1 - P_3 - P_2$, precisely as in §6.5. In this case triangular plots for various combinations of different P_2 and P_3 may be produced.

8 ANALYSIS OF TWO-TREATMENT CROSSOVERS UNDER NON-UNIFORMITY.

We have thus far, in §4-§7, restricted attention to analysing crossover studies under a mixed ANOVA, or uniform covariance, model. In this chapter we provide a framework for a second set of Bayesian analyses for two-treatment crossover designs under the assumption of a general, non-uniform, covariance matrix. We first develop general results covering a Bayesian analysis for comparing multivariate normal samples with a general covariance matrix and then show how these results may be applied to the two-period two-treatment design. We could derive similar analyses for the other designs which we have considered, but we will allow this simple design to stand proxy for the others as it will be clear how to generalise the approach to the more complex designs.

8.1 A Bayesian Analysis of Multivariate Normal Samples under Non-Uniformity.

In contrast to the analysis presented in §3 we suppose that the data in the g groups have a general covariance Ξ. As in §3 suppose at the end of the study that n_i patients in group i complete the study and let $\bar{y}_i$ and B_i be the mean vectors and matrices of sums of squares and cross products respectively. With these definitions the likelihood is proportional to,

$$\prod_{i=1}^{g} |\Xi|^{-\frac{1}{2}} \exp\left(-\frac{n_i}{2}(\bar{y}_i-\mu_i)'\Xi^{-1}(\bar{y}_i-\mu_i)\right) \times |\Xi|^{-(n_i-1)/2} \exp\left(-\frac{1}{2}tr(\Xi^{-1}B_i)\right) \qquad (8.1)$$

Suppose that a realistic "ignorance" prior for the parameters $\mu_1, \mu_2, \ldots, \mu_g$ and Ξ is of the form,

$$p(\mu_1, \mu_2, \ldots, \mu_g, \Xi) \propto |\Xi|^{-(k+1)/2} \qquad (8.2)$$

We will again consider the reasonableness of (8.2) later. Combining (8.1) and (8.2) gives the posterior distribution of the parameters in the form,

$$p(\mu_1, \mu_2, \ldots, \mu_g, \Xi \mid X) \propto |\Xi|^{-(N+k+1)/2} \exp\left(-\frac{1}{2}\sum_i [n_i(\bar{y}_i-\mu_i)'\Xi^{-1}(\bar{y}_i-\mu_i) - tr(\Xi^{-1}B_i)]\right) \qquad (8.3)$$

The marginal distribution of Ξ may be obtained by integrating $\mu_1, \mu_2, \ldots, \mu_g$ out of (8.3) to give,

$$p(\Xi \mid X) \propto |\Xi|^{-(N+k-g+1)/2} \exp\left(-\frac{1}{2}\sum_i tr(\Xi^{-1}B_i)\right). \qquad (8.4)$$

Combining (8.3) and (8.4) gives,

$$p(\mu_1, \mu_2, \ldots, \mu_g \mid \Xi, X) \propto |\Xi|^{-g/2} \exp\left(-\frac{1}{2}\sum_i n_i(\bar{y}_i-\mu_i)'\Xi^{-1}(\bar{y}_i-\mu_i)\right)$$

which implies that ,

$$p(\mu_1, \mu_2, \ldots, \mu_g \mid \Xi, X) = N_{gk}[(\bar{y}_1\bar{y}_2\ldots\bar{y}_g)', \Sigma] \qquad (8.5)$$

where,

$$\Sigma = \begin{pmatrix} \frac{1}{n_1} & & & \\ & \frac{1}{n_2} & & \\ & & \ddots & \\ & & & \frac{1}{n_g} \end{pmatrix} \otimes \Xi$$

Let ,

$$\mu_i = (\mu_{i1}, \mu_{i2}, \ldots, \mu_{ik})' \quad , \quad \bar{x}_i = (\bar{x}_{i1}, \bar{x}_{i2}, \ldots, \bar{x}_{ik})',$$

and let K_{kg} be the commutation matrix defined by MacRae(1974) (see also Magnus and Neudecker , 1979), for example,

$$K_{32} = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

Make the transformation ,

$$\mu^* = K_{kg} \begin{pmatrix} \mu_1 \\ \mu_2 \\ \cdot \\ \cdot \\ \cdot \\ \mu_g \end{pmatrix}$$

to give,

$$p(\mu^* \mid \Xi, X) = N_{gk}[K_{kg}(\bar{x}_1 \bar{x}_2 \ldots \bar{x}_g)' \quad , \quad K_{kg}' \Sigma K_{kg}] \tag{8.6}$$

which using Theorem 3.1 (viii) of Magnus and Neudecker(1979) implies that ,

$$p((\mu_{(1)}, \mu_{(2)} \cdots \mu_{(k)}) \mid \Xi, X) = N_{gk}[(\bar{x}_{(1)} \bar{x}_{(2)} \ldots \bar{x}_{(k)})', \Sigma_1] \tag{8.7}$$

where,

$$\mu_{(l)} = (\mu_{1l}\mu_{2l}\ldots\mu_{gl})' \quad , \quad \bar{x}_{(l)} = (\bar{x}_{1l}\bar{x}_{2l}\ldots\bar{x}_{gl})' \quad , \quad \Sigma_l = \Xi \otimes \begin{pmatrix} \frac{1}{n_1} & & & \\ & \frac{1}{n_2} & & \\ & & . & \\ & & & \frac{1}{n_g} \end{pmatrix}$$

Equation (8.4) implies that ,

$$p(\Xi \mid X) = W_k^{-1}\left(\sum_{i=1}^{g} B_i, N-g-k+1\right) \tag{8.8}$$

Combining (8.7) and (8.8) implies that ,

$$p\left[\begin{pmatrix} \mu_{11} & \mu_{12} & \cdots & \mu_{1k} \\ \mu_{21} & \mu_{22} & \cdots & \mu_{2k} \\ . & . & & . \\ . & . & & . \\ \mu_{g1} & \mu_{g2} & \cdots & \mu_{gk} \end{pmatrix} \middle| X\right] =$$

$$t_{gk}\left[\begin{pmatrix} \bar{x}_{11} & \bar{x}_{12} & \cdots & \bar{x}_{1k} \\ \bar{x}_{21} & \bar{x}_{22} & \cdots & \bar{x}_{2k} \\ . & . & & . \\ . & . & & . \\ \bar{x}_{g1} & \bar{x}_{g2} & \cdots & \bar{x}_{gk} \end{pmatrix}, \begin{pmatrix} n_1^{-1} & & & \\ & n_2^{-1} & & \\ & & . & \\ & & & n_g^{-1} \end{pmatrix}, \sum_{i=1}^{g} B_i, N-g-k+1\right] \tag{8.9}$$

using Theorem 8.5.1 of Box and Tiao(1973). The distribution defined in (8.9) is a matric-variate t-distribution given by,

$$p\left[\mu = \begin{pmatrix} \mu_{11} & \mu_{12} & \cdots & \mu_{1k} \\ \mu_{21} & \mu_{22} & \cdots & \mu_{2k} \\ . & . & & . \\ . & . & & . \\ \mu_{g1} & \mu_{g2} & \cdots & \mu_{gk} \end{pmatrix} \middle| X\right] =$$

$$\frac{\Gamma_k(N/2)}{\Gamma(1/2)^{gk}\Gamma_k[(N-k)/2]}\left(\prod_{i=1}^{g} n_i\right)^{k/2}\left|\left(\sum_{i=1}^{g} B_i\right)^{-1}\right|^{g/2}\left|I_k + \left(\sum_{i=1}^{g} B_i\right)^{-1}(\mu-\hat{\mu})'\begin{pmatrix} n_1 & & & \\ & n_2 & & \\ & & . & \\ & & & n_g \end{pmatrix}(\mu-\hat{\mu})\right|^{-N/2}$$

where

$$\Gamma_p(b) = [\Gamma(1/2)]^{p(p-1)/2}\prod_{\alpha=1}^{p}\Gamma\left(b+\frac{\alpha-p}{2}\right) \qquad b > \frac{p-1}{2}$$

8.2 The Two-Period Two-Treatment Crossover.

As in §4.1, the cell means model shown in Table 2.1 may be put into the general structure of §8.1 by setting $k = g = 2$ and by noting that,

$$\begin{pmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{21} \\ \mu_{22} \end{pmatrix} = \begin{pmatrix} 1 & 1 & 1 & 0 \\ 1 & -1 & -1 & 1 \\ 1 & 1 & -1 & 0 \\ 1 & -1 & 1 & -1 \end{pmatrix} \begin{pmatrix} \mu \\ \pi \\ \tau \\ \lambda \end{pmatrix}$$

From (8.9) the posterior distribution of $\mu_{11}, \mu_{12}, \mu_{21}$ and μ_{22} may be written as,

$$p\left[\begin{pmatrix} \mu_{11} & \mu_{12} \\ \mu_{21} & \mu_{22} \end{pmatrix} \middle| X \right] = t_{22}\left[\begin{pmatrix} \bar{x}_{11} & \bar{x}_{12} \\ \bar{x}_{21} & \bar{x}_{22} \end{pmatrix}, \begin{pmatrix} n_1^{-1} & \\ & n_2^{-1} \end{pmatrix}, \sum_{i=1}^{2} B_i, N-3 \right]$$

We concentrate on the treatment and carryover effects, τ and λ and note that they may be written as,

$$(\tau \;\; \lambda) = (1/2 \;\; -1/2) \begin{pmatrix} \mu_{11} & \mu_{12} \\ \mu_{12} & \mu_{22} \end{pmatrix} \begin{pmatrix} 1 & 1 \\ 0 & 1 \end{pmatrix}$$

Then from standard properties of matric-variate and multivariate t-distributions (see Box and Tiao,1973, §8.4.3) the following posterior distributions may be derived,

$$p(\tau, \lambda \mid X) = t_2\left[\begin{pmatrix} \tilde{\tau} \\ \hat{\lambda} \end{pmatrix}, \frac{q}{4} \begin{pmatrix} C_{11} & C_{12} \\ C_{12} & C_{22} \end{pmatrix}, N-3 \right] \tag{8.10}$$

$$p(\tau \mid X) = t\left(\tilde{\tau}, \frac{q}{4} \frac{C_{11}}{N-3}, N-3 \right) \tag{8.11}$$

$$p(\lambda \mid X) = t\left(\hat{\lambda}, \frac{q}{4} \frac{C_{22}}{N-3}, N-3 \right) \tag{8.12}$$

$$p(\tau \mid \lambda = 0, X) = t\left(\tilde{\tau} - \hat{\lambda} \frac{C_{12}}{C_{22}}, \frac{q}{4} \frac{C_{11} - C_{12}^2 / C_{22}}{N-3}, N-3 \right) \tag{8.13}$$

where $\hat{\lambda}$ and $\tilde{\tau}$ are defined in (2.1) and (2.3) and

$$C_{11} = \sum_{i=1}^{2} \{B_i\}_{11} \quad , \quad C_{12} = C_{21} = \sum_{i=1}^{2} [\{B_i\}_{11} + \{B_i\}_{12}] \quad , \quad C_{22} = \sum_{i=1}^{2} [\{B_i\}_{11} + 2\{B_i\}_{12} + \{B_i\}_{22}]$$

8.3 Discussion.

There are great similarities between the analysis presented in the previous section and the analysis based upon a uniform covariance matrix developed in §4; but there are important differences. To illustrate the similarities and to highlight the differences we return to the anginal attack rate data from Wheatley(1987) displayed in Table 2.3.

These data give rise to the following summary statistics :

$$\bar{y}_{1.1} = 8.065$$
$$\bar{y}_{1.2} = 4.226$$
$$\bar{y}_{2.1} = 6.344$$
$$\bar{y}_{2.2} = 9.813$$

$$B_1 = \begin{pmatrix} 945.871 & 235.548 \\ 235.548 & 327.419 \end{pmatrix}$$

$$B_2 = \begin{pmatrix} 1727.219 & 1401.063 \\ 1401.063 & 2204.875 \end{pmatrix}$$

from which the following may be derived,

$$\bar{\tau} = 0.861$$
$$\hat{\lambda} = -1.933$$
$$C_{11} = 2673.090$$
$$C_{12} = C_{21} = 4309.701$$
$$C_{22} = 8478.606$$

Based upon these statistics the results in §8.2 give rise to posterior distributions each of which is a t-distribution as follows,

$$p(\tau \mid X) = t(0.861, 0.707, 60)$$
$$p(\lambda \mid X) = t(-1.933, 2.244, 60)$$
$$p(\tau \mid \lambda = 0, X) = t(1.843, 0.128, 60)$$

the corresponding posterior distributions based upon a uniform covariance matrix are,

$$p(\tau \mid X) = t(0.861, 0.684, 85.7)$$
$$p(\lambda \mid X) = t(-1.933, 2.207, 61)$$
$$p(\tau \mid \lambda = 0, X) = t(1.827, 0.126, 61)$$

There are a number of issues which arise by comparing these two sets of posterior distributions :

i) The posterior distributions for λ are identical in the two models, except that in the general covariance matrix case there is one degree of freedom less than in the uniform covariance case. This should not really be surprising since in the former case there is an extra unknown parameter and part of the information in the data is used in estimating this parameter, with a consequent loss of a single degree of freedom. In practical terms this makes little difference with a reasonably sized study, but there are theoretical issues which are related to the marginalization paradoxes considered by Dawid *et al*(1973).

ii) In the general covariance, in contrast to the uniform case, the posterior marginal distribution for τ is based solely on data from the first period, as in Grizzle's(1965) approach, although again a single degree of freedom is lost. This arises because in this case the second period provides no useful information concerning variability since the variances in the two periods are no longer assumed to be equal. A marginal advantage is that one need no longer consider a Behrens-Fisher distribution, although there is therefore a loss in sensitivity.

iii) The near equality of the conditional posterior distributions for τ given no carryover effect will not in general be the case. In this particular instance it arises because the sample variances in the two periods are nearly equal and of necessity are close to the estimated single variance in the uniform case, namely 43.82 and 41.51 for the first and second periods as opposed to 42.67 in the pooled case.

iv) Since the posterior for λ is again a t-distribution we may use a similar Bayes factor for model M_0 versus M_1 as was used in the uniform case. In the more complex crossover designs the necessary Bayes factors need to be determined from the more general multivariate results derived by Smith and Spiegelhalter(1981).

9 TREATMENT OF MISSING VALUES IN CROSSOVER DESIGNS.

9.1 Introduction.

The development thus far has, in a sense, taken place divorced from the realities of practical life. We have, for example, assumed :

i) that the original measurement metric of each of the clinical parameters which we have considered allows an analysis based on linear models and Gaussian random variation.

ii) that our data are free from outliers, or influential observations.

iii) that our data are complete; there are no missing data.

Potentially, at least, (i) is particularly important. Firstly, it is not clear in what metric one should choose to measure beliefs. Conceivably, one particular metric may be preferable. Alternatively, if the metric is largely irrelevant, then our inferences may be considered robust (c.f. Box and Tiao,1973,§3.2). Secondly, experience suggests that certain metrics are preferable in terms of approximating normality. For example, commenting on Racine *et al*(1986), Cox(1986) suggested "there is prior evidence based on careful analysis of data that for detailed analysis log blood pressure and perhaps reciprocal pulse rate are good variables to analyze ...". Interestingly Jones(1986) arrived at the reciprocal transformation for the blood pressure data considered by Racine *et al*(1986) which was confirmed by these authors in the reply to the discussion; they also expressed a preference for the logarithmic transformation for the pulse rate data. The analysis which they used was based on Perrichi's(1981) Bayesian approach to determining a transformation to normality. There is no great difficulty in applying this approach to crossover designs and therefore we do not pursue it further here.

As far as outliers are concerned they too are important, particularly in crossover designs where they can influence the choice of model in which treatment effects are estimated. Berry(1990) has shown that an outlier in the data given by Brown(1980) has a major impact on the perception, at least, of the relationship between the measurements taken in the two periods. Indeed in this case the outlier has an even greater impact since if it is not excluded one concludes that there is significant carryover effect - $p < 0.10$, and if it is excluded one concludes, if one uses Grizzle's procedure, that there is not a significant carryover effect - $p > 0.10$. Again the work of Pettit and Smith(1984) is relatively easily applied to crossover designs and therefore we again do not pursue it further here.

The work of Patel(1985) suggests that there is much to be gained from the use of all data from a crossover design, and that the exclusion of data from patients for whom all data are not available is potentially wasteful. However, care needs to be taken when considering whether data from a patient for whom some data are misssing should be used, since if the reason that the data are missing is related to treatment then potentially one may produce a biased estimate of the treatment effect.

In the present chapter we consider how one can tackle missing value problems from a Bayesian perspective for the simple two-treatment, two-period crossover design answering directly one of the questions posed by Freeman(1986) - "what happens with real data sets that have missing values, outliers, early crossovers and so on?"

9.2 Missing Values in the Two-Period Crossover.

Suppose in a two-treatment, two-period crossover that complete information is available for $n_1 + n_2$ patients, $n_{11} + n_{21}$ patients have only data in the first period and $n_{12} + n_{22}$ only in the second, where in the light of the comments above the incidence of missing data is unrelated to treatments. The pattern of the data is as shown in Table 9.1.

TABLE 9.1 Pattern of Missing Data in a Two-Treatment, Two-Period Crossover.

Sequence A → B			Sequence B → A		
Patients	Period 1	Period 2	Patients	Period 1	Period 2
n_1	y_{111} y_{121} . $y_{1n_{11}}$	y_{112} y_{122} . $y_{1n_{12}}$	n_2	y_{211} y_{221} . $y_{2n_{21}}$	y_{212} y_{222} . $y_{2n_{22}}$
n_{11}	x_{11} . $x_{1n_{11}}$	Missing	n_{21}	x_{21} . $x_{2n_{21}}$	Missing
n_{12}	Missing	z_{11} . $z_{1n_{12}}$	n_{22}	Missing	z_{21} . $z_{2n_{22}}$

The $n_1 + n_2$ patients with complete data make the following contribution to the likelihood,

$$\prod_{i=1}^{2} \exp\left(\frac{-n_i}{2\sigma^2(1-\rho^2)}\left[(\bar{y}_{i.1}-\mu_{i1})^2 - 2\rho(\bar{y}_{i.1}-\mu_{i1})(\bar{y}_{i.2}-\mu_{i2}) + (\bar{y}_{i.2}-\mu_{i2})^2\right]\right)$$

$$\times\ (\sigma^2)^{-(n_1+n_2)}(1-\rho^2)^{-(n_1+n_2)/2} \prod_{i=1}^{2} \exp\left(\frac{-1}{2\sigma^2(1-\rho^2)}[S_{i11} - 2\rho S_{i12} + S_{i22}]\right) \qquad (9.1)$$

where $\mu_{11} = \mu + \pi + \tau$, $\mu_{12} = \mu - \pi - \tau + \lambda$, $\mu_{21} = \mu + \pi - \tau$, $\mu_{22} = \mu - \pi + \tau - \lambda$, $\sigma^2 = (\sigma_A^2 + \sigma_\epsilon^2)/2$, $\rho = (\sigma_A^2 - \sigma_\epsilon^2)/(\sigma_A^2 + \sigma_\epsilon^2)$ and S_{ijk} are the relevant elements of the matrix of corrected sums of squares and cross-products in sequence i . Suppose that the patients with missing data values give means $\bar{x}_1, \bar{x}_2, \bar{z}_1, \bar{z}_2$ and corrected sums of squares S_{ij}^2, then their contribution to the likelihood takes the form,

$$\exp\left(\frac{-1}{2\sigma^2}\left[n_{11}(\bar{x}_1-\mu_{11})^2+n_{12}(\bar{z}_1-\mu_{12})^2+n_{21}(\bar{x}_2-\mu_{21})^2+n_{22}(\bar{z}_2-\mu_{22})^2\right]\right)$$

$$\times\ (\sigma^2)^{-(n_{11}+n_{12}+n_{21}+n_{22})/2}\exp\left(\frac{-1}{2\sigma^2}\left[S_{11}^2+S_{12}^2+S_{21}^2+S_{22}^2\right]\right) \qquad (9.2)$$

The first lines in (9.1) and (9.2) may be respectively rewritten as,

$$\prod_{i=1}^{2}\exp\left[\frac{-1}{2}(\mu_{i1}-\bar{y}_{i.1}\quad \mu_{i2}-\bar{y}_{i.2})\Sigma_{i0}^{-1}\begin{pmatrix}\mu_{i1}-\bar{y}_{i.1}\\ \mu_{i2}-\bar{y}_{i.2}\end{pmatrix}\right] \qquad (9.3)$$

and

$$\prod_{i=1}^{2}\exp\left[\frac{-1}{2}(\mu_{i1}-\bar{x}_i\quad \mu_{i2}-\bar{z}_i)\Sigma_{i1}^{-1}\begin{pmatrix}\mu_{i1}-\bar{x}_i\\ \mu_{i2}-\bar{z}_i\end{pmatrix}\right] \qquad (9.4)$$

where

$$\Sigma_{i0} = \frac{\sigma^2}{n_i}\begin{pmatrix}1 & \rho\\ \rho & 1\end{pmatrix}$$

and

$$\Sigma_{i1} = \sigma^2\begin{pmatrix}\frac{1}{n_{i1}} & 0\\ 0 & \frac{1}{n_{i2}}\end{pmatrix}$$

Using (A7.1.1) from Box and Tiao(1973) (9.3) and (9.4) may be combined to give,

$$\prod_{i=1}^{2}\exp\left[\frac{-1}{2}(\mu_{i1}-\hat{\mu}_{i1}\quad \mu_{i2}-\hat{\mu}_{i2})\Sigma_i^{*-1}\begin{pmatrix}\mu_{i1}-\hat{\mu}_{i1}\\ \mu_{i2}-\hat{\mu}_{i2}\end{pmatrix}\frac{-1}{2}(\bar{y}_{i.1}-\bar{x}_i\quad \bar{y}_{i.2}-\bar{z}_i)\Sigma_2^{*-1}\begin{pmatrix}\bar{y}_{i.1}-\bar{x}_i\\ \bar{y}_{i.2}-\bar{z}_i\end{pmatrix}\right] \qquad (9.5)$$

where,

$$\hat{\mu}_{i1} = \bar{y}_{i.1} + \frac{n_{i1}(n_i+n_{i2}(1-\rho^2))(\bar{x}_i-\bar{y}_{i.1})+n_in_{i2}\rho(\bar{z}_i-\bar{y}_{i.2})}{n_i^2+n_in_{i1}+n_in_{i2}+n_{i1}n_{i2}(1-\rho^2)}$$

$$\hat{\mu}_{i2} = \bar{y}_{i.2} + \frac{n_in_{i1}\rho(\bar{x}_i-\bar{y}_{i.1})+n_{i2}(n_i+n_{i1}(1-\rho^2))(\bar{z}_i-\bar{y}_{i.2})}{n_i^2+n_in_{i1}+n_in_{i2}+n_{i1}n_{i2}(1-\rho^2)}$$

$$\Sigma_{i1}^{*} = \frac{\sigma^2}{n_i^2+n_in_{i1}+n_in_{i2}+n_{i1}n_{i2}(1-\rho^2)}\begin{pmatrix}n_i+n_{i2}(1-\rho^2) & n_i\rho\\ n_i\rho & n_i+n_{i1}(1-\rho^2)\end{pmatrix}$$

and

$$\Sigma_{i2}^{*} = \frac{\sigma^2}{n_i n_{i1} n_{i2}} \begin{pmatrix} n_{i2}(n_i + n_{i1}) & n_{i1} n_{i2} \rho \\ n_{i1} n_{i2} \rho & n_{i1}(n_i + n_{i2}) \end{pmatrix}$$

and therefore the full likelihood may be written as,

$$\prod_{i=1}^{2} \exp\left[\frac{-1}{2} (\mu_{i1} - \hat{\mu}_{i1} \quad \mu_{i2} - \hat{\mu}_{i2}) \Sigma_1^{*-1} \begin{pmatrix} \mu_{i1} - \hat{\mu}_{i1} \\ \mu_{i2} - \hat{\mu}_{i2} \end{pmatrix} \right]$$

$$\times \prod_{i=1}^{2} \exp\left(\frac{-1}{2\sigma^2(1-\rho^2)} [S_{i11} - 2\rho S_{i12} + S_{i22}] \frac{-1}{2} (\bar{y}_{i.1} - \bar{x}_i \quad \bar{y}_{i.2} - \bar{z}_i) \Sigma_2^{*-1} \begin{pmatrix} \bar{y}_{i.1} - \bar{x}_i \\ \bar{y}_{i.2} - \bar{z}_i \end{pmatrix} \right)$$

$$\times \ (\sigma^2)^{-(2n_1 + 2n_2 + n_{11} + n_{12} + n_{21} + n_{22})/2} (1-\rho^2)^{-(n_1 + n_2)/2} \exp\left(\frac{-1}{2\sigma^2} [S_{11}^2 + S_{12}^2 + S_{21}^2 + S_{22}^2] \right)$$

In the current parametrization the prior density has the form $p(\mu_{11}, \mu_{12}, \mu_{21}, \mu_{22}, \sigma^2, \rho) \propto [\sigma^2(1-\rho^2)]^{-1}$ and therefore the posterior distribution of the parameters may be written in the form,

$$p(\mu_{11}, \mu_{12}, \mu_{21}, \mu_{22}, \sigma^2, \rho \mid X) = p(\mu_{11}, \mu_{12}, \mu_{21}, \mu_{22} \mid \sigma^2, \rho, X) p(\sigma^2, \rho \mid X)$$

where

$$p(\mu_{11}, \mu_{12}, \mu_{21}, \mu_{22} \mid \sigma^2, \rho, X) = N[(\hat{\mu}_{11}, \hat{\mu}_{12}, \hat{\mu}_{21}, \hat{\mu}_{22})', \Sigma] \tag{9.6}$$

$$\Sigma = \begin{pmatrix} \Sigma_{11}^{*} & 0 \\ 0 & \Sigma_{21}^{*} \end{pmatrix}$$

and

$$p(\sigma^2, \rho \mid X) \propto \prod_{i=1}^{2} \exp\left(\frac{-1}{2\sigma^2(1-\rho^2)} [S_{i11} - 2\rho S_{i12} + S_{i22}] \frac{-1}{2} (\bar{y}_{i.1} - \bar{x}_i \quad \bar{y}_{i.2} - \bar{z}_i) \Sigma_2^{*-1} \begin{pmatrix} \bar{y}_{i.1} - \bar{x}_i \\ \bar{y}_{i.2} - \bar{z}_i \end{pmatrix} \right)$$

$$\times \frac{(\sigma^2)^{-(2n_1 + 2n_2 + n_{11} + n_{12} + n_{21} + n_{22} - 2)/2} (1-\rho^2)^{-(n_1 + n_2)/2}}{[n_1^2 + n_1 n_{11} + n_1 n_{12} + n_{11} n_{12}(1-\rho^2)][n_2^2 + n_2 n_{21} + n_2 n_{22} + n_{21} n_{22}(1-\rho^2)]^{1/2}}$$

$$\times \exp\left(\frac{-1}{2\sigma^2} [S_{11}^2 + S_{12}^2 + S_{21}^2 + S_{22}^2] \right) \tag{9.7}$$

Applying that part of the inverse transformation (4.1) relating to τ and λ to (9.6) gives the following posterior distributions,

$$p(\tau, \lambda \mid \sigma^2, \rho, X) = N\left[\begin{pmatrix} \tau(\rho) \\ \lambda(\rho) \end{pmatrix}, \begin{pmatrix} \sigma_\tau^2 & \sigma_{\tau\lambda} \\ \sigma_{\tau\lambda} & \sigma_\lambda^2 \end{pmatrix} \right] \tag{9.8}$$

where

$$\tau(\rho) = \frac{\hat{\mu}_{11}+\hat{\mu}_{21}}{2}$$

$$\lambda(\rho) = \frac{\hat{\mu}_{11}+\hat{\mu}_{12}+\hat{\mu}_{21}+\hat{\mu}_{22}}{2}$$

$$\sigma_\tau^2 = \frac{\sigma^2}{4}\left(\frac{n_1+n_{12}(1-\rho^2)}{n_1^2+n_1n_{11}+n_1n_{12}+n_{11}n_{12}(1-\rho^2)}+\frac{n_2+n_{22}(1-\rho^2)}{n_2^2+n_2n_{21}+n_2n_{22}+n_{21}n_{22}(1-\rho^2)}\right)$$

$$\sigma_{\tau\lambda} = \frac{\sigma^2}{4}\left(\frac{n_1(1+\rho)+n_{12}(1-\rho^2)}{n_1^2+n_1n_{11}+n_1n_{12}+n_{11}n_{12}(1-\rho^2)}+\frac{n_2(1+\rho)+n_{22}(1-\rho^2)}{n_2^2+n_2n_{21}+n_2n_{22}+n_{21}n_{22}(1-\rho^2)}\right)$$

$$\sigma_\lambda^2 = \frac{\sigma^2}{4}\left(\frac{2n_1(1+\rho)+(n_{11}+n_{12})(1-\rho^2)}{n_1^2+n_1n_{11}+n_1n_{12}+n_{11}n_{12}(1-\rho^2)}+\frac{2n_2(1+\rho)+(n_{21}+n_{22})(1-\rho^2)}{n_2^2+n_2n_{21}+n_2n_{22}+n_{21}n_{22}(1-\rho^2)}\right)$$

$$p(\tau\,|\,\sigma^2,\rho,X) = N(\tau(\rho),\sigma_\tau^2) \qquad (9.9)$$

$$p(\lambda\,|\,\sigma^2,\rho,X) = N(\lambda(\rho),\sigma_\lambda^2) \qquad (9.10)$$

$$p(\tau\,|\,\lambda=0,\sigma^2,\rho,X) = N\left(\tau(\rho)-\lambda(\rho)\frac{\sigma_{\tau\lambda}}{\sigma_\lambda^2},\sigma_\tau^2-\frac{(\sigma_{\tau\lambda})^2}{\sigma_\lambda^2}\right) \qquad (9.11)$$

The standard way to proceed would be to combine (9.7) with, in turn, (9.9),(9.10) and (9.11) and integrate out both σ^2 and ρ. The result of such a process is a hypergeometric function of 2 variables and therefore cannot be considered a practical solution. Two alternatives methods suggest themselves.

First, Gelfand *et al*(1990) have proposed a method based on Gibbs sampling - see Geman and Geman(1984). We do not intend to pursue this approach here since whilst we can agree with Gelfand *et al* that the main advantage of the Gibbs sampler approach is its ease of implementation to problems involving complex likelihoods we do not agree that other potential methods are 'likely to be "one-off" and, in any case, not routinely implementable by most applied statisticians', indeed applied statisticians may also have difficulty in applying the Gibbs sampler approach since the concept is likely to be novel to most of them.

A second, pragmatic, way forward is to integrate σ^2 analytically out of the above combinations and then to use numerical methods to integrate out ρ. A program to carry out this type of analysis is presented in §A6.2 in which the final numerical integral is performed using Gaussian quadrature. In the next section this method is illustrated using the example considered by Gelfand *et al*(1990).

9.3 An Example of a Two-Period Two-Treatment Crossover with Missing Data.

Gelfand *et al*(1990) take data from Maas *et al*(1987) to illustrate their proposed method for treating missing data in the two-period crossover based on the Gibbs sampler. We present the original data taken from Maas *et al*(1987) in Table 9.1 since the data presented in Gelfand *et al*(1990) are incorrect. The context of this data is a bioequivalence study in which it was desired to test whether a new, chewable (C), formulation of the

anti-epileptic treatment Carbamazepine was bioequivalent to the standard (S) tablet formulation. The standard approach in bioequivalence studies is to assume that the logarithms of the response variables, routinely either the area under the plasma concentration curves (AUC) and/or the maximum plasma concentration (CMAX), follow the standard linear model for crossovers and interest centres on the making inferences about the ratio of AUC's or CMAX's - see for example Racine-Poon *et al*(1987). In our parametrization, therefore, we will need to transform in the case of the treatment effect to $\exp(2\tau)$ and a corresponding transformation exists for the carryover effect. In order to illustrate their technique with missing data, Gelfland *et al* treated three observations as missing. These observations are shown in bold print in Table 9.1.

TABLE 9.1 Bioequivalence Data (CMAX - $\mu g/ml$)Taken from Maas *et al*(1987)
(C = Chewable Tablet , S = Standard Tablet).

		Period				Period	
Sequence	Subject	1	2	Sequence	Subject	1	2
C→S	1	**5.19**	4.07	S→C	3	4.21	**4.86**
	2	4.83	5.16		4	3.89	5.39
	6	3.72	**2.94**		5	5.23	5.41
	7	4.19	2.98		9	3.50	4.01
	8	4.20	3.48		10	3.68	4.55

The data in Table 9.1 give rise to the following summary statistics ;

$n_1 = 3$ $n_2 = 4$

$n_{11} = 1$ $n_{12} = 1$ $n_{21} = 0$ $n_{22} = 1$

$\bar{y}_{1.1} = 1.480877$ $\bar{y}_{1.2} = 1.326631$ $\bar{y}_{2.1} = 1.39212$ $\bar{y}_{2.2} = 1.56918$

$\bar{x}_1 = 1.31371$ $\bar{z}_1 = 1.40364$ $\bar{x}_2 = 0$ $\bar{z}_2 = 1.58104$

$S_{111} = 0.0132482$ $S_{112} = 0.0444875$ $S_{122} = 0.1602117$

$S_{211} = 0.0973115$ $S_{212} = 0.0573021$ $S_{222} = 0.0629484$

$S^2_{11} = 0$ $S^2_{12} = 0$ $S^2_{21} = 0$ $S^2_{22} = 0$

Applying the method described in the previous section to these data gives the posterior distribution for τ , λ and $\tau \mid \lambda = 0$ as shown in Figure 9.1. Included in this Figure are the posterior distributions derived from all the data and also those derived by ignoring those subjects for whom complete data is not available. The resulting posterior distributions reveal a typical pattern in such trials with missing data: firstly, if there is missing data from a subject then if we can assume that there is no carryover we may as well ignore data from that subject completely; secondly, if we cannot assume that there is no carryover effect, or if we wish to make inferences

about the carryover effect itself, then we should take into account the missing data; finally, the loss of such a considerable amount of data results in substantially increased inferential uncertainty. As far as this particular example is concerned, the objective of bioequivalence studies is to determine whether the ratio of CMAX's lies within 0.8 to 1.2 and therefore, since none of the posterior distributions for the treatment effect assign high probability to this interval the conclusion is that the two formulations are not bioequivalent.

9.4 Relative Efficiencies and Bayes Factors.

We saw in the previous section that depending on which model is appropriate for making inferences we may gain little from including data from subjects for whom complete data are not available. We may investigate this phenomenon further by considering the posterior variances of the parameters under various conditions, assuming that the variance components are known.

Suppose (i) $n_1 = n_2 = n$; (ii) $n_{11} = n_{21} = n_{12} = n_{22} = k$; (iii) $k = \alpha n$. Then using the above results the posterior variances of τ , λ and $\tau \mid \lambda = 0$ are

$$\sigma^2_{\tau.1} = \frac{\sigma^2}{2}\frac{1+\alpha(1-\rho^2)}{n(1+2\alpha)+\alpha^2 n(1-\rho^2)}$$

$$\sigma^2_{\lambda.1} = \sigma^2\frac{(1+\rho)+\alpha(1-\rho^2)}{n(1+2\alpha)+\alpha^2 n(1-\rho^2)}$$

$$\sigma^2_{\tau|\lambda=0.1} = \frac{\sigma^2}{4}\frac{(1-\rho)+\alpha(1-\rho^2)}{n(1+2\alpha)+\alpha^2 n(1-\rho^2)}$$

Corresponding to these we may also calculate the conditional variances which would arise if we were to ignore those patients with missing data which are,

$$\sigma^2_{\tau.2} = \frac{\sigma^2}{2n}$$

$$\sigma^2_{\lambda.2} = \frac{\sigma^2(1+\rho)}{n}$$

$$\sigma^2_{\tau|\lambda=0.2} = \frac{\sigma^2(1-\rho)}{4n}$$

and finally we may calculate the conditional variances which would have arisen if complete data had been available on all $2n + 4k$ patients. These are,

$$\sigma^2_{\tau.3} = \frac{\sigma^2}{2n(1+2\alpha)}$$

$$\sigma^2_{\lambda.3} = \frac{\sigma^2(1+\rho)}{n(1+2\alpha)}$$

$$\sigma^2_{\tau|\lambda=0.3} = \frac{\sigma^2(1-\rho)}{4n(1+2\alpha)}$$

In §2.8 we measured relative efficiency by the ratio of variances. Adopting that approach in the present context, using of course in this instance conditional posterior variances, gives the following relative efficiencies :

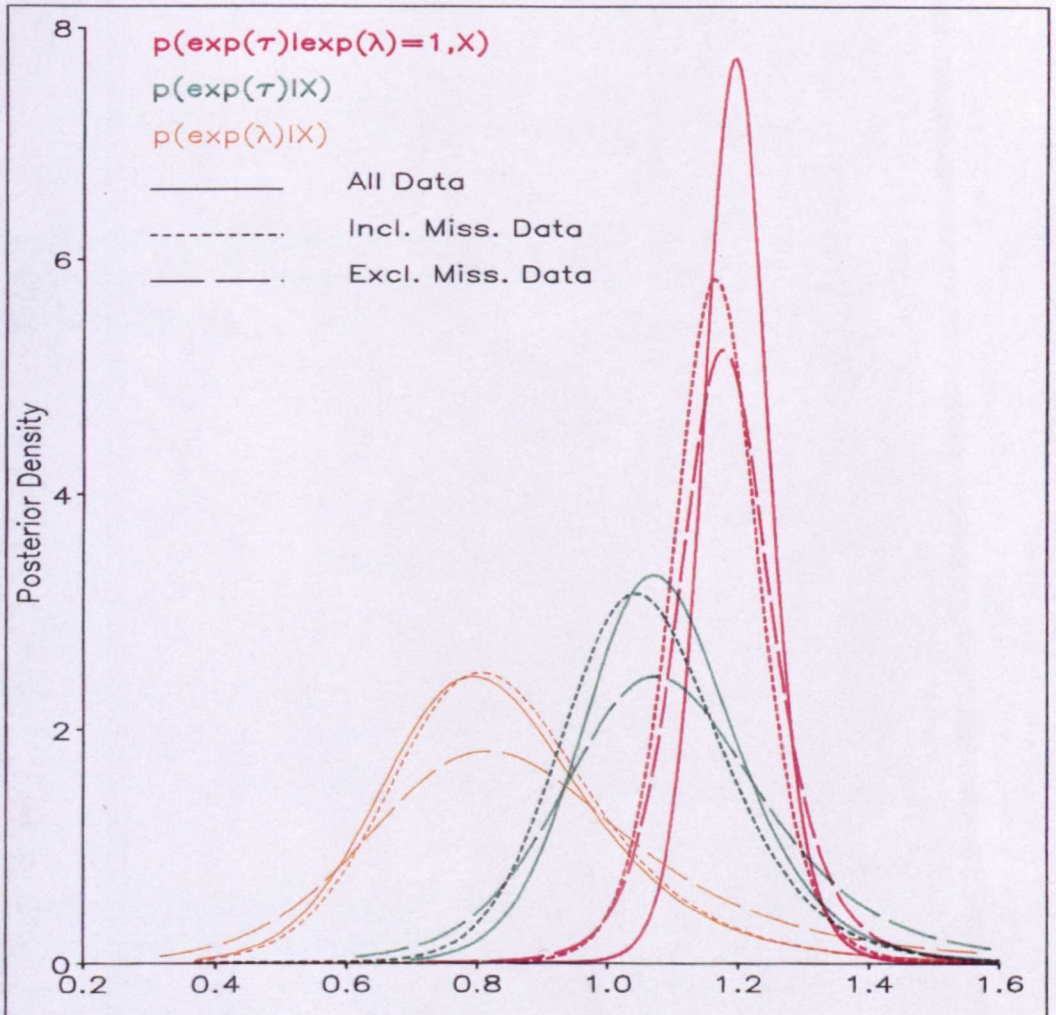


FIGURE 9.1 Posterior Distributions for Data from Maas et al (1987)

$$RE_{1,2}(\tau) = \frac{\sigma^2_{\tau,1}}{\sigma^2_{\tau,2}} = \frac{(1+\alpha(1-\rho^2))/(1+2\alpha)}{1+\alpha^2(1-\rho^2)/(1+2\alpha)}$$

$$RE_{1,2}(\lambda) = \frac{\sigma^2_{\lambda,1}}{\sigma^2_{\lambda,2}} = \frac{(1+\alpha(1-\rho))/(1+2\alpha)}{1+\alpha^2(1-\rho^2)/(1+2\alpha)}$$

$$RE_{1,2}(\tau \mid \lambda = 0) = \frac{\sigma^2_{\tau|\lambda=0,1}}{\sigma^2_{\tau|\lambda=0,2}} = \frac{(1+\alpha(1+\rho))/(1+2\alpha)}{1+\alpha^2(1-\rho^2)/(1+2\alpha)}$$

$$RE_{1,3}(\tau) = \frac{\sigma^2_{\tau,1}}{\sigma^2_{\tau,3}} = \frac{1+\alpha(1-\rho^2)}{1+\alpha^2(1-\rho^2)/(1+2\alpha)}$$

$$RE_{1,3}(\lambda) = \frac{\sigma^2_{\lambda,1}}{\sigma^2_{\lambda,3}} = \frac{1+\alpha(1-\rho)}{1+\alpha^2(1-\rho^2)/(1+2\alpha)}$$

$$RE_{1,3}(\tau \mid \lambda = 0) = \frac{\sigma^2_{\tau|\lambda=0,1}}{\sigma^2_{\tau|\lambda=0,3}} = \frac{1+\alpha(1+\rho)}{1+\alpha^2(1-\rho^2)/(1+2\alpha)}$$

Since in most crossover studies the correlation between observations on the same patient, ρ , is likely to be large, it is of interest to study the behaviour of the above relative efficiencies as ρ tends to 1. In the limit the relative efficiencies become,

$$\lim_{\rho \to 1} RE_{1,2}(\tau) = \frac{1}{1+2\alpha}$$

$$\lim_{\rho \to 1} RE_{1,2}(\lambda) = \frac{1}{1+2\alpha}$$

$$\lim_{\rho \to 1} RE_{1,2}(\tau \mid \lambda = 0) = 1$$

$$\lim_{\rho \to 1} RE_{1,3}(\tau) = 1$$

$$\lim_{\rho \to 1} RE_{1,3}(\lambda) = 1$$

$$\lim_{\rho \to 1} RE_{1,3}(\tau \mid \lambda = 0) = 1+2\alpha$$

Whilst these limiting relative efficiencies are of interest, in practice $\rho \neq 1$, and therefore it is of interest to investigate further these efficiencies by considering other values of ρ. In Table 9.2 we present values of $RE_{1,2}(\tau)$,$RE_{1,2}(\lambda)$,$RE_{1,2}(\tau \mid \lambda)$,$RE_{1,3}(\tau)$,$RE_{1,3}(\lambda)$ and $RE_{1,3}(\tau \mid \lambda)$ for different values of $\alpha = 0.1, 0.2, 0.3, 0.4, 0.5$ and $\rho = 0.3, 0.5, 0.7, 0.9$.

The limiting relative efficiencies, and those in Table 9.2, mirror precisely the behaviour of the posterior distributions in Figure 9.1 and therefore we are forced to conclude :

(i) if we may assume that there is no carryover effect then there is nothing to be gained by taking account of patients for whom complete data is not available.

TABLE 9.2 Relative Efficiencies in Two Period Crossovers with Missing Data

		Relative Efficiencies					
α	ρ	$RE_{1.3}(\tau)$	$RE_{1.3}(\lambda)$	$RE_{1.3}(\tau \mid \lambda)$	$RE_{1.2}(\tau)$	$RE_{1.2}(\lambda)$	$RE_{1.2}(\tau \mid \lambda)$
0.1	0.3	1.083	1.062	1.122	0.902	0.885	0.935
	0.5	1.068	1.043	1.143	0.890	0.870	0.952
	0.7	1.047	1.026	1.165	0.872	0.855	0.971
	0.9	1.017	1.008	1.188	0.847	0.840	0.990
0.2	0.3	1.152	1.111	1.228	0.823	0.794	0.877
	0.5	1.126	1.077	1.273	0.804	0.769	0.909
	0.7	1.086	1.045	1.321	0.776	0.746	0.943
	0.9	1.032	1.014	1.373	0.737	0.725	0.980
0.3	0.3	1.211	1.151	1.322	0.757	0.719	0.826
	0.5	1.175	1.103	1.391	0.734	0.690	0.870
	0.7	1.121	1.060	1.468	0.701	0.662	0.917
	0.9	1.046	1.019	1.553	0.654	0.637	0.971
0.4	0.3	1.262	1.184	1.406	0.701	0.658	0.781
	0.5	1.219	1.125	1.500	0.677	0.625	0.833
	0.7	1.152	1.071	1.607	0.640	0.595	0.893
	0.9	1.058	1.023	1.731	0.588	0.568	0.962
0.5	0.3	1.306	1.212	1.481	0.653	0.606	0.741
	0.5	1.257	1.143	1.600	0.629	0.571	0.800
	0.7	1.180	1.081	1.739	0.590	0.541	0.870
	0.9	1.070	1.026	1.905	0.535	0.513	0.952

(ii) if we need to make inferences about the carryover effect, or if the assumption of no carryover effect is not tenable and therefore the marginal posterior of the treatment effect needs to be used rather than the conditional posterior, considerable gains may be made by taking into account missing data.

The above results suggest, potentially at least, that if we are to perform the Bayes factor analysis derived in §4.4 then we need to use patients for whom not all data are available. In this instance the calculation of the Bayes factor needs to be carried out wholly numerically. The program given in Appendix A6.3 was written to carry out the required numeric integrations. No further work is required to determine the ratio of undefined constants in this approach, since Good's device of imaginary results provides exactly the same value, namely $\sqrt{\frac{3}{4}}$, for both the missing and complete data cases. The Bayes factors for the Maas *et al* example are :

Complete	: 1.050
Including patients with missing data	: 1.035
Excluding patients with missing data	: 1.243

and as might be expected, taking into account missing data gives a closer reflection of the complete data case than does excluding patients with missing data.

10 ACUTE TOXICITY TESTING AND LD50 ESTIMATION - A REVIEW.

10.1 Introduction.

The basis of all modern work on acute toxicity testing and LD_{50} estimation is an article by Trevan(1927), although as Stigler(1986) points out the most familiar model associated with LD_{50} estimation, the probit model, can be traced back to Fechner's work on stimulus-response model during the last century (Fechner, 1860). Trevan's objective was to investigate whether the then popular "minimum lethal dose" was a good measure of the toxicity of a drug or whether other measures could be determined which were in some sense better. Trevan concluded that,

> '... toxicity should be stated primarily in terms of "median lethal dose", that is the dose which kills 50 percent of a large group of animals. As a convenient abbreviation I would suggest for this the symbol LD 50, ...' (Trevan, 1927, p. 490)

There were two major reasons for Trevan's conclusion. First, he argued that the median lethal dose was a simply-understood concept which scientists would readily recognize. Second, he pointed out that the median lethal dose has the advantage that it is in a region of doses which can be estimated with the smallest variance.

Interestingly, Trevan was primarily interested in assaying biologically substances such as insulin and digitalis which could not then be analysed chemically and we will see in §13 that such applications are still relevant today. The method was in time adopted for toxicological purposes and was for a long time considered to be a very valuable means of determining the likely consequences to man of, for example, accidental overdosage with a drug or inadvertent ingestion of a chemical. In addition to its role in safeguarding human health, the LD_{50} test also became a mandatory requirement for the registration of both pharmaceutical and industrial chemicals.

For this latter purpose, the need for a precise determination of the LD_{50} value led to the routine use of large numbers of animals in order to minimise statistical variability even though it has long be known, by toxicologists and statisticians working in the area, that the LD_{50} value is susceptible to minor changes in experimental conditions and that, however many animals are used, it is subject to wide variability. Hence, a 'classical' or 'formal' LD_{50} test is one in which the primary aim is the determination of a 'precise' LD_{50} value, using a defined set of experimental conditions. In general, this requires between 80 and 100 animals, although pre-1970 many more than 100 animals were used. The test was often required in two rodent species and by a variety of routes of administration, depending on the type of chemical being used.

In the present section we concentrate on the traditional methods of estimation in 'classical' LD_{50} tests, concentrating on maximum likelihood estimation. At the end of the section we review the modern controversy surrounding LD_{50} tests and the alternatives which have been put forward.

10.2 Tolerance Distributions.

One of the primary concepts in biological assays in general and in LD_{50} tests in particular is that of the tolerance distribution. Essentially the idea behind the tolerance distribution is that for each individual in a population there is a specific stimulus, or dose, below which no reaction, or response, occurs and above which it does. Clearly it is unlikely that each individual in the population has the same cut-off dose or tolerance and therefore the idea of a distribution of tolerances across the population is a logical development.

Suppose that the tolerance dose is given by δ which has a distribution in the population which may be denoted by $f(\delta)$. If a dose δ_0 were to be given to the whole population then all individuals within the population whose tolerances are less than δ_0 will respond, in the present context die. Clearly the proportion of the population who will die is given by,

$$P(\delta_0) = \int_0^{\delta_0} f(\delta) d\delta$$

The median of the tolerance distribution, δ_μ is by definition given by,

$$\int_0^{\delta_\mu} f(\delta) d\delta = 0.5$$

and it is this quantity , that is the dose which will kill 50% of the population subjected to it which is the LD_{50} and which we need to estimate.

Clearly, any estimate of the LD_{50} will depend upon the particular tolerance distribution which is assumed. Traditionally it has been assumed that the tolerance distribution is lognormal although other distributions, for example the log-logistic, have been used. Under a lognormal distribution with parameters μ and σ the probability of a response given a dose δ_0 may be expressed as

$$P(\delta_0) = \Phi[(\log(\delta_0) - \mu)/\sigma]$$

and where μ is the $\log(LD_{50})$.

In the next section we outline how maximum likelihood may be used to estimate μ.

10.3 Maximum Likelihood Estimation.

Suppose in k dose groups each of n_i animals are exposed to a dose d_i of a test substance, and further that a log-normal tolerance distribution is appropriate. As we have seen above under this model the probability of dying given a dose d_i is

$$P_i = \Phi[\alpha + \beta \log(d_i)] \qquad (10.1)$$

where $\Phi(x)$ is the standard normal cumulative distribution function, α and β are related to the parameters μ and σ of the tolerance distribution by

$$\alpha = -\mu/\sigma \ , \ \beta = 1/\sigma$$

Suppose that of the n_i animals dosed with d_i, r_i die within the observational period, then the log-likelihood function has the form

$$l = \sum_{i=1}^{k} r_i \log(P_i) + (n_i - r_i)\log(1 - P_i) \qquad (10.2)$$

The maximum of the log-likelihood function defined by (10.1) and (10.2) is not available analytically and therefore numerical methods need to be resorted to.

From (10.1) and (10.2) the first and second partial derivatives of l with respect to α and β may be shown to have the form

$$\frac{\partial l}{\partial \alpha} = \sum_{i=1}^{k} \left(\frac{r_i}{P_i} - \frac{n_i - r_i}{1 - P_i} \right) \phi[\alpha + \beta \log(d_i)]$$

$$\frac{\partial l}{\partial \beta} = \sum_{i=1}^{k} \left(\frac{r_i}{P_i} - \frac{n_i - r_i}{1 - P_i} \right) \phi[\alpha + \beta \log(d_i)] \log(d_i)$$

$$\frac{\partial^2 l}{\partial \alpha^2} = -\sum_{i=1}^{k} \left[\left(\frac{r_i}{P_i^2} + \frac{n_i - r_i}{(1 - P_i)^2} \right) \phi^2[\alpha + \beta \log(d_i)] + \left(\frac{r_i}{P_i} - \frac{n_i - r_i}{1 - P_i} \right) \phi[\alpha + \beta \log(d_i)](\alpha + \beta \log(d_i)) \right]$$

$$\frac{\partial^2 l}{\partial \alpha \partial \beta} = -\sum_{i=1}^{k} \left[\left(\frac{r_i}{P_i^2} + \frac{n_i - r_i}{(1 - P_i)^2} \right) \phi^2[\alpha + \beta \log(d_i)] + \left(\frac{r_i}{P_i} - \frac{n_i - r_i}{1 - P_i} \right) \phi[\alpha + \beta \log(d_i)](\alpha + \beta \log(d_i)) \right] \log(d_i)$$

$$\frac{\partial^2 l}{\partial \beta^2} = -\sum_{i=1}^{k} \left[\left(\frac{r_i}{P_i^2} + \frac{n_i - r_i}{(1 - P_i)^2} \right) \phi^2[\alpha + \beta \log(d_i)] + \left(\frac{r_i}{P_i} - \frac{n_i - r_i}{1 - P_i} \right) \phi[\alpha + \beta \log(d_i)](\alpha + \beta \log(d_i)) \right] \log^2(d_i)$$

From these derivatives an iterative procedure may be derived as follows. Suppose that α_r and β_r are the current estimates of α and β, then the next estimates are given by,

$$\begin{pmatrix} \alpha_{r+1} \\ \beta_{r+1} \end{pmatrix} = \begin{pmatrix} \alpha_r \\ \beta r \end{pmatrix} - \begin{pmatrix} \frac{\partial^2 l}{\partial \alpha^2} & \frac{\partial^2 l}{\partial \alpha \partial \beta} \\ \frac{\partial^2 l}{\partial \alpha \partial \beta} & \frac{\partial^2 l}{\partial \beta^2} \end{pmatrix}^{-1} \begin{pmatrix} \frac{\partial l}{\partial \alpha} \\ \frac{\partial l}{\partial \beta} \end{pmatrix}$$

where the second and third terms on the right-hand side are evaluated at α_r and β_r. At convergence the asymptotic variance of the estimates are given by,

$$\begin{pmatrix} \hat{\sigma}_\alpha^2 & \hat{\sigma}_{\alpha\beta} \\ \hat{\sigma}_{\alpha\beta} & \hat{\sigma}_\beta^2 \end{pmatrix} = -\begin{pmatrix} \frac{\partial^2 l}{\partial \alpha^2} & \frac{\partial^2 l}{\partial \alpha \partial \beta} \\ \frac{\partial^2 l}{\partial \alpha \partial \beta} & \frac{\partial^2 l}{\partial \beta^2} \end{pmatrix}^{-1}$$

10.4 Fieller's Theorem.

The analysis in the previous section provides an estimate of the $\log(LD_{50})$, $\hat{\mu} = -\hat{\alpha}/\hat{\beta}$. A 'confidence interval' for the $\log(LD_{50})$ is available from Fieller's theorem.

Under the assumption that the estimates $\hat{\alpha}$ and $\hat{\beta}$ are asymptotically normally distributed with means α and β with covariance matrix having elements $\hat{\sigma}_\alpha^2$, $\hat{\sigma}_{\alpha\beta}$ and $\hat{\sigma}_\beta^2$ then from standard properties of a normal distribution we have

$$\frac{\hat{\alpha} + \hat{\beta}\mu}{(\hat{\sigma}_\alpha^2 + 2\mu\hat{\sigma}_{\alpha\beta} + \mu^2\hat{\sigma}_\beta^2)^{1/2}} \sim N(0,1)$$

This asymptotic property may be used to derive a 95% confidence interval μ by setting the left-hand side equal to the 2.5% point of the normal distribution and solving for μ. This procedure gives rise to a quadratic equation in μ which does not necessarily have real roots. When this occurs the implied 95% confidence interval covers the whole real line, a well-known defect of the approach.

10.5 The Modern Controversy.

Whilst the campaign against the use of large numbers of animals in LD_{50} experiments is a campaign based firmly in the 1980's, some of the basic arguments of the campaigners are not new. For example C.W.Hume, the then secretary general of the Universities Federation for Animal Welfare, wrote over 30 years ago,

> "One cannot help wondering how far the extensive use of the 50%-survival test is a hangover due to habit and custom, and whether suitable continuous variates have been sought as diligently as could be desired. Even for testing toxicity with an L.D.50, death might not be the only possible end-point that could be chosen if the phenomena of the moribund state were to be adequately analysed" (Hume,1957).

The sentiments expressed in this passage can be seen to be precursors of the views of the harsher environment of the 1980's :

> "If I want to keep my job, I am better off doing toxicology *their* way and forgetting about creativity. And if I hope to market my drug on a worldwide basis, I am going to use the guidelines that are

the most demanding with regard to number of species, subjects and dose levels, and duration of treatment. I can be sure that no regulatory agency will object to a toxicological dossier that is more voluminous than the one it might consider desirable or necessary" (Zbinden,1988).

"Lethality as an endpoint, although definite and incontravertible [sic], is crude and causes much suffering" (Anon,1989).

The fight against the LD_{50} has been on two fronts. Firstly the more radical animal rights groups refer to the test as the 'death test' and use photographs in their literature of animals killed by agrochemicals and cosmetics. The less radical animal welfare groups argue that since the LD_{50} cannot be determined precisely, the performance of such tests is unnecessary and morally unacceptable. The second front has been manned by toxicologists who whilst they have recognized the need to measure the acute toxicity of chemicals are also concerned to reduce both the suffering of animals and number of animals used in acute toxicity tests.

In the early 1980's most regulatory authorities based their testing guidelines on those of the OECD whose guideline required the use of, in general, no more than 30 animals per test and , where no mortality was anticipated at a dose level of 5000 *mg/kg* bodyweight, as few as 10 animals - the so-called 'limit' test. Whilst most regulatory authorities supported the principle that acute toxicity tests should not be solely lethality tests, the determination of a statistically-derived LD_{50} was required as were 95% confidence limits for the estimate, it was also recognised that acute toxicity tests give other extremely important information, which is essential for safeguarding human health. For example the 1984 EEC guidelines required documentation of the relationship between the animals' exposure to the test substance and the incidence and severity of behavioural and clinical abnormalities, effects on major organs and bodyweight changes.

The pressure, from animal welfare activists, toxicologists and regulators led to a number of suggestions for altering the basic procedure for estimating acute toxicity and the LD_{50}, example of these are provided by Müller and Kleyt(1982), Schütz and Fuchs(1982), Lorke(1983) and Bruce(1985,1987). In 1986 a meeting of 'experts' in Paris considered three alternative procedures for acute toxicity testing, namely the Fixed Dose Procedures of the British Toxicology Society (BTS) and German Bundesgesundheitsamt and the so-called Up-and-Down Procedure. The BTS procedure alone amongst the three goes further in that it positively discourages lethality as an endpoint and therefore the suffering of animals is dramatically reduced.

One potential argument against the use of a procedure, such as the BTS procedure, which is not based on the formal determination of an LD_{50} is that it will prove difficult to classify substances against existing classification schemes which are based on the LD_{50}. In fact the validation work reported by van den Heuvel *et al*(1987) has shown that the BTS procedure gives extremely similar results when compared with the 1981 OECD procedure both in terms of ranking compounds according to their acute toxicity and in providing information for human risk assessment. The procedure also offers significant reductions in animal numbers and, from an animal welfare perspective, is preferable as the severity of effects which are seen is considerably reduced.

It is likely that in the future the BTS procedure will become the standard for acute toxicity testing. In the meantime classical acute toxicity tests are still carried out and while that is the case there is still a need to optimise the extraction of information from such tests and therefore it is the role of the statistician to develop statistical methods with that objective. The Bayesian approach developed in the following chapter is aimed at providing a classification of a substance on the basis of a classification scheme based on the LD_{50}, as such it may be seen as belonging to those procedures developed during the 1980's referred to above.

11 A BAYESIAN APPROACH TO LD50 EXPERIMENTS.

11.1 Introduction.

As we have noted, the recent controversy surrounding the validity and usefulness of the acute toxicity test has markedly increased. On the one hand animal protection groups question the biological relevance of such tests citing examples in which limited, or insignificant, information is obtained. Toxicologists, on the other hand, emphasize the need to quantify the toxic potential of a chemical while at the same time they encourage procedures designed to limit the number of animals required to give an assessment of lethality (Bass *et al*, 1982; Dayan *et al*, 1984). This desire to limit the number of experimental animals has given rise to a number of recent suggestions for modifying the standard practice in acute toxicity testing (see Müller and Kley, 1982; Schütz and Fuchs, 1982; Lorke, 1983).

In such toxicity tests the response of an animal to the test substance is dichotomous; alive/dead or no response/response. The design of such a test consists of k dose levels on an appropriate scale. The experiments may be characterized by the triplets $d_i, n_i, r_i (i = 1, \ldots k)$ where d_i is the dose administered to n_i animals of which r_i respond in the i^{th} dose group. A mathematical dose-response function relating the probability of response to the dose, usually the probit or logit model, is specified. Based on the above triplets, the parameters of either model are traditionally estimated by maximum likelihood, weighted least-squares or minimum chi-square (Finney,1971). In this type of experiment the median lethal dose, or $LD50$, is of main interest, being defined as the dose, or quantity, of the substance which kills 50% of the animals exposed to it (in this thesis we regard the median lethal dose and the $LD50$ as being synonymous in contrast to some authors who view the $LD50$ as that dose *in the current experiment* which killed 50% of the test animals).

It is well known that under certain conditions the traditional methods of analysis give rise to inadequate results, in that although they provide a point estimate of the $LD50$, the fiducial limits, at some specified level of confidence, will consist of the whole real line (Fieller, 1954;Finney,1971, Section 4.7). In this chapter the view is taken that the object of estimating the $LD50$ is to determine an index of the toxicity of a substance by means of some predefined toxicity classes. For instance, the European Economic Community has defined the following toxicity classes for classifying the lethality of substances based on the $LD50$ values from oral studies in rats (Annex VI of the Council Directive 67/548/EEC - Sixth Amendment) :

TABLE 11.1 Toxicity Classes - Annex VI of the Council Directive 67/548/EEC - Sixth Amendment.

Toxicity Class	Description	Range of $LD50$ (mg./kg.)
1	very toxic	< 25
2	toxic	25 - 200
3	harmful	200 - 2000
4	practically non-toxic	> 2000

A second example comes from the 1983 Swiss poison regulation again using oral $LD50$ values in rats:

TABLE 11.2 Toxicity Clas ses - 1983 Swiss Poison Regulation.

Toxicity Class	Range of $LD50$ (mg./kg.)
1	< 5
2	5 - 50
3	50 - 500
4	500 - 2000
5	2000 - 5000

The motivation for the present work arose from the need to classify a substance which in an acute toxicity test gave the data in Table 11.3.

TABLE 11.3 Results from an Acute Toxicity Experiment

Dose (mg./kg.)	Number of Animals Exposed	Number of Animals Dying
500	5	1
1000	5	2
2500	5	3
5000	5	2

Using maximum likelihood to estimate the parameters of the probit model (using a log dose scale) gives 4049 mg./kg. as a point estimate for the $LD50$. However this is one of the above examples for which the 95% fiducial limits comprise the whole positive real axis, a result practically useless for classifying the substance. We would argue that classical methods cannot answer the question of interest - Which toxicity class does the substance belong to ? - whereas a Bayesian approach can. However even if the regulatory authorities require a point estimate and a confidence interval, a Bayesian approach is preferable since a highest posterior density (H.P.D.) interval will always exist, if a proper prior is used; and will exist in all but pathological cases if an improper prior is used (Tsutakawa,1975). This is not the case for fiducial limits, based on Fieller's Theorem.

In this chapter a Bayesian analysis is developed in which emphasis is placed on calculating the posterior probabilities of a substance belonging to predetermined toxicity classes. Two cases are considered: (i) an improper prior distribution for the parameters of the model; (ii) a normal prior distribution for the parameters of the model. Methods of determining from toxicologists their prior beliefs in the parameters of the model are considered. Approximations to the various posterior distributions are developed.

We have already seen that it has been argued (Zbinden and Flury-Roversi,1981; Kimber,1986) that it is incorrect to judge a substance's toxicity solely on the basis of the $LD50$. We do not dispute this point of view but would agree with the following sentiments :

"... if the LD_{50} is wanted it should be obtained as efficiently as possible in respect of number of test animals used and in relation to optimal extraction of information from the data".

"as long as the LD_{50} is used, there is no excuse (scientific or economic) for not estimating according to some accepted criterion of optimality". (Finney,1985).

11.2 A Bayesian Analysis Using an Improper prior.

In this thesis we choose in the main to use the probit model, although the methods have also been successfully implemented using the logit. Let k doses of a substance $d_i (i = 1, \ldots, k)$ be administered to $n_i (i = 1, \ldots, k)$ animals of which $r_i (i = 1, \ldots, k)$ respond, then the likelihood $L(\alpha, \beta \mid X)$, where α and β are the parameters of the probit model and X denotes the data, is given by,

$$L(\alpha, \beta \mid X) = \prod_{i=1}^{k} \Phi(\alpha + \beta x_i)^{r_i} [1 - \Phi(\alpha + \beta x_i)]^{n_i - r_i} \qquad (11.1)$$

where $\Phi(.)$ is the standard normal distribution function and $x_i = \log(d_i)$. Assuming an improper prior for α and β, that is

$$p_C(\alpha, \beta) = constant \quad -\infty < \alpha < \infty \;,\; 0 < \beta < \infty \qquad (11.2)$$

(C denotes the constraint $\beta > 0$) use of Bayes' theorem gives,

$$p_C(\alpha, \beta \mid X) = \frac{L(\alpha, \beta \mid X) p_C(\alpha, \beta)}{p_C(X)} \qquad (11.3)$$

where,

$$p_C(X) = \int_{-\infty}^{\infty} \int_{0}^{\infty} L(\alpha, \beta \mid X) p_C(\alpha, \beta) d\beta d\alpha \qquad (11.4)$$

Letting $w = -\alpha/\beta$ be the $\log(LD50)$ we have,

$$p_C(w \mid X) = \int_{0}^{\infty} \beta p_C(-w\beta, \beta \mid X) d\beta \quad -\infty < w < \infty \qquad (11.5)$$

and supposing a toxicity class, on the log-scale, to be defined by w_L and w_U, we may calculate,

$$P[w_L < w < w_U \mid X] = \int_{w_L}^{w_U} p_C(w \mid X) dw \qquad (11.6)$$

Equations (11.1) to (11.6) provide all the necessary information to make inferences concerning the $LD50$. However because of the non-linearity of the probit model the integrations in (11.4),(11.5) and (11.6) cannot be performed analytically. Thus either numerical integration methods need to be resorted to, or approximations sought.

The numerical integration problems may be simplified by redefining the range of β in (11.2). Thus if β is not constrained to be greater than zero, and writing $p_U(\alpha,\beta)$ for this unconstrained prior distribution then,

$$p_U(\alpha,\beta \mid X) = \frac{L(\alpha,\beta \mid X)p_U(\alpha,\beta)}{p_U(Y)} \qquad (11.7)$$

where,

$$p_U(X) = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} L(\alpha,\beta \mid X)p_U(\alpha,\beta)d\beta d\alpha \qquad (11.8)$$

Using the results in Box and Tiao(1973, Section 1.5) we have,

$$p_C(\alpha,\beta \mid X) = \frac{p_U(\alpha,\beta \mid X)P(\beta>0 \mid \alpha,\beta,X)}{P(\beta>0 \mid X)} = \frac{p_U(\alpha,\beta \wedge \beta>0 \mid X)}{P(\beta>0 \mid X)} \qquad (11.9)$$

and

$$p_C(w \mid X) = \frac{\int_0^{\infty} p_U(-w\beta,\beta \wedge \beta>0 \mid X)d\beta}{P(\beta>0 \mid X)} \quad , -\infty < w < \infty \qquad (11.10)$$

The methods described by Naylor and Smith(1982) could be used to perform the integrations in (11.8),(11.9),(11.11) and (11.6). However this is not recommended since it would involve using indicator functions for calculating $P(\beta>0 \mid X)$ and for calculating (11.6), which practice has shown can seriously underestimate or overestimate the required probabilities. Alternatively a modification of the quadrature rules developed by Galant(1969) and Steen *et al*(1969) may be used to integrate over β . These rules were developed for integrals of the form,

$$\int_0^b \exp(-x^2)f(x)dx$$

but may be simply modified for integrals of the form,

$$\int_b^{\infty} \exp(-x^2)f(x)dx$$

see Appendix A2.2.

If the doses have been chosen on a true log-scale, or if they are not far from it, instead of using numerical integration an approximation can be developed which may be used even for small sample sizes. We illustrate how this may be achieved using the hypothetical example shown in Table 11.4.

Using the Gauss-Hermite quadrature described by Naylor and Smith(1982) the double integration in (11.8) is efficiently performed from which (11.7) is simply obtained. Figure 11.1 shows the bivariate 50% and 95% H.P.D. regions for α and β for the data in Table 11.4.

TABLE 11.4 Results from a Hypothetical Experiment

Dose (mg./kg.)	Number of Animals Exposed	Number of Animals Dying
100	3	1
1000	3	2

The contours in Figure 11.1 are very nearly elliptical, suggesting that a bivariate normal (*BN*) approximation to $p_U(\alpha, \beta \mid X)$ may be reasonable. The parameters of the *BN* approximation may be obtained as a by-product of the Naylor and Smith approach, or by a second approximation.

Denoting by $\hat{\alpha}, \hat{\beta}, \hat{\sigma}_\alpha^2, \hat{\sigma}_\beta^2, \hat{\sigma}_{\alpha\beta}$ the maximum likelihood estimates of α and β and their asymptotic variances and covariance, and by $\tilde{\alpha}, \tilde{\beta}, \tilde{\sigma}_\alpha^2, \tilde{\sigma}_\beta^2, \tilde{\sigma}_{\alpha\beta}$ the posterior means,variances and covariance, then from Lindley(1980) the following results are obtained,

$$\tilde{\alpha} = \hat{\alpha} + \frac{1}{2}\hat{L}_{30}\hat{\sigma}_\alpha^4 + \frac{3}{2}\hat{L}_{21}\hat{\sigma}_\alpha^2\hat{\sigma}_{\alpha\beta} + \frac{1}{2}\hat{L}_{12}(\hat{\alpha}_\alpha^2\hat{\sigma}_\beta^2 + 2\hat{\sigma}_{\alpha\beta}^2) + \frac{1}{2}\hat{L}_{03}\hat{\sigma}_\beta^2\hat{\sigma}_{\alpha\beta} + O(N^{-1}) \qquad (11.11)$$

$$\tilde{\beta} = \beta + \frac{1}{2}\hat{L}_{03}\hat{\sigma}_\beta^4 + \frac{3}{2}\hat{L}_{12}\hat{\sigma}_\beta^2\hat{\sigma}_{\alpha\beta} + \frac{1}{2}\hat{L}_{21}(\hat{\alpha}_\alpha^2\hat{\sigma}_\beta^2 + 2\hat{\sigma}_{\alpha\beta}^2) + \frac{1}{2}\hat{L}_{30}\hat{\sigma}_\alpha^2\hat{\sigma}_{\alpha\beta} + O(N^{-1}) \qquad (11.12)$$

where, for example,

$$L_{30} = \frac{\partial^3\{\log[L(\alpha,\beta \mid X)]\}}{\partial\alpha^3}\Big|_{\alpha=\hat{\alpha}} \quad \text{and} \quad N = \sum_{i=1}^{k} n_i$$

The required differentials may be derived as follows :

$$l = \log[L(\alpha,\beta \mid X)] = \sum_{i=1}^{k} r_i\log(P_i) + (n_i - r_i)\log(1-P_i)$$

where $P_i = \Phi(\Delta_i)$ and $\Delta_i = \alpha + \beta x_i$ then,

$$L_{10} = \frac{\partial l}{\partial\alpha} = \sum_{i=1}^{k}\left(\frac{r_i}{P_i} - \frac{n_i - r_i}{1-P_i}\right)\phi(\Delta_i)$$

$$L_{01} = \frac{\partial l}{\partial\beta} = \sum_{i=1}^{k}\left(\frac{r_i}{P_i} - \frac{n_i - r_i}{1-P_i}\right)x_i\phi(\Delta_i)$$

$$L_{20} = \frac{\partial^2 l}{\partial\alpha^2} = \sum_{i=1}^{k}\left(-\frac{r_i}{P_i^2} - \frac{n_i - r_i}{(1-P_i)^2}\right)\phi^2(\Delta_i) - \sum_{i=1}^{k}\left(\frac{r_i}{P_i} - \frac{n_i - r_i}{1-P_i}\right)\Delta_i\phi(\Delta_i)$$

$$L_{11} = \frac{\partial^2 l}{\partial\alpha\partial\beta} = \sum_{i=1}^{k}\left(-\frac{r_i}{P_i^2} - \frac{n_i - r_i}{(1-P_i)^2}\right)x_i\phi^2(\Delta_i) - \sum_{i=1}^{k}\left(\frac{r_i}{P_i} - \frac{n_i - r_i}{1-P_i}\right)x_i\Delta_i\phi(\Delta_i)$$

$$L_{02} = \frac{\partial^2 l}{\partial\beta^2} = \sum_{i=1}^{k}\left(-\frac{r_i}{P_i^2} - \frac{n_i - r_i}{(1-P_i)^2}\right)x_i^2\phi^2(\Delta_i) - \sum_{i=1}^{k}\left(\frac{r_i}{P_i} - \frac{n_i - r_i}{1-P_i}\right)x_i^2\phi\Delta_i(\Delta_i)$$

$$L_{30} = \frac{\partial^2 l}{\partial\alpha^3} = 2\sum_{i=1}^{k}\left(\frac{r_i}{P_i^3} - \frac{n_i - r_i}{(1-P_i)^2}\right)\phi^3(\Delta_i) - 3\sum_{i=1}^{k}\left(-\frac{r_i}{P_i^2} - \frac{n_i - r_i}{(1-P_i)^2}\right)\Delta_i\phi^2(\Delta_i)$$
$$+ \sum_{i=1}^{k}\left(\frac{r_i}{P_i} - \frac{n_i - r_i}{1-P_i}\right)(\Delta_i^2 - 1)\phi(\Delta_i)$$

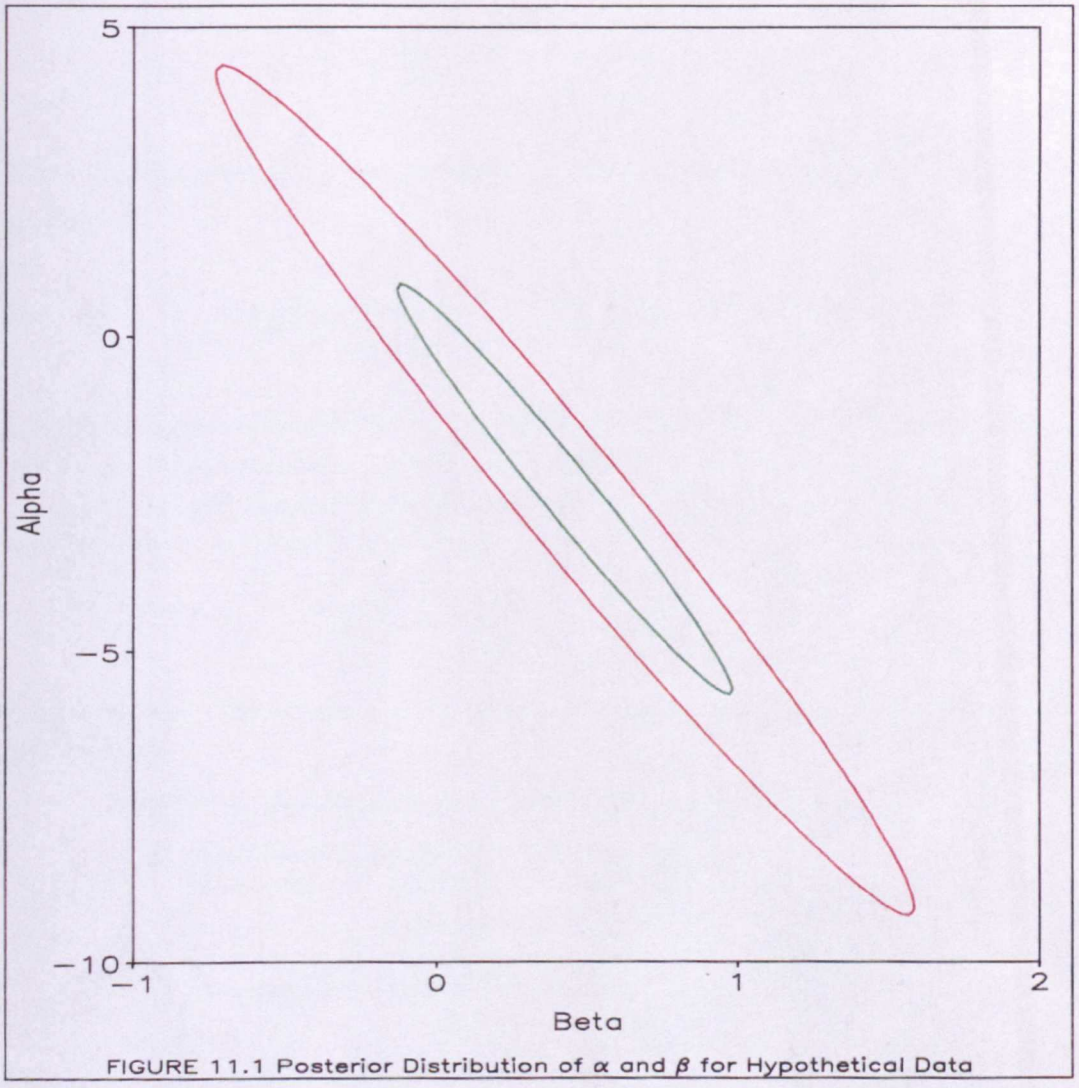


FIGURE 11.1 Posterior Distribution of α and β for Hypothetical Data

$$L_{21} = \frac{\partial^2 l}{\partial\alpha^2\partial\beta} = 2\sum_{i=1}^{k}\left(\frac{r_i}{P_i^3}-\frac{n_i-r_i}{(1-P_i)^2}\right)x_i\phi^3(\Delta_i) - 3\sum_{i=1}^{k}\left(-\frac{r_i}{P_i^2}-\frac{n_i-r_i}{(1-P_i)^2}\right)x_i\Delta_i\phi^2(\Delta_i) + \sum_{i=1}^{k}\left(\frac{r_i}{P_i}-\frac{n_i-r_i}{1-P_i}\right)x_i(\Delta_i^2-1)\phi(\Delta_i)$$

$$L_{12} = \frac{\partial^2 l}{\partial\alpha\partial\beta^2} = 2\sum_{i=1}^{k}\left(\frac{r_i}{P_i^3}-\frac{n_i-r_i}{(1-P_i)^2}\right)x_i^2\phi^3(\Delta_i) - 3\sum_{i=1}^{k}\left(-\frac{r_i}{P_i^2}-\frac{n_i-r_i}{(1-P_i)^2}\right)x_i^2\Delta_i\phi^2(\Delta_i) + \sum_{i=1}^{k}\left(\frac{r_i}{P_i}-\frac{n_i-r_i}{1-P_i}\right)x_i^2(\Delta_i^2-1)\phi(\Delta_i)$$

$$L_{03} = \frac{\partial^2 l}{\partial\beta^3} = 2\sum_{i=1}^{k}\left(\frac{r_i}{P_i^3}-\frac{n_i-r_i}{(1-P_i)^2}\right)x_i^3\phi^3(\Delta_i) - 3\sum_{i=1}^{k}\left(-\frac{r_i}{P_i^2}-\frac{n_i-r_i}{(1-P_i)^2}\right)x_i^3\Delta_i\phi^2(\Delta_i) + \sum_{i=1}^{k}\left(\frac{r_i}{P_i}-\frac{n_i-r_i}{1-P_i}\right)x_i^3(\Delta_i^2-1)\phi(\Delta_i)$$

Each of the above expressions is to be evaluated at the maximum likelihood estimates $\hat{\alpha}$ and $\hat{\beta}$.

Additionally,

$$\hat{\sigma}_\alpha^2 = \frac{-L_{02}}{L_{20}L_{02}-L_{11}^2} \; ; \; \hat{\sigma}_{\alpha\beta} = \frac{L_{11}}{L_{20}L_{02}-L_{11}^2} \; ; \; \hat{\sigma}_\beta^2 = \frac{-L_{20}}{L_{20}L_{02}-L_{11}^2}$$

As Lindley notes similar corrections to $O(N^{-1})$ are not available for the variances and covariance. However, although it has not been possible to prove the following result, in a large number of cases over a wide range of total sample sizes and different values of k, the number of groups, it has been found to be very accurate. Define $\delta = (\tilde{\alpha}-\hat{\alpha})/\tilde{\alpha} \approx (\tilde{\beta}-\hat{\beta})/\tilde{\beta}$ then take,

$$\frac{\tilde{\sigma}_\alpha^2-\hat{\sigma}_\alpha^2}{\tilde{\sigma}_\alpha^2} \approx \frac{\tilde{\sigma}_\beta^2-\hat{\sigma}_\beta^2}{\tilde{\sigma}_\beta^2} \approx \frac{\tilde{\sigma}_{\alpha\beta}-\hat{\sigma}_{\alpha\beta}}{\tilde{\sigma}_{\alpha\beta}} \approx \delta/2$$

To illustrate the use of these corrections we have applied them to the data of Table 11.4, the results being shown in Table 11.5.

TABLE 11.5 Approximations to Posterior Moments for Hypothetical Example

Parameter	Maximum Likelihood Estimates	Posterior Moments	Approximate Posterior Moments
α	-2.154	-2.443	-2.436
β	0.374	0.424	0.423
σ_α^2	7.284	7.730	7.706
σ_β^2	0.211	0.224	0.224
$\sigma_{\alpha\beta}$	-1.217	-1.291	-1.287

The results in Table 11.5 are satisfactory in that they correspond, in the case of approximate posterior means to a relative error of less than 0.3%, while the corresponding relative errors for approximate second moments are less than 0.4%. (An alternative approach would be to use the approximation developed by Tierney and Kadane(1986) which has the advantage that it also provides corrections for second order moments).

Suppose now that $p_U(\alpha, \beta \mid X)$ may be approximated by a *BN* density with means $\tilde{\alpha}, \tilde{\beta}$ variances $\tilde{\sigma}_\alpha^2, \tilde{\sigma}_\beta^2$ and covariance $\tilde{\sigma}_{\alpha\beta}$ denoted by $BN(\mu, \Sigma)$where,

$$\mu = \begin{pmatrix} \tilde{\alpha} \\ \tilde{\beta} \end{pmatrix} \text{ and } \Sigma = \begin{pmatrix} \tilde{\sigma}_\alpha^2 & \tilde{\sigma}_{\alpha\beta} \\ \tilde{\sigma}_{\alpha\beta} & \tilde{\sigma}_\beta^2 \end{pmatrix} \tag{11.13}$$

then

$$p_C(\alpha, \beta \mid X) = \frac{BN(\mu, \Sigma)}{\Phi(\tilde{\beta}/\tilde{\sigma}_\beta)}, \quad \beta > 0$$

Using the results in the Appendix the posterior distribution of $w = \log(LD50)$ given the constraint $\beta > 0$ may be calculated from (A4.2), while inferences of the form (11.6) may be derived from (A4.4).

Application of the double-fold approximation, the *BN* distribution for $p_U(\alpha, \beta \mid X)$ and the approximate means, variances and covariance is shown in Table 11.6 using the Swiss toxicity classes, from which it can be seen that the approximations are satisfactory. The exact probabilities in this table were calculated using subroutine DBLIN from the IMSL library of subroutines.

TABLE 11.6 Exact Posterior Probabilities of Toxicity Classes and Approximate Probabilities for the Data in Table 11.4.

	Toxicity Classes					
	1	2	3	4	5	>5000 mg/kg
Exact Probabilities	0.041	0.062	0.570	0.224	0.038	0.065
Probabilities based on Normal Approx. (exact Moments)	0.042	0.061	0.576	0.219	0.037	0.065
Probabilities based on Normal Approx. (approx. moments)	0.042	0.061	0.576	0.219	0.037	0.066

Returning to the example in Table 11.3., which was the motivation behind this work, the probabilities that the substance belongs to the various toxicity classes are shown in Table 11.7. From these results it may be seen that, although we may not definitely decide into which class the substance should be placed, it is extremely unlikely that it belongs to classes 1, 2, or 3, since their total probability is 0.03. Further experimentation would be necessary to determine which of classes 3 or 4 it belongs to or whether the $LD50$ is greater than 5000 mg./kg.

TABLE 11.7 Posterior Probabilities of Toxicity Classes for the Data in Table 11.3.

	Toxicity Classes					
	1	2	3	4	5	>5000 mg/kg
Probabilities	0.005	0.004	0.021	0.232	0.402	0.336

We need not be restricted to calculating the posterior probabilities of the toxicity classes. The results in the Appendix allow us to simply calculate the posterior distribution of $\log(LD50)$ and its cumulative distribution function, or to calculate H.P.D. limits for $\log(LD50)$. To illustrate, Figures 11.2 and 11.3 show the posterior distribution and cumulative posterior distribution respectively, for the data of Table 11.3 whose 95% H.P.D. limits for $\log(LD50)$ are *4.71* and *15.67* corresponding to *111* and $6.38 * 10^6$ mg/kg.

11.3 Exact Analysis for a Logit Model and Two Dose Groups.

We noted in the previous section that numerical methods were needed to calculate the posterior distribution of the LD50 and to make inferences because the necessary integrations could not be performed analytically. This is certainly true for the probit model which we have been considering; however in the case of the logit model there exists one special case for which some progress can be made analytically.

Suppose that an experiment has only two dose groups and that the probability of dying may be described by a logit model so that the likelihood is proportional to,

$$\prod_{i=1}^{2} \frac{\exp(\alpha+\beta x_i)^{r_i}}{(1+\exp(\alpha+\beta x_i))^{n_i}}$$

If the prior for α and β has the form,

$$p_U(\alpha,\beta) = constant \quad ; \quad -\infty < \alpha < \infty \ , \ -\infty < \beta < \infty$$

then

$$p(\alpha,\beta \mid X) = \prod_{i=1}^{2} \frac{\exp(\alpha+\beta x_i)^{r_i}}{(1+\exp(\alpha+\beta x_i))^{n_i}} / p_U(X) \qquad (11.14)$$

where

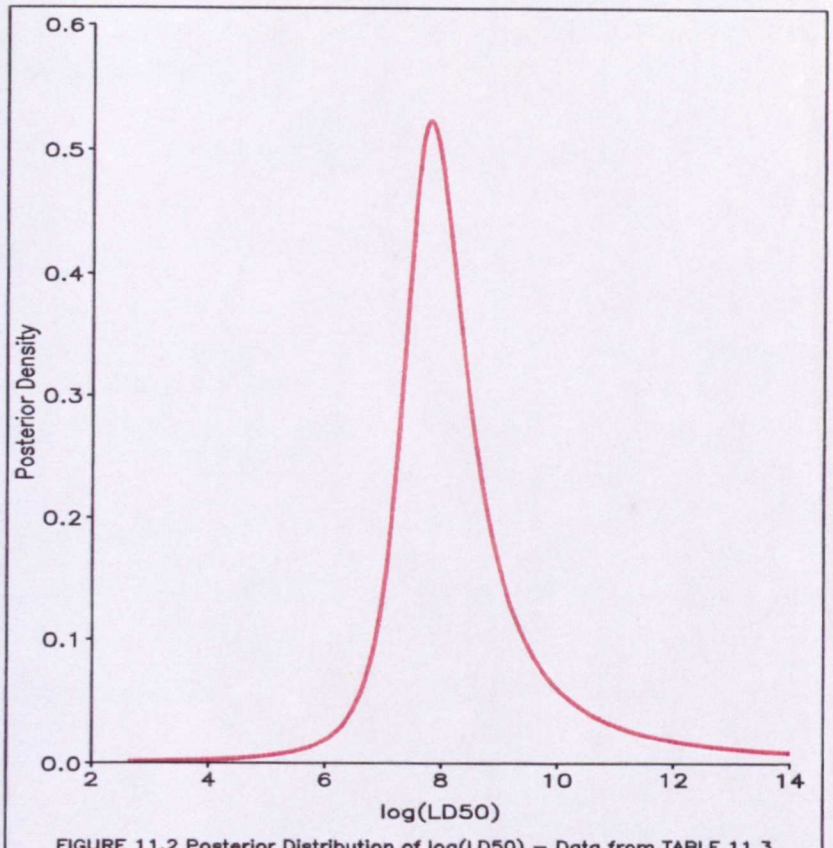


FIGURE 11.2 Posterior Distribution of log(LD50) — Data from TABLE 11.3

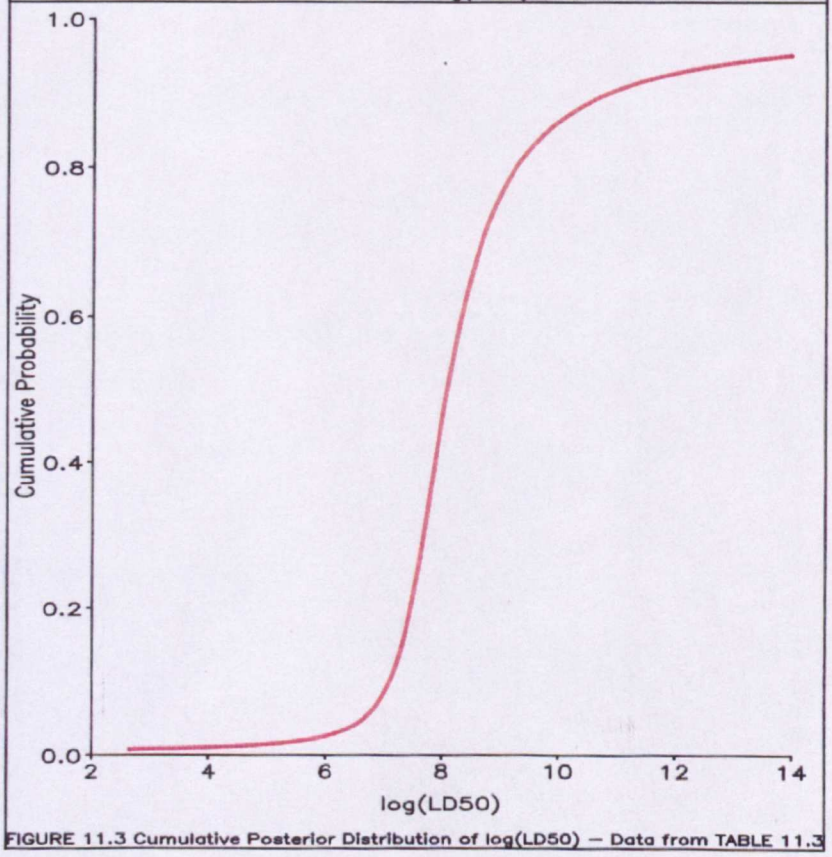


FIGURE 11.3 Cumulative Posterior Distribution of log(LD50) — Data from TABLE 11.3

$$p_U(X) = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\prod_{i=1}^{2}\frac{\exp(\alpha+\beta x_i)^{r_i}}{(1+\exp(\alpha+\beta x_i))^{n_i}}d\alpha d\beta \qquad (11.15)$$

In (11.14) make the transformation

$$\pi_i = \frac{\exp(\alpha+\beta x_i)}{(1+\exp(\alpha+\beta x_i))} \quad (i=1,2) \qquad (11.16)$$

to give,

$$p_U(X) = \int_0^1\int_0^1 \frac{1}{x_2-x_1}\pi_1^{r_1-1}(1-\pi_1)^{n_1-r_1-1}\pi_2^{r_2-1}(1-\pi_2)^{n_2-r_2-1}d\pi_1 d\pi_2$$

$$= \frac{B(r_1,n_1)B(r_2,n_2)}{x_2-x_1}$$

In the case of the constrained prior,

$$p_C(\alpha,\beta) = constant \quad ; \quad -\infty<\alpha<\infty \ , \ 0<\beta<\infty$$

the transformation (11.16) applied to

$$p_C(X) = \int_{-\infty}^{\infty}\int_{0}^{\infty}\prod_{i=1}^{2}\frac{\exp(\alpha+\beta x_i)^{r_i}}{(1+\exp(\alpha+\beta x_i))^{n_i}}d\alpha d\beta$$

gives

$$p_C(X) = \int_0^1\int_0^{\pi_2} \frac{1}{x_2-x_1}\pi_1^{r_1-1}(1-\pi_1)^{n_1-r_1-1}\pi_2^{r_2-1}(1-\pi_2)^{n_2-r_2-1}d\pi_1 d\pi_2$$

$$= \frac{1}{x_2-x_1}\frac{\Gamma(r_2)\Gamma(n_2-r_2)}{\Gamma(n_1+n_2+1)}\sum_{t=0}^{r_2-1}\frac{\Gamma(r_1+r_2-t-1)\Gamma(n_1+n_2-r_1-r_2+t)}{\Gamma(r_2-t)\Gamma(n_2-r_2+t+1)}$$

In order to progress towards the marginal posterior distribution of the $\log(LD50)$, and hence the $LD50$ itself, consider the transformation,

$$y = e^{\beta(x_2-x_1)} \ , \ z = \frac{\alpha}{\beta(x_2-x_1)} + \frac{x_1}{x_2-x_1}$$

with jacobian $\log(y)/(y(x_2-x_1))$ applied to (11.14) which gives,

$$p(y,z\mid X) = \frac{y^{z(r_1+r_2)+r_2-1}\log(y)}{P_U(X)(x_2-x_1)(1+y^z)^{n_1}(1+y^{1-z})^{n_2}} \qquad (11.17)$$

Now since $\log(LD50) = x_1 - z(x_2 - x_1)$, in other words it is a simple linear transformation of z, if we are able to integrate y from (11.17), or its counterpart obtained by replacing $p_U(X)$ by $p_C(X)$, then we may easily obtain the marginal posterior distribution of $\log(LD50)$. One possible method to carry out the integration might be found in the contour integration results given by Whittaker and Watson(1963). We do not propose to take this analysis further since the case of two dose groups is not intrinsically of interest except insofar as it highlights the integration difficulties involved in such problems, and insofar as it might provide a bench-mark against which the analytic approximation derived in §11.2, or other analytic approximations, could be tested.

11.4 A Bayesian Analysis Using an Informative Prior for α and β.

To begin we suppose that prior to performing the current experiment a previous experiment has been performed yielding data X_0. Assuming further that prior to the previous experiment our joint prior distribution for α and β was improper, it follows from standard Bayesian arguments that we may pool the data as if it came from a single experiment. The analysis in §11.2 may then be carried out.

Suppose now, however, that we can approximate our unconstrained prior distribution for α and β by a *BN* distribution; an assumption which will be justified in §11.5. Denoting this unconstrained prior by $BN(\mu_0, \Sigma_0)$, then, since as we have seen in the previous Section for doses on a log-scale the likelihood may be approximated by $BN(\mu, \Sigma)$ - see (11.13), standard Bayesian calculations give,

$$p_U(\alpha, \beta \mid X) = BN(\mu^*, \Sigma^*) \qquad (11.18)$$

where,

$$\Sigma^* = (\Sigma_0^{-1} + \Sigma^{-1})^{-1} \text{ and } \mu^* = \Sigma^*(\Sigma_0^{-1}\mu_0 + \Sigma^{-1}\mu)$$

(see for instance Lindley and Smith,1972, §2). Since $p_U(\alpha, \beta \mid X)$ in (11.18) is approximated by a *BN* distribution the results in the Appendix may be used to make posterior inferences concerning $w = \log(LD50)$ exactly as in §11.2.

If the normal approximation (11.13) does not hold, which can be checked by calculating the third and fourth moments of the posterior marginal distributions of α and β, Lindley's or Tierney and Kadane's approximations for marginal distributions may be directly applied to the product of the prior and likelihood in the parametrisation w and β.

11.5 Determining a Prior Distribution for α and β.

In this section we consider ways in which one can determine an experimenter's prior belief in the parameters of the probit model. Each method which is considered leads to a normal prior distribution for α and β, so that the methods in the previous section may then be used.

For the logit model Tsutakawa(1975) suggests that a parametrisation of the model which is familiar to the experimenter should be chosen. He considers two methods using an experimenter's prior beliefs in the probabilities of response P_1 and P_2 at two dose levels d_1 and d_2. First we investigate the implications of Tsutakawa's methods for the probit model, and second consider a method based on eliciting the experimenter's prior beliefs in the toxicity class to which the test substance belongs.

11.5.1 A Semi-Uninformative Prior Distribution for α and β Determined using Probabilities of Response.

Following Tsutakawa(1975) suppose that P_1 and P_2 are uniformly distributed over the region $0 < P_1 < P_2 < 1$. Tsutakawa shows this to imply that the $LD50$ lies between d_1 and d_2 with probability $1/2$, d_1 and d_2 are respectively the lower and upper prior quartiles for the $LD50$. Further he shows that the prior distribution in terms of α and β belongs to the natural conjugate family of distributions. We now show that the above construction leads, for the probit model, to a BN prior for α and β.

Suppose that P_1 and P_2 are *a priori* uniformly distributed such that $0 < P_1 < P_2 < 1$, then,

$$p(P_1, P_2) = 2 \quad , \quad 0 < P_1 < P_2 < 1$$

Make the transformation,

$$P_i = \Phi(\alpha + \beta x_i) \quad ; \quad x_i = \log(d_i) \quad , \quad i = 1, 2 \tag{11.19}$$

with Jacobian,

$$(x_2 - x_1)\phi(\alpha + \beta x_1)\phi(\alpha + \beta x_2) \tag{11.20}$$

so that,

$$\begin{aligned} p_1(\alpha, \beta) &= \frac{2(x_2 - x_1)}{2\pi} \exp\left[\frac{-1}{2}\{(\alpha + \beta x_1)^2 + (\alpha + \beta x_2)^2\}\right] \\ &= 2BN(\mu_1, \Sigma_1) \quad -\infty < \alpha < \infty \quad , \quad 0 < \beta < \infty \end{aligned} \tag{11.21}$$

where,

$$\mu_1 = \begin{pmatrix} 0 \\ 0 \end{pmatrix} \text{ and } \Sigma_1 = \begin{pmatrix} \frac{x_1^2 + x_2^2}{(x_2 - x_1)^2} & \frac{-(x_1 + x_2)}{(x_2 - x_1)^2} \\ \frac{-(x_1 + x_2)}{(x_2 - x_1)^2} & \frac{2}{(x_2 - x_1)^2} \end{pmatrix}$$

For practical applications (11.21) is replaced by $BN(\mu_1, \Sigma_1)$ and the analysis given in §11.4 is carried out.

It is clear from the form of Σ_1 that this method should not be used for cases in which x_1 and x_2 are chosen such that $x_2 - x_1$ is very small or very large. In the former case the variances of α and β tend to infinity and ρ tends to -1, while in the latter cases the variance of β tends to 0. A second disadvantage is the zero prior modal values for α and β.

11.5.2 An Alternative Determination of $p(\alpha, \beta)$ using Probabilities of Response.

A second suggestion of Tsutakawa for the logit model, when moderate amounts of prior information are available, is that the experimenter should specify the modal probabilities of response, $\hat{P}_1$ and $\hat{P}_2$, corresponding to doses d_1 and d_2. Supposing that the prior distribution of P_1 and P_2 is a member of the family of natural conjugate prior densities, that is

$$p(P_1, P_2) \propto P_1^{t_1 - 1}(1 - P_1)^{m_1 - t_1 - 1} P_2^{t_2 - 1}(1 - P_2)^{m_2 - t_2 - 1} \tag{11.22}$$

then,

$$l_i = 1 + \hat{P}_i(m_i - 2) \quad (l_i > 1,\ m_i > 2) \tag{11.23}$$

The values of m_i, and hence from (11.23) l_i, should be chosen to reflect the weight to be given to the two dose levels.

Supposing that the m_i's and l_i's have been chosen, combining (11.19),(11.20) and (11.22) gives,

$$p_2(\alpha,\beta) \propto [(x_2 - x_1)\phi(\alpha+\beta x_1)\phi(\alpha+\beta x_2)]$$
$$\times \left[\Phi(\alpha+\beta x_1)^{l_1-1}\{1-\Phi(\alpha+\beta x_1)\}^{m_1-l_1-1}\Phi(\alpha+\beta x_2)^{l_2-1}\{1-\Phi(\alpha+\beta x_2)\}^{m_2-l_2-1}\right] \tag{11.24}$$

The expression in the first square bracket in (11.24) is the same as (11.20) so that it may be written as $BN(\mu_1, \Sigma_1)$ c.f. (11.21), while the expression in the second square bracket may be approximated by $BN(\mu, \Sigma)$as in §11.2. Thus using (11.18) gives,

$$p_2(\alpha,\beta) = BN(\mu^*, \Sigma^*) \tag{11.25}$$

where,

$$\Sigma^* = (\Sigma_1^{-1} + \Sigma^{-1})^{-1} \text{ and } \mu^* = \Sigma^*(\Sigma_1^{-1}\mu_1 + \Sigma^{-1}\mu)$$

In practice it is recommended that the experimenter is given information as to the consequences of his choice of d_1, d_2, m_1 and m_2. Thus (11.25) could be used to show the implied *a priori* probabilities of the test substance being in the toxicity classes of interest. Using (11.25) the analysis in §11.4 may be carried out.

11.5.3 Determining $p(\alpha,\beta)$ using Prior Probabilities of the Toxicity Classes.

Suppose that the experimenter is prepared to supply the following information:

i) prior information concerning the $LD50$ in terms of a discrete probability distribution,

ii) the most likely value for the slope parameter β (modal value).

If an experimenter is prepared to choose the dose levels in an experiment it is necessary for him to have some idea, albeit subconscious, of the likely values of the $LD50$ and the slope since he will not choose dose levels for which he is *a priori* sure he will get no response or 100% response.

To illustrate how the above information may be used, suppose that prior to the experiment in Table 11.3 the experimenter specifies the probabilities of the substance being in each of the Swiss toxicity classes, as shown in Table 11.8.

TABLE 11.8 Prior Probabilities of Toxicity Classes.

	Toxicity Classes					
	1	2	3	4	5	>5000 mg/kg
Probabilities	0.01	0.04	0.10	0.35	0.40	0.10

Suppose further that the experimenter's unconstrained prior distribution for α and β is $BN(\mu, \Sigma)$, where μ and Σ are defined in Appendix 4. By equating the cumulative distribution given in Table 11.8 to the theoretical cumulative distribution defined by (A4.4) and (A4.5) it might be hoped that μ and Σ can be determined. However, in the Appendix 4, h and γ may be written as,

$$h = \frac{w\frac{x_0}{\sigma_x}\frac{\sigma_x}{\sigma_y} - \frac{y_0}{\sigma_y}}{\sqrt{\left(w^2\frac{\sigma_x^2}{\sigma_y^2} - 2\rho w\frac{\sigma_x}{\sigma_y} + 1\right)}} \quad , \quad \gamma = \frac{w\frac{\sigma_x}{\sigma_y} - 1}{\sqrt{\left(w^2\frac{\sigma_x^2}{\sigma_y^2} - 2\rho w\frac{\sigma_x}{\sigma_y} + 1\right)}}$$

so that (A4.5) depends only on the four parameters,

$$c_1 = \frac{x_0}{\sigma_x} \quad , \quad c_2 = \frac{y_0}{\sigma_y} \quad , \quad c_3 = \frac{\sigma_x}{\sigma_y} \quad , \quad c_4 = \rho$$

c.f. Hinkley(1970). This result implies that any four of the prior probabilities in Table 11.8 are sufficient to determine c_1, c_2, c_3 and c_4, but additional information is required to determine μ and Σ. We choose to do this through the specification of x_0, that is the slope parameter.

11.5.4 Numerical Examples of the Determination of $p(\alpha, \beta)$.

Each of the three methods given above for determining a prior distribution $p(\alpha, \beta)$ lead to a *BN* prior. Thus the methods in §11.4 may be used to make inferences. In this section we compare the inferences which are made when these methods are applied to the experiment in Table 11.3. In order to use these methods a number of subjective assessments need to be made. These are as follows :

i) In order to use the method of §11.5.1, two doses, d_1 and d_2, need to be chosen within which *a priori* the $LD50$ lies with probability *1/2*. These were chosen to be 1000 mg./kg. and 3000 mg./kg.

ii) For the method of §11.5.2, in addition to the doses d_1 and d_2, which were taken to be as above, the modal responses P_1 and P_2 at these doses and the weights m_1 and m_2 need to be chosen. P_1 and P_2 were chosen to be 1/4 and 3/4 while the influence of the weights was investigated by choosing m_i = 3,4 and 5.

iii) For the method based on the prior probabilities of the toxicity classes, in addition to the probabilities, given in Table 11.8, the modal value of β needs to be chosen. In this case it was set to 0.5.

In Table 11.9 are shown the prior distributions which are given by (i), (ii) and (iii) together with their corresponding inferences; for completeness the inferences for the improper prior is given again.

TABLE 11.9 Prior Distributions and Posterior Inferences.

Parameter of Prior	Prior Moments					
	Improper	Sec 11.5.1	Sec 11.5.2 $m_i = 3$	Sec 11.5.2 $m_i = 4$	Sec 11.5.2 $m_i = 5$	Sec 11.5.3
α	-	0.000	-4.227	0.224	-6.350	-3.786
β	-	0.000	0.567	0.748	0.852	0.500
σ_α^2	-	92.646	63.197	46.645	36.817	5.282
σ_β^2	-	1.657	1.130	0.834	0.659	0.070
$\sigma_{\alpha\beta}$	-	-0.997	-0.997	-0.997	-0.997	-0.987
Toxicity Class	Probability					
1	0.005	0.000	0.005	0.005	0.004	0.002
2	0.004	0.000	0.004	0.003	0.003	0.002
3	0.021	0.000	0.020	0.019	0.018	0.017
4	0.232	0.008	0.271	0.289	0.306	0.323
5	0.402	0.206	0.428	0.441	0.453	0.561
> 5000 mg/kg	0.336	0.794	0.272	0.243	0.216	0.094

The results in Table 11.9 are worthy of comment for a number of reasons:

i) The prior based on the results in §11.5.1 is not recommended. Although the choice of α_1 and α_2 does not lead to either a very small or a very large variance, the *a priori* modal value of β, i.e. 0, tends to have a relatively extreme effect on the modal posterior value of β thus increasing the most likely value of the $LD50$.

ii) For fixed values of the modal responses $\hat{P}_1$ and $\hat{P}_2$, increasing the variable parameters m_i has a smooth effect on the posterior probabilities of the toxicity classes; $m_i = 3$ may be considered as semi-uninformative.

iii) The method of §11.5.3, based on prior probabilities of the toxicity classes allows a considerable amount of prior information to be incorporated.

iv) For the present data set an analysis based on the improper prior, or on any of the informative priors, shows that there is a very small probability that the $LD50$ is less than 500 mg./kg. (toxicity classes 1, 2 and 3), the maximum posterior probability being 0.03.

11.6 H.P.D. Intervals for the LD50 - Choosing the Scale for Making Inferences.

We noted in §11.2 that one need not be content with calculating the posterior probabilities of the toxicity classes; indeed one great advantage of a Bayesian approach to inference is the richness offered by the posterior distribution. One alternative approach which we suggested previously would be to calculate the 95% H.P.D. limits for the $\log(LD50)$. A question which naturally arises is Why use $\log(LD50)$ and not $LD50$? The answer to this question highlights the potential dangers of an automatic, unthinking adoption of a single inferential summary.

The data displayed in Table 11.10 arose in a rabies vaccine of the type described by Thraenhart(1986). In contrast to standard $LD50$ experiments, the dose metameter in such studies is in the form of dilutions of the vaccine. For the purposes of this section we will treat the results as if they arose from a standard $LD50$ experiment although $LD50$ is not an appropriate term since the vaccine is given to protect against the rabies virus. Perhaps $ED50$ (50% Effective Dose) would be a more appropriate description.

TABLE 11.10 Results from a Rabies Vaccine Experiment

Dose (Dilution)	Number of Animals	Number of Animals Dying
128.20	16	13
25.64	16	14
5.13	16	14
1.03	16	6

The maximum likelihood estimator of the $LD50$ for this data is a dilution of 0.775; the data did not lend themselves to the calculation of asymptotic fiducial limits. The Bayesian approach which we have outlined gives rise to a posterior median of 0.760 dilutions, a posterior mode of 1.252 dilutions and 95% H.P.D. limits of 0.011 and 5.386 dilutions. The posterior probability that the $LD50$ is less than the lower H.P.D. limit is 0.047; in other words this 95% interval is practically a one-sided interval (the actual one-sided 95% interval has the value 0.013 as its lower limit).

If we recall how this interval was determined we see that it was based not on the $LD50$ directly but on the $\log(LD50)$ with a final transformation to the original scale. Suppose we were to work directly with the $LD50$, then by definition of an H.P.D. we would expect such an interval to be shorter. This is the case, the interval ranging from 0 to 2.888 dilutions so that this latter interval, again a 95% interval, is approximately 50% of the former interval. We see that again the 95% H.P.D. interval is one-sided, but interestingly in the other direction. The difference in the two parameterizations is strikingly illustrated by their respective posterior distributions displayed in Figures 11.4 and 11.5.

An argument can be made that the difference between the intervals 0.011-5.386 and 0-2.888 is not relevant in the context of the 5-fold dilutions used in the experiment. We will however see in §13 that such a difference can be of practical significance in the context of rabies vaccine experiments. For the purposes of argument suppose that the data arose from an acute toxicity experiment and that the doses in mg/kg were 100 times

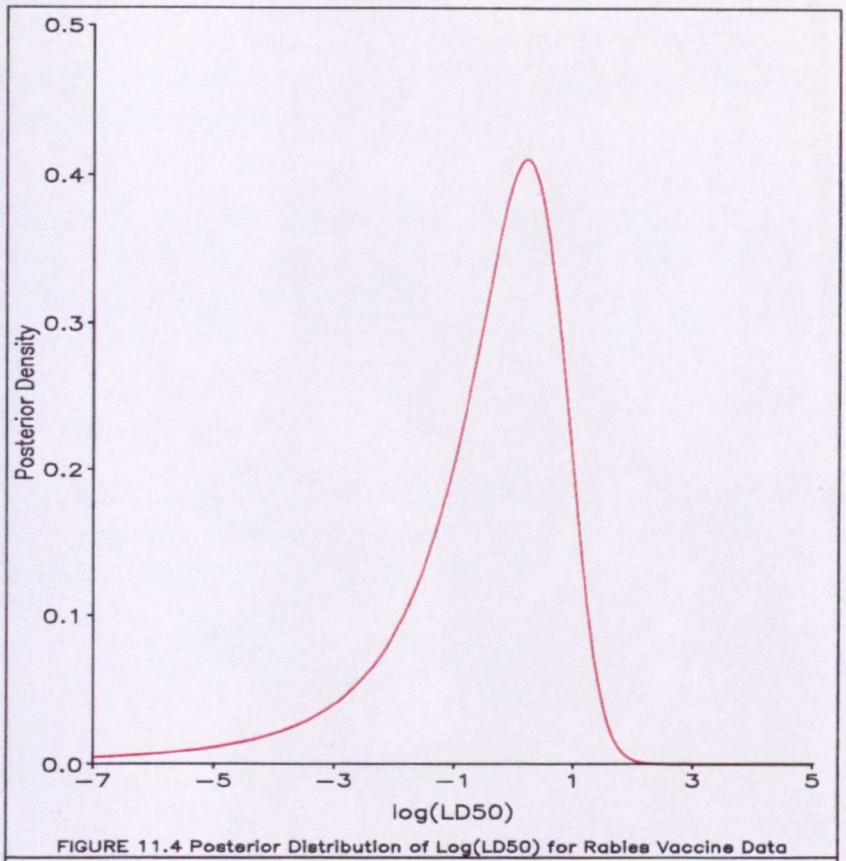


FIGURE 11.4 Posterior Distribution of Log(LD50) for Rabies Vaccine Data

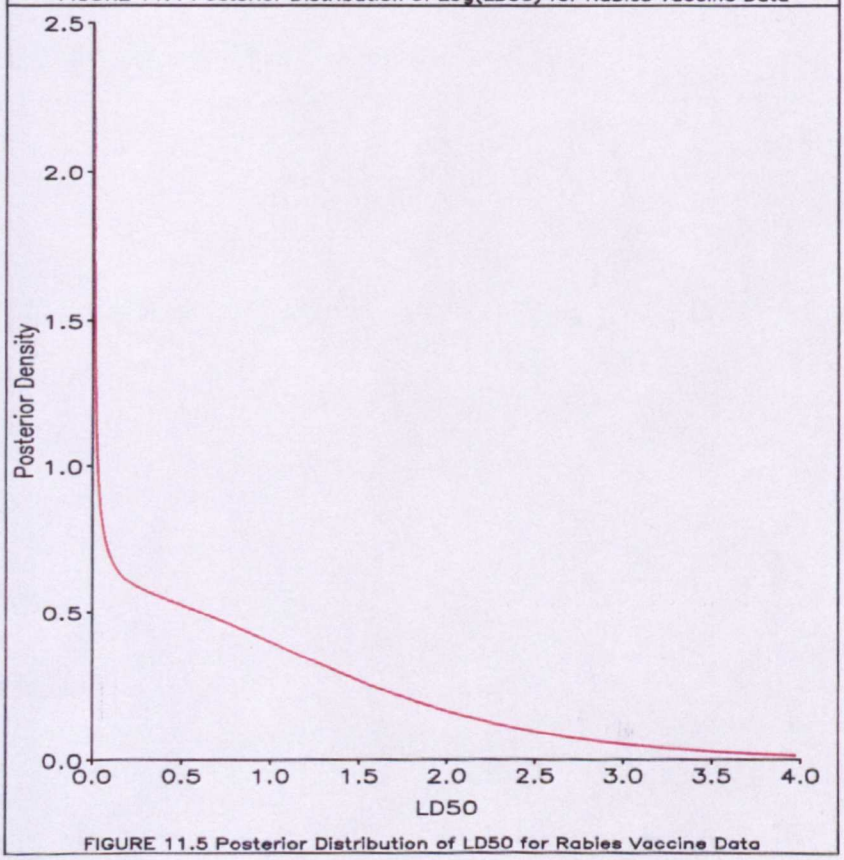


FIGURE 11.5 Posterior Distribution of LD50 for Rabies Vaccine Data

larger than the dilutions. In such circumstances the two intervals would be 1.1-538.6 mk/kg and 0-288.8 mg/kg and the difference might have profound implications with respect to the classification of the substance using either the EEC or Swiss toxicity classes.

Two obvious questions need to be answered. Does the problem arise with classical confidence intervals? Which is the appropriate scale for inference ?

To answer the first question we investigate a problem considered by Bartoszynski and Powers(1990). These authors were interested in determining a shortest confidence interval for the half-life of a drug based on estimating the elimination rate constant. In particular if β is the elimination half-life, $\hat{\beta}$ an estimate of it and s its corresponding standard error then a $(1-\alpha)\%$ confidence interval for β is ,

$$\hat{\beta} - t_{\alpha/2}s \;<\; \beta \;<\; \hat{\beta} + t_{\alpha/2}s \qquad (11.26)$$

where $t_{\alpha/2}$ is the $(1-\alpha/2)\%$ quantile of the appropriate t-distribution. Such an interval is in general only approximately a 95% interval since $\hat{\beta}$ and s would normally be estimated by non-linear least squares. The half-life is given by $h = \log(2)/\beta$ so that (11.26) may be written as,

$$\frac{\log(2)\hat{h}}{\log(2)+\hat{h}st_{\alpha/2}} \;<\; h \;<\; \frac{\log(2)\hat{h}}{\log(2)-\hat{h}st_{\alpha/2}} \qquad (11.27)$$

Although (11.26) is, approximately at least, the shortest confidence interval for β this is not true of the interval (11.27) for h.

Suppose, therefore, that we may choose u and v such that,

$$\int_u^v g(t)dt \;=\; 1-\alpha$$

where $g(t)$ is the t-density with the appropriate degrees of freedom, say M. Then a $(1-\alpha)\%$ confidence interval for β is,

$$\hat{\beta} - vs \;<\; \beta \;<\; \hat{\beta} - us$$

so that,

$$\frac{\log(2)}{\hat{\beta}-us} \;<\; h \;<\; \frac{\log(2)}{\hat{\beta}-vs} \qquad (11.28)$$

is the corresponding $(1-\alpha)\%$ confidence interval for h. The conditions under which (11.28) is of minimum length may be derived either as Bartoszynski and Powers(1990) or as follows. The length of the interval is,

$$\phi(u,v) = \frac{\log(2)}{\beta - vs} - \frac{\log(2)}{\beta - us} \tag{11.29}$$

which we need to minimise subject to the condition,

$$\int_u^v g(t)dt = 1-\alpha \tag{11.30}$$

From (11.29) and (11.30) we get,

$$\frac{d\phi(u,v)}{dv} = \frac{\log(2)}{(\beta - vs)^2} - \frac{\log(2)}{(\beta - us)^2}\frac{du}{dv}$$

and

$$g(v) - g(u)\frac{du}{dv} = 0$$

which implies that,

$$\frac{d\phi(u,v)}{dv} = \frac{\log(2)}{(\beta - vs)^2} - \frac{\log(2)}{(\beta - us)^2}\frac{g(v)}{g(u)} \tag{11.31}$$

From (11.31) the solution to $d\phi(u,v)/dv = 0$ is given by,

$$g(v)(\beta - vs)^2 = g(u)(\beta - us)^2$$

or equivalently by

$$\frac{(\beta - vs)^4}{(M+v^2)^{M+1}} = \frac{(\beta - us)^4}{(M+u^2)^{M+1}} \tag{11.32}$$

c.f. Bartoszynski and Powers(1990) equation (24).

The analysis provided by Bartoszynski and Powers(1990) in which they assume that $\beta \sim N(\beta, \sigma^2)$ and $Ms^2/\sigma^2 \sim \chi^2_M$ may be thought of as providing sufficient statistics for β and σ^2; β and s^2 can be thought of as summarizing almost all of the information about β and σ^2 contained in the data. When the usual uninformative priors are assumed for β and σ^2 the posterior distribution of the parameters may be approximated by,

$$p(\beta, \sigma^2 \mid X) = \frac{1}{(2\pi\sigma^2)^{1/2}}\exp\left(\frac{-(\beta-\hat{\beta})^2}{2\sigma^2}\right)\frac{(Ms^2/2)^{M/2}}{\Gamma(M/2)}(\sigma^2)^{-(M/2+1)}\exp\left(\frac{-Ms^2}{2\sigma^2}\right)$$

from which the marginal posterior distribution of β may be derived in the form,

$$p(\beta \mid X) = \frac{(Ms^2)^{-1/2}}{B\left(\frac{1}{2},\frac{M}{2}\right)}\left(1+\frac{(\beta-\hat{\beta})^2}{Ms^2}\right)^{-(M+1)/2}$$

It follows that the posterior distribution of $h = \log(2)/\beta$ is,

$$p(h \mid X) = \frac{\log(2)(Ms^2)^{-1/2}}{B\left(\frac{1}{2}, \frac{M}{2}\right)h^2}\left(1 + \frac{(\log(2) - h\hat{\beta})^2}{Mh^2s^2}\right)^{-(M+1)/2}$$

An interval (a, b) is said to be a $100(1-\alpha)\%$ H.P.D. interval for a parameter ϕ if

1) (a, b) is a $100(1-\alpha)\%$ posterior interval, i.e. $\int_a^b p(\phi \mid X)d\phi = 1-\alpha$

2) for all $\phi \in (a, b)$ and $\phi' \notin (a, b)$, $p(\phi \mid X) \geq p(\phi' \mid X)$

Condition 2) requires that there be no values of ϕ within the interval (a, b) which have a posterior ordinate lower in value than any value of ϕ without the interval. A second implication of 2) is that $p(a \mid X) = p(b \mid X)$; a third implication is that for fixed α the H.P.D. interval is the shortest interval.

The requirement of equal ordinates reduces in the case of inference about h to,

$$\frac{1}{a^2}\left(1 + \frac{(\log(2) - a\hat{\beta})^2}{Ma^2s^2}\right)^{-(M+1)/2} = \frac{1}{b^2}\left(1 + \frac{(\log(2) - b\hat{\beta})^2}{Mb^2s^2}\right)^{-(M+1)/2}$$

Let $v = (\beta a - \log(2))/(as)$ and $u = (\beta b - \log(2))/(bs)$ then the above ordinate condition may be shown to be equivalent to

$$\frac{(\bar{\beta} - vs)^4}{(M + v^2)^{M+1}} = \frac{(\bar{\beta} - us)^4}{(M + u^2)^{M+1}}$$

which is identical to (11.32). Since the transformation $t = (\beta h - \log(2))/(hs)$ applied to $\int_a^b p(h \mid X)dh$ gives $\int_u^v g_M(t)$ where $g_M(t)$ is the standard t-density on M degrees of freedom. It is clear that the $100(1-\alpha)\%$ H.P.D. interval is identical to the shortest interval developed by Bartoszynski and Powers(1990).

Whilst we have considered a specific transformation, a similar result would have arisen had we taken instead a general nonlinear transformation $\psi(\beta)$. It is clear from the above analysis that the answer to the first question which we posed is that classical intervals in general suffer from the same problems as do Bayesian H.P.D. intervals.

Turning to the second question, two separate considerations suggest that $\log(LD50)$ is the more appropriate scale for making inferences. The first consideration is statistical. Box and Tiao(1973) argue for so-called *standardized* H.P.D. intervals. Such intervals are calculated in the metric for which the uninformative prior is locally uniform. In this metric different sets of data translate the likelihood in the parameter space but otherwise leave it unchanged; for this region such likelihoods are termed *data translated*. In the present context, our constrained prior,

$$p_c(\alpha, \beta) = constant \quad \beta > 0 \quad , -\infty < \alpha < \infty$$

becomes in the parametrization β and ω ,

$$p_c(w,\beta) \propto \beta$$

and in the parametrization e^w, i.e. $LD50$, and β,

$$p_c(LD50,\beta) \propto \frac{\beta}{LD50}$$

Clearly $\log(LD50)$ is the parametrization in which, with respect to the parameter of interest, the prior is locally uniform.

The second consideration concerns the dose scale itself. Since the scale on which a dose is measured is essentially arbitrary, for example in risk assessment doses may be measured either in mg/kg or in parts per million, it is advantageous to have a scale on which a proportionate increase in the dose has the same scale value at all levels of dose.

11.7 Profile Likelihood.

In discussion of Racine *et al*(1986), Ross(1986), Bailey and Gower(1986) and Cox(1986) all suggest that the failure of the traditional method of setting confidence intervals based on Fieller's theorem to give an adequate result is a direct result of the invalidity of the normal approximation to the binomial for small numbers of animals. They conclude that the use of likelihood intervals solves the problem. In this section we show that in exactly the same way as with the fiducial intervals based on Fieller's theorem, there always exist a "confidence level" for which this likelihood method fails to produce an interval. We establish this result for a logit model, although the same result may be empirically demonstrated for the probit model.

Definition :

Suppose $L(\theta,\phi \mid X)$ is a two parameter likelihood then the profile likelihood of θ, $PL(\theta)$, is defined as,

$$PL(\theta) = L(\theta,\hat{\phi}(\theta))$$

where $\hat{\phi}(\theta)$ is the solution to $\partial L(\theta,\phi \mid X)/\partial\phi = 0$.

Theorem :

The profile likelihood for $w = \log(LD50)$ for a logit response model has a minimum given by,

$$w^* = \frac{\sum_{i=1}^{k} x_i(r_i - n_i/2)}{\sum_{i=1}^{k}(r_i - n_i/2)}, \quad \beta(w^*) = 0.$$

Proof :

From the log-likelihood $l(w,\beta(w))$ which, for convenience, we denote by l and regarding it as a function of w alone, we have

$$\frac{\partial l}{\partial w} = \sum_{i=1}^{k}(r_i - n_i P_i)\left[(x_i - w)\frac{d\beta(w)}{dw} - \beta(w)\right]$$

When $\beta(w) = 0$, $P_i = 1/2$ and substitution of $w = w^*$ gives $\partial l/\partial w = 0$. Differentiation of $\partial l/\partial w$ gives,

$$\frac{\partial^2 l}{\partial w^2} = \sum_{i=1}^{k}(r_i - n_i P_i)\left[(x_i - w)\frac{d^2\beta(w)}{dw^2} - 2\frac{d\beta(w)}{dw}\right] - \sum_{i=1}^{k} n_i P_i(1-P_i)\left[(x_i - w)\frac{d\beta(w)}{dw} - \beta(w)\right]^2$$

At the turning point w^*, $\beta(w^*) = 0$, $P_i = 1/2$ so that,

$$\frac{\partial^2 l}{\partial w^2} = -2\frac{d\beta(w^*)}{dw}\sum_{i=1}^{k}(r_i - n_i/2) - \frac{1}{4}\sum_{i=1}^{k} n_i(x_i - w^*)^2\left[\frac{d\beta(w^*)}{dw}\right]^2 \qquad (11.33)$$

By definition $\beta(w)$ is defined as an implicit function of w by the equation,

$$\frac{\partial l}{\partial w} = \sum_{i=1}^{k}(x_i - w)(r_i - n_i P_i) = 0.$$

A second differentiation gives,

$$\sum_{i=1}^{k}(r_i - n_i P_i)(-1) - \sum_{i=1}^{k} n_i P_i(1-P_i)(x_i - w)\left[(x_i - w)\frac{d\beta(w)}{dw} - \beta(w)\right] = 0$$

giving

$$\frac{d\beta(w)}{dw} = \frac{\beta(w)\sum_{i=1}^{k} n_i P_i(1-P_i)(x_i - w) - \sum_{i=1}^{k}(r_i - n_i P_i)}{\sum_{i=1}^{k} n_i P_i(1-P_i)(x_i - w)^2}$$

At the turning point w^*, $\beta(w^*) = 0$, $P_i = 1/2$ so that,

$$\frac{d\beta(w)}{dw} = -\frac{\sum_{i=1}^{k}(r_i - n_i/2)}{\frac{1}{4}\sum_{i=1}^{k} n_i(x_i - w^*)^2}$$

Substituting this into (11.33) gives,

$$\frac{\partial^2 l}{\partial w^2} = \frac{8\left[\sum_{i=1}^{k}(r_i - n_i/2)\right]^2}{\sum_{i=1}^{k} n_i(x_i - w^*)^2} - \frac{4\left[\sum_{i=1}^{k}(r_i - n_i/2)\right]^2}{\sum_{i=1}^{k} n_i(x_i - w^*)^2} = \frac{4\left[\sum_{i=1}^{k}(r_i - n_i/2)\right]^2}{\sum_{i=1}^{k} n_i(x_i - w^*)^2}$$

which is clearly positive, so that the turning point is a minimum.

This result implies that the profile likelihood function for w has both a maximum and a minimum. Thus the profile likelihood can be characterized, for convenience using the log of the profile likelihood, as in Figure 11.6. The behaviour of the profile likelihood function evidenced in this figure is mirrored in the plots of $L(\mu_0)$, the likelihood ratio statistic, given by Williams(1986), and has also been described explicitly by Aitkin(1986). The asymptote represents the log of the profile likelihood for zero slope and corresponds to,

$$l(\infty, \beta(\infty)) = r\log(r/n) + (n-r)\log(1 - r/n)$$

where

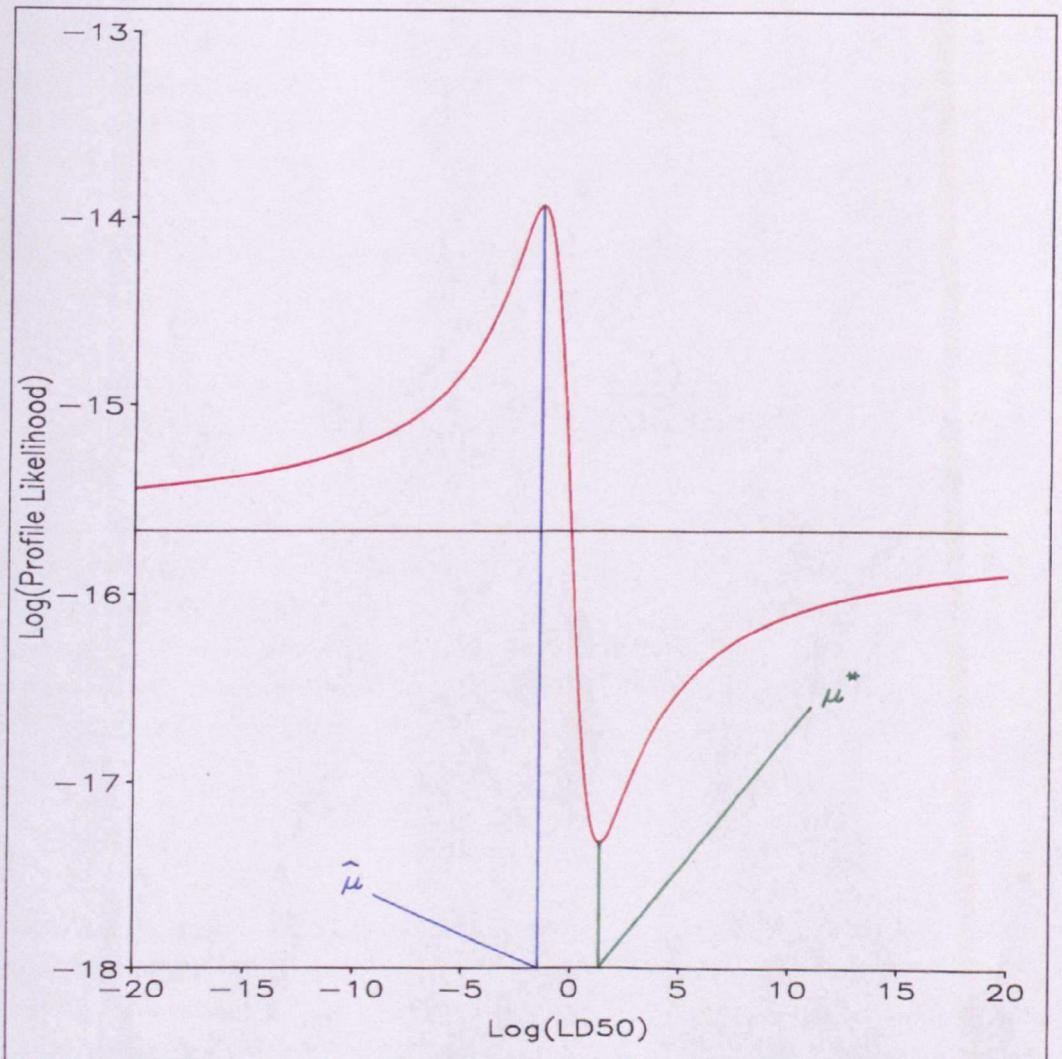


FIGURE 11.6 Profile Log(Likelihood Function) — Example (d) from Williams(1986)

$$r = \sum_{i=1}^{k} r_i \quad , \quad n = \sum_{i=1}^{k} n_i$$

The implication of the form of the log of the profile likelihood, which was apparently not appreciated by either Williams(1986) or Aitkin(1986), is that there will always be a level α for which the likelihood interval will comprise the whole real line. The level at which this occurs will be less than that at which Fieller's Theorem applied to the asymptotic normal approximation breaks down, but it will always occur. This may clearly be seen in Williams'(1986) Figure 1. in which the likelihood ratio statistic always lies above the asymptotic approximation.

The proof of the theorem shows that it is negative values of the slope β which cause problems and it is precisely those values of β which are excluded by the Bayesian analysis based on a prior for β which is uniform on the positive half of the real line. There is clearly justification in conditioning on positive β in toxicity experiments although the argument may be more difficult to sustain in other classes of experiments.

The profile likelihood, or relative likelihood approach, has a second major defect. As Kalbfleisch and Sprott(1969) point out :

> "... the maximum relative likelihood does not take account of the uncertainty due to lack of knowledge of β and so can be misleading in terms of both precision and location".

This comment relates to the effective assumption that for fixed ω , β is known to be equal to its maximum likelihood estimate without weighting for the uncertainty in that estimate. A Bayesian analysis effectively takes account precisely of this uncertainty in the following way. Suppose again that we have two parameters Θ and ϕ and we wish to make inferences about Θ. For a uniform prior on both parameters an asymptotic approximation to the posterior distribution of Θ is given by,

$$p(\theta \mid X) = \left(\frac{H^*(\phi^*)}{2\pi n \mid H(\hat{\theta}, \hat{\phi}) \mid} \right)^{1/2} \frac{e^{l(\theta, \phi^*)}}{e^{l(\hat{\theta}, \hat{\phi})}}$$

where $\hat{\Theta}$ and $\hat{\phi}$ are the global maximum likelihood estimates, ϕ^* is the maximum likelihood estimate of ϕ for fixed Θ , $H(\hat{\theta}, \hat{\phi})$ is minus the inverse of the Hessian of the log likelihood, and H^* is minus the reciprocal of the derivative of the log likelihood function with respect to ϕ for fixed Θ. The profile likelihood function, $\exp(l(\theta, \phi^*))$ is weighted in the above expression by $H^*(\phi^*)^{1/2}$ which represents the uncertainty in ϕ^* measured by the curvature of the log likelihood at that point.

12 PREDICTION IN LD50 EXPERIMENTS.

12.1 Introduction.

Ever since their very beginnings, Bayesian methods have been used for predictive purposes. Richard Price, for example, in his appendix to the posthumously published original paper by Bayes provided applications of Bayes' results to six problems of which three had to do with the prediction of events, albeit that Dale(1982) has pointed out that Price's application of Bayes' results to these prediction problems was incorrect. A recent re-interpretation by Stigler(1982) of Bayes' Scholium in which he defended the use of a uniform prior suggests that Bayes proposed a uniform "uninformative" prior distribution for the parameter of his problem not because he believed in the so-called "principle of the equal distribution of ignorance", but rather because it lead to a uniform predictive distribution for the data. A second obvious example of an early use of predictive ideas is to be found in Laplace's "law of succession".

More recently predictive distributions have been used for a variety of practical applications. Aitchison(1964) used the predictive distribution for setting tolerance limits to be used in normal range applications - an area surveyed in detail by Guttman(1970); Guttman(1965) uses it in goodness-of-fit problems; Box(1980) uses it for testing the compatibility of the prior distribution and the likelihood; Naylor and Smith(1983) use it again for a normal range problem in which there is a mixture of "healthy" and "sick" subjects. Aitchison and Dunsmore(1975), a text devoted solely to predictive distributions, provide a number of further applications as does Grieve(1988) in a pharmaceutical context.

In a series of articles, over a number of years, Geisser has championed predictive inference for its own sake - see for instance Geisser(1971), Geisser(1982) and Geisser(1985) - the latter article providing references to other applications. In essence he argues that predictive inference, since it deals with observable quantities, is of more relevance to practical problems than "estimative inference" which has to do with hypothetical models whose parameters can only have meaning in the limit as the sample size goes to infinity. Such considerations lay behind the procedure for the determination of a prior distribution for α and β in §11.5 in that toxicologists are asked to express beliefs about observable events, namely the deaths of animals, rather than about the parameters α and β themselves. Commenting on Stigler's(1982) re-interpretation of Bayes' Scholium Geisser(1985) concluded that 'Bayes himself is the first Bayesian predictivist'.

In this chapter we develop a predictive approach to a non-standard problem in $LD50$ estimation.

12.2 Background to the Applications.

The first application concerns a claim by a national regulatory authority that a new formulation of an agrochemical product Basudin had an $LD50$ of the order of 200 mk/kg or less. When originally tested on rats this substance gave rise to the data shown in Table 12.1. There is no evidence in this table to suggest that the $LD50$ could be as low as 200 mg/kg. Indeed, the maximum likelihood estimates of the $LD50$ and their respective 95% fiducial limits given in Table 12.2 show that it is highly unlikely that the $LD50$ could be this low and is more likely to be of the order of 700 to 1100 mg/kg. This is confirmed by the Bayesian analysis of §11 which, using uninformative priors, gives rise to the posterior distributions displayed in Figure 12.1 and by the fact that the posterior probabilities that the $LD50$ is less than 200 mg/kg are each less than 0.0001.

TABLE 12.1 Data from Previous Studies with Basudin.

Study	Dose (mg./kg.)	Number of Animals Exposed	Number of Animals Dying
1	600	10	0
	1000	10	6
	1470	10	8
	1670	10	10
2	600	10	0
	775	10	5
	850	10	6
	1000	10	10
3	359	10	1
	600	10	2
	1000	10	7
	2150	10	10
	3590	10	10

In the light of the pressures to reduce the numbers of experimental animals and under the strong conviction that no substantial change in the toxicity of Basudin had taken place it was decided that it was not appropriate to carry out a full *LD50* experiment, particularly since there were 10 batches of the new formulation which had been questioned. It was therefore decided to apply a dose of 200 mg/kg taken from each batch to 10 rats to repudiate the claim of increased toxicity in the expectation that no animals would die at this dose. On the basis of the data in Table 12.1 predictive distributions of the results of these tests may be calculated and the observed results compared to these to give an assessment of changes in the toxicity of Basudin.

TABLE 12.2 Maximum Likelihood Estimates and Fiducial Limits for the Data from Table 12.1.

Study	M.L.E. (mg/kg)	Lower Fiducial Limit	Upper Fiducial Limit
1	1015	808	1183
2	797	719	851
3	780	601	1061

The second application again concerns an agrochemical product, Miral. In this instance there was anecdotal evidence to suggest that when stored for long periods in the humid conditions to be found in S.E. Asia, oxidation of the compound could occur leading to increased toxicity. When originally tested the results given in Table 12.3 were obtained.

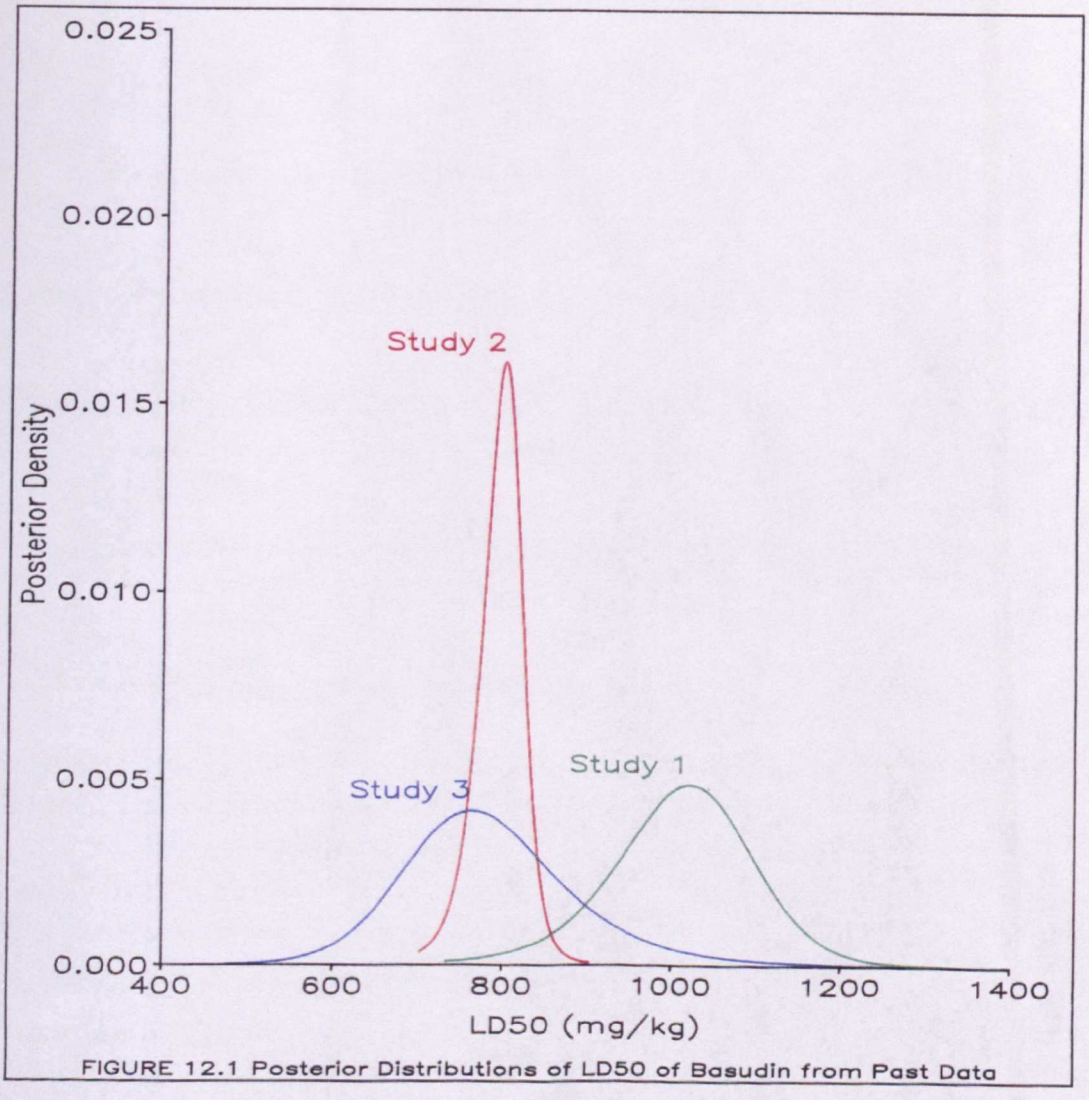


FIGURE 12.1 Posterior Distributions of LD50 of Basudin from Past Data

TABLE 12.3 Data from a Previous Study with Miral.

Study	Dose (mg./kg.)	Number of Animals Exposed	Number of Animals Dying
Males	35.9	5	0
	60	5	0
	129	5	2
	147	5	4
	215	5	5
Males and Females	35.9	10	0
	60	10	5
	129	10	7
	147	10	9
	215	10	10

These results gave rise to the traditional maximum likelihood results displayed in Table 12.4

TABLE 12.4 Maximum Likelihood Estimates and Fiducial Limits for the Data from Table 12.3.

Study	M.L.E. (mg/kg)	Lower Fiducial Limit	Upper Fiducial Limit
Males	133	No Fiducial Limits Calculable	
Males and Females	76	54	100

The Bayesian analysis outlined in §11, again using uninformative priors, gave rise to the posterior distributions shown in Figure 12.2. Both sets of data show that it is extremely unlikely that the $LD50$ for Miral is less than 40 mg/kg. It was therefore decided to apply a dose of 35 mg/kg to each of 5 males and 5 females from each of 6 batches of Miral. The data in Table 12.3 may be used to provide predictive distributions, and a comparison of these distributions with the actual results will again indicate whether a change in toxicity has occurred.

12.3 Predicting the Results of a Future LD50 Experiment.

Suppose we wish to predict the results of a future experiment consisting of a single dose, d , being administered to a group of n animals. Given that we know the values of α and β in our probit model, then the probability distribution of the number, r , of deaths from the n animals is,

$$P(r \mid n, \alpha, \beta) = \binom{n}{r} P^r (1-P)^{n-r}$$

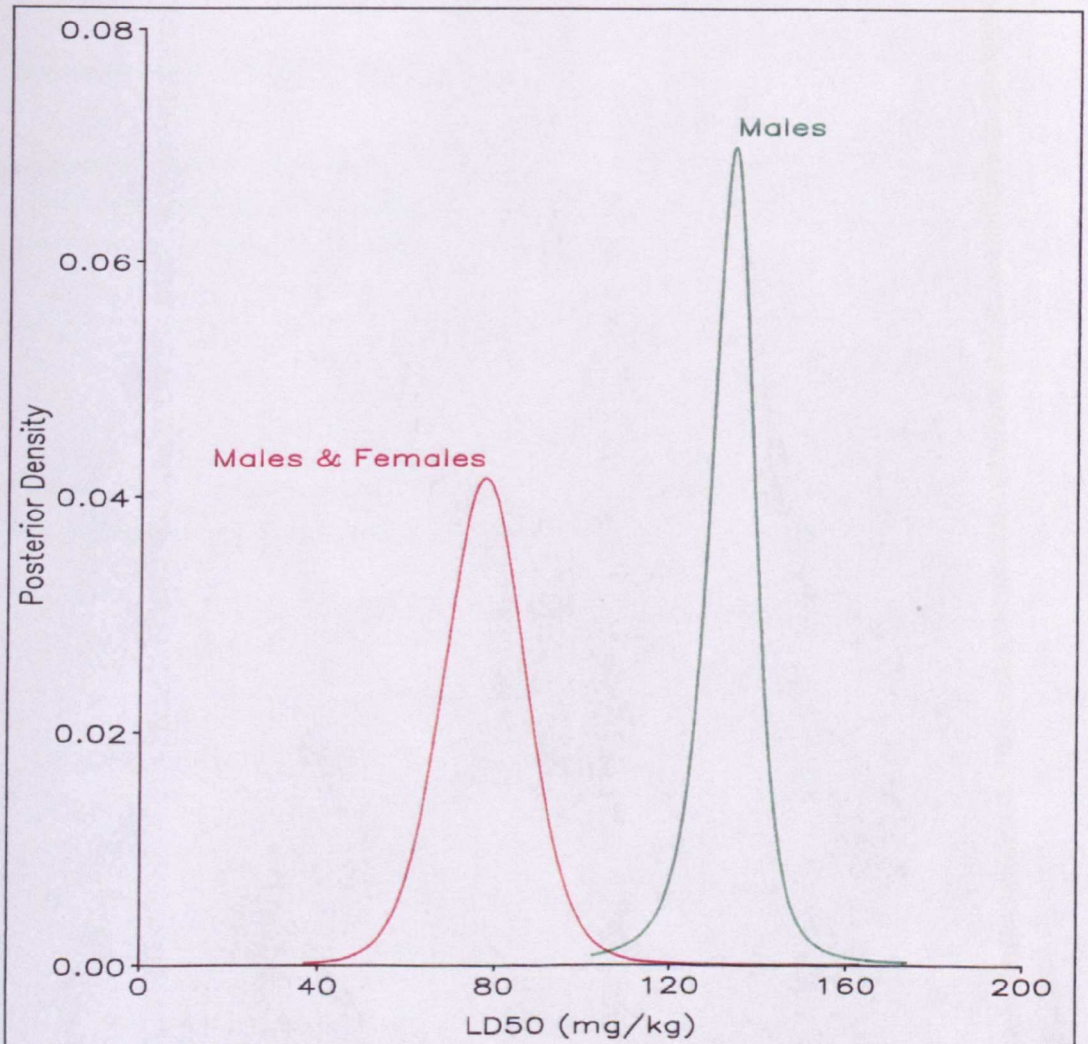


FIGURE 12.2 Posterior Distributions of LD50 of Miral from Past Data

where $P = \Phi(\alpha + \beta x)$ and $x = \log(d)$. If our knowledge concerning α and β is described by a posterior distribution determined as in §11, then the predictive distribution of r deaths from the n animals given our current knowledge is,

$$P(r \mid X) = \int_{\alpha}\int_{\beta} P(r \mid n,\alpha,\beta)p(\alpha,\beta \mid X)d\alpha d\beta$$

$$= \frac{\int_{\alpha}\int_{\beta} P(r \mid n,\alpha,\beta)L(\alpha,\beta \mid X)p(\alpha,\beta)d\alpha d\beta}{\int_{\alpha}\int_{\beta} L(\alpha,\beta \mid X)p(\alpha,\beta)d\alpha d\beta} \qquad (12.1)$$

12.4 Approximating the Predictive Distributions.

We are again confronted with integrals which we cannot determine analytically. The Gaussian quadrature method of Naylor and Smith(1982) is one possibility for calculating (12.1) or we may again use Lindley's(1980) asymptotic results. By noting that (12.1) is of the form,

$$\frac{\int u(\theta)e^{l(\theta)+p(\theta)}d\theta}{\int e^{l(\theta)+p(\theta)}d\theta}$$

where $\theta = (\alpha,\beta)$, $u(\theta) = P(r \mid n,\alpha,\beta)$, $l(\theta) = \log(L(\alpha,\beta \mid X))$ and $\rho(\theta) = \log(p(\alpha,\beta))$ Lindley's equation (16) may be used to show that a good approximation to (12.1) is given by,

$$P(r \mid n,\hat{\alpha},\hat{\beta}) + \frac{1}{2}(\hat{P}_{11}\hat{\sigma}_{\alpha}^2 + 2\hat{P}_{12}\hat{\sigma}_{\alpha\beta} + \hat{P}_{22}\hat{\sigma}_{\beta}^2)$$

$$+ \frac{1}{2}\hat{L}_{30}(\hat{P}_1\hat{\sigma}_{\alpha}^4 + \hat{P}_2\hat{\sigma}_{\alpha}^2\hat{\sigma}_{\alpha\beta}) + \frac{1}{2}\hat{L}_{21}(3\hat{P}_1\hat{\sigma}_{\alpha}^2\hat{\sigma}_{\alpha\beta} + \hat{P}_2(\hat{\sigma}_{\alpha}^2\hat{\sigma}_{\beta}^2 + 2\hat{\sigma}_{\alpha\beta}^2))$$

$$+ \frac{1}{2}\hat{L}_{12}(\hat{P}_1(\hat{\sigma}_{\alpha}^2\hat{\sigma}_{\beta}^2 + 2\hat{\sigma}_{\alpha\beta}^2) + 3\hat{P}_2\hat{\sigma}_{\beta}^2\hat{\sigma}_{\alpha\beta}) + \frac{1}{2}\hat{L}_{03}(\hat{P}_1\hat{\sigma}_{\alpha}^2\hat{\sigma}_{\alpha\beta} + \hat{P}_2\hat{\sigma}_{\beta}^4)$$

where

$$\hat{P}_1 = \left.\frac{\partial P(r \mid n,\alpha,\beta)}{\partial\alpha}\right|_{\alpha=\hat{\alpha},\beta=\hat{\beta}}, \quad \hat{P}_{12} = \left.\frac{\partial^2 P(r \mid n,\alpha,\beta)}{\partial\alpha\partial\beta}\right|_{\alpha=\hat{\alpha},\beta=\hat{\beta}}$$

etc., and where $\hat{L}_{ij}$, $\hat{\sigma}_{\alpha}^2$, $\hat{\sigma}_{\beta}^2$ and $\hat{\sigma}_{\alpha\beta}$ are as previously defined (see §11.2). The required differentials have the following form :

$$P_1 = \frac{\partial P(r \mid n, \alpha, \beta)}{\partial \alpha} = \binom{n}{r}\phi(\Delta)P^{r-1}(1-P)^{n-r-1}(r-nP)$$

$$P_2 = \frac{\partial P(r \mid n, \alpha, \beta)}{\partial \alpha} = \binom{n}{r}\phi(\Delta)P^{r-1}(1-P)^{n-r-1}(r-nP)x$$

$$P_{11} = \frac{\partial^2 P(r \mid n, \alpha, \beta)}{\partial \alpha^2} = \binom{n}{r}\phi^2(\Delta)P^{r-2}(1-P)^{n-r-2}(r^2-r+2Pr+P^2n^2-nP^2-2nPr) - P_1\Delta$$

$$P_{12} = \frac{\partial^2 P(r \mid n, \alpha, \beta)}{\partial \alpha \partial \beta} = \binom{n}{r}\phi^2(\Delta)P^{r-2}(1-P)^{n-r-2}(r^2-r+2Pr+P^2n^2-nP^2-2nPr)x - P_1\Delta x$$

$$P_{22} = \frac{\partial^2 P(r \mid n, \alpha, \beta)}{\partial \beta^2} = \binom{n}{r}\phi^2(\Delta)P^{r-2}(1-P)^{n-r-2}(r^2-r+2Pr+P^2n^2-nP^2-2nPr)x^2 - P_1\Delta x^2$$

in which $\Delta = \alpha + \beta x$, and where again each differential is evaluated at the maximum likelihood estimates $\hat{\alpha}$ and β.

12.5 Results.

12.5.1 Toxicity of Basudin.

Using the above results and the data in Table 12.1 we may calculate the predictive distributions for r deaths among 10 rats receiving a dose 0f 200 mg/kg. The predictive distributions for the three sets of data are displayed in Table 12.5.

TABLE 12.5 Predictive Distributions of r Deaths from 10 Animals Receiving 200 mg/kg. of Basudin.[1]

	Study		
r	1	2	3
0	0.999	1.000	0.943
1	0.001	0.000	0.048
2	0.000	0.000	0.007
3	0.000	0.000	0.001

In the actual experiments which were carried out there were no deaths. Thus the experimental results agree well with the predictive distributions in that the highest predictive probability of a single death from 10 rats is of the order of 1 in 20 (study 3). On the basis of these results it was concluded that the new formulation of Basudin did not have an $LD50$ of the order of 200 mg/kg. or less.

1 The probabilities for $r > 3$ are all essentially zero and are not shown.

12.5.2 Toxicity of Miral.

In the case of Miral, Tables 12.6 and 12.7 provide predictive distributions of r deaths from 5 males receiving 35 mg/kg of Miral and r deaths from 10 male and female animals also receiving 35 mg/kg. These predictive distributions were derived using the results in §12.4 on the basis of the data shown in Table 12.3.

TABLE 12.6 Predictive Distributions of r Deaths from 5 Male Animals Receiving 35 mg/kg. of Miral.[2]

r	Probability
0	1.000
1	0.000

TABLE 12.7 Predictive Distributions of r Deaths from 10 Animals Receiving 35 mg/kg. of Miral.[3]

r	Probability
0	0.536
1	0.246
2	0.141
3	0.060
4	0.016
5	0.002

In Table 12.8 the results of testing 35 mg/kg, taken from each of 6 batches, in 5 males and in 10 males and females are tabulated. It is not so clear in this instance that there has not been a change in toxicity. In the case of males we predict with almost certainty that there will be no deaths from 5 rats and yet one of 6 batches gave rise to one death; for males and females together the predictive probability of less than 3 deaths from 10 rats is 0.923 but one batch gave rise to 3 deaths. Whilst not conclusive, these results do tend to suggest that an increase in toxicity has taken place.

12.6 Discussion.

Whilst the approach taken in this chapter is appealing in terms of saving on the use of animals, nonetheless one needs to be sure that its application is appropriate. In particular applicability of the technique assumes :

> that all experiments, that is those used for prediction, those on which the claims for increased toxicity were based and the new experiments were conducted in a similar fashion and under similar conditions.

2 The probabilities for $r > 1$ are all essentially zero and are not shown.

3 The probabilities for $r > 5$ are all essentially zero and are not shown.

TABLE 12.8 Observed Results from Testing 6 Batches of Miral.

Batch	Males		Males & Females	
	n	*r*	*n*	*r*
1	5	0	10	0
2	5	0	10	0
3	5	1	10	3
4	5	0	10	0
5	5	0	10	0
6	5	0	10	2

This assumption is particularly important since, as we have seen, the *LD50* is not a biological constant but can vary depending on environmental and other factors. Potentially, therefore, whilst in the case of Basudin we concluded that there was no change in toxicity , we may only have concluded this because the conditions under which the test was conducted changed thereby masking the changed toxicity; the converse may be true in the case of Miral.

The importance of this assumption was underlined when it was subsequently revealed that the regulatory authority who had claimed that the *LD50* of Basudin had changed had use mice instead of rats !!

13 DISCUSSION.

In this thesis we have considered two areas of controversy in pharmaceutical research and have provided operational tools for carrying out Bayesian analyses of varying complexity. In particular, where appropriate, we have provided graphical methods for displaying the relationships between prior assumptions concerning the parameters of the relevant models and the posterior inferences which may be derived from these prior assumptions and the experimental data. At least two issues remain open.

Consider first the classical LD_{50} test and the approach developed in §11. We noted in §10 that it is likely that the BTS procedure which is not based upon the LD_{50}, indeed it is not even primarily concerned with lethality, will, become the main procedure for determining the acute toxicity of a test compound and therefore it could be argued that the development in §11 is unnecessary. There are a number of reasons for arguing against this view :

i) In §11 we concurred with Finney's(1985) opinion that while some regulatory authorities still require the estimation of a formal LD_{50} value it is incumbent upon us as statisticians to utilise the most efficient methods available for its determination. Such was the motivation behind Williams'(1986) development of a likelihood-based method for constructing a confidence interval for the LD_{50}, an idea independently developed by Aitkin(1986).

ii) Whilst from a regulatory perspective the need to determine a formal LD_{50} value is likely to disappear there are still instances within pharmaceutical research in which an LD_{50} value is needed. One such instance is the determination of the appropriate dose of cytotoxic drugs to be given to patients in the first human study. Oncologists will in general require either an LD_{50}, or an LD_{10}, based on animal studies before they are prepared to specify a dose in such early human studies and whilst they do not require extreme precision for such estimates since the LD_{10}, as well as the LD_{50}, is required efficient methods are necessary as estimating the LD_{10} requires more resources for the same precision as does estimating the LD_{50}.

iii) There are other areas of toxicology, apart from those associated with pharmaceutical research, for which LD_{50} estimates are needed. One example is in the area of ecotoxicology, that is environmental toxicology, where it is necessary to determine the LD_{50} in fish of, for example, agrochemicals which may enter rivers by being washed there either through irrigation or through rainwater. Apart from animal welfare considerations many of the species of fish which are used in such studies are expensive, for example trout or salmon, and therefore there is again a requirement of efficiency. Interestingly there is one area of ecotoxicology involving LD_{50} estimation for which there has been no effort to increase efficiency and that is where the test system is a water-born insect, the main example being the species *Daphnia*. Apparently insects are considered expendable.

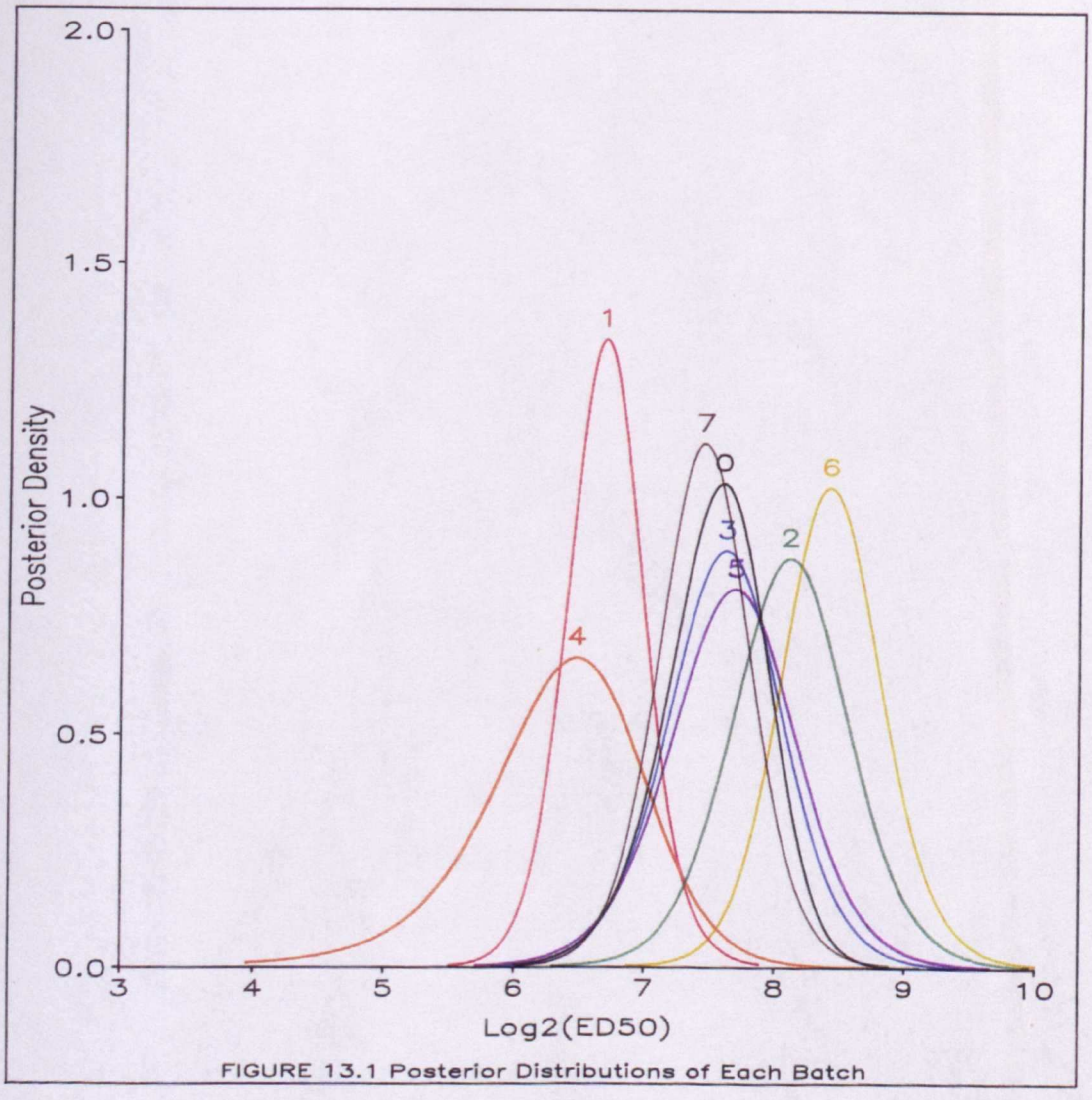


FIGURE 13.1 Posterior Distributions of Each Batch

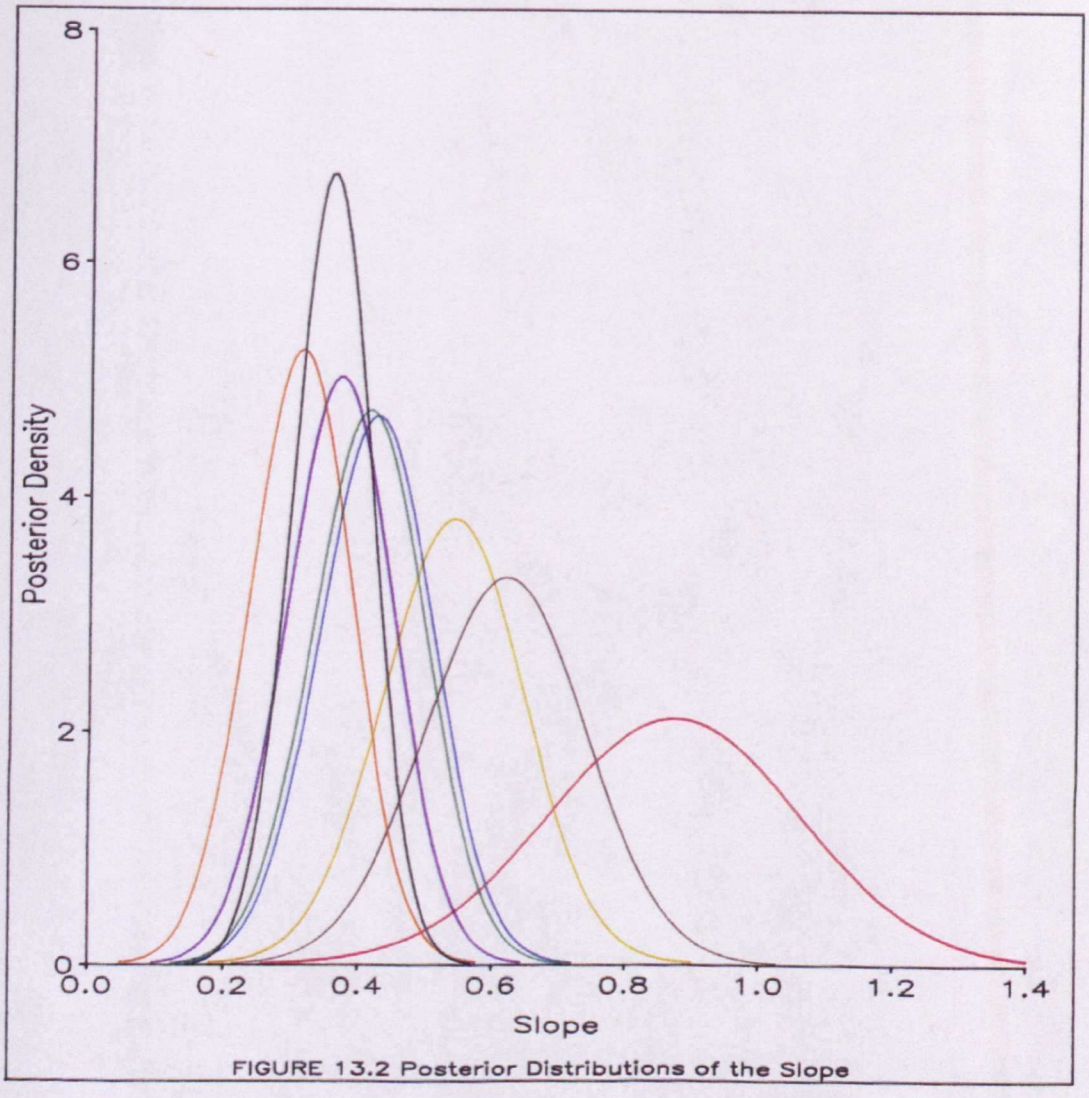


FIGURE 13.2 Posterior Distributions of the Slope

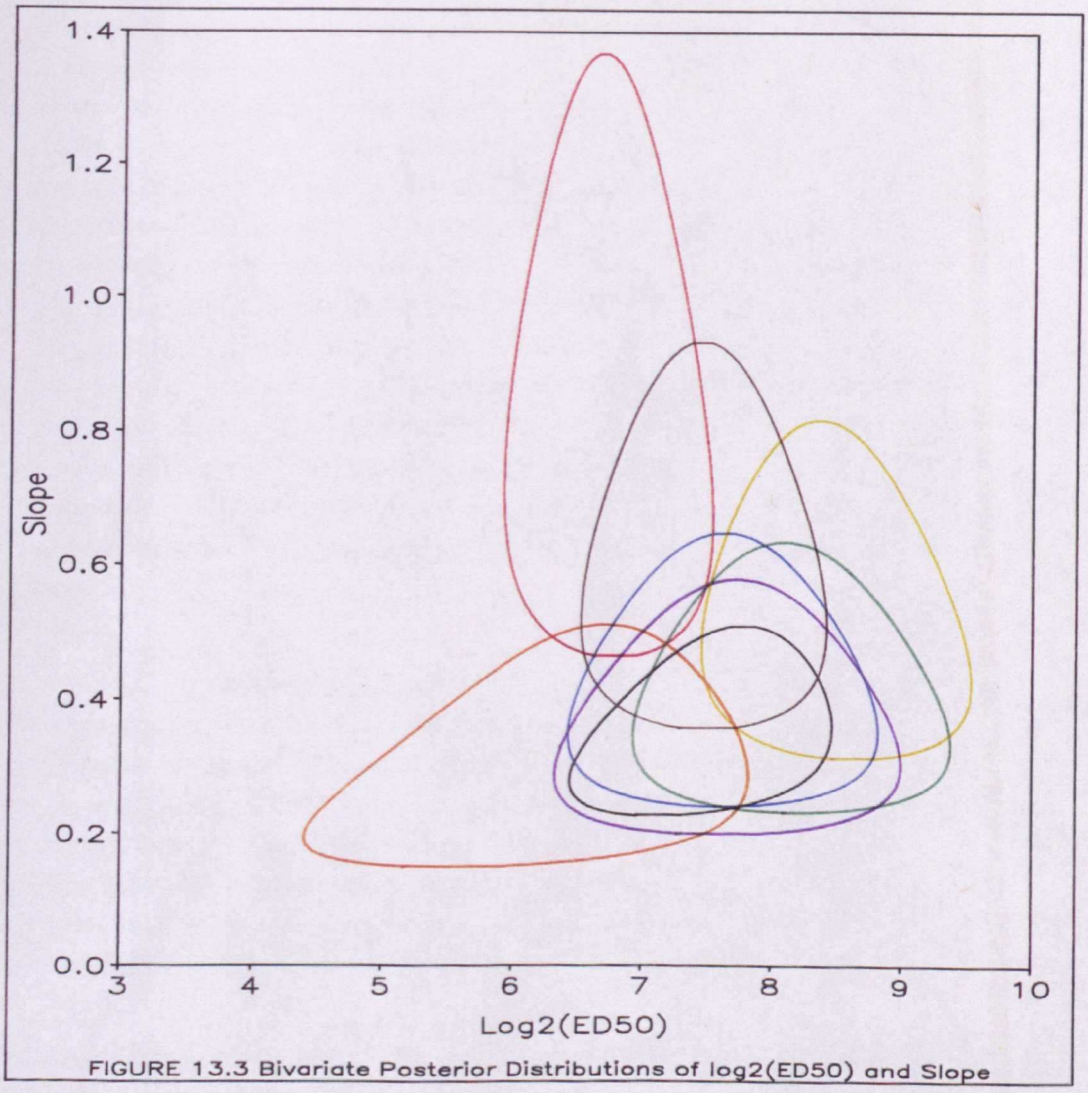


FIGURE 13.3 Bivariate Posterior Distributions of log2(ED50) and Slope

iv) There are a large number of instances within the process of the isolation of new chemical entities for medical research for which the determination of an ED_{50} as opposed to an LD_{50} is required. In some of these cases the model which is being used is an animal model and so once again considerations of efficient resource utilisation suggest that one should optimise the statistical methodology.

v) Finally, returning to the very origins of the LD_{50}, namely Trevan's work on sera, there are still cases in the area of vaccine testing for which a formal LD_{50} is needed. Thraenhardt(1986) has considered the use of Bayesian methods for the evaluation of batches of anti-rabies vaccine based upon the WHO method outlined by Seligmann(1973). The regulatory authorities require that before every new batch of anti-rabies vaccine is released it should be tested against a standard and generally this comparison is based upon the dilution which protects 50% of the animals against the rabies virus. Thraenhardt proposed that the ED_{50}'s should be compared by calculating the posterior probability that the LD_{50} of the test batch is greater than that of the standard vaccine. As illustration we have taken data from Thraenhardt(1986) and in Figures 13.1,13.2 and 13.3 displayed the posterior distributions of the Log_2(ED50), the slope and the joint posterior distribution of Log_2(ED50) and the slope respectively in which the black posterior distributions, labelled '0' in Figure 13.1, relate to the standard vaccine and the remaining seven posteriors in each figure come from seven test batches. From the posteriors displayed in Figure 13.1 we may calculate that probability that the standard has a greater Log_2(ED50) than does batch '1' is 0.057 and perhaps conclude that this batch is not as potent as the standard. It has to be doubted that this approach is a sensible one in the light of the posterior distributions for the slopes displayed in Figure 13.2 from which it is fairly clear that there are large differences. The concept of relative potency requires equality of slopes and this assumption has to be doubted in view of these posteriors. Nonetheless, the log relative potency of two batches has a similar form to the log(ED50) and therefore the techniques which we have developed can quite simply be modified to deal with this case.

The second issue concerns both the LD_{50} problems and the analysis of the two-treatment crossover designs. In both cases we have used vague prior distributions, and there will be arguments about the validity of their use. For example Stone and Springer(1965) have questioned the validity of the vague prior which we have used in §3, and similar concerns have been expressed concerning the vague prior in §8. Despite Box and Tiao's(1973) response to the theoretical arguments of Stone and Springer there are clearly problems with vague priors if one tries to assign to them some semi-philosophical importance which they clearly do not have. Rather they should be thought of merely as a device for expressing that we know little about the parameters of the model under consideration relative to what we may learn from the data.

In the context of pharmaceutical research, particularly when we are dealing with regulatory authorities, it may be very difficult to incorporate prior information into the analysis of the experimental results even if we have a lot of it and believe it to be relevant, notwithstanding the comments of Healy and Newman in §1, and this may be our preferred approach which would circumvent the problems associated with vague priors. However, there seems to be considerable scope for the use of informative priors in in-house research work and this

conflict between the public and private inference may be resolved by the suggestion given in §1, namely to give the data, or likelihood, in a results section, leaving a Bayesian analysis with its posterior distribution to the discussion.

14 REFERENCES

Abeyasekra,S. and Curnow,R.N. (1984). The desirability of adjusting for residual effects in a crossover design. *Biometrics*,40,1071-1078.

Abramowitz,M. and Stegun,I.A. (1972). *Handbook of Mathematical Functions.* New York : Dover

Aitchison,J. (1964). Bayesian tolerance regions. *J. Roy. Statist. Soc. Ser. B*, 26,161-175.

Aitchison,J. and Dunsmore,I.R. (1975). *Statistical Prediction Analysis*. Cambridge : Cambridge University Press.

Aitkin,M. (1982). Direct likelihood inference. In *Lecture Notes in Statistics - GLIM82*. R.Gilchrist (ed.). New York : Springer Verlag.

Aitkin,M. (1986). Statistical modelling: the likelihood approach. *The Statistician*,35,102-113.

Anon (editorial) (1979). Planning a cross-over trial. *Lancet*,i,511.

Anon (1989). Alternatives to the classical LD50 test and their applicability to classification schemes. *Frame News*, November 1989,8-9.

Armitage,P. (1986). In discussion of Racine *et al*(1986).

Armitage,P. (1988). Some aspects of phase-III trials. In *Biometry - Clinical Trials and Related Topics.* T.Okuno (ed.). Amsterdam : Elsevier.

Armitage,P. and Hills,M. (1982). The two-period crossover trial. *The Statistician*,31,119-131.

Bailey,R.A. and Gower,J.C. (1986). In discussion of Racine *et al* (1986).

Balls,M. and Horner,S.A. (1985). The FRAME interlaboratory programme in *in vitro* cytotoxicology. *Fd. Chem. Toxicol.*,23,209-213.

Barker,N.,Hews,R.J.,Huitson,A. and Poloniecki,J. (1982). The two-period crossover trial. *BIAS*,9,67-116.

Barnard,G.A. (1984). Comparing the means of two independent samples. *Appl. Statist.*,33,266-271.

Barnard,G.A. (1986). Comparing the means of two independent samples - a further note. Unpublished manuscript.

Barnes,C.G., Berry,H., Carter,M.E., Downie,W.W., Fowler,P.D., Moll,J.M.H., Perry,J.D., Sawaf,M.S. and Wright,V. (1979). Diclofenac sodium(voltarol) and indomethacin: a multicentre comparative study in rheumatoid arthritis and osteoarthritis. *Rheumatol. Rehabil.*,Supp. 2,135-143.

Bartoszynski,R. and Powers,J.D. (1990). Construction of best confidence intervals for half-lives. *J. Vet. Pharmacol. Ther.*,13,1-6.

Bass,R.,Günzel,P.,Henschler,D.,König,J.,Lorke,D.,Neubert,D.,Schütz,E., Shuppan,D. and Zbinden,G. (1982) LD_{50} versus acute toxicity - critical assessment of the methodology currently in use. *Arch. Toxicol.*,51,183-186.

Beccari,E. (1949). A method for reducing the number of pharmacological assays. *Nature*,163,534-535.

Berger,J and Wolpert,D. (1985). *The Likelihood Principle*. CA : Institute of Mathematical Statistics.

Berry,D.A. (1990). Basic principles in designing and analysing clinical trials. In *Statistics in Pharmaceutical Research*. D.A.Berry (ed.). New York : Marcel Dekker.

Bock,R.D. (1975). *Multivariate Statistical Methods.* New York : McGraw-Hill.

Bouver,H. and Bargmann,R.E. (1979). Comparison of computational algorithms for the evaluation of the univariate and bivariate normal distribution. In *Proceedings of the 12th. Interface of Computer Science and Statistics*. J.F.Gentleman (ed.). Waterloo : University of Waterloo.

Box,G.E.P. (1976). Science and statistics. *J. Am. Statist. Assoc.*,71,791-799.

Box,G.E.P. (1980). Sampling and Bayes' inference in scientific modelling and robustness (with discussion). *J. Roy. Statist. Soc. Ser. A*,143,383-430.

Box,G.E.P. (1983). An apology for ecumenism in statistics. In *Scientific Inference, Data Analysis and Robustness.* G.E.P.Box,T.Leonard and C.-F.Wu (eds). New York : Academic Press.

Box,G.E.P. and Tiao,G.C. (1973). *Bayesian Inference in Statistical Analysis.* Reading,Massachusetts : Addison-Wesley.

Boys,R.J. (1989). Algorithm AS R80. A remark on Algorithm AS 76 : an integral useful in caculating noncentral *t* and bivariate normal probabilities. *Appl. Statist.*,38,580-582.

Breslow,N. (1989). Biostatisticians and Bayes. Presented at the Sesquicentennial Meeting of the American Statistical Association, Washington DC.

British Toxicological Society (1984). A new approach to the classification of substances and preparations on the basis of their acute toxicity. *Human Toxicol.*,3,85-92.

Brogan,D.R., and Kutner,M.H. (1980). Comparative analyses of pretest-posttest research designs. *Am. Statistician*,34,229-232.

Brown,B.W. (1980). The crossover experiment for clinical trials. *Biometrics*,36,69-79.

Brown,V.K.H. (1983). Acute toxicity testing. In *Animals and Alternatives in Toxicity Testing.* M.Balls, R.J.Ridell and A.N.Worden. (eds). New York : Academic Press.

Brown,V.K. (1984). The LD50 value - a frequently misapplied concept. *ATLA*,12,75-79.

Brownlee,K.A.,Hodges,J.L. and Rosenblatt,M. (1953). The up-and-down method with small samples. *J. Am. Statist. Assoc.*,48,262-277.

Bruce,R.D. (1985). An up-and-down procedure for acute toxicity testing. *Fund. Appl. Toxicol.*,5,151-157.

Bruce,R.D. (1987). A confirmatory study of the up-and-method for acute oral toxicity testing. *Fund. Appl. Toxicol.*,8,97-100.

Brunner,E. and Neumann,N. (1987). Non-parametric methods for the 2-period-cross-over design under weak model assumptions. *Biom. J.*,29,907-920.

Chanter,D.O. and Heywood,R. (1982). The LD_{50} test: some considerations of precision. *Toxicol. Letters*,10,303-307.

Chassan,J.B. (1970). A note on relative efficiency in clinical trials. *J. Clin. Pharmacol.*,10,359-360.

Chaubey,Y.P. and Mudholkar,G.S. (1982). A new approximation for the distribution of the difference of two t-variables. *Comm. in Statist. - Theor. Meth.*,11,2335-2342.

Choi,S.C. and Pepple,P.A. (1989). Monitoring clinical trials based on predictive probability of significance. *Biometrics*,45,317-323.

Choi,S.C., Smith,P.J. and Becker,D.P. (1985). Early decision in clinical trials when the treatment differences are small - experience of a controlled trial in head trauma. *Cont. Clin. Trials*,6,280-288.

Cochran,W.G. (1963). The Behrens-Fisher test when the range of the unknown variance ratio is restricted. *Sankhya Ser. A*,25,353-362.

Cochran,W.G.,Autrey,K.M. and Cannon,C.Y. (1941). A double change-over design for dairy cattle feeding experiments. *J. Dairy Sci.*,4,937-951.

Cochran,W.G. and Davis,M. (1965). The Robbins-Munro method for estimating the median lethal dose. *J. Roy. Statist. Soc. Ser. B*,27,,28-44.

Cooper,B.E. (1968). Algorithm AS 4: An auxiliary function for distribution integrals. *Appl. Statist.*,17,190-192. (Correction : *Appl. Statist.*,19,204,1970).

Cox,D.R. (1986). In discussion of Racine *et al* (1986).

Dale,A.I. (1982). Bayes or Laplace ? An examination of the origin and early application of Bayes' theorem. *Arch. Hist. Ex. Sci.*,27,23-47.

Davis,M. (1971). Comparison of sequential bioassay in small samples. *J. Roy. Statist. Soc. Ser. B*,33,78-87.

Dawid,A.P., Stone,M. and Zidek,J.V. (1973). Marginalization Paradoxes in Bayesian and structural inference (with Discussion). *J. Roy. Statist. Soc. Ser. B*,35,189-233.

Dayan,A.D.,Clark,B.,Jackson,M.,Morgan,H. and Charlesworth,F.A. (1984). Role of the LD50 test in the pharmaceutical industry. *Lancet*,i,555-556.

DePass,L.R. (1989). Alternative approaches in median lethality (LD_{50}) and acute toxicity testing. *Toxicol. Lett.*,49,159-170.

DePass,L.R.,Myers,R.C.,Weaver,E.V. and Weil,C.S. (1984). An assessment of the importance of the number of dosage levels, number of animals per dosage level, sex and method of LD50 and slope calculation in acute toxicity studies. In *Alternative Methods in Toxicology* Vol. 2,141-153. A.M.Goldberg(ed.). New York : Mary Ann Liebert Inc.

Disch,D. (1981). Bayesian nonparametric inference for effective doses in a quantal-response experiment. *Biometrics*,37,713-722.

Dixon,W.J. (1965). The up-and-down method for small samples. *J. Am. Statist. Assoc.*,60,967-978.

Dixon,W.J. and Mood,A.M. (1948). A method for obtaining and analyzing sensitivity data. *J. Am. Statist. Assoc.*,43,109-126.

Douglas,M.T.,Chanter,D.O.,Bell,I.B. and Burney,G.M. (1986). A proposal for the reduction of animal numbers required for the acute toxicity to fish test (LC_{50} determination). *Aquatic Toxicol.*,8,243-249.

Dubey,S.D. (1986). Current thoughts on crossover designs. *Clin. Res. Prac. & Drug Reg. Affairs*,4,127-142.

Durbin,J. and Watson,G.S. (1951). Testing for serial correlation in least squares regression II. *Biometrika*,38,159-178.

Durbin,J. and Watson,G.S. (1971). Testing for serial correlation in least squares regression III. *Biometrika*,58,1-19.

Ebbutt,A.F. (1984). Three-period crossover designs for two treatments. *Biometrics*,40,219-224.

ECETOC (1985). Acute toxicity tests, $LD_{50}(LC_{50})$ determinations and alternatives. *ECETOC Monograph* No. 6.

Ekwall,B. (1983). Correlation between cytotoxicity in vitro and LD_{50}-values. *Pharmacol. Toxicol.*,52 Supp. ii,80-99.

Enslein,K. and Craig,P.N. (1978). A toxicity estimation model. *J. Environ. Pathol. Toxicol.*,2,115-121.

Enslein,K.,Lander,T.P.,Tomb,M.E. and Craig,P.N. (1989). A predictive model for estimating LD_{50} values. *Toxicol. Ind. Health*,5,261-387.

Farewell,V.T. (1985). Some remarks on the analysis of cross-over trials with a binary response. *Appl. Statist.*,34,121-128.

Feinstein,A.R. (1977). Clinical biostatistics XXXIX. The haze of BAyes, the aerial palaces of decision analysis and the computerised Ouija board. *Clin. Pharmacol. and Therap.*,72,1178-1181.

FDA (1977). A report on the two-period cross-over design and its applicability in trials of clinical effectiveness. *Minutes of the BEMAC Meeting.*

Fidler,V. (1984). Change-over clinical trial with binary data: mixed-model-based comparison of tests. *Biometrics*,40,1063-1070.

Fieller,E.C. (1954). Some problems in interval estimation. *J. Roy. Statist. Soc. Ser. B*,16,175-186.

Finney,D.J. (1963). Some properties of a distribution specified by its cumulants. *Techno.*,5,63-69.

Finney, D.J. (1971). *Probit Analysis.* Cambridge : Cambridge University Press, 2nd Edition

Finney,D.J. (1985). The median lethal dose and its estimation. *Arch. Toxicol.*,56,215-218.

Fisher,R.A. (1941). The asymptotic approach to Behrens's integral, with further tables for the d test of significance. *Ann. Eugen.*,11,141-172.

Fleiss,J.L.,Wallenstein,S. and Rosenfeld,R. (1985). Adjusting for baseline measurements in the two-period crossover study: a cautionary note. *Cont. Clin. Trials*,6,192-197.

Freeman,P.R. (1970). Optimal Bayesian sequential estimation of the median effective dose. *Biometrika*,57,79-89.

Freeman,P.R. (1986). In discussion of Racine *et al*(1986).

Freeman,P.R. (1989). The performance of the two-stage analysis of two-treatment, two-period crossover trials. *Statist. in Med.*,8,1421-1432.

Frei,A.,Cottier,P.Wunderlich,P. and Lüdin,E. (1987). Glycerol and Dextran combined in the therapy of acute stroke. *Stroke*,18,373-379.

Gad,S.C.,Smith,A.C.,Cramp,A.L.,Gavigan,F.A. and Derelanko,M.J. (1984). Innovative designs and practices for acute systemic toxicity studies. *Drug Chem. Toxicol.*,7,423-434.

Galant,D. (1969). Gauss quadrature rules for the evaluation of $2\pi^{-1/2}\int_0^{\infty}\exp(-x^2)f(x)dx$. *Math. Comp.*,23,674.

Gart,J.J. (1969). An exact test for comparing matched proportions in crossover designs. *Biometrika*,56,75-80.

Gart,J.J. (1975). The Poisson distribution: the theory and application of some conditional tests. In *Statistical Distributions in Scientific Work*, Vol. 2. G.P.Patil et al (eds.) Holland : D.Reidel.

Geisser,S. (1964). Estimation in the uniform covariance case. *J. Roy. Statist. Soc. Ser. B*,26,477-483.

Geisser,S. (1971). The inferential use of predictive distributions. In *Foundations of Statistical Inference.* V.P.Godambe and D.A.Sprott (eds.) New York : Rinehart and Winston.

Geisser,S. (1982). Aspects of the predictive and estimative approaches in the determination of probabilities (with discussion). *Biometrics*, Supp. 38,75-93.

Geisser,S. (1985). On the prediction of observables : a selective update. In *Bayesian Statistics 2.* J.M.Bernardo,M.H.de Groot,D.V.Lindley,A.F.M.Smith (eds.). Oxford : Oxford University Press.

Gelfand,A.E., Hills,S.E., Racine-Poon,A. and Smith,A.F.M. (1990). Illustration of Bayesian inference in normal data models using Gibbs sampling. *J. Am. Statist. Assoc.*,85,972-985.

Gersich,F.M., Blanchard,F.A., Applegarth,S.L. and Park,C.N. (1986). The precision of daphnid (*Daphnia magna* Straus, 1820) static acute toxicity tests. *Arch. Environ. Contam. Toxicol.*,15,741-749.

Gomez-Marin,O. and McHugh,R.B. (1984). Randomization modelling of the crossover experiment for clinical trials. *Biom. J.*,8,901-914.

Gough,K. (1989). Letter to the editor. *Statist. in Med.*,8,891-892.

Govindarajulu,Z. (1988). *Statistical Techniques in Bioassay*. Basel : Karger.

Grieve,A.P. (1982). The two-period changeover design in clinical trials. *Biometrics*,38,517.

Grieve,A.P. (1984). Tests of sphericity of normal distributions and the analysis of repeated measures designs. *Psychom.*,49,257-267.

Grieve,A.P. (1985). A Bayesian analysis of the two-period crossover design in clinical trials. *Biometrics*,41,979-990.

Grieve,A.P. (1986). Correction. *Biometrics*,42,459.

Grieve,A.P. (1987a). Applications of Bayesian software: two examples. *The Statistician*,36,283-288.

Grieve,A.P. (1987b). A note on the analysis of the two-period crossover design when the period-treatment interaction is significant. *Biom. J.*,29,771-775.

Grieve,A.P. (1988a). Some uses of predictive distributions in pharmaceutical research. In *Biometry - Clinical Trial and Related Topics*. T.Okuno (ed.). Amsterdam : Elsevier Science Publishers.

Grieve,A.P. (1988b). A Bayesian approach to the analysis of LD50 experiments. In *Bayesian Statistics 3.* J.M.Bernardo,M.H.de Groot,D.V.Lindley,A.F.M.Smith (eds.). Oxford : Oxford University Press.

Grieve,A.P. (1990). Crossover versus parallel designs. In *Statistics in Pharmaceutical Research*. D.A.Berry (ed.). New York : Marcel Dekker.

Griffin,J.P. (1981). Referring to the paper by Zbinden and Flury-Roversi. *Arch. Toxicol.*,49,99-103.

Griffith,J.F. (1964). Interlaboratory variations in the determination of acute oral LD_{50}. *Toxicol. Appl. Pharmacol.*,6,726-730.

Grizzle,J.E. (1965). The two-period change-over design and its use in clinical trials. *Biometrics*,21,467-480.

Grizzle,J.E. (1974). Correction. *Biometrics*,30,727.

Guttman,I. (1967). The use of the concept of a future observation in goodness-of-fit problems. *J. Roy. Statist. Soc. Ser. B*,29,83-100.

Guttman,I. (1970). *Statistical Tolerance Regions : Classical and Bayesian.* London : Griffin.

Hafner,K.B.,Koch,G.G. and Canada,A.T. (1988). Some analysis strategies for three-period changeover designs with two treatments. *Statist. in Med.*,7,471-481.

Hamilton,M.A. and Bissonnette,G.K. (1975). Statistical inferences about injury and persistence of environmentally stressed bacteria. *J. Hyg.*,74,149-155.

Harper,W.M. (1962). Quadrature formulas for infinite integrals. *Math. Comp.*,16,170-175.

Healy,M.J.R. (1983). In discussion of Lewis(1983).

Healy,M.J.R. (1986). Private communication.

Hecker,H. (1986). Identification and interpretation of effects in two-period crossover designs. *EDV in Med. u. Biol.*,17,60-66.

Hedayat,A. and Afsarinejad,K. (1975). Repeated measures designs, I. In *A Survey of Statistical Design and Linear Models*. J.N.Srivastava(ed.) Amsterdam : North Holland.

Hedayat,A. and Afsarinejad,K. (1978). Repeated measures designs, II. *Ann. Statist.*,6,619-628.

Hews,R.J. (1981). A further note on the interpretation of results from the two-period cross-over clinical trial. *PSI Newsletter*,Vol. 3,no.2.

Hildreth,C. (1963). Bayesian statisticians and remote clients. *Econometrica*,31,422-438.

Hill, I.D. (1973). Algorithm AS 66: The normal integral. *Appl. Statist.*,22,424,427.

Hills,M. and Armitage,A. (1979). The two-period cross-over trial. *Br. J. Clin. Pharmacol.*,8,7-20.

Hinkley,D.V. (1969). On the ratio of two correlated normal variables. *Biometrika*,56,635-639. (Correction : *Biometrika*,57,683,1970).

Huitson,A. (1980). Note on the interpretation of results from the two-period cross-over clinical trial. *PSI Newsletter*,Vol. 2,no.4.

Huitson,A.,Poloniecki,J.,Hews,R. and Barker,N. (1982). A review of crossover trials. *The Statistician*,31,71-80.

Hume,C.W. (1957). The strategy and tactics of experimentation. *Lancet*,ii,1049-1052.

Hunter,W.J.,Lingk,W. and Recht,P. (1979). Intercomparison study on the determination of single administration toxicity in rats. *J. Assoc. Off. Anal. Chem.*,62,864-873.

Huntsberger,D.V. (1955). A generalization of a preliminary testing procedure for pooling data. *Ann. Math. Statist.*,26,734-743.

Jeffreys,H. (1983). *Theory of Probability*, 3rd. ed. Oxford : Clarendon Press.

Jones ,B. (1986). In discussion of Racine *et al* (1986).

Jones,B. and Kenward,M.G. (1987). Modelling binary data from a three-period cross-over trial. *Statist. in Med.*,6,555-564.

Jones,B. and Kenward,M.G. (1989). *Design and Analysis of Cross-Over Trials.* London : Chapman and Hall.

Kaiser,M.S. (1989). Interpretation of confidence intervals for median effective dose estimates. *Environ. Toxicol. and Chem.*,8,181-188.

Kalbfleisch,J.D. and Sprott,D.A. (1969). Application of likelihood methods to models involving large numbers of parameters (with discussion). *J. Roy. Statist. Soc. Ser. B*,32,175-208.

Kaufmann,S.R. and Cohen,M.J. (1987). The clinical relevance of the LD_{50}. *Vet. Hum. Toxicol.*,29,39-41.

Kennedy,G.L., Ferenz,R.L. and Burgess,B.A. (1986). Estimation of acute oral toxicity in rats by determination of the approximate lethal dose rather than the LD_{50}. *J. Appl. Toxicol.*,6,145-148.

Kenward,M.G. and Jones,B. (1987a). A log-linear model for binary cross-over data. *Appl. Statist.*,36,192-204.

Kenward,M.G. and Jones,B. (1987b). The analysis of data from 2 x 2 cross-over trials with baseline measurements. *Statist. in Med.*,6,911-926.

Kershner,R.P. and Federer,W.T. (1981). Two-treatment crossover designs for estimating a variety of effects. *J. Am. Statist. Assoc.*,76,612-619.

Kimber,G.R. (1986). In discussion of Racine *et al* (1986).

Koch,G.G. (1972). The use of non-parametric methods in the statistical analysis of the two-period change-over design. *Biometrics*,28,577-584.

Kunert,J. (1985). Optimal repeated measurements designs for correlated observations and analysis by weighted least squares. *Biometrika*,72,375-389.

Kunert,J. (1987). On variance estimation in crossover designs. *Biometrics*,43,833-845.

Laird,N. (1983). Further comparative analyses of pretest-posttest research designs. *Am. Statistician*,37,329-330.

Lan,K.K.G., DeMets,D.L. and Halperin,M. (1984). More flexible sequential and nonsequential designs in long-term clinical trials. *Comm. in Statist.*,A13,2339-2353.

Lan,K.K.G., Simon,R. and Halperin,M. (1982). Stochastically curtailed tests in long-term clinical trials. *Comm. in Statist. - Seq. Anal.*,1,207-214.

Larson,H.J. and Bancroft,T.A. (1963). Biases in prediction by regression for incompletely specified models. *Biometrika*,50,391-402.

Laska,E.,Meisner,M. and Kushner,H.B. (1985). Optimal crossover designs in the presence of carryover effects. *J. Am. Statist. Assoc.*,80,704-710.

Laska,E.M. and Meisner,M. (1983). A variational approach to optimal two-treatment crossover designs: application to carryover models. *Biometrics*,39,1087-1091.

Layard,M.W.J. and Arvesen,J.N. (1978). Analysis of Poisson data in crossover experimental designs. *Biometrics*,34,421-428.

Layton,D.W.,Mallon,B.J.,Rosenblatt,D.H. and Small,M.J. (1987). Deriving allowable daily intakes for systemic toxicants lacking chronic toxicity data. *Reg. Toxicol. Pharmacol.*,7,96-112.

LeBeau,J.E. (1983). The role of the LD_{50} evaluation in drug safety evaluation. *Reg. Toxicol. Pharmacol.*,3,71-74.

Le Cam,L. (1985). In discussion of Berger and Wolpert(1985).

Lee,J.L. (1980). A note on the comparison of group means based on repeated measurements of the same subject. *J. Chron. Dis.*,33,673-675.

Lewis,J.A. (1983). Clinical trials : statistical developments of practical benefit to the pharmaceutical industry (with discussion). *J. Roy. Statist. Soc. Ser. A*,146,362-393.

Lindley,D.V. (1980). Approximate Bayesian methods. In *Bayesian Statistics* J.M.Bernardo,M.H.de Groot,D.V.Lindley,A.F.M.Smith (eds.). Valencia : Valencia University Press.

Lindley,D.V. and Smith,A.F.M. (1972). Bayes estimates for the linear model (with discussion). *J. Roy. Statist. Soc. Ser. B*,34,1-41.

Little,R.J.A. (1988). Approximately calibrated small samples inference about means from bivariate normal data with missing values. *Comp. Statist. Data Anal.*,7,161-178.

Lord,F.M. (1967). A paradox in the interpretation of group comparisons. *Psychol. Bull.*,68,304-305.

Lorke,D. (1983). A new approach to practical acute toxicity testing. *Arch. Toxicol.*,54,275-287.

Lucas,H.L. (1957). Extra-period Latin-square change-over designs. *J. Dairy Sci.*,40,225-239.

Maas,B., Garnett,W.R., Pollock,I.M. and Carnstock,T.J. (1987). A comparative bioavailability study of carbamazepine tablets and the chewable formulation. *Ther. Drug Monit.*,9,28-33.

McHugh,R. and Gomez-Marin,O. (1987). Randomization and additivity in the two-period crossover clinical trial. *Biom. J.*,29,961-970.

MacRae,E.C. (1974). Matrix derivatives with an application to an adaptive linear decision problem. *Ann. Statist.*,2,337-346.

Magnus,J.R. and Neudeucker,H. (1979). The commutation matrix : some properties and applications. *Ann. Statist.*,7,381-394.

Marks,B.L. (1962). Some optimal sequential schemes for estimating the mean of accumulative normal quantal response curve. *J. Roy. Statist. Soc. Ser. B*,24,393-400.

Matthews,J.N.S. (1988). Recent developments in crossover designs. *Int. Statist. Rev.*,56,117-127.

MehtaJ.S. and Swamy,P.A.V.B. (1973). Bayesian analysis of a bivariate normal distribution with incomplete observations. *J. Am. Statist. Assoc.*,68,922-926.

MehtaJ.S. and Swamy,P.A.V.B. (1974). Bayesian analysis of a bivariate normal distribution when some observations are missing. In *Studies in Bayesian Ecomometrics and Statistics*. S.E. Fienberg and A. Zellner (eds.) Amsterdam : North Holland.

Meier,J. and Theakston,R.D.G. (1986). Approximate LD_{50} determinations of snake venoms using eight to ten experimental animals. *Toxicon.*,24,395-401.

Molinengo,L. (1979). The curve doses vs survival time in the evaluation of acute toxicity. *J. Pharm. Pharmacol.*,31,343-344.

Müller,H. and Kley,H.-P. (1982). Retrospective study on the reliability of an approximate LD_{50} determined with a small number of animals. *Arch. Toxicol.*,51,189-196.

Nagelkerke,N.J.D.,Hart,A.A.M. and Oosting,J. (1986). The two period binary response cross-over trial. *Biom. J.*,7,863-869.

Naylor,J.C. and Smith,A.F.M. (1982). Applications of a method for the efficient computation of posterior distributions. *Appl. Statist.*,31,214-225.

Newman,G.R. (1983). In discussion of Lewis(1983).

Nicholls,D.P.,Moles,K.,Gleadhill,D.N.S.,Booth,K.,Rowan,J. and Morton,P. (1986). Comparison of transdermal nitrate and isosorbide dinitrate in chronic stable angina. *Br. J. Clin. Pharmacol.*,22,15-20.

Odeh, R.E. and Evans, J.D. (1974). Algorithm AS 70: The percentage points of the normal distribution. *Appl. Statist.*,23,96-97.

O'Neill,R.T. (1978). Subject-own-control designs in clinical drug trials: overview of the issues with emphasis on the two treatment problem. Presented at the Annual NSDEU Meeting, Key Biscayne, Florida.

Owen,D.M. (1956). Tables for computing bivariate normal probabilities. *Ann. Math. Statist.*,27,1075-1090.

Pate,I. (1989). Direct use of the likelihood function for ED_{50} estimation.

Patel,H.I. (1983). Use of baseline measurements in the two-period crossover design. *Comm. Statist.-Theor. Meth.*,12(23),2693-2712.

Patel,H.I. (1985). Analysis of incomplete data in a two-period crossover design with reference to clinical trials. *Biometrika*,72,411-418.

Patil,V.M. (1965). Approximation to the Behrens-Fisher distributions. *Biometrika*,52,267-271.

Pericchi,L.R. (1981). A Bayesian approach to transformation to normality. *Biometrika*,68,35-43.

Piegorsch,W.W. (1989). Quantification of toxic response and the development of the median effective dose (ED_{50}) - a historical perspective. *Toxicol. Ind. Health*,5,55-62.

Poloniecki,J. and Daniel,D. (1981). Further analysis of the Hills and Armitage enuresis data. *The Statistician*,30,225-229.

Poloniecki,J. and Pearce,A.C. (1983). Interaction in the two-way crossover trial. *Biometrics*,39,798.

Prescott,R.J. (1981). The comparison of success rates on cross-over trials in the presence of an order effect. *Appl. Statist.*,30,9-15.

Prigge,R. (1935). Die Staatliche Prüfung der Diptherieimpfstoffe und ihre experimentellen Grundlagen. *Arbeiten aus dem Staatsinstitut für experimentelle Therapie und dem Georg Speyer-Hause zur Frankfurt A.M.*,32,1-50.

Racine,A.,Grieve,A.P.,Flühler,H. and Smith,A.F.M. (1986). Bayesian methods in practice: experiences in the pharmaceutical industry (with discussion). *Appl. Statist.*,35,93-150.

Ramsey,F.L. (1972). A Bayesian approach to bioassay. *Biometrics*,28,841-858.

Rekker,R.F. (1980). LD_{50} values: are they about to be predictable ?. *Trends in Pharmacol. Sci.*,1,383-384.

Ritchie,D.M., Boyle,J.A., McInnes,J.M., Jasani,M.K., Dalakos,T.G., Grieveson,P. and Buchanan,W.W. (1968). Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. *Q. J. Med.*,37,393-406.

Ross,G.J.S. (1986). In discussion of Racine *et al* (1986).

Rowan,A.N. (1981). The LD_{50} test: a critique and suggestions for alternatives. *Phar. Techn.*,5,65-94.

Ruben,H. (1960). On the distribution of thw weighted difference of two independent student variables. *J. Roy. Statist. Soc. Ser. B*,22,188-194.

Schafer,W.D. (1981). Letter to the editor. *Am. Statistician*,35,179.

Schütz,E. and Fuchs,H. (1982). A new approach to minimising the number of animals used in toxicity testing and optimising the information of test results. *Arch. Toxicol.*,51,197-220.

Scott,A.J. and Smith,T.M.F. (1971). Interval estimates for linear combinations of means. *Appl. Statist.*,20,276-285.

Seligmann,E.B. (1973). The NIH test for potency. In *Laboratory Techniques in Rabies (3rd. Edition)*. M.M.Kaplan and H.Koprowski(eds.). Geneva : W.H.O.

Selwyn,M.R.,Dempster,A.P. and Hall,N.R. (1981). A Bayesian approach to bioequivalence for the 2 x 2 changeover design. *Biometrics*,37,11-21.

Sevcik,C. (1987). LD_{50} determination : objections to the method of Beccari as modified by Molinengo. *Toxicon.*,25,779-783.

Smith,A.F.M. and Spiegelhalter,D.J. (1981). Bayesian approaches to multivariate structure. In *Interpreting Multivariate Data*. V.Barnett(ed.). New York : Wiley.

Society of Toxicology (1989). Comments on the LD50 and acute eye and skin irritation tests. *Fund. Appl. Toxicol.*,13,621-623.

Spiegelhalter,D.J. (1986a). In discussion of Racine *et al*(1986).

Spiegelhalter,D.J. (1986b). Probabilistic prediction in patient management and clinical trials. *Statist. in Med.*,5,421-423.

Spiegelhalter,D.J. and Freedman,L.S. (1988). Bayesian approach to clinical trials. In *Bayesian Statistics 3*, J.M.Bernardo, M.H.DeGroot, D.V.Lindley and A.F.M.Smith (eds). Oxford : Oxford University Press.

Spiegelhalter,D.J., Freedman,L.S. and Blackburn,P.R. (1986). Monitoring clinical trials : conditional or predictive power? *Cont. Clin. Trials*,7,8-17.

Spiegelhalter,D.J. and Smith,A.F.M. (1982). Bayes factors for linear and log-linear models with vague prior information. *J. Roy. Statist. Soc. Ser. B*,44,377-387.

Steen,N.M.,Byrne,G.D. and Gelbard,E.M. (1969). Gaussian quadrature for the integrals $\int_0^\infty \exp(-x^2)f(x)dx$ and $\int_0^b \exp(-x^2)f(x)dx$. *Math. Comp.*,23,661-671.

Stigler,S.M. (1982). Thomas Bayes' Bayesian inference. *J. Roy. Statist. Soc. Ser. A*, 145, 250-258.

Stigler,S.M. (1986). *The History of Statistics: The Measurement of Uncertainty Before 1900.* Cambridge, Mass. : Harvard University Press.

Stirling, W.D. (1981a). Algorithm AS 168: Scale selection and formatting. *Appl. Statist.*,30,339-344.

Stirling, W.D. (1981b). Algorithm AS 169: An improved algorithm for scatter plots. *Appl. Statist.*,30,345-349.

Stone,M. and Springer,B.G.F. (1965). A paradox involving quasi prior distributions. *Biometrika*,52,623-627.

Sukhatme,P.V. (1938). On Fisher and Behrens test of significance for the difference in means of two normal samples. *Sankhya*,4,39-48.

Tattersall,M.L. (1982). Statistics and the LD_{50} study. *Arch. Toxicol. Suppl.*,5,267-270.

Taulbee,J.D. (1982). A note on the use of nonparametric methods in the statistical analysis of the two-period changeover design. *Biometrics*,38,1053-1055.

Thraenhart,O. (1986). *Wertbemessung von Gewebekultur-Impstoffen gegen Tollwut für Mensch und Hund.* Habilitationsschrift, University of Essen.

Tierney,L. and Kadane,J.B. (1986). Accurate approximations for posterior moments and marginal densities. *J. Am. Statist. Assoc.*,81,82-86.

Trevan,J.W. (1927). The error of determination in toxicity. *Proc. Roy. Soc. Ser. B*,101,483-514.

Tsutakawa,R.K. (1975). Bayesian inference for bioassay. Dept. of Math. Sciences,Univ. of Missouri-Columbia, Tech. Rep. 52.

Tsutakawa,R.K. (1980). Selection of dose levels for estimating a percentage point of a logistic quantal response curve. *Appl. Statist.*,29,25-33.

Tute,M.S. (1981). Computer prediction of LD_{50} values. *ATLA*,9,50-52.

Tute,M.S. (1983). Mathematical modelling. In *Animals and Alternatives in Toxicity Testing.* M.Balls,R.J.Riddell, and A.N.Worden (eds). New York : Academic Press.

Überla,K. and Schnieders,B. (1982). In reference to the paper by Bass *et al. Arch. Toxicol.*,51,183-186.

Van den Heuvel,M.J.,Dayan,A.D. and Shillaker,R.O. (1987). Evaluation of the BTS approach to the testing of substances and preparations for their acute toxicity. *Human Toxicol.*,6,279-291.

Van Noordwijk,A.J. and Van Noordwijk,J. (1988). An accurate method for estimating an approximate lethal dose with few animals, tested with a Monte Carlo procedure. *Arch. Toxicol.*,61,333-343.

Varma,A.O. and Chilton,N.W. (1974). Crossover designs involving two treatments. *J. Periodontal. Res.*,9,160-170.

Vere,D.W. (1979). Validity of cross-over trials. *Br. J. Clin. Pharmacol.*,8,5-6.

Vit,P.J. (1989). Approximate lethal dose versus median lethal dose in acute toxicity testing of pharmaceuticals. *Arch. Toxicol.*,63,343-344.

Wallenstein,S. and Fleiss,J.L. (1988). The two-period crossover design with baseline measurements. *Comm. Statist.-Theor. Meth.*,17,3333-3343.

Weir,J.B. de V. (1960). Significance of the difference between two means when the population variances may be unequal. *Nature*,187,438.

Welch,B.L. (1938). The significance of the difference between two means when the population variances are unequal. *Biometrika*,29,350-362.

Wetherill,G.B. (1963). Sequential estimation of quantal response curves(with discussion). *J. Roy. Statist. Soc. Ser. B*,25,1-48.

Wheatley,D. (1987). Transdermal nitroglycerin in angina pectoris. *Stress Med.*,3,199-203.

Whittaker,E.T. and Watson,G.N. (1963). *A Course of Modern Algebra.* Cambridge : Cambridge University Press.

Willan,A.R. and Pater,J.L. (1986a). Using baseline measurements in the two-period crossover clinical trial. *Cont. Clin. Trials*,7,282-289.

Willan,A.R. and Pater,J.L. (1986b). Carryover and the two-period crossover clinical trial. *Biometrics*,42,593-599.

Williams,D.A. (1986). Interval estimation of the median lethal dose. *Biometrics*,424,641-645.

Young,J.C. and Minder,Ch.E. (1974). Algorithm AS 75 : An integral useful in calculating non-central *t* and bivariate normal probabilities. *Appl. Statist.*,23,455-467. (Correction : *Appl. Statist.*,28, ,1979).

Zbinden,G. (1986). Acute toxicity testing, public responsibility and scientific challenges. *Cell Biol. Toxicol.*,2,325-335.

Zbinden,G. (1988). A look behind drug regulatory guidelines. In *National and International Drug Safety Guidelines.* S.Adler and G.Zbinden (eds.). Zollikon : MTC Verlag.

Zbinden,G. and Flury-Roversi,M. (1981). Significance of the LD_{50}-test for the toxicological evaluation of chemical substances. *Arch. Toxicol.*,47,77-99.

Zeise,L., Wilson,R. and Crouch,E. (1984). Use of acute toxicity to estimate carcinogenic risk. *Risk Anal.*,4,187-199.

Zellner,A. and Rossi,P.E. (1984). Bayesian analysis of dichotomous quantal response models. *J. Econometrics*,25,365-393.

Zimmermann,H. and Rahlfs,W. (1978). Testing hypotheses in the two-period change over trial with binary data. *Biom. J.*,20,133-141.

Zimmermann,H. and Rahlfs,W. (1980). Model building and testing for the change-over design. *Biom. J.*,22,197-220.

Zinner,D.D.,Duany,L.F. and Chilton,N.W. (1970). Controlled study of the clinical effectiveness of a new oxygen gel on plaque, oral debris and gingival inflammation. *Pharm. Ther. Dent.*,1,7-15.

A APPENDICES.

A1 Behrens-Fisher Densities and Orthogonal Polynomials.

Four different methods of calculating Behrens-Fisher densities and/or distribution functions are considered. The first three methods depend on the use of orthogonal polynomials and Gaussian quadrature. As a by-product of one of these methods an alternative to Fisher's(1941) Hermite polynomial expansion of the Behrens-Fisher density is derived.

A1.1 Background.

Suppose $x_{ij}(i = 1, 2; j = 1, \ldots, n_i)$ are two independent samples from $N(\mu_i, \sigma_i^2)$ and further that the prior distributions of $\mu_1, \mu_2, \log(\sigma_1^2)$ and $\log(\sigma_2^2)$ are independently uniform over $(-\infty, \infty)$. If $\bar{x}_1, \bar{x}_2, s_1^2, s_2^2$ are the respective means and variances of the two samples, standard Bayesian calculations show that the posterior distribution of the parameters has the form,

$$\begin{aligned} p(\mu_1, \mu_2, \sigma_1^2, \sigma_2^2 \mid X) &= A_1 A_2 (\sigma_1^2 \sigma_2^2)^{-1/2} \exp\left[-\frac{n_1(\mu_1 - \bar{x}_1)^2}{2\sigma_1^2} - \frac{n_2(\mu_2 - \bar{x}_2)^2}{2\sigma_2^2} \right] \\ &\times B_1 B_2 (\sigma_1^2)^{-(n_1+1)/2} (\sigma_2^2)^{-(n_2+1)/2} \\ &\times \exp\left[-\frac{(n_1 - 1)s_1^2}{2\sigma_1^2} - \frac{(n_2 - 1)s_2^2}{2\sigma_2^2} \right] \end{aligned} \qquad (A1.1.1)$$

where

$$X = (\bar{x}_1, \bar{x}_2, s_1^2, s_2^2) \quad , \quad A_i = \left(\frac{n_i}{2\pi} \right)^{1/2} \quad , \text{ and } \quad B_i = \left[\frac{(n_i - 1)s_i^2}{2} \right]^{(n_i - 1)/2} \Gamma^{-1}\left[\frac{(n_i - 1)}{2} \right].$$

If we are interested in making inferences concerning $\eta = \mu_2 - \mu_1$, a natural way to proceed is to integrate σ_1^2 and σ_2^2 out of (A1.1.1) to obtain,

$$p(\mu_1, \mu_2 \mid X) = C_1 C_2 \left[1 + \frac{n_1(\mu_1 - \bar{x}_1)^2}{\nu_1 s_1^2} \right]^{-n_1/2} \left[1 + \frac{n_2(\mu_2 - \bar{x}_2)^2}{\nu_2 s_2^2} \right]^{-n_2/2} \qquad (A1.1.2)$$

where $\nu_i = n_i - 1, C_i = B^{-1}(1/2, \nu_i/2)(\nu_i s_i^2 / n_i)^{-1/2}$ followed by the transformation $\eta = \mu_2 - \mu_1, \psi = \mu_1$ (with unit jacobian) and to integrate out ψ. Thus,

$$p(\eta \mid X) = \int_{-\infty}^{\infty} C_1 C_2 \left[1 + \frac{n_1(\psi - \bar{x}_1)^2}{\nu_1 s_1^2} \right]^{-n_1/2} \left[1 + \frac{n_2(\eta + \psi - \bar{x}_2)^2}{\nu_2 s_2^2} \right]^{-n_2/2} d\psi. \qquad (A1.1.3)$$

Posterior probabilities concerning η may be obtained by integrating (A1.1.3) over the required range. For example,

$$P(\eta>0\mid X) = \int_0^{\infty}\int_{-\infty}^{\infty} C_1C_2\left[1+\frac{n_1(\psi-\bar{x}_1)^2}{\nu_1 s_1^2}\right]^{-n_1/2}\left[1+\frac{n_2(\eta+\psi-\bar{x}_2)^2}{\nu_2 s_2^2}\right]^{-n_2/2} d\psi d\eta. \qquad (A1.1.4)$$

The problem considered in this appendix is the numerical evaluation of (A1.1.3) and (A1.1.4).

A1.2 Quadrature Using Harper Polynomials.

From (A1.1.3) it is clear that,

$$p(\eta\mid\psi,X) = C_2\left[1+\frac{n_2(\eta+\psi-\bar{x}_2)^2}{\nu_2 s_2^2}\right]^{-n_2/2} \qquad (A1.2.1)$$

and,

$$p(\psi\mid X) = C_1\left[1+\frac{n_1(\psi-\bar{x}_1)^2}{\nu_1 s_1^2}\right]^{-n_1/2} \qquad (A1.2.2)$$

so that (A1.1.3) and (A1.1.4) may be written,

$$p(\eta\mid X) = \int_{-\infty}^{\infty} p(\eta,\psi\mid X)d\psi = \int_{-\infty}^{\infty} p(\eta\mid\psi,X)p(\psi\mid X)d\psi \qquad (A1.2.3)$$

$$P(\eta>0\mid X) = \int_0^{\infty}\int_{-\infty}^{\infty} p(\eta,\psi\mid X)d\psi = \int_0^{\infty}\int_{-\infty}^{\infty} p(\eta\mid\psi,X)p(\psi\mid X)d\eta d\psi$$

$$= \int_{-\infty}^{\infty} P(\eta>0\mid\psi,X)p(\psi\mid X)d\psi \qquad (A1.2.4)$$

In (A1.2.3) and (A1.2.4) make the transformation $u = n_1^{1/2}(\psi-\bar{x}_1)/(\nu_1 s_1^2)^{1/2}$ with jacobian $(\nu_1 s_1^2/n_1)^{1/2}$ then

$$p(\eta\mid X) = \int_{-\infty}^{\infty} p(\eta\mid u,X)p(u\mid X)du$$

$$= \int_{-\infty}^{\infty} C_2\left(1+\frac{n_2[\eta+\bar{x}_1-\bar{x}_2+u(\nu_1 s_1^2/n_1)^{1/2}]^2}{\nu_2 s_2^2}\right)^{-n_2/2} C_1'(1+u^2)^{-n_1/2}du \qquad (A1.2.5)$$

and

$$P(\eta>0\mid X) = \int_{-\infty}^{\infty} P(\eta>0\mid u,X)p(u\mid X)du$$

$$= \int_{-\infty}^{\infty}\left(1-P\left[t(\nu_2)>\frac{\bar{x}_2-\bar{x}_1-u(\nu_1 s_1^2/n_1)^{1/2}}{(s_2^2/n_2)^{1/2}}\right]\right)C_1'(1+u^2)^{-n_1/2}du \qquad (A1.2.6)$$

where $C_1' = B^{-1}(1/2,\nu_1/2)$ and $t(\nu_2)$ is t-distributed with ν_2 degrees of freedom.

Equations (A1.2.5) and (A1.2.6) may both be written in the form,

$$\int_{-\infty}^{\infty} C_1' f(u)(1+u^2)^{-n_1/2} du \qquad (A1.2.7)$$

and may therefore be approximated by,

$$\sum_{i=1}^{n} C_1' w_{1i} f(u_{1i}) \qquad (A1.2.8)$$

where u_{1i} are the zeros of the orthogonal polynomials $\phi_{n,k}(x)$ developed by Harper(1962) and w_{1i} are the associated weights $[k=(\nu_1-1)/2, n<k+1/2]$. Explicit expressions for $\phi_{n,k}(x)$ and w_{1i} are derived in Appendix A2.1.

A1.3 Quadrature Using Hermite Polynomials.

In (A1.1.1) make the transformation $\eta=\mu_2-\mu_1$, $\psi=\mu_1$, $\rho=\sigma_2^2/\sigma_1^2$ and $\theta=\sigma_1^2$ with jacobian θ and integrate out in turn ψ and θ to give,

$$\begin{aligned} p(\eta,\rho\mid X) &= D_1\{(n_1^{-1}+\rho n_2^{-1})(\nu_1 s_1^2+\nu_2 s_2^2\rho^{-1})\}^{-1/2} \\ &\times \left[1+\frac{(\eta-\bar{x}_2+\bar{x}_1)^2}{(n_1^{-1}+\rho n_2^{-1})(\nu_1 s_1^2+\nu_2 s_2^2\rho^{-1})}\right]^{-(n_1+n_2-1)/2} \\ &\times E_1\rho^{-(n_1+1)/2}\left[1+\frac{\nu_2 s_2^2}{\nu_1 s_1^2\rho}\right]^{-(n_1+n_2-2)/2} \end{aligned} \qquad (A1.3.1)$$

where $D_1=B^{-1}[1/2,(\nu_1+\nu_2)/2]$ and $E_1=B^{-1}(\nu_1/2,\nu_2/2)[\nu_2 s_2^2/(\nu_1 s_1^2)]^{-1/2}$. Clearly (A1.3.1) may be written in the form $p(\eta\mid\rho,X)p(\rho\mid X)$ where,

$$p(\rho\mid X) = E_1\rho^{-(\nu_1+2)/2}\left[1+\frac{\nu_2 s_2^2}{\nu_1 s_1^2\rho}\right]^{-(\nu_1+\nu_2)/2} \qquad (A1.3.2)$$

and

$$\begin{aligned} p(\eta,\rho\mid X) &= D_1[(n_1^{-1}+\rho n_2^{-1})(\nu_1 s_1^2+\nu_2 s_2^2\rho^{-1})]^{-1/2} \\ &\times \left[1+\frac{(\eta-\bar{x}_2+\bar{x}_1)^2}{(n_1^{-1}+\rho n_2^{-1})(\nu_1 s_1^2+\nu_2 s_2^2\rho^{-1})}\right]^{-(n_1+n_2-1)/2} \end{aligned} \qquad (A1.3.3)$$

This structure is similar to (A1.3) and therefore,

$$p(\eta\mid X) = \int_0^{\infty} p(\eta\mid\rho,X)p(\rho\mid X)d\rho \qquad (A1.3.4)$$

and

$$P(\eta>0\mid X) = \int_0^\infty\int_0^\infty p(\eta\mid\rho,X)p(\rho\mid X)d\eta d\rho = \int_0^\infty P(\eta>0\mid\rho,X)p(\rho\mid X)d\rho \qquad (A1.3.5)$$

where $P(\eta>0\mid\rho,X) = 1-P[t(\nu_1+\nu_2)>t_1]$ and

$$t_1 = \frac{(\nu_1+\nu_2)^{1/2}(\bar{x}_2-\bar{x}_1)}{[(n_1^{-1}+\rho n_2^{-1})(\nu_1 s_1^2+\nu_2 s_2^2\rho^{-1})]^{1/2}}.$$

Equations (A1.3.4) and (A1.3.5) may both be written in the form,

$$\int_{-\infty}^{\infty} f(\rho)p(\rho\mid X)d\rho \qquad (A1.3.6)$$

and therefore we may use the following argument due to Barnard(1984). Since $p(\rho\mid X)$ is a continuous density there will exist a monotonic function $g(.)$ with inverse $h(.)$ such that $g(\rho)$ has a standard normal distribution. Therefore we may write (A1.3.6) as,

$$(2\pi)^{-1/2}\int_{-\infty}^{\infty} f[h(z)]e^{-z^2/2}dz \quad , \quad z=g(\rho),$$

which may be approximated by,

$$\sum_{i=1}^{n} w_{2i}^{*} f[h(u_{2i}^{*})]$$

where $w_{2i}^{*} = w_{2i}\pi^{-1/2}$, $u_{2i}^{*} = u_{2i}2^{-1/2}$, and u_{2i} and w_{2i} are the zeros and associated weights of the Hermite polynomials $H_n(x)$ (see for example Abramowitz and Stegun, 1972). Barnard(1984) proposes using $n=3$, so that calculations could be carried out on a calculator. Clearly this approach could also be applied to functions of the type (A1.2.7).

A1.4 Quadrature using Jacobi Polynomials.

In (A1.3.4) and (A1.3.5) make the transformation $u = \nu_2 s_2^2/(\nu_2^2+\nu_1 s_1^2\rho)$ with jacobian $\nu_2 s_2^2/(u^2\nu_1 s_1^2)$ giving,

$$p(\eta\mid X) = \int_0^1 p(\eta\mid u,X)p(u\mid X)du \qquad (A1.4.1)$$

$$P(\eta>0\mid X) = \int_0^1 P(\eta>0\mid u,X)p(u\mid X)du \qquad (A1.4.2)$$

where,

$$p(u\mid X) = B^{-1}(\nu_1/2,\nu_2/2)u^{\nu_2/2-1}(1-u)^{\nu_1/2-1}$$

$$p(\eta \mid u, X) = D_1 \left[\frac{\nu_1 s_1^2}{n_1(1-u)} + \frac{\nu_2 s_2^2}{n_2 u} \right]^{-1/2} \left[1 + \frac{(\eta - \bar{x}_2 + \bar{x}_1)^2}{\frac{\nu_1 s_1^2}{n_1(1-u)} + \frac{\nu_2 s_2^2}{n_2 u}} \right]^{-(\nu_1+\nu_2+1)/2}$$

and

$$P(\eta > 0 \mid X) = 1 - P[t(\nu_1 + \nu_2) > t_2]$$

where

$$t_2 = \frac{(\bar{x}_2 - \bar{x}_1)(\nu_1 + \nu_2)^{1/2}}{\left[\frac{\nu_1 s_1^2}{n_1(1-u)} + \frac{\nu_2 s_2^2}{n_2 u} \right]^{1/2}}$$

Both (A1.4.1) and (A1.4.2) may be written in the form,

$$\int_0^1 f(u) u^{\nu_2/2-1} (1-u)^{\nu_1/2-1} du$$

which may be approximated by,

$$\sum_{i=1}^{n} w_{3i} f(u_{3i})$$

where w_{3i} and u_{3i} are the zeros and associated weights of the Jacobi polynomials $G_n(p, q, x)$, $p = \nu_1/2 + \nu_2/2 - 1$, $q = \nu_2/2$ (see for example Abramowitz and Stegun, 1972).

A similar approach is considered by Barnard(1986) except that he takes the transformation $\gamma = n_2/(n_2 + n_1\rho)$ with jacobian $n_2/(n_1\gamma^2)$ giving,

$$p(\eta \mid X) = \int_0^1 p(\eta \mid \gamma, X) p(\gamma \mid X) d\gamma \qquad (A1.4.3)$$

and

$$P(\eta > 0 \mid X) = \int_0^1 P(\eta > 0 \mid \gamma, X) p(\gamma \mid X) d\gamma \qquad (A1.4.4)$$

where

$$p(\gamma \mid X) = B^{-1}(\nu_1/2, \nu_2/2) \frac{(\nu_1 s_1^2/n_1)^{\nu_1/2} (\nu_2 s_2^2/n_2)^{\nu_2/2}}{\left[\frac{\nu_1 s_1^2 (1-\gamma)}{n_1} + \frac{\nu_2 s_2^2 \gamma}{n_2} \right]^{-(\nu_1+\nu_2)/2}} (1-\gamma)^{\nu_1/2-1} \gamma^{\nu_2/2-1}$$

$$p(\eta \mid \gamma, X) = D_1 \left[\frac{\nu_1 s_1^2}{n_1 \gamma} + \frac{\nu_2 s_2^2}{n_2(1-\gamma)} \right]^{-1/2} \left[1 + \frac{(\eta - \bar{x}_2 + \bar{x}_1)^2}{\frac{\nu_1 s_1^2}{n_1 \gamma} + \frac{\nu_2 s_2^2}{n_2(1-\gamma)}} \right]^{-(\nu_1+\nu_2+1)/2}$$

and

$$P(\eta > 0 \mid \gamma, X) = 1 - P[t(\nu_1 + \nu_2) > t_3]$$

where

$$t_3 = \frac{(\bar{x}_2 - \bar{x}_1)(\nu_1 + \nu_2)^{1/2}}{\left[\frac{\nu_1 s_1^2}{n_1 \gamma} + \frac{\nu_2 s_2^2}{n_2(1-\gamma)}\right]^{1/2}}$$

This latter approach has two disadvantages. First, the form of $p(\gamma \mid X)$ is such that no orthogonal polynomials are available. Second, in the form in which Barnard(1986) implements the method it is not assumed that the constant D_1 is known so that two numerical integrations need to be calculated each time, thus making it largely impractical.

A1.5 Expansion in Terms of Harper Polynomials.

The expected value of a Behrens-Fisher variate may be obtained from (A1.1.2),

$$E(\mu_2 - \mu_1 \mid X) = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} (\mu_2 - \mu_1) p(\mu_2, \mu_1 \mid X) d\mu_2 \mu_1$$

$$= \int_{-\infty}^{\infty} \mu_2 p(\mu_2 \mid X) d\mu_2 - \int_{-\infty}^{\infty} \mu_1 p(\mu_1 \mid X) d\mu_1 = \bar{x}_2 - \bar{x}_1,$$

where $p(\mu_i \mid X) = t(\bar{x}_i, s_i^2/n_i, \nu_i)$. The central moments may be similarly calculated,

$$E(\mu_2 - \mu_1 - \bar{x}_2 + \bar{x}_1 \mid X)^r = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} [(\mu_2 - \bar{x}_2) - (\mu_1 - \bar{x}_1)]^r p(\mu_2, \mu_1 \mid X) d\mu_2 \mu_1$$

$$= \sum_{m=0}^{r} (-1)^{m+r} \binom{r}{m} \int_{-\infty}^{\infty} (\mu_2 - \bar{x}_2)^m p(\mu_2 \mid X) d\mu_2 \int_{-\infty}^{\infty} (\mu_1 - \bar{x}_1)^{r-m} p(\mu_1 \mid X) d\mu_1$$

$$= \sum_{m=0}^{r} (-1)^{m+r} \binom{r}{m} \beta_{m,\nu_2} \beta_{r-m,\nu_1} = \gamma_r \quad (r < \min[\nu_1/2, \nu_2/2]) \qquad (A1.5.1)$$

using (A3.2.1) where,

$$\beta_{l,\nu_i} = (s_i^2/n_i)^{l/2} \alpha_{l,\nu_i}$$

$$\alpha_{l,\nu_i} = \nu_i^{l/2} \frac{B[(l+1)/2, (\nu_i - l)/2]}{B(1/2, \nu_i/2)} \quad , \qquad l \text{ even}$$

$$= 0 \qquad l \text{ odd.}$$

From (A1.5.1) we have,

$$E(\mu_2 - \mu_1 - \bar{x}_2 + \bar{x}_1)^2 = \gamma_2 = \frac{\nu_1 s_1^2/n_1}{\nu_1 - 2} + \frac{\nu_2 s_2^2/n_2}{\nu_2 - 2} \quad . \qquad (A1.5.2)$$

$$E(\mu_2-\mu_1-\bar{x}_2+\bar{x}_1)^4 = \gamma_4 = \frac{3(\nu_1 s_1^2/n_1)^2}{(\nu_1-2)(\nu_1-4)}+\frac{6(\nu_1 s_1^2/n_1)(\nu_2 s_2^2/n_2)}{(\nu_1-2)(\nu_2-2)}+\frac{3(\nu_2 s_2^2/n_2)^2}{(\nu_2-2)(\nu_2-4)}\,. \tag{A1.5.3}$$

Suppose that η is approximately distributed as $t(\bar{x}_2-\bar{x}_1, s^{*2}, \nu^*)$ then from (A3.2.2),

$$E(\eta-\bar{x}_2+\bar{x}_1)^2 \approx \frac{\nu^* s^{*2}}{\nu^*-2} \tag{A1.5.4}$$

and

$$E(\eta-\bar{x}_2+\bar{x}_1)^4 \approx \frac{3(\nu^* s^{*2})^2}{(\nu^*-2)(\nu^*-4)} \tag{A1.5.5}$$

Equate (A1.5.2) and (A1.5.3) to (A1.5.4) and (A1.5.5) to give,

$$\nu^* = 4+\frac{6\gamma_2^2}{\gamma_4-3\gamma_2^2} = 4+\frac{6\kappa_2^2}{\kappa_4} \tag{A1.5.6}$$

$$s^{*2} = \gamma_2\frac{\nu^*-2}{\nu^*} \tag{A1.5.7}$$

so that,

$$p(\eta\,|\,X) \approx p_0(\eta) = C^*\left[1+\frac{(\eta-\bar{x}_2+\bar{x}_1)^2}{\nu^* s^{*2}}\right]^{-(k+1)}$$

where $C^* = [(\nu^* s^{*2})^{1/2}B(1/2, \nu^*/2)]^{-1}$ and $k = (\nu^*-1)/2$. This approximation was given by Patil(1965). Suppose,

$$p(\eta\,|\,X) \approx p_0(\eta)\left\{1+\sum_{j=3}^{l} C_{2j}\phi_{2j,k}\left[\frac{\eta-\bar{x}_2+\bar{x}_1}{(\nu^* s^{*2})^{1/2}}\right]\right\} \tag{A1.5.8}$$

(it is not necessary to consider odd terms). Multiply (A1.5.8) by

$$\phi_{2j,k}\left[\frac{\eta-\bar{x}_2+\bar{x}_1}{(\nu^* s^{*2})^{1/2}}\right]$$

and integrate over the range of η. The right hand side may be written,

$$C_{2j}\int_{-\infty}^{\infty} p_0(\eta)\phi_{2j,k}^2\left[\frac{\eta-\bar{x}_2+\bar{x}_1}{(\nu^* s^{*2})^{1/2}}\right]d\eta. \tag{A1.5.9}$$

Let

$$w = \frac{\eta-\bar{x}_2+\bar{x}_1}{(\nu^* s^{*2})^{1/2}}$$

with jacobian $(\nu^* s^{*2})^{1/2}$ then (A1.5.9) becomes,

$$C_{2j}\nu^{*1/2}s^{*}C^{*}\int_{-\infty}^{\infty}(1+w^2)^{-(k+1)}\phi^2_{2j,k}(w)dw = \frac{C_{2j}(2j)!\Gamma(k-2j+3/2)^2 2^{2k-4j+2}}{B(1/2,k+1/2)(2k-4j+1)\Gamma(2k-2j+2)} \quad (A1.5.10)$$

using (A2.1.7). The left hand side may be written,

$$\int_{-\infty}^{\infty} p(\eta \mid X)\phi_{2j,k}\left[\frac{\eta-\bar{x}_2+\bar{x}_1}{(\nu^* s^{*2})^{1/2}}\right]d\eta$$

$$= \Gamma(k-2j+3/2)(2j)!\sum_{m=0}^{j}\frac{(-1)^m 2^{-2m}(\nu^* s^{*2})^{-(j-m)}}{m!(2j-2m)!\Gamma(k-2j+3/2+m)}\int_{-\infty}^{\infty} p(\eta \mid X)(\eta-\bar{x}_2+\bar{x}_1)^{2j-2m}d\eta$$

$$= \Gamma(k-2j+3/2)(2j)!\sum_{m=0}^{j}\frac{(-1)^m 2^{-2m}(\nu^* s^{*2})^{-(j-m)}}{m!(2j-2m)!\Gamma(k-2j+3/2+m)}\gamma_{2j-2m} \quad (A1.5.11)$$

using (A2.1.5) and (A1.5.1). Equating (A1.5.10) and (A1.5.11) gives,

$$C_{2j} = \frac{B(1/2,k+1/2)(2k-4j+1)\Gamma(2k-2j+2)}{\Gamma(k-2j+3/2)2^{2k-4j+2}}\sum_{m=0}^{j}\frac{(-1)^m 2^{-2m}(\nu^* s^{*2})^{-(j-m)}}{m!(2j-2m)!\Gamma(k-2j+3/2+m)}\gamma_{2j-2m} \quad (A1.5.12)$$

Suppose we wish to calculate,

$$P(\eta>0 \mid X) = \int_0^{\infty} p(\eta \mid X)d\eta \approx \int_0^{\infty} p_0(\eta)\left[1+\sum_{j=3}^{l}Q_{2j}\sum_{m=0}^{j}R_{2j,m}(\eta-\bar{x}_2+\bar{x}_1)^{(2j-2m)}\right]d\eta \quad (A1.5.13)$$

where

$$Q_{2j} = C_{2j}\Gamma(k-2j+3/2)(2j)!$$

and

$$R_{2j,m} = \frac{(-1)^m 2^{-2m}(\nu^* s^{*2})^{-(j-m)}}{m!(2j-2m)!\Gamma(k-2j+3/2+m)}$$

In (A1.5.13) make the transformation,

$$w = \left[1+\frac{(\eta-\bar{x}_2+\bar{x}_1)^2}{\nu^* s^{*2}}\right]^{-1}$$

with jacobian,

$$\frac{\nu^{*1/2}s^{*}}{2w^2}\left(\frac{1-w}{w}\right)^{-1/2}$$

so that,

$$P(\eta > 0 \mid X) \approx C^* \int_0^{\xi} \left[w^{k+1} + \sum_{j=3}^{L} Q_{2j} \sum_{m=0}^{L} R_{2j,m} (v^* s^{*2})^{j-m} w^{k+1} \left(\frac{1-w}{w} \right)^{j-m} \right] \frac{v^{*1/2} s^*}{2w^2} \left(\frac{1-w}{w} \right)^{-1/2} dw$$

$$= \frac{C^*}{2} \int_0^{\xi} \left[v^{*1/2} s^* w^{k-\frac{1}{2}} (1-w)^{-\frac{1}{2}} + \sum_{j=3}^{L} Q_{2j} \sum_{m=0}^{L} R_{2j,m} (v^* s^{*2})^{j-m+\frac{1}{2}} w^{k-j+m-\frac{1}{2}} (1-w)^{j-m-\frac{1}{2}} \right] dw$$

$$= \frac{C^*}{2} \left[v^{*1/2} s^* B_{\xi}\left(k+\frac{1}{2}, \frac{1}{2} \right) + \sum_{j=3}^{L} Q_{2j} \sum_{m=0}^{L} R_{2j,m} (v^* s^{*2})^{j-m} B_{\xi}\left(k-j+m+\frac{1}{2}, j-m+\frac{1}{2} \right) \right]$$

(A1.5.14)

where,

$$\xi = \left[1 + \frac{(\bar{x}_2 - \bar{x}_1)^2}{v^* s^{*2}} \right]^{-1}.$$

This expansion was motivated, in part, by Durbin and Watson's(1951,1971) approximation to their *d* statistic for testing serial correlation based on Jacobi polynomials which in turn led to the development by Grieve(1984) of an approximation to the distribution of the locally best invariant statistic for testing sphericity of multivariate normal distributions again based on Jacobi polynomials. Whilst this expansion is of some theoretical interest it should be clear from the form of (A1.5.14) that it is not a practical expansion.

An alternative expansion of the Behrens-Fisher distribution with respect to a t-kernel was proposed by Finney(1963). Finney's expansion uses polynomials defined by,

$$\psi_n = \frac{\sigma^n}{f(x)} \frac{d^n}{dx^n} [f(x)] \qquad (A1.5.15)$$

where $f(x)$ is the t-kernel and σ is the standard deviation of the relevant Behrens-Fisher distribution. These polynomials should be contrasted with the Harper polynomials defined by (see A2.1.1)

$$\phi_{n,k} = (-1)^n \frac{\Gamma(2k-2n+2)}{\Gamma(2k-n+2)} (1+x^2)^{k+1} \frac{d^n}{dx^n} [(1+x^2)^{n-k-1}]$$

Whilst there is some similarity between the expressions defining $\psi_n(x)$ and $\phi_{k,n}(x)$ they are not the same. In the same way that (A1.5.14) is impractical so too is Finney's approach based on (A1.5.15).

A1.6 Application of the Approximations.

The approximations in §A1.2-A1.5 were developed for calculating Behrens-Fisher densities and probabilities in the context of the two-treatment, two-period crossover design (see §2.4 and §4.3). To illustrate these approximations, therefore, three well-known crossover examples - Grizzle,1965; Hills and Armitage,1979; Brown,1980 - are used. The results from these studies are shown in Table A1.1.

We noted in §A1.4 and in §A1.5 that Barnard's(1986) alternative method, closely related to the Jacobi polynomial method was largely impractical as was the expansion in terms of Harper polynomials. For this reason these methods are not applied to the data in Table A1.1., however we have applied two other methods

TABLE A1.1 Sufficient Statistics for Data from Grizzle(1965), Hills and Armitage(1979) and Brown(1980).

Data Set	Group sizes		Degrees of Freedom	$\hat{T}$	$\hat{R}$	SSP	SSE
	n_1	n_2					
Grizzle	8	6	12	0.360	-0.409	14.944	12.007
Hills & Armitage	17	12	27	1.019	0.793	565.517	145.360
Brown	32	31	62	-0.387	-0.083	17.658	29.487

of approximation to these data. The first set of approximations was developed by Fisher(1941) using a general Cornish-Fisher expansion; the second method was originally proposed by Weir(1960) and was independently investigated by Scott and Smith(1971). The Fisher method is based on expanding the Behrens-Fisher density about a Normal kernel using Hermite polynomials in a similar way to that considered in A1.5. The Weir method approximates the density by a normal distribution with the correct mean and variance.

In Table A2.2 the results of applying the approximations to the data in Table A2.1 are presented, in which we have concentrated on the probability of a positive treatment effect. There are a number of points to be made concerning the results in this table:

(i) Of the simpler methods, i.e. Barnard's, Patil's and Weir's, Weir's is the least, Patil's the most accurate. Barnard's method could be made more accurate by increasing the degree of the Hermite polynomial used at the cost of simplicity. The accuracy of Patil's approximation is somewhat surprising in the light of the Chaubey and Mudholkar's(1982) results. These authors conclude that "Patil's approximation is very poor" this conclusion is not however supported by our results, indeed recalculation of the cases considered by them throws doubt on their original calculations.

(ii) The Gaussian quadrature method based on Harper polynomials is uniformly more accurate than when based on Jacobi polynomials. On initial consideration this is somewhat surprising since the Harper method is restricted with respect to the maximum degree of the orthogonal polynomial which can be used whereas the Jacobi method is
not. However if we consider the form of,

TABLE A1.2 Application of the Approximations to the Data Sets in Table A1.1

Method	Data Sets					
	Grizzle		Hills & Armitage		Brown	
Exact	0.9912		0.6268		0.00008	
PB	0.9588		0.5905		0.00007	
PF0	0.9964		0.6292		0.00004	
PF1	0.9930		0.6268		0.00007	
PF2	0.9912		0.6268		0.00008	
PF3	0.9911		0.6268		0.00008	
PP	0.9912		0.6269		0.00008	
PE	0.9929		0.6245		0.00005	
Key :	PB = Barnard's Hermite Method PF = Fisher's Method PP = Patil's Approximation PE = Weir and Scott and Smith's Method					
Quadrature	Polynomial		Polynomial		Polynomial	
Degree	Harper	Jacobi	Harper	Jacobi	Harper	Jacobi
3	0.9912	0.9875	0.6272	0.6262	0.00001	0.00012
4	0.9900	0.9874	0.6267	0.6262	0.00004	0.00012
5	0.9924	0.9874	0.6268	0.6262	0.00007	0.00012
6	0.9901	0.9874	0.6268	0.6262	0.00009	0.00012
7		0.9874	0.6268	0.6262	0.00008	0.00012
8		0.9874	0.6268	0.6262	0.00008	0.00012
9		0.9874	0.6268	0.6262	0.00008	0.00012
10		0.9874	0.6268	0.6262	0.00008	0.00012
Welch	0.9935		0.6283		0.00007	
Grizzle	0.9790		0.6317		0.00054	

$$1 - P\left(t(\nu_2) > \frac{\bar{x}_2 - \bar{x}_1 - u(\nu_1 s_1^2/n_1)^{1/2}}{(s_2^2/n_2)^{1/2}} \right) \qquad (A1.6.1)$$

in the case of the Harper method and of

$$1 - P\left(t(\nu_1 + \nu_2) > \frac{(\bar{x}_2 - \bar{x}_1)(\nu_1 + \nu_2)^{1/2}}{\left[\frac{\nu_1 s_1^2}{n_1(1-u)} + \frac{\nu_2 s_2^2}{n_2 u} \right]^{1/2}} \right) \qquad (A1.6.2)$$

in the case of the Jacobi method which are shown for the three examples in Figures A1.1 and A1.2 in which the t- and beta-variates correspond to u in (A1.6.1) and (A1.6.2) respectively then the reason for the superiority of the Harper method is easier to understand. Gaussian quadrature formulae work well if in the following formula,

$$\int g(x)\phi(x)dx \approx \sum_{i=1}^{n} w_i g(x_i)$$

$g(x)$ may be approximated by a polynomial of degree less than (2n-1). The form of $g(x)$ is such that it is more difficult to approximate it by a polynomial than is the case for the Harper method.

(iii) It is illuminating to compare the results based on a Behrens-Fisher distribution to those which would arise if Grizzle's(1965) procedure were used for those cases in which the carryover effect is significant. For Grizzle's and Brown's examples the Behrens-Fisher approach gives rise to increased sensitivities in comparison with Grizzles procedure, whilst for the Hills and Armitage example this is not the case. This difference arises because for the Hills and Armitage example the sample variance in the first period is smaller than that in the second period, whilst the reverse is true for the other two examples. In general one can expect an increased sensitivity using the Behrens-Fisher approach since our knowledge about variability is based on data from both periods. For completeness Welch's(1938) approximate frequency approach to the Behrens-Fisher problem has also been given in Table A1.2.

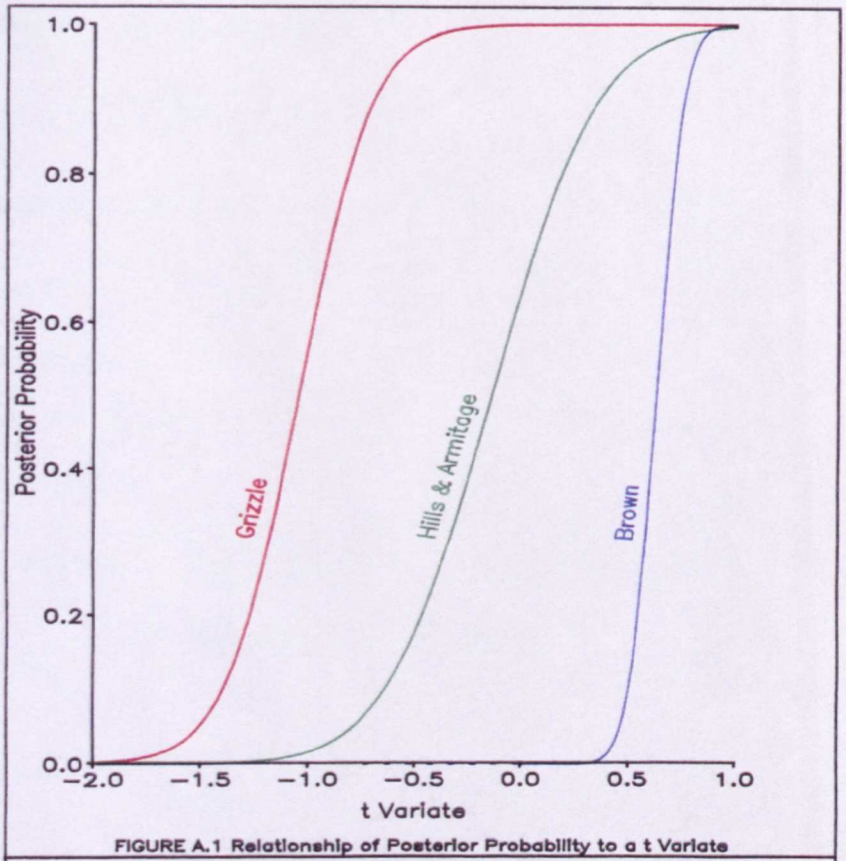


FIGURE A.1 Relationship of Posterior Probability to a t Variate

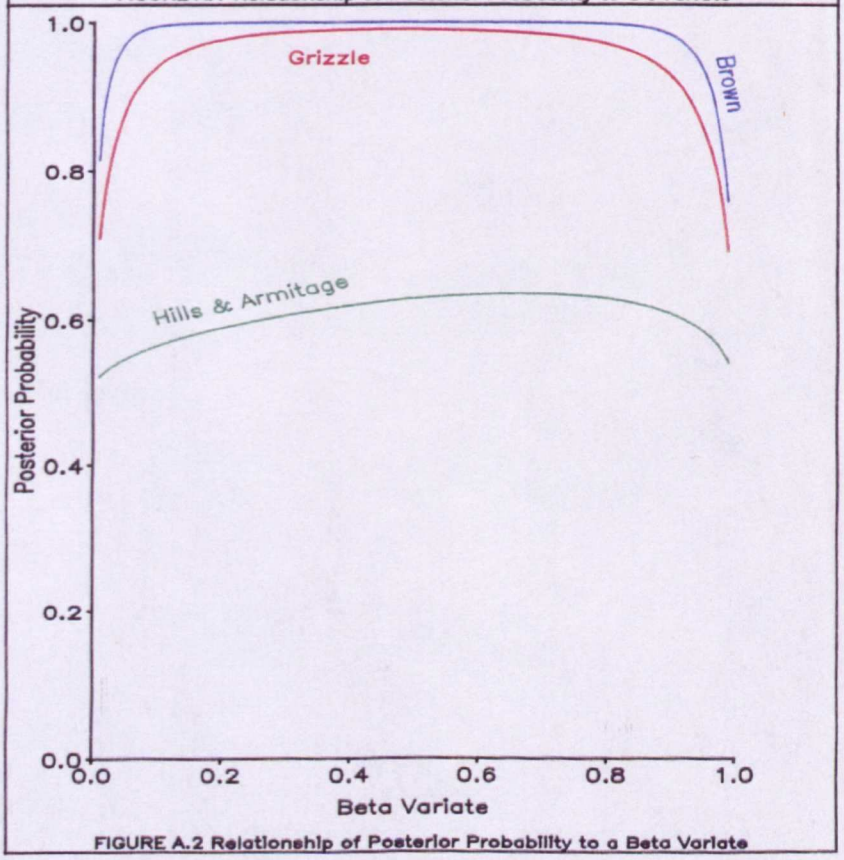


FIGURE A.2 Relationship of Posterior Probability to a Beta Variate

A2 ORTHOGONAL POLYNOMIALS.

A2.1 Harper Polynomials.

Harper(1962) develops n^{th} degree polynomials $\phi_{n,k}(x)$ which satisfy the orthogonality conditions,

$$\int_{-\infty}^{\infty}(1+x^2)^{-(k+1)}\phi_{m,k}(x)\phi_{n,k}(x)dx = 0 \quad ; \quad m \neq n, m+n > 2k+1.$$

He shows that this orthogonal system of polynomials may be defined either by Rodrigues' formula,

$$\phi_{n,k}(x) = (-1)^n \frac{\Gamma(2k-2n+2)}{\Gamma(2k-n+2)}(1+x^2)^{k+1}\frac{d^n}{dx^n}[(1+x^2)^{n-k-1}]. \qquad (A2.1.1)$$

or by the differential equation,

$$(1+x^2)\phi''_{n,k}(x) - 2kx\phi'_{n,k}(x) + n(2k-n+1)\phi_{n,k} = 0. \qquad (A2.1.2)$$

Writing (A2.1.2) in the form,

$$\phi_{n,k}(x) = \frac{2kx}{n(2k-n+1)}\phi'_{n,k}(x) - \frac{1+x^2}{n(2k-n+1)}\phi''_{n,k}(x) \qquad (A2.1.3)$$

$$= Q_0\phi'_{n,k}(x) + P_1\phi''_{n,k}(x)$$

implies that,

$$\frac{\phi_{n,k}(x)}{\phi'_{n,k}(x)} = Q_0 + \frac{P_1}{\phi'_{n,k}(x)/\phi''_{n,k}(x)} \qquad (A2.1.4)$$

Differentiation of (A2.1.3) r times gives,

$$\phi^{(r)}_{n,k}(x) = Q_r\phi^{(r+1)}_{n,k}(x) + P_{r+1}\phi^{(r+2)}_{n,k}(x) \quad , \quad r = 0,\ldots,n-1,$$

where,

$$Q_r = \frac{2(k-r)x}{(n-r)[2(k-r)-(n-r)+1]} \quad , \quad P_{r+1} = \frac{-(1+x^2)}{(n-r)[2(k-r)-(n-r)+1]}$$

$$0 = 2(k-n)x\phi^{(n+1)}_{n,k}(x) - (1+x^2)\phi^{(n+2)}_{n,k}(x).$$

Successive substitution of the ratios,

$$\frac{\phi^{(r)}_{n,k}(x)}{\phi^{(r+1)}_{n,k}(x)} = Q_r + \frac{P_{r+1}}{\phi^{(r+1)}_{n,k}(x)/\phi^{(r+2)}_{n,k}(x)}$$

into (A2.1.4) gives,

$$\frac{\phi_{n,k}(x)}{\phi'_{n,k}(x)} = Q_0 + \cfrac{P_1}{Q_1 + \cfrac{P_2}{Q_2 + \ddots \cfrac{P_{n-1}}{Q_{n-1}}}}.$$

Calculation of the successive convergents of this continued fraction shows that,

$$\phi_{n,k}(x) = \frac{\Gamma(k-n+3/2)n!}{2^n}\sum_{m=0}^{N}\frac{(-1)^m(2x)^{n-2m}}{m!(n-2m)!\Gamma(k-n+3/2+m)}, \quad N=[n/2] \quad (A2.1.5)$$

Harper gives the associated weights,

$$w_{1j} = \frac{2^{2k-2n+2}n!\Gamma(k-n+3/2)^2}{\phi'_{n,k}(a_j)\Gamma(2k-n+2)(1+a_j^2)}$$

where a_j are the zeros of $\phi_{n,k}(x)$. Using equation (7) of Harper(1962) a more convenient form for the weights may be derived,

$$w_{1j} = \frac{2^{2k-2n+2}n!\Gamma(k-n+3/2)^2(2k-2n+3)^2(1+a_j^2)}{n^2\Gamma(2k-n+2)(2k-n+2)^2\phi_{n-1,k}^2(a_j)}. \quad (A2.1.6)$$

Harper also derives the result,

$$h_n = \int_{-\infty}^{\infty}(1+x^2)^{-(k+1)}\phi_{n,k}^2(x)dx = \frac{2^{2k-2n+2}n!\Gamma(k-n+3/2)^2}{(2k-2n+1)\Gamma(2k-n+2)}. \quad (A2.1.7)$$

For the special cases $k = n-1$ and $k = n$ the quadrature formulae have the simple representations,

$$\sum_{i=1}^{n}\frac{\pi}{n}\left[1-\cos^2\left(\frac{(2i-1)\pi}{2n}\right)\right]^{n-1}f\left[\cot\left(\frac{(2i-1)\pi}{2n}\right)\right]$$

and

$$\sum_{i=1}^{n}\frac{\pi}{n+1}\left[1-\cos^2\left(\frac{i\pi}{n+1}\right)\right]^{n}f\left[\cot\left(\frac{i\pi}{n+1}\right)\right]$$

respectively.

A2.1.1 Zeros and Weights of Harper Polynomials.

The SAS macro in Appendix 7.2 may be used to calculate the zeros and weights of Harper Polynomials. These are tabulated in the following tables for n = 3(1)19 and k = n-1(.5)20 in which the weights are given in the form

$$w_{1i}^{*} = \frac{\Gamma(k+1)}{\Gamma\left(\frac{1}{2}\right)\Gamma\left(k+\frac{1}{2}\right)}w_{1i}$$

see (A1.2.8).

Zeros and Weights of Harper Polynomials

$n = 3(1)19$; $k = n\text{-}1(0.5)20$

n	k	t	w
3	2.0	0.000000000000	0.888888888889
		1.732050807569	0.055555555556
	2.5	0.000000000000	0.833333333333
		1.224744871392	0.083333333333
	3.0	0.000000000000	0.800000000000
		1.000000000000	0.100000000000
	3.5	0.000000000000	0.777777777778
		0.866025403784	0.111111111111
	4.0	0.000000000000	0.761904761905
		0.774596669241	0.119047619048
	4.5	0.000000000000	0.750000000000
		0.707106781187	0.125000000000
	5.0	0.000000000000	0.740740740741
		0.654653670708	0.129629629630
	5.5	0.000000000000	0.733333333333
		0.612372435696	0.133333333333
	6.0	0.000000000000	0.727272727273
		0.577350269190	0.136363636364
	6.5	0.000000000000	0.722222222222
		0.547722557505	0.138888888889
	7.0	0.000000000000	0.717948717949
		0.522232967867	0.141025641026
	7.5	0.000000000000	0.714285714286
		0.500000000000	0.142857142857
	8.0	0.000000000000	0.711111111111
		0.480384461415	0.144444444444
	8.5	0.000000000000	0.708333333333
		0.462910049886	0.145833333333
	9.0	0.000000000000	0.705882352941
		0.447213595500	0.147058823529
	9.5	0.000000000000	0.703703703704
		0.433012701892	0.148148148148
	10.0	0.000000000000	0.701754385965
		0.420084025208	0.149122807018
	10.5	0.000000000000	0.700000000000
		0.408248290464	0.150000000000
	11.0	0.000000000000	0.698412698413
		0.397359707120	0.150793650794
	11.5	0.000000000000	0.696969696970
		0.387298334621	0.151515151515
	12.0	0.000000000000	0.695652173913
		0.377964473009	0.152173913043
	12.5	0.000000000000	0.694444444444
		0.369274472938	0.152777777778
	13.0	0.000000000000	0.693333333333
		0.361157559257	0.153333333333
	13.5	0.000000000000	0.692307692308
		0.353553390593	0.153846153846
	14.0	0.000000000000	0.691358024691
		0.346410161514	0.154320987654

n	k	t	w
	14.5	0.000000000000	0.690476190476
		0.339683110243	0.154761904762
	15.0	0.000000000000	0.689655172414
		0.333333333333	0.155172413793
	15.5	0.000000000000	0.688888888889
		0.327326835354	0.155555555556
	16.0	0.000000000000	0.688172043011
		0.321633760451	0.155913978495
	16.5	0.000000000000	0.687500000000
		0.316227766017	0.156250000000
	17.0	0.000000000000	0.686868686869
		0.311085508419	0.156565656566
	17.5	0.000000000000	0.686274509804
		0.306186217848	0.156862745098
	18.0	0.000000000000	0.685714285714
		0.301511344578	0.157142857143
	18.5	0.000000000000	0.685185185185
		0.297044262893	0.157407407407
	19.0	0.000000000000	0.684684684685
		0.292770021885	0.157657657658
	19.5	0.000000000000	0.684210526316
		0.288675134595	0.157894736842
	20.0	0.000000000000	0.683760683761
		0.284747398726	0.158119658120
4	3.0	0.414213562373	0.497487373415
		2.414213562372	0.002512626585
	3.5	0.361515706764	0.493432247780
		1.693902710832	0.006567752220
	4.0	0.324919696233	0.489578711875
		1.376381920472	0.010421288125
	4.5	0.297593972106	0.486227795631
		1.188039489145	0.013772204369
	5.0	0.276183025245	0.483371910391
		1.060057987360	0.016628089609
	5.5	0.258819045102	0.480940107676
		0.965925826290	0.019059892324
	6.0	0.244368311755	0.478858106821
		0.892987673685	0.021141893179
	6.5	0.232097362185	0.477062192047
		0.834344541821	0.022937807953
	7.0	0.221507813690	0.475500757684
		0.785875915867	0.024499242316
	7.5	0.212247554333	0.474132725872
		0.744950317591	0.025867274128
	8.0	0.204059786870	0.472925474533
		0.709798667819	0.027074525467
	8.5	0.196752220617	0.471852991866
		0.679182275742	0.028147008134
	9.0	0.190177623828	0.470894395380
		0.652204671046	0.029105604620

n	k	t	w
	9.5	0.184221094924	0.470032787328
		0.628199026389	0.029967212672
	10.0	0.178791470481	0.469254381578
		0.606657737182	0.030745618422
	10.5	0.173815369282	0.468547838916
		0.587186697228	0.031452161084
	11.0	0.169232966864	0.467903759433
		0.569474652111	0.032096240567
	11.5	0.164994936016	0.467314292606
		0.553272088960	0.032685707394
	12.0	0.161060191084	0.466772835657
		0.538376344700	0.033227164343
	12.5	0.157394197827	0.466273798408
		0.524620878817	0.033726201593
	13.0	0.153967688527	0.465812418549
		0.511867401388	0.034187581451
	13.5	0.150755672289	0.465384615385
		0.500000000000	0.034615384616
	14.0	0.147736663584	0.464986873164
		0.488920692393	0.035013126836
	14.5	0.144892074344	0.464616147349
		0.478546013244	0.035383852651
	15.0	0.142205730145	0.464269788774
		0.468804362516	0.035730211226
	15.5	0.139663481610	0.463945481890
		0.459633922457	0.036054518111
	16.0	0.137252889653	0.463641194140
		0.450981004594	0.036358805860
	16.5	0.134962968519	0.463355134240
		0.442798725624	0.036644865760
	17.0	0.132783974501	0.463085717572
		0.435045937620	0.036914282428
	17.5	0.130707231021	0.462831537349
		0.427686356760	0.037168462651
	18.0	0.128724982908	0.462591340443
		0.420687848496	0.037408659557
	18.5	0.126830274292	0.462364007043
		0.414021837013	0.037635992957
	19.0	0.125016845697	0.462148533446
		0.407662814235	0.037851466554
	19.5	0.123279046894	0.461944017436
		0.401587929141	0.038055982564
	20.0	0.121611762711	0.461749645808
		0.395776642311	0.038250354192
5	4.0	0.000000000000	0.731428571429
		0.726542528006	0.134224896468
		3.077683537177	0.000060817818
	4.5	0.000000000000	0.700000000000
		0.639022639400	0.149701788083
		2.142813586463	0.000298211917

n	k	t	w
	5.0	0.000000000000	0.677248677249
		0.577350269190	0.160714285714
		1.732050807570	0.000661375661
	5.5	0.000000000000	0.660000000000
		0.530805202921	0.168914639168
		1.489377667534	0.001085360832
	6.0	0.000000000000	0.646464646465
		0.494035478464	0.175239310717
		1.325114691646	0.001528366051
	6.5	0.000000000000	0.635555555556
		0.464022405431	0.180255315148
		1.204719832129	0.001966907074
	7.0	0.000000000000	0.626573426573
		0.438913639943	0.184324550635
		1.111722197872	0.002388736079
	7.5	0.000000000000	0.619047619048
		0.417499809062	0.187688127943
		1.037156646526	0.002788062534
	8.0	0.000000000000	0.612649572650
		0.398952748516	0.190512503007
		0.975678131129	0.003162710668
	8.5	0.000000000000	0.607142857143
		0.382683432365	0.192916086766
		0.923879532512	0.003512484663
	9.0	0.000000000000	0.602352941176
		0.368259780191	0.194985292987
		0.879474640558	0.003838236425
	9.5	0.000000000000	0.598148148148
		0.355356597638	0.196784590580
		0.840865638404	0.004141335345
	10.0	0.000000000000	0.594427244582
		0.343723769333	0.198363009608
		0.806898221355	0.004423368101
	10.5	0.000000000000	0.591111111111
		0.333165318464	0.199758473626
		0.776715253397	0.004685970819
	11.0	0.000000000000	0.588137009190
		0.323525197076	0.201000757631
		0.749665334348	0.004930737775
	11.5	0.000000000000	0.585454545455
		0.314677388833	0.202113552815
		0.725243504595	0.005159174457
	12.0	0.000000000000	0.583022774327
		0.306518856833	0.203115936561
		0.703051551825	0.005372676276
	12.5	0.000000000000	0.580808080808
		0.298964417098	0.204023437665
		0.682770702993	0.005572521931
	13.0	0.000000000000	0.578782608696
		0.291942945136	0.204848820699
		0.664142384025	0.005759874954

n	k	t	w
	13.5	0.000000000000	0.576923076923
		0.285394524096	0.205602671942
		0.646954376765	0.005935789597
	14.0	0.000000000000	0.575209876543
		0.279268270006	0.206293842919
		0.631030672439	0.006101218809
	14.5	0.000000000000	0.573626373626
		0.273520651850	0.206929790199
		0.616223910244	0.006257022988
	15.0	0.000000000000	0.572158365262
		0.268114178619	0.207516838621
		0.602409657890	0.006403978749
	15.5	0.000000000000	0.570793650794
		0.263016362145	0.208060387288
		0.589482026792	0.006542787315
	16.0	0.000000000000	0.569521690768
		0.258198889747	0.208565072302
		0.577350269189	0.006674082314
	16.5	0.000000000000	0.568333333333
		0.253636958281	0.209034896444
		0.565936107710	0.006798436889
	17.0	0.000000000000	0.567220593027
		0.249308733624	0.209473333354
		0.555171618249	0.006916370132
	17.5	0.000000000000	0.566176470588
		0.245194908596	0.209883411871
		0.544997535720	0.007028352835
	18.0	0.000000000000	0.565194805195
		0.241278338796	0.210267784777
		0.535361886423	0.007134812625
	18.5	0.000000000000	0.564270152505
		0.237543740616	0.210628785221
		0.526218875211	0.007236138526
	19.0	0.000000000000	0.563397683398
		0.233977439264	0.210968473298
		0.517527973231	0.007332685003
	19.5	0.000000000000	0.562573099415
		0.230567157296	0.211288674738
		0.509253164916	0.007424775554
	20.0	0.000000000000	0.561792561793
		0.227301836159	0.211591013219
		0.501362322386	0.007512705885
6	5.0	0.267949192431	0.478835065332
		1.000000000000	0.021164021164
		3.732050807572	0.000000913504
	5.5	0.245717163998	0.472419603657
		0.881375831261	0.027571619358
		2.581239957730	0.000008776985
	6.0	0.228243474390	0.466938828892
		0.797473388882	0.033032982708
		2.076521396571	0.000028188400

n	k	t	w
	6.5	0.214039848701	0.462254971217
		0.733975352318	0.037685884011
		1.779175968070	0.000059144772
	7.0	0.202198091878	0.458229360849
		0.683704722789	0.041671102644
		1.578500485802	0.000099536507
	7.5	0.192128214588	0.454743905488
		0.642600209766	0.045109270247
		1.431835088119	0.000146824264
	8.0	0.183428003727	0.451702918691
		0.608163004728	0.048098360249
		1.318843838362	0.000198721060
	8.5	0.175812529131	0.449030011754
		0.578757970834	0.050716605095
		1.228466184230	0.000253383151
	9.0	0.169073525623	0.446664289697
		0.553263210576	0.053026305216
		1.154114651767	0.000309405087
	9.5	0.163054749238	0.444557000454
		0.530879433878	0.055077247914
		1.091595243411	0.000365751632
	10.0	0.157636374878	0.442668848423
		0.511019449009	0.056909471937
		1.038097423022	0.000421679640
	10.5	0.152724758554	0.440967913529
		0.493240737223	0.058555417953
		0.991659580334	0.000476668518
	11.0	0.148245511715	0.439428058265
		0.477202543339	0.060041577835
		0.950866528349	0.000530363900
	11.5	0.144138691229	0.438027710292
		0.462637585381	0.061389755675
		0.914668832809	0.000582534033
	12.0	0.140355381171	0.436748929017
		0.449332832327	0.062618034201
		0.882270011261	0.000633036782
	12.5	0.136855214107	0.435576685760
		0.437116099560	0.063741519245
		0.853053436706	0.000681794995
	13.0	0.133604541150	0.434498304775
		0.425846487160	0.064772916996
		0.826533445865	0.000728778229
	13.5	0.130575059181	0.433503025923
		0.415407422067	0.065722984823
		0.802321731567	0.000773989255
	14.0	0.127742766075	0.432581659890
		0.405701504747	0.066600885986
		0.780103684757	0.000817454124
	14.5	0.125087155167	0.431726314336
		0.396646631603	0.067414470804
		0.759621388094	0.000859214860

n	k	t	w
	15.0	0.122590586776	0.430930174766
		0.388173035637	0.068170501136
		0.740661161885	0.000899324098
	15.5	0.120237792558	0.430187327945
		0.380220998722	0.068874830885
		0.723044291305	0.000937841170
	16.0	0.118015480734	0.429492618642
		0.372739062360	0.069532552111
		0.706620018640	0.000974829247
	16.5	0.115912018785	0.428841532652
		0.365682613335	0.070148114074
		0.691260175481	0.001010353274
	17.0	0.113917176277	0.428230100684
		0.359012754768	0.070725420828
		0.676855020564	0.001044478488
	17.5	0.112021914778	0.427654818946
		0.352695396873	0.071267911686
		0.663309976223	0.001077269368
	18.0	0.110218215026	0.427112583143
		0.346700518564	0.071778627955
		0.650543043203	0.001108788902
	18.5	0.108498933764	0.426600633341
		0.341001563223	0.072260268560
		0.638482733491	0.001139098099
	19.0	0.106857684413	0.426116507682
		0.335574940700	0.072715236651
		0.627066402996	0.001168255668
	19.5	0.105288737040	0.425658003335
		0.330399614163	0.073145678837
		0.616238895895	0.001196317828
	20.0	0.103786934016	0.425223143409
		0.325456755199	0.073553518377
		0.605951434163	0.001223338214
7	6.0	0.000000000000	0.633271490414
		0.481574618807	0.181178788849
		1.253960337663	0.002185456610
		4.381286267534	0.000000009333
	6.5	0.000000000000	0.612857142857
		0.444060143928	0.190159611954
		1.105247947452	0.003411635749
		3.013509177560	0.000000180868
	7.0	0.000000000000	0.596736596737
		0.414213562373	0.196968834909
		1.000000000000	0.004662004662
		2.414213562372	0.000000862061
	7.5	0.000000000000	0.583673469388
		0.389718323235	0.202278901265
		0.920325609716	0.005882002418
		2.061824531970	0.000002361623
	8.0	0.000000000000	0.572867132867
		0.369136907940	0.206517018742
		0.857241434763	0.007044578173
		1.824520502961	0.000004836651

n	k	t	w
	8.5	0.000000000000	0.563775510204
		0.351522310895	0.209965885039
		0.805658472099	0.008138052677
		1.651467980701	0.000008307182
	9.0	0.000000000000	0.556018099548
		0.336221237037	0.212819091164
		0.762443331718	0.009159154604
		1.518431903539	0.000012704459
	9.5	0.000000000000	0.549319727891
		0.322766162507	0.215213130615
		0.725544647898	0.010109091679
		1.412234742615	0.000017913761
	10.0	0.000000000000	0.543476337904
		0.310812335226	0.217246685379
		0.693554496408	0.010991342096
		1.325032522664	0.000023803572
	10.5	0.000000000000	0.538333333333
		0.300099115521	0.218992674013
		0.665469602794	0.011810416404
		1.251834944639	0.000030242916
	11.0	0.000000000000	0.533771403298
		0.290425252308	0.220506018582
		0.640552824498	0.012571169260
		1.189300702488	0.000037110508
	11.5	0.000000000000	0.529696969697
		0.281632513291	0.221828791704
		0.618248594526	0.013278424627
		1.135099908740	0.000044298820
	12.0	0.000000000000	0.526035585859
		0.273594521053	0.222993711529
		0.598129089739	0.013936780358
		1.087553329931	0.000051715183
	12.5	0.000000000000	0.522727272727
		0.266208942579	0.224026566941
		0.579858729331	0.014550515386
		1.045416975619	0.000059281309
	13.0	0.000000000000	0.519723158829
		0.259391901814	0.224947933394
		0.563170047739	0.015123555153
		1.007747656213	0.000066932039
	13.5	0.000000000000	0.516983016983
		0.253073903346	0.225774408295
		0.547846867076	0.015659469424
		0.973815901328	0.000074613789
	14.0	0.000000000000	0.514473429952
		0.247196806295	0.226519514631
		0.533712292323	0.016161487437
		0.943047743027	0.000082282957
	14.5	0.000000000000	0.512166405024
		0.241711542627	0.227194371513
		0.520619974981	0.016632521558
		0.914984720353	0.000089904417

n	k	t	w
	15.0	0.000000000000	0.510038314176
		0.236576372485	0.227808198352
		0.508447642109	0.017075194389
		0.889255741118	0.000097450171
	15.5	0.000000000000	0.508069073783
		0.231755533181	0.228368698513
		0.497092227126	0.017491866434
		0.865556867324	0.000104898161
	16.0	0.000000000000	0.506241502904
		0.227218180900	0.228882354541
		0.486466153589	0.017884662748
		0.843636521068	0.000112231258
	16.5	0.000000000000	0.504540816327
		0.222937552953	0.229354657651
		0.476494462348	0.018255497784
		0.823284476582	0.000119436401
	17.0	0.000000000000	0.502954220418
		0.218890298197	0.229790287837
		0.467112564673	0.018606098085
		0.804323546554	0.000126503869
	17.5	0.000000000000	0.501470588235
		0.215055937109	0.230193256460
		0.458264466183	0.018938022740
		0.786603218242	0.000133426682
	18.0	0.000000000000	0.500080196301
		0.211416422815	0.230567020072
		0.449901349191	0.019252681681
		0.769994722164	0.000140200096
	18.5	0.000000000000	0.498774509804
		0.207955781508	0.230914571969
		0.441980430950	0.019551351946
		0.754387168028	0.000146821183
	19.0	0.000000000000	0.497546006117
		0.204659815799	0.231238516358
		0.434464036482	0.019835192094
		0.739684485831	0.000153288488
	19.5	0.000000000000	0.496388028896
		0.201515858381	0.231541128852
		0.427318839859	0.020105254956
		0.725802981478	0.000159601744
	20.0	0.000000000000	0.495294666723
		0.198512566228	0.231824406113
		0.420515238923	0.020362498892
		0.712669366478	0.000165761634
8	7.0	0.198912367380	0.454797243666
		0.668178637919	0.045043488372
		1.496605762665	0.000159267892
		5.027339492127	0.000000000069
	7.5	0.186600903819	0.448397668947
		0.617711247332	0.051298924164
		1.318069523759	0.000303404134
		3.441846255738	0.000000002755

n	k	t	w
	8.0	0.176326980708	0.442876073253
		0.577350269189	0.056643356643
		1.191753592594	0.000480550266
		2.747477419455	0.000000019837
	8.5	0.167583760821	0.438078255130
		0.544085363882	0.061241586146
		1.096179457710	0.000680086641
		2.339717375328	0.000000072084
	9.0	0.160025111951	0.433878605670
		0.516036937124	0.065227903906
		1.020550294723	0.000893308252
		2.065568914128	0.000000182172
	9.5	0.153405481366	0.430176336268
		0.491960121251	0.068709172579
		0.958745990727	0.001113582311
		1.865988957449	0.000000368843
	10.0	0.147545172920	0.426890718102
		0.470992115274	0.071772578895
		0.906997197521	0.001336058566
		1.712820169482	0.000000644438
	10.5	0.142309240320	0.423956835512
		0.452512910601	0.074484858511
		0.862836033439	0.001557291139
		1.590752691419	0.000001014837
	11.0	0.137594102972	0.421322151960
		0.436063631221	0.076901472664
		0.824568839261	0.001774894822
		1.490675589384	0.000001480553
	11.5	0.133318751854	0.418943831751
		0.421296215062	0.079066862805
		0.790988942455	0.001987267319
		1.406794975288	0.000002038125
	12.0	0.129418793476	0.416786677798
		0.407941111521	0.081017264536
		0.761209970976	0.002193376225
		1.335233594157	0.000002681440
	12.5	0.125842309081	0.414821547487
		0.395785819343	0.082782449818
		0.734564076420	0.002392599893
		1.273289538722	0.000003402802
	13.0	0.122546909351	0.413024132425
		0.384660202985	0.084387063641
		0.710537130410	0.002584610195
		1.219016785530	0.000004193739
	13.5	0.119497596928	0.411374013464
		0.374426189336	0.085851654154
		0.688725985332	0.002769286804
		1.170974752159	0.000005045577
	14.0	0.116665187265	0.409853924047
		0.364970376830	0.087193471344
		0.668809429192	0.002946654779
		1.128072015524	0.000005949829

n	k	t	w
	14.5	0.114025123226	0.408449171808
		0.356198629761	0.088427090524
		0.650527929534	0.003116839232
		1.089465107438	0.000006898435
	15.0	0.111556572395	0.407147181080
		0.348032055832	0.089564902532
		0.633669184496	0.003280032482
		1.054490875930	0.000007883905
	15.5	0.109241730724	0.405937128377
		0.340403966543	0.090617501926
		0.618057609384	0.003436470304
		1.022620032499	0.000008899392
	16.0	0.107065278980	0.404809649879
		0.333257548224	0.091593996590
		0.603546550799	0.003586414820
		0.993424483358	0.000009938710
	16.5	0.105013953877	0.403756605079
		0.326544055076	0.092502256366
		0.590012429171	0.003730142227
		0.966553869688	0.000010996327
	17.0	0.103076206360	0.402770884541
		0.320221391163	0.093349114057
		0.577350269189	0.003867934068
		0.941718406066	0.000012067334
	17.5	0.101241926840	0.401846252543
		0.314252986006	0.094140528968
		0.565470245343	0.004000071087
		0.918676116700	0.000013147402
	18.0	0.099502222417	0.400977217509
		0.308606894455	0.094881720778
		0.554294980751	0.004126828973
		0.897223200264	0.000014232739
	18.5	0.097849234840	0.400158924702
		0.303255069738	0.095577279775
		0.543757412476	0.004248475484
		0.877186657994	0.000015320040
	19.0	0.096275990704	0.399387066870
		0.298172771630	0.096231258120
		0.533799088014	0.004365268574
		0.858418584088	0.000016406436
	19.5	0.094776277318	0.398657809463
		0.293338080960	0.096847245822
		0.524368793627	0.004477455262
		0.840791694007	0.000017489452
	20.0	0.093344539223	0.397967727726
		0.288731498603	0.097428434297
		0.515421440720	0.004585271014
		0.824195786324	0.000018566963
9	8.0	0.000000000000	0.565794699128
		0.363970234266	0.209137512110
		0.839099631177	0.007956504984
		1.732050807569	0.000008633342
		5.671281819613	0.000000000000

n	k	t	w
	8.5	0.000000000000	0.551247165533
		0.342773382953	0.214385128733
		0.776621471983	0.009970942280
		1.523707789330	0.000020346189
		3.867516007714	0.000000000032
	9.0	0.000000000000	0.539169066228
		0.324919696233	0.218493653776
		0.726542528006	0.011883997999
		1.376381920470	0.000037814756
		3.077683537174	0.000000000356
	9.5	0.000000000000	0.528974552784
		0.309609165203	0.221773490132
		0.685192108727	0.013678533991
		1.264990443345	0.000060697749
		2.614278699222	0.000000001737
	10.0	0.000000000000	0.520250853378
		0.296287540179	0.224435677751
		0.650272225161	0.015350572512
		1.176912751227	0.000088317572
		2.303092725601	0.000000005477
	10.5	0.000000000000	0.512698412698
		0.284556761717	0.226627822156
		0.620257438181	0.016903083264
		1.104991158242	0.000119875028
		2.076849224174	0.000000013202
	11.0	0.000000000000	0.506094367572
		0.274122412035	0.228455721104
		0.594088390777	0.018342495683
		1.044816254984	0.000154572837
		1.903452658551	0.000000026590
	11.5	0.000000000000	0.500269360269
		0.264761326273	0.229996844536
		0.571002499763	0.019676750111
		0.993501020996	0.000191678072
		1.765449887891	0.000000047147
	12.0	0.000000000000	0.495092316103
		0.256300799974	0.231308996707
		0.550434490711	0.020914221115
		0.949064384983	0.000230548047
		1.652455313926	0.000000076080
	12.5	0.000000000000	0.490460157127
		0.248604776446	0.232436033793
		0.531954999219	0.022063137438
		0.910095213324	0.000270635957
		1.557865927037	0.000000114248
	13.0	0.000000000000	0.486290674927
		0.241564399221	0.233411728716
		0.515231092295	0.023131285470
		0.875557245418	0.000311486186
		1.477264480479	0.000000162165
	13.5	0.000000000000	0.482517482517
		0.235091385234	0.234262439607
		0.500000000000	0.024125874126
		0.844669960705	0.000352724974
		1.407574047100	0.000000220034

n	k	t	w
	14.0	0.000000000000	0.479086368632
		0.229113273132	0.235008987659
		0.486051119485	0.025053490643
		0.816832714141	0.000394049579
		1.346579557123	0.000000287803
	14.5	0.000000000000	0.475952618810
		0.223569949468	0.235668001501
		0.473213371928	0.025920106330
		0.791574699982	0.000435217550
		1.292642119111	0.000000365214
	15.0	0.000000000000	0.473079016048
		0.218411065011	0.236252894773
		0.461346122891	0.026731108462
		0.768520948691	0.000476036887
		1.244520756354	0.000000451855
	15.5	0.000000000000	0.470434327577
		0.213594083300	0.236774587124
		0.450332534432	0.027491344499
		0.747368615249	0.000516357381
		1.201256978732	0.000000547207
	16.0	0.000000000000	0.467992144907
		0.209082786178	0.237242042942
		0.440074613433	0.028205170739
		0.727870067476	0.000556063189
		1.162097649439	0.000000650676
	16.5	0.000000000000	0.465729984301
		0.204846114864	0.237662678696
		0.430489466350	0.028876500956
		0.709820582727	0.000595066569
		1.126442021999	0.000000761629
	17.0	0.000000000000	0.463628581785
		0.200857260931	0.238042674356
		0.421506427094	0.029508852688
		0.693049238289	0.000633302652
		1.093804501757	0.000000879412
	17.5	0.000000000000	0.461671335201
		0.197092945852	0.238387213897
		0.413064826848	0.030105390019
		0.677412059520	0.000670725112
		1.063787911725	0.000001003373
	18.0	0.000000000000	0.459843858668
		0.193532844521	0.238700672792
		0.405112242593	0.030668962406
		0.662786792756	0.000707302598
		1.036063941379	0.000001132870
	18.5	0.000000000000	0.458133623820
		0.190159119909	0.238986765474
		0.397603107270	0.031202139527
		0.649068866358	0.000743015804
		1.010358610245	0.000001267285
	19.0	0.000000000000	0.456529668696
		0.186956044377	0.239248662244
		0.390497596401	0.031707242310
		0.636168233324	0.000777855068
		0.986441298249	0.000001406029

n	k	t	w
	19.5	0.000000000000	0.455022359821
		0.183909689180	0.239489082693
		0.383760728348	0.032186370441
		0.624006876731	0.000811818411
		0.964116355735	0.000001548545
	20.0	0.000000000000	0.453603196460
		0.181007668106	0.239710370856
		0.377361631324	0.032641426670
		0.612516819564	0.000844909932
		0.943216607701	0.000001694311
10	9.0	0.158384440324	0.431403490444
		0.509525449494	0.067543083092
		1.000000000000	0.001053064582
		1.962610505506	0.000000361882
		6.313751514671	0.000000000000
	9.5	0.150552072824	0.425586308562
		0.480907155427	0.072945123412
		0.925929815979	0.001467501651
		1.724392757235	0.000001066374
		4.291291877265	0.000000000000
	10.0	0.143778293995	0.420480466642
		0.456684697903	0.077610991743
		0.866504932543	0.001906193139
		1.556030372976	0.000002348472
		3.405687238888	0.000000000005
	10.5	0.137844149909	0.415968097097
		0.435826716156	0.081671333072
		0.817402215697	0.002356256119
		1.428822820231	0.000004313679
		2.886411791477	0.000000000034
	11.0	0.132589291201	0.411954413669
		0.417613959250	0.085230175236
		0.775911453558	0.002808401485
		1.328316714778	0.000007009476
		2.538021824645	0.000000000135
	11.5	0.127893225361	0.408362919786
		0.401526850550	0.088370524187
		0.740231531855	0.003256119304
		1.246310730658	0.000010436333
		2.284991543330	0.000000000389
	12.0	0.123663416752	0.405131500435
		0.387179099517	0.091158964801
		0.709110476972	0.003694972536
		1.177751239998	0.000014561317
		2.091276041311	0.000000000910
	12.5	0.119827461052	0.402209354990
		0.374276542499	0.093649273646
		0.681646339803	0.004122039240
		1.119329194085	0.000019330294
		1.937270985693	0.000000001830
	13.0	0.116327781365	0.399554623584
		0.362590577765	0.095885204940
		0.657170089551	0.004535490732
		1.068774077100	0.000024677457
		1.811310400158	0.000000003287

n	k	t	w
	13.5	0.113117938451	0.397132555866
		0.351940431057	0.097902626978
		0.635173256239	0.004934279537
		1.024468851105	0.000030532203
		1.705977951985	0.000000005415
	14.0	0.110160004784	0.394914095044
		0.342180970508	0.099731161571
		0.615261367113	0.005317911272
		0.985226335053	0.000036823775
		1.616313263737	0.000000008337
	14.5	0.107422657888	0.392874777582
		0.333194123741	0.101395447072
		0.597122941529	0.005686278966
		0.950152595363	0.000043484224
		1.538862010286	0.000000012156
	15.0	0.104879771081	0.390993872777
		0.324882699723	0.102916116945
		0.580508236287	0.006039543177
		0.918559937829	0.000050450148
		1.471138251420	0.000000016952
	15.5	0.102509355186	0.389253705235
		0.317165855825	0.104310562912
		0.565214304642	0.006378045476
		0.889909516770	0.000057663591
		1.411303372090	0.000000022787
	16.0	0.100292752352	0.387639117533
		0.309975715110	0.105593534238
		0.551074260908	0.006702246161
		0.863772333225	0.000065072369
		1.357965734173	0.000000029698
	16.5	0.098214013935	0.386137041020
		0.303254803409	0.106777611672
		0.537949416664	0.007012679551
		0.839802038474	0.000072630050
		1.310050950521	0.000000037707
	17.0	0.096259414758	0.384736150589
		0.296954080832	0.107873584855
		0.525723420960	0.007309922040
		0.817715538545	0.000080295701
		1.266715202857	0.000000046815
	17.5	0.094417069745	0.383426585112
		0.291031411082	0.108890754941
		0.514297826520	0.007594569422
		0.797278885627	0.000088033514
		1.227285728294	0.000000057011
	18.0	0.092676628382	0.382199719582
		0.285450357761	0.109837178836
		0.503588688411	0.007867220938
		0.778296833385	0.000095812372
		1.191218980911	0.000000068272
	18.5	0.091029028991	0.381047978239
		0.280179228074	0.110719867569
		0.493523922087	0.008128468230
		0.760604982311	0.000103605397
		1.158070600287	0.000000080564

n	k	t	w
	19.0	0.089466299448	0.379964680404
		0.275190305899	0.111544948411
		0.484041227915	0.008378887839
		0.744063788793	0.000111389499
		1.127473453145	0.000000093846
	19.5	0.087981394313	0.378943912580
		0.270459231392	0.112317798108
		0.475086443782	0.008619036287
		0.728553936969	0.000119144951
		1.099121310741	0.000000108073
	20.0	0.086568060772	0.377980421770
		0.265964495094	0.113043153019
		0.466612225057	0.008849447023
		0.713972721550	0.000126854995
		1.072756534188	0.000000123194
11	10.0	0.000000000000	0.515951259548
		0.293626492938	0.225654839335
		0.642660977169	0.016260979338
		1.154061520533	0.000108539468
		2.189694562989	0.000000012085
		6.955152771773	0.000000000000
	10.5	0.000000000000	0.504930254930
		0.279902832547	0.228686811442
		0.607331805696	0.018678421386
		1.068591105274	0.000169594796
		1.921508111638	0.000000044911
		4.713673950193	0.000000000000
	11.0	0.000000000000	0.495477003217
		0.267949192431	0.231092909498
		0.577350269190	0.020926538632
		1.000000000000	0.000241932130
		1.732050807568	0.000000118131
		3.732050807568	0.000000000000
	11.5	0.000000000000	0.487275350912
		0.257413561077	0.233028441476
		0.551474610337	0.023010186972
		0.943313195171	0.000323445975
		1.588994141027	0.000000250121
		3.156718525353	0.000000000001
	12.0	0.000000000000	0.480089518645
		0.248035064120	0.234603928783
		0.528836030409	0.024938736303
		0.895409006787	0.000412118630
		1.476044852168	0.000000456959
		2.770982743517	0.000000000003
	12.5	0.000000000000	0.473739924497
		0.239615626326	0.235899675168
		0.508805090454	0.026723469566
		0.854211454228	0.000506142045
		1.383952976708	0.000000750963
		2.491057074405	0.000000000010
	13.0	0.000000000000	0.468087280679
		0.232001733793	0.236975107659
		0.490912589708	0.028376151827
		0.818276749066	0.000603959868
		1.307017097158	0.000001140280
		2.276939250748	0.000000000026

n	k	t	w
	13.5	0.000000000000	0.463021826658
		0.225072291913	0.237874924685
		0.474800375817	0.029908265469
		0.786564338407	0.000704267333
		1.241503549226	0.000001629123
		2.106867946820	0.000000000060
	14.0	0.000000000000	0.458455855150
		0.218730304494	0.238633238005
		0.460189515301	0.031330624981
		0.758302142724	0.000805990986
		1.184850474279	0.000002218331
		1.967892524748	0.000000000121
	14.5	0.000000000000	0.454318408864
		0.212897027260	0.239276421695
		0.446858993930	0.032653207135
		0.732903234574	0.000908260466
		1.135233521858	0.000002906053
		1.851780115167	0.000000000220
	15.0	0.000000000000	0.450551443855
		0.207507769300	0.239825108730
		0.434631049654	0.033885101769
		0.709912190271	0.001010378796
		1.091313535832	0.000003688408
		1.753024764507	0.000000000369
	15.5	0.000000000000	0.447107005549
		0.202508819432	0.240295613994
		0.423360820085	0.035034528213
		0.688969350985	0.001111794357
		1.052082373379	0.000004560081
		1.667792864965	0.000000000581
	16.0	0.000000000000	0.443945117699
		0.197855157337	0.240700964101
		0.412928876155	0.036108885476
		0.669786313597	0.001212075895
		1.016764686004	0.000005514812
		1.593326136777	0.000000000867
	16.5	0.000000000000	0.441032182104
		0.193508722839	0.241051653146
		0.403235734109	0.037114817814
		0.652128696467	0.001310890952
		0.984753125777	0.000006545797
		1.527585084377	0.000000001239
	17.0	0.000000000000	0.438339750051
		0.189437089126	0.241356204435
		0.394197753097	0.038058285204
		0.635803752976	0.001407987637
		0.955564309750	0.000007645990
		1.469026488876	0.000000001708
	17.5	0.000000000000	0.435843568197
		0.185612432900	0.241621592921
		0.385744022010	0.038944632941
		0.620651296257	0.001503179425
		0.928808112928	0.000008808335
		1.416459329472	0.000000002281

n	k	t	w
	18.0	0.000000000000	0.433522829721
		0.182010725897	0.241853566330
		0.377813964766	0.039778657339
		0.606536935401	0.001596332581
		0.904165769819	0.000010025924
		1.368948511820	0.000000002966
	18.5	0.000000000000	0.431359580869
		0.178611093612	0.242056891735
		0.370355475535	0.040564666102
		0.593346956822	0.001687355838
		0.881373946223	0.000011292121
		1.325748773443	0.000000003769
	19.0	0.000000000000	0.429338246422
		0.175395301803	0.242235546630
		0.363323450365	0.041306532890
		0.580984397053	0.001776191944
		0.860212948617	0.000012600632
		1.286258222147	0.000000004694
	19.5	0.000000000000	0.427445247105
		0.172347341702	0.242392868274
		0.356678619105	0.042007746107
		0.569365991982	0.001862810773
		0.840497858419	0.000013945551
		1.249984989369	0.000000005744
	20.0	0.000000000000	0.425668688760
		0.169453092257	0.242531671378
		0.350386607511	0.042671452228
		0.558419779998	0.001947203708
		0.822071770901	0.000015321387
		1.216522850853	0.000000006920
12	11.0	0.131652497588	0.410139840453
		0.414213562373	0.086808272238
		0.767326987979	0.003042915578
		1.303225372841	0.000008971402
		2.414213562374	0.000000000329
		7.595754112718	0.000000000000
	11.5	0.126227156154	0.404978254900
		0.395563481338	0.091261179941
		0.725660570242	0.003744740338
		1.206438949286	0.000015823267
		2.115961140688	0.000000001554
		5.135000144775	0.000000000000
	12.0	0.121421983222	0.400378272893
		0.379249975406	0.095149065890
		0.690250161969	0.004447710493
		1.128766660088	0.000024945811
		1.905340811302	0.000000004914
		4.057159485637	0.000000000000
	12.5	0.117127115286	0.396254854354
		0.364818853333	0.098566771577
		0.659651241143	0.005142079034
		1.064580086599	0.000036282968
		1.746388522849	0.000000012066
		3.425616010247	0.000000000000

n	k	t	w
	13.0	0.113258148886	0.392538763343
		0.351931397113	0.101590253418
		0.632851360001	0.005821267603
		1.010345128149	0.000049690709
		1.620965693386	0.000000024926
		3.002413859292	0.000000000000
	13.5	0.109749021937	0.389173236342
		0.340328978713	0.104280742219
		0.609115854462	0.006481002366
		0.963710371776	0.000064973619
		1.518769762200	0.000000045454
		2.695498088117	0.000000000000
	14.0	0.106547186531	0.386111393364
		0.329810138698	0.106687954987
		0.587896313753	0.007118664289
		0.923039894134	0.000081911878
		1.433448609291	0.000000075481
		2.460903240817	0.000000000001
	14.5	0.103610249342	0.383314233778
		0.320215234155	0.108852559198
		0.568773588625	0.007732810638
		0.887154378999	0.000100279792
		1.360841783842	0.000000116593
		2.274706678256	0.000000000002
	15.0	0.100903579739	0.380749081958
		0.311415859681	0.110808063734
		0.551420861411	0.008322826508
		0.855178643409	0.000119857733
		1.298094447333	0.000000170063
		2.122669849630	0.000000000004
	15.5	0.098398572482	0.378388376193
		0.303307376228	0.112582275032
		0.535578901395	0.008888672634
		0.826447315760	0.000140439301
		1.243173689067	0.000000236832
		1.995740867428	0.000000000008
	16.0	0.096071363257	0.376208719288
		0.295803520453	0.114198424450
		0.521039005108	0.009430703577
		0.800444078194	0.000161835155
		1.194587417736	0.000000317515
		1.887866283578	0.000000000014
	16.5	0.093901863833	0.374190129274
		0.288832441073	0.115676046606
		0.507630941686	0.009949537039
		0.776761177437	0.000183874626
		1.151212536238	0.000000412430
		1.794831707328	0.000000000024
	17.0	0.091873026886	0.372315443905
		0.282333735178	0.117031668337
		0.495214249966	0.010445960174
		0.755071650094	0.000206405911
		1.112185459302	0.000000521634
		1.713605333735	0.000000000039

n	k	t	w
	17.5	0.089970278554	0.370569844050
		0.276256198748	0.118279352850
		0.483671835397	0.010920862697
		0.735109787698	0.000229295381
		1.076829878358	0.000000644963
		1.641945840965	0.000000000059
	18.0	0.088181075278	0.368940469617
		0.270556096055	0.119431132459
		0.472905179288	0.011375189353
		0.716657094181	0.000252426406
		1.044607663713	0.000000782078
		1.578157668463	0.000000000087
	18.5	0.086494553996	0.367416107984
		0.265195811909	0.120497355044
		0.462830700176	0.011809906435
		0.699531995800	0.000275697920
		1.015084625627	0.000000932495
		1.520932544893	0.000000000122
	19.0	0.084901253295	0.365986939628
		0.260142790327	0.121486963240
		0.453376952690	0.012225978435
		0.683582171150	0.000299022905
		0.987906096794	0.000001095625
		1.469243596201	0.000000000167
	19.5	0.083392889107	0.364644329179
		0.255368690227	0.122407720845
		0.444482444649	0.012624352074
		0.668678746309	0.000322326877
		0.962779172184	0.000001270803
		1.422272646508	0.000000000222
	20.0	0.081962172790	0.363380652782
		0.250848707500	0.123266397534
		0.436093916944	0.013005945628
		0.654711840915	0.000345546458
		0.939459563020	0.000001457310
		1.379359115359	0.000000000288
13	12.0	0.000000000000	0.477248752262
		0.246477863032	0.235169907192
		0.524840487364	0.025748548203
		0.885922693643	0.000456559921
		1.448750112781	0.000000608545
		2.636783295581	0.000000000007
		8.235740954500	0.000000000000
	12.5	0.000000000000	0.468533991261
		0.236833349087	0.236844222279
		0.501789595797	0.028282093582
		0.838125387578	0.000605470164
		1.340677992210	0.000001218299
		2.308373041386	0.000000000045
		5.555507125731	0.000000000000
	13.0	0.000000000000	0.460885937899
		0.228243474390	0.238165347225
		0.481574618808	0.030623008691
		0.797473388882	0.000766541148
		1.253960337663	0.000002133815
		2.076521396572	0.000000000172
		4.381286267537	0.000000000000

n	k	t	w
	13.5	0.000000000000	0.454117560761
		0.220528421300	0.239215553433
		0.463651698956	0.032785717090
		0.762322132064	0.000936555449
		1.182313345447	0.000003393155
		1.901623150714	0.000000000492
		3.693402744119	0.000000000000
	14.0	0.000000000000	0.448083550735
		0.213548681195	0.240055299548
		0.447613843043	0.034785136355
		0.731517732089	0.001112769466
		1.121789116797	0.000005018108
		1.763690240652	0.000000001155
		3.232631517569	0.000000000000
	14.5	0.000000000000	0.442669218893
		0.207194106881	0.240729718868
		0.433149312756	0.036635752175
		0.704222117608	0.001292901007
		1.069759833098	0.000007016155
		1.651364409645	0.000000002348
		2.898643298174	0.000000000000
	15.0	0.000000000000	0.437782779454
		0.201376400031	0.241272979207
		0.420014580095	0.038351157980
		0.679809177277	0.001475085621
		1.024396747359	0.000009383183
		1.557640500429	0.000000004282
		2.643505116088	0.000000000000
	15.5	0.000000000000	0.433349866916
		0.196023826229	0.241711273371
		0.408016157276	0.039943857928
		0.657800029883	0.001657821791
		0.984381292204	0.000012106271
		1.477929497318	0.000000007180
		2.441129752419	0.000000000000
	16.0	0.000000000000	0.429309564368
		0.191077415610	0.242064908315
		0.396998039403	0.041425216622
		0.637821042501	0.001839915396
		0.948734836736	0.000015166222
		1.409082212839	0.000000011261
		2.275988244563	0.000000000000
	16.5	0.000000000000	0.425611476436
		0.186488178747	0.242349788990
		0.386832812014	0.042805488028
		0.619575678074	0.002020428350
		0.916713323816	0.000018539684
		1.348856111627	0.000000016730
		2.138207750885	0.000000000000
	17.0	0.000000000000	0.422213538511
		0.182215031584	0.242578488195
		0.377415218532	0.044093884515
		0.602825072027	0.002198633403
		0.887739374789	0.000022200860
		1.295605332140	0.000000023771
		2.021185811426	0.000000000000

n	k	t	w
	17.5	0.000000000000	0.419080354035
		0.178223225133	0.242761028564
		0.368657419182	0.045298663572
		0.587374298265	0.002373975486
		0.861357029764	0.000026122818
		1.248091162511	0.000000032541
		1.920326050539	0.000000000001
	18.0	0.000000000000	0.416181916532
		0.174483140799	0.242905461321
		0.360485437995	0.046427219506
		0.573062447769	0.002546039266
		0.837200692742	0.000030278469
		1.205361254422	0.000000043170
		1.832322176893	0.000000000002
	18.5	0.000000000000	0.413492615981
		0.170969354688	0.243018299564
		0.352836460292	0.047486173169
		0.559755324932	0.002714522248
		0.814973285304	0.000034641270
		1.166669916552	0.000000055756
		1.754730266947	0.000000000003
	19.0	0.000000000000	0.410990458114
		0.167659902599	0.243104846089
		0.345656749390	0.048481456135
		0.547339980154	0.002879212635
		0.794430540207	0.000039185710
		1.131423931869	0.000000070370
		1.685701787970	0.000000000004
	19.5	0.000000000000	0.408656445034
		0.164535696708	0.243169443842
		0.338900021090	0.049418387724
		0.535720555312	0.003039971227
		0.775369490769	0.000043887628
		1.099144769625	0.000000087056
		1.623810701720	0.000000000006
	20.0	0.000000000000	0.406474079453
		0.161580058224	0.243215669007
		0.332526161318	0.050301744357
		0.524815084027	0.003196716668
		0.757619890418	0.000048724400
		1.069441635538	0.000000105834
		1.567937928727	0.000000000008
14	13.0	0.112672939900	0.391173779355
		0.349915133947	0.102676174284
		0.628341645367	0.006093751357
		0.999999999999	0.000056260490
		1.591490882983	0.000000034513
		2.857835809272	0.000000000000
		8.875245474975	0.000000000000
	13.5	0.108691344894	0.386612204152
		0.336716981246	0.106274841992
		0.601195028255	0.007032088266
		0.946188690487	0.000080786793
		1.472135548957	0.000000078796
		2.499184216277	0.000000000001
		5.975365641090	0.000000000000

n	k	t	w
	14.0	0.105104235266	0.382495449570
		0.324919696233	0.109446434186
		0.577350269190	0.007948445282
		0.900404044297	0.000109516947
		1.376381920471	0.000000154010
		2.246036773905	0.000000000005
		4.704630109480	0.000000000000
	14.5	0.101850472582	0.378762168269
		0.314290174109	0.112258280424
		0.556179303475	0.008837267331
		0.860802227731	0.000142015071
		1.297288924030	0.000000268888
		2.055142906115	0.000000000017
		3.960298140021	0.000000000000
	15.0	0.098881415672	0.375361600991
		0.304646527089	0.114764950547
		0.537211175882	0.009695210066
		0.826088608297	0.000177807222
		1.230493481452	0.000000431127
		1.904661879646	0.000000000046
		3.461869962786	0.000000000000
	15.5	0.096157816095	0.372251446722
		0.295844403741	0.117010994995
		0.520084492459	0.010520494413
		0.795322318654	0.000216416780
		1.173090345438	0.000000646986
		1.782177314605	0.000000000105
		3.100737657516	0.000000000000
	16.0	0.093647607238	0.369396206950
		0.287767541642	0.119033047468
		0.504516457604	0.011312437630
		0.767800088019	0.000257386598
		1.123057181145	0.000000921143
		1.680029152739	0.000000000211
		2.824997477929	0.000000000000
	16.5	0.091324298069	0.366765892840
		0.280321082672	0.120861443519
		0.490282034671	0.012071114799
		0.742983782505	0.000300291755
		1.078935595177	0.000001256703
		1.593198368310	0.000000000385
		2.606395121482	0.000000000000
	17.0	0.089165785308	0.364335009777
		0.273426741472	0.122521472917
		0.477199520093	0.012797115441
		0.720453379049	0.000344745888
		1.039643073859	0.000001655326
		1.518240293499	0.000000000651
		2.428109270133	0.000000000000
	17.5	0.087153460991	0.362081754519
		0.267019247331	0.124034354595
		0.465120311840	0.013491369094
		0.699875412033	0.000390403355
		1.004356544256	0.000002117402
		1.452701874501	0.000000001035
		2.279444602259	0.000000000000

n	k	t	w
	18.0	0.085271532357	0.359987376048
		0.261043679921	0.125418000658
		0.453921497395	0.014155020728
		0.680981192240	0.000436958745
		0.972437315424	0.000002642258
		1.394782767592	0.000000001563
		2.153248435384	0.000000000000
	18.5	0.083506496801	0.358035663218
		0.255453444434	0.126687619164
		0.443500383227	0.014789342149
		0.663551398704	0.000484144852
		0.943381029174	0.000003228356
		1.343128074643	0.000000002262
		2.044541439128	0.000000000000
	19.0	0.081846731785	0.356212531273
		0.250208711919	0.127856192918
		0.433770389795	0.015395669378
		0.647404943350	0.000531729788
		0.916783310926	0.000003873488
		1.296696222313	0.000000003155
		1.949742051938	0.000000000000
	19.5	0.080282171073	0.354505685940
		0.245275203300	0.128934862338
		0.424657925328	0.015975358790
		0.632390770655	0.000579513731
		0.892315601482	0.000004574934
		1.254671760699	0.000000004267
		1.866203109943	0.000000000000
	20.0	0.078804046622	0.352904348817
		0.240623230838	0.129933233560
		0.416099973083	0.016529756800
		0.618381716993	0.000627325585
		0.869707778779	0.000005329618
		1.216406077889	0.000000005619
		1.791922584091	0.000000000000
15	14.0	0.000000000000	0.446092068288
		0.212556561670	0.240296548744
		0.445228685308	0.035470642279
		0.726542528005	0.001180969142
		1.110612514829	0.000005804029
		1.732050807570	0.000000001662
		3.077683537176	0.000000000000
		9.514364454223	0.000000000000
	14.5	0.000000000000	0.438980308736
		0.205394117052	0.241115539293
		0.428870308767	0.037947040889
		0.695485316667	0.001438200465
		1.050853551792	0.000009060641
		1.601400332610	0.000000004344
		2.688715997790	0.000000000000
		6.394702007121	0.000000000000
	15.0	0.000000000000	0.432632393813
		0.198912367380	0.241733708608
		0.414213562373	0.040232721616
		0.668178637920	0.001704160464
		1.000000000001	0.000013202893

n	k	t	w
		1.496605762666	0.000000009512
		2.414213562372	0.000000000000
		5.027339492122	0.000000000000
	15.5	0.000000000000	0.426929868888
		0.193009614634	0.242196437027
		0.400979690096	0.042344907643
		0.643912684129	0.001975465091
		0.956008741188	0.000018237493
		1.410067112325	0.000000018301
		2.207277105248	0.000000000001
		4.226467181723	0.000000000000
	16.0	0.000000000000	0.421777817625
		0.187604284943	0.242537838391
		0.388950436784	0.044299712927
		0.622154543472	0.002249362881
		0.917444439472	0.000024145063
		1.337004884813	0.000000031924
		2.044210759368	0.000000000002
		3.690306481009	0.000000000000
	16.5	0.000000000000	0.417099246907
		0.182630071672	0.242783865277
		0.377952043916	0.046111924144
		0.602494816099	0.002523648531
		0.883263511572	0.000030887001
		1.274235459231	0.000000051591
		1.911538112258	0.000000000004
		3.301967612642	0.000000000000
	17.0	0.000000000000	0.412831015433
		0.178032440941	0.242954473140
		0.367844159305	0.047794952154
		0.584612809315	0.002796577055
		0.852685627858	0.000038411486
		1.219542185876	0.000000078440
		1.800942714107	0.000000000009
		3.005573556750	0.000000000000
	17.5	0.000000000000	0.408920830301
		0.173766069115	0.243065153321
		0.358511964297	0.049360874323
		0.568253086357	0.003066785305
		0.825113513001	0.000046658389
		1.171326281624	0.000000113494
		1.706974355610	0.000000000018
		2.770700982867	0.000000000000
	18.0	0.000000000000	0.405324996970
		0.169792931616	0.243128035113
		0.349860466133	0.050820522240
		0.553209215689	0.003333223382
		0.800080869229	0.000055563123
		1.128400909924	0.000000157624
		1.625891956745	0.000000000033
		2.579234688647	0.000000000000
	18.5	0.000000000000	0.402006709982
		0.166080855809	0.243152688719
		0.341810282550	0.052183588825
		0.539312234068	0.003595096324
		0.777217417899	0.000065059547

n	k	t	w
		1.089863636421	0.000000211538
		1.555031199244	0.000000000057
		2.419655657931	0.000000000000
	19.0	0.000000000000	0.398934738009
		0.162602410227	0.243146717502
		0.334294476822	0.053458740187
		0.526422281310	0.003851815363
		0.756224758165	0.000075082076
		1.055014185051	0.000000275777
		1.492436655320	0.000000000091
		2.284260011575	0.000000000000
	19.5	0.000000000000	0.396082400572
		0.159334041379	0.243116199734
		0.327256146229	0.054653724306
		0.514422420979	0.004102957646
		0.736859283085	0.000085567170
		1.023299583070	0.000000350718
		1.436636751552	0.000000000140
		2.167684676127	0.000000000000
	20.0	0.000000000000	0.393426763322
		0.156255395399	0.243066021515
		0.320646560095	0.055775472491
		0.503213999845	0.004348233219
		0.718919829390	0.000096454320
		0.994276505290	0.000000436588
		1.386500289594	0.000000000205
		2.066072176639	0.000000000000
16	15.0	0.098491403357	0.374308853883
		0.303346683607	0.115522042394
		0.534511135950	0.009977309853
		0.820678790829	0.000191284615
		1.218503525589	0.000000509186
		1.870868411790	0.000000000069
		3.296558208939	0.000000000000
		10.153170387615	0.000000000000
	15.5	0.095444292318	0.370265748727
		0.293480457248	0.118404923812
		0.515237192204	0.011081712650
		0.785826789706	0.000246747445
		1.152833557833	0.000000867159
		1.728903640392	0.000000000207
		2.877208571690	0.000000000000
		6.813611694672	0.000000000000
	16.0	0.092663646242	0.366579026763
		0.284524531046	0.120965529617
		0.497940833903	0.012146491272
		0.755164946041	0.000307589084
		1.096947745158	0.000001362756
		1.615055453835	0.000000000509
		2.581297554200	0.000000000000
		5.349527505510	0.000000000000
	16.5	0.090112751866	0.363203767382
		0.276346245659	0.123251624489
		0.482301383434	0.013169595148
		0.727902809446	0.000373000340
		1.048603357506	0.000002011558

n	k	t	w
		1.521063574108	0.000000001082
		2.358275043644	0.000000000000
		4.492036369026	0.000000000000
	17.0	0.087761610310	0.360102223005
		0.268838646456	0.125302415809
		0.468067229337	0.014150322727
		0.703446435052	0.000442211812
		1.006224131920	0.000002824586
		1.441731021182	0.000000002060
		2.182588118636	0.000000000000
		3.918077797474	0.000000000000
	17.5	0.085585436127	0.357242464099
		0.261914389525	0.127150310551
		0.455037663902	0.015088900088
		0.681339198490	0.000514513154
		0.968663618605	0.000003808511
		1.373594971539	0.000000003595
		2.039698821781	0.000000000000
		3.502477690334	0.000000000000
	18.0	0.083563547150	0.354597313266
		0.255501331298	0.128822274022
		0.443050271682	0.015986178656
		0.661223175932	0.000589262089
		0.935064330698	0.000004966112
		1.314243809566	0.000000005854
		1.920633113988	0.000000000000
		3.185383817132	0.000000000000
	18.5	0.081678530307	0.352143501283
		0.249539276695	0.130340886943
		0.431971959587	0.016843419116
		0.642813101964	0.000665886806
		0.904769790549	0.000006296845
		1.261937847192	0.000000009006
		1.819508646867	0.000000000001
		2.934202291773	0.000000000000
	19.0	0.079915605793	0.349860994323
		0.243977541551	0.131725173201
		0.421692441998	0.017662137547
		0.625878310532	0.000743884270
		0.877267391840	0.000007797437
		1.215385514482	0.000000013222
		1.732287160053	0.000000000002
		2.729522812287	0.000000000000
	19.5	0.078262136167	0.347732453970
		0.238773098169	0.132991252345
		0.412119420878	0.018443996397
		0.610229905743	0.000822816164
		0.852150028524	0.000009462460
		1.173604686535	0.000000018661
		1.656092448698	0.000000000003
		2.559001692202	0.000000000000
	20.0	0.076707242879	0.345742800901
		0.233889145639	0.134152857386
		0.403174961038	0.019190727769
		0.595711453939	0.000902303619
		0.829089587738	0.000011284848

n	k	t	w
		1.135833236861	0.000000025473
		1.588813493549	0.000000000005
		2.414383065346	0.000000000000
17	16.0	0.000000000000	0.420318378809
		0.186932397108	0.242611082395
		0.387402063885	0.044867037344
		0.619173786030	0.002336327384
		0.911620452673	0.000026324983
		1.324214008134	0.000000038487
		2.008270725985	0.000000000002
		3.514635438717	0.000000000000
		10.791718657268	0.000000000000
	16.5	0.000000000000	0.414373108038
		0.181396911366	0.242879366570
		0.375131964989	0.047194057819
		0.597142296606	0.002703867182
		0.873047477202	0.000036082683
		1.252651726260	0.000000071718
		1.854969222580	0.000000000009
		3.064845205251	0.000000000000
		7.232168212462	0.000000000000
	17.0	0.000000000000	0.408996671636
		0.176326980708	0.243035311684
		0.363970234266	0.049344361401
		0.577350269190	0.003074406230
		0.839099631178	0.000047462940
		1.191753592594	0.000000121903
		1.732050807568	0.000000000024
		2.747477419456	0.000000000000
		5.671281819619	0.000000000000
	17.5	0.000000000000	0.404109997003
		0.171660660109	0.243104626013
		0.353758068757	0.051334790721
		0.559437002277	0.003445007509
		0.808906270335	0.000060384379
		1.139076835386	0.000000192821
		1.630593766169	0.000000000056
		2.508329094314	0.000000000000
		4.757104352468	0.000000000000
	18.0	0.000000000000	0.399648176284
		0.167346984160	0.243106930427
		0.344367016748	0.053180593768
		0.543119093901	0.003813356589
		0.781812810126	0.000074743025
		1.092903942778	0.000000287931
		1.544982737425	0.000000000117
		2.319988742932	0.000000000000
		4.145291095934	0.000000000000
	18.5	0.000000000000	0.395557404474
		0.163343580979	0.243057332258
		0.335691861989	0.054895479837
		0.528170191000	0.004177653929
		0.757315747321	0.000090421272
		1.051985356391	0.000000410247
		1.471474984523	0.000000000221
		2.166855656035	0.000000000000
		3.702381715731	0.000000000000

n	k	t	w
	19.0	0.000000000000	0.391792683876
		0.159614891733	0.242967554112
		0.327645455935	0.056491725281
		0.514406909693	0.004536521220
		0.735020231725	0.000107294806
		1.015386249712	0.000000562257
		1.407463358847	0.000000000386
		2.039297237132	0.000000000000
		3.364547249833	0.000000000000
	19.5	0.000000000000	0.388316078992
		0.156130821843	0.242846754240
		0.320154895056	0.057980299929
		0.501678808851	0.004888922043
		0.714611438894	0.000125237753
		0.982390805371	0.000000745905
		1.351066811594	0.000000000633
		1.930998217263	0.000000000000
		3.097022043002	0.000000000000
	20.0	0.000000000000	0.385095373040
		0.152865705271	0.242702129933
		0.313158646534	0.059370997845
		0.489861099418	0.005234095746
		0.695834707622	0.000144126379
		0.952440005359	0.000000962592
		1.300888670729	0.000000000985
		1.837622520618	0.000000000000
		2.879099718071	0.000000000000
18	17.0	0.087488663526	0.359272071776
		0.267949192431	0.125836963283
		0.466307658155	0.014424274026
		0.700207538210	0.000463567984
		1.000000000000	0.000003120397
		1.428148006742	0.000000002534
		2.144506920508	0.000000000000
		3.732050807571	0.000000000000
		11.430052302755	0.000000000000
	17.5	0.085081295580	0.355669332366
		0.260278420697	0.128136799732
		0.451830159824	0.015628597429
		0.675523496518	0.000560708302
		0.957753484413	0.000004556991
		1.350701039926	0.000000005181
		1.979845168001	0.000000000000
		3.251768245603	0.000000000000
		7.650429084747	0.000000000000
	18.0	0.082862362451	0.352355976125
		0.253234392197	0.130192503247
		0.438640668996	0.016781886110
		0.653332607462	0.000663283228
		0.920564850211	0.000006341741
		1.284800026266	0.000000009549
		1.847838152016	0.000000000001
		2.912900486157	0.000000000000
		5.992671458522	0.000000000000

n	k	t	w
	18.5	0.080808492300	0.349298493630
		0.246735761075	0.132038213296
		0.426556791951	0.017884543895
		0.633235129719	0.000770246969
		0.887483389253	0.000008485984
		1.227801710621	0.000000016225
		1.738901777502	0.000000000003
		2.657590191425	0.000000000000
		5.021749217290	0.000000000000
	19.0	0.078900181093	0.346468333612
		0.240715294379	0.133702289661
		0.415430679671	0.018937700123
		0.614916699482	0.000880657685
		0.857794004318	0.000010993088
		1.177846989397	0.000000025826
		1.647001551480	0.000000000006
		2.456566108962	0.000000000000
		4.372031618021	0.000000000000
	19.5	0.077121006557	0.343841026682
		0.235116861346	0.135208440171
		0.405140986468	0.019942954624
		0.598126021375	0.000993679811
		0.830946434954	0.000013859729
		1.133582927604	0.000000038972
		1.568114220975	0.000000000012
		2.293163806878	0.000000000000
		3.901770594074	0.000000000000
	20.0	0.075457029002	0.341395486021
		0.229893174629	0.136576603240
		0.395587017599	0.020902196614
		0.582659343707	0.001108580664
		0.806509019652	0.000017077178
		1.093997148396	0.000000056261
		1.499436616920	0.000000000023
		2.157091343627	0.000000000000
		3.543159244304	0.000000000000
19	18.0	0.000000000000	0.398541117624
		0.166870486213	0.243091662675
		0.343300433624	0.053645499713
		0.541172937094	0.003912883226
		0.778331241872	0.000079073197
		1.086289575113	0.000000322230
		1.530613945453	0.000000000147
		2.279770369417	0.000000000000
		3.948910696227	0.000000000000
		12.068205279491	0.000000000000
	18.5	0.000000000000	0.393475523398
		0.162461084550	0.242999925570
		0.333727322209	0.055781239285
		0.524620947944	0.004380352790
		0.751065865827	0.000100217747
		1.040399893816	0.000000502579
		1.447283046608	0.000000000330
		2.103724991414	0.000000000000
		3.438089987082	0.000000000000
		8.068439975722	0.000000000000

n	k	t	w
	19.0	0.000000000000	0.388846874223
		0.158384440324	0.242848732256
		0.324919696233	0.057758909212
		0.509525449495	0.004844536215
		0.726542528006	0.000123642878
		0.999999999999	0.000000741667
		1.376381920471	0.000000000661
		1.962610505506	0.000000000000
		3.077683537175	0.000000000000
		6.313751514678	0.000000000000
	19.5	0.000000000000	0.384600135652
		0.154600624234	0.242652845448
		0.316779951843	0.059593682324
		0.495681863478	0.005303203410
		0.704322954225	0.000149153644
		0.964059095451	0.000001046140
		1.315066413309	0.000000001209
		1.846179658454	0.000000000000
		2.806178490797	0.000000000000
		5.286033589664	0.000000000000
	20.0	0.000000000000	0.380689247491
		0.151076119279	0.242423624548
		0.309227171735	0.061299127394
		0.482924120462	0.005754654770
		0.684062254843	0.000176546122
		0.931801563065	0.000001421365
		1.261335500301	0.000000002055
		1.747978198162	0.000000000000
		2.592442868515	0.000000000000
		4.598368023855	0.000000000000

A2.1.2 An Application of Harper Polynomials - Predictive Probability in Clinical Trials.

Whilst, potentially at least, Harper polynomials might find application to general Bayesian integration problems, for example replacing Hermite polynomials in Naylor and Smith(1982) approach, the fact that they would need to be recalculated at each iteration mitigates against their use. Apart from using Harper polynomials to calculate Behrens-Fisher densities and cumulative distribution functions we have also applied them to the following problem involving predictive probabilities in clinical trials.

The idea of 'stochastic curtailment' embodied in the work of Lan *et al*(1982) and Lan *et al*(1984) which allows for the early termination of clinical studies can be criticised on the grounds that the conditional probabilities involved are calculated on the basis of parameter values which may have little support from current experimental data. Spiegelhalter *et al*(1986) take this view and provide a general argument in favour of a Bayesian predictive approach, illustrating the argument with the comparison of two binomial samples - a problem tackled independently by Choi *et al*(1985). The comparison of two normal means has been considered by Spiegelhalter(1986b), Spiegelhalter and Freedman(1988) and Armitage(1988). In each of these three papers it is assumed that the population variances are known. That such considerations are not only of theoretical interest is lent credence by the published report of Frei *et al*(1987) of a study of Glycerol, Glycerol and Dextran and placebo in the treatment of acute stroke. This study was terminated after the inclusion of only 1/3 of the proposed number of patients because a Bayesian analysis based on predictive probabilities showed that there was a probability of only 0.06 that the trial would reach a successful conclusion if allowed to run its course.

Choi and Pepple(1989) consider the case of two normal means and, under the assumption of known variances, recreate the results of Spiegelhalter(1986b). When the variances are not known they propose two approximations, P_1 and P_2, to the predictive probability of success and compare them by simulation. A by-product of this simulation is their conclusion that both P_1 and P_2 are conservative estimates of the "true" predictive probability termed P_s. Whilst our primary interest is in the calculation of P_2, nonetheless it is of interest to investigate Choi and Pepple's claim of conservatism.

Without loss of generality, suppose that n patients are treated in each of the two treatment groups, and that the posterior distribution of δ, the difference between population means, is $N(d_n, \sigma_\delta^2/n)$ where $d_n = \bar{x} - \bar{y}$ is the difference in sample means and $\sigma_\delta^2 = \sigma_x^2 + \sigma_y^2$. The posterior probability that δ is positive is,

$$P_n = P(\delta > 0 \mid d_n) = \left(\frac{n}{2\pi\sigma_\delta^2}\right)^{1/2} \int_0^\infty \exp\left[\frac{-n(\delta - d_n)^2}{2\sigma_\delta^2}\right] d\delta$$

$$= \Phi\left(\frac{n^{1/2} d_n}{\sigma_\delta}\right) \qquad (A2.1.8)$$

By analogy the posterior probability after $n + m = N$ patients in each group is,

$$P_N = \Phi\left(\frac{N^{1/2} d_N}{\sigma_\delta}\right)$$

where $d_N = (nd_n + md_m)/N$ and d_m is the difference in means based on a further $2m$ patients.

Suppose a trial is regarded as a success if $P_N > 1 - \alpha$ implying,

$$d_m > \frac{N^{1/2}\sigma_\delta z_\alpha - nd_n}{m}$$

By definition,

$$p(d_m \mid \delta) = \left(\frac{m}{2\pi\sigma_\delta^2}\right)^{1/2} \exp\left[\frac{-m(d_m-\delta)^2}{2\sigma_\delta^2}\right]$$

so that

$$P_s = P\left[d_m > \frac{N^{1/2}\sigma_\delta z_\alpha - nd_n}{m} \mid \delta\right] = 1 - \Phi\left[\left(\frac{N}{m}\right)^{1/2} z_\alpha - \frac{nd_n + m\delta}{m^{1/2}\sigma_\delta}\right] \qquad (A2.1.9)$$

Similarly,

$$p(d_m \mid d_n) = \left(\frac{nm}{2\pi N\sigma_\delta^2}\right)^{1/2} \exp\left[\frac{-nm(d_m-d_n)^2}{2N\sigma_\delta^2}\right]$$

so that

$$P_1 = P\left[d_m > \frac{N^{1/2}\sigma_\delta z_\alpha - nd_n}{m} \mid d_n\right] = 1 - \Phi\left[\left(\frac{n}{m}\right)^{1/2} z_\alpha - \left(\frac{nN}{m}\right)^{1/2}\frac{d_n}{\sigma_\delta}\right] \qquad (A2.1.10)$$

This result is given in a slightly different form in Spiegelhalter(1986b) and Spiegelhalter and Freedman(1988) and is equivalent to Choi and Pepple's equation (10).

Choi and Pepple's simulation comparing P_s and P_1 is equivalent to comparing their expectations with respect to $p(d_n \mid \delta)$. By definition,

$$p(d_n \mid \delta) = \left(\frac{n}{2\pi\sigma_\delta^2}\right)^{1/2} \exp\left[\frac{-n(d_n-\delta)^2}{2\sigma_\delta^2}\right]$$

so that

$$E(P_s) = \frac{(2\pi)^{-1/2}\int_{-\infty}^{z_\alpha - n^{1/2}\delta/\sigma_\delta}\left[\int_{\left(\frac{N}{m}\right)^{1/2} z_\alpha - \frac{N\delta}{m^{1/2}\sigma_\delta} - \frac{n^{1/2}w}{m^{1/2}}}^{\infty} (2\pi)^{-1/2} e^{-z^2/2} dz\right] e^{-w^2/2} dw}{\Phi(z_\alpha - n^{-1/2}\delta/\sigma_\delta)}$$

We may use properties of bivariate normal distributions to show that the above expression can be written as,

$$E(P_s) = 1 - \frac{B\left[z_\alpha - n^{1/2}\delta/\sigma_\delta \;,\; z_\alpha - N^{1/2}\delta/\sigma_\delta \;:\; \left(\frac{n}{N}\right)^{1/2}\right]}{\Phi(z_\alpha - n^{1/2}\delta/\sigma_\delta)} \qquad (A2.1.11)$$

where

$$B(h,k;\rho) = \frac{1}{2\pi(1-\rho^2)^{1/2}} \int_{-\infty}^{h} \int_{-\infty}^{k} \exp\left[\frac{-(x^2-2\rho xy+y^2)}{2(1-\rho^2)}\right] dy\,dx$$

Similar calculations give,

$$E(P_1) = 1 - \frac{B\left[z_\alpha - n^{1/2}\delta/\sigma_\delta \;,\; \left(\frac{n}{N+m}\right)^{1/2}(z_\alpha - N^{1/2}\delta/\sigma_\delta) \;;\; \left(\frac{N}{N+m}\right)^{1/2}\right]}{\Phi(z_\alpha - n^{1/2}\delta/\sigma_\delta)} \qquad (A2.1.12)$$

The denominators in (A2.1.11) and (A2.1.12) arise since Choi and Pepple consider only those cases for which P_n is less than $1-\alpha$. If this restriction is ignored these expressions reduce to,

$$E(P_s) = 1 - \Phi[z_\alpha - N^{1/2}\delta/\sigma_\delta] \qquad (A2.1.13)$$

and

$$E(P_1) = 1 - \Phi\left[\left(\frac{n}{N+m}\right)^{1/2}(z_\alpha - N^{1/2}\delta/\sigma_\delta)\right] \qquad (A2.1.14)$$

respectively.

In Table A2.3 we evaluate (A2.1.11) and (A2.1.12) for those cases considered by Choi and Pepple in their Table 1 using the Gaussian quadrature algorithm suggested by Bouver and Bargmann(1979) to calculate $B(h,k;\rho)$. The near equality of all entries in these two tables suggests that we need only consider (A2.1.11) and (A2.1.12) when looking at "conservatism" of P_1 and renders superfluous the simulation results, particularly those associated with the test statistics Z_i which Choi and Pepple calculate to test the equality of P_1 and P_s , since it is unnecessary to test the equality of quantities which are by definition different.

Since $E(P_1)$ and $E(P_s)$ are by definition different, the only question which remains to be answered is whether they are sensible measures of performance. Now P_s, defined in (A2.1.9), is the probability of success conditional on the value of δ ; denote this by $\pi \mid \delta$. The probability P_1, defined in (A2.1.10), is the probability of success conditional on the difference d_n; denote this by $\pi \mid d_n$. Using properties of bivariate normal distributions it can be shown that,

$$\pi \mid d_n = \int_\delta \pi \mid \delta\, p(\delta \mid d_n)\, d\delta \qquad (A2.1.15)$$

where $p(\delta \mid d_n)$ is the posterior distribution of δ . Equation (A2.1.15) shows that the probability of success given the results currently available is the result of averaging the probability of success given the value of δ , $\pi \mid \delta$, with respect to our current beliefs about δ as represented by $p(\delta \mid d_n)$.

Choi and Pepple's simulations involve the calculation of the expected values of $\pi \mid \delta$ and $\pi \mid d_n$ with respect to $p(d_n \mid \delta)$. The notation $\pi \mid \delta$ does not make it clear that this probability depends on d_n but this is explicitly shown in (A2.1.9). The expectation of $\pi \mid d_n$ has the form,

TABLE A2.3 Evaluation of $E(P_s)$ and $E(P_1)$ $(n_1 = n_2 = n, N = n + m, \mu_y = 0, \sigma_x = \sigma_y)$.

n_1	μ_x	σ_x^2	$N = 40$		$N = 60$	
			$E(P_s)$	$E(P_1)$	$E(P_s)$	$E(P_1)$
20	-.2	1	.004	.062	.002	.101
		2	.007	.080	.006	.126
	0	1	.032	.134	.037	.196
		2	.032	.134	.037	.196
	.2	1	.146	.229	.225	.310
		2	.099	.200	.146	.276
	.5	1	.536	.373	.771	.465
		2	.323	.306	.507	.394
10	0	1	.040	.233	.042	.278
		2	.040	.233	.042	.278
	.5	1	.646	.442	.824	.496
		2	.404	.384	.564	.437

$$E(\pi \mid d_n) = \int_{d_n} \pi \mid d_n p(d_n \mid \delta) dd_n$$

$$= \int_{d_n} \left(\int_{\delta} \pi \mid \delta p(\delta \mid d_n) d\delta \right) p(d_n \mid \delta) dd_n$$

$$= \int_{d_n} \left(\int_{\delta} \pi \mid \delta \frac{pd_n \mid \delta) p\delta}{\int_{\delta} p(d_n \mid \delta) p(\delta) d\delta} d\delta \right) p(d_n \mid \delta) dd_n \qquad (A2.1.16)$$

The illogicality of using $E(P_1) = E(\pi \mid d_n)$ as a measure of the performance of the predictive probability P_1 is apparent from (A2.1.16). A Bayesian analysis proceeds by averaging the conditional distribution of the data given a specific parameter value with respect to the prior distribution of the parameter to give the posterior distribution of the parameter, from which the predictive distribution and hence P_1 can be determined. A consequence of this procedure is a down-weighting of the contribution of specific values δ as measured in $p(d_n \mid \delta)$. To reintroduce the importance of specific values by averaging with respect to $p(d_n \mid \delta)$ seems strange; indeed $p(d_n \mid \delta)$ appears twice in the last line of (A2.1.16).

I would argue that if one wishes to compare P_1 and P_s it should be done solely on the basis of (A2.1.9) and (A2.1.10) and that the "conservatism" noted by Choi and Pepple is implicit in the down-weighting of extreme probabilities given by the relationship (A2.1.15). The Bayesian argument against P_s mirrors the argument against the use of "stochastic curtailment" in that in reality δ is unknown, so that when predictions are to be made all that is known about δ is contained in $p(\delta \mid d_n)$ which may give little support to any particular hypothesized value for δ.

In practice, in order to use P_1 some value has to be substituted for σ_0 in (A2.3.3). Choi and Pepple suggest using the sample variances. In the Appendix to their paper Choi and Pepple develop a second form for the required predicted probability which they term P_2. Formulae (12) and (13) in the Appendix to Choi and Pepple's paper are incorrect and should read :

$$f(\bar{X} \mid x_1, \ldots, x_{n_1}) = \frac{\sqrt{m_1 n_1}\,\Gamma\left(\frac{n_1}{2}\right)}{\sqrt{N\pi(n_1-1)}\,\Gamma\left(\frac{n_1-1}{2}\right)s_{x_0}}\left[1 + \frac{m_1 n_1(\bar{x}-\bar{x}_0)^2}{(n_1-1)Ns_{x_0}^2}\right]^{-n_1/2} \qquad (A2.1.17)$$

and

$$P_2 = K\int_c^{\infty}\int_{-\infty}^{\infty}\left[1 + m_1\frac{[(z+t)/m_1 - \bar{x}_0^{\,2}]}{(n_1-1)Ns_{x0}^2/n_1}\right]^{-n_1/2}\left[1 + \frac{m_2[t/m_2 - \bar{y}_0]^2}{(n_2-1)Ns_{y0}^2/n_2}\right]^{-n_2/2} dt\,dz \qquad (A2.1.18)$$

respectively, where

$$K = \frac{\sqrt{n_1 n_2}\,\Gamma\left(\frac{n_1}{2}\right)\Gamma\left(\frac{n_2}{2}\right)}{\sqrt{m_1 m_2}N\pi\,\Gamma\left(\frac{n_1-1}{2}\right)\Gamma\left(\frac{n_2-1}{2}\right)\sqrt{(n_1-1)(n_2-1)}\,s_{x_0}s_{y_0}}$$

The error has arisen because Jeffreys(1983, p.143) uses the mean square deviation $s' = \sqrt{\Sigma(x_i-\bar{x})^2/n}$ not the standard deviation $\sqrt{\Sigma(x_i-\bar{x})^2/(n-1)}$.

The necessity of carrying out the double integration in (A2.1.18) in order to determine P_2 may be obviated in the following way. The transformation

$$w = \sqrt{\frac{m_1 n_1}{Ns_{x_0}^2}}\left(\frac{z+t}{m_1} - \bar{x}_0\right) \quad , \quad u = \sqrt{\frac{m_2 n_2}{Ns_{y_0}^2(n_2-1)}}\left(\frac{t}{m_2} - \bar{y}_0\right)$$

applied to (A2.1.18) gives,

$$P_2 = \frac{\Gamma\left(\frac{n_2}{2}\right)}{\Gamma\left(\frac{1}{2}\right)\Gamma\left(\frac{n_2-1}{2}\right)}\int_{-\infty}^{\infty} P\left[t(n_1-1) < \frac{\eta - c - \sqrt{(n_2-1)Ns_{y_0}^2 m_2/n_2}\,u}{\sqrt{Ns_{x_0}^2 m_1/n_1}}\right](1+u^2)^{-n_2/2}\,du$$

so since this expression is of the form

$$\int_{-\infty}^{\infty} f(u)(1+u^2)^{-n_1/2}\,du$$

P_2 may be approximated by

$$\sum_{i=1}^{t}\frac{\Gamma\left(\frac{n_2}{2}\right)}{\Gamma\left(\frac{1}{2}\right)\Gamma\left(\frac{n_2-1}{2}\right)}w_i P\left[t(n_1-1) < t_i = \frac{\eta - c - \sqrt{(n_2-1)Ns_{y_0}^2 m_2/n_2}\,u_i}{\sqrt{Ns_{x_0}^2 m_1/n_1}}\right]$$

where u_i are the zeros of the Harper polynomials $\phi_{t,k}(x)\,(k = (n_1-2)/2)$ and w_i are the associated weights.

To illustrate we use Choi and Pepple's data concerning the number of episodes of urinary incontinence. We have the following,

$$\hat{c} = 14.20$$

$$\eta = 46.46$$

$$\sqrt{(n_2-1)Ns_{y_0}^2 m_2/n_2} = \sqrt{17\times 90\times 1.24^2\times 72/18} = 97.01$$

$$\sqrt{Ns_{x_0}^2 m_1/n_1} = \sqrt{90\times 1.30^2\times 70/20} = 23.70$$

$$k = 8$$

The results presented in A2.2 may be used to calculate the following :

u_i	t_i	$P(t_{19}<t_i)$	w_i^*	$w_i^*\times P(t_{19}<t_i)$]
-5.671	25.242	1	$3.8671\ 10^{-13}$	$3.8671\ 10^{-13}$
-1.732	8.681	1	$8.6333\ 10^{-6}$	$8.6333\ 10^{-6}$
-0.839	4.926	0.99995	$7.9565\ 10^{-3}$	$7.9561\ 10^{-3}$
-0.364	2.929	0.99569	$2.0914\ 10^{-1}$	$2.0823\ 10^{-1}$
0	1.398	0.91095	$5.6579\ 10^{-1}$	$5.1541\ 10^{-1}$
0.364	-0.132	0.44826	$2.0914\ 10^{-1}$	$9.3747\ 10^{-2}$
0.839	-2.219	0.02326	$7.9565\ 10^{-3}$	$1.8505\ 10^{-4}$
1.732	-5.884	0.00001	$8.6333\ 10^{-6}$	$4.9655\ 10^{-11}$
5.671	-22.446	0.00000	$3.8671\ 10^{-13}$	0
				0.8255

The value of P_2 calculated in this way is very close to the value of 0.84 given by Choi and Pepple for P_1, in marked contrast to their calculated value for P_2. This difference cannot be attributed to their use of the incorrect formulae, since using the above orthogonal polynomial method on their formula gives the value 0.8373. The difference is most probably caused by an ill-advised choice of the method of numerical integration for a double integral which Choi and Pepple describe as having an "ill-behaved" integrand. The "ill behaviour" is likely to be caused by the high correlation between z and t which in our method is allowed for by the transformation to w and u. The corresponding value for "volume loss" using this method is 0.6609 again close to Choi and Pepple's value for P_1.

The investigations in this section are based either wholly, or partially, on the assumption of known variances. In the partial case the assumption is only made in calculating P_n or P_N. It could be argued that if P_2 is more appropriate than P_1 then at least P_n if not both P_n and P_N, should not be based on an assumption of the

equality of the variances, in which case P_n and P_N should be determined from Behrens-Fisher distributions. This makes the calculation of the predictive probabilities considerably more complicated although progress might possibly be made using Patil's(1964) approximation to Behrens-Fisher distribution. However for reasonable sample sizes it is doubtful whether this added complexity would be worthwhile. In fact the results above suggest that the approximate predictive probability P_1 will be accurate enough for practical purposes.

A2.1.3 Additional Applications of Harper Polynomials - Missing Data in Bivariate Normal Samples.

Little(1988) notes that one problem with frequentist methods is that exact inferences are rarely available for problems involving missing data even in the most simple cases. Bayesian inference, on the other hand, provides exact solutions to such problems although the computational difficulties involved, particularly in multiparameter problems, may force one to resort to approximation. As Little puts it, "Bayesians, *approximate an exact solution*; frequentists *seek an approximate answer where no exact solution exists*."

To illustrate a Bayesian approach to missing values Little(1988) considered the following problem. A random sample of n observations $y_{1i}, y_{2i}; i = 1, \ldots, n$ are taken from a bivariate normal distribution Y_1 and Y_2 with means μ_1 and μ_2, variances σ_{11} and σ_{22} and covariance σ_{12}; of these n observations m are complete and $n-m$ values of Y_2 are missing. This problem was also considered by Mehta and Swamy(1973,1974) who, using Jeffreys' prior, derived the posterior marginal distribution for μ_1 in t-form and noted that given μ_1, μ_2 has a t-distribution. Since their primary objective was to make inferences about $\delta = \mu_1 - \mu_2$ they did not consider in detail the marginal distribution of μ_2. Little shows that the posterior distribution of μ_2 may be written in the form,

$$p(\mu_2 \mid X) = \int_{-\infty}^{\infty} p(\mu_2 \mid \mu_1, X) p(\mu_1 \mid X) d\mu_1 \qquad (A2.1.19)$$

where

$$p(\mu_1 \mid X) = C_1 \left[1 + \frac{n(\mu_1 - \bar{y}_1^*)^2}{s_1^*} \right]^{-(a+1)/2}$$

$$p(\mu_2 \mid \mu_1, X) = C_2 \left[1 + \frac{(\mu_2 - b_{20} - b_{21}\mu_1)^2}{ss_{2.1}\left(\frac{1}{m} + \frac{(\mu_1 - \bar{y}_1)^2}{ss_1}\right)} \right]^{-(b+1)/2}$$

$$C_1 = \frac{\Gamma\left(\frac{a+1}{2}\right) n^{1/2}}{\Gamma\left(\frac{1}{2}\right)\Gamma\left(\frac{a}{2}\right) s_1^{*1/2}}$$

$$C_2 = \frac{\Gamma\left(\frac{b+1}{2}\right)}{\Gamma\left(\frac{1}{2}\right)\Gamma\left(\frac{b}{2}\right)\left[ss_{2.1}\left(\frac{1}{m} + \frac{(\mu_1 - \bar{y}_1)^2}{ss_1}\right)\right]^{1/2}}$$

$\bar{y}_1^*$ and s_1^* are the sample mean and variance of Y_1 based on all n cases; $\bar{y}_1$ and ss_1 are the sample mean and variance of Y_1 based on the m complete cases; b_{21} and b_{20} are the slope and intercept from the regression of Y_2 on Y_1 based on the m complete cases and $ss_{2.1}$ is the associated residual sum of squares and the prior distribution of all the parameters is proportional to $\sigma_{11}^{-(a_0-b_0)}(\sigma_{11}\sigma_{22}-\sigma_{12}^2)^{-b_0}$.

The cumulative posterior distribution function may be written as,

$$\begin{aligned}\int_{-\infty}^{z} p(\mu_2 \mid X)d\mu_2 &= \int_{-\infty}^{z}\int_{-\infty}^{\infty} p(\mu_2 \mid \mu_1, X)p(\mu_1 \mid X)d\mu_1 d\mu_2 \\ &= \int_{-\infty}^{\infty}\int_{-\infty}^{z} p(\mu_2 \mid \mu_1, X)d\mu_2 p(\mu_1 \mid X)d\mu_1 \\ &= \int_{-\infty}^{\infty} P\left[t_b < \frac{b^{1/2}(z-b_{20}-b_{21}\mu_1)}{\left(ss_{2.1}\left[\frac{1}{m}+\frac{(\mu_1-\bar{y}_1)^2}{ss_1}\right]\right)^{1/2}}\right] p(\mu_1 \mid X)d\mu_1 \qquad (A2.1.20)\end{aligned}$$

In both (A2.1.19) and (A2.1.20) we may make the transformation $u = n^{1/2}(\mu_1 - \bar{y}_1^*)/s_1^{*1/2}$ to give,

$$\begin{aligned}p(\mu_2 \mid X) = C_1'C_2' \int_{-\infty}^{\infty} &\left[ss_{2.1}\left(\frac{1}{m}+\frac{\left(u\frac{s_1^{*1/2}}{n^{1/2}}+\bar{y}_1^*-\bar{y}_1\right)^2}{ss_1}\right)\right]^{-1/2} \\ &\times\left[1+\frac{\left(\mu_2-b_{20}-b_{21}\left(u\frac{s_1^{*1/2}}{n^{1/2}}+\bar{y}_1^*\right)\right)^2}{ss_{2.1}\left(\frac{1}{m}+\frac{\left(u\frac{s_1^{*1/2}}{n^{1/2}}+\bar{y}_1^*-\bar{y}_1\right)^2}{ss_1}\right)}\right]^{-(b+1)/2} (1+u^2)^{-(a+1)/2}du \qquad (A2.1.21)\end{aligned}$$

and

$$\int_{-\infty}^{z} p(\mu_2 \mid X)d\mu_2 = \int_{-\infty}^{\infty} P\left[t_b < \frac{b^{1/2}\left(z-b_{20}-b_{21}\left(u\frac{s_1^{*1/2}}{n^{1/2}}+\bar{y}_1^*\right)\right)}{\left[ss_{2.1}\left(\frac{1}{m}+\frac{\left(u\frac{s_1^{*1/2}}{n^{1/2}}+\bar{y}_1^*-\bar{y}_1\right)^2}{ss_1}\right)\right]^{1/2}}\right](1+u^2)^{-(a+1)/2}du \qquad (A2.1.22)$$

where

$$C_1' = \frac{\Gamma\left(\frac{a+1}{2}\right)}{\Gamma\left(\frac{1}{2}\right)\Gamma\left(\frac{a}{2}\right)}$$

and

$$C_2' = \frac{\Gamma\left(\frac{b+1}{2}\right)}{\Gamma\left(\frac{1}{2}\right)\Gamma\left(\frac{b}{2}\right)}$$

Both (A2.1.21) and (A2.1.22) have the form

$$\int_{-\infty}^{\infty} f(u)(1+u^2)^{-(k+1)}du$$

and therefore may again be approximated by

$$\sum_{i=1}^{I} w_{ii} f(u_{ii})$$

where u_{ii} are the zeros of the orthogonal polynomials $\phi_{I,k}(x)$ and w_{ii} are the associated weights.

A2.2 Polynomials for Normal Kernels Over a Truncated Range.

Contemporaneously Galant(1969) and Steen *et al*(1969) considered Gaussian quadrature rules for integrals of the form,

$$\int_{0}^{\infty} e^{-x^2} f(x)dx \quad ;$$

the latter authors also developed rules for integrals of the form,

$$\int_{0}^{b} e^{-x^2} f(x)dx. \qquad (A2.2.1)$$

In §11 we noted that one method for evaluating some of the integrals involved in our Bayesian analysis of *LD50* experiments required quadrature rules for integrals of the form,

$$\int_{b}^{\infty} e^{-x^2} f(x)dx \quad . \qquad (A2.2.2)$$

To see how such integrals may arise suppose, following Naylor and Smith(1982), that the linear transformation,

$$\beta^* = \beta$$
$$\alpha^* = \alpha + c\beta$$

achieves approximate independence of β^* and α^*, then (11.4) is approximately,

$$p_c(X) = \int_{-\infty}^{\infty} f(\alpha^* \mid X)d\alpha^* \int_{0}^{\infty} g(\beta^* \mid X)d\beta^*.$$

Suppose that,

$$g(\beta^* \mid X) = h(\beta^*)(2\pi\sigma^2)^{-1/2}\exp\left(\frac{-(\beta^*-\beta_0)^2}{2\sigma^2}\right) \qquad (A2.2.3)$$

then

$$\int_0^\infty g(\beta^* \mid X)d\beta^* = \int_0^\infty h(\beta^*)(2\pi\sigma^2)^{-1/2}\exp\left(\frac{-(\beta^*-\beta_0)^2}{2\sigma^2}\right)d\beta^*.$$

Let $u = (\beta^* - \beta_0)/(\sqrt{2}\sigma)$ with jacobian $\sqrt{2}\sigma$ which implies that,

$$\int_0^\infty g(\beta^* \mid X)d\beta^* = \pi^{-1/2}\int_{-\beta_0/(\sqrt{2}\sigma)}^\infty h(\beta_0+\sqrt{2}\sigma u)e^{-u^2}du$$

If the integral (A2.2.2) may be approximated by

$$\sum_{i=1}^n w_{4i}f(u_i)$$

then

$$g(\beta^* \mid X) = \pi^{-1/2}\sum_{i=1}^n w_{4i}h(\beta_0+\sqrt{2}\sigma u_i)$$

$$= \sum_{i=1}^n w^*_{4i}g(\beta_0+\sqrt{2}\sigma u_i \mid X)$$

where $w^*_{4i} = \sqrt{2}\sigma w_{4i}e^{u_i^2}$.

Orthogonal polynomials for integrals of the form (A2.2.2) have not previously been studied. However the undoubted similarity between (A2.2.1) and (A2.2.2) show that they may be simply generated following the approach given by Steen *et al* (1969). If we denote the required polynomials by θ_i then they may be generated by the following recursion:

$$\theta_1(x) = 1 \qquad (A2.2.4)$$

$$\theta_2(x) = x - \frac{e^{-b^2}}{\pi^{1/2}(1-erf(b))} \qquad (A2.2.5)$$

$$\theta_{k+1}(x) = (x+\alpha_k)\theta_k(x)+\beta_k\theta_{k-1}(x) \quad k = 1,. \qquad (A2.2.6)$$

where

$$\alpha_k = \frac{1}{2\gamma_k}\left[e^{-x^2}\theta_k^2(x)\right]_0^\infty \qquad (A2.2.7)$$

$$\beta_k = \frac{\gamma_k}{\gamma_{k-1}} \qquad (A2.2.8)$$

and

$$\gamma_k = \frac{1}{2}k\gamma_{k-1} - \frac{1}{2}\left[e^{-x^2}\theta_k(x)\theta_{k-1}(x)\right]_b^{\infty} \qquad (A2.2.9)$$

The SAS macro given in Appendix A7.3 uses the recursion defined by (A2.2.4)-(A2.2.9) to generate, for given b and n, the zeros and associated weights of $\theta_n(x)$.

A4 DENSITY AND DISTRIBUTION FUNCTIONS OF THE RATIO OF NORMAL VARIABLES.

Suppose that the posterior distribution of two variables y and x is bivariate normal with means y_0 and x_0, variances σ_y^2 and σ_x^2, and correlation ρ so that,

$$p(y,x) = BN(\mu,\Sigma)$$

where,

$$\mu = \begin{pmatrix} y_0 \\ x_0 \end{pmatrix} \text{ and } \Sigma = \begin{pmatrix} \sigma_y^2 & \rho\sigma_y\sigma_x \\ \rho\sigma_y\sigma_x & \sigma_x^2 \end{pmatrix}$$

Then,

$$p\left(w = \frac{y}{x} \mid x > 0\right) = \frac{\int_0^{\infty} x\,p(wx,x)dx}{\int_0^{\infty}\int_{-\infty}^{\infty} p(x,y)dydx} = \frac{A}{B} \qquad (A4.1)$$

Following Hinkley (1969) it may be shown that,

$$A = \frac{b(w)d(w)}{\sqrt{(2\pi)}\sigma_y\sigma_x a^3(w)}\Phi\left(\frac{b(w)}{\sqrt{(1-\rho^2)}a(w)}\right) + \frac{\sqrt{(1-\rho^2)}}{2\pi\sigma_y\sigma_x a^2(w)}\exp\left(\frac{-c}{2(1-\rho^2)}\right) \qquad (A4.2)$$

where,

$$a^2(w) = \frac{w^2}{\sigma_y^2} - \frac{2\rho w}{\sigma_y\sigma_x} + \frac{1}{\sigma_x^2}\ ,\quad b(w) = \frac{wy_0}{\sigma_y^2} - \frac{\rho(y_0 + wx_0)}{\sigma_y\sigma_x} + \frac{x_0}{\sigma_x^2}\ ,$$

$$c = \frac{y_0^2}{\sigma_y^2} - \frac{2\rho y_0 x_0}{\sigma_y\sigma_x} + \frac{x_0^2}{\sigma_x^2}\ ,\quad d(w) = \exp\left[\frac{b^2(w) - ca^2(w)}{2(1-\rho^2)a^2(w)}\right]$$

It is simply shown that,

$$B = \Phi\left(\frac{x_0}{\sigma_x}\right) \qquad (A4.3)$$

(A4.1),(A4.2) and (A4.3) define the posterior distribution of w.

The cumulative distribution, $F(w)$, can be written as,

$$F(w) = \frac{\int_0^{\infty}\int_{-\infty}^{wx} p(y,x)dydx}{\Phi\left(\frac{x_0}{\sigma_x}\right)} = \frac{B(h,k,\gamma)}{\Phi(k)} \qquad (A4.4)$$

where,

$$B(h,k,\gamma) = \frac{\int_{-\infty}^{h}\int_{-\infty}^{k} \exp\left[\frac{-(u^2-2\gamma uv+v^2)}{2(1-\gamma^2)}\right]dudv}{2\pi\sqrt{(1-\rho^2)}} \qquad (A4.5)$$

$$h = \frac{wx_0 - y_0}{\sigma_y \sigma_x a(w)} \quad , \quad k = \frac{x_0}{\sigma_x} \quad , \quad \gamma = \frac{w\sigma_x - \rho\sigma_y}{\sigma_y \sigma_x a(w)}$$

Numerical evaluation of (A4.5) may be carried out using equation (2.1) of Owen(1956) together with a program for evaluating the integral,

$$T(h,a) = (2\pi)^{-1}\int_0^a \frac{\exp\left[\frac{-h^2(1+x^2)}{2}\right]}{1+x^2}dx$$

Two such programs are given by Cooper(1968) and Young and Minder (1974) - see also Boys(1989).

A5 FORTRAN PROGRAM FOR LD50 ESTIMATION.

A5.1 Introduction.

This program is designed to perform a Bayesian analysis of acute toxicity studies. As a by-product, a classical, maximum-likelihood analysis is available - see Finney(1971). The program carries out the analyses developed in §11.2,§11.4 and §11.5 although it is also able to deal with the more general problem of making inferences about the ED"X", where "X" is between 0 and 100 %. This program has been implemented at the laboratory level in the Toxicology Department of CIBA-GEIGY's Pharmaceutical Division in Basel, Switzerland.

The program was developed on an IBM PC AT 02, but with slight modification will run on any machine with a FORTRAN 77 compiler. These slight modifications relate solely to input and output.

In this appendix descriptions and listings of the main program, all subroutines and functions are given. Input to, and output from the program are given for three examples, chosen to illustrate the various features of the program.

A5.2 Program Descriptions.

This program is written in DOUBLE PRECISION FORTRAN 77 and consists of 1 main routine, 21 subroutines and 9 functions. The program will handle up to 10 dose groups. The program is self-contained, requiring no additional functions. In what follows, the main program, all subroutines, and all functions are described.

A5.2.1 MAIN PROGRAM

Purpose :	Reads the input parameters and data; calls the principal subroutines; outputs some results.	
Input :	FILE1	character string , data file
	FILE2	character string , output file
	IOUT	integer, controls whether plot data is output IOUT = 0 no plot data output to file IOUT = 1 plot data output to file
	FILE3	character string , plot file
	TITLE	character string , title
		the above are input fron the terminal, the remainder from the data file (FILE1)
	ILOOP	integer, number of data sets to be analysed
	IED	integer, defines the effective dose sought for instance IED = 50 defines the ED50, IED = 90 defines the ED90
	K	integer, number of dose groups
	CLASS	logical, controls whether a Bayesian analysis is carried out. CLASS = .TRUE. - Bayesian analysis CLASS = .FALSE. - only maximum likelihood
	PRIOR	logical, controls use of prior information PRIOR = .TRUE. - use prior information PRIOR = .FALSE. - no prior information
	NR	integer, number of class boundaries
	TLIM(NR)	real array, toxicity class boundaries,
		NR and TLIM only read if CLASS = .TRUE.
	ALPHA0	real, prior mean for alpha
	BETHA0	real, prior mean for beta
	V0(2,2)	real array, prior covariance matrix for alpha and beta
		ALPHA0,BETHA0 and V0 only read if PRIOR = .TRUE.
	D(K)	real array, doses
	IN(K)	integer array, number of animals
	IR(K)	integer array, number of responses

Routines called :	ESTIM SCORE SHOW CTEST FIDUC SHOW1 HPD SHOW2 COMBIN SHOW3

A5.2.2 AXIS(VALMIN,STEP,NVALS,MAXPR,IR,IRPIN,OFFSET,IFACT,VALS,IV,IFAULT)

Purpose :	Optimization of axis for plotting
Parameters:	For definition of parameters see Stirling(1981a)
Called by :	SCATPL

A5.2.3 COMBIN(ALPHA0,BETA0,V0)

Purpose :	To combine prior moments with moments from an analysis using an uninformative prior	
Parameters:	ALPHA0	real - input : prior mean for alpha
	BETA0	real - input : prior mean for beta
	V0	real array - input : prior covariance matrix
Routines called :	DINV DMULT	
Called by :	MAIN	

A5.2.4 CON(W,A,B,D,H,RHO)

Purpose :	To set up constants for bivariate normal integrals	
Parameters:	W	real - input : value of log(ED"X")
	A	real - output : see Appendix A4
	B	real - output : see Appendix A4
	D	real - output : see Appendix A4
	H	real - output : see Appendix A4
	RHO	real - output : see Appendix A4
Called by :	DMED DMODE OT HPD	

A5.2.5 CTEST(Y,K,T,H,D,IR,IN)

Purpose :	To perform goodness-of-fit test; output results from the test including the expected number of responses in each dose group and the chi-squared test	
Parameters:	Y(2)	real array - input : final estimates
	K	see main program
	T	real - output : 95 % point of normal distribution or t-distribution with (K-2) degrees of freedom
	H	real - output : heterogeneity factor
	D(K)	see main program
	IR(K)	see main program
	IN(K)	see main program
Routines called :	FNORM	
Called by :	MAIN	

A5.2.6 DERIV(Y,K,D,IR,IN,D1,D2,DA,DB,V3)

Purpose :	To calculate first,second and third derivatives of the log-likelihood at the current parameter estimates and to calculate the Lindley corrections and the estimated posterior covariance matrix	
Parameters:	Y(2)	real array - input : current estimates
	K	see main program
	D(K)	see main program
	IR(K)	see main program
	IN(K)	see main program
	D1(2)	real array - output : first partial derivatives
	D2(2,2)	real array - output : second partial derivatives
	DA	real - output : Lindley correction for alpha
	DB	real - output : Lindley correction for beta
	V3(2,2)	real - output : estimated posterior covariance matrix
Routines called :	FNORM DV1 DV2 DV3	
Called by :	SCORE	

A5.2.7 DINV(D2,V)

Purpose :	To calculate the inverse of a matrix	
Parameters:	D2(2,2)	real array - input : matrix whose inverse is required
	V(2,2)	real array - output : inverse of D2
Called by :	SCORE COMBIN	

A5.2.8 DMED(DLMED)

Purpose :	To calculate posterior median ED"X"	
Parameters:	DLMED	real - output : posterior median ED"X"
Routines called :	CON BIVL	
Called by :	HPD	

A5.2.9 DMODE(DLMOD)

Purpose :	To calculate posterior mode ED"X"	
Parameters:	DLMOD	real - output : posterior mode ED"X"
Routines called :	CON DEN	
Called by :	HPD	

A5.2.10 DMULT(B1,B2,A,C1,C2)

Purpose :	To multiply a vector by a matrix	
Parameters:	B1	real - input : 1st element of vector
	B2	real - input : 2nd element of vector
	A	real - input : matrix
	C1	real - output : 1st element of vector
	C2	real - output : 2nd element of vector
Called by :	COMBIN	

A5.2.11 ESTIM(XMIN,K,D,IR,IN)

Purpose :	To calculate initial estimates of alpha and beta by linear least squares

Parameters:	XMIN(2)	real array - output : initial estimates
	K	see main program
	D(K)	see main program
	IR(K)	see main program
	IN(K)	see main program
Routines called :	PROBIT	
Called by :	MAIN	

A5.2.12 FIDUC(Y,V,T,H,D,DL,DU,IED)

Purpose :	To estimate ED"X" and 95 % fiducial limits if possible	
Parameters:	Y(2)	real array - input : final estimates of alpha and beta
	V(2,2)	real array - input : asymptotic covariance matrix
	T	real - input : 95 % point of normal distribution or t-distribution with (K-2) degrees of freedom
	H	real - input : heterogeneity factor
	D	real - output : estimated ED"X"
	DL	real - output : estimated lower 95 % limit
	DU	real - output : estimated upper 95 % limit
	IED	integer - input : see main program
Routines called :	PROBIT	
Called by :	MAIN	

A5.2.13 HPD(TLIM,NR,IED)

Purpose :	To calculate 95 % HPD interval for log(ED"X") , posterior probabilities of toxicity classes, posterior density of log(ED"X") and posterior distribution function of log(ED"X")	
Parameters:	TLIM(NR)	real - input : toxicity class boundaries
	NR	integer - input : number of boundaries
	IED	integer - inout : see main program
Routines called :	FNORM TFN OT CON BIVL DMED DMODE SPLOT PROBIT	
Called by :	MAIN	

A5.2.14 OT(W,F00,U2,F)

Purpose :	Given a value for log(ED"X") to find another value with the same posterior density	
Parameters:	W	real - input : value of log(ED"X")
	F00	real - output : posterior density for W
	U2	real - output : value of log(ED"X") with the same posterior density as W
	F	real - output : posterior density for U2
Routines called :	CON DEN	
Called by :	HPD	

A5.2.15 SCALE(FMN,FMX,N,MPV,VALMIN,STEP,NVALS,IR,IFAULT)

Purpose :	Optimization of scale for plotting
Parameters:	For definition of parameters see Stirling(1981a)
Called by :	SCATPL

A5.2.16 SCATPL(A,N,M,ICY,NCY,ICX,NY,NX,SCALEY,SCALEX,ISTAND,IFAULT)

Purpose :	To produce line printer plots
Parameters:	For definition of parameters see Stirling(1981b)
Routines called :	SCALE AXIS
Called by :	SPLOT

A5.2.17 SCORE(XMIN,K,D,IR,IN,V,DLOGLO,DA,DB,V3)

Purpose :	To estimate maximum likelihood estimates of alpha and beta	
Parameters:	XMIN(2)	real array - input : initial estimates output : final estimates
	K	see main program
	D(K)	see main program
	IR(K)	see main program
	IN(K)	see main program
	V(2,2)	real array - output : estimated covariance matrix
	DLOGLO	real - output : maximised log-likelihood
	DA	real - output : Lindley correction for alpha
	DB	real - output : Lindley correction for beta
	V3(2,2)	real array - output : posterior covariance matrix using uninformative prior
Routines called :	DERIV DINV FN	
Called by :	MAIN	

A5.2.18 SHOW(A,B,V)

Purpose :	Displays maximum likelihood parameter estimates and asymptotic covariance matrix	
Parameters:	A	real, estimate of alpha
	B	real, estimate of beta
	V(2,2)	real array, asymptotic covariance matrix
Called by :	MAIN	

A5.2.19 SHOW1(A,B,V)

Purpose :	Displays posterior moments using an uninformative prior	
Parameters:	A	real, posterior mean of alpha
	B	real, posterior mean of beta
	V(2,2)	real array, posterior covariance matrix
Called by :	MAIN	

A5.2.20 SHOW2(A,B,V)

Purpose :	Displays prior moments	
Parameters:	A	real, prior mean of alpha
	B	real, prior mean of beta
	V(2,2)	real array, prior covariance matrix
Called by :	MAIN	

A5.2.21 SHOW3(A,B,V)

Purpose :	Displays posterior moments using an informative prior asymptotic covariance matrix	
Parameters:	A	real, posterior mean of alpha
	B	real, posterior mean of beta
	V(2,2)	real array, posterior covariance matrix
Called by :	MAIN	

A5.2.22 SPLOT(PLOT,IED)

Purpose :	Controls plotting	
Parameters:	PLOT(161,3)	real array - input : plot data
	IED	integer - input : see main program
Routines called :	SCATPL	
Called by :	HPD	

A5.2.23 BIVL(H,RHO)

Purpose :	Calculates bivariate normal probabilities
Parameters:	See CON
Routines called :	FNORM TFN
Called by :	DMED HPD

A5.2.24 DEN(A,B,D)

Purpose :	Calculates posterior density for log(ED"X")
Parameters:	See CON
Routines called :	FNORM
Called by :	DMODE HPD OT

A5.2.25 DV1(D,X,IE)

Purpose :	To calculate the first partial derivative of the response function	
Parameters:	D	real - input : log(dose)
	X	real - input : alpha + beta*log(dose)
	IE	integer - input : derivative indicator IE = 0 derivative wrt alpha IE = 1 derivative wrt beta
Called by :	DERIV	

A5.2.26 DV2(D,X,IE)

Purpose :	To calculate the second partial derivative of the response function	
Parameters:	D	real - input : log(dose)
	X	real - input : alpha + beta*log(dose)
	IE	integer - input : derivative indicator IE = 0 2nd derivative wrt alpha IE = 1 2nd derivative wrt alpha and beta IE = 2 2nd derivative wrt beta
Called by :	DERIV	

A5.2.27 DV3(D,X,IE)

Purpose :	To calculate the third partial derivative of the response function	
Parameters:	D	real - input : log(dose)
	X	real - input : alpha + beta*log(dose)
	IE	integer - input : derivative indicator IE = 0 3rd derivative wrt alpha IE = 1 3rd derivative wrt alpha**2 and beta IE = 2 3rd derivative wrt alpha and beta**2 IE = 3 3rd derivative wrt beta
Called by :	DERIV	

A5.2.28 FN(Y)

Purpose :	To calculate the negative maximised log-likelihood	
Parameters:	Y(2)	real array - input : maximimum likelihood estimates of alpha and beta
Routines called :	FNORM	
Called by :	SCORE	

A5.2.29 FNORM(X,UPPER)

Purpose :	To evaluate the distribution function of the standard normal distribution - Hill(1973)	
Parameters:	X	real - input : point at which the function is to be evaluated
	UPPER	logical - input : indicator function UPPER = .TRUE. upper tail probability UPPER = .FALSE. lower tail probability
Called by :	BIVL CTEST DEN DERIV FN HPD TFN	

A5.2.30 PROBIT(P)

Purpose :	To evaluate the inverse normal distribution function -Odeh and Evans(1974)	
Parameters:	P	real - input : probability for which inverse is required
Called by :	ESTIM	

A5.2.31 TFN(HI,AI)

Purpose :	To calculate the integral of a special function
Parameters:	For definition of function and parameters see Cooper(1968)
Called by :	BIVL HPD

A5.3 Program Listings.

A5.3.1 MAIN PROGRAM

```
      PROGRAM ACUTE
      IMPLICIT REAL*8 (A-H,O-Z)
      CHARACTER*80 TITLE
      CHARACTER*12 FILE1
      CHARACTER*12 FILE2
      CHARACTER*12 FILE3
      DIMENSION XMIN(2),D(10),IR(10),IN(10),V(2,2),A(15),TLIM(10)
      DIMENSION V0(2,2)
      COMMON /COM1/ALPHA,BETHA,V3(2,2)
      COMMON /COMFIL/IOUT
      LOGICAL CLASS,PRIOR
      WRITE(*,100)
      READ(*,200) FILE1
      OPEN(UNIT=1,FILE=FILE1,STATUS='OLD',IOSTAT=IERR)
      WRITE(*,300)
      READ(*,200) FILE2
      OPEN(UNIT=3,FILE=FILE2,STATUS='NEW',IOSTAT=IERR)
      IOUT=0
      WRITE(*,400)
      READ(*,*) IOUT
      IF(IOUT.EQ.0) GOTO 10
      WRITE(*,500)
      READ(*,200) FILE3
      OPEN(UNIT=8,FILE=FILE3,STATUS='NEW',IOSTAT=IERR)
   10 READ(1,*) ILOOP
      ILOO=0
   20 ILOO=ILOO+1
      IF(ILOO.GT.ILOOP) STOP
      READ(1,700) TITLE
      READ(1,*) IED,K,CLASS,PRIOR
      IF (CLASS) THEN
       READ(1,*) NR
       READ(1,*) (TLIM(I),I=1,NR)
      END IF
      IF (PRIOR) READ(1,*) ALPHA0,BETHA0,V0
      ISUM=0
      DO 30 I=1,K
      READ(1,*) D(I),IN(I),IR(I)
   30 IF (IN(I).NE.IR(I).AND.IR(I).NE.0) ISUM=ISUM+1
      WRITE(3,800) TITLE
      WRITE(3,600) IED
      WRITE(3,900)
      WRITE(3,1000)
      IF (ISUM.GE.2) GOTO 40
      WRITE(3,1100)
      WRITE(*,1100)
      GOTO 50
   40 CALL ESTIM(XMIN,K,D,IR,IN)
      CALL SCORE(XMIN,K,D,IR,IN,V,DLOGLO,DA,DB,V3)
      CALL SHOW(XMIN(1),XMIN(2),V)
      WRITE(3,1200) DLOGLO
      CALL CTEST(XMIN,K,T,H,D,IR,IN)
      CALL FIDUC(XMIN,V,T,H,ED,EDL,EDU,IED)
      IF (EDL.EQ.-999.0D0) WRITE(3,1400) IED,ED
      IF (EDL.NE.-999.0D0) WRITE(3,1300) IED,ED,EDL,IED,EDU
      IF (.NOT.CLASS) GOTO 50
      WRITE(3,800) TITLE
      WRITE(3,1500)
      ALPHA=XMIN(1)+DA
      BETHA=XMIN(2)+DB
      CALL SHOW1(ALPHA,BETHA,V3)
      CALL HPD(TLIM,NR,IED)
      IF (PRIOR) THEN
       WRITE(3,800) TITLE
       WRITE(3,1600)
       CALL SHOW2(ALPHA0,BETHA0,V0)
       CALL COMBIN(ALPHA0,BETHA0,V0)
       CALL SHOW3(ALPHA,BETHA,V3)
      CALL HPD(TLIM,NR,IED)
```

```
      END IF
   50 GOTO 20
  100 FORMAT(2x,'INPUT FILE : ')
  200 FORMAT(A12)
  300 FORMAT(2X,'OUTPUT FILE(SHOULD NOT ALREADY EXIST) : ')
  400 FORMAT(2X,'ENTER "1" IF PLOT OUTPUT REQUIRED : ')
  500 FORMAT(2X,'PLOT OUTPUT FILE(SHOULD NOT ALREADY EXIST) : ')
  600 FORMAT(//,5X,'MAXIMUM LIKELIHOOD ESTIMATION OF ED',I2/)
  700 FORMAT(A80)
  800 FORMAT('^L',/5X,80A/)
  900 FORMAT(/ ,5X,'MODEL : PROBIT')
 1000 FORMAT(/  ,5X,'INDEPENDENT VARIABLE : LOG(DOSE)'/)
 1100 FORMAT(/ ,4X,'NO CALCULATIONS WITH LESS THAN TWO RESPONSES BETWEE
     1N 0% AND 100%  (0 < IN(I)/IR(I) < 1) !')
 1200 FORMAT(/ ,5X,'MAXIMISED LOG-LIKELIHOOD'//14X,F10.4)
 1300 FORMAT(/ ,5X/5X,'ESTIMATE OF ED',I2//15X,F15.4//5X,
     1 'FIDUCIAL LIMITS (95%)'//3X,F15.4,' < ED',I2,' < ',F15.4)
 1400 FORMAT(/ ,5X/5X,'ESTIMATE OF ED',I2//8X,F15.4//5X,'NO FIDUCIAL',
     1' LIMITS')
 1500 FORMAT(/ ,5X,'BAYESIAN ANALYSIS'/)
 1600 FORMAT(/ ,////6X,'PRIOR INFORMATION :')
      END
```

A5.3.2 AXIS

```
      SUBROUTINE AXIS(VALMIN,STEP,NVALS,MAXPR,IR,IRPRIN,OFFSET,IFACT,
     1 VALS,IV,IFAULT)
      REAL VALS(IV)
      DATA IRMAX/20/,MPRMAX/20/
      IFAULT=0
      IF(NVALS.LT.2) IFAULT=IFAULT+1
      FMAX=VALMIN+STEP*FLOAT(NVALS-1)
      IF(NVALS.GE.2.AND.FMAX.LE.VALMIN) IFAULT=IFAULT+2
      IF(MAXPR.LT.2.OR.MAXPR.GT.MPRMAX) IFAULT=IFAULT+4
      IF(NVALS.GT.IV) IFAULT=IFAULT+8
      IF(IR.GT.IRMAX) IFAULT=IFAULT+16
      IF(IFAULT.GT.0) RETURN
      TMAX=10.**MAXPR
      FL=ABS(FMAX)
      FS=ABS(VALMIN)
      IL=0
   10 IF(FL.LT.1..AND.FS.LT.1.) GOTO 20
      FL=FL/10.
      FS=FS/10.
      IL=IL+1
      GOTO 10
   20 IF(FL.GE..1.OR.FS.GE..1) GOTO 30
      FL=FL*10.
      FS=FS*10.
      IL=IL-1
      GOTO 20
   30 IS=IL+IR
      IT=IS
      IF(VALMIN.LE.0..AND.FMAX.GE.0.) GOTO 50
   40 FL=AMOD(FL,1.)*10.
      FS=AMOD(FS,1.)*10.
      IF(IT.LE.0) GOTO 1016
      IF(INT(FL).NE.INT(FS)) GOTO 50
      IT=IT-1
      GOTO 40
   50 IFACT=0
      OFFSET=0.
      IRPRIN=MAX0(IR,0)
      ILPRIN=MAX0(IL,0)
      IF(IRPRIN+ILPRIN.LE.MAXPR) GOTO 70
      IF(IS.LE.MAXPR) GOTO 60
      IRPRIN=MAXPR-1
      IFACT=MAX0(IT,MAXPR)-1-IR
```

```
      GOTO 70
   60 IFACT=IL-1
      IRPRIN=IS-1
   70 FS=10.**(-IFACT)
      VSTEP=STEP*FS
      VMIN=VALMIN*FS
      IF(IS.LE.MAXPR) GOTO 80
      OFFSET=AINT(VMIN/10.)*10.
      VMIN=VMIN-OFFSET
   80 DO 90 I=1,NVALS
      VALS(I)=VMIN
   90 VMIN=VMIN+STEP
      FS=.1**IRPRIN
      IF(ABS(VALS(1))*FS+.5.LT.TMAX.AND.ABS(VALS(NVALS))
     1 *FS+.5.LT.TMAX) RETURN
      IL=IL+1
      IS=IS+1
      IT=IT+1
      GOTO 50
 1016 IFAULT=16
      RETURN
      END
```

A5.3.3 COMBIN

```
      SUBROUTINE COMBIN(ALPHA0,BETHA0,V0)
      IMPLICIT REAL*8 (A-H,O-Z)
      DIMENSION V0(2,2),V1(2,2),V2(2,2),V4(2,2)
      COMMON /COM1/ALPHA,BETHA,V3(2,2)
       CALL DINV(V3,V1)
       CALL DINV(V0,V2)
       V4(1,1)= V1(1,1) +V2(1,1)
       V4(2,1)= V1(2,1) +V2(2,1)
       V4(1,2)= V1(1,2) +V2(1,2)
       V4(2,2)= V1(2,2) +V2(2,2)
       CALL DINV(V4,V3)
       CALL DMULT(ALPHA,BETHA,V1,ALPHA1,BETHA1)
       CALL DMULT(ALPHA0,BETHA0,V2,ALPHA2,BETHA2)
       CALL DMULT(ALPHA1+ALPHA2,BETHA1+BETHA2,V3,ALPHA,BETHA)
      RETURN
      END
```

A5.3.4 CON

```
      SUBROUTINE CON(W,A,B,D,H,RHO)
      IMPLICIT REAL*8 (A-H,O-Z)
      COMMON /COM1/ALPHA,BETHA,V3(2,2)/COM2/R,SX,SY,C
      A=DSQRT(W*W/V3(1,1) -2.D0*R*W/SX/SY +1.D0/V3(2,2))
      B=ALPHA*W/V3(1,1) -R*(ALPHA+BETHA*W)/SX/SY +BETHA/V3(2,2)
      D=DEXP((B*B -(C*A*A))/2.D0/(1.D0-R*R)/A/A)
      H=(W*BETHA -ALPHA)/SX/SY/A
      RHO=(SX*W-R*SY)/SX/SY/A
      RETURN
      END
```

A5.3.5 CTEST

```
      SUBROUTINE CTEST(Y,K,T,H,D,IR,IN)
      IMPLICIT REAL*8 (A-H,O-Z)
      DIMENSION Y(2),D(10),IR(10),IN(10),EXP(10),PCHI(10),PT(10)
      DATA PCHI/3.841D+00,5.991D+00,7.815D+00,9.488D+00,11.070D+00,
     1    12.592D+00,14.067D+00,15.507D+00,16.919D+00,18.307D+00/
      DATA PT/12.7062D+00,4.3027D+00,3.1824D+00,2.7764D+00,2.5706D+00,
     1     2.4469D+00,2.3646D+00,2.3060D+00,2.2622D+00,2.2281D+00/
      WRITE(3,100)
      WRITE(3,200)
      IDF=K-2
      CHI=0.0D+00
      DO 10 I=1,K
```

```
      X=Y(1)+Y(2)*DLOG(D(I))
      P=FNORM(X,.FALSE.)
      Q=FNORM(X,.TRUE.)
      EXP(I)=FLOAT(IN(I))*P
      CHI=CHI+((FLOAT(IR(I))-EXP(I))**2)/(EXP(I)*Q)
   10 WRITE(3,300) D(I),IN(I),IR(I),EXP(I)
      WRITE(3,400) CHI,IDF
      H=1.00D+00
      IF(CHI.GT.PCHI(IDF)) H=CHI/FLOAT(IDF)
      T=1.96D+00
      IF(H.GT.1.00D+00) GOTO 20
      WRITE(3,500) T
      GOTO 30
   20 T=PT(IDF)
      WRITE(3,600) T
   30 CONTINUE
  100 FORMAT(/ ,5X,'FIT OF THE MODEL')
  200 FORMAT(/ ,5X,'  DOSE   NO   RESP   EXP')
  300 FORMAT(/ ,2X,F9.2,1X,I3,2X,I3,2X,F6.1)
  400 FORMAT(/ ,/5X,'CHI-VALUE = ',F5.2/5X,'D.F.      = ',I5)
  500 FORMAT(/ ,5X,'NOTE : SINCE CHI-SQUARE VALUE SMALL (P>0.05)'/13X,'
     1FIDUCIAL LIMITS CALCULATED USING A T-VALUE OF',F6.2)
  600 FORMAT(/ ,5X,'NOTE : SINCE CHI-SQUARE VALUE LARGE (P<0.05)'/13X,'
     1FIDUCIAL LIMITS CALCULATED USING A T-VALUE OF',F6.2)
      RETURN
      END
```

A5.3.6 DERIV

```
      SUBROUTINE DERIV(Y,K,D,IR,IN,D1,D2,DA,DB,V3)
      IMPLICIT REAL*8 (A-H,O-Z)
      DIMENSION Y(2),D(10),IR(10),IN(10),D1(2),D2(2,2),D3(4),V3(2,2)
      SUM1=0.0D+00
      SUM2=SUM1
      SUM3=SUM1
      SUM4=SUM1
      SUM5=SUM1
      D3(1)=SUM1
      D3(2)=SUM1
      D3(3)=SUM1
      D3(4)=SUM1
      HALF=0.5D+0
      ONE=1.0D+0
      HALF3=1.5D+0
      TWO=2.0D+0
      THREE=3.0D+0
      DO 40 I=1,K
         DX=DLOG(D(I))
         X=Y(1)+Y(2)*DX
         DR=FLOAT(IR(I))
         DNR=FLOAT(IN(I)-IR(I))
         P=FNORM(X,.FALSE.)
         Q=FNORM(X,.TRUE.)
         IF(IR(I).EQ.0) GOTO 10
         IF(IR(I).EQ.IN(I)) GOTO 20
         C1=DR/P-DNR/Q
         C2=DR/(P*P)+DNR/(Q*Q)
         C3=TWO*( DR/(P*P*P) - DNR/(Q*Q*Q) )
         GOTO 30
   10    C1=-DNR/Q
         C2=DNR/(Q*Q)
         C3=TWO*(-DNR)/(Q*Q*Q)
         GOTO 30
   20    C1=DR/P
         C2=DR/(P*P)
         C3=TWO*DR/(P*P*P)
   30    DV10=DV1(DX,X,0)
         DV11=DV1(DX,X,1)
         DV20=DV2(DX,X,0)
         DV21=DV2(DX,X,1)
         DV22=DV2(DX,X,2)
         SUM1=SUM1+C1*DV10
```

```
      SUM2=SUM2+C1*DV11
      SUM3=SUM3+C1*DV20-C2*DV10*DV10
      SUM4=SUM4+C1*DV22-C2*DV11*DV11
      SUM5=SUM5+C1*DV21-C2*DV10*DV11
      D3(1)=D3(1)+C3*DV10*DV10*DV10-THREE*C2*DV10*DV20+
     1       C1*DV3(DX,X,0)
      D3(2)=D3(2)+C3*DV10*DV10*DV11-TWO*C2*DV10*DV21-C2*DV20*DV11+
     1       C1*DV3(DX,X,1)
      D3(3)=D3(3)+C3*DV10*DV11*DV11-TWO*C2*DV11*DV21-C2*DV22*DV10+
     1       C1*DV3(DX,X,2)
      D3(4)=D3(4)+C3*DV11*DV11*DV11-THREE*C2*DV11*DV22+
     1       C1*DV3(DX,X,3)
   40 CONTINUE
      D1(1)=-SUM1
      D1(2)=-SUM2
      D2(1,1)=-SUM3
      D2(1,2)=-SUM5
      D2(2,1)=-SUM5
      D2(2,2)=-SUM4
      DET=SUM3*SUM4-(SUM5*SUM5)
      S20=-SUM4/DET
      S11=SUM5/DET
      S02=-SUM3/DET
      PR1=S20*S20
      PR2=S20*S11
      PR3=S20*S02+TWO*S11*S11
      PR4=S11*S02
      PR5=S02*S02
      DA=HALF*D3(1)*PR1+ HALF3*D3(2)*PR2+HALF*D3(3)*PR3+ HALF*D3(4)*PR4
      DB=HALF*D3(1)*PR2+ HALF*D3(2)*PR3+HALF3*D3(3)*PR4+ HALF*D3(4)*PR5
      PR6= 1+ DABS( (DA/(Y(1)+DA) +DB/(Y(2)+DB)) /4)
      V3(1,1)=S20*PR6
      V3(2,2)=S02*PR6
      V3(2,1)=S11*PR6
      V3(1,2)=V3(2,1)
      RETURN
      END
```

A5.3.7 DINV

```
      SUBROUTINE DINV(D2,V)
      IMPLICIT REAL*8 (A-H,O-Z)
      DIMENSION D2(2,2),V(2,2)
      DET=D2(1,1)*D2(2,2)-D2(1,2)*D2(2,1)
      V(1,1)=D2(2,2)/DET
      V(2,2)=D2(1,1)/DET
      V(1,2)=-D2(2,1)/DET
      V(2,1)=-D2(1,2)/DET
      RETURN
      END
```

A5.3.8 DMED

```
      SUBROUTINE DMED(DLMED)
      IMPLICIT REAL*8 (A-H,O-Z)
      COMMON /COM1/ALPHA,BETHA,V3(2,2)/COM2/R,SX,SY,C
      W=ALPHA/BETHA
   10 CALL CON(W,A,B,D,H,RHO)
      FW=BIVL(H,RHO)
      DIF=FW-0.5D0
      W1=W+0.001D0
      CALL CON(W1,A,B,D,H,RHO)
      FW1=BIVL(H,RHO)
      DER=(FW1-FW)/.001D0
      W=W-DIF/DER
      IF (DABS(DIF).GT.1.D-7) GOTO 10
      DLMED=DEXP(W)
      RETURN
      END
```

A5.3.9 DMODE

```
      SUBROUTINE DMODE(DLMOD)
      IMPLICIT REAL*8 (A-H,O-Z)
      COMMON /COM1/ALPHA,BETHA,V3(2,2)/COM2/R,SX,SY,C
      W=ALPHA/BETHA
      CALL CON(W,A,B,D,H,RHO)
      F=DLOG(DEN(A,B,D))
      W1=W+0.001D0
      CALL CON(W1,A,B,D,H,RHO)
      F1=DLOG(DEN(A,B,D))
      DER=(F1-F)/1.0D-3
      IF (DABS(DER).LT.0.1D0) GOTO 20
      STEP=0.001D0
      ISIGN0=1
      IF (DER.GT.0.0D0) GOTO 10
      ISIGN0=-1
      STEP=-0.001D0
      W=W+STEP
      CALL CON(W,A,B,D,H,RHO)
      F=DLOG(DEN(A,B,D))
   10 W1=W+STEP
      CALL CON(W1,A,B,D,H,RHO)
      F1=DLOG(DEN(A,B,D))
      DER=(F1-F)/STEP
      IF (DABS(DER).LT.0.1D0) GOTO 40
      ISIGN=1
      IF(DER.GT.0.0D0) GOTO 20
      ISIGN=-1
   20 IF (ISIGN0.EQ.ISIGN) GOTO 30
      STEP=-STEP/2.0D0
   30 ISIGN0=ISIGN
      W=W1
      F=F1
      GOTO 10
   40 CALL CON(W,A,B,D,H,RHO)
      F=DLOG(DEN(A,B,D))
      W1=W+0.001D0
      CALL CON(W1,A,B,D,H,RHO)
      F1=DLOG(DEN(A,B,D))
      W2=W+0.002D0
      CALL CON(W2,A,B,D,H,RHO)
      F2=DLOG(DEN(A,B,D))
      DER1=(F1-F)/1.0D-3
      DER2=(F+F2-2.0D0*F1)/1.0D-6
      W=W-DER1/DER2
      IF(DABS(DER1).GT.1.D-7) GOTO 40
      DLMOD=DEXP(W)
      RETURN
      END
```

A5.3.10 DMULT

```
      SUBROUTINE DMULT(B1,B2,A,C1,C2)
      IMPLICIT REAL*8 (A-H,O-Z)
      DIMENSION A(2,2)
       C1= A(1,1)*B1 +A(1,2)*B2
       C2= A(2,1)*B1 +A(2,2)*B2
      RETURN
      END
```

A5.3.11 ESTIM

```
      SUBROUTINE ESTIM(XMIN,K,D,IR,IN)
      IMPLICIT REAL*8 (A-H,O-Z)
      DIMENSION D(10),IR(10),IN(10),X(10),PI(10),XMIN(2)
      SUMD=0.0D+00
      SUMP=SUMD
      DIG=0.0D+00
      DO 10 I=1,K
         IF(IR(I).EQ.0.OR.IR(I).EQ.IN(I)) GOTO 10
         X(I)=DLOG(D(I))
```

```
      P1=DFLOAT(IR(I))/DFLOAT(IN(I))
      PI(I)=PROBIT(P1)
      SUMD=SUMD+X(I)
    SUMP=SUMP+PI(I)
    DIG=DIG+1.0D+00
 10 CONTINUE
    SUMX=0.0D+00
    SUMXY=0.0D+00
    DO 20 I=1,K
      IF(IR(I).EQ.0.OR.IR(I).EQ.IN(I)) GOTO 20
      SUMX=SUMX+(X(I)-SUMD/DIG)**2
    SUMXY=SUMXY+(X(I)-SUMD/DIG)*(PI(I)-SUMP/DIG)
 20 CONTINUE
    XMIN(2)=SUMXY/SUMX
    XMIN(1)=(SUMP/DIG)-XMIN(2)*SUMD/DIG
    RETURN
    END
```

A5.3.12 FIDUC

```
    SUBROUTINE FIDUC(Y,V,T,H,D,DL,DU,IED)
    IMPLICIT REAL*8 (A-H,O-Z)
    DIMENSION Y(2),V(2,2)
    DO 10 I=1,2
    DO 10 J=1,2
 10 V(I,J)=V(I,J)*H
    DM=(PROBIT(FLOAT(IED)/100.0D0)-Y(1))/Y(2)
    G=T*T*V(2,2)/(Y(2)**2)
    TERM1=V(1,1)+2.D+00*DM*V(1,2)+DM*DM*V(2,2)-
   1     G*(V(1,1)-V(1,2)*V(1,2)/V(2,2))
    DL=-999.0D0
    D=DEXP(DM)
    IF(TERM1.LT.0.0D0.OR.G.GT.1.0D0) RETURN
    TERM1=DSQRT(TERM1)*T/(Y(2)*(1.D+00-G))
    TERM2=G*(DM+V(1,2)/V(2,2))/(1.D+00-G)
    DML=DM+TERM2-TERM1
    DMU=DM+TERM2+TERM1
    DL=DEXP(DML)
    DU=DEXP(DMU)
    RETURN
    END
```

A5.3.13 HPD

```
    SUBROUTINE HPD(TLIM,NR,IED)
    IMPLICIT REAL*8 (A-H,O-Z)
    CHARACTER*50 CH
    DIMENSION TLIM(NR),PROB(10),CLASS(10),PLOT(161,3)
    COMMON //PBO,STD/COM1/ALPHA,BETHA,V3(2,2)/COM2/R,SX,SY,C
    COMMON /COM3/X,TK
    COMMON /COM4/WS,IOT
    COMMON /COMFIL/IOUT
    ALPHA0=ALPHA
    ALPHA=PROBIT(FLOAT(IED)/100.0D0)-ALPHA
    TWO= 2.DO
    IOT=0
    SX=  DSQRT(V3(2,2))
    SY=  DSQRT(V3(1,1))
    R=   -V3(1,2)/SX/SY
    X=   BETHA/SX
    PBO= FNORM(X,.FALSE.)
    TK=  TFN(X,(BETHA*R*SY -SX*ALPHA) /BETHA/SY/DSQRT(1-R*R))
    C=   ALPHA*ALPHA/V3(1,1) -TWO*R*BETHA*ALPHA/SX/SY+BETHA*BETHA/
   1      V3(2,2)
    STD= DSQRT(V3(1,1) +TWO*ALPHA*V3(1,2)/BETHA +V3(2,2)*ALPHA*ALPHA/
   1   BETHA/BETHA) /BETHA
    WO=  ALPHA/BETHA -1.96D0*STD
    CALL OT(WO,F00,W1,F01)
    WS=W1
    IOT=1
 10 CALL OT(WO+1.D-3,DMY1,W11,DMY2)
```

```
      FX2=F00* ((W11-W1)/1.D-3 -1)
      CALL CON(W0,DUMMY1,DUMMY2,DUMMY3,H,RHO)
      FX1=-BIVL(H,RHO)
      CALL CON(W1,DUMMY1,DUMMY2,DUMMY3,H,RHO)
      FX1=FX1+BIVL(H,RHO)-.95D0
      DEL=FX1/FX2
      IF (DABS(DEL).LT.1D-7) GOTO 30
      DEL=DEL*TWO
   20 DEL=DEL/TWO
      W2=W0-DEL
      IF (W2.GT.ALPHA/BETHA) GOTO 20
      CALL OT(W2,F00,W3,DUMMY2)
      WS=W3
      CALL CON(W2,DUMMY1,DUMMY2,DUMMY3,H,RHO)
      FX3=-BIVL(H,RHO)
      CALL CON(W3,DUMMY1,DUMMY2,DUMMY3,H,RHO)
      FX3=FX3+BIVL(H,RHO)-.95D0
      IF (DABS(FX3).GE.DABS(FX1)) GOTO 20
      W0=W2
      W1=W3
      GOTO 10
   30 CALL DMED(DLMED)
      CALL DMODE(DLMOD)
      WRITE(3,100) IED,DLMED,IED,DLMOD
      W0=DEXP(W0)
      W1=DEXP(W1)
      WRITE(3,200) IED,W0,W1
      IF(IED.NE.50) GOTO 95
      DO 40 I=1,NR
         CALL CON(DLOG(TLIM(I)),DUMMY1,DUMMY2,DUMMY3,H,RHO)
   40 PROB(I)=BIVL(H,RHO)
      WRITE(3,300)
      CLASS(1)=PROB(1)
      WRITE(3,400) 1,TLIM(1),CLASS(1)
      DO 50 I=2,NR
         CLASS(I)=PROB(I)-PROB(I-1)
   50 WRITE(3,500) I,TLIM(I-1),TLIM(I),CLASS(I)
      CLASS(NR+1)=1-PROB(NR)
      TOTAL= 0
      DO 60 I=1,NR+1
   60 TOTAL=TOTAL+CLASS(I)
      WRITE(3,600) TLIM(NR),CLASS(NR+1),TOTAL
      WRITE(3,700)
      DO 80 I=1,NR
         CH= ' '
         DO 70 J=1,IDNINT(CLASS(I)*50.D0)
   70    CH(J:J)= '+'
   80 WRITE(3,800) I,CH
      CH= ' '
      DO 90 I=1,IDNINT(CLASS(NR+1)*50.D0)
   90    CH(I:I)= '+'
      WRITE(3,900) CH
   95 W=ALPHA/BETHA -4.D0*STD
      WU=ALPHA/BETHA +4.D0*STD
      IPLOT=0
  105 CALL CON(W,A,B,D,H,RHO)
      IPLOT=IPLOT+1
      F=DEN(A,B,D)
      FW=BIVL(H,RHO)
      PLOT(IPLOT,1)=W
      PLOT(IPLOT,2)=F
      PLOT(IPLOT,3)=FW
      IF(IOUT.EQ.1) WRITE(8,1000) W,F,FW
      W=W+ STD/20.D0
      IF (W.LE.WU) GOTO 105
      CALL SPLOT(PLOT,IED)
      ALPHA=ALPHA0
  100 FORMAT(// ,5X,'POSTERIOR MEDIAN FOR ED',I2//5X,F15.4//5X,
     1             'POSTERIOR MODE FOR ED',I2//5X,F15.4//)
  200 FORMAT(/ ,5X,'95% H.P.D. LIMITS FOR ED',I2//2(5X,F15.4)//)
  300 FORMAT('^L',/7X,47('-')/7X,'|  PROBABILITY OF TOXICITY CLASSES',
     112X,'|'//7X,'|',5X,'CLASS',22X,'PROBABILITY  |')
```

```
  400 FORMAT(/ ,7X,'|',3X,I1,' :          < ',F7.1,8X,F10.8,3X,'|')
  500 FORMAT(/ ,7X,'|',3X,I1,' : ',F7.1,' - ',F7.1,8X,F10.8,3X,'|')
  600 FORMAT(/ ,7X,'|',15X,'> ',F7.1,8X,F10.8,3X,'|'/39X,
     1     12('  ')/7X,'|',45X,'|'/33X,'TOTAL: ',F10.8/7X,47('-')/)
  700 FORMAT(//, 9X,'0.0-------0.2-------0.4-------0.6-------0.8-------
     11.0')
  800 FORMAT(/  , 7X,I1,' : ',A50)
  900 FORMAT(/  , 7X,'> : ',A50)
 1000 FORMAT(5X,F15.10,5X,F15.10,12X,F15.10)
      RETURN
      END
```

A5.3.14 OT

```
      SUBROUTINE OT(W,F00,U2,F)
      IMPLICIT REAL*8(A-H,O-Z)
      COMMON //PB0,STD/COM1/ALPHA,BETHA,V3(2,2)/COM2/R,SX,SY,C
      COMMON /COM4/WS,IOT
      STEP=STD/10.0D0
      ST=1.0D0
      CALL CON(W,A,B,D,DUMMY1,DUMMY2)
      F00=DEN(A,B,D)
      U0=W+STEP
      IF(IOT.GT.0) U0=WS
      CALL CON(U0,A,B,D,DUMMY1,DUMMY2)
      F0=DEN(A,B,D)
      IF(F0.LT.F00) ST=-1.0D0
   10 U0=U0+STEP*ST
      CALL CON(U0,A,B,D,DUMMY1,DUMMY2)
      F0=DEN(A,B,D)
      IF (ST*(F0-F00).GT.0.0D0) GOTO 10
      U1=U0
      U0=U0-STEP*ST
      F1=F0
      CALL CON(U0,A,B,D,DUMMY1,DUMMY2)
      F0=DEN(A,B,D)
   20 U2=(U0*(F1-F00) -U1*(F0-F00))/(F1-F0)
      CALL CON(U2,A,B,D,DUMMY1,DUMMY2)
      F=DEN(A,B,D)
      IF (DABS((F-F00)/F00).LT.1.D-8) RETURN
      IF (F.LT.F00) GOTO 30
      U0=U2
      F0=F
      GOTO 20
   30 U1=U2
      F1=F
      GOTO 20
   40 RETURN
      END
```

A5.3.15 SCALE

```
      SUBROUTINE SCALE(FMN,FMX,N,MPV,VALMIN,STEP,NVALS,IR,IFAULT)
      REAL UNIT(12),TOL,BIAS
      DATA NUNIT/12/
      DATA UNIT(1),UNIT(2),UNIT(3),UNIT(4),UNIT(5),UNIT(6),
     1 UNIT(7),UNIT(8),UNIT(9),UNIT(10),UNIT(11),UNIT(12)/
     2 12.,15.,20.,25.,30.,40.,50.,60.,80.,100.,120.,150./
      DATA TOL/5.E-6/,BIAS/1.E-5/,MINN/2/,MAXN/10000/,COVER/.7/
      FMAX=FMX
      FMIN=FMN
      IFAULT=0
      IF(FMAX.LT.FMIN) IFAULT=IFAULT+1
      IF(N.LT.MINN.OR.N.GT.MAXN) IFAULT=IFAULT+2
      IF(MPV.LE.0.OR.MPV.GE.N) IFAULT=IFAULT+4
      IF(IFAULT.NE.0) RETURN
      NVALS=(N-1)/MPV+1
      IF(FMAX-FMIN.GT.TOL*AMAX1(ABS(FMAX),ABS(FMIN))) GOTO 40
      IFAULT=-1
```

```
      IF(FMAX)10,20,30
   10 FMAX=0.0
      GOTO 40
   20 FMAX=1.0
      GOTO 40
   30 FMIN=0.0
   40 FINTER=FLOAT(N)/FLOAT(MPV)
      S=(FMAX-FMIN)*(1.+2.*BIAS)/FINTER
      IR=0
   50 IF(S.GT.10.) GOTO 60
      S=S*10.
      IR=IR+1
      GOTO 50
   60 IF(S.LE.100.) GOTO 70
      S=S/10.
      IR=IR-1
      GOTO 60
   70 DO 80 I=1,NUNIT
         IF(S.LE.UNIT(I)) GOTO 90
   80 CONTINUE
   90 STEP=10.**(-IR)*UNIT(I)
      AJ=0.
  100 AJ=AJ+1.
      IF(UNIT(I)-.1.GT.AINT((UNIT(I)+.1)/AJ)*AJ) GOTO 100
      TSTEP=STEP/AJ
      TEMP=FMIN/TSTEP+AJ*(.5/FLOAT(MPV)-FINTER*BIAS)
      VALMIN=AINT(TEMP)*TSTEP
      IF(TEMP.LT.0..AND.TEMP.NE.AINT(TEMP)) VALMIN=VALMIN-TSTEP
      IF(FMAX.LT.VALMIN+STEP*(FINTER*(1.-BIAS)-.5/FLOAT(MPV))) GOTO 110
      IF(UNIT(I)/UNIT(I+1)*(1.-1./(AJ*FINTER)).LT.COVER) GOTO 100
      I=I+1
      GOTO 90
  110 DO 120 J=1,2
         AJ=AJ*10.
         IF(UNIT(I)-.1.LT.AINT((UNIT(I)+.1)/AJ)*AJ) IR=IR-1
  120 CONTINUE
      RETURN
      END
```

A5.3.16 SCATPL

```
      SUBROUTINE SCATPL(A,N,M,ICY,NCY,ICX,NY,NX,SCALEY,SCALEX,ISTAND,
     1 IFAULT)
      DIMENSION IOUT(161),VALS(20),A(N,M),ICY(NCY),SCALEX(2),
     2 SCALEY(2),INTCH(11),MARKCH(5),IFORM1(19),IFORM2(20)
      DATA IWRITE/3/,MAXWID/132/,MAXHT/62/,MAXY/5/,MPVX/10/,MPVY/5/
      DATA INTCH(1),INTCH(2),INTCH(3),INTCH(4),INTCH(5),INTCH(6),
     1 INTCH(7),INTCH(8),INTCH(9),INTCH(10),INTCH(11)
     2 /1H0,1H1,1H2,1H3,1H4,1H5,1H6,1H7,1H8,1H9,1H9/
      DATA MARKCH(1),MARKCH(2),MARKCH(3),MARKCH(4),MARKCH(5)
     1 /1H*,1H0,1H+,1HX,1H-/
      DATA IBLANK/1H /,IDOT/1H./,ICOLON/1H:/,ICOMMA/1H,/,IAPOST/1H'/,
     1 ISEMI/1H;/,ITWO/1H2/,IDASH/1H-/
      DATA IFORM1(1),IFORM1(2),IFORM1(3),IFORM1(4),IFORM1(5),
     1     IFORM1(6),IFORM1(7),IFORM1(8),IFORM1(9),IFORM1(10),
     2     IFORM1(11),IFORM1(12),IFORM1(13),IFORM1(14),IFORM1(15),
     3     IFORM1(16),IFORM1(17),IFORM1(18),IFORM1(19)
     4 /1H(,1H1,1HH,1H ,1H,,1HF,1H8,1H.,1H0,1H,,1H1,1HX,1H,,1H1,1H5,1H2,
     5 1HA,1H1,1H)/
      DATA IFORM2(1),IFORM2(2),IFORM2(3),IFORM2(4),IFORM2(5),
     1     IFORM2(6),IFORM2(7),IFORM2(8),IFORM2(9),IFORM2(10),
     2     IFORM2(11),IFORM2(12),IFORM2(13),IFORM2(14),IFORM2(15),
     3     IFORM2(16),IFORM2(17),IFORM2(18),IFORM2(19),IFORM2(20)
     4 /1H(,1H1,1HH,1H ,1H,,1H5,1HX,1H,,1H1,1H6,1H(,1HF,1H8,1H.,1H0,1H,,
     5 1H2,1HX,1H),1H)/
    1 FORMAT(1H ,10X, 1H:, 151A1)
    2 FORMAT(11H TIMES 10**, I3)
    3 FORMAT(7H OFFSET,F10.0)
    4 FORMAT(1H ,14X,10HTIMES 10**,I3)
    5 FORMAT(1H ,14X,6HOFFSET,F10.0)
```

```
  6 FORMAT(1H ,2X,16(9X,A1))
    IFAULT=0
    IF(N.LT.1) IFAULT=IFAULT+1
    IF(M.LT.2) IFAULT=IFAULT+2
    IF(ICX.LT.1.OR.ICX.GT.M) IFAULT=IFAULT+4
    IF(NCY.LE.0.OR.NCY.GT.MAXY) IFAULT=IFAULT+8
    IF(IFAULT.GT.0) RETURN
    DO 10 I=1,NCY
    IF(ICY(I).LT.1.OR.ICY(I).GT.M) GOTO 1016
 10 CONTINUE
    NLY=MAXHT-5
    IF(NLY.GT.NY) NLY=NY
    IF(NLY.LE.MPVY) NLY=MPVY+1
    NLX=MAXWID-11
    IF(NLX.GT.NX) NLX=NX
    IF(NLX.LE.MPVX) NLX=MPVX+1
    XMIN=SCALEX(1)
    XMAX=SCALEX(2)
    IF(XMAX.GE.XMIN) GOTO 30
    XMIN=A(1,ICX)
    XMAX=XMIN
    IF(N.EQ.1) GOTO 30
    DO 20 I=2,N
    AI=A(I,ICX)
    IF(AI.LT.XMIN) XMIN=AI
 20 IF(AI.GT.XMAX) XMAX=AI
 30 CALL SCALE(XMIN,XMAX,NLX,MPVX,TEMP,XVSTEP,NXVALS,IRX,IFAIL)
    IF(IFAIL.GT.0) GOTO 1032
    XMIN=TEMP
    XSTEP=XVSTEP/FLOAT(MPVX)
    YMIN=SCALEY(1)
    YMAX=SCALEY(2)
    IF(YMAX.GE.YMIN) GOTO 50
    K=ICY(1)
    YMIN=A(1,K)
    YMAX=YMIN
    DO 40 J=1,NCY
    K=ICY(J)
    DO 40 I=1,N
    AI=A(I,K)
    IF(AI.LT.YMIN) YMIN=AI
 40 IF(AI.GT.YMAX) YMAX=AI
 50 CALL SCALE(YMIN,YMAX,NLY,MPVY,TEMP,YVSTEP,NYVALS,IRY,IFAIL)
    IF(IFAIL.GT.0) GOTO 1064
    YMIN=TEMP
    YSTEP=YVSTEP/FLOAT(MPVY)
    CALL AXIS(YMIN,YVSTEP,NYVALS,6,IRY,IRPR,OFFSET,IFACT,VALS,
   1 20,IFAIL)
    IF(IFAIL.GT.0) GOTO 1064
    IFORM1(9)=INTCH(IRPR+1)
    IF(IFACT.NE.0) WRITE(IWRITE,2) IFACT
    IF(OFFSET.NE.0.) WRITE(IWRITE,3) OFFSET
    IF(ISTAND.EQ.0) INTCH(3)=ISEMI
    IPLTED=0
    DO 140 I=1,NLY
    IY=NLY-I
    DO 60 IX=1,NLX
 60 IOUT(IX)=IBLANK
    DO 120 L=1,N
    INDX=(A(L,ICX)-XMIN)/XSTEP+1.5
    IF(INDX.LT.1.OR.INDX.GT.NLX) GOTO 120
    DO 110 J=1,NCY
    K=ICY(J)
    Y=(A(L,K)-YMIN)/YSTEP
    INDY=Y+0.5
    IF(INDY.NE.IY) GOTO 110
```

```
      IPLTED=IPLTED+1
      IF(IOUT(INDX).NE.IBLANK) GOTO 80
      IF(ISTAND.EQ.0) GOTO 70
      IOUT(INDX)=MARKCH(J)
      GOTO 110
   70 IOUT(INDX)=ICOMMA
      IF(INT(Y).EQ.IY) IOUT(INDX)=IAPOST
      GOTO 110
   80 DO 90 IC=3,10
   90 IF(IOUT(INDX).EQ.INTCH(IC)) GOTO 100
      IC=2
  100 IOUT(INDX)=INTCH(IC+1)
  110 CONTINUE
  120 CONTINUE
      IF(MOD(IY,MPVY).EQ.0) GOTO 130
      WRITE(IWRITE,1) (IOUT(IX),IX=1,NLX)
      GOTO 140
  130 WRITE(IWRITE,IFORM1) VALS(NYVALS),IDASH,ICOLON,
     1 (IOUT(IX),IX=1,NLX)
      NYVALS=NYVALS-1
  140 CONTINUE
      WRITE(IWRITE,1) (IDOT,I=1,NLX)
      CALL AXIS(XMIN,XVSTEP,NXVALS,6,IRX,IRPR,OFFSET,IFACT,VALS,
     1 20,IFAIL)
      INTCH(3)=ITWO
      IFORM2(15)=INTCH(IRPR+1)
      IF(IFAIL.GT.0) GOTO 1032
      WRITE(IWRITE,6) (ICOLON,I=1,NXVALS)
      WRITE(IWRITE,IFORM2) (VALS(I),I=1,NXVALS)
      IF(IFACT.NE.0) WRITE(IWRITE,4) IFACT
      IF(OFFSET.NE.0.0) WRITE(IWRITE,5) OFFSET
      IFAULT=IPLTED-N*NCY
      RETURN
 1064 IFAULT=IFAULT+32
 1032 IFAULT=IFAULT+16
 1016 IFAULT=IFAULT+16
      RETURN
      END
```

A5.3.17 SCORE

```
      SUBROUTINE SCORE(XMIN,K,D,IR,IN,V,DLOGLO,DA,DB,V3)
      IMPLICIT REAL*8 (A-H,O-Z)
      DIMENSION XMIN(2),D(10),IR(10),IN(10),D1(2),D2(2,2),DEL(2),V(2,2)
      DIMENSION V3(2,2)
   10 CALL DERIV(XMIN,K,D,IR,IN,D1,D2,DA,DB,V3)
      CALL DINV(D2,V)
      DDMAX=DMAX1(DABS(D1(1)),DABS(D1(2)))
      IF(DDMAX.LT.1.D-10) GOTO 30
      DEL(1)=V(1,1)*D1(1)+V(1,2)*D1(2)
      DEL(2)=V(2,1)*D1(1)+V(2,2)*D1(2)
      DO 20 I=1,2
   20 XMIN(I)=XMIN(I)-DEL(I)
      GOTO 10
   30 DLOGLO=-FN(XMIN,K,D,IR,IN)
      RETURN
      END
```

A5.3.18 SHOW

```
      SUBROUTINE SHOW(A,B,V)
      IMPLICIT REAL*8 (A-H,O-Z)
      DIMENSION V(2,2)
      WRITE(3,100)
      WRITE(3,200)
      WRITE(3,300) A,B
      WRITE(3,400)
      WRITE(3,200)
      WRITE(3,500) V(1,1),V(1,2),V(2,1),V(2,2)
```

```
100 FORMAT(/ ,5X,'PARAMETER ESTIMATES')
200 FORMAT(/ ,14X,'   ALPHA  ','   BETA   ')
300 FORMAT(/ ,13X,2F10.4)
400 FORMAT(/ ,5X,'COVARIANCE MATRIX OF PARAMETER ESTIMATES')
500 FORMAT(/ ,5X,'ALPHA   ',2F10.4/6X,'BETA   ',2F10.4/)
    RETURN
    END
```

A5.3.19 SHOW1

```
    SUBROUTINE SHOW1(A,B,V)
    IMPLICIT REAL*8 (A-H,O-Z)
    DIMENSION V(2,2)
    WRITE(3,100)
    WRITE(3,200)
    WRITE(3,300) A,B
    WRITE(3,400)
    WRITE(3,200)
    WRITE(3,500) V(1,1),V(1,2),V(2,1),V(2,2)
100 FORMAT(/ ,5X,'POSTERIOR EXPECTAIONS (UNINFORMATIVE PRIOR)')
200 FORMAT(/ ,14X,'   ALPHA  ','   BETA   ')
300 FORMAT(/ ,13X,2F10.4)
400 FORMAT(/ ,5X,'POSTERIOR COVARIANCE MATRIX (UNINFORMATIVE PRIOR)')
500 FORMAT(/ ,5X,'ALPHA   ',2F10.4/6X,'BETA   ',2F10.4/)
    RETURN
    END
```

A5.3.20 SHOW2

```
    SUBROUTINE SHOW1(A,B,V)
    IMPLICIT REAL*8 (A-H,O-Z)
    DIMENSION V(2,2)
    WRITE(3,100)
    WRITE(3,200)
    WRITE(3,300) A,B
    WRITE(3,400)
    WRITE(3,200)
    WRITE(3,500) V(1,1),V(1,2),V(2,1),V(2,2)
100 FORMAT(/ ,5X,'POSTERIOR EXPECTAIONS (UNINFORMATIVE PRIOR)')
200 FORMAT(/ ,14X,'   ALPHA  ','   BETA   ')
300 FORMAT(/ ,13X,2F10.4)
400 FORMAT(/ ,5X,'POSTERIOR COVARIANCE MATRIX (UNINFORMATIVE PRIOR)')
500 FORMAT(/ ,5X,'ALPHA   ',2F10.4/6X,'BETA   ',2F10.4/)
    RETURN
    END
```

A5.3.21 SHOW3

```
    SUBROUTINE SHOW3(A,B,V)
    IMPLICIT REAL*8 (A-H,O-Z)
    DIMENSION V(2,2)
    WRITE(3,100)
    WRITE(3,200)
    WRITE(3,300) A,B
    WRITE(3,400)
    WRITE(3,200)
    WRITE(3,500) V(1,1),V(1,2),V(2,1),V(2,2)
100 FORMAT(/ ,5X,'POSTERIOR EXPECTAIONS (INFORMATIVE PRIOR)')
200 FORMAT(/ ,14X,'   ALPHA  ','   BETA   ')
300 FORMAT(/ ,13X,2F10.4)
400 FORMAT(/ ,5X,'POSTERIOR COVARIANCE MATRIX (INFORMATIVE PRIOR)')
500 FORMAT(/ ,5X,'ALPHA   ',2F10.4/6X,'BETA   ',2F10.4/)
    RETURN
    END
```

A5.3.22 SPLOT

```
    SUBROUTINE SPLOT(PLOT,IED)
    REAL*8 PLOT(161,3)
    DIMENSION A(161,3),ICY(2),SCALEY(2),SCALEX(2)
    N=161
    M=3
    DO 10 I=1,N
```

```
      DO 10 J=1,M
   10 A(I,J)=PLOT(I,J)
      ICY(1)=2
      NCY=1
      ICX=1
      NY=35
      NX=95
      SCALEX(1)=2.
      SCALEX(2)=1.
      SCALEY(1)=2.
      SCALEY(2)=1
      ISTAND=0
      WRITE(3,100) IED
      CALL SCATPL(A,N,M,ICY,NCY,ICX,NY,NX,SCALEY,SCALEX,ISTAND,IFAULT)
      WRITE(3,300) IED
      ICY(1)=3
      SCALEY(1)=0.
      SCALEY(2)=1.
      WRITE(3,200) IED
      CALL SCATPL(A,N,M,ICY,NCY,ICX,NY,NX,SCALEY,SCALEX,ISTAND,IFAULT)
      WRITE(3,300) IED
  100 FORMAT('^L',5X,'POSTERIOR DENSITY OF LOG(ED',I2,')'/)
  200 FORMAT('^L',5X,'CUMULATIVE POSTERIOR DISTRIBUTION OF LOG(ED',I2,
     1 ')'/)
  300 FORMAT(// ,30X,'LOG(ED',I2,')')
      RETURN
      END
```

A5.3.23 BIVL

```
      FUNCTION BIVL(H,RHO)
      IMPLICIT REAL*8 (A-H,O-Z)
      COMMON //PBO,STD/COM3/X,TK
      ROOT=DSQRT(1-RHO*RHO)
      AH=X/H/ROOT -RHO/ROOT
      IF (DABS(H).GE.1.D-10) THEN
      BIVL=(FNORM(H,.FALSE.)+PBO)/2.DO -TFN(H,AH)-TK
      IF (H*X.LT.0.DO) BIVL=BIVL-.5DO
      ELSE
      BIVL= PBO/2.DO -TK
      END IF
      BIVL=BIVL/PBO
      RETURN
      END
```

A5.3.24 DEN

```
      FUNCTION DEN(A,B,D)
      IMPLICIT REAL*8(A-H,O-Z)
      COMMON //PBO,STD/COM2/R,SX,SY,C
      PI2=4.DO*DACOS(0.DO)
      PR=1.DO-R*R
      F=B*D*FNORM(B/A/DSQRT(PR),.FALSE.) /DSQRT(PI2)/SX/SY/A/A/A
      DEN=(F +DSQRT(PR)*DEXP(-C/2.DO/PR) /PI2/SX/SY/A/A) /PBO
      RETURN
      END
```

A5.3.25 DV1

```
      FUNCTION DV1(D,X,IE)
      IMPLICIT REAL*8(A-H,O-Z)
      DATA PI2/.398942280444D+00/
      DIE=1.0D+00
      IF(IE.EQ.1) DIE=D
      DV1=DIE*PI2*DEXP(-X*X/2.00D+00)
      RETURN
      END
```

A5.3.26 DV2

```
      FUNCTION DV2(D,X,IE)
      IMPLICIT REAL*8 (A-H,O-Z)
      DATA PI2/.398942280444D+00/
      DIE=1.0D+00
      IF(IE.EQ.1) DIE=D
      IF(IE.EQ.2) DIE=D*D
      DV2=-DIE*PI2*X*DEXP(-X*X/2.0D+00)
      RETURN
      END
```

A5.3.27 DV3

```
      FUNCTION DV3(D,X,IE)
      IMPLICIT REAL*8 (A-H,O-Z)
      DIE=1.D0
      IF (IE.EQ.1) DIE=D
      IF (IE.EQ.2) DIE=D*D
      IF (IE.EQ.3) DIE=D*D*D
      DV3=DIE*0.398942280444D0*DEXP(-X*X/2.D0)*(X*X-1.D0)
      RETURN
      END
```

A5.3.28 FN

```
      FUNCTION FN(Y,K,D,IR,IN)
      IMPLICIT REAL*8 (A-H,O-Z)
      DIMENSION Y(2),IR(10),IN(10),D(10)
      SUM=0.0D+00
      DO 10 I=1,K
         X=Y(1)+Y(2)*DLOG(D(I))
         X1=FLOAT(IR(I))*DLOG(FNORM(X,.FALSE.))
         X2=FLOAT(IN(I)-IR(I))*DLOG(FNORM(X,.TRUE.))
         SUM=SUM-X1-X2
   10 CONTINUE
      FN=SUM
      RETURN
      END
```

A5.3.29 FNORM

```
      FUNCTION FNORM(X,UPPER)
      IMPLICIT REAL*8 (A-H,O-Z)
      LOGICAL UPPER,UP
      LTONE=7.0D+00
      UTZERO=18.66D+00
      UP=UPPER
      Z=X
      IF(Z.GE.0.0D+00) GOTO 10
      UP=.NOT.UP
      Z=-Z
   10 IF(Z.LE.LTONE.OR.UP.AND.Z.LE.UTZERO) GOTO 20
      FNORM=0.0D+00
      GOTO 40
   20 Y=0.5D+00*Z*Z
      IF(Z.GT.1.28D+00) GOTO 30
      FNORM=0.5D+00-Z*(0.398942280444D+00-0.399903438504D+00*Y/
     1  (Y+ 5.75885480458D+00-29.8213557808D+00/
     2  (Y+ 2.62433121679D+00+48.6959930692D+00/
     3  (Y+ 5.92885724438D+00))))
      GOTO 40
   30 FNORM=0.398942280385D+00*DEXP(-Y)/
     1  (Z-3.8052D-08+1.00000615302D+00/
     2  (Z+3.98064794D-04+1.98615381364D+00/
     3  (Z-0.151679116635D+00+5.29330324926D+00/
     4  (Z+4.8385912808D+00-15.1508972451D+00/
     5  (Z+0.742380924027D+00+30.789933034D+00/
     6  (Z+3.99019417011D+00))))))
```

```
 40 IF(.NOT.UP) FNORM=1.0D+00-FNORM
    RETURN
    END
```

A5.3.30 PROBIT

```
    FUNCTION PROBIT(P)
    IMPLICIT REAL*8 (A-H,O-Z)
    P0= -0.322232431088D+00
    P1= -1.0D+00
    P2= -0.3422432088547D+00
    P3= -0.204231210245D-01
    P4= -0.453642210148D-04
    Q0= 0.99348462606D-01
    Q1= 0.588581570495D+00
    Q2= 0.531103462366D+00
    Q3= 0.10353775285D+00
    Q4= 0.3856070063D-02
    PROBIT= 0.0D+00
    PS= P
    IF(PS.GT.0.5D+00) PS= 1.0D+00-PS
    IF(PS.EQ.0.5D+00) RETURN
    YI= DSQRT(DLOG(1.0D+00/(PS*PS)))
    PROBIT= YI+((((YI*P4+P3)*YI+P2)*YI+P1)*YI+P0)
   1          /((((YI*Q4+Q3)*YI+Q2)*YI+Q1)*YI+Q0)
    IF(P.LT.0.5D+00) PROBIT= -PROBIT
    RETURN
    END
```

A5.3.31 TFN

```
    FUNCTION TFN(HI,AI)
    IMPLICIT REAL*8 (A-H,O-Z)
    DATA G1/.1591549431D0/
    H=DABS(HI)
    A=DABS(AI)
    EPS=1.D-6
    TFN=0.D0
    IF (A.EQ.0.D0) RETURN
    ATA=DATAN(A)
    IF (H*A.LE.4.D0) GOTO 10
    TFN=G1*(ATA+DATAN(1.D0/A)) -.5D0*(FNORM(H,.FALSE.)-.5D0)
    GOTO 50
 10 HSQ2=.5D0*H*H
    EXPH2=DEXP(-HSQ2)
    ASQ=A*A
    A4=ASQ*ASQ
    H4=HSQ2*HSQ2
    A4H4=A4*H4
    BBJ=A*HSQ2
    BJ=A*H4*.5D0
    FJ=1.D0
    DJ=3.D0
    SUM=0.D0
 20 EJ=DJ
    SER=0.D0
    TERM=BJ
 30 SER=SER+TERM
    IF (TERM.LE.SER*EPS) GOTO 40
    TERM=TERM*HSQ2/EJ
    EJ=EJ+1.D0
    GOTO 30
 40 CONTR1=(SER+BBJ)/FJ
    CONTR2=SER*ASQ/(FJ+2.D0)
    CONTR=CONTR1-CONTR2
    SUM=SUM+CONTR
    TFN=ATA-SUM*EXPH2
    EPSA=EPS*TFN
    BBJ=BBJ*A4H4/DJ/(DJ-1.D0)
    BJ=BJ*A4H4/DJ/(DJ+1.D0)
    FJ=FJ+4.D0
```

```
      DJ=DJ+2.D0
      IF (CONTR2*EXPH2.GE.EPSA) GOTO 20
      TFN=TFN*G1
   50 IF (AI.LT.0.D0) TFN=-TFN
      RETURN
      END
```

A5.4 Input.

CARD	1	:	TITLE (upto 80 characters)
CARD	2	:	ILOOP
CARD	3	:	IED , K , CLASS , PRIOR
CARD	4	:	NR
CARD	5	:	TLIM(1) , TLIM(2) , . . . , TLIM(NR)
CARD	6	:	ALPHA0 , BETA0 , V0(1,1) , V0(1,2) , V0(2,1) , V0(2,2)
CARD	7	:	D(1) , IN(1) , IR(1)
CARD	8	:	D(2) , IN(2) , IR(2)
	.		
	.		
	.		
CARD	K+6	:	D(K) , IN(K) , IR(K)

Cards 4-6 are optional. Cards 4 and 5 are only necessary if CLASS = .TRUE.; Card 6 is only necessary if PRIOR = .TRUE. Cards 2 - (K + 6) should be repeated ILOOP times for each data set.

A5.5 Examples.

A5.5.1 Input for Examples.

```
3
EXAMPLE FROM GRIEVE(1988b) - UNINFORMATIVE PRIOR - ED50
50 4 .TRUE. .FALSE.
5
5 50 500 2000 5000
500 5 1
1000 5 2
2500 5 3
5000 5 2
EXAMPLE FROM GRIEVE(1988b) - INFORMATIVE PRIOR - ED50
50 4 .TRUE. .TRUE.
5
5 50 500 2000 5000
-3.0 0.5 9.0 -.96 -.96 .16
500 5 1
1000 5 2
2500 5 3
5000 5 2
CGP 35127 (ip) IN FEMALE MICE - SINGLE DOSE STUDY - ED90
90 8 .TRUE. .FALSE.
3
1 4 16
 0.62 6 0
 0.93 6 0
 1.85 6 2
 2.78 6 3
 5.56 6 4
 8.33 6 6
16.67 6 6
25.00 6 6
```

A5.5.2 Example 1.

```
EXAMPLE FROM GRIEVE(1988b) - UNINFORMATIVE PRIOR - ED50

MAXIMUM LIKELIHOOD ESTIMATION OF ED50

MODEL : PROBIT
INDEPENDENT VARIABLE : LOG(DOSE)

PARAMETER ESTIMATES
            ALPHA      BETA
           -2.3187     0.2791
COVARIANCE MATRIX OF PARAMETER ESTIMATES
            ALPHA      BETA
ALPHA        6.1247    -0.8146
 BETA       -0.8146     0.1098

MAXIMISED LOG-LIKELIHOOD
           -13.1007
FIT OF THE MODEL
   DOSE  NO   RESP   EXP
 500.00   5    1     1.4
1000.00   5    2     1.7
2500.00   5    3     2.2
5000.00   5    2     2.6

CHI-VALUE =  1.00
D.F.      =     2
NOTE : SINCE CHI-SQUARE VALUE SMALL (P>0.05)
         FIDUCIAL LIMITS CALCULATED USING A T-VALUE OF  1.96

ESTIMATE OF ED50
         4049.3035
NO FIDUCIAL LIMITS
```

EXAMPLE FROM GRIEVE(1988b) - UNINFORMATIVE PRIOR - ED50

BAYESIAN ANALYSIS

POSTERIOR EXPECTAIONS (UNINFORMATIVE PRIOR)

	ALPHA	BETA
	-2.4390	0.2937

POSTERIOR COVARIANCE MATRIX (UNINFORMATIVE PRIOR)

	ALPHA	BETA
ALPHA	6.2760	-0.8347
BETA	-0.8347	0.1125

POSTERIOR MEDIAN FOR ED50

3199.3200

POSTERIOR MODE FOR ED50

2436.6822

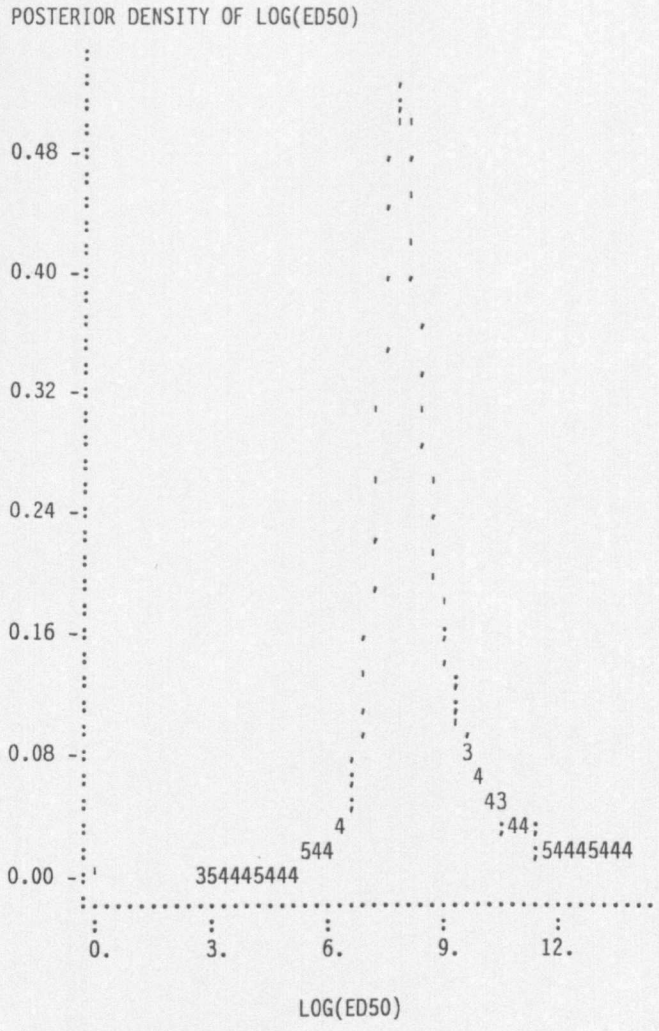
95% H.P.D. LIMITS FOR ED50

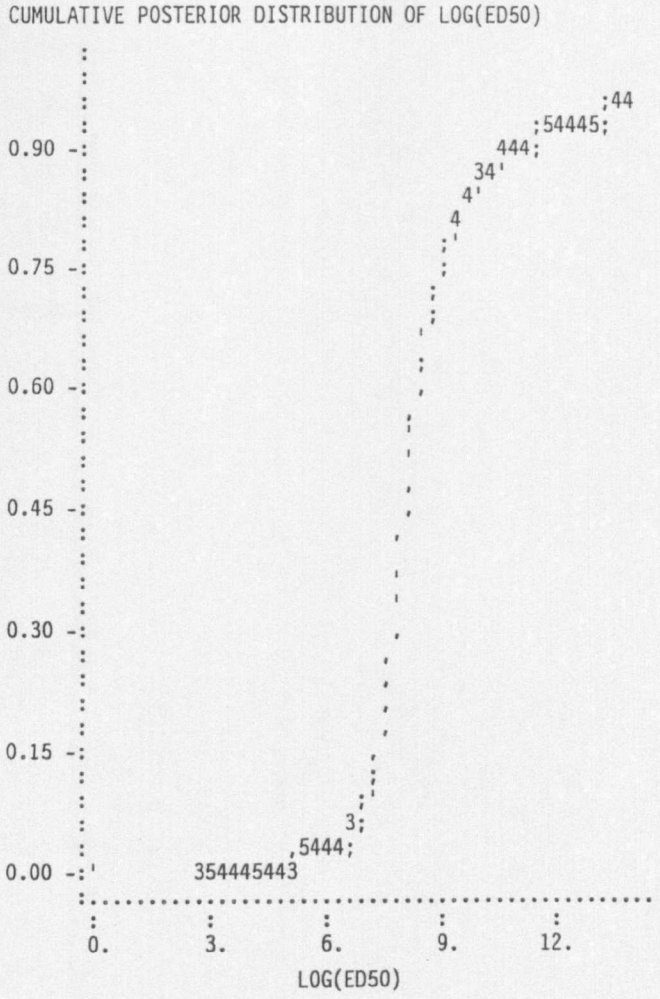
110.7882 6378274.8083

PROBABILITY OF TOXICITY CLASSES

CLASS				PROBABILITY
1 :		<	5.0	0.00534677
2 :	5.0	-	50.0	0.00381713
3 :	50.0	-	500.0	0.02061723
4 :	500.0	-	2000.0	0.23352378
5 :	2000.0	-	5000.0	0.40106765
		>	5000.0	0.33562744
			TOTAL:	1.00000000

```
  0.0-------0.2-------0.4-------0.6-------0.8-------1.0
1 :
2 :
3 : +
4 : ++++++++++++
5 : ++++++++++++++++++++
> : ++++++++++++++++++
```


POSTERIOR DENSITY OF LOG(ED50)
0.48
0.40
0.32
0.24
0.16
0.08
0.00
0.
3.
6.
9.
12.
LOG(ED50)


CUMULATIVE POSTERIOR DISTRIBUTION OF LOG(ED50)
0.90
0.75
0.60
0.45
0.30
0.15
0.00
0.
3.
6.
9.
12.
LOG(ED50)

A5.5.3 Example 2.

```
EXAMPLE FROM GRIEVE(1988b) - INFORMATIVE PRIOR - ED50

MAXIMUM LIKELIHOOD ESTIMATION OF ED50

MODEL : PROBIT
INDEPENDENT VARIABLE : LOG(DOSE)

PARAMETER ESTIMATES
            ALPHA     BETA
           -2.3187    0.2791
COVARIANCE MATRIX OF PARAMETER ESTIMATES
            ALPHA     BETA
ALPHA       6.1247   -0.8146
 BETA      -0.8146    0.1098

MAXIMISED LOG-LIKELIHOOD
           -13.1007
FIT OF THE MODEL
   DOSE  NO   RESP   EXP
 500.00   5    1     1.4
1000.00   5    2     1.7
2500.00   5    3     2.2
5000.00   5    2     2.6

CHI-VALUE =  1.00
D.F.      =    2
NOTE : SINCE CHI-SQUARE VALUE SMALL (P>0.05)
         FIDUCIAL LIMITS CALCULATED USING A T-VALUE OF  1.96

ESTIMATE OF ED50
         4049.3035
NO FIDUCIAL LIMITS
```

EXAMPLE FROM GRIEVE(1988b) - INFORMATIVE PRIOR - ED50

BAYESIAN ANALYSIS

POSTERIOR EXPECTAIONS (UNINFORMATIVE PRIOR)

ALPHA	BETA
-2.4390	0.2937

POSTERIOR COVARIANCE MATRIX (UNINFORMATIVE PRIOR)

	ALPHA	BETA
ALPHA	6.2760	-0.8347
BETA	-0.8347	0.1125

POSTERIOR MEDIAN FOR ED50

3199.3200

POSTERIOR MODE FOR ED50

2436.6822

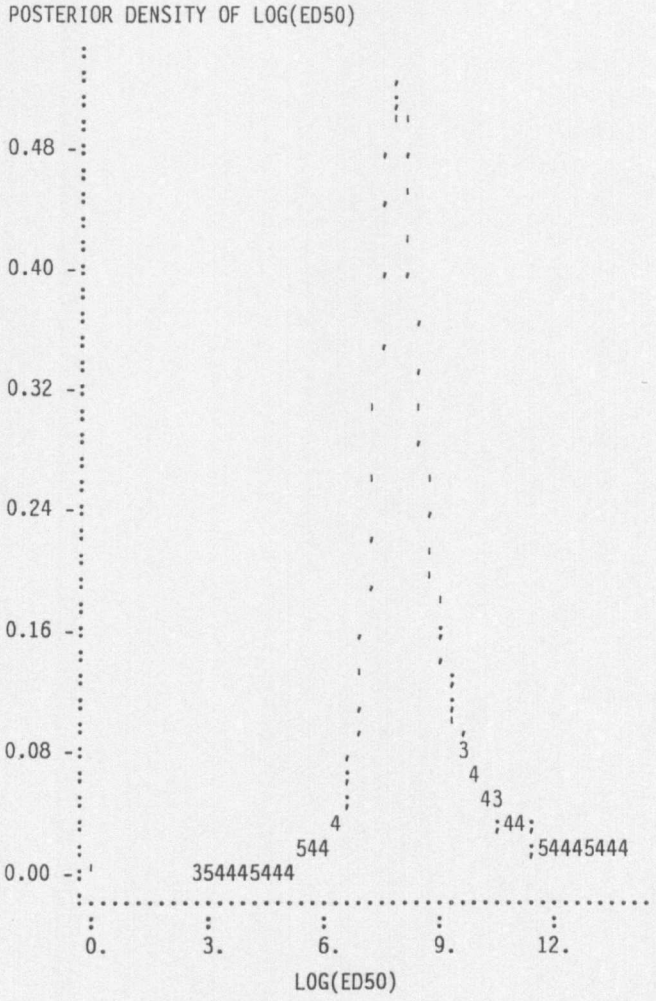
95% H.P.D. LIMITS FOR ED50

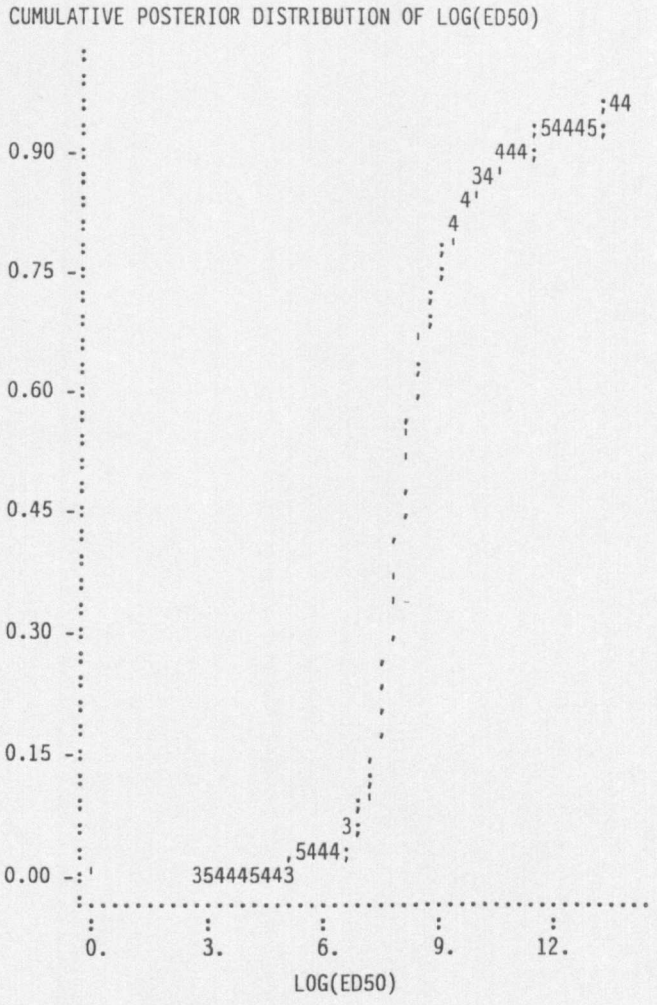
110.7882 6378274.8083

PROBABILITY OF TOXICITY CLASSES

CLASS				PROBABILITY
1 :		<	5.0	0.00534677
2 :	5.0	-	50.0	0.00381713
3 :	50.0	-	500.0	0.02061723
4 :	500.0	-	2000.0	0.23352378
5 :	2000.0	-	5000.0	0.40106765
		>	5000.0	0.33562744
			TOTAL:	1.00000000

```
  0.0-------0.2-------0.4-------0.6-------0.8-------1.0
1 :
2 :
3 : +
4 : ++++++++++++
5 : ++++++++++++++++++++
> : ++++++++++++++++++
```


POSTERIOR DENSITY OF LOG(ED50)
0.48
0.40
0.32
0.24
0.16
0.08
0.00
0.
3.
6.
9.
12.
LOG(ED50)


CUMULATIVE POSTERIOR DISTRIBUTION OF LOG(ED50)
0.90
0.75
0.60
0.45
0.30
0.15
0.00
0.
3.
6.
9.
12.
LOG(ED50)

EXAMPLE FROM GRIEVE(1988b) - INFORMATIVE PRIOR - ED50

PRIOR INFORMATION :

PRIOR EXPECTAIONS

	ALPHA	BETA
	-3.0000	0.5000

PRIOR COVARIANCE MATRIX

	ALPHA	BETA
ALPHA	9.0000	-0.9600
BETA	-0.9600	0.1600

POSTERIOR EXPECTAIONS (INFORMATIVE PRIOR)

	ALPHA	BETA
	-2.8912	0.3573

POSTERIOR COVARIANCE MATRIX (INFORMATIVE PRIOR)

	ALPHA	BETA
ALPHA	3.5438	-0.4690
BETA	-0.4690	0.0635

POSTERIOR MEDIAN FOR ED50

3059.9890

POSTERIOR MODE FOR ED50

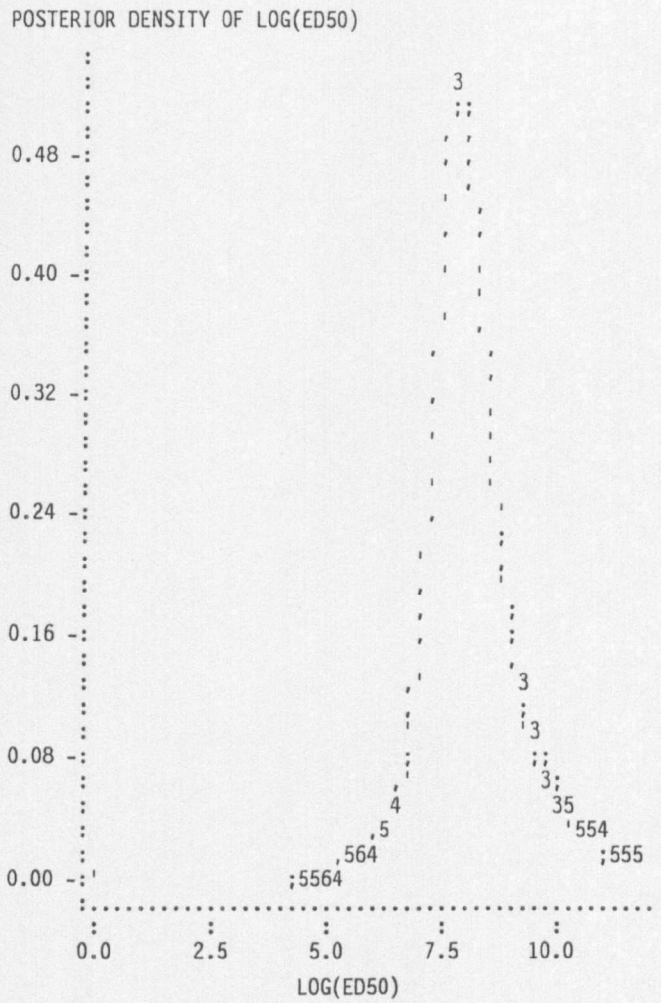
2450.6319

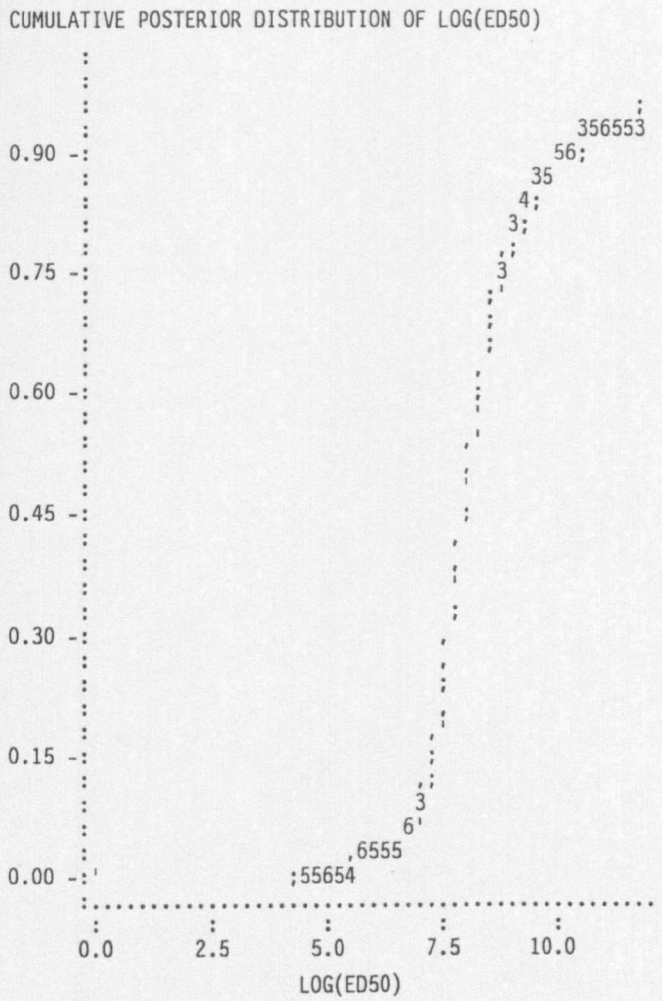
95% H.P.D. LIMITS FOR ED50

200.7817 602999.9368

PROBABILITY OF TOXICITY CLASSES			
CLASS			PROBABILITY
1 :	<	5.0	0.00365551
2 :	5.0 -	50.0	0.00293979
3 :	50.0 -	500.0	0.01979330
4 :	500.0 -	2000.0	0.25631111
5 :	2000.0 -	5000.0	0.40916296
	>	5000.0	0.30813733
		TOTAL:	1.00000000

```
  0.0-------0.2-------0.4-------0.6-------0.8-------1.0
1 :
2 :
3 : +
4 : ++++++++++++
5 : ++++++++++++++++++++
> : ++++++++++++++++
```


POSTERIOR DENSITY OF LOG(ED50)
0.48
0.40
0.32
0.24
0.16
0.08
0.00
0.0
2.5
5.0
7.5
10.0
LOG(ED50)


CUMULATIVE POSTERIOR DISTRIBUTION OF LOG(ED50)
0.90
0.75
0.60
0.45
0.30
0.15
0.00
0.0
2.5
5.0
7.5
10.0
LOG(ED50)

A5.5.4 Example 3.

```
CGP 35127 (ip) IN FEMALE MICE - SINGLE DOSE STUDY - ED90

MAXIMUM LIKELIHOOD ESTIMATION OF ED90

MODEL : PROBIT
INDEPENDENT VARIABLE : LOG(DOSE)

PARAMETER ESTIMATES
            ALPHA      BETA
           -1.7000     1.5469
COVARIANCE MATRIX OF PARAMETER ESTIMATES
            ALPHA      BETA
ALPHA        0.2832   -0.1852
 BETA       -0.1852    0.1667

MAXIMISED LOG-LIKELIHOOD
          -13.1075
FIT OF THE MODEL
  DOSE  NO   RESP   EXP
  0.62   6    0     0.0
  0.93   6    0     0.2
  1.85   6    2     1.4
  2.78   6    3     2.7
  5.56   6    4     5.0
  8.33   6    6     5.7
 16.67   6    6     6.0
 25.00   6    6     6.0

CHI-VALUE =  2.22
D.F.      =     6
NOTE : SINCE CHI-SQUARE VALUE SMALL (P>0.05)
        FIDUCIAL LIMITS CALCULATED USING A T-VALUE OF  1.96

ESTIMATE OF ED90
                  6.8724
FIDUCIAL LIMITS (95%)
       4.5602 < ED90 <         18.8023
```

CGP 35127 (ip) IN FEMALE MICE - SINGLE DOSE STUDY - ED90

BAYESIAN ANALYSIS

POSTERIOR EXPECTAIONS (UNINFORMATIVE PRIOR)

ALPHA	BETA
-1.8937	1.7215

POSTERIOR COVARIANCE MATRIX (UNINFORMATIVE PRIOR)

	ALPHA	BETA
ALPHA	0.2976	-0.1947
BETA	-0.1947	0.1752

POSTERIOR MEDIAN FOR ED90

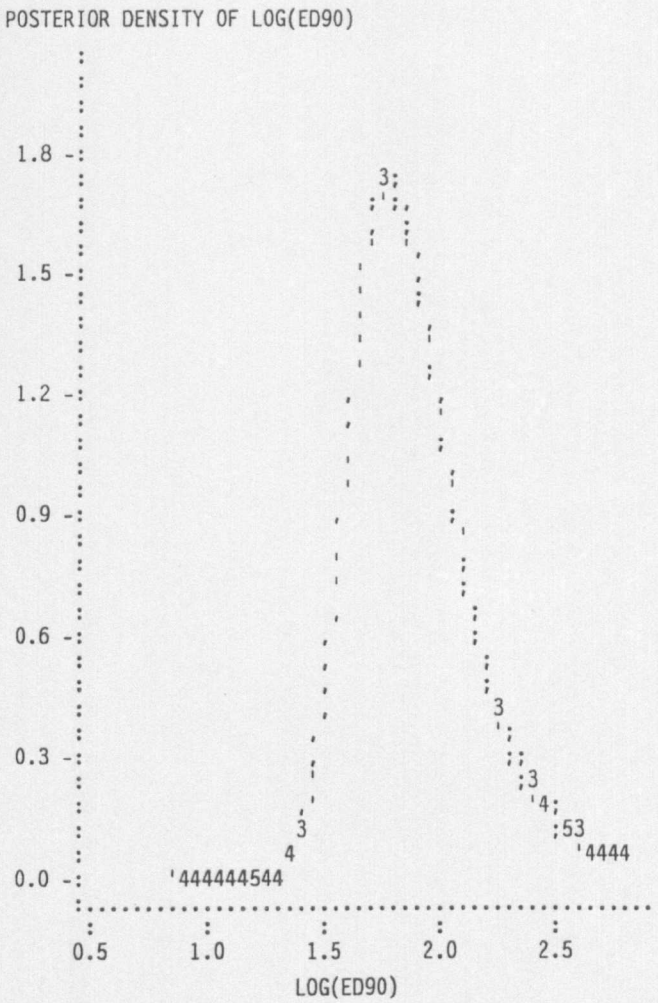
6.3249

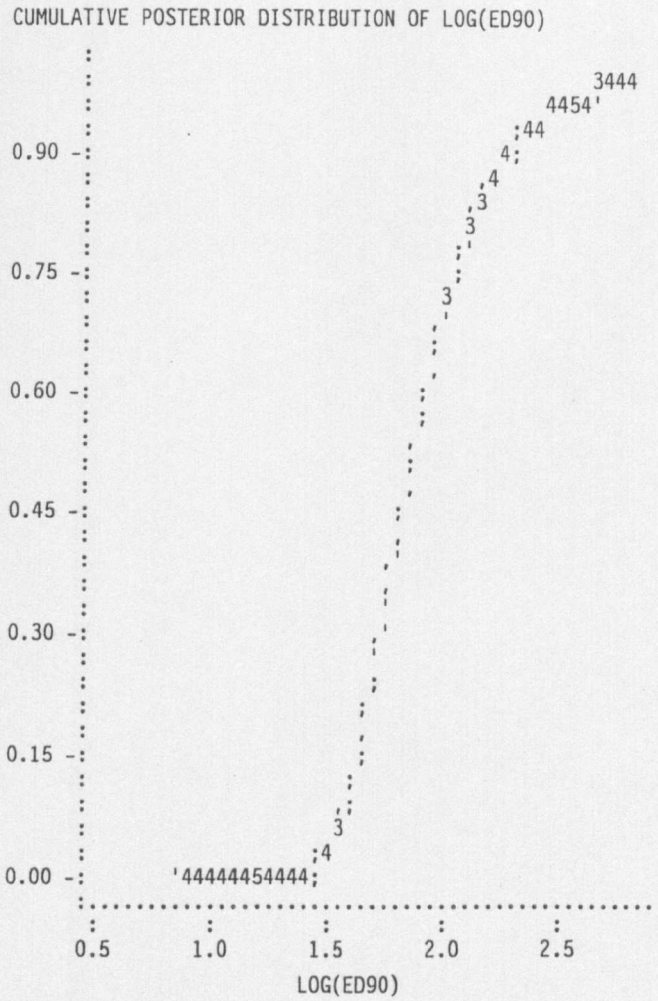
POSTERIOR MODE FOR ED90

5.8814

95% H.P.D. LIMITS FOR ED90

4.0923 12.0673


POSTERIOR DENSITY OF LOG(ED90)
1.8
1.5
1.2
0.9
0.6
0.3
0.0
0.5
1.0
1.5
2.0
2.5
LOG(ED90)


CUMULATIVE POSTERIOR DISTRIBUTION OF LOG(ED90)
0.90
0.75
0.60
0.45
0.30
0.15
0.00
0.5
1.0
1.5
2.0
2.5
LOG(ED90)

A6 SAS PROGRAMS FOR BAYESIAN ANALYSES ASSOCIATED WITH THE TWO-TREATMENT, TWO-PERIOD CROSSOVER.

A6.1 A SAS Program for the Bayesian Analysis of §4.

A6.1.1 Introduction.

This program is designed to perform a Bayesian analysis of a two-treatment, two-period crossover design. The program carries out the analyses developed in §4.

The program was written in SAS in order that the strengths of the SAS system in the realms of graphics could be utilised. In this Appendix a listing of the program including an example of data taken from Patel(1983) is given.

A6.1.2 Program Description.

This program has been written utilising the SAS data step language, without resorting to the use of the SAS library of procedures. In what follows the most important variables in the most important DATA SETS are described.

DATA SET A6 :

- N1 - Number of patients in sequence group $A \rightarrow B$
- N2 - Number of patients in sequence group $B \rightarrow A$
- Y11 - Cell mean $\bar{y}_{1.1}$
- Y12 - Cell mean $\bar{y}_{1.2}$
- Y21 - Cell mean $\bar{y}_{2.1}$
- Y22 - Cell mean $\bar{y}_{2.2}$
- SSP - Patient sum of squares
- SSE - Error sum of squares
- N - Total number of patients
- M - 1/N1 + 1/N2
- RH - Least squares estimate of λ
- TH - Least squares estimate of τ

DATA SET B3 :

- R - Carryover effect
- T - Treatment effect
- P_UNC - Constrained Conditional Density

DATA SET C3 :

- R - Carryover effect
- T - Treatment effect
- P_CON - Constrained Conditional Density

DATA SET D :

- T - Treatment effect
- P_UNC - Unconstrained Conditional Density
- P_CON - Constrained Conditional Density

DATA SET E :

- T - Treatment effect
- P_UNC - Unconstrained Density
- P_CON - Constrained Density

DATA SET F :

- R - Carryover effect
- P_UNC - Unconstrained Density
- P_CON - Constrained Density

DATA SET G :

- P_0 - Prior belief in a carryover effect
- M_W - Posterior mean treatment effect
- P_W - Posterior probability of a +ve Treatment effect
- X_U - Upper 95% H.P.D. limit
- X_L - Lower 95% H.P.D. limit

B01 - Bayes factor
P_1 - Posterior belief in a carryover effect

A6.1.3 Program Listing.

```
****************************************
INPUT DATA FROM PATEL (1983)
****************************************;

DATA A0;INPUT PAT SEQ Y1 Y2;CARDS;
 1 1 1.28 1.33
 2 1 1.60 2.21
 3 1 2.46 2.43
 4 1 1.41 1.81
 5 1 1.40 0.85
 6 1 1.12 1.20
 7 1 0.90 0.90
 8 1 2.41 2.79
 9 2 2.68 2.10
10 2 2.60 2.32
11 2 1.48 1.30
12 2 2.08 2.34
13 2 2.72 2.48
14 2 1.94 1.11
15 2 3.35 3.23
16 2 1.16 1.25
17 2 3.06 1.38
;
*********************************************
CALCULATION OF SUFFICIENT STATISTICS
*********************************************;

DATA A1; SET A0; Y=(Y1+Y2)/2;
PROC MEANS NOPRINT; BY SEQ; VAR Y1 Y2; OUTPUT OUT=A2 N=NO MEAN=Y1 Y2;
DATA A3; SET A2; RETAIN N1 Y11 Y12;
IF _N_=1 THEN DO; N1=NO; Y11=Y1; Y12=Y2; END;
ELSE DO; N2=NO; Y21=Y1; Y22=Y2; OUTPUT; END; KEEP N1 N2 Y11 Y12 Y21 Y22;
PROC MEANS NOPRINT DATA=A0; VAR Y Y1 Y2; OUTPUT OUT=A4 USS=SIJ SIJ1 SIJ2;
DATA A5; MERGE A3 A4 ; KEEP N1 N2 Y11 Y12 Y21 Y22 SSP SSE;
SSP=2*(SIJ-(N1*((Y11+Y12)/2)**2+N2*((Y21+Y22)/2)**2));
SE=SIJ1+SIJ2-(SSP+N1*Y11**2+N1*Y12**2+N2*Y21**2+N2*Y22**2);
DATA A6; SET A5;
N=N1+N2; M=N/(N1*N2); DF=(N-1)/2;
CONST=EXP(LGAMMA(DF)-(LGAMMA(DF-.5)+LGAMMA(.5)));
DF1=N-1; DF2=N-1;
RH= .5*(Y11+Y12-(Y21+Y22)) ; TH= 0.25*(Y11+Y22-(Y12+Y21));
****************************************
BASIC DATA
****************************************;

PROC PRINT;
****************************************
CALCULATION OF P(T,R|DATA)

P_UNC = UNCONSTRAINED DENSITY
P_CON = CONSTRAINED DENSITY
****************************************;

DATA B0; SET A6;
SER=SQRT(M*SSP/(2*(N-2))); RL=RH-(3*SER); RU=RH+3*SER;
C=4/(M*(SSE*SSP)**0.5); LM=C*(CONST**2);
DO CASE=1 TO 19 BY 3;PROB=(100-5*CASE)/100;
   LS=LOG(PROB*LM); KEEP CASE PROB R T IND LL L_L LN;
   DO R=RL TO RU BY (SER/10);
   IND=0; T=RL; DEL=SER/10; L_L=-10000;
   LOOP1:T=T+DEL;
         LINK LOGLIK;
         IF IND=0 THEN DO;
            IF LL > LS THEN DO;
               T=T-DEL;
               DEL=DEL/1000;
```

```
            IND=1; GOTO LOOP1;
         END;
         ELSE IF LL < L_L THEN GOTO LOOP2;
         ELSE L_L=LL;
      END;
      IF IND=1 THEN DO;
         IF LL > LS THEN DO;LN=LL;
            X=DEL*(LL-LS)/(LL-L_L);
            T=T-X;
            LINK LOGLIK;
            OUTPUT;
            DEL=SER/10;
            IND=2;
         END;
         ELSE L_L=LL;
      END;
      IF IND=2 THEN DO;
         IF LL < LS THEN DO;
            T=T-DEL;
            DEL=DEL/1000;
            IND=3;GOTO LOOP1;
         END;
         ELSE L_L=LL;
      END;
      IF IND=3 THEN DO;
         IF LL < LS THEN DO;LN=LL;
            X=DEL*(LS-LL)/(L_L-LL);
            T=T-X;
            OUTPUT;
            GOTO LOOP2;
         END;
         ELSE L_L=LL;
      END;
      IF T GT RU  THEN GOTO LOOP2;
      GOTO LOOP1;
   LOOP2:END;
END;
LOGLIK:
Y1=2*((R-RH)**2)/M;
Y2=8*((T-(R/2+TH))**2)/M;
W2=(Y2/SSE)**0.5; W1=(Y1/SSP)**0.5;
LL=LOG(LM)-DF*LOG((1+W1*W1)*(1+W2*W2));
RETURN;
RUN;
DATA B1; SET B0; BY CASE; RETAIN NIND;
IF FIRST.CASE THEN NIND=1; ELSE NIND=NIND+1;
IF IND=3 THEN ID=-NIND;
PROC SORT; BY CASE IND ID;
DATA B2; SET B0; BY CASE; IF FIRST.CASE;
DATA B3; SET B1 B2; P_UNC=PROB;
KEEP P_UNC R T;
PROC SORT; BY P_UNC;
PROC PRINT;

DATA C0; SET A6;
SER=SQRT(M*SSP/(2*(N-2))); RL=RH-(3*SER); RU=RH+3*SER;
C=4/(M*(SSE*SSP)**0.5);
PR2=PROBF((SSP/SSE),(DF2-1),(DF1-1));
PR1=PROBF((SSP/SSE),(DF2),(DF1));
LM=C*(CONST**2)*PR1/PR2;
DO CASE=1 TO 19 BY 3;PROB=(100-5*CASE)/100;
   LS=LOG(PROB*LM); KEEP CASE PROB R T IND LL L_L LN;
   DO R=RL TO RU BY (SER/10);
   IND=0; T=RL; DEL=SER/10; L_L=-10000;
   LOOP1:T=T+DEL;
         LINK LOGLIK;
         IF IND=0 THEN DO;
            IF LL > LS THEN DO;
               T=T-DEL;
               DEL=DEL/1000;
               IND=1; GOTO LOOP1;
            END;
            ELSE IF LL < L_L THEN GOTO LOOP2;
```

```
            ELSE L_L=LL;
         END;
         IF IND=1 THEN DO;
            IF LL > LS THEN DO;LN=LL;
               X=DEL*(LL-LS)/(LL-L_L);
               T=T-X;
               LINK LOGLIK;
               OUTPUT;
               DEL=SER/10;
               IND=2;
            END;
            ELSE L_L=LL;
         END;
         IF IND=2 THEN DO;
            IF LL < LS THEN DO;
               T=T-DEL;
               DEL=DEL/1000;
               IND=3;GOTO LOOP1;
            END;
            ELSE L_L=LL;
         END;
         IF IND=3 THEN DO;
            IF LL < LS THEN DO;LN=LL;
               X=DEL*(LS-LL)/(L_L-LL);
               T=T-X;
               OUTPUT;
               GOTO LOOP2;
            END;
            ELSE L_L=LL;
         END;
         IF T GT RU  THEN GOTO LOOP2;
         GOTO LOOP1;
     LOOP2:END;
END;
LOGLIK:
Y1=2*((R-RH)**2)/M;
Y2=8*((T-(R/2+TH))**2)/M;
PR2=PROBF((SSP/SSE),(DF2-1),(DF1-1));
SS1=DF1*(SSP+Y1);
SS2=DF2*(SSE+Y2);
PR1=PROBF((SS1/SS2),(DF2),(DF1));
W2=(Y2/SSE)**0.5; W1=(Y1/SSP)**0.5;
LL=LOG(LM)-DF*LOG((1+W1*W1)*(1+W2*W2)) + LOG(PR1) - LOG(PR2) ;
RETURN;
RUN;
DATA C1; SET C0; BY CASE; RETAIN NIND;
IF FIRST.CASE THEN NIND=1; ELSE NIND=NIND+1;
IF IND=3 THEN ID=-NIND;
PROC SORT; BY CASE IND ID;
DATA C2; SET C0; BY CASE; IF FIRST.CASE;
DATA C3; SET C1 C2; P_CON=PROB;
PROC SORT; BY CASE;
DATA C3; SET C3;
KEEP P_CON R T;
PROC PRINT;
*****************************************
CALCULATION OF P(T|R = 0,DATA)
P_UNC = UNCONSTRAINED DENSITY
P_CON = CONSTRAINED DENSITY
*****************************************;
DATA D; SET A6; CONST=CONST*(8/(M*SSE))**0.5;
SER=SQRT(M*SSP/(2*(N-2))); SET=SQRT(M*SSE/(8*(N-2)));
RL=MIN(0,ROUND(RH-(2*SER),1)); RU=MAX(0,ROUND(RH+2*SER));
SS1= DF1   *(SSP+2*(RH**2)/M);
SS3=(DF1-1)*(SSP+2*(RH**2)/M);
DO T=(TH-(8*SET)) TO (TH+8*SET) BY (SET/10);
   Y=8*((T-TH)**2)/M;
   SS2=DF2*(SSE+Y);
   SS4=SSE*DF2;
   PR1=PROBF((SS1/SS2),(DF2),(DF1));
```

```
   PR2=PROBF((SS3/SS4),(DF2),(DF1-1));
   W=(Y/SSE)**0.5;
   P_UNC=CONST*(1+W*W)**-DF;
   P_CON=P_UNC*PR1/PR2;
   OUTPUT;
END;
KEEP T P_UNC P_CON PR1 PR2;
****************************************
```

APPROXIMATION OF P(T|DATA)

P_UNC = UNCONSTRAINED DENSITY
P_CON = CONSTRAINED DENSITY

```
*****************************************;

DATA E(KEEP=T P_UNC P_CON)
     E1(KEEP=M1 M2 V1 V2 DF1 DF2 P_T1 P_T2 B01);SET A6;
P=1/(2*ARCOS(0))**0.5;
B1=(N-6)*((SSE+SSP)**2)/(SSE*SSE+SSP*SSP)+4; B0=(B1-2)*(SSE+SSP)/(N-4);
A=M*B0/8;
SET=SQRT(A/B1);TL=(TH+RH/2)-(4*SET);TU=(TH+RH/2)+4*SET;
X=SSP/(SSE+SSP);DF1=N-2;
IX1=PROBBETA(X,DF1/2,DF1/2+1);
IX2=PROBBETA(X,DF1/2,DF1/2+2);
IX3=PROBBETA(X,DF1/2,DF1/2);
IX4=PROBBETA(X,DF1/2+1,DF1/2);
IX5=PROBBETA(X,DF1/2+2,DF1/2);
E1=(DF1/2+1)*IX2/IX1-(DF1*IX1/(IX3*2));
E2=(DF1/2+1)*IX5/IX4-(DF1*IX4/(IX3*2));
F1=DF1*IX1/(E1*IX3);
F2=DF1*IX4/(E2*IX3);
SSE1=SSE/E1; SSP1=SSP/E2; E=SSE1/(F1-2)+SSP1/(F2-2);
V=2*SSE1*SSE1/((F1-2)**2*(F1-4))+2*SSP1*SSP1/((F2-2)**2*(F2-4));
B11=2*E*E/V+4; B01=(B11-2)*E; A1=M*B01/8;
DO T=TL TO TU BY (SET/10);
   C=P*EXP(LGAMMA(B1/2+.5)-LGAMMA(B1/2))/A**0.5;
   P_UNC=C*(1+((T-(TH+RH/2))**2)/A)**-(B1/2+.5);
   C=P*EXP(LGAMMA(B11/2+.5)-LGAMMA(B11/2))/A1**0.5;
   P_CON=C*(1+((T-(TH+RH/2))**2)/A1)**-(B11/2+.5);
   OUTPUT E;
END;
M1=TH; M2=TH+RH/2; V1=M*SSE/(8*(N-2)); V2=A/B1; DF1=N-2;DF2=B1;
P_T1=PROBT(M1/SQRT(V1),DF1); P_T2=PROBT(M2/SQRT(V2),DF2);
B01=SQRT(3/(2*M))/(1+(2*RH*RH)/(M*SSP))**(N/2);
OUTPUT E1;
****************************************
```

CALCULATION OF P(R|DATA)

P_UNC = UNCONSTRAINED DENSITY
P_CON = CONSTRAINED DENSITY

```
*****************************************;

DATA F;SET A6;C=(2/(M*SSP))**0.5;PR2=PROBF((SSP/SSE),(DF1-1),(DF2-1));
SER=SQRT(M*SSP/(2*(N-2)));RL=RH-(4*SER);RU=RH+4*SER;
DO R=RL TO RU BY (SER/10);
Y=2*((R-RH)**2)/M;W=(Y/SSP)**0.5;
SS1=(DF1-1)*(SSP+Y);SS2=DF2*SSE;PR1=PROBF((SS1/SS2),DF2,(DF1-1));
P_UNC=C*CONST*((1+W*W)**-DF);P_CON=P_UNC*PR1/PR2;OUTPUT;END;
KEEP R P_UNC P_CON PR1 PR2;
****************************************
```

POSTERIOR INFERENCE FOR TREATMENT EFFECT

```
*****************************************;

DATA G;SET E1 ;KEEP P_0 M_W P_W XL XU B01 P_1;
XUS=M2+1.96*SQRT(V2);XLS=M2-1.96*SQRT(V2);
DO P_0=0 TO 1   BY 0.01;IF P_0=1 THEN PI=10000000;ELSE PI=P_0/(1-P_0);
   P=(PI*B01)/(1+PI*B01);P_1=1-P;
   M_W=  P*M1  +P_1*M2   ;
   V_W=  P*V1+P_1*V2 +P*P_1*(M1-M2)**2 ;
   P_W=P*P_T1+P_1*P_T2   ;
   XU=XUS;XU1=XU;
LO:XA1=(XU-M1)/SQRT(V1);XA2=(XU-M2)/SQRT(V2);
```

```
   P1=P*(1-PROBT(XA1,DF1))+P_1*(1-PROBT(XA2,DF2));
   LINK XOTHER;XA1=(XL-M1)/SQRT(V1);XA2=(XL-M2)/SQRT(V2);
   XL1=XL;DENOM=DEN0;XU1=XU1+0.001;LINK XOTHER;XU1=XU1-0.001;
   P2=P*PROBT(XA1,DF1)+P_1*PROBT(XA2,DF2);
   PL=1-(P1+P2);
   NUM=PL-0.95;
   DENOM=DENOM*(1-((XL-XL1)/0.001));
   XU=XU-(NUM/DENOM);DIFF1=ABS(XU-XU1);
   IF ABS(XU-XU1) LT 1E-6 THEN DO;XUS=XU;OUTPUT;END;ELSE DO;XU1=XU;GOTO L0;
   END;END;
XOTHER:
      A=V1*DF1;DF=DF1;M=M1;X=XU1;LINK TDIS;DEN1=PX;
      A=V2*DF2;DF=DF2;M=M2;X=XU1;LINK TDIS;DEN2=PX;
      DEN=P*DEN1+P_1*DEN2;
      XL=XLS;XL0=XL;
L1:   A=V1*DF1;DF=DF1;M=M1;X=XL;LINK TDIS;DEN1=PX;DER1=DER;
      A=V2*DF2;DF=DF2;M=M2;X=XL;LINK TDIS;DEN2=PX;DER2=DER;
      DEN0=P*DEN1+P_1*DEN2;NUM1=DEN0-DEN;
      DER=P*DER1+P_1*DER2;
      XL=XL-(NUM1/DER);DIFF2=ABS(XL-XL0);
      IF ABS(XL-XL0) LT 1E-6 THEN DO;XLS=XL;RETURN;END;ELSE DO;XL0=XL;GOTO L1;
END;
TDIS: C=1/(2*ARCOS(0))**0.5;
C=C*EXP(LGAMMA(DF/2+.5)-LGAMMA(DF/2))/A**0.5;
PX=C*(1+((X-M)*(X-M))/A)**-(DF/2+.5);
DER=-(DF/2+.5)*PX*2*(X-M)/(A*(1+((X-M)*(X-M))/A));RETURN;
```

A6.2 A SAS Program for the Bayesian Analysis of §9.2

A6.2.1 Introduction.

This program is designed to perform a Bayesian analysis of a two-treatment, two-period crossover design with missing data. The program carries out the analyses developed in §9.

A6.2.2 Program Description.

This program has been written utilising the SAS data step language, without resorting to the use of the SAS library of procedures. In what follows the most important variables in the most important DATA SETS are described.

DATA SET INP :

- N1 - Number of patients in sequence group $A \rightarrow B$ with complete data,
- N2 - Number of patients in sequence group $A \rightarrow B$ with complete data,
- N11 - Number of patients in sequence group $A \rightarrow B$ with missing 1st period data,
- N12 - Number of patients in sequence group $B \rightarrow A$ with missing 2nd period data,
- N21 - Number of patients in sequence group $B \rightarrow A$ with missing 1st period data,
- N22 - Number of patients in sequence group $B \rightarrow A$ with missing 2nd period data,
- Y11 - Cell mean $\bar{y}_{1.1}$,
- Y12 - Cell mean $\bar{y}_{1.2}$,
- Y21 - Cell mean $\bar{y}_{2.1}$,
- Y22 - Cell mean $\bar{y}_{2.2}$,
- X1 - Cell mean $\bar{x}_1$,
- Z1 - Cell mean $\bar{z}_1$,
- X2 - Cell mean $\bar{x}_2$,
- Z2 - Cell mean $\bar{z}_2$,
- S111 - Corrected sum of squares S_{111} ,
- S112 - Corrected sum of cross products S_{112} ,

S122 - Corrected sum of squares S_{122} ,
S211 - Corrected sum of squares S_{211} ,
S221 - Corrected sum of cross products S_{212} ,
S222 - Corrected sum of squares S_{222} ,
S11 - Corrected sum of squares S_{11} ,
S12 - Corrected sum of squares S_{12} ,
S21 - Corrected sum of squares S_{21} ,
S22 - Corrected sum of squares S_{22} .

DATA SET T : T - Treatment effect
DEN - Posterior Density

DATA SET L : L - Carryover effect
DEN - Posterior Density

DATA SET TL : T - Treatment effect
DEN - Posterior Density

A6.2.3 Program Listing.

```
*************************************************
INPUT DATA TAKEN FROM GELFLAND ET AL(1990)
*************************************************;

DATA INP;
N1= 3          ; N2= 4          ;
N11= 1         ; N12= 1         ; N21= 0         ; N22= 1         ;
Y11= 1.480877  ; Y12= 1.326631  ; Y21= 1.39212   ; Y22= 1.56918   ;
X1= 1.31372    ; Z1= 1.40364    ; X2= 0          ; Z2= 1.58104    ;
S111= 0.01324816 ; S112= 0.04448745 ; S122= 0.1602117 ;
S211= 0.0973115  ; S212= 0.0573021  ; S222= 0.0629484 ;
S11= 0         ; S12= 0         ; S21= 0         ; S22= 0         ;
*************************************************
DATA SET - T
CALCULATION OF P(T | DATA)

DATA SET - L
CALCULATION OF P(L | DATA)

DATA SET - TL
CALCULATION OF P(T | L = 0,DATA)

*************************************************;


DATA T (KEEP=T INDIC DEN DEN_0)
DATA L (KEEP=L INDIC DEN DEN_0)
DATA TL(KEEP=T INDIC DEN DEN_0);
SET INP;
ARRAY GAUSS{20} GAUSS1-GAUSS20;ARRAY WT{20} WT1-WT20;
GAUSS{1}= -.9931285992;WT{1}= .0176140071;
GAUSS{2}= -.9639719273;WT{2}= .0406014298;
GAUSS{3}= -.9122344282;WT{3}= .0626720483;
GAUSS{4}= -.8391169718;WT{4}= .0832767415;
GAUSS{5}= -.7463319065;WT{5}= .1019301198;
GAUSS{6}= -.6360536807;WT{6}= .1181945320;
GAUSS{7}= -.5108670019;WT{7}= .1316886385;
GAUSS{8}= -.3737060887;WT{8}= .1420961093;
GAUSS{9}= -.2277858511;WT{9}= .1491729865;
GAUSS{10}=-.0765265211;WT{10}=.1527533871;
DO I=11 TO 20;GAUSS{I}=-GAUSS{21-I};WT{I}=WT{21-I};END;
INDIC=1;
P=(2*N1+2*N2+N11+N12+N21+N22-3)/2;
DEN_0=0;
START1  = -.3 ;
```

```
FINISH1 =  .4 ;
DEL1    = .002;
DO T = START1 TO FINISH1 BY DEL1;
   DEN=0.0;
   DO IGAUSS=1 TO 20;
      R=GAUSS{IGAUSS};
      R12=1-R*R;
      LINK CGEN;
      LINK MEANS;
      LINK COVS;
      LINK MEVA1;
      LINK CON;
      LINK FAC1;
      DENTR=-0.5*(N1+N2)*LOG(R12)-0.5*LOG(C1)-0.5*LOG(C2)-P*LOG(FACT)
            -0.5*LOG(VAR);
      DEN=DEN+WT{IGAUSS}*EXP(DENTR);
   END;DEN_0=DEN_0+DEN*DEL;
OUTPUT T;
END;
DEN_0=0;
START2  = -.3 ;
FINISH2 =  .4 ;
DEL2    = .002;
DO L = START2 TO FINISH2 BY DEL2;
   DEN=0.0;
   DO IGAUSS=1 TO 20;
      R=GAUSS{IGAUSS};
      R12=1-R*R;
      LINK CGEN;
      LINK MEANS;
      LINK COVS;
      LINK MEVA2;
      LINK CON;
      LINK FAC2;
      DENTR=-0.5*(N1+N2)*LOG(R12)-0.5*LOG(C1)-0.5*LOG(C2)-P*LOG(FACT)
            -0.5*LOG(VAR);
      DEN=DEN+WT{IGAUSS}*EXP(DENTR);
   END;DEN_0=DEN_0+DEN*DEL;
OUTPUT 1;
END;
DEN_0=0;
START3  = -.3 ;
FINISH3 =  .4 ;
DEL3    = .002;
DO T = START3 TO FINISH3 BY DEL3;
   DEN=0.0;
   DO IGAUSS=1 TO 20;
      R=GAUSS{IGAUSS};
      R12=1-R*R;
      LINK CGEN;
      LINK MEANS;
      LINK COVS;
      LINK MEVA3;
      LINK CON;
      LINK FAC1;
      DENTR=-0.5*(N1+N2)*LOG(R12)-0.5*LOG(C1)-0.5*LOG(C2)-P*LOG(FACT)
            -0.5*LOG(VAR);
      DEN=DEN+WT{IGAUSS}*EXP(DENTR);
   END;DEN_0=DEN_0+DEN*DEL;
OUTPUT TL;
END;
STOP;
CGEN : C1= N1*N1 + N1*N11 + N1*N12 + N11*N12*R12;
       C2= N2*N2 + N2*N21 + N2*N22 + N21*N22*R12; RETURN;
MEANS: MU11=Y11 + ( N11*(N1+N12*R12)*(X1-Y11) + N1*N12*R*(Z1-Y12) ) /C1;
       MU12=Y12 + ( N1*N11*R*(X1-Y11) + N12*(N1+N11*R12)*(Z1-Y12) ) /C1;
       MU21=Y21 + ( N21*(N2+N22*R12)*(X2-Y21) + N2*N22*R*(Z2-Y22) ) /C2;
       MU22=Y22 + ( N2*N21*R*(X2-Y21) + N22*(N2+N21*R12)*(Z2-Y22) ) /C2;
       TH=0.50*(MU11-MU21); LH=0.50*(MU11+MU12-MU21-MU22);
       RETURN;
COVS : A11 = N1+N12*R12; A12 = N1*R ; A22 = N1+N11*R12;
       B11 = N2+N22*R12; B12 = N2*R ; B22 = N2+N21*R12;
```

```
      SIG11 = A11/C1 + B11/C2 ;
      SIG12 = (A11+A12)/C1 + (B11+B12)/C2 ;
      SIG22 = (A11+2*A12+A22)/C1 + (B11+2*B12+B22)/C2;
      RETURN;
MEVA1: MEAN=TH ;
      VAR =SIG11/4;
      RETURN;
MEVA2: MEAN=LH ;
      VAR =SIG22/4;
      RETURN;
MEVA3: MEAN=TH-SIG12*LH/SIG22;
      VAR =(SIG11-SIG12*SIG12/SIG22)/4;
      RETURN;
FAC1 : FACT=(CON+(S111+S211+S122+S222-2*R*(S112+S212))/R12
          + (T-MEAN)**2/VAR)/2;
      RETURN;
FAC2 : FACT=(CON+(S111+S211+S122+S222-2*R*(S112+S212))/R12
          + (L-MEAN)**2/VAR)/2;
      RETURN;
CON  : CON= S11 + S12 + S21 + S22 +
           N1*(N11*(N1+N12)*(Y11-X1)**2-2*N11*N12*R*(Y11-X1)*(Y12-Z1)
             + N12*(N1+N11)*(Y12-Z1)**2)/(N1**2+N1*N11+N1*N12+N11*N12*R12) +
           N2*(N21*(N2+N22)*(Y21-X2)**2-2*N21*N22*R*(Y21-X2)*(Y22-Z2)
             + N22*(N2+N21)*(Y22-Z2)**2)/(N2**2+N2*N21+N2*N22+N21*N22*R12) ;
      RETURN;

PROC UNIVARIATE NOPRINT DATA=T;BY INDIC;VAR DEN_0;OUTPUT OUT=MAX MAX=MAX_DEN;
DATA T;MERGE T MAX; BY INDIC;DEN=DEN/MAX_DEN;KEEP DEN T;

PROC UNIVARIATE NOPRINT DATA=L;BY INDIC;VAR DEN_0;OUTPUT OUT=MAX MAX=MAX_DEN;
DATA L;MERGE L MAX; BY INDIC;DEN=DEN/MAX_DEN;KEEP DEN T;

PROC UNIVARIATE NOPRINT DATA=TL;BY INDIC;VAR DEN_0;OUTPUT OUT=MAX MAX=MAX_DEN;
DATA TL;MERGE TL MAX; BY INDIC;DEN=DEN/MAX_DEN;KEEP DEN T;
```

A6.3 A SAS Program for Determining the Bayes Factor in a Two Period Crossover with Missing Data.

A6.3.1 Introduction.

This program is designed to determine the Bayes factor against carryover in a two-treatment, two-period crossover design with missing data. The program carries out the necessary numerical integrations mentioned in §9.

A6.3.2 Program Description.

This program has been written utilising the SAS data step language, without resorting to the use of the SAS library of procedures. The input to this program is identical to that in A6.2.2.

The important difference between these two programs is that the current one has the following additional data set.

DATA SET BF : B01 - Bayes factor.

A6.3.3 Program Listing.

```
*****************************************************
INPUT DATA TAKEN FROM GELFLAND ET AL(1990)
*****************************************************;

DATA INP;
N1=  3          ; N2=  4          ;
N11=  1         ; N12=  1         ; N21=  0         ; N22=  1         ;
Y11=  1.480877  ; Y12=  1.326631  ; Y21=  1.39212   ; Y22=  1.56918   ;
X1=   1.31372   ; Z1=   1.40364   ; X2=   0         ; Z2=   1.58104   ;
S111= 0.01324816 ; S112= 0.04448745 ; S122= 0.1602117 ;
S211= 0.0973115  ; S212= 0.0573021  ; S222= 0.0629484 ;
S11=  0         ; S12=  0         ; S21=  0         ; S22=  0         ;
```

```
DATA T (KEEP=T INDIC DEN DEN_0)
DATA TL(KEEP=T INDIC DEN DEN_0);
SET INP;
ARRAY GAUSS{20} GAUSS1-GAUSS20;ARRAY WT{20} WT1-WT20;
GAUSS{1}= -.9931285992;WT{1}= .0176140071;
GAUSS{2}= -.9639719273;WT{2}= .0406014298;
GAUSS{3}= -.9122344282;WT{3}= .0626720483;
GAUSS{4}= -.8391169718;WT{4}= .0832767415;
GAUSS{5}= -.7463319065;WT{5}= .1019301198;
GAUSS{6}= -.6360536807;WT{6}= .1181945320;
GAUSS{7}= -.5108670019;WT{7}= .1316886385;
GAUSS{8}= -.3737060887;WT{8}= .1420961093;
GAUSS{9}= -.2277858511;WT{9}= .1491729865;
GAUSS{10}=-.0765265211;WT{10}=.1527533871;
DO I=11 TO 20;GAUSS{I}=-GAUSS{21-I};WT{I}=WT{21-I};END;
INDIC=1;
P=(2*N1+2*N2+N11+N12+N21+N22-3)/2 +2;
DEN_0=0;
START1  = -.3 ;
FINISH1 =  .4 ;
DEL1    = .002;
DO T = START1 TO FINISH1 BY DEL1;
   DEN=0.0;
   DO IGAUSS=1 TO 20;
      R=GAUSS{IGAUSS};
      R12=1-R*R;
      LINK CGEN;
      LINK MEANS;
      LINK COVS;
      LINK MEVA1;
      LINK CON;
      LINK FAC1;
      DENTR=-0.5*(N1+N2)*LOG(R12)-.5*LOG(C1)-.5*LOG(C2)-P*LOG(FACT)
            -0.5*LOG(VAR)-LOG(R12);
      DEN=DEN+WT{IGAUSS}*EXP(DENTR);
   END;DEN_0=DEN_0+DEN*DEL1;
OUTPUT T;
END;
P=(2*N1+2*N2+N11+N12+N21+N22-3)/2 +2  ;
DEN_0=0;
START3  = -.3 ;
FINISH3 =  .4 ;
DEL3    = .002;
DO T = START3 TO FINISH3 BY DEL3;
   DEN=0.0;
   DO IGAUSS=1 TO 20;
      R=GAUSS{IGAUSS};
      R12=1-R*R;
      LINK CGEN;
      LINK MEANS;
      LINK COVS;
      LINK MEVA2;
      LINK CON;
      LINK FAC2;
      DENTR=-0.5*(N1+N2)*LOG(R12)-.5*LOG(C1)-.5*LOG(C2)-P*LOG(FACT)
            -0.5*LOG(VAR)-0.5*LOG(1+R) - LOG(1-R) -.5*LOG(SIG22/4);
      DEN=DEN+WT{IGAUSS}*EXP(DENTR);
   END;DEN_0=DEN_0+DEN*DEL3;
OUTPUT TL;
END;
STOP;
CGEN : C1= N1*N1 + N1*N11 + N1*N12 + N11*N12*R12;
       C2= N2*N2 + N2*N21 + N2*N22 + N21*N22*R12; RETURN;
MEANS: MU11=Y11 + ( N11*(N1+N12*R12)*(X1-Y11) + N1*N12*R*(Z1-Y12) ) /C1;
       MU12=Y12 + ( N1*N11*R*(X1-Y11) + N12*(N1+N11*R12)*(Z1-Y12) ) /C1;
       MU21=Y21 + ( N21*(N2+N22*R12)*(X2-Y21) + N2*N22*R*(Z2-Y22) ) /C2;
       MU22=Y22 + ( N2*N21*R*(X2-Y21) + N22*(N2+N21*R12)*(Z2-Y22) ) /C2;
       TH=0.50*(MU11-MU21); LH=0.50*(MU11+MU12-MU21-MU22);
       RETURN;
COVS : A11 = N1+N12*R12; A12 = N1*R ; A22 = N1+N11*R12;
       B11 = N2+N22*R12; B12 = N2*R ; B22 = N2+N21*R12;
       SIG11 = A11/C1 + B11/C2 ;
```

```
       SIG12 = (A11+A12)/C1 + (B11+B12)/C2 ;
       SIG22 = (A11+2*A12+A22)/C1 + (B11+2*B12+B22)/C2;
       RETURN;
MEVA1: MEAN=TH ;
       VAR =SIG11/4;
       RETURN;
MEVA2: MEAN=TH-SIG12*LH/SIG22;
       VAR =(SIG11-SIG12*SIG12/SIG22)/4;
       RETURN;
FAC1 : FACT=(CON+(S111+S211+S122+S222-2*R*(S112+S212))/R12
           + (T-MEAN)**2/VAR)/2   ;
       RETURN;
FAC2 : FACT=(CON+(S111+S211+S122+S222-2*R*(S112+S212))/R12
           + (T-MEAN)**2/VAR)/2  + 2*LH*LH/SIG22 ;
       RETURN;
CON  : CON= S11 + S12 + S21 + S22 +
            N1*(N11*(N1+N12)*(Y11-X1)**2-2*N11*N12*R*(Y11-X1)*(Y12-Z1)
              + N12*(N1+N11)*(Y12-Z1)**2)/(N1**2+N1*N11+N1*N12+N11*N12*R12) +
            N2*(N21*(N2+N22)*(Y21-X2)**2-2*N21*N22*R*(Y21-X2)*(Y22-Z2)
              + N22*(N2+N21)*(Y22-Z2)**2)/(N2**2+N2*N21+N2*N22+N21*N22*R12) ;
       RETURN;

PROC UNIVARIATE NOPRINT DATA=T; BY INDIC;VAR DEN_0;OUTPUT OUT=MAX1 MAX=MAX_DEN1;
DATA T; MERGE T  MAX1; BY INDIC;DEN=DEN/MAX_DEN1;
PROC UNIVARIATE NOPRINT DATA=TL;BY INDIC;VAR DEN_0;OUTPUT OUT=MAX2 MAX=MAX_DEN2;
DATA TL;MERGE TL MAX2; BY INDIC;DEN=DEN/MAX_DEN2;
DATA BF;MERGE MAX1 MAX2;BO1=SQRT(3/4)*MAX_DEN2/MAX_DEN1;KEEP BO1;
```

A7 SAS MACROS FOR CALCULATING THE ZEROS AND WEIGHTS OF ORTHOGONAL POLYNOMIALS.

A7.1 Introduction.

The SAS macros in this Appendix were developed to calculate the zeros and associated weights of the orthogonal polynomials defined by the following orthogonality conditions :

Harper Polynomials :

$$\int_{-\infty}^{\infty}(1+x^2)^{-(k+1)}\phi_{m,k}(x)\phi_{n,k}(x)dx = 0 \quad ; \quad m \neq n, m+n > 2k+1.$$

Polynomials for a Truncated Normal :

$$\int_{b}^{\infty} e^{-x^2}\theta_m(x)\theta_n(x)dx$$

Jacobi Polynomials :

$$\int_{0}^{1} x^{v_2/2-1}(1-x)^{v_1/2-1}G_m(p,q,x)G_n(p,q,x)dx$$

A7.2 Harper Polynomials

```
%MACRO HARPER(K,DEGREE);
%LET RANGE=%EVAL(&DEGREE+1);
DATA HARPER;
ARRAY A{&RANGE} A1-A&RANGE;
ARRAY XT{&DEGREE} XT1-XT&DEGREE; ARRAY XW{&DEGREE} XW1-XW&DEGREE;
ARRAY ROW1  (W) R1W1-R1W&RANGE;   ARRAY ROW2  (W) R2W1-R2W&RANGE;
ARRAY ROW3  (W) R3W1-R3W&RANGE;   ARRAY ROW4  (W) R4W1-R4W&RANGE;
ARRAY ROW5  (W) R5W1-R5W&RANGE;   ARRAY ROW6  (W) R6W1-R6W&RANGE;
ARRAY ROW7  (W) R7W1-R7W&RANGE;   ARRAY ROW8  (W) R8W1-R8W&RANGE;
ARRAY ROW9  (W) R9W1-R9W&RANGE;   ARRAY ROW10 (W) R10W1-R10W&RANGE;
ARRAY ROW11 (W) R11W1-R11W&RANGE; ARRAY ROW12 (W) R12W1-R12W&RANGE;
ARRAY ROW13 (W) R13W1-R13W&RANGE; ARRAY ROW14 (W) R14W1-R14W&RANGE;
ARRAY ROW15 (W) R15W1-R15W&RANGE; ARRAY ROW16 (W) R16W1-R16W&RANGE;
ARRAY ROW17 (W) R17W1-R17W&RANGE; ARRAY ROW18 (W) R18W1-R18W&RANGE;
ARRAY ROW19 (W) R19W1-R19W&RANGE; ARRAY ROW20 (W) R20W1-R20W&RANGE;
ARRAY B (Z) ROW1-ROW&RANGE;
N=&DEGREE;
K=&K;
KEEP K N XT1-XT&DEGREE XW1-XW&DEGREE;
      DO L=1 TO N ; XT{L}=0; END;
      DO IX=1 TO 2;
         IF IX EQ 1 THEN N=N-1; ELSE N=N+1;
         Z=1; W=1; B=1;
         W=2; B=0;
         DK=K-N+1.5; C1=LGAMMA(DK);
         Z=N;
         DO W=1 TO (N+1);
            A{W}=0; B=0;
         END;
         NI=FLOOR(1+N/2); C=-1;
         DO I=1 TO NI;
            C=-C; M=I-1; IN=N-2*M; W=N+1-IN;
            IF M EQ 0 THEN CO=1;
                      ELSE CO=C*EXP(LGAMMA(N+1)-LGAMMA(M+1)-LGAMMA(IN+1)+C1
                              -LGAMMA(DK+M)-(2*M)*LOG(2));
            A{W}=CO;
            B=CO;
         END;
         IF IX EQ 1 THEN GOTO L50;
         LINK ZPOLR;
```

```
         F=2*(K-N+1)*LOG(2)+LGAMMA(N+1)+2*C1+2*LOG(2*DK);
         F=F-( 2*LOG(N)+LGAMMA(2*K-N+2)+2*LOG(2*K-N+2));
         N_1=N;
         DO J=1 TO N;
            TI=XT{J}; T_I=TI;
            LINK POLY;
            P=0.5;Q=K+0.5;
            BETL=LGAMMA(P)+LGAMMA(Q)-LGAMMA(P+Q);
            XW{J}=EXP(F-2*LOG(ABS(C))-BETL)*(1+TI*TI);
         END;
L50:  END;
      OUTPUT HARPER;
POLY:C=0;
     DO W=1 TO N_1;
        NL=N_1-W;
        Z=N_I-1;
        IF NL EQ 0 THEN C=C+B;
                   ELSE C=C+B*T_I**NL;
     END;
     RETURN;
ZPOLR:IF N=3 THEN DO;
           XT{1}=SQRT(3/(2*K-3)); XT{2}=0;XT{3}=-XT{1}; RETURN;
      END;
           ELSE DO;
           NI=FLOOR(1+N/2);
           X_FINISH=SQRT(-A{3}); X_START=SQRT(-A{2*NI-1}/A{2*NI-3});
           DEL=(X_FINISH-X_START)/500; S1=SIGN(A{W});
           N_1=N+1; I_L=FLOOR((N+.1)/2); X1=0; U1=-10;
           DO TI=X_START TO X_FINISH BY DEL;
           X2=TI; T_I=TI;
           LINK POLY;
           S2=SIGN(C); U2=C;
           IF S1 NE S2 THEN DO;
           DEL_1=(X2-X1)/100;X1_1=X1;U1_1=U1;S1_1=S1;IT=0;
           DO TI_1=X1 TO X2 BY DEL_1;
              X2_1=TI_1;T_I=TI_1;
              LINK POLY;
              S2_1=SIGN(C);U2_1=C;
              IF S1_1 NE S2_1 THEN DO;
              S0_1=S1_1;U0_1=U1_1;X0_1=X1_1;S1_1=S2_1;U1_1=U2_1;X1_1=X2_1;
LC:           XN_1=(X0_1+X1_1)/2;
              IT=IT+1;IF IT EQ 100 THEN STOP;
              T_I=XN_1;LINK POLY;UN_1=C;SN_1=SIGN(C);
              IF ABS((X0_1-XN_1)/X0_1) LT 1E-14 AND
                 ABS((X1_1-XN_1)/X1_1) LT 1E-14 THEN GOTO LD;
              IF SN_1 EQ S0_1 THEN DO;S0_1=SN_1;U0_1=UN_1;X0_1=XN_1;GOTO LC;
                              END;
                              ELSE DO;S1_1=SN_1;U1_1=UN_1;X1_1=XN_1;GOTO LC;
                              END;
LD:           XT{I_L}=-XN_1;XT{N+1-I_L}=XN_1;I_L=I_L-1;
              IF I_L=0 THEN GOTO LF;ELSE  GOTO LE;END;
           END;
           END;
LE:      S1=S2;U1=U2;X1=X2;
      END;
LF:   RETURN;
      END;
RUN;
%MEND;
```

A7.3 Polynomials for a Normal Kernel Over a Truncated Range.

```
%MACRO TRUNC(LIMIT,DEGREE);
%LET RANGE=%EVAL(&DEGREE+1);
DATA TRUNCATE;
ARRAY XT{&DEGREE} XT1-XT&DEGREE; ARRAY XW{&DEGREE} XW1-XW&DEGREE;
ARRAY GAM{&DEGREE} GAM1-GAM&DEGREE; ARRAY BET{&DEGREE} BET1-BET&DEGREE;
ARRAY ALP{&DEGREE} ALP1-ALP&DEGREE;
ARRAY ROW1  (W) R1W1-R1W&RANGE;   ARRAY ROW2  (W) R2W1-R2W&RANGE;
ARRAY ROW3  (W) R3W1-R3W&RANGE;   ARRAY ROW4  (W) R4W1-R4W&RANGE;
ARRAY ROW5  (W) R5W1-R5W&RANGE;   ARRAY ROW6  (W) R6W1-R6W&RANGE;
ARRAY ROW7  (W) R7W1-R7W&RANGE;   ARRAY ROW8  (W) R8W1-R8W&RANGE;
```

```
ARRAY ROW9  (W) R9W1-R9W&RANGE;   ARRAY ROW10 (W) R10W1-R10W&RANGE;
ARRAY ROW11 (W) R11W1-R11W&RANGE; ARRAY ROW12 (W) R12W1-R12W&RANGE;
ARRAY ROW13 (W) R13W1-R13W&RANGE; ARRAY ROW14 (W) R14W1-R14W&RANGE;
ARRAY ROW15 (W) R15W1-R15W&RANGE; ARRAY ROW16 (W) R16W1-R16W&RANGE;
ARRAY ROW17 (W) R17W1-R17W&RANGE; ARRAY ROW18 (W) R18W1-R18W&RANGE;
ARRAY ROW19 (W) R19W1-R19W&RANGE; ARRAY ROW20 (W) R20W1-R20W&RANGE;
ARRAY B (Z) ROW1-ROW&RANGE;
NO=&DEGREE;
BO=&LIMIT;
KEEP BO NO XT1-XT&DEGREE XW1-XW&DEGREE;
BO=1;
PI=2*ARCOS(0);
Z=1; W=1; B=1;
Z=2; W=1; B=1;
ARG=BO; LINK ERF;
W=2; B=-(1-EXP(-BO*BO))/(SQRT(PI)*ERFOUT);
GAM{1}=SQRT(PI)*ERFOUT/2;
DO N=2 TO NO;
   K=N-1;
   LINK PARNEXT;
   DO L=1 TO N ; XT{L}=0; END;
   Z=N+1;
   DO W=1 TO (N+1);
      B=0;
   END;
   DO L=0 TO N;
      IF L=0 THEN DO;
                  C=0; Z=N  ; W=N  ; C=C+ALP{K+1}*B;
                       Z=N-1; W=N-1; C=C+BET{K+1}*B;
                  Z=N+1; W=N+1; B=C;
                  END;
      ELSE IF L=N THEN DO;
                       Z=N+1; W=1  ; B=1;
                       END;
      ELSE IF L=(N-1) THEN DO;
                           C=0; Z=N ; W=2 ; C=C+B;
                                      W=1 ; C=C+ALP{K+1}*B;
                           Z=N+1; W=2 ; B=C;
                           END;
      ELSE DO;
           C=0; Z=N ;  W=Z-L+1; C=C+B;
                       W=Z-L  ; C=C+ALP{K+1}*B;
                Z=N-1; W=Z-L  ; C=C+BET{K+1}*B;
                Z=N+1; W=Z-L  ; B=C;
           END;
   END;
END;
LINK ZPOLR;
DO I=1 TO NO;
   T_I=XT{I};
   POLY_N=NO-1;  LINK POLY;
   POLY_N=NO  ;  LINK POLY_DER;
   XW{I}=GAM{NO}/(C*D);
END;
OUTPUT TRUNCATE;
ERF :ERFOUT=2*PROBNORM(SQRT(2)*ARG)-1; RETURN;
PARNEXT: POLY_N=K-1; T_I=BO ; LINK POLY; C_K_11=C;
         POLY_N=K-1; T_I=0  ; LINK POLY; C_K_12=C;
         POLY_N=K  ; T_I=BO ; LINK POLY; C_K_1 =C;
         POLY_N=K  ; T_I=0  ; LINK POLY; C_K_2 =C;
         GAM{K+1}=K*GAM{K}/2-(EXP(-BO*BO)*C_K_1*C_K_11-C_K_2*C_K_12)/2;
         ALP{K+1}=(EXP(-BO*BO)*C_K_1*C_K_1-C_K_2*C_K_2)/(2*GAM{K+1});
         BET{K+1}=-GAM{K+1}/GAM{K};
         RETURN;
POLY:C=0; Z=POLY_N+1;
     DO W=1 TO Z;
        NL=Z-W;
        IF NL EQ 0 THEN C=C+B;
                   ELSE DO;
                        PROD=1;
                        DO INL=1 TO NL;
                           PROD=PROD*T_I;
```

```
                    END;
                    C=C+B*PROD;
                END;
    END;
    RETURN;
POLY_DER:D=0; Z=POLY_N+1;
        DO W=1 TO Z;
          NL=Z-W;
          IF NL EQ 0 THEN GOTO LOOPEND;
          IF NL EQ 1 THEN D=D+B;
          IF NL NE 1 THEN DO;
                          PROD=1;
                          DO INL=1 TO (NL-1);
                             PROD=PROD*T_I;
                          END;
                          D=D+B*NL*PROD;
                      END;
LOOPEND: END;
        RETURN;
ZPOLR:POLY_N=NO;
      Z=NO+1; W=2;
      X_FINISH=-B;
      W=Z; B_0=B; W=Z-1; B_1=B;
      X_START=-B_0/B_1;
      DEL=(X_FINISH-X_START)/500; S1=SIGN(B_0);
      I_L=1; X1=0; U1=-10;
      DO TI=X_START TO X_FINISH BY DEL;
         X2=TI; T_I=TI;
         LINK POLY;
         S2=SIGN(C); U2=C;
         IF S1 NE S2 THEN DO;
         DEL_1=(X2-X1)/100; X1_1=X1; U1_1=U1; S1_1=S1; IT=0;
         DO TI_1=X1 TO X2 BY DEL_1;
            X2_1=TI_1; T_I=TI_1;
            LINK POLY;
            S2_1=SIGN(C); U2_1=C;
            IF S1_1 NE S2_1 THEN DO;
            S0_1=S1_1; U0_1=U1_1; X0_1=X1_1; S1_1=S2_1; U1_1=U2_1; X1_1=X2_1;
LC:         XN_1=(X0_1+X1_1)/2;
            IT=IT+1; IF IT EQ 100 THEN STOP;
            T_I=XN_1; LINK POLY; UN_1=C; SN_1=SIGN(C);
            IF ABS((X0_1-XN_1)/X0_1) LT 1E-12 AND
            ABS((X1_1-XN_1)/X1_1) LT 1E-12 THEN GOTO LD;
            IF SN_1 EQ S0_1 THEN DO; S0_1=SN_1; U0_1=UN_1; X0_1=XN_1; GOTO LC;
                            END;
                            ELSE DO; S1_1=SN_1; U1_1=UN_1; X1_1=XN_1; GOTO LC;
                            END;
LD:         XT{I_L}=XN_1; I_L=I_L+1;
            IF I_L=(NO+1) THEN GOTO LF; ELSE  GOTO LE;END;
        END;
    END;
LE:  S1=S2; U1=U2; X1=X2;
    END;
LF:  RETURN;
RUN;
%MEND;
```

A7.4 Jacobi Polynomials

```
%MACRO JACOBI(V1,V2,DEGREE);
%LET RANGE=%EVAL(&DEGREE+1);
DATA JACOBI;
ARRAY A{&RANGE} A1-A&RANGE;
ARRAY XT{&DEGREE} XT1-XT&DEGREE; ARRAY XW{&DEGREE} XW1-XW&DEGREE;
ARRAY ROW1  (W) R1W1-R1W&RANGE;   ARRAY ROW2  (W) R2W1-R2W&RANGE;
ARRAY ROW3  (W) R3W1-R3W&RANGE;   ARRAY ROW4  (W) R4W1-R4W&RANGE;
ARRAY ROW5  (W) R5W1-R5W&RANGE;   ARRAY ROW6  (W) R6W1-R6W&RANGE;
ARRAY ROW7  (W) R7W1-R7W&RANGE;   ARRAY ROW8  (W) R8W1-R8W&RANGE;
ARRAY ROW9  (W) R9W1-R9W&RANGE;   ARRAY ROW10 (W) R10W1-R10W&RANGE;
ARRAY ROW11 (W) R11W1-R11W&RANGE; ARRAY ROW12 (W) R12W1-R12W&RANGE;
ARRAY ROW13 (W) R13W1-R13W&RANGE; ARRAY ROW14 (W) R14W1-R14W&RANGE;
ARRAY ROW15 (W) R15W1-R15W&RANGE; ARRAY ROW16 (W) R16W1-R16W&RANGE;
```

```
ARRAY ROW17 (W) R17W1-R17W&RANGE; ARRAY ROW18 (W) R18W1-R18W&RANGE;
ARRAY ROW19 (W) R19W1-R19W&RANGE; ARRAY ROW20 (W) R20W1-R20W&RANGE;
ARRAY B (Z) ROW1-ROW&RANGE;
N=&DEGREE;
V1=&V1; V2=&V2;
Q=V2/2; P=(V1+V2)/2 -1;
KEEP V1 V2 N XT1-XT&DEGREE XW1-XW&DEGREE;
      DO L=1 TO N ; XT{L}=0; END;
      DO IX=1 TO 2;
         IF IX EQ 1 THEN N=N-1; ELSE N=N+1;
         Z=1; W=1; B=1;
         W=2; B=0;
         C1=LGAMMA(Q+N)-LGAMMA(P+2*N);
         Z=N;
         DO W=1 TO (N+1);
            A{W}=0; B=0;
         END;
         NI=N; C=-1;
         DO I=1 TO (N+1);
            C=-C; M=I-1; IN=N-M; W=N+1-IN;
            IF M EQ 0 THEN C0=1;
                      ELSE C0=C*EXP(LGAMMA(N+1)-LGAMMA(M+1)-LGAMMA(IN+1)+C1
                              +LGAMMA(P+2*N-M)-LGAMMA(Q+N-M));
            A{W}=C0;
            B=C0;
         END;
         IF IX EQ 1 THEN GOTO L50;
         LINK ZPOLR;
         F=LGAMMA(N)+LGAMMA(Q+N-1)+LGAMMA(P+N-1)+LGAMMA(P-Q+N)+2*LOG(P+2*N-1);
         F=F-2*LGAMMA(P+2*N-2)-LOG(N)-LOG(Q+N-1)-LOG(P+Q+N)-LOG(P+N-1);
         N_1=N;
         DO J=1 TO N;
            TI=XT{J}; T_I=TI;
            LINK POLY;
            BETPQ=LGAMMA(P)+LGAMMA(Q)-LGAMMA(P+Q);
            XW{J}=EXP(F-2*LOG(ABS(C))      )*TI*(1-TI);
         END;
L50:  END;
      OUTPUT JACOBI;
POLY:C=0;
     DO W=1 TO N_1;
        NL=N_1-W;
        Z=N_1-1;
        IF NL EQ 0 THEN C=C+B;
                   ELSE C=C+B*T_I**NL;
     END;
     RETURN;
ZPOLR:DEL=1/1000; S1=SIGN(A{W});
      N_1=N+1; I_L=1; X1=0.000001; U1= 10;
      DO TI=X1  TO (1-DEL)  BY DEL;
         X2=TI; T_I=TI;
         LINK POLY;
         S2=SIGN(C); U2=C;
         IF S1 NE S2 THEN DO;
         DEL_1=(X2-X1)/100;X1_1=X1;U1_1=U1;S1_1=S1;IT=0;
             DO TI_1=X1 TO X2 BY DEL_1;
                X2_1=TI_1;T_I=TI_1;
                LINK POLY;
                S2_1=SIGN(C);U2_1=C;
                IF S1_1 NE S2_1 THEN DO;
                S0_1=S1_1;U0_1=U1_1;X0_1=X1_1;S1_1=S2_1;U1_1=U2_1;X1_1=X2_1;
LC:             XN_1=(X0_1+X1_1)/2;
                IT=IT+1;IF IT EQ 100 THEN STOP;
                T_I=XN_1;LINK POLY;UN_1=C;SN_1=SIGN(C);
                IF ABS((X0_1-XN_1)/X0_1) LT 1E-12 AND
                   ABS((X1_1-XN_1)/X1_1) LT 1E-12 THEN GOTO LD;
                IF SN_1 EQ S0_1 THEN DO;S0_1=SN_1;U0_1=UN_1;X0_1=XN_1;GOTO LC;
                                END;
                                ELSE DO;S1_1=SN_1;U1_1=UN_1;X1_1=XN_1;GOTO LC;
                                END;
LD:             XT{I_L}=XN_1; I_L=I_L+1;
                IF I_L=N_1 THEN GOTO LF;ELSE  GOTO LE;END;
```

```
            END;
            END;
LE:       S1=S2;U1=U2;X1=X2;
      END;
LF:   RETURN;
RUN;
%MEND;
```