

1346R

718421

NOV 15 1988

ER-122:Wallace

REPORT OF FOREIGN TRAVEL BY FRED SNYDER, ORAU

Robert W. Wood, Director of Physical and Technological Research, ER-74,
Headquarters, Germantown, Maryland

Attached is a copy of a trip report prepared by Fred Snyder covering his travel to Milan, Italy, during the period August 28 through September 2, 1988. At the request of the organizing committee of the XXII Congress of the International Society of Hematology, the traveler presented a primary lecture entitled, "PAF and PAF Antagonists" at one of their main symposia.

The report has been reviewed and does not contain any classified information.

ORIGINAL SIGNED BY
M. C. WALLACE

for

Larry L. Radcliffe, Acting Director
Research and Waste Management Division

Attachment

cc w/atchmt:

- R. O. Hunter, ER-1, HQ, FORS
- D. B. Waller, IE-1, HQ, FORS
- J. G. Covne, MA-28, OSTI
- J. A. Lenhard, ER-10, ORO
- D. J. Cook, DP-82, ORO

ER-122:Wallace:CB:6-0714:10-10-88
Processed by ac: 10/21/88

REPOSITORY Oak Ridge Operations
 COLLECTION Records Holding Area
 BOX No. A-58-7 7 of 8 9164 Bldg. 2714-H
 FOLDER 1515-ORAU

CONCURR
ER-122
WALLACE
INITIALS
<i>MC</i>
DATE
<i>10/21</i>
ER-122
ATCHLE
INITIALS
<i>✓</i>
DATE
<i>10/21</i>
ER-122
BROWN
INITIALS
<i>B</i>
DATE
<i>10/21</i>
ER-122
WALLACE
INITIALS
<i>MC</i>
DATE
<i>11/15</i>
RTG. SYN
.....
INITIALS
.....
DATE
.....
RTG. SYN
.....
INITIALS
.....
DATE
.....
RTG. SYN
.....
INITIALS
.....
DATE
.....
RTG. SYN
.....
INITIALS
.....
DATE

1128196
DOE F 1325.10
(8-87)

T-2219

COVER SHEET
FOR TRIP REPORTS SUBMITTED TO THE
OFFICE OF ENERGY RESEARCH

Destination(s) and Dates for
Which Trip Report Being Submitted: Milan, Italy August 28-September 2, 1988

Name of Traveler: Fred Snyder

Joint Trip Report Yes

No

If so, Name of Other Traveler(s): _____

FOREIGN TRIP REPORT

**XXII Congress of the International Society of Hematology
Milan, Italy**

August 28 - September 2, 1988

by

**Fred Snyder
Vice Chairman**

**Medical and Health Sciences Division
Oak Ridge Associated Universities
Oak Ridge, TN 37831**

1128198

TABLE OF CONTENTS

<u>Subject</u>	<u>Page</u>
Summary	2
Comprehensive Trip Report	3
Appendix	7
I) Full itinerary	7
I) List of persons contacted	7
II) Conference attendees according to country	8
III) Abstracts of plenary lectures in PAF Symposium.	12-16
a) Cellular Regulation of Enzymes in the Metabolism of Platelet-Activating Factor (PAF)	
b) Immune Response and Vascular Injury: Platelet-Activating Factor Primes Blood Cell/Endothelium Interactions	
c) Effect of Platelet-Activating Factor on Platelets	
d) Short and Long Time Anti-Anaphylactic Properties of PAF-Acether Antagonists	

SUMMARY

1. **Traveler** -- Fred Snyder, Vice Chairman, Medical and Health Sciences Division, Oak Ridge Associated Universities. Phone 615/576-3110. Report prepared September 19, 1988.
2. **Contractor** -- Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN 37831 (USA)
(Contract No. DE-AC05-76OR00033).
3. **Destination** -- Milan, Italy, August 28 - September 2, 1988.
4. **Purpose** -- The Organizing Committee of the XXII Congress of the International Society of Hematology invited me to give a primary lecture at one of their main symposia, "PAF and PAF Antagonists". I was the only invited speaker from the USA at the PAF symposium.
5. **Abstract of Full Report** -- This Congress was attended by more than 1,800 biologists, biochemists, and clinicians. Participation was open to all scientists throughout the world who were interested in exchanging information on any aspect of research in the area of hematology. The purpose of the Congress was not only to provide a framework for presenting multidisciplinary research results that might catalyze some advanced working hypotheses in the hematology field but also to give practical information about recent therapeutic advances in the treatment of clinical disorders. The format of the program consisted of invited lectures, selected oral presentations, and posters on a wide range of issues related to both basic and clinical hematology.
6. **Actual travel costs and sources of funding** --
 - a) **Airline fare**-- The airline ticket (roundtrip) costing 2,850,000 lira (approximately \$2048) was sent to the traveler by the Organizing Committee of the XXII Congress of the International Society of Hematology.
 - b) **Lodging** -- Lodging was arranged by the Organizing Committee of the XXII Congress of the International Society of Hematology; the cost is not available.
 - c) **Meals and Miscellaneous expenses**--\$ 265.00 paid by DOE

COMPREHENSIVE TRIP REPORT

The purpose of this trip was to present an invited lecture at one of the main symposia at the *XXII International Congress of Hematology* held in Milan, Italy from August 28-September 2, 1988. My lecture was given at the PAF symposium on "PAF and PAF Antagonists" held Tuesday morning, August 30th. Because of the large number and diverse range of topics covered at this huge scientific Congress, only the general areas of subject matter (see below), the countries represented (see Appendix), and the complete abstracts of the PAF symposium (see Appendix) are provided in this report.

The program format of the Congress consisted of invited lectures, oral presentations selected from the submitted abstracts, and poster sessions. Quality of the presentations ranged from first class to below average, which was undoubtedly due to the diversity of topics on the agenda. I felt the the PAF symposium was excellent since it covered the most recent developments of both clinical and basic research investigations in the PAF field. My presentation was the only invited lecture from the USA at this symposium.

Topics of various scientific sessions for the 5-day Congress were as follows:

Monday, August 29, 1988

1. Regulatory Cell Factors: tumor necrosis factor, Interleukins, etc.
2. Biotechnologies and Production of Coagulant Factors
3. New Strategies in Bone Marrow Transplantation
4. Oncogenes-gene Rearrangements
5. Hematopoietic Growth Factors and Intron A
6. Plasminogen Activator Inhibitors
7. Myelodysplastic Syndromes
8. Recent Advances with Idarubicin in Acute Leukemia
9. Scientific Bases and Practical Implications of Standardization in Hematology
10. Iron Metabolism in Cellular Proliferation and Differentiation
11. Immunoglobulins Gammopathies and Immunological Diseases
12. Interferon ALFA-2b in Hematologic Malignancies
13. Iron Metabolism and Overload
14. Medical Relevance of Flow Cytochemistry Information
15. Heparins
16. Hemochromatosis Update
17. Plasma Cell Myeloma

Tuesday, August 30, 1988

1. Endothelium and Blood Cell Interaction in Vascular Diseases
2. PAF and PAF Antagonists
3. Stem Cell Features and Hemic Differentiation
4. Recombinant DNA Technologies
5. CYA and Intravenous Immunoglobulins in Bone Marrow Transplantation
6. Progress and Problems in Hemophilia
7. Advances in Biotherapy: Interleukins, Colony Stimulating Factors, Etc.
8. Biologically Active Peptides
9. Beyond Heparin: The Antithrombotic Properties of Dermatan Sulfate
10. Bone Marrow Biopsy in Clinical Hematology
11. Bone Marrow Transplantation
12. Congenital and Acquired Thrombocytopathy
13. Recent Progress in Autologous Bone Marrow Transplantation
14. Therapeutic Approach to Multiple Myeloma
15. Therapies of Leukemia
16. Biologically Active Peptides
17. Assessment of Platelet Function in Man
18. Drug-Induced Agranulocytosis: Epidemiology and Pathogenic Mechanisms
19. Immune and Non Immune Thrombocytopenia

Wednesday, August 31, 1988

1. Growth Factors - Endogenous Growth Control
2. Cell Separation and Identification
3. New Fibrinolytic Agents
4. Predictive Diagnosis of Blood Diseases

Thursday, September 1, 1988

1. Manipulation and Gene Transfer in Blood Diseases
2. Normal Cell Homing and Neoplastic Cell Invasion
3. Cellular and Humoral markers in Blood Malignancies
4. Intercellular Messengers
5. Recent Progress in Allogeneic Bone Marrow Transplantation (BMT)
6. Thalassemias
7. Differential Antitumor Therapies in the Elderly and in Infancy
8. Low Molecular Weight Heparin (CY216): A New Approach to the Prevention and Treatment of Venous Thromboembolic Disease
9. New Technologies in Cell Analysis (Coulter VCS)
10. Erythrocytes As Carriers and Bioreactors
11. Myeloproliferative and Myelodysplastic Syndromes
12. Treatment of Acute Leukemias
13. Malaria
14. Topics in Hemostasis and Thrombosis
15. Ticlopidine in the prevention of major Thrombotic Events in Ischemic Vascular Diseases
16. Genetic Events Underlying hemopoietic Proliferation and Differentiation
17. Hodgkins Lymphoma

Friday, September 2, 1988

1. Biochemistry of Platelet Components
2. "In Vitro" and "In Vivo" Methodological Approaches
3. Immunological Deficiencies
4. Interferons
5. Sulfomucopolysaccharides (Ateroid) Activity in Protecting Vascular Wall
6. Laboratory Methods and Automation
7. Hemopoietic Consequences of Exposure to Ionizing Radiation and Chemicals
8. Supportive Care and Conditioning Regimen in Bone Marrow Transplantation
9. Aspirin and Platelets: 20 Years After
10. In Vivo uses of Hemopoietic Hormones in Animals and in Humans
11. Supportive Therapy

This Congress provided a unique forum for basic biologists and physicians to discuss clinical problems of hematologic disease from the viewpoints of diagnostic, therapeutic, and research interests. My overall impression is that the meeting was very successful and effective in providing a truly international exchange of ideas in the field of hematology and related areas of research.

APPENDIX I: Full itinerary and List of persons contacted

- a) **Full itinerary--**
Oak Ridge, Tennessee to Milan, Italy and return

- b) **List of persons contacted--**
None, except for discussions with participants at the conference

APPENDIX II: Conference attendees according to country

Algeria	7	Libya	1
Argentina	7	Macau	2
Austria	20	Malaysia	1
Australia	45	Mexico	3
Brazil	10	New Zealand	6
Chile	4	Nigeria	2
China	3	Norway	18
Cuba	2	Poland	6
Czechoslovakia	11	Portugal	15
Egypt	10	Qatar	1
Denmark	28	Taiwan	16
Finland	22	Rumania	5
France	111	Saudi Arabia	5
West Germany	76	South Africa	13
East Germany	2	Spain	27
Greece	18	Sweden	59
Hong Kong	2	Switzerland	24
Hungary	7	Thailand	2
India	8	The Netherlands	35
Iran	1	Turkey	15
Ireland	4	United Kingdom	122
Israel	24	United Arab Emirates	3
Italy	518	Uruguay	1
Japan	265	USA	217
Jordan	1	USSR	6
		Venezuela	4
		Yugoslavia	19
GRAND TOTAL	1887	(does not include late registrants)	

APPENDIX III: Abstracts of plenary lectures in PAF Symposium

CELLULAR REGULATION OF ENZYMES IN THE METABOLISM OF PLATELET-
ACTIVATING FACTOR (PAF)

Fred Snyder, Ten-ching Lee, Merle L. Blank, Boyd Malone, Tomio Kawasaki, and David Vallari

Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, Tennessee 37831 (USA)

PAF can be formed de novo by synthesis from 1-alkyl-2-lyso-sn-glycero-3-P or by a remodeling pathway that involves the modification of the sn-2 position of alkylacylglycerophosphocholines (1). We have recently demonstrated that even though some of the transfer and hydrolytic reactions are of a similar type in both pathways, the specific enzymes responsible possess distinctly different properties. For example the acetyltransferases that utilize alkyllysoglycero-P or alkyllysoglycerophosphocholine (lyso-PAF) appear to be separate entities (2); the same is true for the dithiothreitol-insensitive cholinephosphotransferase (produces PAF) and dithiothreitol-sensitive cholinephosphotransferase (produces phosphatidylcholine) (3), as well as for the phosphohydrolases that utilize alkylacetyl-glycero-P or phosphatidic acid (4). The current status of our studies concerning the properties of the enzymes involved in the de novo and remodeling pathways of PAF synthesis will be summarized.

Enzymes responsible for catalyzing the rate-limiting steps in the de novo synthesis of PAF have been identified as CTP:phosphocholine cytidyltransferase (5) and acetyl-CoA:1-alkyl-2-lyso-sn-glycero-3-P acetyltransferase (2). PAF production by the de novo pathway can be stimulated up to 10-fold when cytidyltransferase is activated by being translocated from the cytosol to a membrane form after the addition of oleic acid to cell cultures (5).

In the remodeling pathway for PAF synthesis, it appears that either the phospholipase A_2 that produces lyso-PAF from alkylacylglycerophosphocholine or the acetyltransferase that utilizes lyso-PAF to produce PAF can be rate-limiting, depending on the conditions. For example, indirect evidence obtained with 20:4-depleted and 20:4-supplemented HL-60 cells (differentiated with dimethylsulfoxide) suggests an arachidonoyl-specific phospholipase A_2 can be rate limiting in PAF production. Also it is clear that the acetyltransferase in the remodeling pathway requires activation (phosphorylation) by various stimuli before significant quantities of PAF can be produced. Other factors that play a role in triggering the turning on and off of enzymatic activities involved in PAF metabolism include divalent cations (Ca^{2+} , Mg^{2+}), pH, and

APPENDIX III: Abstracts of plenary lectures in PAF Symposium (cont.)

Fred Snyder (cont.)

cellular compartmentalization. Catabolic enzymes (acetylhydrolases, lysophospholipase D, and the Pte-H₄-dependent alkyl cleavage monooxygenase) are also important in regulating PAF levels.

Alkylacylglycerophosphocholines, a membrane constituent, are the source of the lyso-PAF that is acetylated to form PAF in the remodeling pathway. This precursor pool is highly enriched in arachidonate and other polyenes that appear to be derived exclusively via a transacylation reaction that does not involve CoA or acyl-CoAs. Thus, when PAF is synthesized by the remodeling route, precursors of eicosanoid mediators are simultaneously generated. We have determined the nature of the molecular species of alkylacylglycerophosphocholines produced (a) through inactivation of PAF via the transacylation of lyso-PAF and (b) through de novo synthesis derived from alkylglycerols or alkylacetyl glycerols in rabbit platelets. The major molecular species found when platelets were incubated with [³H]PAF was 16:0-20:4 (75%), whereas in the incubations with [³H]alkylacetyl glycerol or [³H]alkylglycerol, the primary species of alkylacylglycerophosphocholines produced was 16:0-16:0 (67-71%). These findings are consistent with the proposal that saturated species of alkylacylglycerophosphocholines are derived by the de novo pathway involving alkylacylglycerols (their immediate precursor) and that the polyunsaturated species of this subclass are obtained when PAF is inactivated to lyso-PAF and subsequently acylated by a CoA-independent transacylase.

In related work we have shown 1-alkyl-2-acetyl-3-acyl-sn-glycerols can be synthesized from alkylacetyl glycerols in intact HL-60 cells and microsomes by a specific acyltransferase, which differs from acyl-CoA:diacylglycerol acyltransferases (6). The significance of this potential neutral lipid storage pool of alkylacetylacylglycerols to the biosynthesis of PAF by the de novo and remodeling pathways is speculative at the present time.

References (only our recent publications are cited)

1. Snyder, F. In: Platelet Activating Factor and Related Mediators, (Snyder, F., ed.), pp. 89-114, Plenum Press, NY, 1987
2. Lee, T-c., Malone, B., and Snyder F. J. Biol. Chem. 261, 5373-5377, 1986
3. Woodard, D. S., Lee, T-c., and Snyder, F. J. Biol. Chem. 262, 2520-2527, 1987
4. Lee, T-c., Malone, B., and Snyder, F. J. Biol. Chem. 263, 1755-1760, 1988
5. Blank, M. L., Lee, Y. J., Cress, E. A., and Snyder, F. J. Biol. Chem (in press)
6. Kawasaki, T. and Snyder F. J. Biol. Chem. (in press)

Support: USDOE (DE-AC05-76OR00033); NHLBI (27109-07, 35495-03); ACS (BC-70S).

APPENDIX III: Abstracts of plenary lectures in PAF Symposium (cont.)

IMMUNE RESPONSE AND VASCULAR INJURY : PLATELET-ACTIVATING FACTOR PRIMES BLOOD CELL/ENDOTHELIAL INTERACTIONS.

P. Braquet, M. Paubert-Braquet¹ and R.H. Bourgain²

Institute Henri Beaufour, 17 Avenue Descartes, Le Plessis-Robinson, Paris, France.

¹Unité de recherche clinique, Burn Center, Hopital Percy F92141, Clamart, France.

²Vrije Universiteit Brussel, Laboratorium voor Fysiologie en Fysiopathologie, Learbeeklaan 103, Brussels, Belgium.

Topical superfusion of an injured mesenteric artery with 10^{-7} M PAF results in local platelet thromboformation. PAF alters proteins which control permeability : human endothelial cells (EC) stimulated by PAF retract and lose reciprocal contact, while stress fibers disappear or become less regular, causing blood formation. Sequential optoelectronic measurement shows the following : (i) only platelets are initially present following PAF superfusion ; (ii) there is a gradual enlargement of the platelet mass with each new thromboformation ; (iii) subsequently neutrophils (PMN), eosinophils (PE), and monocytes/macrophages (M ϕ) arrive in an around the thrombus, increasing in number as a function of time. New thrombi may spontaneously reappear after embolization of the PAF thrombus. These effects are antagonized by PAF antagonists BN 52021, BN 52215 (a new, very potent synthetic PAF antagonist $IC_{50} = 8.7 \times 10^{-9}$ M on [³H]-PAF binding to platelet membrane), WEB 2086, 48740 RP.

Similar microscopic observations are observed after endotoxin (LPS) or antigen challenge in actively sensitized guinea-pig : a significant increase in thromboformation in comparison with control is recorded ; this thrombus is abolished by BN 52021, suggesting that PAF is produced by ECs during antigen challenge.

The PAF/interleukin-1 (IL-1) and tumor necrosis factor (TNF) interactions may play a major role in the immune injury of the vascular wall observed in shock, acute respiratory distress syndrome, sepsis and stroke. Indeed, PAF is a potent amplifier of platelet and leukocyte responses. At very low concentrations (10^{-15} -> 10^{-11} M), it dramatically potentiates not only the LPS-induced release of IL-1 and TNF by M ϕ , but also the TNF-induced production of free radicals from PMNs or PEs. PAF also primes PMNs or PEs to produce more leukotrienes when activated by A 23187. Similarly, PAF activates platelets to form thrombin and ATP, which in turn, as IL-1 and TNF, act on ECs to produce more PAF. Thus, positive feedback loops are established which sustain and amplify the EC/blood cell interactions leading in time to EC injury, de-endothelialization and cell infiltration. Other colony-stimulating factors (CSFs) may be involved in this "cross talk" : i.e., granulocyte/monocyte CSF (GM-CSF) produced by ECs under TNF activation.

APPENDIX III: Abstracts of plenary lectures in PAF Symposium (cont.)

EFFECT OF PLATELET-ACTIVATING FACTOR ON PLATELETS

Jean Michel Mencia-Huerta and Pierre Braquet

Institut Henri Beaufour, 1 avenue des Tropiques, 91952 LES ULIS
(France).

Platelet-Activating Factor (PAF) is a phospholipid mediator named after its activity on platelets. Surprisingly, although PAF is one of the most potent aggregating agent for human and rabbit platelets, only a limited number of studies have been devoted to its action of these blood elements. PAF induces platelets to aggregate and to release their granule constituents at concentrations, depending on the species, ranging from 10 pM to 10 nM. Platelet activation by PAF is calcium- and energy- dependent. However, rabbit platelet aggregation by PAF does not require intact cyclooxygenase enzyme or the presence of ADP. In contrast, human platelet aggregation by PAF is inhibited by ADP scavengers but not by cyclooxygenase blockers. Although independent from arachidonic acid metabolite generation, PAF-induced platelet activation leads to the formation of thromboxane A₂. Platelet activation by PAF is inhibited by prostacyclin, by agents increasing cAMP levels and by some calcium channel antagonists.

Since activation of platelets by PAF leads to specific desensitization, the presence of receptors/binding sites for the autacoid on platelets was postulated. Indeed, studies conducted by several groups have demonstrated the presence of specific receptors/ binding sites on human and rabbit platelets. Although the PAF binding protein on platelets has been shown to exhibit an apparent molecular weight ranging from 160 000 to 180 000 daltons, as assessed by exclusion gel chromatography, its precise characterization is not yet performed. From structure/activity relationship studies, a putative conformation for the PAF receptor/ binding site has been proposed, involving the presence of an hydrophobic pocket for the alkyl chain, and recognition sites for respectively, the ether oxyde bound, the acetate moiety and the polar head group. Such receptor model is in agreement with all the experimental data obtained with structurally unrelated antagonists such as BN 52021, kadsurenone, WEB 20 86, L 652,731 and 48 740 RP.

Platelet challenge with PAF induces a series of metabolic events leading to activation. The initial signal is supposed to be the electronic charge transfer from the ether bond of the alkyl chain to a not yet identified target protein, possibly a guanine nucleotide regulatory protein. Indeed, GTP hydrolysis is observed

APPENDIX III: Abstracts of plenary lectures in PAF Symposium (cont.)

Jean Michel Mencia-Huerta (cont.)

within seconds after PAF challenge. This activation of the guanylate cyclase leads to the stimulation of phospholipase C as demonstrated by the formation of phosphatidic acid, increase in phosphatidyl inositol turnover and calcium mobilization. Indeed, numerous steps in the sequence of events leading to platelet activation by PAF are still missing. However, studies in progress in our and other laboratories indicate that activation of the guanine nucleotide regulatory subunit is of critical importance in the activation process of various cell types and platelets by the autacoid.

Upon interaction with platelets, PAF is readily catabolised by the consecutive action of an acetylhydrolase and an acyltransferase, the latter enzyme using preferentially arachidonic acid. The catabolism of PAF by platelets is a receptor/binding site-mediated event since it is prevented by the PAF antagonist, BN 52021

PAF is generated by endothelial cells when stimulated by thrombin, interleukin 1 and more recently, by tumor necrosis factor. Interestingly, endothelial cells generate PAF but do not release it into the microenvironment. This indicates that alterations of the endothelium, whatever the initial cause, will be restricted to a very limited area, as demonstrated by the works of Bourgain et al. (Prostaglandins, 30: 185-197, 1985). Thus, the interaction between endothelial cells and platelets may have a critical importance in the development of thrombotic and vascular lesions associated with ischemia, shock and various immune and non-immune pathological conditions leading to damage of the endothelium.

APPENDIX III: Abstracts of plenary lectures in PAF Symposium (cont.)

SHORT AND LONG TIME ANTI-ANAPHYLACTIC PROPERTIES OF PAF-ACETHER ANTAGONISTS.

M. Bachelet, S. Desquand, C. Dumarey, J. Lefort, A. Lellouch-Tubiana*, M. Pretolani, E. Vannier and B.B. Vargaftig.

Unité de Pharmacologie cellulaire, Unité Associée Institut Pasteur/INSERM n° 285, 25, rue du Dr. Roux, 75015, Paris and *Laboratoire d'Histologie, Faculté de Médecine Necker-Enfants Malades, 156 Rue de Vaugirard, 75015, Paris, France.

PAF-acether (1-alkyl-2-acetyl- α -phosphoryl-3-choline, PAF) and antigen share the ability to induce acute effects, such as bronchoconstriction, leukopenia, thrombocytopenia, hemoconcentration and hypotension, suggesting that PAF is involved in allergic reactions. Accordingly, PAF antagonists (CV 3988, BN 52021, WEB 2086, 48740 RP and Ro 19-3704; for review, see Braquet et al., *Pharmacol. Rev.*, 39, 97-145, 1987) suppress the acute effects of PAF and reduce anaphylaxis.

Different models of acute anaphylaxis can be used to test the potential anti-allergic ability of drugs. Sensitization with 10 μ g ovalbumin dispersed in aluminium hydroxyde raises circulating homocytotropic IgE as well as IgG1 and IgG, which sensitize guinea-pigs *in vivo* and their lungs *in vitro*. When perfused lungs from these animals are challenged with antigen by the intra-arterial route an intense bronchoconstriction develops which is accompanied by massive release of histamine and thromboxane A₂; in presence of indomethacin, bronchoconstriction is not reduced and the formation of leukotriene C₄ is enhanced. Injected or aerosolized with ovalbumin, the actively sensitized animals undergo bronchoconstriction followed by desensitization to subsequent administrations. The intra-tracheal instillation of PAF or of antigen also leads to bronchoconstriction, accompanied by limited systemic effects. Overall, the PAF antagonists do not suppress bronchoconstriction of active anaphylactic shock triggered by the i.v. or aerosol administration of antigen, but their combination with the anti-histamine mepyramine appears to be more effective, even though such positive results were not confirmed by all laboratories. Guinea-pigs sensitized by homologous serum from the actively sensitized animals also undergo anaphylactic shock after the administration of antigen either by the intravenous route or by inhalation. The systemic effects of passive anaphylaxis tend to be less marked than those of active anaphylaxis; thrombocytopenia is relatively mild but leukopenia is intense. Anaphylactic bronchoconstriction accompanying *in vivo* passive homologous shock is inhibited by the PAF antagonists, such as BN 52021, which do not interfere with leukopenia. Another antagonist, compound WEB 2086, suppressed bronchoconstriction and also considerably reduced leukopenia. This is a selective property of the drug, since leukopenia of endotoxic shock is not modified by the different PAF antagonists. In experiments in which guinea-pigs were passively sensitized with serum from sensitized rabbits (heterologous anaphylaxis),

APPENDIX III: Abstracts of plenary lectures in PAF Symposium (cont.)

B.B. Vargaftig (cont.)

bronchoconstriction accompanying shock triggered within 48 hours was blocked by the PAF antagonists studied. Similarly, bronchoconstriction following antigen administration to guinea-pigs transfused with mice ascitic fluid containing exclusively IgE was blocked by PAF antagonists.

Bronchopulmonary hyperresponsiveness, a characteristic feature of asthma, can be modified by the PAF antagonists. Lungs from guinea-pigs sensitized by two injections of ovalbumin undergo bronchoconstriction when injected with 100-1000 fold lower amounts of PAF-acether, as compared to those from naive or from single-injected sensitized animals. This hyperresponsiveness is accompanied by an enhanced formation of thromboxane A₂, LTC₄ and by the turning-on of histamine secretion, which is not released by PAF-stimulated lungs from naive animals. Hyperresponsiveness persists for at least three months after sensitization, when the IgG titers and the lung responses to ovalbumin return to basal levels. The differences between boosted and single-injected animals are probably accounted for by the infiltration of circulating cells (eosinophils?), i.e., inflammation, and/or by a modification of resident cells (alveolar macrophages?) starting 3-4 days after the ovalbumin booster, which operates as a trigger. These results demonstrate that hypersensitivity and hyperresponsiveness in isolated lungs start together but that the latter overlasts the former, probably via the persistence of local inflammation.

The pharmacological modulation of *in vitro* bronchoconstriction by PAF is different when lungs from actively sensitized are compared to those from naive guinea-pigs; thus, cyclooxygenase-dependency in the latter is transformed into lipoxygenase-dependency for the former. In addition, macrophages from sensitized animals become refractory to the cyclic AMP-increasing effect of PGE₂ and salbutamol, confirming that systemic sensitization induces intra-pulmonary modifications which may be involved with hyperresponsiveness.

Ovalbumin administration to sensitized animals is followed within 6-24 h by a marked eosinophil lung infiltration and by eosinophil-enriched mucous plugs located in the bronchial lumen, epithelial desquamation and mucous metaplasia, as induced by PAF. Two of its antagonists (BN 52021 and WEB 2086), anti-platelet serum and prostacyclin prevented the eosinophil infiltration, suggesting that platelets mediate not only the effects of PAF but of ovalbumin as well. PAF may thus mediate eosinophil recruitment after *in vivo* anaphylaxis.



Oak Ridge
Associated Universities Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Executive
Office

October 7, 1988

Mr. Larry L. Radcliffe, Acting Director
Research and Waste Management Division
Department of Energy
Oak Ridge, Tennessee 37831

Subject: TRANSMITTAL OF FOREIGN TRIP REPORT
FRED SNYDER - MILAN, ITALY

Dear Mr. Radcliffe:

Seven copies of the subject report are enclosed. This report
does not contain any proprietary data.

Sincerely,

A handwritten signature in cursive script, appearing to read 'Jon M. Veigel', written over a large, stylized flourish.

Jon M. Veigel
Executive Director

BAKER

Enclosures

1128213

11/2/88

REQUEST FOR APPROVAL OFFICIAL FOREIGN TRAVEL

(Previous Editions are Obsolete)

PART B—To be completed by traveler's administrative officer

Budget and Reporting Classification to be charged: HA 02 02 03
(see Chapter II, Accounting Practices and Procedures Handbook)

PART C—To be completed by traveler

1a. NAME OF TRAVELER Snyder, Fred	c. DATE AND PLACE OF BIRTH [REDACTED], MN
b. CITIZENSHIP USA	d. PASSPORT NUMBER (if available) [REDACTED]
2a. HOME ADDRESS [REDACTED]	b. BUSINESS ADDRESS P.O. Box 117, Oak Ridge, TN 37831
3a. EMPLOYER Oak Ridge Associated Universities	c. TELEPHONE NUMBER 615 576-3110
b. ORGANIZATIONAL UNIT Medical and Health Sciences Division	c. CONTRACT NUMBER DE-AC05-76OR00033
	d. POSITION TITLE (including profession) Vice Chairman (Biochemist)

4. PURPOSE OF TRAVEL—Include all pertinent background information leading to travel and attach copies of invitations and correspondence regarding travel to present papers, give speeches, or to attend conference or symposia. Justification for travel must be provided including benefit to be derived by the government if trip is taken. Also identify by name and organization other DOE and contractor personnel who, to the traveler's knowledge, are going to the same destination at the same time as the traveler. In addition, specify nature and classification of information to be disclosed including titles of papers to be presented; nature of information to be obtained at each of the places to be visited and conferences to be attended and its relation to traveler's work. Travelers are responsible for obtaining clearances for papers or speeches when necessary. If more space is required, attach a separate sheet. NOTE: IF THIS INFORMATION IS CLASSIFIED BE SURE TO CLASSIFY THIS FORM APPROPRIATELY.

The Organizing Committee of the XXII Congress of the International Society of Hematology has invited me to give one of the official lectures during the Main Symposium on "PAF and PAF Antagonists." This conference will be held in Milan, Italy August 28 to September 2, 1988 (see attached letter). Air travel, lodging, and breakfast at the Congress will be covered by the organizers. The title of my talk will be "Cellular Regulation of Enzymes in PAF Metabolism. The conference is directly related to our DOE-sponsored program concerning PAF and related phospholipids. Information gained at this conference will be of great importance to our research program and will provide excellent international visibility to our own accomplishments sponsored by DOE. To my knowledge no other DOE contractor or personnel will participate in this meeting.

DOE-DOE E. [unclear] / [unclear]
to [unclear] [unclear] / [unclear]

1128214

15150RAU

memorandum

DATE:

REPLY TO

ATTN OF: ER-622

SUBJECT: Approved 1512.1's

AUG 11 1988

TO: Felix Ortiz, Jr., Director
Human Resource Management
and Evaluation Division
San Francisco Operations Office

Please find attached approved 1512.1's for the foreign travel of the following individuals:

Grab, Christoph - SLAC
Green, Michael I. - LBL
Kole, Francisco - UC Davis
Maeshima, Kaori - UC Davis
Mossbarger, Lawrence E. - CALTECH
Nobel, Park S. - UC Los Angeles
Nolte, David D. - LBL
Shoashani, Arie - LBL
~~Stokstad, Robert G. - LBL~~
Stokstad, Robert G. - LBL

A trip report is required from each traveler upon completion of his/her travel. If the travel was cancelled or revised in any way, please advise us.

Robert L. Main

Robert L. Main
Office of Management
Office of Energy Research

Attachment(s)

RECEIVED
8/16/88

1128215

LIPOPROTEINS AND PHOSPHOLIPASES : PRESENT AND FUTURE

*International Conference in the honour of
Pr J. Polonovski and Pr L. Douste-Blazy
14 - 16 Septembre 1988*

ORGANIZING COMMITTEE

Marise AYRAULT JARRIER
Gilbert BEREZIAT
Laboratoire de Biochimie UA CNRS 524
27 Rue de Chaligny 75012 PARIS
(1) 43 41 71 00 p 1341,1323

Hugues CHAP
Michel RECORD
INSERM Unité 101 Biochimie des Lipides
Hôpital Purpan 31059 TOULOUSE Cedex
61 49 18 53

Paris, 24th July, 1987

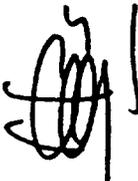
Dr Fred SNYDER
Medical and Health Sciences Division
Oak Ridge Associated Universities
PO Box 117 Oak Ridge
Tennessee 37831-0117

Dear Dr Snyder,

Thank you for your positive answer. We will be very pleased to hear your lecture on "transacylation of polyenic fatty acids between phospholipids". The organizing committee will cover your travel expenses as well as your stay in Paris during the meeting.

With best regards.

Sincerely yours.



G.BEREZIAT

LIPOPROTEINS AND PHOSPHOLIPASES : PRESENT AND FUTURE

*International Conference in the honour of
Pr J. Polonovski and Pr L. Douste-Blazy*

ORGANIZING COMMITTEE

Maryse AYRAULT JARRIER
Gilbert BEREZIAT
Laboratoire de Biochimie UA CNRS 524
27 Rue de Chaligny 75012 PARIS
(1) 43 41 71 00 p 1341,1323

Hugues CHAP
Michel RECORD
INSERM Unité 101 Biochimie des Lipides
Hôpital Purpan 31059 TOULOUSE Cedex
61 49 18 53

Pr F. SNYDER
Medical and Health Science Division
Oak Ridge associated University

Paris, June 5th 1987

Dear Professor Snyder,

Professor Polonovski and Professor Douste-Blazy are retiring in 1988 and 1989.

As suggested by their numerous friends and fellows, we have taken this opportunity to organize an International Conference centered in the two fields they have been mostly active, e.g. lipoproteins and phospholipases. This Conference will be held in Paris probably in the Faculte de Medecine (rue des Saints-Pères) built when Pr Polonovski's father was in charge of the Biochemistry department of the faculty of medecine. The best time could be from September, 14th to September, 16th, just after the European Club on lipoproteins Meeting and just before the ICBL in Tokyo.

We would be honoured if you could give us a lecture (30 min. and 10 min. discussion) on the transacylation processes between phospholipids. You will find enclosed the tentative program of the meeting.

I am looking forward to this excellent next occasion, with best regards.

Pr G. Béréziat



JUL 18 1988

ER-122:Wallace

PROPOSED FOREIGN TRAVEL BY FRED L. SNYDER, ORAU

Robert W. Wood, Director of Physical and Technological Research, ER-74,
Headquarters, Germantown, Maryland

Attached for DOE Headquarters approval are three copies of DOE F 1512.1 covering the proposed travel by Fred L. Snyder to Milan, Italy, during the period August 26 through September 4, 1988. At the invitation of the Organizing Committee of the XXII Congress of the International Society of Hematology, Dr. Snyder will lecture on lipid biochemistry, membranes, and hematological diseases at the Main Symposium on "PAF and PAF Antagonists." It is anticipated that the information learned at this symposium will be important to ORAU's DOE-sponsored program concerning PAF and membrane lipids.

As noted in Part D, Block 8b., DOE F 1512.1, the Organizing Committee will pay airfare, lodging, and breakfast. Specific dollar values are not known at this time. However, the remaining expenses, estimated to be \$445.25, will be charged to DOE Budget Activity HA 02 02 03.

Please have Margie Wallace (FTS 626-0714) notified as soon as a determination is made regarding the travel and return the signed original of DOE F 1512.1 to this office.

ORIGINAL SIGNED BY
M. C. WALLACE

W. D. Adams, Director
Research and Waste Management Division

Attachment

cc w/atchmt:
J. A. Lenhard, ER-10, ORO
M. M. Dare, AD-43, ORO
D. J. Cook, DP-82, ORO

*8/22/88 Rec'd verbal approval
from Bob Main, ER-HS,
Notified Carol Baker, ORAU.
M.C.W.*

ER-122:MWallace:AAlexander:6-0733:7/12/88

CONCURREN
RTG SYMBOL ER-122 WALLACE M.C.W. DATE 7/12/88
RTG SYMBOL ER-122 ATCHEE DATE 7/12/88
RTG SYMBOL AD-40 MARGIE DATE 7/12/88
RTG SYMBOL ER-122 WALLACE M.C.W. DATE 7/12/88
RTG SYMBOL
INITIALS/SIG.
DATE
RTG SYMBOL
INITIALS/SIG.
DATE
RTG SYMBOL
INITIALS/SIG.
DATE
RTG SYMBOL
INITIALS/SIG.
DATE
RTG SYMBOL
INITIALS/SIG.
DATE

1120218

REQUEST FOR APPROVAL OFFICIAL FOREIGN TRAVEL

All Other Editions Are Obsolete

PART A-SUMMARY TRAVEL INFORMATION

ORGANIZATION: Oak Ridge Associated Universities

STI FAXED TO IE-1
7/12/88

COST TO DOE: \$445.25

FUND SOURCE: HA 02 02 03

NAME OF TRAVELER: Fred Snyder

DOE/CONTRACTOR/UNIVERSITY: C

DESTINATION: Milan, Italy

DATES: 8/27/88 TO 9/03/88

PURPOSE: To present an invited lecture on lipid biochemistry, membranes, and hematological diseases.

AGREEMENT: None

DESTINATION: _____

DATES: / / TO / /

PURPOSE: _____

AGREEMENT: _____

DESTINATION: _____

DATES: / / TO / /

PURPOSE: _____

AGREEMENT: _____

DESTINATION: _____

DATES: / / TO / /

PURPOSE: _____

AGREEMENT: _____

REQUEST FOR APPROVAL OFFICIAL FOREIGN TRAVEL

(Previous Editions are Obsolete)

PART B--To be completed by traveler's administrative officer

Budget and Reporting Classification to be charged: HA 02 02 03
(see Chapter II, Accounting Practices and Procedures Handbook)

PART C--To be completed by traveler

1a. NAME OF TRAVELER Snyder, Fred	c. DATE AND PLACE OF BIRTH ██████████, MN
b. CITIZENSHIP USA	d. PASSPORT NUMBER (if available) ██████████
2a. HOME ADDRESS ██████████	b. BUSINESS ADDRESS P.O. Box 117, Oak Ridge, TN 37831
3a. EMPLOYER Oak Ridge Associated Universities	c. TELEPHONE NUMBER 615 576-3110
b. ORGANIZATIONAL UNIT Medical and Health Sciences Division	c. CONTRACT NUMBER DE-AC05-76OR00033
	d. POSITION TITLE (including profession) Vice Chairman (Biochemist)

4. PURPOSE OF TRAVEL--include all pertinent background information leading to travel and attach copies of invitations and correspondence regarding travel to present papers, give speeches, or to attend conference or symposia. Justification for travel must be provided including benefit to be derived by the government if trip is taken. Also identify by name and organization other DOE and contractor personnel who, to the traveler's knowledge, are going to the same destination at the same time as the traveler. In addition, specify nature and classification of information to be disclosed including titles of papers to be presented; nature of information to be obtained at each of the places to be visited and conferences to be attended and its relation to traveler's work. Travelers are responsible for obtaining clearances for papers or speeches when necessary. If more space is required, attach a separate sheet. NOTE: IF THIS INFORMATION IS CLASSIFIED BE SURE TO CLASSIFY THIS FORM APPROPRIATELY.

The Organizing Committee of the XXII Congress of the International Society of Hematology has invited me to give one of the official lectures during the Main Symposium on "PAF and PAF Antagonists." This conference will be held in Milan, Italy August 28 to September 2, 1988 (see attached letter). Air travel, lodging, and breakfast at the Congress will be covered by the organizers. The title of my talk will be "Cellular Regulation of Enzymes in PAF Metabolism. The conference is directly related to our DOE-sponsored program concerning PAF and related phospholipids. Information gained at this conference will be of great importance to our research program and will provide excellent international visibility to our own accomplishments sponsored by DOE. To my knowledge no other DOE contractor or personnel will participate in this meeting.

1128220

1515 ORAU
~~X-3695~~

8. PROPOSED ITINERARY (Account for all time from beginning and ending dates of travel. Vacation dates taken in conjunction with this travel shall be indicated. NOTE: IF INFORMATION IS CLASSIFIED, CLASSIFY THIS FORM APPROPRIATELY.)

DATES	LOCATION (Installation, City, Country)	INDIVIDUALS TO BE CONTACTED	SUBJECTS OF DISCUSSION	(Check One)	
				Classified	Unclassified
8/26/88 8/27-9/3/88 9/4/88	Depart for Italy Milan, Italy Return to Oak Ridge	International Conference	Lipid biochemistry, membranes, and hematological diseases		X

6. HAS TRAVELER SUBMITTED DOE FORM 1512.2 TO COGNIZANT DOE SECURITY OFFICE? (Required for travel to a sensitive country by an individual who currently holds or has ever held, within the last 5 years, a DOE Access Authorization.)

N A

YES

NO: Have not held a DOE Access Authorization within last 5 years.

7. SIGNATURE OF TRAVELER: By signing, the traveler acknowledges the obligation to file a trip report within 30 days of return to duty station.

Fred Snyder

(Signature)

7 June 1988

(Date)

PART D--To be completed by official responsible for travel funds

8a. ESTIMATED COST OF TRAVEL TO DOE

Transportation \$ 140.00 To airport and taxi
Per Diem and Miscellaneous \$ 305.25
Total \$ 445.25

8b. IF PART OF COST OF TRAVEL IS TO BE PAID OR HAS BEEN REQUESTED FROM SOURCES OTHER THAN DOE, INDICATE SOURCE AND AMOUNT. The Organizing Committee is committed to paying the airfare, lodging, and breakfast. Specific dollar values are not known at this time.

TRAVEL FUNDS ARE NOW AVAILABLE FOR THIS TRIP

at this time.

E.S. Butterlin 6/7/88
for Division Business Office (Signature and Title) (Date)

William F. Cousins 7/7/88
William F. Cousins, Asst. Dir. Finance (Date)

PART E--To be completed by Traveler's supervisor

9. REVIEW AND COMMENTS:

William W. Burr 6/9/88
Division Chairman (Signature and Title of Supervisor) (Date)

William E. Felling 7/7/88
William E. Felling, Executive Director (Date)

PART F--To be completed at DOE Field Organization

10. NON SENSITIVE TRAVEL: Review/Approval by Head of DOE Field Organization. (Approval may be given if such authority has been delegated by the Cognizant Secretarial Officer.)

Approval recommended.

M.C. Wallace
(Signature)

for W. D. Adams, Director
Research & Waste Management Div.
(Title)

7/18/88
(Date)

11. SENSITIVE TRAVEL: Review by Head of DOE Field Organization. Has Field Security reviewed DOE F 1512.2 and completed DOE F 1512.37

YES

NO

PART G--To be completed at Headquarters

12. REVIEW/COMMENTS BY DIRECTOR OF DIVISION OR OFFICE

(Signature)

(Title)

(Date)

13. COGNIZANT SECRETARIAL OFFICER

IF DOE EMPLOYEE TRAVEL IE Determination Received

IF SENSITIVE TRAVEL

IE Determination Received

ISA Determination Received

OSS Determination Received

1128221

(Signature)

(Date)



XXII Congress of the International Society of Hematology

President: Elio E. Polli

Milan, September 18, 1987

Prot.: HMT/88

Air mail - Express Letter

Dr. F. SNYDER
Medical Health Science Division
Oakridge Associated University
P.O. Box 117
OAKRIDGE, TN 37831
(USA)

Dear Dr. Snyder,

I am pleased to inform you that the XXII Congress of the International Society of Hematology will be held in Milan on August 28 - September 2, 1988.

On behalf of the Scientific Programme Committee and in consideration of your recognized experience in the field I am honoured to invite you to give one of the official lectures during the Main Symposium on "PAF AND PAF ANTAGONISTS" scheduled on Tuesday, August 30, 1988.

Regarding the Chairmen and Speakers of your session, please refer to the enclosed programme.

In case of your acceptance, please communicate to the Organizing Secretariat (FONDAZIONE GIOVANNI LORENZINI, Via Monte Napoleone, 23, 20121 Milan, Italy) the title of your lecture at your earliest convenience, but in any case no later than October 5, 1987 (better if by cable or telefax: 02/78 15 11). A copy of your acceptance letter with the title will also have to be sent by you to the Chairpersons of your session (Prof. T. Abe, Dean of Med. School, Teikyo University, School of Medicine, 11-1 Kaga 2-Chome, Itabashi-ku, Tokyo 173 - Japan and Prof. R. Paoletti, Dirett. Ist. di Scienze Farmacologiche, Via A. del Sarto 21, 20129 Milan - Italy).

As for your travel (round trip, economy fare) and accommodation expenses (first class hotel on a bed and breakfast basis), I am pleased to inform you that they will be taken care by the Congress Organizers. Further information will be given you upon receipt of your acceptance.

An early reply would be highly appreciated.

At your disposal for any information you may need, please accept kindest regards.

Yours sincerely,

Elio E. Polli, M.D.

Encl.: 2nd Announcement of the Congress
Preliminary Programme of your session
Scientific Secretariat ISH 88
FONDAZIONE GIOVANNI LORENZINI

1120222