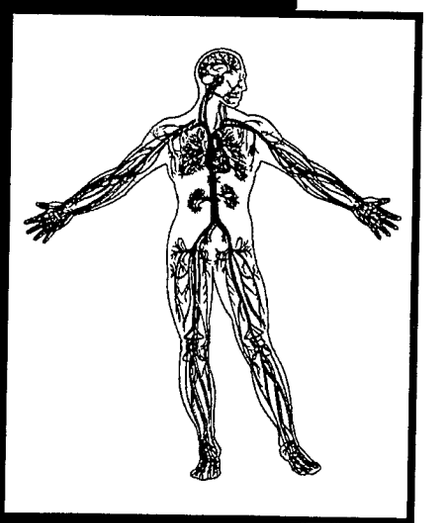
COUNCIL NEWSLETTER



American Heart Association℠

Fighting Heart Disease and Stroke

Thrombosis

Fall 1995 **Edwin G. Bovill, MD, Editor**

Editor's Note

This newsletter addresses a number of critical issues for members of the Council on Thrombosis. Dr Thomas Deuel reviews a meeting with Dr Claude Lenfant, director of NHLBI, that occurred during the December 1994 meeting of the American Society of Hematology. The meeting with Dr Lenfant focused on ways to improve communication between our council and the NIH. Dr Deuel also gives an update on the important ongoing work with respect to the future of vascular biology and its role in the AHA. There is serious consideration about consolidation of the Council on Thrombosis with the Council on Arteriosclerosis and the Working Group on Vascular Biology. Dr Samuel Rapaport, incoming chair of the Thrombosis Council, discusses this in his report on page 2.
Drs Pan Ganguly (Blood) and David Robinson (Heart) have replaced Dr Carol Letendre as our liaison with the NHLBI. Dr Ganguly's report covers new initiatives and reviews recent changes in funding guidelines. Dr Kenneth Mann reviews the status of the AHA grant system and discusses a number of approved and pending changes. Dr Jack Hawiger reports that our journal *Arteriosclerosis, Thrombosis, and Vascular Biology* is doing well.

This issue of the newsletter also includes a new feature, an invited review of a topical area. Dr Frits Rosendaal from the Departments of Clinical Epidemiology and Hematology, Leiden, The Netherlands, has contributed a review entitled "Resistance to Activated Protein C by Factor V Leiden: Clinical Implications." Finally, there is a review of the programs for the Council on Thrombosis at the 1995 ASH meeting and the 1996 AHA meetings along with a report on the budget for fiscal year 1995-1996.

Edwin G. Bovill, MD

Report From the Chair

Report From Thomas F. Deuel, MD, Immediate Past Chair

Two most important events need your closest attention.

During the American Society of Hematology Meeting in December, Sam Rapaport and I met for an hour and a half with Claude Lenfant, director of the NHLBI. The meeting was very productive. We primarily discussed ways in which the Council on Thrombosis might enhance communications with Dr Lenfant and the NHLBI and mechanisms to maintain the highest levels of communication. Dr Lenfant expressed great interest in the activities of the Council on Thrombosis and the community that it represents. He invited our input into all issues related to the activities of the NHLBI. We discussed changes in the focus of the Council on Thrombosis that have evolved over the past several years and emphasized that many investigators within the council are now focusing on issues of vascular biology, atherosclerosis, and cardiovascular disease as the natural outgrowth of research in hemostasis and thrombosis. The vigor and energy of these investigators and the importance of their contributions to an understanding from a variety of perspectives of phenomena within the blood vessel wall was stressed. We emphasized the importance of recognizing within NHLBI the extent to which contributions of the thrombosis community could overlap the activities of the Vascular Biology Program of the Division of Heart and Vascular Diseases. In response, Dr Lenfant agreed to appoint Dr David Robinson, director of the Vascular Biology Program, as an additional liaison to the Council on Thrombosis. Thus, both our present liaison, Dr Pan Ganguly, leader of the Thrombosis and Hemostasis Scientific Research Group within the Division of Blood Diseases and Resources, and Dr Robinson will now work with the council. This is a wonderful commitment to us, and we enthusiastically look forward to working with both of them. Sam Rapaport and I hope to meet periodically with Dr Lenfant to maintain a fruitful, continuing interaction between the Council on Thrombosis and the NHLBI.

The second issue of major importance to the Council on Thrombosis is the future of vascular biology in the AHA. Sam Rapaport, Ralph Nachman, and I represented the Council on Thrombosis on the Task Force on Intercouncil Cooperation, a committee appointed by Dr James Moller, president of the AHA during 1993-1994, to find ways to integrate activities of the Working Group on Vascular Biology, the Council on Thrombosis, and the Council on Arteriosclerosis.

The Working Group on Vascular Biology was formed in 1991 to address interests related to vascular biology, but its activities will cease in mid-1997. The gain to the Council on Thrombosis of merging with the working

group and the Council on Arteriosclerosis would be a far larger council with far greater impact within the AHA and far greater opportunities to influence the content of meetings as well. Coordinated programs and activities can only enhance our visibility and strength within the AHA and will better serve its mandates for consolidation of councils and coordination of activity. Such a union would also help emphasize our areas in the research community. We plan to have a separate meeting in addition to the AHA meeting that will represent all three groups; this will be a highly visible and important meeting. However, it will not replace the importance of the contributions to the annual meeting.

This consolidation of the Councils of Thrombosis and Atherosclerosis with the Working Group on Vascular Biology was discussed at great length at the meeting of the Executive Committee in May. It was concluded that such a consolidation was highly desirable and consistent with the long-range goals of the council. It was also stressed that the needs of the diverse interests of council members had to be met in full in order to consolidate the three groups. The Executive Committee unanimously voted to bring this matter to full discussion at the November meeting of the council with the goal of a vote of the council members to follow.

The opportunities for advancing the cause of thrombosis are striking but can be done only if members of the council are enthusiastic and utmost consideration is given to our best interests. I invite your comments and very much urge each of you to write.

In closing, I thank the Council on Thrombosis for the privilege to serve as chair. It has been a most rewarding experience. I look forward to helping Sam Rapaport and Bob Rosenberg, the new chair and vice-chair, in any way possible.

. . .

Report From Samuel I. Rapaport, MD, Chair

In July of this year I succeeded Dr Deuel as chair of the Council on Thrombosis. As recommended at the May 1995 meeting of the Executive Committee, I am proceeding with plans for a proposed merger of the Councils on Thrombosis and Arteriosclerosis to be followed by a proposal from a merged council to the Working Group on Vascular Biology to incorporate their interests within a combined Council on Arteriosclerosis, Thrombosis, and Vascular Biology.

In August I wrote a letter to all present and past members of the Executive Committee (since 1988) to summarize the background of the proposed merger and the reason why it is necessary for the Executive Committee to decide without delay at its meeting in Anaheim this November on whether to proceed with the merger with the Council on Arteriosclerosis. A copy of this letter, which includes how to contact me by regular mail, fax, and e-mail, follows to inform all council members of how we got to where we are now.

There are many advantages to a proposed combined larger council, but there will be issues to resolve as a merger with the Council on Arteriosclerosis proceeds. If you have specific feelings about the proposal or issues it raises, I invite you to send them to me before the November meeting of the Executive Committee.

Since this is our "off year" at the AHA Scientific Sessions, I know that many of you will not be present at the meeting. For those of you who will be there, please make a special effort to attend the business meeting of the council, which will be held at noon on Monday, November 13.

. . .

TO: Present and Recent Past Members of the Executive Committee of the Council on Thrombosis

FROM: Samuel I. Rapaport, Chairperson, Council on Thrombosis

SUBJECT: Proposed Merger With Council on Thrombosis and Vascular Biology Working Group

I am writing for two purposes:

(1) To inform you of the status of considerations for a proposed merger of the Councils on Arteriosclerosis and Thrombosis to be followed by a proposal from the merged council to the Vascular Biology Working Group to incorporate their interests within a combined Council on Arteriosclerosis, Thrombosis, and Vascular Biology.

(2) To seek advice in defining issues in this regard that need advance thought before the forthcoming Council on Thrombosis Executive Committee meeting next November at the AHA Scientific Sessions in Anaheim.

Two years ago the Council Affairs Committee and the Steering Committee of the AHA commissioned a task force to examine the current structure of the Councils on Arteriosclerosis and Thrombosis, assess the relationship of vascular biology and the Vascular Biology Working Group of AHA to these councils, and develop options to integrate and enhance the functions and activities of all three groups. Drs Scott Grundy and Ken Mann were appointed by AHA to serve as cochairs of the task force. Membership included the chairpersons, vice chairpersons, and immediate past chairpersons of the two councils (Drs Deuel, Rapaport, and Nachman for the Council on Thrombosis; Drs Small, Grundy, and St. Clair

for the Council on Arteriosclerosis) and Dr Victor Dzau, chairperson of the Vascular Biology Working Group.

After long discussions at three meetings of pros and cons, the task force recommended that the two councils and the working group be integrated into a new scientific council structured to accommodate the overlapping interests of the participating groups. Dr Deuel and I, as your representatives on the task force, concurred fully with this recommendation (Dr Nachman was not present at the meeting). We believe that the bringing into a single AHA "scientific tent" of investigators interested in diverse aspects of the pathogenesis and treatment of thrombotic disorders would have many advantages. A new scientific council created out of the existing Councils on Arteriosclerosis and Thrombosis and the Working Group on Vascular Biology should have a greater say in the structure of the scientific program at the annual national meeting in November. It would support an expanded scope and influence of our journal *Arteriosclerosis, Thrombosis, and Vascular Biology.* Moreover, the new amalgamated council should have the critical mass needed to sponsor a yearly stand-alone meeting on vascular biology in the spring of the year. Indeed, at the instigation of the task force, a scientific meeting that could serve as a prototype for future spring symposia will be held in Salt Lake City on February 18-20, 1996 [see announcement on page 13]. I hope that many of you will participate in this meeting.

After the last meeting of the task force in April 1995, Drs Grundy and Deuel wrote a draft memorandum from the task force to the Councils on Arteriosclerosis and Thrombosis and the Working Group oin Vascular Biology proposing the creation of an enlarged and integrated council involving the three groups. This memorandum was reviewed at the May meeting of the Executive Committee of the Council on Thrombosis, which was held in San Diego in conjunction with the clinical meetings. At that meeting it was moved, seconded, and carried that the Council on Thrombosis pursue the feasibility of an amalgamation as described in the memorandum. Since a number of members of the Executive Committee were unable to attend this May meeting, I am enclosing with this letter a copy of the memorandum.

In June 1995 Dr Grundy, as cochair of the task force, reviewed the task force memorandum at a meeting of the Council Affairs Committee. A proposed merger of the Councils of Arteriosclerosis and Thrombosis evoked no substantive comment from other council chairs present at that meeting. Subsequently, Dr Rodman D. Starke, Senior Vice President, Office of Scientific Affairs, advised Dr Grundy, as chairperson of the Council on Arteriosclerosis, and me, as the incoming chairperson of the Council on Thrombosis, that the next step in moving forward a merger of the Councils on Arteriosclerosis and Thrombosis would be a vote in favor of such a merger from the Executive Committee of each council.

Dr Grundy informs me that the Executive Committee of the Council on Arteriosclerosis met earlier this month and enthusiastically endorsed the recommendation of the task force that the Councils on Arteriosclerosis and Thrombosis merge and jointly make a proposal for creation of a new scientific council that will incorporate vascular biology. The Executive Committee of Arteriosclerosis also recommended that this larger council have three subsections identified as (a) lipid and lipoprotein metabolism, (b) thrombosis, and (c) vascular biology and that the Executive Committee of the new council be composed primarily of representatives of these three subsections.

Working Groups of AHA have a five-year term, which for the Working Group on Vascular Biology expires in 1997. Therefore, the Vascular Biology Working Group must soon decide whether their continuing activities within AHA are best served within a combined Arteriosclerosis, Thrombosis, Vascular Biology Council. At the June meeting of the Council Affairs Committee, chairpersons of several other councils expressed interest in the future of the Vascular Biology Working Group. A real possibility exists that the working group will receive within the next several months competing specific proposals to affiliate with other AHA councils, eg, Circulation and High Blood Pressure Research.

Since the Executive Committee of the Council on Arteriosclerosis has approved a merger with the Council on Thrombosis and since such a merger must precede a timely preparation of a joint proposal to the Vascular Biology Working Group, I will call for a motion to merge the two councils at the next meeting of our Executive Committee in November at Anaheim. Because of the importance of this motion, I urge all present members of the Executive Committee to attend the meeting in November. Present plans are for our Executive Committee to meet jointly with the Executive Committee of the Arteriosclerosis Council at a luncheon meeting on Sunday, November 12, and separately later that afternoon.

I apologize for the length of this letter, but I wanted you to be fully informed of how we got to where we now are. Again, I invite your comments on issues related to the proposed amalgamation with the Council on Arteriosclerosis and the Vascular Biology Working Group. You can reach me as follows:

Samuel I. Rapaport, MD
UCSD Medical Center (8423)
200 West Arbor Drive
San Diego, CA 92103
Telephone No: (619) 543-3552
Fax No: (619) 543-3231
e mail: SRAPAPORT@ucsd.edu

Invited Review

Resistance to Activated Protein C by Factor V Leiden: Clinical Implications

Until recently, no abnormality of hemostasis could be found in over 80% of patients with familial thrombophilia. The conditions detectable were primarily deficiencies of protein C, protein S, and antithrombin. Among all patients with venous thrombosis these deficiencies are present in less than 5%.[1,2] This has changed dramatically with the reports on resistance to activated protein C (APC).

Protein C is a major natural inhibitor of coagulation. It is activated by the negative feedback system of activated thrombin and membrane-bound thrombomodulin. Activated protein C, when the coenzyme protein S is present, inhibits clotting by inactivating the procoagulant factors Va and VIIIa. Addition of APC to plasma in vitro therefore lengthens the clotting time. The first report on APC resistance showed that some individuals with thrombophilia do not exhibit the expected prolongation of the clotting time; ie, they are resistant to APC.[3] It has been shown that this resistance is the result of a mutation in the factor V gene (factor V Leiden), a single-base substitution of adenine for guanine, corresponding to the cleavage site of protein C.[4]

Two tests are available to diagnose this abnormality, a clotting test for APC resistance and a DNA test (polymerase chain reaction [PCR]) for the mutation. The clotting test consists of performing two APTTs, one before and one after adding APC to the test plasma. The ratio of the two, preferably normalized to the APTT of normal pool plasma, is the APC-sensitivity ratio, which is reduced in APC resistance. This clotting test cannot be used for patients who are taking warfarin. The DNA test is based on a PCR amplification, showing loss of an *MnlI* restriction site at position 1691 when the substitution of adenine for guanine is present.

APC resistance increases the risk of venous thrombosis about eightfold and thereby is a risk factor for thrombosis of similar strength as protein C and antithrombin deficiency.[5,6] The rare patient with homozygous factor V Leiden has a risk of thrombosis that is increased up to 100-fold.[7] The risk in absolute terms is highly dependent on age: in those under age 30, the risk for a first thrombotic event is about 1 per 10,000 per year for those without factor V Leiden and still only 6 per 10,000 per year for heterozygous carriers. For those aged 50 and older, the risk is 2 per 10,000 per year for those with the normal genotype and over 15 per 10,000 per year for carriers of the mutation. For homozygous carriers, the risk is one to several percentage points per year.

There are other modifying factors besides age. First, risk estimates given apply to those without malignancy, in which circumstance the risk may be higher. Second, oral contraceptives appear to increase the risk synergistically with factor V Leiden: for women aged 15 to 49 who carried the mutation and used oral contraceptives, the risk of venous thrombosis is approximately 30 per 10,000 per year, ie, at least a 30-fold increase.[8] These risk estimates are based on studies conducted in the Netherlands, where there is an estimated overall risk of first thrombosis of about 2 in 10,000 per year. Risk of thrombosis with and without factor V Leiden may vary between populations.

It is becoming more clear that the presence of several risk factors is needed to manifest thrombosis. This is illustrated by the reports in individuals with more than one genetic defect, eg, protein C deficiency and APC resistance, in whom the risk of thrombosis is greatly increased.[9] These data may help to explain previously reported differences in clinical penetrance of thrombophilic defects between and within families.[10,11]

Whereas it is clear that factor V Leiden is the most common determinant for deep-vein thrombosis, its role in arterial thrombosis remains unclear. Some reports suggest that it increases the risk of myocardial infarction as well as ischemic stroke, whereas other studies found no association.[12-14] Although it may seem logical that a risk factor for deep-vein thrombosis would also increase the risk of pulmonary embolism, no studies have specifically examined this.

It is still unclear whether factor V Leiden is the etiology for all cases of hereditary APC resistance.[15] If there are cases of APC resistance caused by other defects, however, these are very rare. Most discrepancies between the clotting test and the DNA test appear to result from laboratory problems with the clotting assay.[16,17] It therefore seems advisable to perform the DNA test as a first screen rather than the clotting test and certainly not to base a diagnosis solely on the clotting test.

The most remarkable feature of APC resistance by factor V Leiden is its high prevalence. It is found in about 50% of patients with familial thrombophilia, in 20% of all patients with a first deep-vein thrombosis, and in 3% to 5% of the general population.[4-6] This leads to much wider implications than the rare deficiencies of protein C, protein S, and antithrombin because so many more individuals are affected.

Most importantly, in testing for factor V Leiden, there is little reason to think in terms of "familial" thrombophilia. For deficiencies of protein C, protein S, and antithrombin, even if diagnostic tests are limited to those with a clear family history and no known explanation for the

thrombosis, the probability of a positive test is about 10%. For APC resistance this probability is already twice as high if we would just test all patients with thrombosis. Indiscriminate screening of the total population would still yield about a 5% incidence of carriers. Very few would advocate such a screening policy; still, the example forces us to reexamine the benefits of diagnostic testing.

Generally there are two possible benefits of a diagnostic test: first, the psychological benefit of knowing, and second, the medical benefit of subsequent preventive interventions. The former may differ from case to case; obviously, this is more important in families that have suffered from unexplained thrombosis for many generations. The benefit may be less obvious for a single patient with a first thrombosis, and the psychological benefit may then reside mainly with the physician.

Because of the synergistic effect of APC resistance and oral contraceptives, it is advisable to test for the mutation before prescribing oral contraceptives in women with a suspected family history of thrombosis and in all women who experience venous thrombosis while using oral contraceptives. The decision of whether or not to prescribe oral contraceptives in a carrier may be difficult since all other reversible methods of contraception have a considerably higher risk of unwanted pregnancies (and subsequent postpartum thrombosis).

The benefit of preventive interventions is mainly to prescribe short-term anticoagulation in high-risk situations (eg, surgery, plaster casts, immobilization, and postpartum periods). Aspirin is not a proven therapy for venous thrombosis prophylaxis. It seems reasonable to follow the same clinical policy as is done with deficiencies of protein C and protein S. It is presently unclear whether patients benefit from long-term therapy with warfarin. This treatment does carry a well-documented risk of bleeding of about 3% per year even in dedicated anticoagulation clinics,[18] which is especially relevant in considering long-term prophylaxis.

Most centers would therefore not prescribe long-term anticoagulation after parturition in an asymptomatic patient with a thrombophilic abnormality. Some would after a first thrombotic event, and most would after recurrent events. There is less agreement on whether or not to anticoagulate during pregnancy because of the need for prolonged treatment with heparin and the risk of bleeding, although the risk of thrombosis in pregnancy in thrombophilia is high.[19] The high frequency of postpartum thrombosis, which can be prevented by a few weeks of anticoagulation, justifies short-term anticoagulation parturition.

Part of the expected benefits paradoxically depend on the local anticoagulation policy in patients without thrombophilia: if this is extensive, as in the Netherlands, where short-term anticoagulation is prescribed for all individuals in most high-risk situations (except pregnancy and puerperium), there may be little preventive gain in diagnosing thrombophilia. If anticoagulation is less widespread, individuals may gain more from a diagnosis of thrombophilia and subsequent prophylaxis when indicated.

References

1. Heijboer H, Brandjes DPM, Büller HR, Sturk A, ten Cate JW. Deficiencies of coagulation-inhibiting and fibrinolytic proteins in outpatients with deep-vein thrombosis. *N Engl J Med.* 1990; 323:1512-1516.

2. Koster T, Rosendaal FR, Briët E, Van der Meer FJM, Colly LP, Trienekens PH, Poort SR, Vandenbroucke JP. Protein C deficiency in a controlled series of unselected outpatients: An infrequent but clear risk factor for venous thrombosis (Leiden Thrombophilia Study). *Blood.* 1995;85:2756-2761.

3. Dahlbäck B, Carlsson M, Svensson PJ. Familial thrombophilia due to a previously unrecognized mechanism characterized by poor anticoagulant response to activated protein C: Prediction of a cofactor to activated protein C. *Proc Natl Acad Sci USA.* 1993; 90:1004-1008.

4. Bertina RM, Koeleman RPC, Koster T, Rosendaal FR, Dirven RJ, Ronde H de, Van der Velden PA, Reitsma PH. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature.* 1994;369:64-67.

5. Koster T, Rosendaal FR, Ronde H de, Briët E, Vandenbroucke JP, Bertina RM. Venous thrombosis due to poor anticoagulant response to activated protein C: Leiden Thrombophilia Study. *Lancet.* 1993;342:1503-1506.

6. Svensson PJ, Dahlbäck B. Resistance to activated protein C as a basis for venous thrombosis. *N Engl J Med.* 1994;330:517-522.

7. Rosendaal FR, Koster T, Vandenbroucke JP, Reitsma PH. High risk of thrombosis in patients homozygous for factor V Leiden (activated protein C resistance). *Blood.* 1995;85:1504-1508.

8. Vandenbroucke JP, Koster T, Briët E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. *Lancet.* 1994;344:1453-1457.

9. Koeleman BPC, Reitsma PH, Allaart CF, Bertina RM. APC-resistance as an additional risk factor for thrombosis in protein C deficient families. *Blood.* 1994;84:1031-1035.

10. Miletich J, Sherman L, Broze G. Absence of thrombosis in subjects with heterozygous protein C deficiency. *N Engl J Med.* 1987;317:991-996.

11. Bovill EG, Bauer KA, Dickermann JD, Callas P, West B. The clinical spectrum of heterozygous protein C deficiency in a large New England kindred. *Blood.* 1989;73:712-717.

12. Halbmayer W-M, Hanshofer A, Schön R, Fischer M. The prevalence of poor anti-coagulant response to activated protein C (APC resistance) among patients suffering from stroke or venous thrombosis and among healthy subjects. *Blood Coag Fibrinol.* 1994;5:51-57.

13. März W, Seydewitz H, Winkelmann B, Chen M, Nauck M, Witt I. Mutation in coagulation factor V associated with resistance to activated protein C in patients with coronary artery disease. *Lancet.* 1995;345:526-527.

14. Ridker PM, Hennekens CH, Lindpainter K, Stampfer MJ, Eisenberg PR, Miletich JP. Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. *N Engl J Med.* 1995;332:912-917.

15. Zöller B, Svensson PJ, Xuhua H, Dahlbäck B. Identification of the same factor V gene mutation in 47 out of 50 thrombosis-prone families with inherited resistance to activated protein C. *J Clin Invest.* 1994;94:2521-2524.

16. Legnani C, Palareti G, Biagi R, Coccheri S. Activated protein C resistance in deep-vein thrombosis. *Lancet.* 1994;343:452-542.

17. Rosendaal FR, Bertina RM, Reitsma PH. Evaluation of activated protein C resistance in stored plasma. *Lancet.* 1994;343:1289-1290.

18. van der Meer FJM, Rosendaal FR, Vandenbroucke JP, Briët E. Bleeding complications in oral anticoagulant therapy. *Arch Intern Med.* 1993;153:1557-1562.

19. Conard J, Horellou MH, van Dreden P, Lecompte T, Samama M. Thrombosis and pregnancy in congenital deficiencies in AT III, protein C or protein S: Study of 78 women. *Thromb Haemost.* 1990;63:319-320.

Dr Frits Rosendaal
Departments of Clinical Epidemiology and Hematology
Leiden, The Netherlands

Committee and Liaison Reports

Report From the NHLBI

All divisions of the NHLBI—Blood (DBDR), Heart (DHVD), Lung (DLD), Epidemiology (DECA), and Extramural (DEA)—have moved to a new location in Bethesda, Maryland. The Office of the Director, NHLBI, continues to be located in the main NIH campus. The Thrombosis and Hemostasis Scientific Research Group has a new telephone number, 301-435-0070; fax number, 301-480-1046; and mail stop code (MSC), 7950.

With the reorganization of the NHLBI, the Division Advisory Committee has been replaced by the Special Emphasis Panel (SEP), which is convened as needed. The Blood Division SEP met on April 27 and 28, 1995. The panel reviewed the old initiatives on hold as well as new, timely ideas for possible implementation. The following is a partial list of ideas that were enthusiastically recommended for further development. It was recognized that the budgetary environment may permit implementation of only the top priority initiatives by the NHLBI.

- Genetic and other risk factors of thrombosis
- Homing determinants in embryonic and hematopoietic stem cells
- Identification and characterization of human histocompatibility antigens
- Immunogenetics of inhibitor formation in hemophilia
- Effects of sickle cell disease on the lung
- Thrombopoietin, megakaryocytopoiesis, and platelet production
- New approaches to improve the function and viability of platelets

The following are highlights of some of the funding guidelines being followed at NHLBI at this time. Since these guidelines may change, investigators considering submitting a research grant application are urged to call the appropriate program office for the latest information.

Beginning fiscal year 1995, NHLBI has adopted a more flexible funding plan in that a small amount of money is allocated to the divisions to fund applications with innovative ideas of high risk or potential clinical impact. Applications from young or minority investigators will also receive consideration for support.

Competitive renewal applications are funded at no more than 10% higher than the amount of direct costs awarded for the last year of the preceding project period. Investigators contemplating a significant expansion of their research program may consider submitting a new application. Competitive renewal of FIRST Awards to a regular R01 grant is exempt from this budgetary restriction. Future year commitments is usually escalated at 4% per year.

To achieve an overall average project period of 4 years, NHLBI may reduce the duration of grants over a certain percentile by 1 year.

Program project grants are funded with a set-aside fund and do not compete with other regular grants. However, these grants must meet the budgetary ceiling for that year. Any investigator contemplating submitting an application for a program project grant should consult with the appropriate program person as soon as possible.

A variety of information about NHLBI programs is now available through the gopher on Internet at gopher.nhlbi.nih.gov.port:70. Although the gopher has been in place only for short time, we are pleased to find that it is being increasingly used by our community. Please contact me at 301-435-0070 if you have any questions.

Pan Ganguly, PhD

Report From the Research Committee

The good news is that there has been an increase in the number of funded national Grant-in-Aid applications on a percentage basis for the AHA. This year, 185 out of 938 applications were approved for funding at 19.7%. This percentage of funding was also achieved in the thrombosis study section; however, the numbers of grants received by the thrombosis community this year was low. Only 40 grants were received compared with a normal year in which approximately 70 to 80 grants are received. I would encourage colleagues who are eligible for a Grant-in-Aid to compete for these awards.

At the last research committee meeting, March 31, 1995, a number of alterations to existing national programs and a new program called the "AHA Scientist Development Grant" were approved. These changes were approved by the Research Program and Evaulation Committee and the Steering Committee.

A summary of these three proposed grant areas is provided in the table beginning on page 8. The new AHA Scientist Development Grant is intended to support highly promising, beginning scientists in progress toward independence by encouraging and adequately funding research projects that can serve to bridge the gap between completion of research training and readiness for successful competition as an independent investigator. The Scientist Development Grant will be supported at the level of $65,000 per year with up to 4 years of funding. The Established Investigator Grant continues but has been increased in budget to $75,000 per year and modified to include both salary and project support. The Grant-in-Aid award is also proposed to be altered to remove any restrictions from candidacy (such as those implemented in the past 2 years to limit access to beginning investigators). The award value has been increased to $55,000. Note that renewals will not be permitted; only newly initiated research projects will be considered for a Grant-in-Aid.

It is anticipated that these changes will take place in awards initiated in 1997 based on applications submitted in 1996.

Kenneth G. Mann, PhD

PROPOSED NATIONAL AHA RESEARCH PROGRAM PORTFOLIO

Summary of Award Characteristics
Approved by Research Committee March 31, 1995

Characteristics	***AHA Scientist Development Grant***	***EI Grant***	***Grant-in-Aid***
Program Objective	To fund projects that will bridge the gap between research training & readiness for competition as independent investigator	To support career development of newly independent investigators by funding projects for which support has not been obtained	To fund distinct, highly meritorious, innovative projects from independent investigators
Science Focus	Research broadly related to CV function and disease, stroke, or to related clinical, basic science, and public health problems		
Disciplines	All basic disciplines as well as epidemiological and clinical investigations that bear on cardiovascular and stroke problems		
Faculty Rank Maximum	Assistant Professor (or equivalent)	Associate Professor (or equivalent)	Professor (or equivalent)
Degree Requirement	MD, PhD, DO, or equivalent		
Experience Restrictions	No more than 4 years elapsed since first faculty appointment	At least 4 years but no more than 9 years elapsed since first faculty appointment	None
Citizenship	US citizen, permanent resident	US citizen, permanent resident	US citizen, exchange visitor, permanent resident
Other Restrictions	Non-renewable. Awardees may apply for EI Grant in final year.	Non-renewable. Prior EIs ineligible. Awardees may apply for GIA in final year.	Awardees may reapply in final year for a different project.
Unique Peer Review Criteria	Evidence that award will promote independence	Prior national-level award(s), evidence of independence from mentor	Evidence of scientific independence; innovative, distinct nature of proposal
Common Peer Review Criteria	Scientific merit of research proposal; qualifications, relevant experience and productivity of applicant; relationship to supervisor; adequacy of available resources, facilities		
PI Salary, Fringes Paid?	Yes, consistent with % total effort, $ cap	Yes, consistent with % total effort, $ cap	No
Common Budget Items	Salaries of technical personnel essential to the project, supplies, equipment, travel, volunteer subject costs, publication costs, and 10% institutional indirect costs		

Characteristics	*AHA Scientist Development Grant*	*EI Grant*	*Grant-in-Aid*
Annual Award Payment Components	Up to $30,000 for PI salary/fringes. At least $35,000 for project.	Up to $35,000 for PI salary/fringes. At least $40,000 for project.	Up to $50,000 for project.
Total Annual Award Amount	$65,000 including 10% indirect costs	$75,000 including 10% indirect costs	$55,000 including 10% indirect costs
Award Duration Maximum	4 years	4 years	3 years
Total Award Commitment	$260,000	$300,000	$165,000
Interim Reporting	Assessment of annual progress reports to include research findings, abstracts, publications and names of trainees supported (optional for Scientist Development Grants)		
Evaluation	Publications, citations by others, ability to attract ongoing research funding, faculty advancement, other evidence of career progression, etc.		

* Final decisions concerning award characteristics will be made by the Research Committee at its November meeting.

Progress Report on *Arteriosclerosis, Thrombosis, and Vascular Biology*

It is approximately 4.5 years since a separate editorial office for Thrombosis was established. During this time, the journal has grown, expanding from a bimonthly to a monthly publication. Its scope has expanded as well, as reflected in the addition of the phrase "vascular biology" to the title.

The impact of the journal continues to have a high ranking according to the Institute for Scientific Information (ISI) measurements, and the journal compares favorably with the top publications in the field of cardiovascular biology and medicine. Among those journals categorized by the ISI under the rubric "cardiovascular system," *Arteriosclerosis, Thrombosis, and Vascular Biology* was ranked fourth with an impact factor of 5.3 in the latest Scientific Citation Index. What is of great significance to the Council on Thrombosis is that our journal outranks those of its competitors that are specifically directed to the field of thrombosis. For example, in the 1993 rankings (the latest available), *Thrombosis and Haemostasis* ranked sixth and *Thrombosis Research* ranked 36th. The thrombosis portion of the journal continues to develop and is attracting quality submissions. The number of thrombosis-related submissions to the Vanderbilt editorial office alone grew 25% in 1994, which followed 22% and 38% increases in 1993 and 1992, respectively. Plans for the journal currently being implemented include future publication of minireviews on focused topics of current research.

We have been trying to improve the function of our editorial offices. Statistics for the Thrombosis editorial office show that 43.6% of 1994 manuscripts were accepted, 43.6% were rejected, and 12.7% remain under revision. The interval from submission of all manuscripts to first decision was 6.9 weeks, while for accepted papers, the interval from submission to final decision was 21.0 weeks. The average priority rating for manuscripts ultimately accepted for publication was 2.7.

Examples of recently published thrombosis articles in *Arteriosclerosis, Thrombosis, and Vascular Biology* are listed below:

Platelet Biology

- AM Vicari, ML Monzani, F Pellegatta, P Ronchi, L Galli, F Folli. Platelet calcium homeostasis is abnormal in patients with severe arteriosclerosis (vol 14, no 9)
- PS Tsao, G Theilmeier, AH Singer, LLK Leung, JP Cooke. L-Arginine attenuates platelet reactivity in hypercholesterolemic rabbits (vol 14, no 10)
- C Legrand, V Morandi, S Mendelovitz, H Shaked, JR Hartman, A Panet. Selective inhibition of platelet macroaggregate formation by a recombinant heparin-binding domain of human thrombospondin (vol 14, no 11)
- J-C Ruf, J-L Berger, S Renaud. Platelet rebound effect of alcohol withdrawal and wine drinking in rats: Relation to tannins and lipid peroxidation (vol 15, no 1)
- A Notarbartolo, G Davì, M Averna, CM Barbagallo, A Ganci, C Gianmarresi, FP La Placa, C Patrono. Inhibition of thromboxane biosynthesis and platelet function by simvastatin in type IIa hypercholesterolemia (vol 15, no 2)
- E Malle, A Ibovnik, HJ Leis, GM Kostner, PFJ Verhallen, W Sattler. Lysine modification of LDL or lipoprotein(a) by 4-hydroxynonenal or malondialdehyde decreases platelet serotonin secretion without affecting platelet aggregability and eicosanoid formation (vol 15, no 3)
- H Ariyoshi, A Oda, EW Salzman. Participation of calpain in protein-tyrosine phosphorylation and dephosphorylation in human blood platelets (vol 15, no 4)

Vascular Biology

- AM Schmidt, O Hori, J Brett, S Du Yan, J-L Wautier, D Stern. Cellular receptors for advanced glycation end products: implications for induction of oxidant stress and cellular dysfunction in the pathogenesis of vascular lesions (vol 14, no 10)
- H-J Kruse, B Grünberg, W Siess, PC Weber. Formation of biologically active autacoids is regulated by calcium influx in endothelial cells (vol 14, no 11)
- SL Diamond, F Sachs, WJ Sigurdson. Mechanically induced calcium mobilization in cultured endothelial cells is dependent on actin and phospholipase (vol 14, no 12)
- KB Lemström, PT Aho, CA Bruggeman, PJ Häyry. Cytomegalovirus infection enhances mRNA expression in platelet-derived growth factor-BB and transforming growth factor-J_1 in rat aortic allografts: possible mechanism for cytomegalovirus-enhanced graft arteriosclerosis (vol 14, no 12)
- PL Walpola, AI Gotlieb, MI Cybulsky, BL Langille. Expression of ICAM-1 and VCAM-1 and monocyte adherence in arteries exposed to altered shear stress (vol 15, no 1)
- F Mohamed, JC Monge, A Gordon, P Cernacek, D Blais, DJ Stewart. Lack of role for nitric oxide (NO) in the selective destabilization of endothelial NO synthase mRNA by tumor necrosis factor-I (vol 15, no 1)
- TW Wakefield, RM Strieter, CA Wilke, AM Kadell, SK Wrobleski, MD Burdick, R Schmidt, SL Kunkel, LJ Greenfield. Venous thrombosis-associated inflammation and attenuation with neutralizing antibodies to cytokines and adhesion molecules (vol 15, no 2)

- T Inaba, M Kawamura, T Gotoda, K Harada, M Shimada, J-I Ohsuga, H Shimano, Y Akanuma, Y Yazaki, N Yamada. Effects of platelet-derived growth factor on the synthesis of lipoprotein lipase in human monocyte-derived macrophages (vol 15, no 4)

Pathways of Blood Coagulation

- E Tremoli, S Eligini, S Colli, P Maderna P Risè, F Pazzucconi, F Marangoni, CR Sirtori, C Galli. n-3 fatty acid ethyl ester administration to healthy subjects and to hypertriglyceridemic patients reduces tissue factor activity in adherent monocytes (vol 14, no 10)
- RM Epand, A Stafford, B Leon, PE Lock, EM Tytler, JP Segrest, GM Anantharamaiah. HDL and apolipoprotein A-1 protect erythrocytes against the generation of procoagulant activity (vol 14, no 11)
- N Narahara, T Enden, M Wiiger, H Prydz. Polar expression of tissue factor in human umbilical vein endothelial cells (vol 14, no 11)
- N Saha, Y Liu, CK Heng, S Hong, PS Low, FSH Tay. Association of Factor VII genotype with plasma Factor VII activity and antigen levels in healthy Indian adults and interaction with triglycerides (vol 14, no 12)
- U Orvim, HE Roald, RW Stephens, N Roos, KJ Sakariassen. Tissue factor-induced coagulation triggers platelet thrombus formation as efficiently as fibrillar collagen at arterial blood flow conditions (vol 14, no 12)
- RM Barstad, MJAG Hamers, P Kierulf, Å-B Westvik, KJ Sakariassen. Procoagulant human monocytes mediate tissue factor/Factor VIIa-dependent platelet-thrombus formation when exposed to flowing nonanticoagulated human blood (vol 15, no 1)
- BJ Warn-Cramer, SI Rapaport. Evidence suggestive of activation of the intrinsic pathway of blood coagulation after injection of Factor Xa/phospholipid into rabbits (vol 15, no 1)
- Sakata T, Kario K, Matsuo T, Katayama Y, Matsuyama T, Kato K, Miyata T. Suppression of plasma-activated Factor VII levels by warfarin therapy (vol 15, no 2)
- T Kokawa, T Abumiya, T Kimura, M Harada-Shiba, H Koh, M Tsushima, A Yamamoto, H Kato. Tissue factor pathway inhibitor activity in human plasma: measurement of lipoprotein-associated and free forms in hyperlipidemia (vol 15, no 4)

Plasminogen Activator and Plasminogen Activator Inhibitor

- HAR Stringer, P van Swieten, HFG Heijnen, JJ Sixma, H Pannekoek. Plasminogen activator inhibitor-1 released from activated platelets plays a key role in thrombolysis resistance: Studies with thrombi generated in the Chandler loop (vol 14, no 9)
- T Padró, PHA Quax, CM van den Hoogen, P Roholl, JH Verheijen, JJ Emeis. Tissue-type plasminogen activator and its inhibitor in rat aorta: effect of endotoxin (vol 14, no 9)
- M Margaglione, G Di Minno, E Grandone, G Vecchione, E Celentano, G Cappucci, M Grilli, P Simone, S Panico, M Mancini. Abnormally high circulation levels of tissue plasminogen activator and plasminogen activator inhibitor-1 in patients with a history of ischemic stroke (vol 14, no 11)
- LM Szymanski, RR Pate. Fibrinolytic responses to moderate intensity exercise: comparison of physically active and inactive men (vol 14, no 11)
- H Noda-Heiny, A Daugherty, BE Sobel. Augmented urokinase receptor expression in atheroma (vol 15, no 1)
- X-N Li, VK Varma, JM Parks, RL Benza, JC Koons, JR Grammer, H Grenett, EM Tabengwa, FM Booyse. Thrombin decreases the urokinase receptor and surface-localized fibrinolysis in cultured endothelial cells (vol 15, no 3)

Experimental Models of Thrombosis

- A Gast, TB Tschopp, HR Baumgartner. Thrombin plays a key role in late platelet thrombus growth and/or stability: effect of a specific thrombin inhibitor on thrombogenesis induced by aortic subendothelium exposed to flowing rabbit blood (vol 14, no 9)
- RM Barstad, HE Roald, Y Cui, VT Turitto, KJ Sakariassen. A perfusion chamber developed to investigate thrombus formation and shear profiles in flowing native human blood at the apex of well-defined stenoses (vol 14, no 12)

Prothrombotic Risk Factors

- RS Rosenson, CC Tangney, JM Hafner. Intraindividual variability of fibrinogen levels and cardiovascular risk profile (vol 14, no 12)
- J Emmerich, D Vidaud, M Alhenc-Gelas, G Chadeuf, M Gouault-Heilmann, M-F Aillaud, M Aiach. Three novel mutations of antithrombin inducing high-molecular-mass compounds (vol 14, no 12)
- SE Humphries, S Ye, P Talmud, L Bara, L Wilhelmsen, L Tiret (European Atherosclerosis Research Study group). European Atherosclerosis Research Study: Genotype at the fibrinogen locus (G_{-455}-A J-gene) is associated with differences in plasma fibrinogen levels in young men and women from different regions in Europe: Evidence for gender-genotype-environment interaction (vol 15, no 1)
- CA Spek, T Koster, FR Rosendaal, RM Bertina, PH Reitsma. Genotypic variation in the promoter region of the protein C gene is associated with plasma protein C levels and thrombotic risk (vol 15, no 2)

New Antithrombotic Agents

- J Strony, A Song, L Rusterholtz, B Adelman. Aurintricarboxylic acid prevents acute rethrombosis in a canine model of arterial thrombosis (vol 15, no 3)

Jack J. Hawiger, MD, PhD

Agenda for Thrombosis Council Program at ASH Meeting

The program for the session to be jointly sponsored by the Thrombosis Council of the American Heart Association and the American Hematology Society at this year's meeting in Seattle is shown below. The speakers will give a 30-minute lecture that will be followed by a question-and-answer session on Saturday, December 2, beginning at 4:15. It will be cochaired by Sam Rapaport and Steve Prescott.

Staying in Control: Plasma Proteins That Regulate Thrombosis and Inflammation

Platelet-Activating Factor Acetylhydrolase: An Anti-Inflammatory Phospholipase
Stephen M. Prescott, MD
University of Utah

Plasma Proteins That Prevent Thrombosis: Unexpected Interactions
Joseph P. Miletich, MD, PhD
Washington University

Thermolabile Serpin Protease Inhibitor Mutants: Thrombotic and Inflammatory Consequences
Mark Wardell, PhD
University of Cambridge MRC Centre

Report From the Program Committee

Dr Prescott reported that the Program Committee will meet in Fall 1995 to begin planning the National Thrombosis Conference to be held in conjunction with the 1996 Scientific Sessions of the AHA. He encouraged the committee members to submit suggestions for program topics and speakers.

He also reported that the number of evening sessions will be decreased and the selection of speakers will be coordinated to eliminate overlap. It was moved, seconded, and carried to continue to sponsor Sunday afternoon programs on topics attractive to broader communities.

Stephen M. Prescott, MD

Budget Report

Dr Rapaport reported that the Council will have $19,060 in new discretionary funds for fiscal year 1995-1996 plus any unexpended funds from fiscal year 1994-1995. It was moved, seconded, and carried to approve the discretionary budget for fiscal year 1995-1996:

Membership recruitment	$2,000.00
Newsletter	4,000.00
Intercouncil working groups	1,500.00
Young Investigator Prizes	N/A
Thrombosis travel stipends	N/A
Arteriosclerosis/Thrombosis/ Vascular Biology Conference	5,000.00
Gordon Conf. on Hemostasis	4,000.00
Integration Initiative	1,000.00
Total	$17,500.00

It was moved, seconded, and carried to defer increasing the monetary award for the Thrombosis Young Investigator Prize until a final decision and details of amalgamation with the Council on Arteriosclerosis and the Working Group on Vascular Biology are made.

Samuel I. Rapaport, MD

Announcements

Joint Conference on Arteriosclerosis/ Thrombosis/Vascular Biology

February 18–20, 1996. Salt Lake City, Utah. Sponsored by the Councils on Arteriosclerosis and Thrombosis and the Intercouncil Working Group on Vascular Biology.

This conference will bring together scientists from atherosclerosis, thrombosis, and vascular biology to discuss the interrelationships of their areas of research and to provide information on the latest advances in these areas. Emphasis will be given to modern technologies involving molecular genetics.

Abstracts for this conference are due Friday, November 17, 1995. For more information, call 214-706-1100, fax 214-373-3406, or write to the American Heart Association, Scientific and Corporate Meetings, 7272 Greenville Avenue, Dallas, TX 75231-4596.

TRIGGER: An Electronic Newsletter for Researchers Working on the Biology of Tissue Factor and Factor VII

An electronic newsletter has been started to facilitate communication among researchers working on the biology of the triggering complex of the blood clotting system (tissue factor and factor VII). TRIGGER will carry titles and brief descriptions (or abstracts) of papers recently accepted for publication, meeting announcements and reports, positions available, technical questions, etc. The newsletter will be sent via e-mail.

For more information (including how to subscribe), send a message with your preferred e-mail address to trigger@omrf.uokhsc.edu. Information can also be obtained via the World Wide Web at http://omrf.uokhsc.edu/~trigger/or by contacting either James H. Morrissey (morrisseyj@omrf.uokhsc.edu) or Pierre F. Neuenschwander (pierren@omrf.uokhsc.edu) at the Oklahoma Medical Research Foundation, 825 NE 13th Street, Oklahoma City, OK 73104. Tel 405-271-7892. Fax 405-271-3137.

Application for Membership

Council on Thrombosis

Council dues are $25/year

The purpose of the council is to achieve the objectives of the AHA in the field of thrombosis, specifically as they relate to research, professional education, and the application of these matters to clinical science. A chief objective is to view thrombosis in all its ramifications, rather than solely through its effect on the heart, brain, and kidney.

The council conducts postgraduate seminars and scientific sessions, either separately or in cooperation with other scientific councils. It also assists in development of educational materials, evaluates medical knowledge with respect to its application in controlling thrombosis, and collaborates with other councils in areas of mutual concern and interest.

Council members represent a large number of disciplines, enabling a forum for eventual solutions to the problems of thrombosis at all levels—basic research, clinical investigation, community health problems, and public understanding.

This offer expires December 31, 1995

Please mail completed form along with payment to:

American Heart Association
Scientific Publishing
PO Box 843543
Dallas, TX 75284-3543

OR

fax credit card orders to
214-691-6342

Questions?
Call 214-706-1310 or 214-706-1201

Please share this with interested colleagues

5NEWS1/2

_____YES! I want to join the Council on Thrombosis.

Name_____

Address_____

_____

City/State/Postal Code_____

Country_____

Telephone_____ Fax_____

E-Mail Address_____

Month and Year of Birth _____/_____ Gender: ☐ M ☐ F

Race/Ethnicity:
☐ American Indian
☐ Asian
☐ Black
☐ Hispanic
☐ White

% of time spent (=100%):
___ Administrative
___ Patient Care
___ Research
___ Teaching
___ Other (specify)_____

Are you interested in Vascular Biology? ☐ Yes ☐ No

Specialty_____

_____YES! As an AHA Council Member, I want to subscribe at these special prices.

	United States Member	United States Non-Member	Outside US Member	Outside US Non-Member
☐ *Arteriosclerosis, Thrombosis, and Vascular Biology*	$109	$146	$145	$182
☐ *Cardiovascular Nursing*	6	6	15	15
☐ *Circulation*	101	135	203	237
☐ *Circulation Research*	128	171	194	237
☐ *Currents in Emergency Cardiac Care*	12	12	16	16
☐ *Hypertension*	101	135	141	175
☐ *Stroke*	101	135	155	189

Please start my subscription with the _____issue

ADVANCE PAYMENT REQUIRED

☐ Check or money order enclosed (payable to the American Heart Association drawn on US bank in US dollars)

☐ MasterCard ☐ Visa ☐ American Express

Card Number _____

Expiration date _____

Signature as it appears on card:

_____

Total payment $_____

AHA Services

To provide you with the best customer service, listed below are the services and contact numbers you are most likely to need.

To ensure timely delivery of your newsletter, journals, and other important information, please send us your address changes and phone and fax numbers using the coupon below.

AHA National Center
7272 Greenville Avenue
Dallas, TX 75231-4596
Tel 214-373-6300 Fax 214-691-6342
gopher.amhrt.org

Service	Department	Telephone	Fax	E-Mail
Address Changes	Customer Service	214-706-1310 or 1201	214-691-6342	pubcust@amhrt.org
Awards				
Council New Investigator Award	Meetings	214-706-1685	214-373-3406	
Research Award	Research Administration	214-706-1453	214-706-1341	
Student Scholarship (Council)	Scientific Councils	214-706-1476 or 1261	214-373-0268	
Conferences				
Annual Scientific Sessions	Meetings	214-706-1253	214-373-3406	
Scientific Conferences	Meetings	214-706-1511 or 1414	214-373-3406	daphner@amhrt.org
Council Membership				
Applications—Catalog	Customer Service	214-706-1201	214-691-6342	pubcust@amhrt.org
Billing Information	Customer Service	214-706-1310 or 1201	214-691-6342	pubcust@amhrt.org
Donations/Memorials	Finance	214-706-1417	214-368-1228	
Journals				
Advertising	Scientific Publishing	214-706-1426	214-691-6342	
Billing Information	Customer Service	214-706-1310	214-691-6342	pubcust@amhrt.org
Permissions	Scientific Publishing	214-706-1309 or 1313	214-691-6342	pubauth@amhrt.org
Reprints	Scientific Publishing	214-706-1466	214-691-6342	pubauth@amhrt.org
Subscriptions—Catalog	Customer Service	214-706-1310	214-691-6342	pubcust@amhrt.org
Publications				
Public/Patient Education	Local AHA Offices	800-242-8721		
Scientific Statements	Inquiries	214-706-1220	214-706-1341	

MOVING?

Please print your new address below:

Name

Address

City State/Province/Country Zip/Post Code

Phone Fax

E-mail

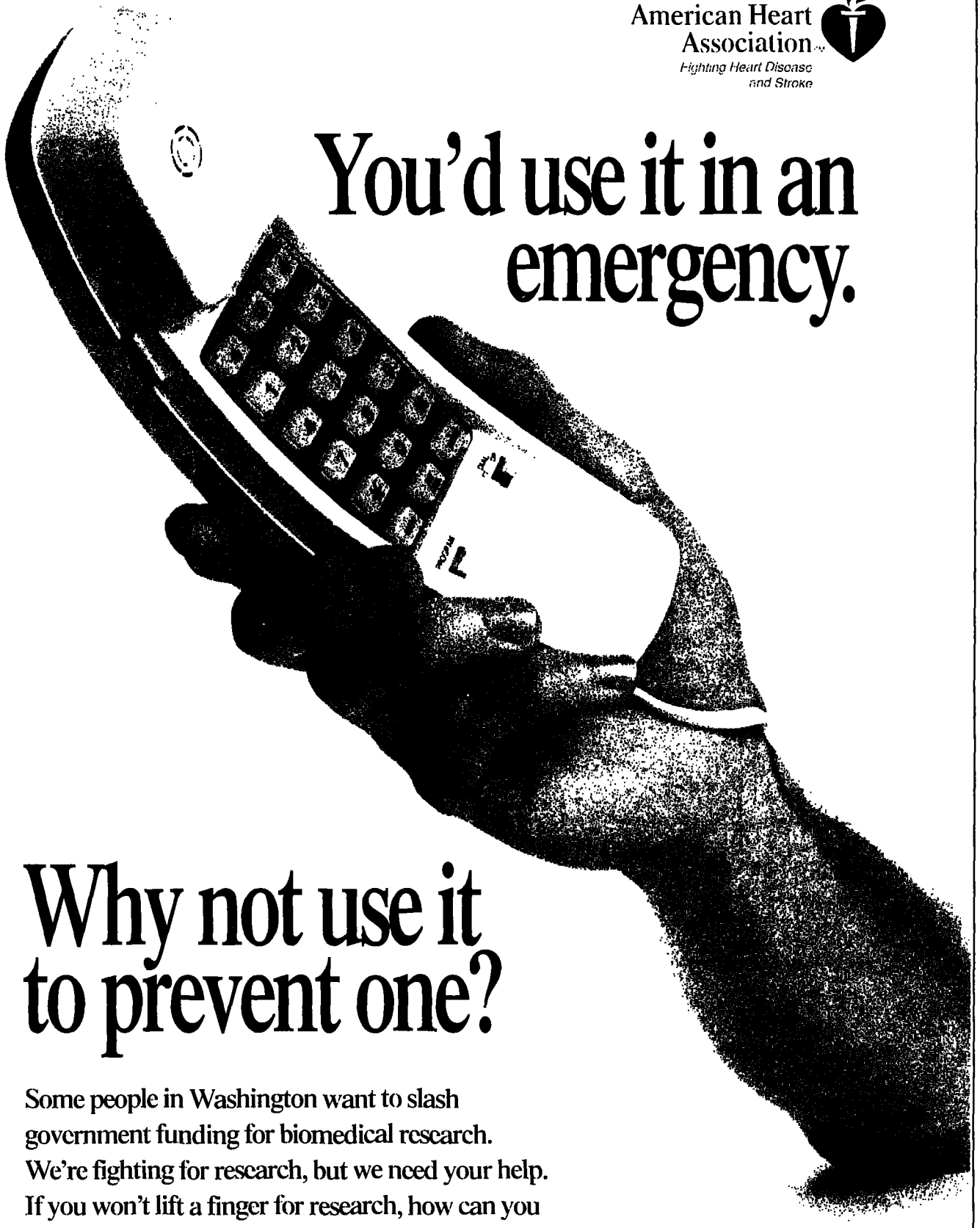
Moving date

IMPORTANT!
ATTACH ADDRESS LABEL HERE

Clip this form including your mailing label and send to:
AMERICAN HEART ASSOCIATION
Scientific Publishing
7272 Greenville Ave
Dallas, TX 75231-4596
Fax 214-691-6342
Tel 214-706-1310

American Heart Association
Fighting Heart Disease and Stroke

You'd use it in an emergency.



Why not use it to prevent one?

Some people in Washington want to slash government funding for biomedical research. We're fighting for research, but we need your help. If you won't lift a finger for research, how can you expect anyone else to?

White House Comment Line: (202) 456-1111 – Capitol Switchboard: (202) 224-3121 – President Clinton's e-mail: president@whitehouse.gov

Research Funding. Talk it up.