Outline of the Fund

Objectives and Projects: Grants for promoting medical science and human welfare are available to investigators engaged in specialized research on the basic and clinical aspects of cerebrovascular disorders.

Fund Name: The Mihara Cerebrovascular Research Promotion Fund, a Public Utility Trust Fund.

Consignor: The late Hiroshi Mihara, M.D.

Trust Executor: Yosoji Kobayashi, Pres.

Commissioners: Toyozo Aizawa, M.D., and six others.

Date Established: April 10, 1981.

Initial Trust Endowment; ¥300 million.

Ministry in Charge: Ministry of Education
International Academic Department
Research Aid Division

Previous Grants: Annual donation of ¥10 million to each selected candidate, since 1981.

Grants-In-Aid

Value: ¥10 million to the selected candidate.
Application Procedure: Those making recommendations should fill in the required details on the designated form and return it to the Trustee together with copies of three major papers by the candidate. The copies are non-returnable.

Status of the Recommender: The recommender should be the dean of a faculty of medicine at a university having such a faculty, the president of a medical college, the chairman of an academic society, or the representative in charge of other research organizations. The number of recommendations is limited to one item per recommender.

Candidates: Corporations or individuals engaged in specialized research in basic, prophylactic and clinical areas of cerebrovascular diseases, whose achievements are expected to exert a far-reaching influence on studies of the etiology and therapy of cerebrovascular disorders.

Languages to be used: English or Japanese

Deadline: September 30, 1990 (valid if postmarked by that date).

Selection Procedure: The final selection will be made by the commissioners after assessment by the evaluation committee. Each recommender will be notified on the following January as to whether the candidate concerned has been selected or not.

Donation of the Grant and the Award Ceremony: A ceremony for donation of the Grant and Awards will be held in March of each year. The cost of transportation and accommodation for attending the ceremony will be borne by this fund.

Request for Recommendation Form: Each recommender should request the designated form from the Trustee in writing. Recommendations, inquiries and correspondence should be directed to:

Mail to

Trustee
Address
Personal Trust Section
Individual Service’s Planning Dept.
The Yasuda Trust & Banking Co. Ltd.
1-2-1 Yaesu, Chuo-ku, Tokyo 103,
JAPAN
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THE AMERICAN HEART ASSOCIATION
PHARMACEUTICAL ROUND TABLE

Some of the biggest names in medicine have joined forces with us in the fight against a common enemy — heart disease. They've teamed up to form the AHA Pharmaceutical Roundtable, a group committed to funding cardiovascular research projects that have been approved as promising, but that could not be funded because we lacked the resources.

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Boehringer Ingelheim Pharmaceuticals, Inc.

We ask you to join us in recognizing these companies for the important commitment they represent.

The AHA Pharmaceutical Roundtable: It's powerful medicine.
Notice

The Scientific Conference on Acute Lung Injury: From Bench to Bedside
(formerly "Lung Injury and Vascular Permeability")

has been rescheduled.

NEW DATES
May 30-June 1, 1990
Fairmont Hotel
Dallas, Texas

OLD DATES
December 14-16, 1989

Information may be obtained through:
Scientific Conference on Acute Lung Injury: From Bench to Bedside,
American Heart Association
Scientific and Corporate Meetings
7320 Greenville Avenue
Dallas, TX 75231
(214) 706-1253

Two CEREBROVASCULAR DISEASE FELLOWSHIPS are available, one or two years, beginning July 1, 1990, in the Department of Neurology, Henry Ford Hospital. These fellowships offer comprehensive training programs in pathophysiology, diagnosis and management of cerebrovascular disorders, including migraine, within an NIH funded center for cerebrovascular disease research. A Javits Junior Clinical Investigator Fellowship is available to one competitive candidate. The department evaluates almost 600 patients with cerebrovascular disease yearly, has a stroke and migraine clinic, and a clinical/clinical research four bed acute stroke unit. Clinical and basic science research opportunities available in: in-vivo NMR spectroscopy of human and animal cerebral ischemia, 133-Xenon inhalation regional cerebral blood flow, non-invasive carotid dopplers, transcranial doppler, platelet function laboratory, HFH stroke center data bank, and experimental drug studies in stroke and migraine. Applicants should have completed an accredited neurology residency and be board eligible/certified. Salary commensurate with experience. Please send letter of inquiry to: K.M.A. Welch, M.D., Chairman, or Steven R. Levine, M.D., Director, Center for Stroke Research, Department of Neurology, Henry Ford Hospital, 2799 West Grand Blvd., Detroit, Michigan 48202-2689 (ph 313-876-3396).

Just what heart researchers have been hoping for.

The member companies of the AHA Pharmaceutical Roundtable offer new hope for the future of vital cardiovascular research. With their unprecedented commitment of time, expertise and funding, these pharmaceutical leaders have the opportunity to exchange ideas and information relevant to heart research, while also supporting promising projects. Altogether, cardiovascular researchers couldn't hope for a more dedicated circle of friends and supporters.

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American Heart Association

Sponsored by the Cardiopulmonary Council
Editor
Dennis Krikler

The British Heart Journal is found throughout the world in leading libraries, and is read by physicians and surgeons with more general interests, as well as by cardiologists. Articles are accepted only after rigorous review and all submissions are subject to peer review by experienced cardiologists.

The editors are practising cardiologists with academic responsibilities who have published research papers and continue to write articles and contribute towards cardiological education. The editors have earned accolades for clarity and crispness—clear communication of the intended message is always in the forefront of the editor's mind. The British Heart Journal publishes original articles, editorials, and reviews and nearly half of the original papers come from abroad.

The British Heart Journal is intended to be read by clinical cardiologists and academic physicians and is ideal for personal subscription. From the British Heart Journal readers will get an international distillation of views on topics of clinical and research interest.

The journal is published monthly in two volumes a year. The title page, contents list, and an author and subject index are included in the June and December issues, reading for binding.

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MILES INTRODUCES

CEREBROSELECTIVE

NIMOTOP®
nimodipine/Miles
CAPSULES 30mg

THE FIRST PHARMACOLOGIC AGENT TO IMPROVE NEUROLOGIC OUTCOME ASSOCIATED WITH VASOSPASM IN ANEURYSMAL SUBARACHNOID HEMORRHAGE
(Hunt and Hess Grades I-III Patients)

SIGNIFICANT REDUCTION IN THE SEVERITY OF DELAYED ISCHEMIC DEFICITS ASSOCIATED WITH VASOSPASM IN GOOD GRADE PATIENTS

- As demonstrated in four double-blind, randomized clinical studies involving 823 evaluable patients
- Treatment initiated within 96 hours of the event

LOW INCIDENCE OF SIDE EFFECTS AT RECOMMENDED DOSAGE REGIMEN

- Decreased blood pressure is most common side effect, occurring in 3.8% (19/494) of patients. Carefully monitor blood pressure during therapy — see Precautions section in the prescribing information
- Other side effects occurring at a frequency of ≥1.0% include headache, nausea, and bradycardia
- No clinically significant effects on hematologic factors, renal or hepatic function, or carbohydrate metabolism have been causally associated with NIMOTOP

For more information call 1-800-642-4776.

LOW INCIDENCE OF SIDE EFFECTS AT RECOMMENDED DOSAGE REGIMEN

HEMODYNAMIC EFFECTS COMPATIBLE WITH SURGERY

- Minimal decreases in arterial blood pressure
- Minimal changes in heart rate

DOSAGE RECOMMENDATION

- NIMOTOP therapy should begin within 96 hours of the aneurysmal subarachnoid hemorrhage regardless of angiographic evidence of vasospasm
- Recommended dosage regimen is 60 mg (two 30 mg liquid-filled capsules) every 4 hours for 21 consecutive days in Hunt and Hess Grades I-III patients
- NIMOTOP can be given orally or can be administered via nasogastric tubing as described in the prescribing information

Please see references and Brief Summary of full prescribing information on next page.
CEREBROSELECTIVE
NIMOTOP® (nimodipine/Miles) CAPSULES
30 mg
FOR IMPROVED NEUROLOGIC OUTCOME

BRIEF SUMMARY

NIMOTOP® (nimodipine/Miles) CAPSULES
For Oral Use

INDICATIONS AND USAGE

Nimotop® (nimodipine) is indicated for the improvement of neurological deficits due to spasm following subarachnoid hemorrhage from ruptured aneurysms in patients who are in good neurological condition post-ictus (e.g. Hunt and Hess Grades I-III). Oral Nimotop® therapy should begin within 96 hours of the subarachnoid hemorrhage and continue for 21 days.

CONTRAINDICATIONS

None known.

PRECAUTIONS

General: Blood Pressure: Nimodipine has the hemodynamic effect expected of a calcium channel blocker, although they are generally not marked. In patients with subarachnoid hemorrhage given Nimotop® in clinical studies, about 5% were reported to have had lowering of the blood pressure and about 1% left the study because of this (not all could be attributed to nimodipine). Nevertheless, blood pressure should be carefully monitored during treatment with Nimotop® based on its known pharmacology and the known effects of calcium channel blockers.

Hepatic Disease: The metabolism of Nimotop® is decreased in patients with impaired hepatic function. Such patients should have their blood pressure and pulse rate monitored closely and should be given a lower dose (see Dosage and Administration).

Laboratory Test Interactions: None known.

Drug Interaction: It is possible that the cardiovascular action of other calcium channel blockers could be enhanced by the addition of Nimotop®.

In Europe, Nimotop® was observed to occasionally interfere the effect of antihypertensive compounds taken concomitantly by patients suffering from hypertension: this phenomenon was not observed in North American clinical trials.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study, higher incidences of adenocarcinoma of the uterus and Leydig-cell adenomas of the testes were observed in rats given a diet containing 1800 ppm nimodipine (equivalent to 91 to 121 mg/kg/day nimodipine) than in placebo controls. The differences were not statistically significant; however, the higher rates were well within historical control range for these tumors in the Wistar strain. Nimodipine was found not to be carcinogenic in a 21-week mouse study but the high dose of 1800 ppm nimodipine in feed (546 to 774 mg/kg/day) shortened the life expectancy of the animals. Mutagenic studies, including the Ames, micronucleus and chromosomal aberration tests were negative.

Nimodipine did not impair the fertility and general reproductive performance of male and female Wistar rats administered orally nimodipine (up to 150 mg/kg/day administered daily for more than 10 weeks in the males and 3 weeks in the females prior to mating and continued to day 7 of pregnancy. This dose in a rat is about 4 times the equivalent clinical dose of 60 mg/dos in a 60 kg patient).

Pregnancy: Pregnancy Category C: Nimodipine has been shown to have a teratogenic effect in the rabbit. Incidences of malformations and stillbirths were increased at oral (in pregnant) doses of 1 mg/kg/day or greater administered from day 6 through day 15 of pregnancy but not at 0.3 mg/kg/day in one of 2 identical rabbit studies. In the second study an increased incidence of stunted fetuses but not at higher doses. Nimodipine was embryotoxic, causing resorption and stunted growth of fetuses, in Long Evans rats at 100 mg/kg/day administered by gavage from day 6 through day 15 of gestation. In one other rabbit study, doses of 10 mg/kg/day of nimodipine administered by gavage from day 6 of gestation and continued until sacrifice (day 20 of pregnancy or day 21 post partum) were associated with higher incidences of skeletal variations, stunted fetuses and stillbirths but no malformedities. There are inadequate and well-controlled studies in pregnant women to directly assess the effect on human fetuses. Nimodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Nimodipine and/or its metabolites have been shown to appear in rat milk at concentrations much higher than in maternal plasma. It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk, nursing mothers are advised not to breast feed their babies when taking the drug.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions were reported by 92 of 821 patients with subarachnoid hemorrhage (11.2%) who were given nimodipine. The most frequently reported adverse reaction was decreased blood pressure in 4.4% of these patients. Twenty-nine of 479 (6.1%) placebo treated patients also reported adverse experiences. The events reported with a frequency greater than 1% are displayed below in dose.

DOSE 4th Number of Patients (%)

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Nimodipine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.35 mg/kg</td>
<td>(n = 82)</td>
<td>(n = 71)</td>
</tr>
<tr>
<td>0.6 mg/kg</td>
<td>(n = 494)</td>
<td>(n = 472)</td>
</tr>
<tr>
<td>1.2 mg/kg</td>
<td>(n = 172)</td>
<td>(n = 4)</td>
</tr>
<tr>
<td>2.4 mg/kg</td>
<td>(n = 12)</td>
<td>(n = 4)</td>
</tr>
<tr>
<td>4.8 mg/kg</td>
<td>(n = 2)</td>
<td>(n = 1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs/Symptoms</th>
<th>Nimodipine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Blood Pressure</td>
<td>1 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal Liver Function Test</td>
<td>1 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (2.4)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Gastrointestinal Symptoms</td>
<td>2 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>EKG Abnormalities</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

There were no other adverse experiences reported by the patients who were given 0.35 mg/kg, 0.6 mg/kg or 1.2 mg/kg. Adverse experiences with an incidence rate of less than 1% in the 0.6 mg/kg dose group were: headache; nausea; gastrointestinal hemorrhage; thrombocytopenia; anemia; proteinuria; vomiting; flushing; diaphoresis; wheezing; phlebitis; toxicity; lightheadedness; dizziness; reduced vision; jaundice; hypertension; hematoma; edema. Adverse experiences with an incidence rate less than 1% in the 0.6 mg/kg dose group were: nausea; gastrointestinal hemorrhage; thrombocytopenia; hepatitis; pulmonary infiltration; vomiting; diaphoresis; conjunctival hemorrhage; hypertension; decreased platelet count; disseminated intravascular coagulation; deep vein thrombosis.

As can be seen from the table, side effects that appear related to nimodipine use based on increased incidence with higher doses or a higher rate compared to placebo control included decreased blood pressure, edema and headaches which are known pharmacologic actions of calcium channel blockers. It must be noted, however, that SAFB is frequently accompanied by alterations in consciousness which lead to an under-reporting of adverse experiences. Patients who received nimodipine in clinical trials for other indications reported flushing (1.2%), headache (4.1%) and fluid retention (0.3%), typical responses to calcium channel blockers. As a calcium channel blocker, nimodipine may have the potential to exacerbate heart failure in susceptible patients or to interfere with A-V conduction, but these events were not observed.

It is clinically significant to note in hamodynamic factors, renal or hepatic function or carbohydrate metabolism have been causally associated with oral nimodipine. Isolated cases of non-fasting elevated blood pressure (0.6%), elevated LDH levels (0.4%), decreased platelet counts (0.1%), elevated alkaline phosphatase levels (0.2%) and elevated SGPT levels (0.2%) have been reported rarely.

OVERDOSAGE

Nimodipine overdose may be expected to be related to cardiovascular effects such as excessive peripheral vasodilation and marked systemic hypotension. Clinically significant hypotension due to Nimotop® overdose may require active cardiovascular support. Nortephrine or dopamine may be helpful in restoring blood pressure. Since Nimotop® is highly protein-bound, dialysis is unlikely to be of benefit.

Dosage and Administration

Nimotop® is given orally in the form of colorless, soft gelatin 30 mg capsules for subarachnoid hemorrhage.

The oral dose is 60 mg (two 30 mg capsules) every 4 hours for 21 consecutive days. Oral Nimotop® therapy should commence within 96 hours of the subarachnoid hemorrhage. The capsule should then be emptied into the patient's naso-gastric tube and washed down with the tube with 30 ml of normal saline (0.9%).

Patients with hepatic failure have substantially reduced clearance and approximately double. Dosage should be reduced to 30 mg every 4 hours, with close monitoring of blood pressure and heart rate.

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