

International Society of Hypertension HYPERTENSION NEWS

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IN THIS ISSUE

From the Editor	1
From the President	3
May Measurement Month	4
The Secretary's Voice	5
Hypertension News DOIs	6
Hot off the Press:	7
- Effector CD4+ T cells recognize intravascular antigen presented by patrolling monocytes	
- Novel ways for cholesterol testing to improve risk prediction	8
Institute Focus:	
- The Division of Cardiovascular Sciences, The University of Manchester, UK	10
Scientific Report:	
- The Angiotensin AT2 Receptor: A major constituent of the "Protective Arm" of the Renin-Angiotensin System	12
Report from NIC Chair:	
- The 1st International Congress of Hypertension in Children and Adolescents (ICHCA)	15
2017 APSH / ISH Summer School	17
ISH Hypertension News team & Corporate Member Information	18

FROM THE EDITOR

DOI: 10.30824/1803-1

Hypertension News getting a 'going-over'

Lars H. Lindholm
Editor, Hypertension News

Dear ISH member,



It is now 15 years since we started the *ISH Hypertension News – an Electronic Newsletter* and it is time to give the newsletter a 'going-over'. To help, we have invited Professor Tony Heagerty from Manchester, UK and Miss Charlotte Swindall from the ISH Secretariat in London to join the Editorial team. The changes will be made in three steps.

First, the number of pages will be reduced by about a third, leaving room for novelties. We will keep the format as before, but not all titles will appear in every issue. Most texts will also be shorter and the list of references will be considerably shorter. I will also be more reluctant to print contributions from other societies and leagues, unless we have asked for them. Needless to say, the ISH Young investigators will have their previously agreed space in the newsletter.

Second, we will work on the distribution figures, adding Facebook and Twitter to our usual send-out by email to ISH members (with one reminder) and National Societies. This should increase the number of members who download the full or part of the newsletter. From September 2017, each issue of Hypertension News was given an ISSN number and from this issue (March 2018) all texts will carry a unique DOI number. This means that what is published in Hypertension News can now be properly cited, which is of special importance when original data are given. It will also make it possible to download part of the newsletter, which we hope will be appreciated especially by our younger members. The references in Hypertension News will also carry DOI numbers. Our Deputy Editor, Dr. Dylan Burger, Ottawa, Canada will follow the distribution figures carefully and he will update you on the progress in coming issues of the newsletter.

Third, this autumn - when there will be two issues of HT News instead of one - we will gradually let Hypertension News expand again. Hence, it is not the reduction of the texts in itself which is our goal, rather making room for some novelties which we hope will be of interest to you.

Continued overleaf

FROM THE EDITOR

Working on Hypertension News is a time consuming *pro-bono* commitment and I am very grateful indeed for the help I am receiving from the members of our Editorial team ([see page 18](#)). I also want to thank our authors for their valuable contributions. Over the years, the ISH Council members (except the odd one...) have kindly contributed with their views on hypertension (under the title "Council's Corner"). On the ISH web site, you can now find a list of where these texts have been published (please [click here](#)). Several members have told me that they want to get to know the members of the ISH Council better. Reading about their views on hypertension is one way of doing that.

In the current issue, there is a report from the May Measurement Month (MMM) team on 1.2 million people that have been screened for hypertension. Since all reports in Hypertension News now carry a DOI number, the major results from MMM can't be released until they have been published in a leading medical journal. The MMM team should be congratulated on this major undertaking which will be repeated in May 2018, hopefully with even more people screened!

Lars H. Lindholm

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Join us for the ISH 2018 Scientific Meeting in Beijing

For more information,
visit

www.ish2018.org



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Professor Thomas Unger

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15 May 2018

Neil Poulter

President 2016 - 2018

This fifth report of my Presidency allows me to wish all members a Happy New Year – albeit rather belatedly!

The end of 2017 saw the final bits of MMM data being submitted from around the world. Since then the two statisticians, Tom Beaney and his mentor Cono Ariti, have been working on the analysis. That work goes on!

The main ISH event in January was a MMM investigator meeting held at a hotel strategically located between London Gatwick and Heathrow airports and thereby providing easy access for representatives from 50 countries who took part in MMM17 to fly to the meeting. In total 76 delegates attended the meeting at which the results of MMM so far were presented and discussed. Equally importantly, the details of the MMM18 campaign were thrashed out with a view to improving the quality and possibly to a lesser extent, the quantity of the data.

Over the weekend of February 16th - 18th a second ISH meeting was held at the same hotel for all ISH officers – all those on the Council, Regional Advisory Group (RAG) chairs and the secretariat.

Twenty one members attended the meeting and received an update of the ISH activities carried out over the last year and helped to set the strategy going forward. Reports of the activities of all five RAGs, the New Investigator Committee, the Membership Committee and the Women in Hypertension Research Committee among others served to emphasise just what a dynamic society ISH is increasingly becoming. This is reflected in an expanding membership year after year particularly of younger people interested in hypertension.

The Vice President, Professor Alta Schutte, presented plans for extending the society membership even further to include nurses and other health care workers who are frequently at the coal-face of hypertension management and critical to the effective detection and control of the problem of the world.

In the next few months I look forward to visiting National Hypertension or CV Society meetings in Portugal, Greece and Finland.

The inaugural face-to-face meeting dedicated to the development of a Certified Course of Hypertension Management in Africa took place in Nairobi at the end of February. The meeting represents a collaboration between the Pan African Society of Cardiology (PASCAR), the Public Health foundation of India (PHFI) and the Centre for Chronic Disease Control (CCDC) from Delhi (India), the British and Irish Hypertension Society (BIHS) and the ISH. This educational programme is expected to be rolled out to 25,000 primary care doctors in Africa over the next two years. The original course, which began in India, is currently running in India with over 1,200 primary care doctors either having completed or now going through the programme.

Looking ahead to the next biennial ISH meeting in Beijing from 20th-23rd September, the programme is largely completed by the relevant ISH committee superbly led by Professor Thomas Unger in collaboration with the local organising committee in China. We hope that you will all put the dates of this meeting in your diary, send in an abstract (deadline 22nd March) and be there along with your colleagues!

With very best wishes for the next few months.

Neil Poulter

Neil Poulter
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2017 Investigator Meeting & Planning MMM18

A simple measure to save lives
maymeasure.com

Over 70 delegates including representatives from 52 of the countries involved in May Measurement Month (MMM) 2017 met in a hotel near Dorking, outside London, on the 19th and 20th of January 2018 to share their experiences in preparation for MMM18.

During May 2017, the BPs of over 1.2 million people were screened across over **100 countries**, with site locations varying from major cities to remote rural communities in developing countries. Large numbers of those being screened were found to be hypertensive and not treated, and similar large numbers were on treatment but not controlled. These individuals are now aware of their hypertension and have been given advice on the next steps needed to address their condition. As a result, we hope that large numbers of cardiovascular events have been averted as a direct result of MMM.

From these screenings we are able to analyse data from **1.2 million** people and the first tranche of these analyses were presented in mid-January to investigators from 50 countries. Findings from this unique data set will shed light on the links between BP levels and multiple other variables including age, sex, day of the week, hour of the day, pregnancy, body weight, height, diabetes, smoking, alcohol ingestion, established vascular disease and ethnicity. These data will be used to create valuable scientific evidence to help influence public health policies and treatment to reduce the burden of global disease due to raised BP at a local and global level.

We hope to complete and submit our initial global results for publication during March 2018 with the aim of appearing in a top-ranking journal ahead of MMM18 which will take place around the globe from May 1st – 31st 2018. In total, we expect to generate at least 20 publications based on global, regional and national data. Meanwhile, we have asked collaborators to bear with us while we complete the initial global data analysis, and not to compromise the main global publication by publishing at a local level.

During the meeting in Dorking, several investigators presented examples from their respective national efforts on how recruitment of those being screened was optimised and on how the MMM campaign could be improved in 2018.



Emphasis will be placed on producing better quality data in 2018. To do so, significant changes to the bespoke MMM App and data collection have been made based on advice given at the meeting.

It is expected that several countries around the world – including Ethiopia, Finland, France, Latvia, Morocco, Senegal and Seychelles - which were not involved with MMM17 will take part in the 2018 campaign. Furthermore, this year, we will ensure the timely distribution of blood pressure (BP) machines, kindly donated by OMRON, whereas time was more limited last year.

Streamlined logistics and more countries involved and improved resources and support will ensure even more people are screened in 2018.

To enhance public awareness Servier will be launching a BP awareness campaign in over 100 countries, the aim of which is to persuade young people to encourage their parents to get their BP measured. This links perfectly with MMM18 which will provide people with the facilities to do so!

Unlike the 2017 campaign we plan to collate all the 2018 data within 2 months of the end of May and be able to clean and analyse the data in time to present the results at the Beijing ISH meeting (September 20th-23rd).

If you are not already involved, please get in touch to join in!

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Maciej Tomaszewski

**ISH Secretary
University of Manchester, UK**

I am delighted to provide you with the next update on the activities of the ISH Executive Committee, the Council and the Society.

1) Professor Neil Poulter, ISH President, chaired a May Measurement Month (MMM) 17 results and review meeting in Dorking (near London) from 19th to 21st January. This meeting brought together the ISH Council members, the National Leaders for May Measurement 2017 and May Measurement Month (MMM) initiative supporters from over 50 countries. Professor Poulter provided the first glimpse into the outcomes of MMM17. He congratulated the leaders in over 50 countries who contributed to the success of MMM17. We are now getting ready for MMM18 and I very much count on your kind support for this key initiative of the Society. Further news is available on our [website](#) and through contact with the MMM Project Manager: Email: manager@maymeasure.com

2) The senior leadership of the Society met on 17th February 2018 in Dorking for the ISH Council meeting. The agenda included key Society business, including MMM, Council elections, alliances with health organisations and sister Societies, finances, forthcoming meetings in Beijing and Glasgow and updates from the key committees of the Society. The Council will meet again prior to the ISH Beijing 2018 meeting.



Left:
ISH Council dinner in Dorking.

Right:
Professor Neil Poulter receiving the World Hypertension League Peter Sleight Excellence in Hypertension Clinical Research Award.



3) The ISH Beijing 2018 Committee (chaired by Professor Thomas Unger) in co-operation with the Beijing 2018 Local Organising Committee is finalising the scientific programme of the meeting. You should expect an exciting and intellectually stimulating programme with several keynote addresses delivered by world leaders in cardiovascular research. Please note that the deadline for abstract submissions has been extended to 22nd March 2018. I strongly encourage you to submit an abstract and if you are a New Investigator and low and middle income countries – apply for one of the travel grants to support your attendance at the meeting.

4) In partnership with the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) we will hold joint ISH/ESH and ISH/ESC sessions during the ESH 2018 and ESC 2018 congresses in Barcelona and Munich, respectively. I strongly encourage you to attend these sessions.

5) ISH has joined the coalition for access to NCD medicines and products. The first meeting of this coalition took place in Geneva (13th -14th February 2018) - ISH was represented at this event by the ISH Forum Officer, Professor Louise Burrell.

6) ISH has partnered with the European Association for the Study of Obesity (EASO) to deliver a meeting on 8 May 2018 in London. Further information on this collaboration and the meeting will be available on the ISH and [EASO](#) websites.

7) Congratulations to ISH President, Professor Neil Poulter, for receiving the World Hypertension League Peter Sleight Excellence in Hypertension Clinical Research Award.

Continued overleaf

8) Congratulations to Professor Fadi Charchar (the Chair of our ISH Mentorship and Training Committee) for winning the High Blood Pressure Research Council of Australia Colin Johnston Lecture and Award.

9) The ISH Mentorship and Training Committee (chaired by Professor Fadi Charchar) has added a new award to the portfolio of ISH prizes. The new ISH Distinguished Mentor Award will honour a member of the ISH who has made outstanding contributions to the mentoring of students and trainees/junior faculty in the field of hypertension and cardiovascular disease. The call for nominees is out – please submit your nominations to the ISH Secretariat by **30th April**.

<http://ish-world.com/news/a/ISH-Distinguished-Mentor-Award/>

10) I am delighted to confirm that ISH members who author a manuscript accepted for publication in the Journal of Hypertension will receive a 15% discount on the open access fees.

11) Please note that our Social Media accounts have been updated @ISHBP will now serve as the official Twitter account for the Society. Our Facebook page can now be found at <https://www.facebook.com/ISHBP/>

Maciej Tomaszewski

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HYPERTENSION NEWS

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Hypertension News Now Provides Digital Object Identifiers (DOIs) for All Content!

In recent years there has been a push to identify scholarly content through universal digital identifiers that can be used to identify, cite, and share articles. The identifiers provide a consistent and easily recognized format for referencing and they remain constant even if the content's location changes. The most universally adopted object identifier for titles/journals is the International Standard Serial Number (ISSN) which was described briefly in the June 2017 issue of Hypertension News. For Hypertension News this number is (ISSN: 2520-2782). Similarly, the Open Researcher and Contributor ID (ORCID) provides an identifier that distinguishes one researcher from all others. This identification is increasingly used by journals and granting agencies to identify individual contributors and ensure recognition of work.

For manuscripts, the Digital Object Identifier (DOI) is the most universally employed method of digital identification, particularly for online content. Unlike a web URL, the DOI of an article specifies not the location of an online object, but rather the location of the content itself. Accordingly, the DOI remains associated with the object irrespective of changes in the object's web address. This is particularly desirable for citation of online content because the article can be cited/linked with the confidence that the resource will be available in the future through the same identifier even if it moves from location to location online.

Beginning with the current issue, all Hypertension News content will be assigned a unique DOI beginning with the prefix "10.30824". Similarly, all content cited in Hypertension News will now be linked directly with their own DOI (when available). This will dramatically increase the visibility of contributions to Hypertension News and assist authors wishing to reference Hypertension News in future contributions.

Dylan Burger

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Effector CD4+ T cells recognize intravascular antigen presented by patrolling monocytes

Westhorpe CLV et al. *Nature Communications* (2018) 9:747.
<http://dx.doi.org/10.1038/s41467-018-03181-4>

Dylan Burger
 Deputy Editor, Hypertension News
 ISH Communications Committee Member
 University of Ottawa, Canada



In recent years advances in imaging technology have brought attention to the concept of immune patrolling of the vasculature.¹ Classically, monocytes were viewed as being abundant in blood but then readily extravasating to inflammatory sites in target tissues. "Non-classical" monocytes (also known as patrolling monocytes) remain in the vascular system and will engage in long-term migration along the endothelium either with or against blood flow. Recognition of "non-classical" monocyte migration along the endothelium has been made possible due to advances in multi-photon intravital imaging platforms and this process has been described in numerous tissues and several small animal models.

Last month Westhorpe and colleagues published an impressive manuscript in *Nature Communications*² that provides exciting new details on how the immune system interacts with the glomerulus in glomerulonephritis. Using intravital multiphoton imaging of the kidney, the authors examined immune cell interactions with the glomerulus. First they established that CD4+T-cells migrate constitutively to an uninflamed glomerulus with increased retention in antigen-bearing glomerular capillaries. The authors subsequently showed that MHCII+monocytes also migrate to glomerular capillaries, that T-cells interact with these monocytes, and (most importantly) that MHCII+ monocytes were required for T-cell induced neutrophil activation and glomerular inflammation in a mouse model of ovalbumin-induced glomerulonephritis.

While the role of T-cells in glomerulonephritis has been described previously³, this study provides convincing evidence that MHCII+"patrolling" macrophages play a critical role in at least one form of experimental glomerulonephritis. In my opinion, the methodology used is sound and, indeed, at the very leading edge of this

field. The multiphoton images in the main body of the document are clear and the videos in the data supplement strongly support the authors' conclusions. It is important, however, to acknowledge that the process of immune surveillance is far more completely understood in mice than it is in humans where many of the labeling techniques employed for visualization of immune cell-endothelial interactions are not possible. In addition, this is a single animal model of glomerulonephritis and whether this is conserved across other forms of glomerulonephritis is unclear. It is worth noting that the authors observed immune patrolling in the non-diseased state which is at least suggestive of the process being conserved across multiple pathological states. Regardless, the results must be corroborated by other groups in other experimental models and ultimately in human glomerulonephritis. If this process proves true however, patrolling macrophages may represent a novel target to interfere with intraglomerular antigen presentation and ultimately, T-cell-mediated glomerular inflammation.

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Novel ways for cholesterol testing to improve risk prediction

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Cholesterol testing is one important component in risk equations such as the Framingham Risk Score or the Systematic Coronary Risk Evaluation (SCORE), which are widely used to assess the risk for incident cardiovascular mortality. Low-density lipoprotein (LDL) cholesterol provides stronger prognostic information than total cholesterol values. Direct methods to measure LDL cholesterol are available but more often LDL cholesterol is calculated indirectly by the Friedewald formula from total cholesterol, high-density cholesterol, and triglyceride values. However, this formula has several limitations in subjects with low LDL cholesterol and/or high triglyceride levels. Furthermore, fasting lipid assessment is often recommended as triglyceride values are highly variable, which may be inconvenient.

Martin and collaborators recently presented a method for improved LDL cholesterol estimation using an adjustable ratio of triglyceride to very low-density lipoprotein cholesterol levels¹. The same authors now present results² from a large database of more than 1.5 million patients (one third were fasting) to show that this novel estimated LDL cholesterol is more closely related to directly measured LDL cholesterol and less affected by fasting status than LDL cholesterol derived by conventional measurements and the Friedewald formula. The advantage for this novel estimated LDL cholesterol method was strongest for patients with low LDL cholesterol and high triglycerides. These findings have several clinical implications. Cholesterol testing in non-fasting conditions is often much simpler for the patient than the request for fasting samples. The availability of more potent lipid lowering drugs and more aggressive targets for lipid lowering therapy in secondary prevention currently recommended make it more important to have accurate determinations also at lower values of LDL cholesterol. Taken together, this novel LDL cholesterol calculation provides a simpler way to obtain a more accurate lipid profile, and may improve risk stratification³.

Another interesting aspect of how the evaluation of cholesterol levels could be improved was recently published by Kim and co-workers⁴. Increased blood pressure variability and decreased heart rate variability has been recognised as markers of increased cardiovascular risk. Whether the visit-to-visit variability in cholesterol levels relates to incident cardiovascular events has, however, not been well studied. These authors analysed data on the visit-to-visit variability of total cholesterol and future cardiovascular events and death in more than 3.5 million people in South Korea with no previous history of an acute myocardial infarction or stroke, who underwent three or more health examinations from 2002 to 2007. The median follow-up was 8.3 years.

The authors showed that increased variability in total cholesterol values (assessed as standard deviation, coefficient of variation, or variability independent of the mean) in a multi-variable adjusted statistical model all related to all cause mortality, acute myocardial infarction, and stroke, independent of mean total cholesterol levels and other potentially confounding factors⁴. Although the results of this study should be viewed in the light of its potential limitations, it appears that the variability in total cholesterol, similar to blood pressure, heart rate, and other physiologic measures provides independent prognostic information. Whether this association represents causation, and if a reduction in cholesterol variability improves prognosis, remains to be shown and warrant further study⁵.

References overleaf

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ISH SOCIAL MEDIA ACCOUNTS UPDATED

We are pleased to announce that our social media accounts have been updated. @ISHBP will now serve as the official Twitter account for the International Society of Hypertension.

Our Facebook page can now be found at www.facebook.com/ISHBP/

Existing followers will continue to receive updates and the accounts will continue to serve New Investigators as they have in the past.

[Follow us on Twitter at @ISHBP](#)



[Like us on Facebook](#)





The Division of Cardiovascular Sciences The University of Manchester, UK

Tony Heagerty

Tony Heagerty, a former President of the ISH is Head of the Division of Cardiovascular Sciences situated in Manchester which is the largest Medical School in the United Kingdom graduating 500 students annually. His personal duties still include everyday clinical practice which is carried out in Manchester Royal Infirmary, the hospital adjacent to the laboratories where the Division’s research is conducted. The clinical service was recognised as an ESH Hypertension Centre of Excellence when the scheme began in 2005 and has been renewed since.

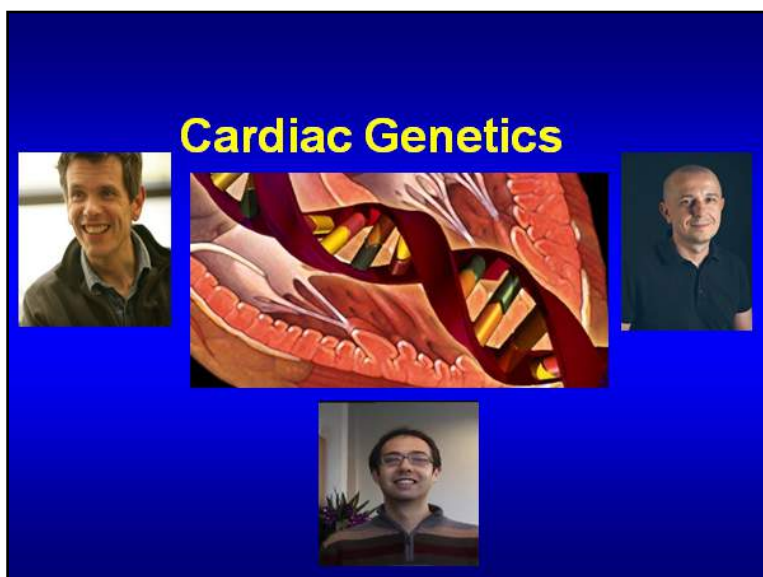
The clinic acts as a tertiary referral centre for the North Western region and receives referrals from far and wide as well as patients from overseas and offers comprehensive workup for secondary hypertension as well as non-adherence testing which is increasing in popularity and academic interest as a result of the recent appointment of Professor Maciej Tomaszewski who is the current Secretary of the ISH. The Division itself comprises 36 principal investigators and currently has 79 postgraduate students reading for PhD or MD degrees. In addition, there are 18 MRes students and very vibrant Academic Clinical Fellowship and Academic Clinical Lectureship programmes for young clinicians interested in cardiovascular research. Also, the group has had a 4 Year PhD Scheme sponsored by the British Heart Foundation for the last 10 years offering 6 research positions annually. In the last full academic year, the group won 25 research awards worth a total of £4.6million. In the current year there have been awards already in excess of £2million and in the last 18 months the group has published 188 papers.

Not all of the activity is focused on hypertension per se and Tony Heagerty’s group is interested in perivascular adipose tissue and its role in the pathogenesis of obesity related hypertension and diabetes. There is an internationally recognised Stroke group looking at minimising damage following cerebral haemorrhage and a large amount of activity devoted towards the mechanisms responsible for heart failure and the development of new therapies. There is also very vibrant research activity focusing on the distribution of sodium and potassium channels in conducting tissue of the heart and the genesis of atrial dysrhythmias. The success of the group has been augmented by the appointment of a new British Heart Foundation funded Professor (Bernard Keavney) with his interest in cardiac genetics and within 4 years this group has grown into a large and highly successful operation, and perhaps most interesting has been the recruitment of Holly Shiels as a fish biologist interested in cardiac dysrhythmias in salmon and trout (it was fascinating to find out that even a change of temperature in the water can provoke malignant dysrhythmias in fish!).

Continued overleaf

Figure 1

The Cardiogenetics Group is headed by Professor Bernard Keavney (top left) with Professor Maciej Tomaszewski (ISH Secretary) and David Talavera who is a Lecturer recently appointed. They have research grant income which they have raised of over 5million dollars in 3 years. Bernard Keavney’s interests are in the genetics of congenital heart disease. Maciej is of course known for his hypertension genetics research and David Talavera is interested in analysing large datasets.



Tony Heagerty has always been involved in bringing on the careers of young and aspiring clinicians as well as academic scientists. The group has been keen to develop a career track for both non-clinical and clinical principal investigators and this has been rewarded with the appointments at senior academic level of a number of young clinicians who are now working in Manchester as well as Professors in Cardiac Physiology. The reputation of the whole Division is such that there are always visitors from all over the world and given that Manchester has the largest cluster of Chinese people in the United Kingdom, it is hardly surprising that very many graduate students come from mainland China to work with the principal investigators in Manchester, but in addition, the group reaches out all over the world and collaborates in North America, Canada, Australia, New Zealand and of course, in many countries in Europe.

Manchester itself is a highly vibrant city and annually is at the top of the list of preferred cities for young people to come and study. It boasts a road one mile long which is solely full of Indian restaurants as well as some of the finest Chinese eateries in the country and with three universities and over 40,000 students, term-time is extremely lively! The North West of England has the worst rates of heart disease and cancer in England and the Division is striving as hard as possible to put that right quickly!

Tony Heagerty

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Figure 2

The Heart Failure Team is shown on this slide with contributions from Andy Trafford and Kat Dibb (top left), Vicky Liu and Joy Wang (centre and top right), Nick Ashton and Holly Shiels.

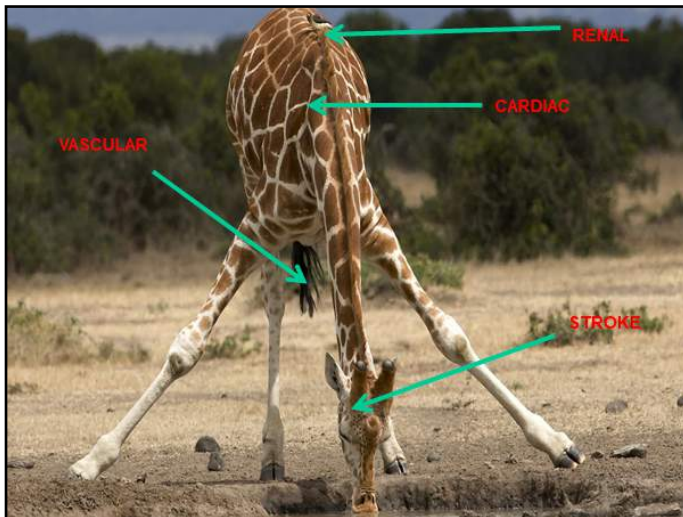


Figure 3

The giraffe which is a much loved creature related to the cow and hypertensive throughout life gives a department focus in cardiovascular research given the fact that all of its organs are exposed to extreme pressures throughout its life.

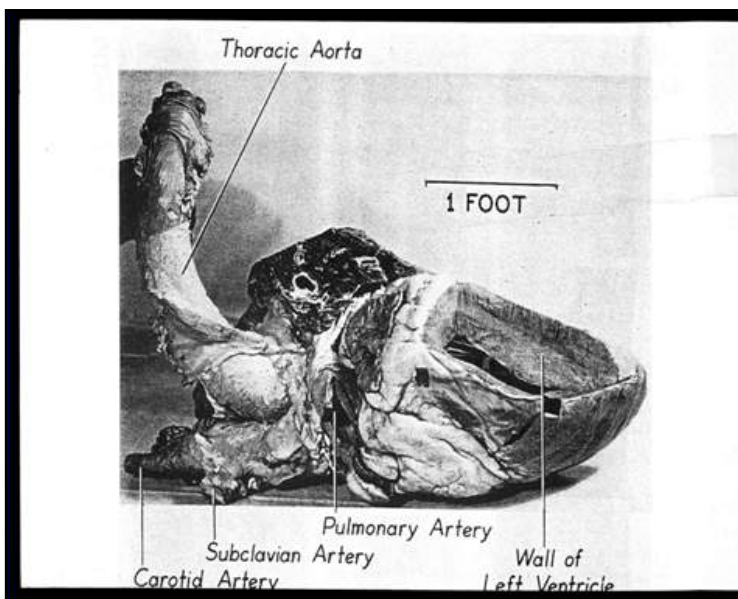


Figure 4

An original illustration from the classic work of Goetz and Keen (*Some Aspects of the Cardiovascular System in the Giraffe*. Goetz RH, Keen EN. *Angiology* 1957;8:542-64) showing a dissected giraffe heart with massive left ventricular hypertrophy which, of course, is important in keeping the giraffe alive but in humans is a sinister adverse cardiovascular risk factor. The research group looking at ways of reducing this comprises Elly Cartwright (top), Delvac Oceandy (centre) and Gina Galli (bottom).



The Angiotensin AT2 Receptor: A major constituent of the "Protective Arm" of the Renin-Angiotensin System

Thomas Unger

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Abstract

Since its discovery, more than twenty-five years ago, the angiotensin AT2 receptor (AT2R) has puzzled the scientific community because of its distinct localization, regulation, signalling pathways and biological effects separating it clearly from the classical features of the renin-angiotensin system (RAS) mediated by the angiotensin AT1 receptor. Intensive research over the years has revealed major characteristics of the AT2R as a modulatory player involved in anti-proliferation, anti-inflammation, natriuresis, neuroregeneration and apoptosis, i.e. biological programs that can counterbalance pathological processes and enable recovery from disease. The AT2R has thus mutated from an "enigmatic" receptor to a significant member of the "protective arm" of the RAS. The recent development of novel, small molecule- and peptide-derived AT2R agonists offers a therapeutic potential in humans with a variety of clinical indications.

The 'enigmatic receptor' is a designation of the angiotensin AT2 receptor (AT2R) from the very beginning of its discovery more than 25 years ago in the late 1980s. 'Enigmatic' because of constitutive action, atypical intracellular signalling and "hidden" (patho) physiological functions that took years, almost decades, to unveil. Even today the various actions, some of them still controversial, the numerous intracellular signalling pathways, the interaction with other membrane receptors and the role of the AT2R in the context of the renin-angiotensin system (RAS), are far from being fully elucidated. We at least know much more than in the early days about the AT2R, we can confidently classify it as an important member of the "protective arm " of the RAS (Figure 1) and we have even identified this receptor as a therapeutic target.

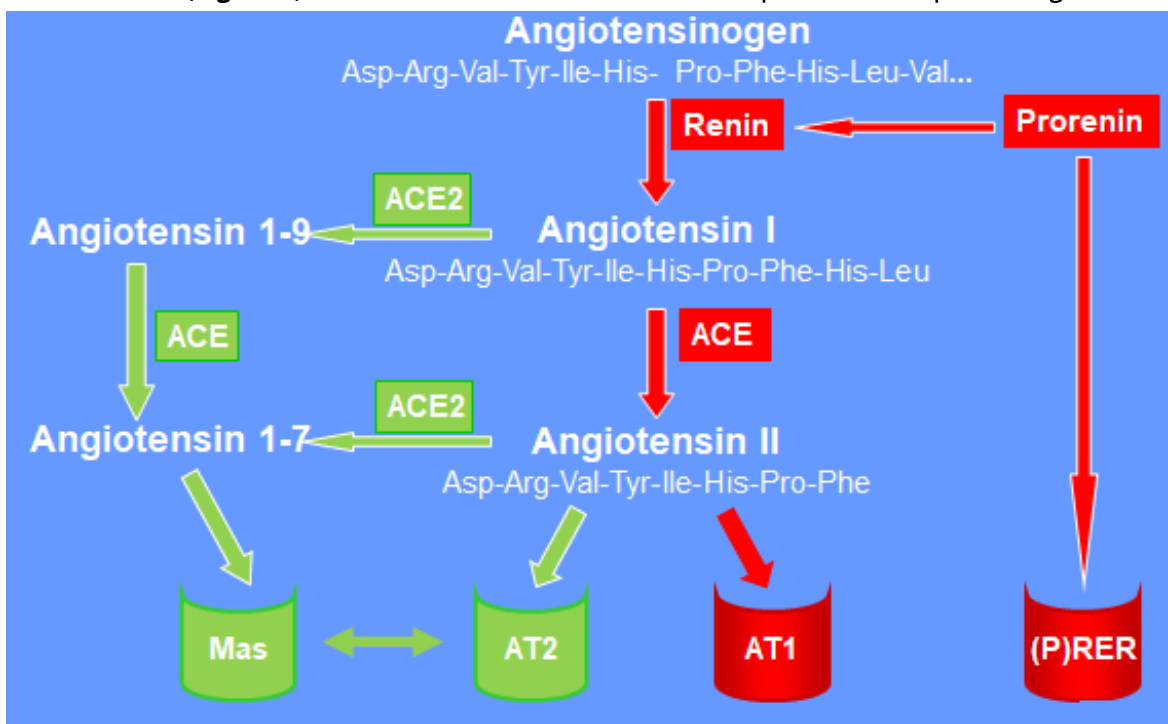


Figure 1
 The Renin-Angiotensin System with its "classical" arms (in red) and its "protective arms" (in green)

Continued overleaf

Until about 1989, the scientific community thought that angiotensin II (Ang II), the main effector peptide of the RAS, used only one single receptor to exert its various actions in the cardiovascular system and beyond: the angiotensin receptor. Several peptidergic angiotensin derivatives such as saralasin, had been developed to antagonize those Ang II actions thought to be harmful or just to serve as pharmaceutical tools to gain more insight into the role of the RAS. However, for several reasons, expectations as to developing these compounds into clinically useful antihypertensives could not be fulfilled.

Around the late 80s, some pharmaceutical companies, searching for new tools and better drugs interfering with the RAS, had developed small compounds that were differentially binding to angiotensin receptors in various tissues pointing to distinct angiotensin receptor populations. While the "sartans" (ARBs) selectively bound to the "classical" angiotensin receptor in blood vessels and other tissues later designated as the angiotensin AT1 receptor (AT1R), some other agents were surprisingly binding to a "new" angiotensin receptor in uterus and adrenal gland, later designed as the angiotensin AT2 receptor (AT2R).

Retrospectively, the surprise about two or even more receptor subtypes in one biological system, such as the RAS, seems to be somewhat out of place since many of these systems operate on several receptors and the effects mediated by different receptors in these systems are often different from- or even opposing each other.

Unexpected pharmacological binding does not necessarily prove the existence of a "new" receptor. Proof of the existence of the AT2R was first provided by the molecular cloning of cDNA of this receptor by Victor Dzau's laboratory at Stanford and Tadashi Inagami's group at Vanderbilt. With further characterization of the genomic structure and the documentation of mouse phenotype by gene deletion experiments, the AT2R was no longer a pharmacologic binding phenomenon but a real biologic entity.

In the following years several groups, including our own, provided ample evidence based on different experimental approaches that Ang II via its AT2R induced effects such as anti-proliferation or anti-inflammation quite opposite to those

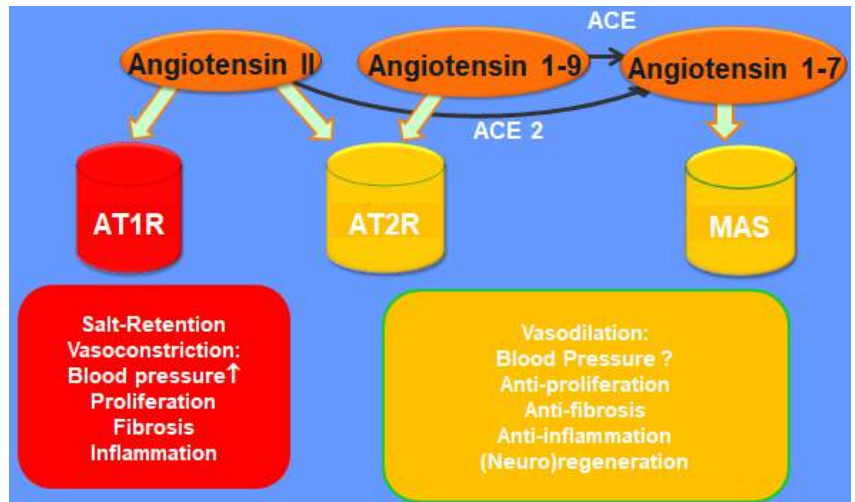


Figure 2 Effects of the two arms of the Renin-Angiotensin System.

"classical" actions of the Renin-Angiotensin System, exerted via its AT1R.

The international research community did not readily accept findings against a mantra of the time stating that Ang II was exclusively acting as a proliferative / hypertrophic agent in cells of the cardiovascular system. It took some more years until it was generally accepted that Ang II, via its AT2R, could act indeed as a growth-inhibiting principle, assigning for the first time a clear biological function to the "enigmatic" AT2R: anti-proliferation with a predominant localization in, among others, fetal tissue, the uterus and some distinct areas of the brain.

It also became apparent that AT2R signalling differed markedly from AT1R signalling. While both receptors, though having only 33-34 % homology, could be assigned to the seven transmembrane domain family of receptors which usually bind G-proteins, the AT2R exhibited some atypical features. It engages a complex intracellular signalling network linked to distinct physiological functions: anti-proliferation (but under some special conditions also hypertrophy), anti-inflammation, cellular differentiation, anti-fibrosis, natriuresis, and induction or inhibition of apoptosis (**Figure 2**).

These findings fuelled a vivid discussion, sometimes controversy, about the "true" biological functions of the AT2R. More recently a model to clear up several contradictions has been proposed in which the type of adapter protein recruited to the receptor, as well as the presence or absence of growth factors, determine the cellular effects assuming a multiple-state receptor model with several activated states. Such a "biased agonism" model could also be the basis for our mechanistic understanding of compounds selectively stimulating the AT2R. In addition, different patterns of homo- or heterodimerization (with the AT1R, the MAS receptor or the bradykinin B2 receptor) have to be considered as functional determinants of AT2R action. It also became apparent that this receptor is distinctly regulated: while being highly expressed in fetal tissues but suppressed in many tissues in the adult organism, its expression can be drastically upregulated under the condition of ischemic or traumatic tissue injury but also in atherosclerotic lesions.

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A further aspect of AT₂R signalling and function deserves particular attention, a feature quite novel and unique for the RAS: Neuroprotection and neuroregeneration, modulation of sympho-excitation, and possibly improvement of cognitive function. Different experimental approaches used by independent groups revealed a fairly consistent picture of the AT₂R in the nervous system, revealing that the AT₂R-induced neuronal differentiation and inhibition of neuro-excitation could be not only part of neuronal development but also the basis for therapeutical considerations about drug-induced AT₂R stimulation. This idea was supported later-on with the help of a wealth of results in different experimental disease models.

Together all these experimental results point to a possible qualification of the AT₂R as a drug target. A decisive step forward in this direction came in 2004 with the publication of the first highly selective, orally active AT₂R agonist by a Swedish group. Until now compound 21, the main representative of this family of AT₂R agonists, has not only helped to unravel many of the secrets of AT₂R signalling and function but, moreover and most importantly, has opened the door to numerous potential clinical indications of AT₂R stimulation not only in the cardiovascular field but also in the areas of renal, metabolic and neuronal diseases as well as in many other indication areas where anti-inflammatory, antifibrotic or anti-proliferative actions are therapeutically required.

One more interesting feature is that despite the fact that activation of the AT₂R can engender the production of cGMP via the nitric oxide (NO) pathway, AT₂R stimulators do not seem to be direct antihypertensive agents such as the AT₁R antagonists. However, they could contribute to lowering blood pressure via indirect mechanisms, for instance by their antifibrotic actions reducing arterial stiffness (**Figure 3**).

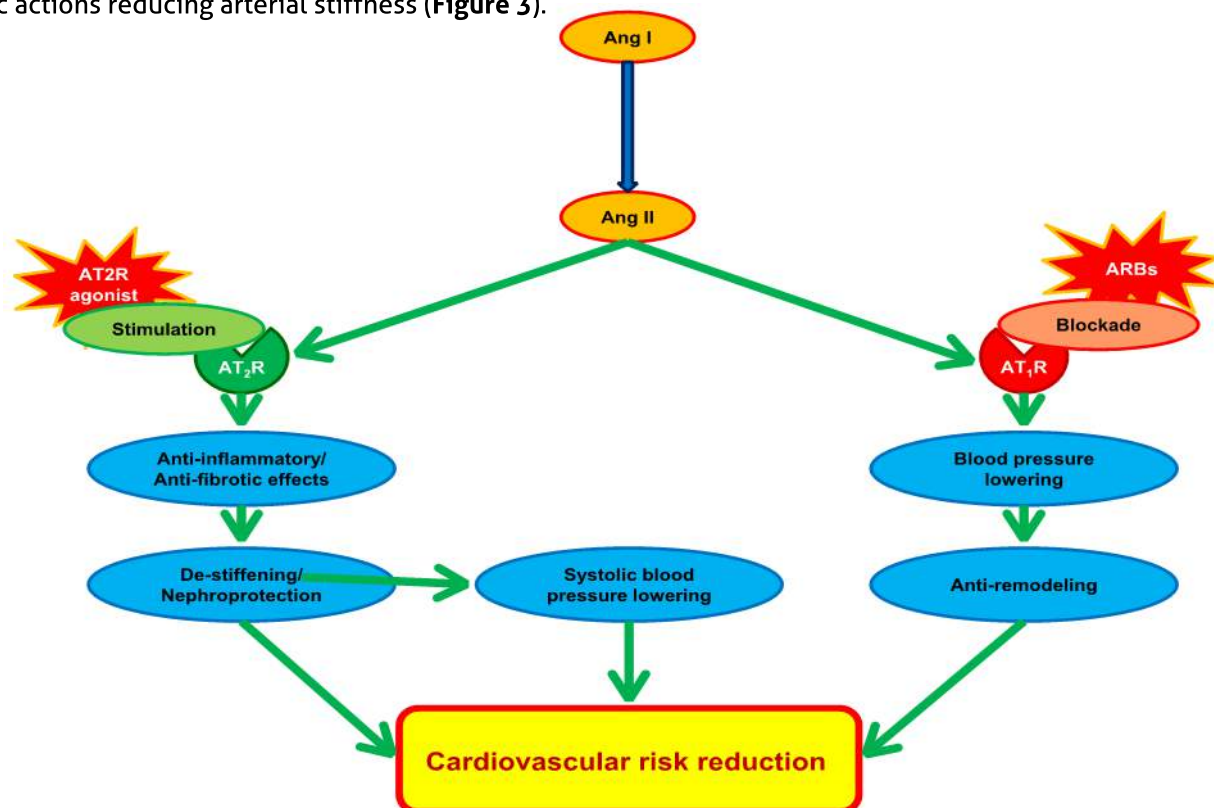


Figure 3

Combined angiotensin receptor modulation. Scheme showing the rationale for combining the stimulation of the AT₂ receptor (AT₂R) with the blockade of the angiotensin AT₁ receptor AT₁R by the AT₁R blockers (ARBs). AT₁R blockade lowers blood pressure directly and AT₂R stimulation reduces arterial stiffness in the long term preventing the increase in the systolic blood pressure without compromising diastolic blood pressure values. Such a combined effect might be of particular significance in the elderly, in patients with isolated systolic hypertension or in end-stage renal patients.

Further reading overleaf

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REPORT FROM NEW INVESTIGATOR COMMITTEE CHAIR



The 1st International Congress of Hypertension in Children and Adolescents (ICHCA)

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Hypertension in Africa Research Team (HART)
South African Medical Research Council Unit for Hypertension and Cardiovascular Disease
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The burden of hypertension in children and adolescents has become a true concern. From the recent 2016 European Society of Hypertension Guidelines for the Management of High Blood Pressure in Children and Adolescents,¹ there was a call to action paediatric hypertension which contributes to the current epidemic of cardiovascular disease. A global effort to improve the identification and treatment of high blood pressure among children and adolescents is therefore anticipated.

In a systematic review published in the *Lancet*, the prevalence of hypertension and slightly elevated blood pressure was 5.5% and 12.7% respectively, with overweight and obesity being important risk factors.² These findings have major implications for health systems as these young people are likely to track to adult hypertension. With these important citations in the backdrop, the first International Congress of Hypertension in Children and Adolescents (ICHCA) was born.

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In a combined effort, Professors Empar Lurbe (Spain), Brian Rayner (South Africa) and Daniel Feig (USA) hosted this exciting congress in the charming setting of Valencia, Spain on 9th- 11th February 2018.

Renowned speakers invited to this meeting included amongst others Professors Anna Dominiczak (UK), Nicholas Webb (UK), Kennedy Cruickshank (UK), Denes Pall (Hungary), Josep Redon (Spain), Mark Mitsnefes (USA), Elke Wühl (Germany), and Mieczyslaw Litwin (Poland). Julie Ingelfinger (USA), Professor of Pediatrics at Harvard Medical School, Senior consultant in Pediatric Nephrology at Mass General Hospital for Children at Massachusetts General Hospital, and Deputy Editor of the New England Journal of Medicine enlightened us with the congress keynote titled *Facing the challenges of hypertension in children and adolescents*. The congress also included a small selection of e-Posters and short scientific communications from peer-reviewed abstracts.

This first ICHCA meeting was attended by 123 delegates from 46 countries endorsed by 22 partners and societies. Whether this will become an annual or biennial meeting is still to be announced, but mention was made that the second meeting will take place in 2019, with no further information confirmed.

Be sure to keep this congress on your list of meetings to attend!

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New Investigator Member Spotlights 2018



Luciana C. Veiras, USA



Yanina Timasheva, Russia



Trefor Morgan APSH Secretary General

The second APSH/ISH Summer School was held from 31st July to 4th August at the Crown Plaza Hotel, Shanghai, China. It was attended by 27 Scholars, 12 Faculty and appropriate support staff. Scholars came from China, Australia, Bangladesh, India, Indonesia, Malaysia, Thailand, Taiwan and Vietnam. The Dean of the Summer School was Trefor Morgan. The Convener and local organizer was Jiguang Wang. The International faculty members supported by ISH were Ernesto Schiffrin (Canada) and Garry Jennings (Australia). The New Investigator Committee of ISH was represented by Akira Nishiyama (Japan). The Member societies of APSH provided the following Faculty members: Markus Schlaich (Australia), Narsingh Verma (India), Arieska Ann Soenarta (Indonesia) and Hiroshi Itoh (Japan). China provided 3 Faculty Members: Zhaosu Wu, Yuqing Zhang and Zhiming Zhu.

The Summer School is an event with presentations by scholars, interspersed by interactive discussion and update lectures by the faculty members. Each day the meeting ran from 08.30 to 17.30 with 1 hour for lunch. Wednesday was a half day with a city tour of Shanghai including a visit to the BUND and a twilight river cruise.

In the meeting there was a strong emphasis on detection and primary prevention balanced by presentations and discussions on modern principles of management. There was discussion of the guidelines from different regions of the world and their relevance to countries at different stages of development. Original work was presented by the faculty and scholars. There was a case management session organized by Markus Schlaich. The role of the New Investigator Committee of ISH was presented by Akira Nishiyama and I am confident this will lead to a number of new applications to ISH to join as Research Fellows and take part in future ISH meetings and New Investigator Committee initiatives.

The participants in the Summer School, both Scholars and faculty, thought that the event was a success and should be continued in the future. The Summer Schools have been able to be conducted due to grants from ISH that have provided fares for the international faculty and some support for the local organization. Member societies of APSH have funded the attendance of faculty members and provided support for scholars to attend. The major cost has been borne by the local hosts, the Chinese Hypertension League and the Shanghai Institute of Hypertension. It is planned to hold a third summer school in 2019 and a search for a host society will be made shortly.

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Society of
Hypertension



International
Society of
Hypertension



Chinese
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