Dear ISH member,

Enclosed, please find a new issue of Hypertension News which I hope you will find worth reading. It contains reports from the president, secretary, treasurer, and chief editor of the Journal of Hypertension, as well as a contribution from South Africa.

Please help us recruit new members to ISH. It would be ideal if each of us could recruit one new member – so why not try! Instructions and an application form are enclosed (at the end).

Best wishes,

Lars H Lindholm
Editor
SOME THOUGHTS ON CLINICAL TRIALS AND THEIR INTERPRETATION

Clinical medicine is increasingly dependent on the randomized, blinded clinical trial (RCT) for therapeutic guidance. The reasons for this rather dramatic acceptance of one particular form of evidence by scientists, practitioners, and policy makers are both sound and compelling. One of several important reasons for embracing the RCT has been that most disease we now confront is complex, and of multiple or unknown aetiology.

The story of blood pressure and its relation to stroke and heart attack are excellent examples of current medical challenges. During the 100 years since the introduction of the sphygmomanometer, a steady progression of different strands of investigation has demonstrated that, in the natural state, the height of the blood pressure is linearly related to the incidence of stroke and heart attack, and that the reduction of blood pressure, by a variety of pharmacological agents, can reduce (and, in the case of stroke, almost exactly to the extent predicted by epidemiological study) blood pressure associated morbidity. At the same time, it has become clear that blood pressure is regulated by a variety of mechanisms. Some of these mechanisms – for example, the renin-angiotensin-aldosterone system – have also been implicated as independent contributors to vascular pathology. In other words, it is possible that the mechanism by which blood pressure is elevated helps to determine, independently, the likelihood of stroke or heart attack.

If this prognostic heterogeneity is true, then a fundamental assumption of the clinical trial may be open to question.

The large, simple hypertensive RCT initially addressed the straightforward question of whether blood pressure reduction prevented strokes and heart attacks. In these placebo controlled trials, mechanism didn’t differentially effect outcomes, the results were remarkably consistent. A 5–6 mmHg decline in diastolic pressure was associated with a roughly 40% reduction in stroke, and about a 15% decline in coronary heart disease events. The fact that the heart attack protection afforded by antihypertensive intervention was only about half of that predicted by epidemiological studies, stimulated the search for additional agents that would be more cardioprotective.

By the late 1980s several new classes of agents had been added to the antihypertensive armamentarium that acted by different mechanisms – both from each other, and from the diuretics and beta blockers that had previously been the mainstay of treatment. To test the hypothesis that these agents had superior cardioprotective capacity, head-to-head RTCs were designed. The trials were designed so that effects of these drugs could be distinguished in a setting where equal blood pressure was achieved. In fact, despite very substantial differences in the actions of the various antihypertensive classes, it has proved difficult to identify consistent differences in outcomes overall.
This inability to distinguish between drugs may accurately reflect the absence of real differences. It is also possible, however, that the results of these clinical trials are confounded by a fundamental design flaw. Patients are eligible for RCTs primarily on the basis of blood pressure. The comparison is simply the difference between the sum of outcomes in the two groups. An underlying assumption is that these participants are phenotypically homogeneous – and that each drug will react pretty much the same in all subjects. The fact, of course, is that there are subgroups within the population with different phenotypes of blood pressure control, who therefore respond differently to one drug or another. Thus, two or more experiments might, unobserved, be coexisting within a single RCT. In one phenotypic group a calcium antagonist might be superior; in another, a converting enzyme inhibitor. The reported result of the RCT would therefore actually be the sum of the two quite distinct experiments. It would be akin to describing two men, one weighing 240 pounds, and the other 120, as being, on average, 180 pounds – it tells us nothing about either man! Were this to occur in an RCT because of an interaction between phenotypic heterogeneity and drug action, it would render the conclusion that a “main” effect applied to the whole group is incorrect and misleading.

Of course, we do not yet have universally agreed upon phenotypic subtypes (although there are candidates), and we certainly are not able to stratify on genetic terms. Thus, this concern can only be described as theoretical. The construction of mechanistically homogeneous groups of hypertensive subjects will permit extrapolation from an RCT to an individual patient with similar phenotype with far greater confidence that his or her response will resemble that seen in the trial. Absent the capacity to phenotype or genotype, my sense is that further large simple RTCs comparing antihypertensive drugs in undifferentiated populations are not likely to be very productive.
Having been asked to write for the Hypertension News at the very end of 2004, I have decided to summarize the ISH activities and news in 2004 as well as our hopes and aspirations for 2005 and beyond. As all of you would be well aware, 2004 was an excellent year for our Society with a successful February meeting in São Paulo. The hospitality of our hosts was matched by excellent scientific presentations, and I was particularly pleased to see several excellent recipients of young investigator awards, including Drs Masato Furuhashi and Sandosh Padmanabhan (Austin Doyle Award), Dr Jose Romero (Pfizer Award) and Drs Armanda Ferreira Vidonho, Jr., Ana Paula Dantas and Maria Franco (Widimsky Award). During the São Paulo Meeting, the Membership Committee considered 26 nominations for new ISH members; these nominations were then approved by the general meeting of the Society bringing the total number of regular members to just above 800. I would like to ask all of you to join our recruitment drive and to invite young (and not so young) clinicians and scientists interested in hypertension to become members of our Society. The electronic application form is included in this issue of the Newsletter. You might also refer to the previous issue of Hypertension News – Opus 5, 14 October 2004, and see the article by Dr Maciej Tomaszewski entitled “A young investigator’s perspective on ISH”. Perhaps this might encourage young clinician scientists to join.

In June 2004, many of our members attended very successful meeting of the European Society of Hypertension (ESH) in Paris. Several landmark studies were presented there including the first presentation of the VALUE trial. Of course our Society has a number of important links with the ESH. First, the Journal of Hypertension is the official journal of both Societies. We are grateful to the Chief Editor, Professor Alberto Zanchetti and his editorial team for their hard work to develop the journal in the current highly competitive publishing environment. In addition, the two Societies also participate together in the Board of Management of the Journal. Again a big thank you is due to Professor Lewis Landsberg, Chairman of the Board of Management, who has led us to a successful completion of the negotiations of our new contract with the publisher, Lippincott Williams and Wilkins.

2005 is going to bring further preparations for the Biennial Scientific Meeting of the ISH in Fukuoka, Japan due in October 15–19, 2006. The theme of the meeting is “Global challenge for overcoming high blood pressure” and the Organizing Committee led by Professor Toshio Oghara is very well advanced in all the preparations, including the cutting-edge scientific programme, excellent support from the Industry as well as many investigator-initiated satellite symposia. I think we can be certain that the 2006 ISH meeting will be a great success for the Society.

Perhaps the most important long-term initiative of the ISH is related to low- and middle-income countries. In a nutshell the idea is to participate early and efficiently in the multidisciplinary efforts to prevent cardiovascular disease epidemic in this part of the world. More details on this important initiative have been published in the previous Hypertension News -- Opus 5 by Professor Robert Fagard.
We also plan to have a new and easily accessible website for our Society; more on this new development will follow soon. Lastly, more observant readers would have noticed by now that I have cited extensively from previous issues of the Hypertension News. I think that it provides a convenient way of exchanging information and ideas. Professor Lars Lindholm, our Editor, and the rest of the editorial group would like to hear your comments and suggestions to make the News useful to all members of the Society.

Happy New Year to all ISH members.
The year 2004 brought good things and less good things to the finances of our Society. Our biennial meeting in São Paulo was scientifically successful but failed in generating any economic profit in spite of the fairly good attendance (about 3,000) and the unrelenting efforts of the local organizers. This outcome mostly resulted from the limited support provided by some pharmaceutical industries which traditionally sponsored our meeting; the explanation for this is the cumbersome phase that many industries are passing through, combined with the difficulties of coping with an increasing number of important congresses organized by national and international scientific Societies. On the other hand the limited support for the scientific meetings is just an aspect of the overall reduction of the resources devoted to the promotion of science and our Society, like others, must be ready to face this problem in future years.

However, there are several positive aspects in the balance of 2004 which I will summarize as follows:

1. The difficult transition period during which we moved the collection of membership fees from the publisher of the Journal of Hypertension to our Secretariat in Geneva is finally over and, so far, more than 500 members have renewed and paid for 2004. Thanks to the production of a more correct and up-to-date list of the postal and e-mail addresses, we hope in future to be able to reach all our active members thus optimizing the income derived for the fees.

   In this respect, on the occasion of the meeting of the ESH last June in Paris the Officers of ISH have renegotiated with the corporate members the amount of their fees which, with 2005, will rise from 2,000 to 10,000 USD per year. In exchange the corporate members will enjoy some privileges at the ISH meeting such as the preferential location of their booths in the congress venue and the priority for the sponsored symposia. As a result of this negotiation the income from these fees will increase from 18,000 to 72,000 USD for 1 year excluding the money for the awards.

2. In recent years the income of the royalties of the Journal of Hypertension has increased steadily from 8,092 USD in 2000 to 26,507 USD in 2001, to 28,203 USD in 2002 and to 57,609 USD in 2003. The figure for 2004 is not yet available but will further and substantially increase in future due to a new contract which has been recently signed with the publisher, Lippincott.

In addition to the efforts made to ameliorate the income the Officers have launched numerous initiatives aimed at reducing the cost of running our Society. These are the following:

1. Some of the activities of STG, the Society which is in charge of keeping the books, and the current accounts of ISH, have been moved to our Secretariat in Geneva, and by year 2005 this should result in a 30–40% saving of this cost.

2. The cost of sharing the facilities of the WHF office in Geneva was recently renegotiated; in particular the cost of the supervisor to our Secretary has been entirely eliminated, resulting in a saving of 11,794 USD.

3. In order to further reduce the burden caused by the travelling of the Officers to get together to discuss Society matters, most of their meetings have been replaced by inexpensive teleconferences. Moreover, the support to the Officers for their participation in relevant meetings as invited speakers in the name of ISH has been limited to the reimbursement for flights at economy class fare for shorter flights.
Finally I would like to remind you that the titles and securities owned by ISH in 2003 for an estimated value of 300,000 USD are still sitting there untouched and that, in addition, our Society possesses liquid funds to a value of 371,000 USD deposited in the Lausanne UBS Branch.

All in all, it appears that despite the lack of profit from the São Paulo meeting the financial health of our Society is quite stable and good enough to allow us to look forward to the coming years with reasonable optimism.
The Journal of Hypertension on the Web
Visits, Hits and Full Text Views

The Journal of Hypertension has been on the web for a few years, and ISH members may be interested to know how much this increasing way of consultation is used for material published in our Journal and which are the types of articles that mostly appeal to the web-readers. I would like to thank Mr Phil Daly, Managing Director of the Journal, for help in getting this type of information.

A few words of caution are necessary before providing some of the available information. Frequency of web-consulting is not necessarily a sign of particular appreciation of an article, it has a quite different meaning from citation (only when an article is cited is agreement or disagreement with its content usually expressed). Furthermore, the timing of web-consulting and citing is quite different: web-consulting has a peak in the months immediately following publication, while citing usually starts and peaks after several months from publication. An important measurement of the interest raised by an article might be the number of months it continues to be visited after its publication, information we have not yet elaborated. Information would also be useful about the time an article continues to be cited, but the usual calculation of the worshipped impact factor is limited to the two years after the year of publication.

There are also different types of web-consulting: visits, hits, full text views and views of the abstract only. The first two types indicate interest in the Journal, the other two a more specific interest in the content of a given article, with viewing of the full article suggesting a high degree of interest.

ISH members may be interested to know that during the six-month period March–August 2004 the Journal of Hypertension received a monthly average of 16,518 visits (range 14,949–18,759) with an average number of 68,193 hits per month (range 59,432–77,045). The top 20 articles whose full text has been viewed during the same period of time are the following:

- 2003 ESH-ESC guidelines for the management of hypertension (JH 2003; 21: 1011)
- Kang et al. Review on uric acid, endothelial dysfunction and pre-eclampsia. (JH 2004; 22: 229)
E SH recommendations for conventional, ambulatory and home BP measurement. (JH 2003; 21: 821)


While several of the papers most often viewed had been published during or immediately before the time period considered, about half of the 20 top papers were published during 2003 and their frequent viewing in 2004 indicates persistence of scientific interest in the papers published in the Journal of Hypertension.

As can be expected, abstract views have mostly concerned the top 20 papers with full text viewing, but other articles are also included in the top 20 abstracts viewed:


Manolis et al. Telmisartan in isolated systolic hypertension. (JH 2004; 22: 1033)

Ferrari et al. PRA or irR for aldosterone-renin ratios. (JH 2004; 22: 377)

Incidence of hypertension. The incidence of hypertension in sub-Saharan Africa is likely to soar by 2025 (He’s group, Lancet, 2005; 365: 217), eventually to involve 151 million hypertensives, an increase of 69% over the year 2000. Mass migration from rural to periurban and urban areas probably accounts, at least in part, for this increasingly high incidence of hypertension. Thus earlier data found a low incidence of only 9% hypertension in rural black South Africans (Seeda t, SA Medical Journal, 1982) a more recent nationwide survey suggests that the incidence of hypertension in this predominantly black population is about 20% while over age 60, the majority are hypertensive (Steyn, J Hypertension, 2001) Furthermore, the incidence of diabetes will also increase, adding a double burden to the heart and kidneys.

Aetiology. Genetic factors such as abnormalities of the epithelial sodium channel and those that govern the renin-angiotensin system are under vigorous investigation. Hypertension in ethnic blacks in general, and probably in South African blacks as well, tends to be low-renin in nature with trends to increased sodium retention and peripheral vasoconstriction (Opie and Seedat, Submitted to Circulation) This pattern argues for preferential therapy by diuretics and calcium channel blockers or other vasodilators unless there are compelling indications for other drugs. However, there are no outcome studies as opposed to many BP-lowering studies. In African-Americans, differences from whites in aetiology and therapeutic responses are graded and overlapping rather than absolute. Whether this conclusion also applies to South African blacks is not known but provides a reasonable working hypothesis. Further studies are needed on South African blacks, who may (or may not) be genetically and environmentally different from African-Americans and from other black populations in different parts of Africa.

Cost implications. At an absolute minimum overall cost of let’s say USD 5 per month for rudimentary management and token therapy, a staggering USD 9.1 billion would be needed per year for countries already saddled by poverty and debt. Similar increases are likely in South Africa. Specifically, Gaziano (paper submitted, Circulation) calculates that implementation of the current South African Hypertension Society guideline would cost $3.9 billion per year for a South African population of 50 million. Thus hypertension in Africa and in South Africa is a widespread problem, of immense economic importance because of its high incidence, its frequent under-diagnosis, and the severity of its complications. Two lifestyle changes that are feasible and should help to stem the epidemic of hypertension in South Africa are a decreased salt intake and a new attitude to obesity in women, currently held to be socially desirable in many African communities.

Congress programme. The upcoming meeting aims both at a wide audience and at the specialists. The first day concerns problems relevant to general practitioners and nurses, such as who should measure the blood pressure, what actually is hypertension, which drugs should be chosen especially for resistant hypertension, and which is the patient at higher risk?
Thereafter separate sessions will be devoted to the interaction between hypertension specialists and epidemiologists, neurologist, obesity experts, nephrologists, dieticians and exercise physiologists. Existing knowledge will be reviewed, but also cutting-edge contentious issues such as the significance of high blood uric acid in renal disease and hypertension. Another issue of community-related importance, because of cost implications, is whether the angiotensin receptor blockers (ARBs) specifically benefit diabetic type 2 nephropathy, and left ventricular hypertrophy, as shown in large trials, or whether the significantly cheaper ACE inhibitors could be used instead. Is the higher incidence of cough and angioedema found in African-Americans with the use of ACE inhibitors also reflected in the South African ethnic black groups? Finally, which preventative measures are not only effective but cost-effective? For example, the high-vegetable, high-fruit diet is beyond the pocket of poorer hypertensives.

**Visiting lecturers.** These will include Richard Johnson, nephrologist, University of Florida, USA, whose forte is the relation between uric acid and renal progression and pathogenesis of essential hypertension; Theodore Kurtz, University of California, San Francisco, USA, Past-president of the American Hypertension Society analyses the metabolic syndrome; Patrick Michel, from the Stroke Unit, Lausanne University Hospital, Switzerland; and Andrew Neil, from the Centre for Diabetes, Endocrinology and Metabolism, Oxford University, United Kingdom, whose interests include both diabetes and lipemias.
SOUTHERN AFRICAN HYPERTENSION CONGRESS 2005
DRAFT PRE-CONFERENCE PROGRAMME
FRIDAY 4 MARCH 2005

Venue to be determined.

10:30 – 13:30 Southern African Hypertension Society Executive Committee meeting.
13:30 – 14:00 Finger lunch – light.
14:00 – 17:00 Hypertension Guideline Workshop. By invitation only.
19:00 Dinner SAHS executive committee, workshop participants and invited speakers. Venue to be determined.

SOUTHERN AFRICAN HYPERTENSION CONGRESS 2005
DRAFT PRIMARY CARE PROVIDER PROGRAMME
SATURDAY 5 MARCH 2005

07:30 – 08:30 Registration.
08:30 – 08:35 Welcome. Prof Brian Rayner.
08:35 – 11:00 SESSION 1: HYPERTENSION THEME.
Chairpersons: Dr Malmo Stoltz and Prof Joe Veriava.
08:35 – 09:05 Should doctors measure BP? Prof John Milne.
09:05 – 09:30 Is my patient hypertensive? Prof Brian Rayner.
09:30 – 10:00 Cardiovascular risk prevention in the community. Dr Thandi Puoane.
10:00 – 10:30 Does my hypertensive patient require drug treatment? Dr Krisela Steyn.
11:00 – 11:30 REFRESHMENT BREAK AND EXHIBITION
11:30 – 13:00 SESSION 2: LIPID THEME
Chairpersons: Dr Shadrick Mazaza and Prof Lionel Opie.
11:30 – 12:00 Lipids: Fire and forget or treat to target? Prof Andrew Neil.
12:00 – 12:30 Management of a hypertensive patient with concomitant ischaemic heart disease. Dr Adrian Horak.
12:30 – 13:00 Controversies in hypertension – case discussion. Prof Rick Johnson, Prof Theo Kurtz and Prof Andrew Neil.
13:00 – 14:00 LUNCH, POSTER & EXHIBITION

SESSION 3: BRAIN ATTACK SYMPOSIUM
in collaboration with the Southern African Stroke Foundation.
Chairpersons: Dr Abul Barday and Prof Gavin Norton.
14:00 – 14:05  Opening remarks.  Prof Alan Bryer.
14:05 – 14:35  Stroke mimics and unusual presentations.  Prof Roland Eastman.

**15:35 – 16:00  REFRESHMENT BREAK & EXHIBITION**

16:00 – 17:00  **SESSION 4: BRAIN ATTACK SYMPOSIUM CONTINUED**
Chairpersons:  Ms Esme Kennel and Dr Martin Mpe.

16:00 – 16:30  Case study: small vessel disease.  Dr Patrik Michel.
16:30 – 17:00  Sex after stroke.  Dr Esther Sapire.

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**SOUTHERN AFRICAN HYPERTENSION CONGRESS 2005**
**DRAFT SCIENTIFIC MEETING PROGRAMME**
**SUNDAY 6 MARCH 2005**

08:00 – 09:00  Registration.
09:00 - 09:05  Welcome.  Prof Brian Rayner.

**SESSION 5: HEART THEME**
Chairpersons:  Prof Pindile Mntla and Prof Brian Rayner.

09:05 – 09:30  **Alumnus Address:**  CRP risk factor and risk marker.  Dr Pinky Sareli.
09:30 – 10:05  Is cardiac fibrosis reversible?  Prof Gavin Norton.
10:05 – 10:35  Genetics of hypertension and related risk factors.  Prof Bongani Mayosi.
10:35 – 11:05  The hypertensive heart.  Prof Lionel Opie.

**11:05 – 11:30  REFRESHMENTS & EXHIBITION**

11:30 – 13:00  **SESSION 6: SYMPOSIUM ON OBESITY & THE METABOLIC SYNDROME.**
Chairpersons:  Prof Y K Seedat and Prof Angela Woodiwiss.  
Sponsored by Boehringer Ingelheim.

11:30 – 12:15  Treating insulin-resistant hypertension and the metabolic syndrome.  
Prof Theodore Kurtz.
12:15 – 12:45  Significance of the metabolic syndrome in South Africa.  Prof Willie Mollentze.
12:45 – 13:00  Discussion.
13:00 – 14:00  LUNCH, EXHIBITION & POSTERS

14:00 – 17:00  SESSION 7: LIPID THEME
Chairpersons: Prof Harry Seftel and Prof John Milne.
14:00 – 14:45  Lipid management: current best clinical practice. Prof Andrew Neil.
15:45 – 16:00  Research presentation 7 A.
16:15 – 16:30  Research presentation 7 B.
16:30 – 16:45  Research presentation 7 C.
16:45 – 17:00  REFRESHMENTS & EXHIBITION

17:00 – 18:00  SESSION 8: ANNUAL GENERAL MEETING.
13:00 – 14:00  LUNCH, EXHIBITION & POSTERS

14:00 – 15:00  SESSION 12: LIFESTYLE THEME.
    Chairpersons: Dr Krisela Steyn and Prof Patrick Mokhobo.

14:00 – 14:30  Is nutritional modification feasible in hypertension management? Ms K Charlton.

14:30 – 15:00  The role of exercise in BP control and cardiovascular risk factor management. Prof Vicki Lambert.

15:00 – 15:30  REFRESHMENTS AND EXHIBITION

15:30 – 17:00  SESSION 13: QUALITY AND CLINICAL STANDARD THEME.
    Chairpersons: Dr Martin Mpe and Dr Pinky Sareli

15:30 – 16:00  Proposed 2005 revision: SA Hypertension Society Guideline. Prof YK Seedat on behalf of the Society.

16:00 – 16:30  Implementing the SAHS guideline in clinical practice. Prof Brian Rayner.

16:30 – 17:00  Challenges facing hypertension management in the public sector. Dr Elamin Mohamed

17:00  Presentation of Awards:
    • Lionel Opie Award for best poster presentation.
    • YK Seedat Award for the best oral presentation.
    Closure: SAHS president.
HOW TO BECOME A MEMBER OF THE
INTERNATIONAL SOCIETY
OF HYPERTENSION

Applications should be made in writing to the Secretary of the Society, Professor Anna F Dominiczak, at the address below, accompanied by a written statement from two members of the Society as to the qualifications of the applicant plus a list of five best and five most recent publications related to hypertension or allied fields and a short CV.

These should then be forwarded to:

Secretary of the Society
Professor A F Dominiczak
c/o S Davenport
Administrator
International Society of Hypertension

c/o World Heart Federation
5 avenue du Mail
CH-1205 Geneva
Switzerland
Telephone: +41 22 807 0326
Fax: +41 22 807 0339
Email: ish@worldheart.org
# APPLICATION FORM FOR MEMBERSHIP OF THE
# INTERNATIONAL SOCIETY OF HYPERTENSION

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**NAMES AND ADDRESSES OF TWO MEMBERS OF ISH WHO SUPPORT YOUR APPLICATION**

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These should then be forwarded to: Secretary of the Society
Professor A F Dominiczak
c/o S Davenport
Administrator
International Society of Hypertension

Telephone: +41 22 807 0326
Fax: +41 22 807 0339
Email: ish@worldheart.org
World Heart Federation
5 avenue du Mail
CH-1205 Geneva, Switzerland

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**ANNUAL MEMBERSHIP FEE AND SUBSCRIPTION TO JOURNAL OF HYPERTENSION**
currently US$ 136.50 (subject to change)

Payment should **not** be made until membership is approved. Applications for membership will be assessed by the Membership Committee and ratified at the next ISH General Business Meeting.