International Society for Clinical Biostatistics News

Number 15 December 1993 Editor: David W. Warne

Executive Committee 1993/94

(= elections at AGM, 1994: see p.18)*

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Editorial

Welcome to the 241 new ISCB members who joined by attending ISCB14-Cambridge'93. This meant 2/3 of the attendees were newcomers. Your attendance also resulted in the number of ISCB members increasing by 50%.

In this even more action-packed issue, continuing the trend of expansion by at least 60% each issue, you'll find some more look backs at Cambridge, including an article on Medical Statistics Education. There are also lots of book reviews (I'd appreciate some new books please, publishers !), and reports on developments in regulation from SEDREG. Recently it was decided that the European Medicines Evaluation Agency will be sited in London, UK.

Thanks to all the contributors to this issue, and to Prof. McPearson who sennt me some typed articles at the last minute. The deadline for the next issue is the end of March 1994, so please send in your articles, on a 3.5" disk, Word format, if at all possible to me by then.

Index

ISCB Membership

The ISCB membership reached a new peak of 715 after Cambridge. Hopefully 1994 will see many new members joining and taking advantage of reduced fees for ISCB15-Basle.

#	Country	31/Dec/92	09/Jun/93	ISCB14	06/Dec/93
1	UK	90	65	128	176
2	Germany	67	45	39	75
3	France	52	38	26	62
4	Sweden	51	42	22	53
5	USA	45	26	16	40
6	Netherlands	30	23	23	38
7	Denmark	58	24	23	38
8	Italy	33	26	23	37
9	Belgium	22	18	13	27
10	Norway	18	18	10	25
11	Switzerland	25	16	8	22
12	Spain	12	11	9	18
13	Hungary	1	21	1	17
14	Canada	12	12	5	14
15	Australia	9	8	2	11
16	Austria	9	5	6	11
17	Poland		11	2	11
18	Finland	7	5	4	7
19	Japan	6	4	4	7
20	Portugal	3	3	2	5
21	Israel	3	2	3	4
22	South Africa	1	1	3	4
23	Ireland	2	2	1	3
24	Slovenia	1	1	1	2
25	China	1		1	1
26	Czech Rep.		1		1
27	Greece	1		1	1
28	Honk Kong	1	1		1
29	India	1	1		1
30	Kenya	1		1	1
31	Thailand	1			1
32	Turkey	1			1
33	New Zealand	1			
	TOTAL	**563**	**430**	**377**	**715**

Questions & Answers

A Question that arose in my mind when I took over editing ISCB News was "who are the ISCB members: what do they do and which other journals and newsletters do they subscribe to ?". Over the past few years, ISCB has asked itself what its role should be. In particular, should it aim to do more than hold a conference each year ? I have included a short questionnaire with this newsletter, to be returned with the subscription form, asking for a little information about the ISCB membership.

Aims of ISCB

The Society was founded to stimulate research on the principles and methodology used in the design and analysis of clinical research, to increase the relevance of statistical theory to the real world of clinical medicine, and to provide a common forum through meetings and publications for the exchange of knowledge, experience and ideas among clinicians, statisticians and members of related disciplines (e.g. epidemiologists, clinical chemists and clinical pharmacologists) working or interested in the field of clinical biostatistics.

The Wife, the Walking Stick and the Adverse Experience, or

The Perils of not Thinking Counterfactually

by Guernsey McPearson

A man used to beat his wife every day with a walking stick. One day the stick broke so he bought a new one in order to continue beating her. This he duly did with the same regularity and application he had shown with the old stick. Some weeks after the purchase of the new stick he decided to take out a life insurance policy on his wife. A stipulation of granting the policy was that his wife be given a medical examination. The doctor on examining the wife found her to be covered with bruises and discovered that she was regularly beaten with a walking stick. He sought an interview with the husband and said, "You must stop beating your wife with your walking stick. It is causing her to have the most horrible bruises." The husband replied, "That's impossible. She had the bruises before I beat her with this walking stick".

I must apologise, gentle reader, for having subjected you to this horrific story. Clearly you have seen through the husband's faulty logic. He was comparing "before" with "after" instead of thinking counterfactually. In order to judge the effect of beating, he should have compared the condition of his beaten wife with the condition she would have been in had he not beaten her.

A number of patients in a clinical trial comparing a new to a standard ACE inhibitor had a cough throughout the trial. However, most of these had a cough before entering the trial and their cough was therefore judged to be unrelated to treatment. At the end of the trial the following table was produced.

	Standard treatment	New treatment	TOTAL
Patients with treatment related cough	5	6	11
Other patients	95	94	189
Total	100	100	200

It was concluded that there was no evidence of any difference between treatments as regards their effect on cough.

Now this, of course, is quite another matter. This is a standard way of looking at adverse experiences and so must be correct, because if it weren't correct, it would imply that many statisticians and physicians working in drug development and regulation were wrong, and this is such a fantastic notion that it may be dismissed out of hand without further discussion.

However, a heretical trouble-maker of a statistician of the McPearson school of statistics was unhappy with this presentation of results and went back to the original data. He produced the following cross-classifications.

Patients having cough at baseline

Status during trial	Standard Treatment	New Treatment	TOTAL
Cough	40	10	50
No cough	5	33	38
TOTAL	45	43	88

Patients not having cough at baseline

Status during trial	Standard Treatment	New Treatment	TOTAL
Cough	5	6	11
No cough	50	51	101
TOTAL	55	57	112

This statistician then had the cheek to calculate the Mantel-Haenzel statistic for the data as cross-classified, coming to the conclusion that there was, indeed, a highly significant difference between the two treatments. He further went on to claim that many of the patients entering the trial were, in fact, receiving treatment from an ACE inhibitor before entry into the trial, that many of these suffered from "cough" and that most of those allocated to standard treatment continued to suffer this treatment related side-effect.

My question to you, gentle reader, is this, "Can you spot the fallacy in this statistician's logic ?", because I can't.

Book Review # 1 by Anna Bartkowiak, Wroclaw, Poland

Handbook Of The Logistic Distribution (Statistics Textbooks and Monographs 123)
edited by N. Balakrishnan
Marcel Dekker (1992)

Having been involved for some time with the logistic distribution, I thought that I knew a thing or two about it. Nonetheless, when I got the book I was surprised that so much could be written about this distribution. I think Balakrishnan should be admired for arranging the authors and the contents of the book. Both more theoretical and applied statisticians can find interesting presentations.

The volume is in 18 chapters and Balakrishnan is the author or co-author of 8 of them. There are, in total, 33 contributing authors: one of them resident in India, one in Europe, 5 in Canada and the remaining in USA. The only European is Dieter Rasch, at the time of writing his contribution still in Rostock, Germany.

Looking at the titles of the chapters, these are: 1. Introduction and Historical Remarks. 2. Logistic Order Statistics and Their Properties. (3) and 4. Maximum Likelihood Estimation Based on Complete (and Type II) Censored Samples. 5. Reliability Estimation Based on MLEs for Complete and Censored Samples. 6. Ranking and Selection Procedures. 7. Characterizations. 8. Translated Families of Distributions. 9. Univariate Generalized Distributions. 10. Some Related Distributions. 11. Multivariate Logistic Distributions. 12. Outliers and Robustness of Estimators. 13. Goodness of Fit Tests. 14. Tolerance Limits and Sampling Plans Based on Censored Samples. 15. Logistic Stochastic Growth Models and Applications. 16. Logistic Growth Models and Related Problems. 17. Applications in Health and Social Sciences. 18. Some other Applications.

From the titles of the chapters, one can see that the major part of the book is a study of the logistic distribution by applying to it some (not all) modern tools of mathematical statistics. The more "practical" chapters are the three last ones. The role of the logistic function in discriminant analysis is not exposed; for instance the role of the logistic function in medical diagnosis is mentioned only marginally. In the index, the keyword "discriminant analysis" does not appear at all, although some relevant papers (e.g. Walker & Duncan, or Anderson) are cited in the references.

The Bibliography comprises 557 references but, to my point of view, some interesting European papers are missing; I think here about the papers by Lesaffre [1,2,3] and Krusinska [4,5,6,7].

[1] Lesaffre E., Albert A., An uncertainty measure in logistic discrimination. Statistics in Medicine (1988), 7, 525-533.
[2] Lesaffre E., Willems J.L., Detection of outliers and influential observations in a multigroup ECG logistic model. In Willems J.L., van Bemmel J.H., Zywietz C. (eds). Computer ECG Analysis: Towards Standarization. North Holland , Amsterdam (1986), 347-352.
[3] Lesaffre E., Willems J.L., Measuring certainty of a decision rule with applications in electro-cardiography. Methods of Information in Medicine (1988), 27, 155-160.
[4] Krusinska E., Generalized Walker-Duncan procedure for obtaining maximum likelihood estimates of parameters of logistic discriminant function, Biometrical Journal (1988), 30, 259-274.
[5] Krusinska E., Logistic discrimination, Applied Mathematics Letters (1988), 1, 357-360.
[6] Krusinska E., Liebhart J., Robust logistic discriminant functions in diagnosing chronic obstructive airways disease. Computers in Biology and Medicine (1990), 20, 351-359.
[7] Krusinska E., An exploratory criterion for variable selection in Logistic discrimination. Applied Mathematics Letters (1993), 6, 39-42.

RANDOM HARVEST

A Muesli of Quotations Culled by Guernsey McPearson (Second helping)

In criticism of randomisation ? *Gott würfelt nicht ?*
(God doesn't play dice.)
Einstein

But had he read the Pentateuch ? ... *the land shall be divided by lot.*
Numbers

I think we have met him. *He would move both heaven and hell, and twist every thing in nature to support his hypothesis.*
Sterne, Tristram Shandy

On the value of statistics ? *I know that two and two make four - and should be glad to prove it if I could, though I must say if by any sort of process I could convert 2 and 2 into five it would give me much greater pleasure.*
Byron

On measuring the quality of life. *Which of your Philosophical Systems is other than a dream theorem; a net quotient, confidently given out, where divisor and dividend are both unknown ?*
Carlyle, Sartor Resartus

On sub-group analysis and patient by treatment interaction. *The play, I remember, pleased not the million; 'twas caviare to the general.*
Shakespeare, Hamlet

On mathemagenic disease:
When the proofs were ranged in columns
When I was shown the charts and diagrams, to add divide and measure them ...
How soon unaccountable I became tired and sick
Walt Whitman

On why the work of the medical statistician is sometimes difficult: *Tout au contraire des Théologiens, les medecins et les philosophes n'admettent pour vrai ce qu'ils peuvent expliquer et fond de leur intelligence la mesure des possibles.*
(Unlike theologians, physicians and philosophers will only accept as true that which they can explain and make their intellect the yardstick of the possible.)
Rousseau

Multivariate analysis ? *It is a tale/ Told by an idiot, full of sound and fury, / Signifying nothing.*
Shakespeare, Macbeth

On the art of reviewing ? *He unravels the web of argument and pieces it together again; folds it up and lays it aside, that he may examine it more and at his leisure. He hugs indecision to his breast and takes home a modest doubt or a nice point to solace himself with it in protracted, luxurious dalliance. Delay seems, in his mind, to be the very essence of justice.*
Hazlitt

Secretary's Report For The Year 1992/1993

by Stephen Senn

Introduction

The honorary secretary of the society has a confession to make: he is sailing under false colours. With the transfer of the membership list from the British Association of Pharmaceutical Physicians in London to our treasurer in Copenhagen it soon became clear that a more efficient way to deal with membership enquiries would be for these to be directed straight to Copenhagen. I therefore owe a deep debt of gratitude to Karsten Schmidt who has effectively been carrying out most of the work of the secretary for me. I report below the few matters that remained for me to deal with.

Newsletter

My most urgent duty was to appoint a newsletter editor for the society, a task that proved remarkably difficult. Having scoured the Earth for a suitable candidate and having received unanimous refusals, I eventually decided to look nearer home and succeeded in persuading David Warne, whose office is only 30 paces from my own, to take over the task. I hope all members have been pleased with the result. David has worked very hard to produce two fine editions of the Newsletter. The future of this is surely secure as the journal can only improve as members rise to the challenge of driving the secretary's articles from the pages of our newsletter by contributing pieces of their own. NOW is an ideal moment to write that piece you always intended to contribute. Why not write a letter ? Ideally this could complain about something. This would then require a reply and in this way the pages get filled up, we are entertained and the activity of the Society is increased.

Future meetings

My other task was to secure a venue for the 1994 meeting of ISCB. Again I decided to look locally and was able to secure the agreement of my boss Jakob Schenker to organise ISCB 15 in Basle. He has put in a great effort to get things organised and our plans are well underway. Unfortunately the skills of a manager include delegation and so some of the work has come home to roost in the Honorary Secretary's office ! Joking apart, however, and speaking on behalf of the ISCB Executive Committee we are all very grateful to Jakob, and the other members of the organising committee Uwe Ferner and Walburga Rieser, for their willingness to take on this task at short notice. My colleague Amy Racine is chairing the Scientific Committee and as you will see from the call for papers her plans are well advanced.

For ISCB16, 1995 we have an offer from Barcelona, Spain that looks very promising. There are as yet no firm plans for ISCB17, 1996, although Budapest is being considered by the ExCom. For ISCB18 in 1997. Ed Gehan has been liaising with Susan Ellenberg of The Society for Clinical Trials regarding the possibility of a joint meeting in the USA.

Constitution

Mats Lörstad did a magnificent job as honorary secretary in attempting to bring clarity into the constitution and succeeded in proposing and steering several necessary amendments through the annual general meetings. I took it upon myself to review the constitution to see if any further work was necessary. Unfortunately I could not turn up a copy of the revised constitution anywhere in the Society's files. Eventually, however, with Mats' help I was able to obtain a copy and this has now been typed onto a diskette that will facilitate the business of future updates, possibly in 1994.

Secretary's Report (continued)

Contact with other Organisations

The Society has made small donations to the Biometry Fund and the Royal Statistical Society's Bradford Hill medal fund. We have continued our connections with John Wiley and *Statistics in Medicine* and the proceedings of the Copenhagen meeting will be published in that journal. Ed Gehan has made informal contacts with the ISI regarding affiliation. He has also been pursuing the possibility of a joint meeting of the ISCB and the Society for Clinical Trials in 1997 (see above). Through SEDREG we have had contact with the EC [now EU, ed.] commission and various local and international statistical organisations. SEDREG activities have been reported in the Newsletter. Karsten Schmidt has been in contact with the Klinikai Biostatisztikai Tarsasag in Hungary who operate as a local group of ISCB [members in Poland and Hungary are supported by ISCB, and each group receives one free copy of *Statistics in Medicine* courtesy of John Wiley, ed.].

Miscellaneous

Various miscellaneous correspondence has been dealt with, in particular many requests for information that, unfortunately, usually have to be answered "no". Thus, for example, the request of a prominent statistical publisher to obtain our membership list was not granted (they have yet to reply to our hint that they might wish to advertise in the Newsletter) and with much regret I had to inform an extremely courteous gentleman writing from Alaska that the society did not have any records regarding the worldwide use of nitrous oxide for medical purposes. But enough of all this gassing on. It is time to bring this report to a close.

Sir Austin Bradford Hill FRS (1897-1991)

from John Matthews, Honorary Secretary, Medical Section, Royal Statistical Society

Sir Austin Bradford Hill made fundamental contributions to most branches of Medical Statistics. In the public mind he is usually remembered for his work with Sir Richard Doll on the link between lung cancer and smoking. This is merely the most widely recognized of his many epidemiological contributions, which also include his well-known criteria for causality.

Perhaps his greatest influence on medical research stems from his early and strong advocacy of controlled clinical trials. He was one of the first to recognize the importance of randomization and of controlled studies, and many of the most important articles can be found in his book "*Statistical Methods in Clinical and Preventive Medicine*" (sadly, now out of print). These luminous accounts of the philosophy behind, and implementation of his ideas in a now famous series of trials for the treatment of tuberculosis, still repay careful study. A fine overview of the many facets of Sir Austin's contributions can be found in the issue of *Statistics in Medicine* (1982, volume 1, number 4) dedicated to him on the occasion of his 85th birthday.

To honour the achievements of one of the most eminent medical statisticians of the century, The Royal Statistical Society has established the Bradford Hill Medal, which will be awarded every three years for excellence in medical statistics. The Society is delighted that the International Society for Clinical Biostatistics has been able to support this venture with a donation of £100, which will not only commemorate Sir Austin, but also promote the subject of which he was such a master.

ISCB Accounts

At the 1992 AGM in Copenhagen, it was asked if the members could have a statement of the society's accounts. The then treasurer promised he would produce a statement up to the end of 1991. As those of you who attended the AGM in Cambridge will know, unfortunately we are still waiting... This also has the unfortunate effect of making it impossible for Karsten Schmidt to produce accounts to the end of 1992. As announced at the 1993 AGM, efforts are being made by the ExCom Officers to check transcripts of the Society's transactions for August 1990 - August 1992 to see if all major amounts can be accounted for. Despite the confusion, the ExCom does not expect there to be further problems.

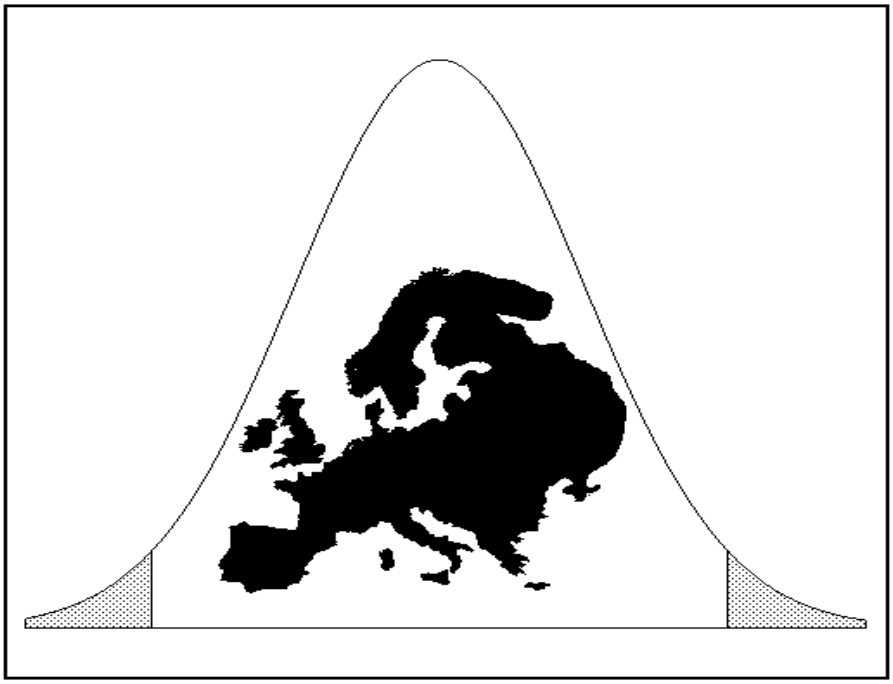
Accounts for ISCB14 will be presented next time (audited by Stephan Evans). The Society's accounts will be audited S. Møller in the future. Meanwhile, here's the statement that was presented to the AGM:

Account as per September 15, 1993

		£
Income		
	Membership fees	6,407.50
	Statistics in Medicine	18,050.00
	Advertising revenue	185.00
	Earned interest	1,233.09
		25,875.59
Expenditure		
	Stationery, postage, fax, photocopies	5,591.57
	Administration	2,715.18
	Bank charges	292.61
	John Wiley, Statistics in Medicine	18,525.00
	SEDREG expenses	457.86
	Printing of Newsletter No. 14	468.32
	Donation to RSS, Sir Bradford Hill Medal	100.00
	Miscellaneous	252.01
		28,402.55
Assets		
	Current bank account	2,369.38
	High interest bank account	47,786.87
	Debtors	185.00
	Seed money ISCB 14	10,000.00
	Seed money ISCB 15	5,000.00
	Revenue ISCB 13	21,354.51
		86,695.76
Liabilities		
	Accrued expenses	2,484.73
EQUITY CAPITAL		84,211.03

from Rolf Holle

EUROPEAN NETWORK FOR EDUCATION IN MEDICAL STATISTICS



In a project funded by the ERASMUS programme of the European Community, several universities with postgraduate courses in the field of Medical Statistics are cooperating with the aim of harmonizing these studies and to prepare future student exchanges.

After one year of work, the project group has presented their first results in the form of a small booklet under the title of "Study Guide on Postgraduate Education in Medical Statistics in Europe". The project and the study guide were presented in an extra session at the ISCB 14 conference in Cambridge. For those members of the ISCB who are interested in education in Medical Statistics, but could not attend the conference or the session, we would like to make information about the project available.

The study guide booklet includes detailed information about 13 existing postgraduate education programmes in Europe as well as short information (contact addresses) about related activities at about 20 other universities. In addition, it contains recommendations for a model curriculum for postgraduate education in Medical Statistics. The study guide is intended to serve as a source of information for students and teachers interested in exchange within Europe and especially for those who are actively engaged in education in Medical Statistics.

If you are interested in receiving a free copy of the study guide booklet, please contact:

Dr. R. Holle, Inst. für Med. Biometrie und Informatik, Universität Heidelberg,
Im Neuenheimer Feld 305, D-69120 Heidelberg, Germany.
Tel: +39 6221 563473 or 564141, Fax: +39 6221 564195

Book Review # 2 by Peter Armitage, Wallingford, England-UK

Biopharmaceutical Sequential Statistical Applications (Statistics Textbooks and Monograph 128)
by Karl Peace
Marcel Dekker (1992)

If, as F.J. Anscombe asserted 30 years ago, 'sequential analysis is a hoax,' it must be one of the most persuasive confidence tricks in the history of statistics. For this interesting volume shows that it is an active concern amongst statisticians in the pharmaceutical industry, a market environment in which ideas are unlikely to survive unless they are commercially viable.

Apart from these introductory chapters on sequential methods and interim analyses, the book contains 19 case studies. Most of these are Phase 2 or 3 clinical trials, with some concentration on cancer, AIDS, cardiovascular and gastrointestinal diseases. Some of the accounts are prospective, describing protocols of trials in progress; some describe analyses of trials recently finished; and one is retrospective, inquiring what would have happened in an already completed trial if sequential methods had been used. There is the expected focusing on topics such as rules for interim stopping (particularly the O'Brien-Fleming rule and the Lan-DeMets alpha-spending approach), and for stochastic curtailment. The latter approach, permitting early termination if it can safely be predicted that the final analysis will show no significant effect, is of dubious value in most large scale Phase 3 trials, but may come into its own in the industrial setting where unpromising regimes need to dropped as soon as possible. There is inevitably some repetition of exposition, as the same themes recur in different chapters. But other topics are raised briefly, such as the sequential revision of sample-size estimates, data-dependent allocation, and Bayesian methods.

Most of these accounts deal in some detail with the practical aspects of data management and decision making. They usefully illustrate the point that, in practice formal sequential procedures are likely to be at best guidelines for action rather than rigid prescriptions to be followed automatically.

The longest chapter, by P.I. Feder and colleagues, takes a broader view of sequential experimentation, as a progression from one stage to another in a programme of related research. the topic here is the estimation of properties of a quantal response curve, where the various features of interest such as the slope, LD50, LD90 etc. make different demands on the design. The choices of doses at each stage depends on the information previously obtained, and on extensive computer calculations of the variances of estimates under alternative designs. The method may unfortunately be made invalid by instability of the response curve between the various stages.

This book is not a manual on sequential methods, but it exemplifies the advantages, as well as the problems, of the sequential approach, and usefully complements the more theoretical expositions found elsewhere. It should be read critically, as there are a number of minor typographical slips.

Books and Software for Review

Books

(1) The following books were all sent to my predecessor, Jørgen Seldrup, in 1992 or earlier, and are still available for review. Please contact the editor if you would like one or more of them. Reviewers are allowed to keep the book(s) that they reviewed (3.5" disks preferred, deadline for reviews: end of March 1994). Publishers: please send me some new books !

Marcel Dekker, New York & Basel:

Kocherlakota S & Kocherlakota C (1992)
Bivariate discrete distributions

Lutz EW (ed) (1991)
Future demographic trends in Europe and North America: What can we assume today ?

Mathai AM & Provost SB (1992)
Quadratic forms in random variables: Theory and applications

Wadsworth, Belmont:

Maxwell SE & Delaney (1990)
Designing experiments and analyzing data: A model comparison perspective

PWS-Kent, Boston:

Ott L & Mendenhall W (1990)
Understanding Statistics

Scheaffer RL (1990)
Introduction to probability and its applications

(2) Reviews to come next time (all Marcel Dekker):
P. North: Chow & Liu: Design and analysis of bioavailability and bioequivalence studies
D. Owens: Guarino: New drug approval process
Singer & Upton: Guidelines for laboratory quality auditing

Software

(3)(a) **RANDOM v5.0**, a commercially produced program for generating randomization lists and labels for a variety of designs has been sent to the editor for review by Dr. Wiedey GmbH, Konstanz, Germany.

It comes on a 3.5" or 5.25" diskette and runs in German and now in English. A 20 page manual accompanies the disks and is also in German, although an English translation will be produced on demand. Since this is a commercial package (not shareware or public domain software), the reviewer will be offered the chance to purchase the program for a reduced price; normally it costs DM 625 (about £250).

(3)(b) **PEST3** is the new version of the highly successful sequential methods program produced by Reading University, England-UK, and used and supported by many leading pharmaceutical companies.

My Biometrics department was lucky enough to have a course recently given by John Whitehead and Caroline Ellwood, during which PEST was available for demonstrations. It's an extremely user-friendly package and could save your trials recruiting too many patients thus saving money whilst allowing decisions to be made earlier, benefitting the patients. The package costs £700, or £400 for academic institutions. If you would like to try it out, please request the disks and manual from the editor. Since this is such a comprehensive package, a review of at least one side of A4 is requested, on a 3.5" disk if possible.

(4) Reviews to come next time:
S. Evans: N, Nsurv, TESTIMATE (IDV, Gauting)

SEDREG: Progress Report

from Karsten Schmidt

At the recent SEDREG meeting at Cambridge, it was agreed that a press release be sent to the media in the EC countries after the DIA *Forum on European Biostatistics Guidelines* in London in October. A copy is enclosed on page 13. Seven principles concerning "Statisticians in European Regulatory Agencies - A Summary" are on page 14.

In the UK, *Scrip* has reacted to the press release and has published a report on 29th October 1993:

Too few statisticians in EC ?

Plans for the European Medicines Evaluation Agency will "perpetuate the inadequacies of the present nationally based drug regulatory procedures", according to the International Society for Clinical Biostatistics, which is calling for a better use of statistics in EC drug licensing procedures.

At a recent Drug Information Association forum, ISCB, a European association for statisticians in the medical and pharmaceutical field, said that "the opportunity to create an EC regulatory body of pre-eminent medical and scientific standing in this important field is apparently being missed. Reliance on variably staffed national authorities will continue, and variations in the appropriateness and consistency of licensing decisions may be expected".

ISCB complains that, although statistical expertise is essential for planning, executing and interpreting the results of clinical trials and other studies on which licence applications are based, very few statisticians are employed by national regulatory agencies in the EC. There was, however, an announcement at the meeting that a statistician is to be appointed to the UK MCA.

... guideline

The forum was organised to promote discussions of a newly drafted guideline on the design, conduct and analysis of phase III clinical trials. The guideline was drawn up at the request of the EC CPMP by a group of statisticians from Germany and the UK, co-ordinated by Professor David Jones of the CSM and Joachim Roehmel of the BGA. The deadline for comments on the draft is November 15th.

Some of the main concerns expressed about the draft at the meeting were that it should stress the role of the statistician rather than statistics; it should not rule out crossover trials in phase III; and that multicentre trials should be presented in a more positive light. The efficiency and usefulness of a log of patients not entered in trials was also questioned.

In Denmark, the press release was cited in a couple of trade & industry magazines. The following is a free translation and a brief summary of 2 replies in *Urgebrevet Danske Erhverv*:

Manager of the Licensing Department of Leo Pharmaceutical Products, Ms Edel K. Seidenschnur, is of the opinion that the need for employing biostatisticians at the Danish National Board of Health is not so pronounced. The Danish National Board of Health and the national authorities in the European Community employ experts within the various therapeutic/medicinal areas; experts with thorough knowledge of statistics, although they are not statisticians. Leo Pharmaceutical Products has not experienced inadequate statistical expertise for the judgement of statistical issues in their product documentation.

In the Danish National Board of Health, Ms Brigitte Kristensen, Head of the Licensing Secretariat, is of the opinion that the tasks of the European Medicines Evaluation Agency comply with the attitudes of the Danish authorities. By utilising the expertise of the national health authorities, it is avoided that an "ivory tower" is built in the European Community, dealing with tasks already being taken care of in the individual member countries. The non-employment of biostatisticians is not a critical issue as the Danish National Board of Health has assigned persons from other areas competent for handling new drug applications; with their professional background they are qualified to evaluate whether statistical requirements for clinical trials are fulfilled.

7/10/93

PRESS RELEASE - ISCB*

New European drug licensing agency fails to win approval

Plans for the European Medicines Evaluation Agency (EMEA) - the body being set up to oversee licensing of new medicines in the European Community (EC) - will perpetuate the inadequacies of the present nationally based drug regulatory procedures, delegates heard in London yesterday at a Drug Information Association forum.

The opportunity to create an EC regulatory body of pre-eminent medical and scientific standing in this important field is apparently being missed. Reliance on variably staffed national authorities (such as the Medicines Control Agency in the UK) will continue, and variations in the appropriateness and consistency of licensing decisions may be expected. Poor licensing decisions may lead to approval of products whose safety is questionable or whose efficacy is inadequate, or to delays in the approval of products representing beneficial advances in therapy.

As a neutral forum, the DIA meeting was organised by member statisticians to promote discussions of newly drafted guidelines intended to improve the statistical quality of licence applications in the EC. Statistical expertise is essential in planning, executing and interpreting the results of clinical trials and other studies providing the evidence on which licence applications are based. Participants included representatives of several key professional groups and organisation in the field of medical statistics, and some of the large number of statisticians employed by pharmaceutical companies in Europe. In contrast, very few statisticians are employed by national regulatory agencies in the EC; most such agencies employ no statisticians. Regulatory statisticians from Germany, Sweden and the UK were present at the DIA forum.

Up to 300 M residents of the EC - potential patients - as well as pharmaceutical companies, may be the losers if the opportunity to upgrade statistical (and other relevant professional - medical, pharmaceutical, etc.) expertise is not taken during development of the EMEA.

Although it is easy to lie with statistics, it is difficult to establish the truth in this important area of drug regulation without statistics and statisticians.

More details from: Professor John Lewis.
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Note: ISCB stands for International Society for Clinical Biostatistics - a major professional society for statisticians in the medical and pharmaceutical field in Europe. A working group of ISCB especially concerned with regulatory issues is led by an executive team consisting of Professor J.A. Lewis (UK, Chair), Dr. Bernhard Huitfeldt (Sweden), Professor David Jones (UK), Dr. Karsten Schmidt (Denmark).

SEDREG: Progress Report (continued)

Statisticians in European Regulatory Agencies - A Summary

1. **Statistical issues of design and analysis are of crucial importance in the proper evaluation of the safety and efficacy of new medicines. (See EC Guideline on Good Clinical Practice).**

2. **Therefore statisticians are essential members of committees and teams who review drug submissions for regulatory purposes.**

3. **Balanced teams containing the right mix of skills are more effective than unbalanced ones, whatever the ceiling on total numbers of staff.**

4. **Currently the number of statisticians employed by European regulatory agencies, either directly or on advisory committees, is far below the level required to achieve balanced review; a great deal of review work is undertaken without access to statistical expertise.**

5. **The development of the European Medicines Evaluation Agency (EMEA) provides an ideal opportunity to get the balance right and to set the standards for Member States.**

6. **Early appointment to EMEA of one or more full-time senior statisticians, well respected in the field of drug development, will provide the best chance of ensuring that the number of statistical staff eventually recruited is right (neither too few nor too many), that they undertake the most valuable tasks, and that they gain appropriate support from academic colleagues.**

7. **The tasks of these staff should include the maintenance of guidelines, and interaction with industry statisticians as well as the review of submissions.**

Book Review # 3 by Anna Bartkowiak, Wroclaw, Poland

Cross-Over Experiments. Design, Analysis, and Application (Statistics Textbooks and Monographs 135)
by David A. Ratkowsky, Marc A. Evans, J. Richard Alldredge.
Marcel Dekker (1993)

A cross-over trial, also called a cross-over experiment, is a kind of repeated measurements design, carried out in such a way that a sequence of two or more treatments is applied to each subject. Multiple use of the same subject may be justified when we can expect an increase in precision resulting from less variability within subjects than between subjects. An important feature of the cross-over design is the presence of, and the ability to measure, "carryover" effects. These may result from a "late response" to a treatment in a clinical trial, or may represent a "learning effect" or a "fatigue" effect in psychological tests. When such an effect is supposed to be present than it is very important to plan the design in such a way that direct treatment effect and the "residual" treatment effect, i.e. the carryover effect, are properly recognized and separated.

The book is in 9 chapters. In the first chapter, an introduction and explanation of all the basic concepts are given. The authors start by presenting a double Latin square design with real data, and part of the corresponding output from SAS. Next the authors immediately start giving comments on the output. At this moment a non-mathematician with a moderate statistical background and without knowledge of the mixed-effects ANOVA may have the feelings of somebody being thrown into a cave where the dwellers speak a slang language (that of SAS people) and address the newcomer in their language: this may be a shock. However, after a while, s/he starts to pick out some repeated expressions and to connect with them some meanings.

After a short time, the newcomer becomes familiar with the model equation, with coding the data for evaluations by SAS and calling the subroutine GLM. S/he knows how to look for the treatment and carry-over effects in the output, and also becomes familiar with the covariance of the estimated effects.

Next quite smoothly the concepts of efficiency of the design, the "direct" treatment effect efficiency and the "carryover" effect efficiency are introduced. Surprisingly, this is done in such a way that even the newcomer knows what it is about.

A real example illustrating the needs of separating direct treatment effects from carryover effects is discussed in detail. Nonetheless, the statistical analysis in that chapter appears like magic: some data are thrown into the black box (SAS); wherefrom some results emerge. The authors' task is interpreting the results. The mathematical background of the operations performed in the black box is hidden. It is said that this is postponed to Chapter 8.

In the chapters 2-6, the authors consider the Latin squares designs (Ch. 2), The 2-treatment, 2 period, 2-sequence design (Ch. 3) and its modifications (Ch. 4), Crossover-designs with variance balance (Ch. 5) and those lacking variance balance (Ch. 6). Chapter 7 is devoted to analysis of categorical data coming from cross-over designs. Some unpublished results of the authors appear here for the first time.

In all these chapters the authors show in detail numerous designs together with the corresponding model equations and macros for SAS. Choosing SAS for calculations is not essential; it is only a matter of convention.

Chapter 8 is entitled "Ordinary Least Squares Estimation Versus Other Criteria of Estimation: Justification of the Methodology Presented in This Book". The assumptions underlying OLS are discussed. A method for checking the assumption of normality (the normal probability plot and the Wilk-Shapiro statistics) were presented and employed already in previous chapters. Another important assumption is that of independent errors. Obviously this assumption cannot be sustained in cross-over designs. However, it is the form in which the dependencies occur which determines whether or not the OLS estimator will be appropriate. In fact, what is needed is the presence of so called Type H covariance structure (Huynh and Feldt, JASA, 1970, pp. 1582-9). This type of structure and consequences of using different covariance structures are neatly explained.

In Chapter 9, entitled "Other topics on Cross-over Designs" we find a section about the Bayesian approach to the cross-over design. Each chapter gives several exercises to be solved by the reader. The book has 94 references.

I found the book especially valuable for the practitioner and I see the book as a must in the library of a researcher involved in cross-over experiments. The book might be used as a reference book or as a help when designing an experiment or/and writing down the model equation for the planned experiment. Chapter 8 is extremely important, discussing the assumptions underlying OLS, in particular the needed form of the covariance structure (the Type H structure is little known).

On the other hand, I felt that the book was somehow unbalanced with respect to the theoretical basis of the analyses. It is not explained how the expected sums of squares are evaluated, what really the type I and type II sums of squares mean and how (on the basis of such principles) the significance tests are constructed. Referring to a SAS manual is not sufficient for a general monograph. The authors do not advise wherefrom such a knowledge might be acquired. Quite popular books by Scheffe [1] and Horton [2] explaining how the expected sums of squares are built when both fixed and random effects are present in the model, are not even mentioned in the references. Recently [3] Wiley has issued a book on the same topic; however neither this book nor any other work by Senn is mentioned in the references.

References:

[1] H. Scheffe: The analysis of variance. Wiley (1959).
[2] R. L. Horton: The general linear model. Data analysis in the social and behavioural sciences. McGraw-Hill (1978).
[3] S.J. Senn: Cross-over trials in clinical research. Wiley (1992).

Organise an ISCB Conference ? - Well, Maybe...

by Simon Day

So last time I wrote full of enthusiasm about how much fun it was doing the organising. This time I write some more.

I thought the organising finished at 11:30pm on Saturday 18th September. That was when I arrived in Cambridge, having spent a rather unpleasant time on our congested M25 (London orbital) motorway. Still, I was finally there. The hotel porter hesitated a bit at the prospect of carrying a very large box of papers to my room - it contained everything I was likely to need, plus a few things extra (you know, the sorts of things that might be useful... perhaps).

Sunday morning, very early I was out running: along the river, then past Queen's College, up to the meeting site at Newnham College and on to Robinson College. Hang on, where is Robinson College ? I'm sure it wasn't this far away last time I came here. Eventually, pulse racing, sweat dripping from all my unmentionable bits I arrived. Hmmm, sorry about that, it was a bit further away than I thought. Ah well just a couple of miles back to the hotel. puff, puff, puff.

Shower and breakfast and it was out again (in the car) to meet Tony Johnson and Kathy Le to check on last minute details. This is when I found out the organising had not finished the night before. There were rooms to be set out and no-one doing it, course notes to be counted and we couldn't get the same answer twice and it now turns out we have two commercial exhibitors arriving whom we didn't know about. They had sent their stuff on ahead and then phoned to say they were on their way. I wanted to send them home but the budget was pretty tight so...

Anyway, back to the hotel for a quick and late lunch, then back to Newnham again. And then, dear delegate, you arrived ! It was nice to find that after all this trouble, some of you were actually going to turn up. One by one, delegates, Alan Phillips (courses organiser), more delegates, course presenters, more delegates, you all started to arrive. I was very pleased that there never seemed to be an unreasonable queue of people waiting to register. Nearly 400 of you, and hardly any waiting - pretty good, I think !

Of course, when you started arriving, a few of you started complaining, but let's face it, anything you didn't like it was too late then. Sorry !

Monday morning was rather frantic getting the courses going but as the last few of you came rushing in after very early trains from home, the whole show was now well and truly running.

I was in an ISCB Executive Committee meeting all afternoon so I had no idea what was going on but what a pleasure to arrive back at Newnham College about 6:30 and find the Welcome Reception going better than a freshers party in a Hall of Residence. This is what it is all about. Meeting old people and new people. Catching up on the year's events. Swapping stories of how long it took you to get there from Heathrow etc. Deborah Ashby from the Organising Committee finally arrived after stopping off in London to examine a few poor unfortunate students and Doug Altman was there too. Everything was slotting into place. When we finally got you all out at the end of the evening, I thought a select two or three of us were going to a nice little pub for a quick half pint before getting an early night in anticipation of the opening ceremony to come. There seemed more than just a few of us and it was more than just a quick half pint. But a good time was had by all.

Going for a run early Tuesday morning was a truly sobering experience.

Organise an ISCB conference ? (continued)

The real hero of the meeting has to be David Clayton. I never fully worked out what happened on his journey on Tuesday morning but suffice to say he arrived just in time to give the opening paper, appearing to be hotter than me on my morning run. It was something to do with his bike breaking down or falling apart, I think.

So we started...

After that, you all know what happened. The weather was kind to us and I stood back with some delight during coffee breaks watching intense discussions between little groups, violent discussions between others and all to a common purpose reflected by the aims of the Society.

The details of the science that went on during the week are better left to someone else since I only managed to attend a few sessions but I thoroughly enjoyed the week, as I hope that you did too. Some of you didn't fully enjoy it - but in a curious way, that pleases me. The only complaints I can remember getting were from British people. Those from other countries may not know this but there is never a happier Englishman than one who is complaining. I'm sure some people would really have had a rotten time if they couldn't find something to complain about. So even they were kept happy.

So there it is. I finally finished clearing up and filing/re-filing all the numerous bits of paper at about 9 o'clock on Friday evening whilst Nikki, my wife, was asking (yet again) 'when can we have dinner ?' Saturday morning: the hotel porter looked even more agasp at me: the piles of papers he had carried up to the room a week ago seemed to have gone through a photocopier and multiplied. It now wouldn't all fit in the boot of the car and so was piled all over the back seat. Saturday lunchtime, we got home. Rest.

Photo 1:

Stephen Senn (Secretary)

Photo 2:

Jørgen Seldrup (President), Wolfgang Köpcke (ex-ExCom), Karsten Schmidt (Treasurer), & ?

English Editor's PS:

Oh don't the days seem lank and long
When all goes right and nothing goes wrong,
And isn't life extremely flat
With nothing whatever to grumble at !
W. S. Gilbert, Princess Ida

Goodbye to:

ISCB 14

ISCB News: News !

ISCB Constitution

This is available from the Treasurer on request. It includes all revisions up to including the last made at the AGM at ISCB13-Copenhagen'92.

ISCB Elections

At next year's conference, you'll have the chance to vote for new officers and members for most of the ISCB Executive Committee. After carefully consulting the constitution, and checking the last few years of ISCB News, I discovered that all three officers (Vice-President, Secretary and Treasurer) and 5 of the 7 Members, along with one of the Nominations Committee, will be completing their first terms in 1994.

The Vice-President (Marc Buyse) automatically becomes President after the 1994 AGM, when Jørgen Seldrup becomes Past-President and, ex officio, a Member of the ExCom (replacing Claude Chastang). An election for the Vice-President will see her/him take that office for 2 years, the Presidency for 2 (1996-1998) and the Past-Presidency for 2 (1998-2000).

The Secretary (Stephen Senn), Treasurer (Karsten Schmidt) and 5 Members (Simon Day, Jan van Houwelingen, Bernhard Huitfeldt, Anthony Johnson, Maria Valsecchi) can choose to stand for re-election for second and final two-year terms (1994-1996) if they so wish. (Irene Guggenmoos-Holzmann and Nancy Geller were elected at ISCB14-Cambridge'93 and their terms run to 1995.)

Stephen Evans will have served his three year term on the Nominations Committee, and must seek re-election in 1994, whilst Roel van Strik (1992-1995) and Maria Valsecchi (1993-1996) have not to be re-elected next year. (There is apparently no limit on the number of terms specified.)

Those are the facts. The Nominations Committee would be delighted to receive suggestions for Officers and Members of the ExCom and NomCom (all of who must be ISCB members). All that's needed is a proposer, seconder and the written consent of the nominee. The deadline is 24 hours before the AGM. If there are some nominations available by the time of the next News (May 1994), I'll publish the names to encourage others to put themselves forward.

ISCB Changes of Address

Please inform the Treasurer who looks after money and also the membership and mailing list databases.

ISCB: The Future

After Brussels, and the aberrations of choosing 2 places starting with C (at least in English !), Copenhagen and Cambridge, the Bs are firmly back in control with Basle (1994), Barcelona (1995), Budapest (1996) and Boston (1997), the latter being offers that the ExCom are considering. We are aware of the 1996 International Biometrics Conference being in the Netherlands in July, so we'll try not to clash with that. Holding a conference across the Atlantic for the first time is a tricky one - would we alienate our European members ? Or since about 1 in 10 members live in North America, isn't it time we visited them, holding a joint meeting with the Society for Clinical Trials (a repeat of the 1991 joint meeting in Brussels) ? See *Controlled Clinical Trials* (1993) 14, 392- for details of this year's SCT conference.

PS I don't expect Zürich will be considered for some time...

Membership Information

THE INTERNATIONAL SOCIETY FOR CLINICAL BIOSTATISTICS

The International Society for Clinical Biostatistics (ISCB) was founded in 1978 to stimulate research into the principles and methodology used in the design and analysis of clinical research and to increase the relevance of statistical theory to the real world of clinical medicine.

The ISCB organises an annual scientific meeting which members and non-members are able to attend. The main objective of the annual scientific meetings is to create an opportunity for the exchange of knowledge, experience and ideas among clinicians, statisticians and members of other disciplines, such as epidemiologists, clinical chemists and clinical pharmacologists, working or interested in, the field of clinical biostatistics.

The scientific meetings cover a broad spectrum of biostatistical interests and regularly include sessions on the design and analysis of clinical trials, epidemiology and statistical methodology, as well as from time to time considering more specialist issues such as, for example, education of biometricians and biometrics users, pharmacokinetics, medical data-bases and pharmacoepidemiology. Each meeting includes a mini-symposium devoted to a particular medical or statistical field. Recent examples have been Organ Transplantation, Regulatory Affairs in Europe and North America, Quality of Life, and Statistics in Medical Journals.

Previous meetings in recent years have been held in Cardiff (1986), Gothenburg (1987), Innsbruck (1988), Maastricht (1989), Nimes (1990), Brussels (1991), Copenhagen (1992). The 1993 meeting was held in Cambridge and Basel will play host in 1994. Future meetings may be held in Barcelona, Budapest and Boston.

The proceedings of these scientific meetings are published in *Statistics in Medicine*. The ISCB benefits from a special journal concession from John Wiley & Sons Limited, the publishers of *Statistics in Medicine*, so that members are able to subscribe to the journal at preferential rates, £120 instead of £130.

The ISCB also organises courses to cover particular statistical topics. These are run to precede or follow on from the annual scientific meeting and are given by the foremost researchers in the field. Recent courses have included Non Parametric Methods in Medical Research, Decision Analysis in Early Phase Drug Trials, Analysis of Longitudinal Data, Martingales in Survival Analysis, Issues in the Design of Clinical Trials, Sample Size Calculations in Clinical Trials, Overdispersion, and Repeated Measures and Longitudinal Data.

The annual general meeting of the ISCB is organised to coincide with the scientific meeting. Membership of the Society is drawn from over 30 countries worldwide and the number of members is over 700.

The current composition of the executive committee is as follows: President, Dr Jørgen Seldrup (France), Vice-President, Dr Marc Buyse (Belgium), Treasurer, Dr Karsten Schmidt (Denmark), Honorary Secretary, Dr Stephen Senn (Switzerland), Past President, Professor Claude Chastang (France), Newsletter Editor, Dr David Warne (Switzerland), and Members: Simon Day (UK), Dr Nancy Geller (USA), Professor Irene Guggenmoos-Holzmann (Germany), Professor Johannes van Houwelingen (Netherlands), Dr Bernhard Huitfeldt (Sweden), Dr Anthony Johnson (UK), and Dr Maria Valsecchi (Italy).

The ISCB also has special working groups dealing with particular aspects of biostatistics. A particular focus in recent years has been statistics in drug regulatory affairs. The chairman of the ISCB working party on Statistics in European Drug Regulation (SEDREG) is Professor John Lewis of the Institute of Mathematics and Statistics, University of Kent, Canterbury, CT2 7NF, UK. The other members of the SEDREG Executive Team are Drs Karsten Schmidt (Denmark) and Bernhard Huitfeldt (Sweden), and Professor David Jones (UK).

The Society publishes a newsletter twice a year. The current editor is Dr David Warne, CIBA, K-490.3.32, CH-4002 Basel, Switzerland. Items for inclusion in the Newsletter should be sent to him (on a 3.5" disk, Word format or text, if possible).

Membership of the Society is open to all with an interest in biostatistics. The current annual (to 31 December 1994) Ordinary membership fee is £15. The Full-time Student Membership fee is £7.50. Members can also choose to receive Statistics in Medicine at a reduced cost (see above), and benefit from the reduced conference fee, at least £15 less than for non-members.

Applications for membership should be addressed to:

ISCB Treasurer,
Dr Karsten Schmidt,
Spadille Biostatistik ApS,
NW Gadesvej 4,
DK-3480 Fredensborg,
Denmark.

Membership Subscription

INTERNATIONAL SOCIETY FOR CLINICAL BIOSTATISTICS

1994 Membership Subscription

Surname _____ Initials/Name _____ Occupation (please tick):

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Business address _____ ☐ Medical Doctor

_____ ☐ Both

Postal code and country _____ ☐ Neither

Phone No. and Fax No. _____

SUBSCRIPTION: (please tick one only)

☐	£	15.00	Ordinary membership of ISCB (to December 31, 1994).
☐	£	7.50	Full-time Student Membership of ISCB (to December 31, 1994).
☐	£	135.00	Ordinary Membership of ISCB (to December 31, 1994) + subscription to *Statistics in Medicine,* 1994.

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ISCB Survey

Please note all replies will be treated in confidence and names won't be attributed to comments.

(1) Age: __, Sex: M ☐/F ☐, Joined ISCB: 19__, Job: Pharma ☐/Univ. ☐/ Other: _____
(2) Other Societies: Biometrics ☐, RSS ☐, PSI ☐, others: _____
(3) Publications Read (including non-statistical journals): _____
(4) Software Packages Used: SAS ☐, GLIM ☐, Genstat ☐, others: _____
(5) Hardware: PC ☐, Mainframe ☐ Workstation ☐ other ☐ details: _____
_____
(6) Comments & Thoughts on ISCB: News, Conferences: _____
_____
(7) Would you like to be an ExCom Member/Officer: Y ☐/N ☐. If Yes, send your name to Secretary !
(8) Would a meeting in USA (e.g. Boston) stop you attending: Y ☐/N ☐. If No, say why: _____

Please return this form to:
ISCB Honorary Treasurer,
Karsten Schmidt,
Spadille Biostatistik ApS,
N.W. Gadesvej 4,
P.O. Box 25,
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Phone: +45 42 284100,
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Cambridge Trip Report

by ISCB's roving reporter

What does a Bayesian reporter without any prior knowledge of conferences do ? Easy, he or she collects some historical data. As this was the first time I'd been let loose on the world of conferences (the chess congress in Liverpool long ago, and the rather philosophical LSE event 2 years before not seeming relevant to the conference at hand), I settled down on the Sunday evening before the course day to start reading David Lodge's novel *Small World.* It turned out to be an extremely accurate prediction:

> *"The modern conference resembles the pilgrimage of medieval Christendom in that allows the participants to indulge themselves in all the pleasures of travel while appearing to be austerely bent in self-improvement. To be sure, there are certain penitential exercises to be performed - the presentation of a paper, perhaps, and certainly listening to the papers of others. But with this excuse you journey to new and interesting places, meet new and interesting people, and form new and interesting relationships with them; exchange gossip and confidences (for your well-worn stories are fresh to them, and vice-versa); eat, drink and make merry in their company every evening; and yet, at the end of it all, return home with an enhanced reputation for seriousness of mind. Today's conferees have an additional advantage over the pilgrims of old in that their expenses are usually paid, or at least subsidised, by the institution to which they belong, be it a government department, a commercial firm, or, most commonly perhaps, a university."*

> *"Dismay had been already plainly written on many faces when they assembled the previous evening for the traditional sherry reception. The conferees had, by that time, acquainted themselves with the accommodation provided in one of the University's halls of residence, a building hastily erected in 1969, at the height of the boom in higher education, and now, only ten years later, looking much the worse for wear. They had glumly unpacked their suitcases in study-bedrooms whose cracked and pitted walls retained, in a pattern of rectangular fade marks, the traces of posters hurriedly removed (sometimes with portions of plaster adhering to them) by their youthful owners at the commencement of the Easter vacation. They had appraised the stained and broken furniture, explored the dusty interiors of cupboards in vain for coat-hangers, and tested the narrow beds, whose springs sagged dejectedly in the middle, deprived of all resilience by the battering of a decade's horseplay and copulation. Each room had a washbasin, though not every washbasin had a plug, or every plug a chain. Some taps could not be turned on, and some could not be turned off. For more elaborate ablutions, or to answer a call of nature, it was necessary to venture out into the draughty and labyrinthine corridors in search of one of the communal washrooms, where baths, showers and toilets were to be found - but little privacy, and unreliable supplies of hot water."*

There was one glaring error, of course, "the pleasures of travel" was clearly not referring to British Rail ! Still I shouldn't grumble - the train I travelled in from Liverpool Street to Cambridge was new and clean. It was also powerful enough to push the train that had broken down in front of it half way to Cambridge and then, once the passengers had alighted, it pushed the "failed train" into the sidings out of the way, before reversing back to the station to pick up the passengers once more. The alternative cross-country coach journey from Heathrow may have been quicker, but missed the possibility of enjoying some of London's many delights, such as Willy Russell's excellent musical "Blood Brothers".

Despite the small travel problems that, as a veteran of missed appointments, I'd allowed for in my planning, I arrived at Newnham College to find accommodation much as described by Lodge. Hot water was discovered eventually, about 24 hours later to be precise when I had found my way to Robinson College, built in 1980 (who said it was 3 minutes' walk away ?!). But still no showers - of course students don't wash, so why build facilities for them ?

Monday was the course day in Newnham. I chose the one on sample sizes, which started off with a group of about 50 people packed into a rather poky Helen Gladstone (presumably some relative of one of my sister's school friends) room in Newnham. Fortunately the afternoon saw us move to Lady Mitchell Hall that accommodates 500. The course was certainly worthwhile especially as a free disk of programs was given out (I've been too busy to test it since then !), but I would think many participants will be happy when the next edition of Campbell and Machin's book (and software) appears in 2 or 3 years' time.

Cambridge Trip Report (continued)

But it was the evening reception that was most enjoyable, putting faces to names, and meeting old friends. Later on, a quick scan of the conference book allowed me to choose what I hoped would be the most interesting and/or entertaining sessions...

Tuesday started with the President's welcome to a packed house that lacked only one person - the first plenary speaker on *Recent Methodological Developments* ! Fortunately David Clayton and bike arrived, and generalised the GLM, and then graphs were considered by Sven Kreiner. After the break the *Controversies in Clinical Trials* plenary started with Wolfgang Köpcke on single patient trials, which are very difficult to combine to produce the infamous N-of-1 trials. Then came the ubiquitous & very controversial Stephen Senn on allocating patients (and blame for the EC guidelines that aren't favourable to crossover designs), with Els Goetghebeur rounding off with non-compliance, including the interesting possibility that electronic monitoring of drug bottles could be used to detect fraud.

In the afternoon, first I opted for the *Clinical Trials* session: the first 2 presentations by U. Frick and P. Kjaersgaard, were especially interesting, concerning sequential test procedures: PEST is becoming very popular. The third talk by L. Mariani concerned breast cancer, and the last by C. Schmoor on Comprehensive Cohort Studies was interesting despite the idea having been dismissed by S. Senn a few hours earlier. During the tea break (sadly no coffee for European non-tea drinkers like me), I took the chance to scrutinise the exhibitions: 3 CROs, 2 publishers and one software firm all doing brisk trade. The poster presentation room was also fascinating, and some of the papers looked, to me at least, more interesting than some of the talks that were accepted. It was disappointing not to be able to take away handouts of the papers or discuss the papers with the authors; some of course couldn't attend, whilst other stands were without even posters !

Returning to the lecture rooms, *Medical Journals* was next on the menu. The presentation on citations by M. Campbell, if it is published, will have the unusual property of destroying the feat of some publications in the first issue of Statistics in Medicine never having been cited. S. Love's review of survival analyses in the same journals reminded us that there's still plenty of room for improvement and more statisticians in the refereeing panels for medical journals. H. Origasa compared the situation with that in Japan where drug trials must be published before a submission to a regulatory authority can be made. Finally, S. Evans talked about ways of preventing fraud in the medical literature, including ideas on data manipulation, invention, and a new term "inliers" or data that are too close to the overall multi-dimensional mean. Other clues to the statistical detective are digit preference tables, inconsistency of sig. tests and confidence intervals, and standard errors constant with varying sample size. The discussion of this paper was also fascinating with P. Meier mentioning the lack of missing data as a clue, the problem of data being selected, and the dangers of whistle-blowing.

Finally, I attended 2 talks by Rolf Holle and Derek Teather during an excellent meeting about *Postgraduate Medical Statistics Education* that is reported elsewhere. As long as there are so few places in Germany and none in Switzerland to study statistics, there'll be a demand for Brits and Yanks in Basel !

Wednesday saw me taking a tour of the Cambridge bookshops instead of the *Measurement and Evaluation of Risk Factors* plenary session. Loaded up with goodies, I staggered back to the session on *Recent Developments*. R. Lancar mentioned that patients and physicians might rate the severity of complications quite differently. D. Teather (standing in for G. Morrey) gave a very good non-technical introduction to Gibbs sampling and illustrated it with some simple examples. D. Spiegelhalter then followed on with a more complicated model that been modelled using BUGS. His quote along the lines that mathematicians have been trying in vain for 40 years to solve problems in Bayesian statistics, yet now we can forget theory and let the humble PC solve the problem using a few hours of simulation was particularly attractive ! Next P. Royston spoke about comparing models and allowing the data to suggest which model fits best. D. Berridge talked about proportional hazards, which seemed appropriate just before lunch: if I'd stayed for the last talk, I would have missed proportionately more of my lunch due to the hazard of a 30 minute round walk back to Robinson College.

Cambridge Trip Report (continued)

In the afternoon, those who took the coach trip to Newmarket to see the National Stud and National Horseracing Museum were disappointed that the former had been cancelled. The fact that neither we (nor the guide) were told rather spoilt things.

Thursday morning started with the plenary session on *Community Intervention Studies.* Mitchell Gail compared cohort and survey designs. Dik Habbema gave a fascinating account of how simulations had been used to model and subsequently affect national health policies in the Netherlands. Stephen Duffy spoke about surrogate variables in a trial for breast screening frequency. After a welcome coffee break came the *Statistics and the Law* plenary. Colin Aitken gave a good introductory talk on the differences between statistical and legal proofs. Paul Meier gave a very entertaining account of some examples from his many years' experience with the American legal system. Finally, a medically trained lawyer, Anthony Barton, explained why it's so difficult for the legal profession to understand probabilities when they want a clear-cut answer. The afternoon saw the final session, again on *Clinical Trials*: P. Thall gave an exciting account of the very latest in Bayesian sequential methods. D. Hasenclever gave examples of another Bayesian approach to finding dose-response curves. S. Senn returned (after a day off back in Basle for a meeting) to talk about baselines, and P. Bauer gave a mathematical paper on testing equivalence. With my mind full of statistics, I decided it was time for a break, and so I missed T. Morikawa and R. Hardy. Finally, the AGM (chaired by S. Senn) saw around 60 old and new members, the latter having been told they were members whether they liked it or not because they'd come to Cambridge ! The evening saw the conference dinner and inevitably that man Senn again, this time giving the after dinner speech. The food was excellent once again, and some of us were back in College at 23.00 ready for sleep, packing and the final day...

Friday morning was the mini-symposium on *Statistics in Medical Journals*. It appeared that many people had left by then, which was a great pity because this was probably the most enjoyable and entertaining session of all. Part (a) was chaired by Marc Buyse, and started with Bjørn Andersen who gave a delightful account of what can and has gone wrong in medical journals in the past and has become carried along by "apostolic succession". Alessandro Liberati then talked about scoring schemes for judging papers. Stuart Pocock gave sound advice on how to present statistics: "keep it clear !". After the break, part (b) started with David Sharp, deputy editor of The Lancet in the chair. Gordon Murray talked about the role of a statistical referee, and Stephen George summarised the results of some recent surveys on the quality of statistics in medical journals. Douglas Altman suggested that a checklist could help reviewers decide if papers were adequate. Lastly, Richard Smith, the editor of the British Medical Journal, and one time co-presenter with Selina Scott on BBC's Breakfast Time TV show, gave an amusing account of the problems of getting over complex medical issues in a few minutes to TV or press journalists. His attitude to statistics, a healthy respect one might say that goes as far as consulting a statistician as a matter of course, is one that we should all hope becomes the norm for editors of other medical journals. Closing remarks were made by some chap called Senn, and everyone departed...

The afternoon was 3.5 hours spent with ISCB's mafiosi, the *ExCom*. If you think it's difficult to get onto such a renowned body, just consider my situation. Two years ago, I hadn't heard of ISCB, one year later I said yes to taking on a small wordprocessing task, and now I have the chance to make decisions about which city (starting with B) hosts ISCB meetings. 17.15 and was all over. A train to Sevenoaks via London, another back up to "home" in Chester, a week's walking in North Wales, Cheshire and the Wirral, and back, via London and Heathrow, to Basel. When I left it had been summer, with ice cream sellers and tennis in the park near my flat; now it was Autumn with hot chestnuts on sale and the courts being used as ice-rinks. A couple of months later, it's now Winter, freezing and snowy, and ISCB14-Cambridge'93 is but a happy memory of my most enjoyable conference, a perfect mix of academic, public health, and industrial medical statistics. Roll on ISCB15 in my new home town when it'll be (very) hot and sunny and you can have fun trying out Basel and Switzerland's wonderful non-disintegrated transport system... See you there !

Book Review # 4 by Jürgen Rehm Lausanne, Switzerland

Sense and Nonsense of Statistical Inference:
Controversy, Misuse and Subtlety.)
by C. Wang
Marcel Dekker (1993

To summarise the overall evaluation of the book before going into critical details: "Sense and Nonsense of Statistical Inference" is an interesting book, well written and deserves many readers.

Its main argumentation can be expressed in three statements:

1. No inference without randomization.
2. No causation without manipulation.
3. No causation without speculation.

Along these lines, Wang discusses a wide range of statistical applications in various sciences to point out misuses of statistics. In short, he feels that statistics are currently overexploited and that the improper use of statistical inferences causes more harm than good to science both for the fields of application and for the field of statistics itself.

While most readers will probably be convinced by his overall line of argumentation, some of Wang's examples show misunderstandings about the fields of application. Probably this is inevitable, since nobody can be an expert about subjects as diverse as astronomy and modern physics on the one hand, and social psychology on the other (to name just a few). To give one example of problematic interpretation of a field of application: contrary to Wang's assumptions, the field of social psychology can be characterized by the experimental method (see Aronson et al., 1990). However, is it really true, that randomized experiments have led this discipline to better (causal) theories compared to other behavioural sciences (as Wang's mottoes would suggest) ?

Personally I also disliked Wang's judgment about whom he considered the "most important" or best statistician at different times. Such judgments are unnecessary and do not add to the value of the book.

In spite of these criticisms, I consider Wang's book thought-provoking and valuable. I especially hope that applied statisticians who work in the medical and social sciences will have a chance to read it. The relatively low price ($39.75) will hopefully add to the diffusion.

Reference: Aronson, E., Ellsworth, P.C., Carlsmith, J.M. & Gonzales, M.H. (1990, 2nd edition). Methods of Research in Social Psychology. New York: McGraw-Hill.

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The Fourth International Conference on Teaching Statistics

ICOTS 4

25-30 July 1994
Congress Palace
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CALL FOR PAPERS

The International Statistical Institute (ISI) and l'Institut National de Statistique et d'Economique Appliqué (I.N.S.E.A.) are pleased to announce that the **Fourth International Conference on Teaching Statistics** will be held in Marrakech, Morocco, from 25-30 July 1994.

The main objectives of the Conference are:
promoting the exchange of ideas about teaching materials, methods and content
fostering international co-operation amongst teachers of statistics.

The programme will include invited lectures, contributed papers and working groups.

People who are intending to present a paper or take part in a working group should get in contact with the organiser before 30th December 1993. After this date, and until 31st May 1994, additional contributed paper proposals may be sent to the chairman of the Programme Committee. The abstract should be limited to a single A4 page before being submitted for acceptance. A proceedings document will be available at the beginning of the conference. It will include abstracts of contributed papers and texts (8 pages) of the invited papers.

ISCB 15 - Bâle asel asilea Basle 94

ISCB-15 in Basle, Switzerland

Jakob Schenker

The fifteenth meeting of ISCB will take place on 25-29 July 1994 in Basle, including a course day on Friday 29 July. The programme Chairperson is Amy Racine. The members of the Local Organising Committee are Jakob Schenker, Uwe Ferner, Walburga Rieser, and Stephen Senn.

Beside the scientific programme of the conference there are other good reasons to attend the congress. The Swiss city of Basle is located on the upper Rhine and has borders with France and Germany. The old city with its Middle Ages character is a charming place, especially in summer, and it is a good starting point for excursions to other parts of Switzerland as well as to France and Germany. With its airport (only 6 km from the centre) and its excellent railway connections it offers good possibilities for travelling.

Basle was founded 2000 years ago by the Romans and became the centre of the upper Rhine region. With its university, founded in 1460, its fair and congress centre, its advanced chemical and pharmaceutical industry and its French and German neighbours, Basle has developed an approach of international openness. Basle is also proud of its place in the history of statistics and of medicine: Paracelsus and James Bernoulli were here. We hope that you too will be amongst us at ISCB-15 and form part of the continuing association of the city with these two subjects.

Barl or Barzel ? Brushing up your Pronunciation for ISCB 15

Stephen Senn

People tend to get rather confused in pronouncing the name of this city on the Rhine/Rhein/Rhin. The situation is, however, perfectly simple. *Barl* is the pronunciation to be used when speaking English and (approximately) when speaking French. The spelling in these two languages is Basle (English) and Bâle (French). In German the spelling is *Basel*, pronounced *Barzel* (In this phonetic representation the letter *z* should be pronounced in the English way.)

There is an increasing tendency amongst English speakers to pronounce the city in the German way. This is not very complimentary. Provided that a place is important enough English speakers always pronounce things in an English way. Nobody says *Paree* for *Paris* except when joking and I bet that all of you who attended ISCB13 (even Jørgen Seldrup and Karsten Schmidt) described themselves (when speaking English) as being in Copenhagen.

So, if you want to pay the locals a compliment, say *Barl* not *Barzel*. After all we like to regard ourselves as being citizens of Switzerland's second city and the rivalry for this status is with Geneva. Now hands up all of you who say *Genève* when speaking English.

(Editorial Note: As those of you who heard him speak at Cambridge (it was difficult to avoid such occasions) know, S.Senn is a Swiss statistician who sounds more English than most English people. This insistence of Anglicising places is rather strange to the English editor who would prefer to use the local place names !)

Swiss-German joke: A Swiss to a German: "and may our common language continue to be the only bond that separates us !"

ISCB15-Basle'94 Update

from Amy Racine-Poon

Reminder:

The scientific programme will commence on Monday 25th July 1994. There will be a half day mini-symposium on Innovative Methods in Drug Development on Thursday 28th July 1994. You should already have received a Call for Papers.

Scientific Programme Committee:

Chair:
A. Racine-Poon (CH)

Members:

P. Bauer (D)	M. Budde (CH)
F. Bühler (CH)	D. Dixon (USA)
A. Grieve (UK)	U. Gugerli (CH)
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C. Minder (CH)	A. Neiss (A)

Local Organising Committee:

Chair:
J. Schenker

Members:
U. Ferner W. Rieser S. Senn

Update:

Further progress has been made with planning the plenary sessions, mini-symposium and short courses:

Session 1: Post-Marketing ADR & Epidemiology
(R. Bruppacher (CH), G. Molenberghs (B))
Session 2: Analysis of Imperfect Data
(R. Little (USA), P. Diggle (UK), J. Lewis (UK))
Session 3: Complex Stochastic Modelling
(D. Spiegelhalter (UK), M. Davidian (USA), A. Grieve (UK))
Session 4: Surrogate & Intermediate Markers
(M. Buyse (B), S. Murray (USA), L. Freedman (USA))
Session 5: Statistics & Statisticians in Regulatory Affairs: An Update
(chaired by J. Lewis (UK))

Mini-Symposium: Innovative Methods in Drug Development
(chaired by S. Vozeh (CH),
J. Gittins (UK), J. O'Quigley (UK), N. Holford (NZ),
Discussants: R. O'Neill (USA), F. Bühler (CH))

Short Courses (each 1 day):
A: Analysis of Ordered Categorical Data
(John Whitehead & Kim Dawes)
B: Crossover Trials in Clinical Research
(Stephen Senn)

Book Review # 5 by Maria Wozniak, Wroclaw, Poland

Total Engineering Quality Management
by Ronald J. Cottman
Marcel Dekker (1993)

The book is the 37th in the series presenting modern methods concerned with quality and reliability of technological products. The methods are oriented not only towards detection of defective material but also towards prevention of quality problems. In the introduction by E.G. Schilling we read that the "series is intended for those in manufacturing, engineering, marketing and management, as well as the consuming public, all of who have an interest and stake in the improvement and maintenance of quality and reliability in the products and services that are lifeblood of the economic system".

The text by R.J. Cottman is along the above principles. He considers in 8 chapters such topics as: Managing Toward Improvement, Processes and Systems, The Engineering Process Team Concept, The Engineering Process Team Approach, Development of the Problem Solution, Statistical Control of Processes, Process Control Charts. This is done having in view "an engineer who finds himself promoted to a management position and who must provide the leadership to accomplish the implementation of new and innovative designs and processes, as well as foster an atmosphere for the improvement of existing processes". We find in the book Deming's fourteen points to success, Deming's five deadly diseases, a fishbone diagram for cause and effect analysis, brainstorming, process flow diagrams, and of course several kinds of control charts.

The book is written in an attractive way. Some situations occurring in a specified plant are described as funny stories, e.g. Good Gilda Goes for Gold, and Opulent Ollie Opts to Operate Ugly. After presenting the story the encountered situations are scrutinized and some guidelines for the process management are deduced.

The edition - as always with Marcel Dekker - is faultless.

Book Review # 6 by Philip M. North, Canterbury, England-UK

Cross-over Trials in Clinical Research
by Stephen Senn
Wiley (1992)

This book provides a discussion of cross-over trials in clinical research for two types of reader. These are the physician or biologist who carries out or wishes to carry out cross-over trials and either has to analyse them or needs to interpret the analysis carried out by others, and the applied statistician with no particular experience as yet with cross-over trials. The depth of the mathematical discussion of the topic has been kept to a level that is sufficient for the purpose of presenting a discussion of the use of the methods in practice. (The book forms part of the series of books on Statistics in Practice, and conforms to that theme very successfully.) The result is a very practical book, with stimulating discussion of the subject area in a style that is appropriate for the types of readers at which it is aimed. Where there is mathematical coverage that can be omitted without detracting from the main thrust of the text, this is indicated.

The author uses a particular convention for dealing with the more controversial issues that he touches upon in his book - and the subject of cross-over trials is one that has generated more controversy than many other areas of statistics in recent years. In his book the author makes it quite clear where he is expressing views that are not necessarily shared by others. This is particularly the case for the discussion of carry-over effects, and whether one should include such effects in the modelling of cross-over data. The last chapter in the book is devoted to this topic. In the author's words, in that chapter, "I have covered various matters which others consider important but I do not". Having presented arguments why one should not adopt mathematical approaches to carry-over, the author states, halfway through the chapter, "I have now finished outlining what I consider the ordinary practitioner needs to know about planning and analysing cross-over trials". He then goes on to summarise how to use the simple carry-over model, for those who are not fully persuaded of his arguments.

So, although the author makes his own views firmly known in this book, he does, on the other hand, present a fair and balanced view of others. And in Chapter 6 (on designs with three or more treatments) he openly admits that "this is a rather unsatisfactory chapter" and states that "there is an open invitation to find better approaches".

This book does provide the "ordinary practitioner" with a full and stimulating discussion of the subject in a very readable style. Of the two types of reader at whom the book is aimed, I suspect that the applied statistician will be able to derive the greater benefit from it. But for both it will be an invaluable aid to their work, and essential reading for those embarking on work with cross-over trials. There needs to be an awareness of other literature in the area too, but this is amply referenced in this book. I am sure that as well as those who are just starting to work in this area of clinical research, those who already have much experience of cross-over trials will also derive great benefit from the book.

The book is laid out as follows. After introducing the subject, mainly through the provision of answers to a number of questions about cross-over trials, consideration is given to some basic issues of estimation in clinical trials. The next two chapters provide extensive coverage of the two-period, two-treatment cross-over design, firstly with normally distributed data and then for other outcomes. This pattern is then repeated in the next two chapters, but now for designs with three or more treatments. Three further chapters then cover some special designs, graphical and tabular presentation of cross-over trials and various design issues, respectively, before the final chapter on mathematical approaches to carry-over. There is some limited provision of SAS code for implementation of procedures presented in the book.

Book Review # 6 (continued)

In this material I particularly liked the way that the author stressed the links with parallel group trials, overcoming the tendency to think of them as falling within a different context from cross-over trials and hence to miss the concepts that are common to both. I also liked the reference back to Fisher from nearly 60 years ago in a discussion of ethical considerations, setting issues of today back into a context that was already being successfully confronted so long ago. In the book this is shortly followed by an interesting, but brief, discussion of bioequivalence studies and, in particular, a questioning of the standard parameters used in such work.

In summary, I found this a stimulating and enjoyable book to read and one that is likely to prove to be extremely useful to many other workers in the area. However, just as with my hobby of birdwatching I find that I can derive most benefit from it by having more than one field guide available to me to help with identification, so when working with cross-over trials I will still want to have more than this one book on cross-over trials available to me. In particular, I will still want access to the book by Jones and Kenward (1989), which I see as a complementary text, and which is amply referred to by Stephen Senn himself.

Reference:

Jones, B. and Kenward, M.G. (1989) Design and Analysis of Cross-Over Trials. Chapman and Hall: London.

Computer Corner

I'm using a brand new Psion Series 3a to type this article. It's a great improvement over the Series 3: 4x the screen area (screen size and number of pixels), twice as fast, more memory, and a wonderful feature for recording and playing digital sounds - up to 2 minutes of music or someone's voice (your boss ?) can be stored and used as an alarm !

At work, we in the Biometrics department have yet another new configuration (or two) for our PCs based on OS/2-2.1 or DOS5/Windows according to whether the PC is "big enough", now with MSMail and Schedule+ to allow greater compatibility with all the departments we work with both in Basel and world-wide. After just getting used to WinWord2 and Excel4, Microsoft has released Word6 and Excel5 - will they ever run out of new ideas that fill up the hard-disk and memory and make us need machines with faster processors ? !

On the mainframe, SAS has now reached version 6.08, bigger and hopefully better than ever. The ability of SAS to extract data direct from our Oracle databases is an interesting possibility, but rather late as I've spent quite a lot of time over the last 12 months checking that our Oracle to SAS conversion program works !

Reminder: please send me articles in the following formats: ASCII (text), WinWord (1, 2), PMWord (1.1 - OS/2), Word for DOS (4, 5.0, 5.5), Word for Mac (4, 5 **but not on a Mac formatted disk !**), Works for Windows, Works 2 for DOS, WordStar (3.3, 3.45, 4, 5.0, 5.5), Lotus 1-2-3 (2, 3), Excel (2, 3), dBase (II, III, III+, IV), WordPerfect (4, 5.2, 5.1 **but not WP6 !**) or RTF. Also graphics files in WMF, EPS, TIF, CGM, HGL, WPG, DRW, PCX, BMP, DXF, PLT or PIC can be used.

Book Review # 7 by H. M. Oranga, Nairobi, Kenya

Statistical Analysis Of Reliability And Life-Testing Models: Theory and Methods
by Lee J. Bain and Max Engelhardt
Marcel Dekker (1991)

In chapter 1, the authors lucidly define various probability models that are commonly used in engineering. The chapter begins with simple definitions on single observations and expands slowly to include the distributions of random variables. The chapter reaches a climax by introducing the hazard function h(x) of various probability models. The moment generating functions are clearly described and their role in defining probability models exemplified.

Chapter 2 covers statistical inference. The coverage is intensive on the mathematical statistics of estimation and inference. The treatment of properties of estimators - sufficiency, unbiasedness, consistency, efficiency and uniformly minimum variance unbiased estimators is exhaustively undertaken. The authors have very carefully discussed some of the fundamental theorems in statistics including the Central Limit Theorem, Rao-Blackwell theorem, Cramer-Rao Lower Bound and Neyman-Pearson Lemma. The chapter also introduces basic estimation and hypothesis testing procedures such as minimax estimation, Bayes estimation, least squares and maximum likelihood estimation. The likelihood ratio test is also introduced.

Chapter 3 describes some properties of the exponential distribution and gives some examples of how and when the distribution may be a useful model in practice. The authors further discuss the theory underlying the statistical inferences based on distributions involving from one to k parameters, cases with censored or non-censored sampling and in situations of sampling with and without replacements.

Chapters 4 to 9 deal with some of the important probability distributions used in reliability and life-testing models. These chapters discuss the Weibull, gamma, extreme-value and logistic probability distributions and are carefully presented with the associated mathematics being carefully and comprehensively presented.

In summary, the book forms a good, compulsory reading in both undergraduate and graduate degree courses in mathematical statistics and actuarial science.

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Calendar

25-27 April 1994 — **Edinburgh, UK**

5th European Workshop on Statistical Methodology in Clinical Research and Development
Info: S.Senn, CIBA-GEIGY, CH-4002 Basel, SWITZERLAND.

5-9 June 1994 — **Valencia, SPAIN**

5th Valencia International Meeting on Bayesian Statistics
Info: J.M. Bernardo, Presidencia de la Generalidad Caballeros 9, E-46001 Valencia, SPAIN.
Tel: +34 6 3866138, Fax: +34 6 3863626, email: bernardo@mac.uv.es

15-17 June 1994 — **Boston, USA**

International Research Conference on Lifetime Data models in Reliability and Survival Analysis
Info: M.-L.T. Lee, Channing Laboratory, Harvard Medical School, 180 Longwood Avenue, Boston, MA 02115, USA.
email: stmei@gauss.med.harvard.edu

15-18 June 1994 — **Cary, North Carolina, USA**

26th Symposium on the Interface of Computing Science and Statistics
Info: J. Sall, SAS Campus Drive, Cary, NC 27512, USA. Fax: +1 919 677 8123

11-15 July 1994 — **Exeter, UK**

9th International Workshop on Statistical Modelling
Info: J. Hinde, MSOR Dep't, University of Exeter, Layer Building, North Park Road, Exeter EX4 4QE. ENGLAND-UK.
Tel: +44 392 264473, Fax: +44 392 264460, email: jph@msor.exeter.ac.uk

25-29 July 1994 — **Basle, SWITZERLAND**

15th Meeting of the International Society for Clinical Biostatistics
Info: ISCB15, Administrative Secretariat, Ciba Convention Services, PO Box, CH-4002 Basel, SWITZERLAND.

25-30 July 1994 — **Marrakech, MOROCCO**

ICOTS-4: The Fourth International Conference on Teaching Statistics
Info: ISI Permanent Office, 428 Prinses Beatrixlaan, P.O. Box 950, NL-2270AZ, Voorburg, NETHERLANDS.
Tel: +31 70 3375737, Fax: +31 70 3860025

8-12 August 1994 — **Hamilton, CANADA**

17th International Biometric Conference
Info: IBC Local Organising Committee, Dep't of Mathematics and Statistics, McMaster University, Hamilton,
Ontario L8S 4K1, CANADA. Tel: +1 416 5297070, Fax: +1 416 5220935

14-16 September 1994 — **Newcastle-upon-Tyne, UK**

RSS International Conference
Info: I.J. Goddard, Executive Secretary, Royal Statistical Society, 25 Enford Street, London W1H 2BH. ENGLAND-UK.
Tel: +44 71 7235882, Fax: +44 71 7061710