I. INTRODUCTION

The prevention and control of chronic "degenerative" diseases and specifically of chronic cardiovascular diseases (CVD) has received special consideration by the World Health Organization (WHO) and by the Pan American Health Organization (PAHO) for many years (1, 2). In 1972 PAHO convened a Symposium on Epidemiologic Studies and Clinical Trials in Chronic Diseases, which reported the deliberations of different panels, including one on Arteriosclerotic and Hypertensive Cardiovascular Disease (Chronic Cardiovascular Diseases, CVD), to the Advisory Committee on Medical Research of that same year. In this report (3), Dr. D. S. Frederickson, who acted as chairman of the Symposium, reiterated the need to carry out research in Latin America and the Caribbean in: a) Comparative epidemiology about Atherosclerosis and Hypertension, using standardized methodology. b) Determination of changes in risk factors of Chronic Cardiovascular Disease (CVD), such as in lipids, in populations undergoing economic and cultural changes. And, c) Ways to avoid the increase in mortality due to atherosclerosis as economic conditions improve; in other words the PREVENTION of CVD. In 1975 the bases for a Cooperative Project consisting of the Establishment of Pilot Programs for the Control of Hypertension in Latin America were proposed to collaborative Centers. This project was begun in 1976, and will be finished this year (1982). It involves 10 countries and a maximum follow up of 4 years of therapy to hypertensive patients. Moreover, six years ago (1976) the PAHO Directing
Council resolved that the Organization should stimulate research and health promotion in CVD in Western Hemisphere countries (4). This resolution was further strengthened in 1978 (5), and WHO initiated a collaborative project to study the precursors of atherosclerosis in childhood and youth (6). In 1980, (7) the same body further emphasized prevention and control of such diseases in the Americas, with cooperative activities and exchange of knowledge and technology as important components. Finally, PAHO's Advisory Committee on Medical Research requested in 1981 that a presentation be made at the 1982 meeting on the state of Research in Chronic Cardiovascular Diseases at PAHO. This presentation obeys such request.

II. BACKGROUND

A. Present Situation of Cardiovascular Disease Conditions in the Western Hemisphere.

Age-adjusted mortality rates due to Chronic Cardiovascular Disease (CVD)* in Latin America and the Caribbean range from 48 to 264/100,000 population. This range has been stable at least for the last ten years even though during this period CVD mortality is contributing more significantly to overall mortality in the Western Hemisphere. Moreover, CVD has progressively appeared among the most important five causes of death essentially in all countries in the Hemisphere, regardless of stage of socioeconomic development. It often is the leading cause of death.

The following characteristics of CVD mortality rates, based on official statistics available to PAHO, are considered worth highlighting:

* Chronic Cardiovascular Disease (CVD) in this section is grouped in two categories: 1. Diseases of the Heart, which are mostly ischemic-atherosclerotic in origin, ("IHD"), and 2. Hypertensive Disease plus Cerebrovascular Accidents ("HD+CVA").
1. During the 1970's 16 of 20 countries in the Western Hemisphere have exhibited an increase in CVD mortality as a proportion of total mortality (both age adjusted). Of the four countries not exhibiting an increase, the USA shows a 2% decline while this is near 1% in Canada, Trinidad & Tobago and Uruguay. In contrast, 14 of the 16 countries whose proportion of CVD deaths has increased, show increments of 2% or more. The countries of the Hemisphere as a whole exhibit a 3% increase in the proportion of CVD/total deaths. This significant increase is not only due to a decline in mortality due to non CVD (this factor appears to be predominant in 6 of the 16 countries showing an increase), but also to an actual elevation in age adjusted CVD mortality rate in 10 countries (Figure 1).

2. The countries with age adjusted CVD mortality rates over 1 per thousand show in general a stable or declining rate in this statistic particularly important in Canada, Chile, Costa Rica and the United States of America. Within this group, however, Colombia and Paraguay exhibit significant increments in rate. The countries with rates below 1 per thousand inhabitants show, in general, increasing rates. An exception to this trend is Peru (Figure 2).

3. Available data shows that within countries, urban higher socioeconomic groups exhibit higher CVD mortality rates than rural lower socioeconomic groups (8). Urban male populations categorized in three socio-economic strata exhibit a progression of 1.7 fold in CVD mortality between successively higher socioeconomic levels (9). Also, as CVD mortality rates increase, the male adult population is more affected than the adult female population.
4. An analysis of the total CVD mortality in the Hemisphere discloses that where the rates are higher, on the average "IHD" mortality contributes with 73% of the total mortality; the other 27% can be explained by increments in "HD+CVA" (Figure 3). However, the USA and Canada exhibit high (and rising) "IHD" in relation to "HD+CVD" deaths ("IHD/HD+CVA" ratio = 4.1 and 3.7 respectively) while the Caribbean exhibits a stable ratio of 1.3 Twice as many countries in Latin America show an increasing ratio rather than a decreasing one. This increment is due primarily to an elevation in "IHD" in the last decade.

5. Within regions and countries, "HD+CVA" is more prevalent among blacks than among other races (10,11).

6. Among the countries in the Hemisphere there is not only a large range of death rates due to CVD but, similarly, there is a large range of socioeconomic and demographic conditions characteristic of different stages of "development." One variable which represents development at a country level, and which can be argued to be more accurate than GNP/capita is total caloric intake per capita. Within this variable, still two others appear to be more specific indicators of development, although less sensitive: Total fat intake/capita and percentage of animal fats and oils. These nutritional components have also been demonstrated to be related to the development of atherosclerosis and CVD. In effect: comparative epidemiologic studies as well as retrospective and prospective studies strongly suggest that diet, and within it, cholesterol intake, and total saturated and polyunsaturated fatty acid intakes play a major role in the development of atherosclerosis and in its clinical repercussions (12-13). Correlations between per capita caloric, total fat and animal fat intakes as predictive variables (14), and total CVD and "IHD" mortality as resultant
variables, taking each country as a unit, yield statistically significant correlations. Importantly, the slopes are not significantly different from 0 for total caloric intake but are significant for total fat and animal fat intakes:

<table>
<thead>
<tr>
<th>1974-79 Intakes:</th>
<th>Total Caloric</th>
<th>Total Fat</th>
<th>Animal Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>slope</td>
<td>0.06</td>
<td>0.65</td>
<td>0.74</td>
</tr>
<tr>
<td>correlation Coeff.</td>
<td>0.72</td>
<td>0.62</td>
<td>0.55</td>
</tr>
<tr>
<td>&quot;IHD&quot; Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>slope</td>
<td>0.05</td>
<td>0.56</td>
<td>0.65</td>
</tr>
<tr>
<td>correlation Coeff.</td>
<td>0.60</td>
<td>0.70</td>
<td>0.48</td>
</tr>
</tbody>
</table>

There are relatively few data on morbidity from CVD in Latin America and the Caribbean. However, available information (15-20) discloses that the prevalence of hypertension in specific adult population groups ranges between 10 and 20 %, increasing as age advances especially in postmenopausal women. Again hypertension is more prevalent among black populations. Studies in the Caribbean suggest that in that region higher levels of blood pressure are better tolerated than, for example, in the USA (21). However, this needs confirmation.

As is almost universally the case "essential hypertension" accounts for over 85% of all hypertension diagnosis in the Western Hemisphere. A few studies also suggest that IHD morbidity in certain population groups resembles that of developed countries (22) while in others it is lower (23). Further studies are needed to determine what this difference is due to. In summary, CVD is already

In summary, CVD is already a universal problem in the Western Hemisphere. Moreover, its importance is increasing in developing countries and within them in urban population groups and as "socioeconomic status" improves.
Significantly, CVD mortality rates are declining consistently in the USA and Canada. Other Latin American countries also show a declining rate in the absence of any specific action to that effect. In certain countries and particularly among black populations, hypertension and related problems are more prevalent but in general and even among blacks, atherosclerosis accounts for the majority of the CVD problem.

B. The cooperative Project on the Control of Hypertension in Latin America.

The Pan American Health Organization in 1976 began a multinational collaborative study on the Control of Hypertension with the following objectives:

1. To study the problem posed by hypertension at the community level or in defined population groups.
2. To provide adequate medical care to hypertensive patients.
3. To evaluate the operation, costs and effectiveness of the program, and
4. To acquire the experience necessary to organize community based programs aimed at increasing the health coverage of the hypertensive population.

The overall objective was that by involving in this program groups concerned with hypertension primarily at the clinical level, a new dimension of concern and a more homogeneous approach to the care of the hypertensive patient, with emphasis on public health and on community participation, would be generalized through Latin America. When the study was planned, evidence was that control of hypertensives with diastolic blood pressure above 105 mm Hg resulted in a reduction in CVD events and death (24,25). Moreover, it was evident that simple therapeutic measures were effective and safe, if properly and continuously provided.

It is also expected that this type of project will serve as the basis for a wider, more comprehensive and integrated effort in the control of CVD and
other non-communicable diseases within existing health systems and thus contribute to the goal of Health for All by the Year 2000.

This effort, which has involved 10 countries (Argentina, Bolivia, Brazil, Chile, Colombia, Cuba, Ecuador, Mexico, Peru and Venezuela) is approaching its conclusion this year. Final analysis of data will take place the second part of 1982, and Norms for the Control of Hypertension are in the process of being completed now, with full collaboration of participants in the study. These Norms, which emphasize primary care, will serve as the basis for action-research.

**Design of the Study:**

The project contemplated the incorporation of centers in different countries where special attention was being given to hypertensive populations. It was hoped that, as a first step, a point prevalence study of hypertension in the selected population would take place. Unfortunately, for various reasons this was not possible in most centers. The study population consisted, then, of known hypertensives who entered the study by being referred or by seeking medical attention at the cooperating centers. Subjects of both sexes and 20 years of age or older were eligible. A standardized initial form was filled and from then on, on a yearly basis, for 4 years maximum, a follow up form was filled on each subject indicating his/her state of hypertension related health or whether no data was available for any reason.

The study began with the participation of 6 countries and progressively 4 additional countries entered the study. As a consequence, 6 centers can provide up to 4 years follow up; 15 centers, up to 3 years; 5 centers up to 2 years, and 1 center up to 1 year follow up. The care of the hypertensive patients was left to the criteria of the responsible health personnel.
All the data from cooperating centers, totalling 27, is now (as of March 15th, 1982) in our hands and the final forms from periodic examinations are being keyed into computer files. A complex and very efficient system for error screening and checking for internal consistency of the information is fully operative and is serving as a model for similar processing of data generated at different centers in other studies. It is expected that by June 1982 all the files will be clean of errors and final analysis can proceed.

Nevertheless, even though results are still partial and tentative, some already highlight the final product of this effort.

Results:

Analysis at present is based on a total of 5,228 initial forms. The range of entries to the project by countries is from 99 to 1,824. Thirty six percent of initial subjects are males and 64% are females.

Age distribution is as follows:

- Less than 30 years old: 3.4%
- 30 to 44 years old: 17.2%
- 45 to 64 years old: 59.2%
- 65 years old and more: 20.2%

Upon admission to the project the patient distribution by phases of hypertension as defined by WHO is as follows:

<table>
<thead>
<tr>
<th>Phase</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I (no cardiovascular organ damage)</td>
<td>43.2</td>
</tr>
<tr>
<td>Phase II (only cardiac hypertrophy)</td>
<td>29.1</td>
</tr>
<tr>
<td>Phase III (lesions in end organs are present)</td>
<td>24.8</td>
</tr>
<tr>
<td>Malignant hypertension</td>
<td>0.3</td>
</tr>
<tr>
<td>Unknown</td>
<td>2.6</td>
</tr>
</tbody>
</table>
The blood pressure levels by age groups upon admission are distributed as follows:

<table>
<thead>
<tr>
<th>Age group</th>
<th>Systolic B.P. (mm Hg) mean</th>
<th>S.D. (median)</th>
<th>Diastolic B.P. (mm Hg) mean</th>
<th>S.D. (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 30 yrs.</td>
<td>160.4</td>
<td>22.3 (160)</td>
<td>101.2</td>
<td>15.7 (100)</td>
</tr>
<tr>
<td>30 - 44 yrs. old</td>
<td>169.5</td>
<td>23.4 (170)</td>
<td>106.1</td>
<td>14.5 (102)</td>
</tr>
<tr>
<td>45 - 64 yrs. old</td>
<td>176.5</td>
<td>26.5 (175)</td>
<td>104.5</td>
<td>14.4 (100)</td>
</tr>
<tr>
<td>65 and more yrs.</td>
<td>182.7</td>
<td>25.4 (180)</td>
<td>100.2</td>
<td>14.5 (100)</td>
</tr>
</tbody>
</table>

The following Table summarizes the mean and maximal success rate of follow up of patients in all the centers up to early 1981:

<table>
<thead>
<tr>
<th>Initial</th>
<th>% Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 5,228</td>
<td>1 year 2 years 3 years 4 years</td>
</tr>
<tr>
<td>100%</td>
<td>mean</td>
</tr>
<tr>
<td>---</td>
<td>maximal</td>
</tr>
</tbody>
</table>

Data for the 4th year follow up is still too scanty at this time for any conclusions.

The causes for no follow up are summarized next:

<table>
<thead>
<tr>
<th></th>
<th>1st Year</th>
<th>2nd Year</th>
<th>3rd Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanent cure (%)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death (%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rejection of program (%)</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lost to follow up (%)</td>
<td>96</td>
<td>98</td>
<td>99</td>
</tr>
</tbody>
</table>

These data point out one problem posed in the care of patients with hypertension: Difficulty in following patients. This is because, among
other reasons, hypertension is very often asymptomatic and unless the community and health team work very closely together, are educated in terms of the disease, and are motivated in solving the problem, follow up is poor.

Moreover, of all the subjects, initial and with follow up, who were aware of being hypertensive the proportion who had taken any medication 3 weeks prior to the examination is as follows:

<table>
<thead>
<tr>
<th>Years of knowing of their hypertension</th>
<th>Percent of Subjects taking some medication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>all</td>
</tr>
<tr>
<td>Less than 1 year</td>
<td>75.4</td>
</tr>
<tr>
<td>1 - 2 years</td>
<td>36.5</td>
</tr>
<tr>
<td>3 - 9 years</td>
<td>23.4</td>
</tr>
<tr>
<td>10 or more years</td>
<td>17.6</td>
</tr>
<tr>
<td>All</td>
<td>32.6</td>
</tr>
</tbody>
</table>

Two facts again become evident from this table: 1. As time elapses from diagnosis the proportion of patients taking medication decreases, and 2. The proportion of subjects taking medication is lower as the phase of hypertension is higher; this is independent of the time elapsed from the original diagnosis.

As indicated before, the therapeutic plan and the follow up program was left to the criteria of the different physicians in charge of the care of each patient. Diet alone (low sodium, weight reducing diets) was used in only 1% of patients. Drugs alone were used in 16% of patients. Diet and drug combinations were used in 80% of patients. One percent of patients received either no treatment or was treated by surgery.

The physicians evaluated the patients' compliance with treatment as follows: Depending on the centers between 53 and 69% of patients followed treatment.
regularly during the first year of follow up, and between 55 and 93% during
the second year of follow up. Irregular compliance with treatment ranged
between 26 and 44% for the first year and between 8 and 45% for the second
year. Treatment was fully abandoned by between 0 and 12% among the patients
followed up.

Physicians evaluation of response to therapy in the different centers
for different levels of systolic and diastolic blood pressure on initial
examination is presented in the following table:

<table>
<thead>
<tr>
<th>Initial Blood Pressure (mm Hg)</th>
<th>Range of Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good</td>
</tr>
<tr>
<td>Systolic</td>
<td></td>
</tr>
<tr>
<td>Lower than 160</td>
<td>60-65</td>
</tr>
<tr>
<td>160 - 219</td>
<td>38-55</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
</tr>
<tr>
<td>Lower than 95</td>
<td>60-65</td>
</tr>
<tr>
<td>95 - 119</td>
<td>41-52</td>
</tr>
<tr>
<td>120 and higher</td>
<td>32</td>
</tr>
</tbody>
</table>

With the data available the evaluation of response is no different in
the first or second year follow ups. The data in files for the 3rd and 4th
year follow ups is still too meager at present to make any statements in this
regard. What appears evident is that the higher the initial blood pressure
the higher the rate of inadequate responses, as judged by the physician.

Other forms of evaluating response is by registering:
1. The change in blood pressure as the patients are followed;
2. The relative success in bringing hypertensive patients to or towards
normality, and
3. The relative presence of complications during follow ups.
The validity of these data and its analysis depends on further characterization of the subjects who continued under control and of those lost to follow up. This may be possible once all the data is available in proper form. What follows are just brief examples of future analyses to be performed with the complete data banks. Age, sex, treatment compliance, etc. by centers will be considered in future analyses.

The following tables present the mean changes observed yearly in systolic and diastolic blood pressure in the 45 to 64 year old group of subjects from all centers, based on initial blood pressure levels.

<table>
<thead>
<tr>
<th>Follow-up Date</th>
<th>Initial Systolic B.P. (mm Hg)</th>
<th>1st. Annual</th>
<th>2nd. Annual</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N differences</td>
<td>N differences</td>
<td></td>
</tr>
<tr>
<td>Less than 160</td>
<td>159 + 6.9</td>
<td>62 + 12.1</td>
<td></td>
</tr>
<tr>
<td>160 - 219</td>
<td>589 -17.4</td>
<td>183 - 18.5</td>
<td></td>
</tr>
<tr>
<td>220 and more</td>
<td>42 -48.2</td>
<td>16 - 54.7</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up Date</th>
<th>Initial Diastolic B.P. (mm Hg)</th>
<th>1st. Annual</th>
<th>2nd. Annual</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N differences</td>
<td>N differences</td>
<td></td>
</tr>
<tr>
<td>Less than 95</td>
<td>226 + 2.4</td>
<td>87 + 4.0</td>
<td></td>
</tr>
<tr>
<td>95 - 119</td>
<td>462 - 7.8</td>
<td>125 - 8.3</td>
<td></td>
</tr>
<tr>
<td>120 and more</td>
<td>102 -20.2</td>
<td>36 -33.2</td>
<td></td>
</tr>
</tbody>
</table>

It is evident that the higher the initial blood pressure the greater the fall in subsequent follow ups. A case for regression to the mean is also observed among the groups with lower systolic and diastolic blood pressures.

When the same group of subjects is viewed with regards to changes in initial classification of blood pressure group (normotensive, intermediate
in successive follow up studies, this picture emerges (as % of cases):

<table>
<thead>
<tr>
<th>Initial Group</th>
<th>Fist Follow-up</th>
<th>Second Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Norm.</td>
<td>Interm.</td>
</tr>
<tr>
<td>Normotensive</td>
<td>23</td>
<td>48</td>
</tr>
<tr>
<td>Intermediate</td>
<td>78</td>
<td>18</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>689</td>
<td>14</td>
</tr>
</tbody>
</table>

Again, a regression towards the mean is observed in that 52 to 70% of normotensives and 42 to 57% of Intermediates appear to increase their blood pressures, while 18 and 14% of Intermediates and 38 to 42% of hypertensives fall to lower blood pressure categories. Only 10 to 14% of the hypertensives appear to reach normotensive values.

Finally, if the point prevalence of end-organ damage is analyzed in the initial and first year follow up, another indication of the effectiveness of the management of the hypertensive population under surveillance can be considered:

Disease Conditions Associated to Hypertension in the Total Study Population (Rates per 1,000 Subjects) -

<table>
<thead>
<tr>
<th>Disease</th>
<th>Initial Rate (N = 4455)</th>
<th>Rate at 1st. Follow up (N = 1317)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>26.9</td>
<td>40.6</td>
</tr>
<tr>
<td>Ischemic Heart disease</td>
<td>16.1</td>
<td>20.7</td>
</tr>
<tr>
<td>Renal Disease</td>
<td>7.1</td>
<td>9.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6.7</td>
<td>13.4</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>5.7</td>
<td>6.0</td>
</tr>
<tr>
<td>Cerebro Vascular Accidents</td>
<td>2.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Hypertensive Encephalopathy</td>
<td>2.0</td>
<td>1.9</td>
</tr>
</tbody>
</table>

* Hypertensive: Systolic B.P. 160 or more mm Hg; diastolic B.P. 95 mm Hg or more. Normotensive: Systolic B.P. 120 mm Hg or less; diastolic B.P. 85 mm Hg or less. Intermediate: Between the above levels.
These prevalences point out again the important fact that initially a substantial proportion of hypertensives present related alterations and end-organ damage due to their disease and that this is observed again in the first follow up in slightly higher proportion of subjects. One can not tell at the moment whether this is progression of damage or that subjects with symptoms due to end-organ damage are more constant in seeking medical attention. Probably both situations apply, although as shown before, compliance with medication appears to be poorest among phase III hypertensives.

This schematic analysis of some aspects related to the response of the hypertensive population to the present level of care is not very optimistic. However, the following considerations are pertinent at present:

1. Centers vary in effectiveness and many have improved since the beginning of this study.

2. Present data is only partial and preliminary.

3. Efforts should be directed towards early detection and control of hypertensives since end-organ damage is present in a substantial proportion of first diagnosed hypertensives. The only way to achieve this is through community based programs and massive education, coupled to adequate support of such programs.

4. The follow up of hypertensives and their proper control is a universal problem (not only applies to Latin America) and, therefore, ideally, primary and primordial prevention of hypertension and of cardiovascular disease in general would be highly desirable. Recent developments suggest that this may be possible though dietary and drug interventions. The following section of this document focuses on a project being initiated along these lines.
C. Cardiovascular Risk Factors and their Possible Control.

Several studies carried out in developed countries have defined the relative contribution of certain characteristics of individuals and populations which are associated with a greater risk of clinical cardiovascular disease and/or cardiovascular death (26.-27). These characteristics include:

1. Age. CVD risk increases with age.
2. Sex. Pre-menopausal women have less CVD risk than men of the same ages. After menopause CVD risk increases briskly in women approaching that of men of the same ages.
3. Family history of CVD. Hereditary factors influence CVD: In the case of atherosclerosis through characteristics of carbohydrate and lipid metabolisms and tendency to hypertension. High arterial pressure itself appears to be determined partly by polygenic hereditary factors which may include higher vascular sensitivity to elevated sodium intakes (28-29).
4. Sociocultural-behavioral-lifestyle variables of various kinds have been associated to CVD manifestations. Prominent among these are: smoking (30), alcohol consumption beyond a mild-moderate intake (31), chronic stress (32,33) (for example, associated to inadequate acculturation), sedentarism as the opposite of the beneficial effect of physical exercise in blood pressure and total cardiovascular fitness (34), and last, but most importantly, dietary habits and practices (12,13,35). When faulty dietary habits are associated to certain life styles and to genetic components, obesity and diabetes can occur. These aggravate further other CVD risk factors (26).

The Framingham study (26) in the USA and studies in other countries have suggested that, in terms of events related to ischemic heart disease 60% of the variance can be explained by three risk factors:
1. Hypercholesterolemia due to elevations in the low density lipoprotein cholesterol fraction (LDLC); 2. Hypertension and, 3. Smoking.

These risk factors operate in age-sex-race adjusted populations. In terms of hypertension, age and body mass index showed the greatest numerical correlation with systolic and diastolic blood pressures in step-wise linear regression analysis in North Karelia, Finland, for example (36).

Of the previously indicated CVD risk factors those amenable to modification through public health measures include lipid metabolism, smoking, alcohol intake, chronic stress, sedentarism, dietary habits and practices, obesity, and hypertension control. Different intervention programs have been designed to determine the effectiveness of a reduction in CVD risk factors on morbidity and mortality related to CVD.

Significantly positive effects have been documented at the population level and in the care of special groups with multiple risk factor intervention trials. Some interventions, by reducing more critical risk factors, appear more effective than others:

1. In obese hypertensive individuals, a reduction in body weight is effective in reducing blood pressure. Weight reduction in non-obese individuals however, is not associated to a decline in blood pressure (37).

2. Salt restriction and a higher ratio of K/Na intake is also effective in reducing blood pressure in a proportion of hypertensive subjects (38).

3. A reduction in the intake of saturated fatty acids (S) and an increase in the intake of polyunsaturated fatty acids (P) to a level of 10% or more of total energy intake with a P/S ratio near 1 is effective in causing a lowering of blood pressure, of LDLC and of the tendency to thrombosis as evidenced by lower platelet adhesiveness and aggregability and favorable changes in platelet factors 3 and 4 (39,40). This nutrition intervention has also been demonstrated
to cause increased sodium excretion in humans and animals, increased renal
cortical blood flow and increased glomerular filtration rates (41,42). These
effects can be blocked by inhibitors of prostaglandin synthesis (43).

4. A recently published experience on a double intervention at a
population level, leading to a decrease in fat intake and an increased P/S
ratio on the one hand, and to a significant decline in smoking on the other, has
clearly shown that over 60% of the observed reduction in CVD-clinical events
and mortality could be attributed to dietary changes while no more than 25%
could be attributed to the smoking factor (44).

From all the above considerations, it would appear that the primary
importance of dietary factors in cardiovascular disease is becoming clearer.
Moreover, it is becoming evident that dietary interventions seem particularly
suited for the control of CVD at population levels.

5. On the other hand, recent intervention studies involving the
treatment of hypertensive subjects (45,46) have demonstrated that among mildly
hypertensive patients (diastolic blood pressure between 90 and 104 mm Hg)
reductions in diastolic blood pressure to levels below 90 mm Hg result in a
decline in total mortality. Significantly, total mortality was 17% less among a
carefully followed up group with strict hypertensive care as compared to a
group receiving routine care. Both groups lowered their mean diastolic blood
pressure; however the decline was 5.4 mm Hg greater in the intensively followed
group. On the other hand, the risk of clinical events (fatal or non-fatal)
related to CVD, increases progressively as both systolic and diastolic blood
pressures increase (26). Therefore, a reduction in blood pressure to values
near 120/80 mm Hg in all age-sex categories appears beneficial.

Moreover, there are indications that the decrease in mortality and
morbidity from cardiovascular diseases in the United States is accompanied by
a progressive decrease in serum cholesterol concentrations and, in white populations, by a decline in the severity of atherosclerotic lesions in major vessels (47). The reason behind these changes is still not certain because simultaneous changes in multiple risk factors have occurred, including a change in dietary pattern with time, which has favored the consumption of polyunsaturated fat while operating a reduction in the intakes of refined carbohydrate and total saturated fat (48).

The new knowledge of cardiovascular risk factors and their possible control; our evaluation of CVD mortality and morbidity in the Hemisphere, and our experiences in hypertension control strategies in Latin America, allow us to consider, as very timely, the intensification of research efforts leading to appropriate techniques for the prevention and control of CVD (including hypertension) in our Hemisphere. These efforts can be extremely important for the countries in our Region since they are aimed at reducing the problem of chronic cardiovascular diseases where these have already reached high rates and preventing further development of such diseases in population groups who are still relatively free of them. This is the importance of the collaborative project to be summarized next, and which is in its initial stages.

D. Collaborative Project "Contribution of Dietary and Drug Interventions in the Prevention and Control of Chronic Cardiovascular Disease" (PRECAVAS project).

1. Background:

The scientific basis and justification of the project have been considered in the previous sections of this report. For clarity purposes the main basis for the project are listed:

a) In Latin America and the Caribbean the range of CVD mortality, its characteristics, and its associations with "development" and dietary
variables strongly suggest that CVD risk factors play substantially different roles in different population groups. Their study should yield a wealth of information on CVD risk factors and CVD upon which intervention strategies can be developed.

b) The control of hypertension in Latin America, although possible, is fraught with serious operational difficulties. A community based approach is essential.

c) New knowledge in the area of CVD risk factors strongly suggest that dietary components (primarily fat, cholesterol, saturated and polyunsaturated fatty acid intakes) play an important role in the development of CVD, including hypertension, through modifications of lipoprotein-lipid transport, tendency to thrombogenicity, renal function and vascular reactivity, apparently through prostaglandin synthesis and metabolism. This does not mean that other risk and conditioning factors are to be neglected in considering the problem of CVD, which is a condition resulting from a variety of factors. However, dietary interventions seem most feasible to implement at the population level as a strategy for the control and prevention of CVD.

d) Reduction of diastolic blood pressure, even in mildly hypertensive subjects (which is nearly 75% of all hypertensive populations), is associated to reduced mortality.

2. Objectives:

a) General:

To develop the knowledge and the technology necessary for the definition of strategies and actions in the fields of nutrition and health
care directed towards the prevention and control of chronic cardiovascular diseases tailored to the different conditions and human ecological characteristics existing in Latin America and the Caribbean as well as to their process of development.

b) Specific:

i) To favor the development of common criteria and of a unified methodology among collaborators in Latin America and the Caribbean in the planning and execution of the necessary studies to reach the general objective of the project.

ii) To develop a descriptive epidemiologic base of indicators of cardiovascular risk factors and of their conditioners with emphasis on dietary aspects. This will be achieved by the study of selected population groups in the different countries participating in the project.

iii) To test interventions centered on food intake and on the control of hypertension derived partly from the previous specific objective and directed towards inducing a favorable change in the indicators of cardiovascular risk factors.

3. Definitions:

In this document terms are used which merit a clear definition.

These are:

1) **Conditioners of risk factors**: Conditions which act inducing or modifying the level or the expressivity of a known cardiovascular risk factor. Among these the following can be considered of importance in the project:

   a) Diet and within this, i) Total caloric intake

   ii) Total fat intake
iii) Total intake of polyunsaturated fatty acids and/or saturated fatty acids, and in consequence, the ratio of polyunsaturated to saturated P/S fatty acids.

iv) Refined carbohydrates

v) Starches

vi) Fiber

vii) Sodium and potassium, and the relation of sodium to potassium (Na/K).

viii) Calcium, etc.

b) Habits:  

i) Alcoholism

ii) Smoking

c) Sociocultural conditions and personal stress, including life styles:  

i) Socioeconomic status

ii) Urban or rural life style

iii) Migration-acculturation

iv) Recent stressing events

v) Chronic stress

vi) Physical activity and sedentarism, etc.

d) Pathologies and conditions which are associated and/or modify the development of chronic atherosclerotic disease:

i) Diabetes

ii) Gout

iii) Multiparity and pregnancy

iv) Obesity, etc.
e) Hereditary factors like longevity or the opposite with familiar tendencies.

2) **Risk Factors:** Situations or states which provoke or accelerate the development of atherosclerotic lesions and/or pathologic events fatal or not, consecutive to atherosclerosis. The following are considered:

   a) High blood pressure
   b) Alterations in the transport and metabolism of lipid and carbohydrates.
   c) Situations which favor the development of thrombosis.
   d) Conditions that accelerate or revert the process of atherosclerosis at the cellular level.

3) **Indicators of Risk Factors:** Variables that can be measured and that are related with the state and severity of risk factors. The following can be considered:

   a) Systolic and diastolic blood pressure levels.
   b) Total plasma cholesterol and cholesterol in lipoprotein fractions.
   c) Plasma triglycerides.
   d) Glycemia and glycosylated hemoglobin.
   e) In vivo coagulation tests (bleeding time) and in vitro coagulation tests (Platelet adhesiveness, recalcified clotting time, activity levels of various platelet factors, etc.).
   f) Hematocrit
   g) Synthesis and metabolic capacity of prostacyclines and thromboxanes.

4) **Atherosclerosis:** The pathologic process resulting in thickening of the arterial intima and its consequences. This can be measured in
in autopsy material and can be estimated by special means or radiologic
diagnosis, ultrasound, etc.

5) **Indicators of Atherosclerosis:** History or presence of clinical
subclinical events which occur primarily as a consequence of the
process of atherosclerosis. Among these, the following can be out-
lined:

a) Rose Questionnaire

b) Electrocardiogram which indicate coronary disease

c) Indicators of inadequate arterial circulation, etc.

4. **Hypotheses:**

a) Among the Cardiovascular disease (CVD) conditioners of risk
factors considered in the study, dietary characteristics can explain
the greater proportion of the total variance for blood pressure, serum
lipids, and indices of thrombogenesis within age, sex, and race-
location categories.

b) Within the dietary characteristics considered in the study,
fat intake and fatty acid composition (P/S ratio) account for the
greater proportion of variance attributable to dietary sources in blood
pressure, serum lipids, and indices of thrombogenesis.

c) Blood pressure, serum lipids, and indices of thrombogenesis
are favorably affected by high dietary P/S ratios.

d) Given polyunsaturated fatty acid intakes equal or greater than
10% of total calories, no conditioners of risk factors explain a
significant amount of blood pressure variance, within age, sex, and
location-race categories. In this hypothesis, other conditioners
include other dietary factors such as fiber and sodium intake, life style
characteristics, and personal stressful situations contemplated in the study, history of CVD and related diseases, and obesity.

e) At the population level, the modification of fat intake towards levels resulting in near 25% of the total caloric intake with a P/S ratio near 1 results in a favorable change in blood pressure, serum lipids and indices of thrombogenesis. These fat intake levels and characteristics are the recommended by FAO/WHO (49).

f) The control of the hypertensive population which requires drug treatment is favored by the dietary modifications stated in the previous hypothesis (e).

The following are suggested as possibilities for preliminary exploration: 1. High P/S ratio intakes result in simultaneous favorable effects on blood pressure, serum lipids and indices of thrombogenesis.

2. Populations chronically consuming favorable dietary components which include the group of high polyunsaturated fatty acid intakes, high P/S ratio and high dietary fiber do not show an increase in blood pressure with age.

5. General Design of the Project:

Stage I: Development and testing of common methodology and of operational aspects in 2 pilot areas: One in Mexico and the other in the State of Sao Paulo. The Caribbean area will conduct partial pilot testing of specific methodology. Duration, 8 months.

Stage II: Description and analysis of the epidemiology of chronic cardiovascular diseases, of the indicators of cardiovascular risk factors and of their conditioners in Latin America and the Caribbean. It involves two areas of action:
a) Analysis of the existing information on the epidemiology of chronic cardiovascular diseases, of the factor and indicators of cardiovascular risk and of their conditioners with emphasis on the dietary characteristics which exist in the different countries participating in the project.

b) Cross-sectional study of the epidemiology of indicators of cardiovascular risk factors and of their conditioners and, ideally, of indicators of cardiovascular pathology in selected population groups in Latin America and the Caribbean. As of now, a total of 6 countries or sub-regions are being contemplated (please see below). The population groups would be chosen so to achieve a large range in the dietary characteristics considered crucial in the project: i) Total caloric intake, ii) Fat calories, iii) Polyunsaturated fatty acid intakes, and iv) Polyunsaturated to saturated fatty acid intake ratio (P/S).

It is also expected that these population groups will also vary in cardiovascular morbidity and mortality and in other conditioners of cardiovascular risk factors such as sociocultural conditions, lifestyle, stress, hereditary characteristics, habits (alcohol intake and smoking), etc. The duration of this Stage is estimated to be 6 months in each country.

Stage III: Dietary and drug interventions to diminish the cardiovascular risk factors based on results of Stage II and of collateral studies centered on: 1. Diet and atherosclerosis, and 2. Control of hypertension. Pilot dietary and drug interventions based on WHO/FAO dietary guidelines on fat intake (49) and WHO proposed management of hypertensive patients (50) can be also conducted in one or two areas. The duration of this Phase should be 12 to 18 months in each site.
This project is conceived as a true collaborative intercountry project where data obtained at the local or Center level belong to the scientist in charge and to the Institution where he/she belongs. However, local data will be shared with all the other collaborative scientists and will form a pool of which PAHO will be depository. PAHO's role is essentially that of promoter, facilitator, and collaborator with the group of scientists towards the fulfillment of the project's final objective. Publications and credits derived from publications that come out of local data gathered by this project will be the responsibility and privilege of the local scientists. With regards to Publications which include data from different regions, a council formed by all the scientists who collaborate in the project will designate a responsible person who will produce the publication and will be the first author and speaker for the group in that topic.

It is essential for an effective collaboration that a fluid and permanent system of communications exists. An important part of the project is that of local consultations and then group meetings for the purpose of arriving at a protocol and a methodology that will allow the gathering of essential and basic information in a similar and homogeneous form with proper standardization and control so that the data obtained is comparable in all data banks, be they local or regional. These data should also serve as the basis to collect more information depending on the local interest and available resources.

The project will be financed in part by PAHO funds and in its majority by extrabudgetary funds which should be obtained by the study collaborators as a group. For now, in order to initiate the project and to bring together the interested scientists funds have been obtained from the U.S. Department
of Agriculture, Georgetown University and IBM Corporation.

It is contemplated that the individuals responsible for the project will be: 1) At the level of the country or Center (like INCAP and CAREC), the scientists in charge of the project at the local or regional level; 2) At the central level in Washington, Drs. Fernando E. Viteri, and Jorge Litvak on behalf of PAHO; Dr. John J. Canary on behalf of Georgetown University and Dr. James M. Iacono on behalf of the U. S. Department of Agriculture.

At present, collaborating institutions and scientists are:

a. Argentina: Ministry of Health (Drs. E. C. Balossi and M. del C. Morasso), and through scientific Institutions to be defined shortly. Argentina's participation is highly desirable because of its unique dietary characteristics, besides the scientific know-how available.

b. Brazil: University of Sao Paulo in two branches:
   a) School of Public Health, Department of Nutrition, (Dr. Yaro Candra),
   b) School of Medicine, Department of Medicine, Section of Nutrition and Metabolic Diseases (Drs. J. Dutra de Oliveira and J. E. dos Santos).

c. Chile: Ministry of Health (Dr. H. Rodríguez); Catholic University, Department of Medicine, Section of Nutrition and Metabolic Diseases (Dr. A. Arteaga), and University of Chile, Institute of Nutrition and Food Technology, (Dr. S. Valiente).

d. English Speaking Caribbean: University of West Indies, Department of Medicine (Dr. C.A.C. Grell), and Department of Nutrition, Ministry of Health of Trinidad & Tobago (Dr. N. Byam).

e. Mexico: National Institute of Nutrition, Division of Renal Diseases and Hypertension (Drs. J. Herrera-Acosta and E. Tovar), and Division of Nutrition (Drs. A. Chavez and A. Mata).
It is hoped that in the near future the Institute of Nutrition of Central America and Panama (INCAP) will be incorporated to the collaborating Institutions (Dr. M. A. Guzmán and Lic. R. Flores). The participation of INCAP is also highly desirable because of the dietary characteristics of the sub-region, besides the scientific know-how available. CAREC and CFNI could collaborate also with the University of the West Indies in this project.

6. Data Areas and Sample Sizes and Characteristics:

The main data areas are: 1) Diet characteristics, 2) Sociocultural characteristics, which include life style, 3) Personal stressful situations, 4) Blood pressure, 5) Serum lipids, 6) Indices of thrombogenesis, and 7) Family and personal data including history of CVD and allied disorders and other recognized CVD risk factors.

Additional information will be collected at the population level for the purpose of proper description in accord with the specific interests of the study. This will include urban-rural environment, race, sex, and age composition. Morbidity and mortality data will be gathered when possible.

At least two population groups should be studied in each country. These population groups, including subjects from 6 to 70 years of age, should differ in: 1) Food intake, with emphasis in: a) Total energy intake, b) Percent of fat energy, c) Percent of fat energy as saturated and polyunsaturated fatty acids, and 2) Morbidity and mortality from cardiovascular diseases. Populations thus can be categorized as, i.e. high and low fat intake populations, or high and low saturated fat intake populations, etc.

The purpose of studying these population categories which differ in these critical variables is precisely to try to achieve the greatest range possible in these variables so that correlations with risk indicators are favored.
Similarly, indicators of the atherosclerotic process can be correlated with these variables whenever the previous information is available. In the process of selection of the population categories on the basis of the previously defined criteria all other known conditioners of cardiovascular risk factors should be taken into consideration. In this sense, and taking into account that the analysis of the information will proceed at the individual level, the population categories to be studied should be selected within the natural range of the selection criteria observed in the country of the region. These population categories should also comply with either of the two following conditions with regards to conditioners of cardiovascular risk factors not considered in their selection: a) That the population categories which differ in the critical variables do not vary in the other conditioners that is, that all categories should have the same habits, life style, hereditary and other pathologies and conditions, etc.; this is essentially impossible; or b) That these other conditioners of risk factors vary within each category so that by well-known statistical methods one can control for their effects on the dependent variables which would be used as risk indicators or as indicators of the chronic atherosclerotic process. This is feasible both at the intracountry level as well as in comparisons between countries. The variability of other conditioners of risk factors not used in the selection of the population categories would be favored if, within each category, a series of small and different clusters of population are sampled. It would also be desirable, but not essential, that the variability in all conditioners and risk factors exhibited by the chosen populations is similar to facilitate the adjustment for this variability. Proper statistical techniques can be applied for this purpose. Finally, even when the population categories are chosen on the basis of clear differences of their average energy intake and/or fat intake
and/or the type of fat consumed there will always be a dispersion of these characteristics around the mean in the different population groups. This dispersion will also result in an overlap in these characteristics among the individuals that conform the sample within each of the population categories to be studied. Figure 4, will clarify these concepts.

From the standpoint of the intervention phase (Stage III), the following groups of subjects will be required:

1. Within each population category (i.e. low fat intake or high fat intake) the population will be randomly divided into two groups: control and dietary experimental. For this purpose paired clusters will be randomly assigned to each group.

2. Within each population group, two blood pressure categories will naturally emerge: Those requiring drug intervention (Diastolic Blood Pressure greater than 104 mm Hg) and those not requiring drug intervention. The first group will be close to 4% of the adult population above 20 years of age; 15% of all adults are expected to be hypertensives, and 25% of these will require drug intervention. This results in 4% of all adults.

This is the most limiting group and together with assumed compliances (in two basal examinations and one final examination at the end of one year of intervention) determines the necessity of extra sampling for hypertensive individuals.

As an example, and considering a 15% coefficient of variation in the determinations; an alpha error of 5%; a power of 90%, and an expected change due to the intervention in blood pressure or in any other variable amounting to 10% of the initial value, the annexed sample scheme has been worked out. This is subject to a critical evaluation in the pilot areas.
7. Progress made to date:

a. A proposal for the study has been presented to all collaborators and a workshop was held at PAHO headquarters in Washington from March 22 to 26, 1982. As a result of this workshop preliminary agreements were reached on sites for the Pilot phases (Mexico, Sao Paulo and Jamaica) and on standardization of procedures for all the study.

b. Dr. M. A. Guzmán (Biostatistician) was consulted on sampling and determinations of errors in the study.

c. Dr. W. Dressler (Medical Anthropologist) was consulted on the development of intraculturally meaningful scores of sociocultural and stress variables which can then be used for intercultural comparisons.

d. Mr. P. Gallagher has joined the project as data manager. He has 12 years of experience in this area, working in international research projects.

e. An estimate of cost (tentative) was drawn for the Stages I and II. The contribution of the project to the local units for the Stage I (pilot study) is considered around U.S.$50,000 per site. For Stage II (cross sectional epidemiologic study) the contribution of the project to the local units in each country is estimated at about U.S.$70,000. These amounts constitute near 40% of the total cost. The rest will be contributed by the local collaborating units. Stage III (intervention phase) will probably cost near U.S.$100,000 per country.

f. Technical collaboration has been received from various U.S. and Latin American Institutions. Support for training and for standardization and control procedures have been officially received from the U.S. Department of Agriculture.

g. Sources for financial support of the project are being sought.

8. REFERENCES:

References are available upon request to Dr. F. E. Viteri.
# Sampling Scheme

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<th>Category b.</th>
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<td>2</td>
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_A. (Similar for category b.)_

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<th>Population</th>
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<tr>
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_Sampling exclusively for Phase II:_ Sixty-five subjects in each of 26 sex-5 year range cells covering between 6 and 70 years of age. If 80% comply with the second basal sampling procedure, each cell will have 50 subjects. Total subjects: 1,690 in approximately 520 families. It is estimated 375 families are needed. Sixty-five families from each of the eight clusters in category a. are randomly selected: 65 x 8 = 520. The same procedure would be used for category b.
This sampling procedure will give rise to 1,690 initial blood samples and 1,350 second basal blood samples. Total: 3,040.

At the end of Phase II 1,000 subjects older than 20 years would have been studied. One hundred and fifty hypertensive subjects would be included. Complete information would be available from 420 families (in two periods).

Sampling for Phase III (Intervention): If a compliance of 75% is assumed during Phase III for those who complete Phase II (with two determinations), sampling for Phase II would proceed as follows:

First examination of Phase II: 100% initial

88 subjects per cell = 2,280 total = 1,760 adults older than 20 years.

Hypertensives (15%) = 260

25% Hypertensives with Diastolic B.P. > 104 = 65

Second examination of Phase II: Compliance = 80%

70 subjects per cell = 1,820 total = 1,400 adults older than 20 years.

Hypertensives (15%) = 210

25% Hypertensives with Diastolic B.P. > 104 = 50

The population clusters are separated into dietary experimental and control groups (4 clusters per group). Therefore, each group will have 910 subjects = 700 adults older than 20 years.

Hypertensives (15%) = 105 per group

25% Hypertensives with Diastolic B.P. > 104 = 26 per group.

Final examination of Phase III: Compliance = 75%

50 subjects per sex-10 year span cells = 600 subjects. This number is needed to fill 6 cells (from 11 to 70 years of age); plus 50 subjects between 6 and 10 years of age. A total of 500 subjects per group will be older than 20 years, considering both sexes together.

Hypertensives in each group (15%) = 75

We have defined that it is necessary to compare 200 hypertensive subjects in each group (including 50 with Diastolic B.P. > 104). An additional sample of hypertensive subjects is needed to complete the 200 needed at the end of Phase III. The number would be 125 which, added to the 75 coming from the population sample, would total 200. To accomplish this the following numbers are needed as follows:
170 additional hypertensives must be available after the second basal examination. This means a total of 215 additional hypertensives must be detected on initial screening. Blood Pressure needs to be measured in a sample of 1,500 adult subjects in each group; this means that approximately 750 families per group will need screening. Families will be selected at random taking the total population of each group (control and dietary experimental), excluding the families already chosen for the population sample.

Note: It is difficult to predict the proportion of hypertensive subjects who will already be under medical care upon their selection as subjects in this study. It will vary from site to site. However a decision to include or exclude them in the study can be taken. For Phase II they should be included and identified for a separate analysis. For Phase III, ideally they should be excluded but this can cause sampling complications throughout the study. On the other hand, their inclusion brings serious problems in terms of data analysis along time.
CHANGES IN THE RELATIVE CONTRIBUTION OF CVD DEATHS TO TOTAL DEATHS BETWEEN 1970 AND 1974-79


XCVD MORTALITY RATES HAVE DECLINED
Fig. 3
Mortality from "IHD" and from "HD+CVA" in relation to total CVD mortality 1974-79

Country: [Country Name]

"C": $\gamma = -2.9 + 0.75x$
$\rho = 0.88$

"H+CVA": $\gamma = 7.8 + 0.25x$
$\rho = 0.53$

"IHD": Dis. of the Heart; "HD+CVA": Hypertensive Disease + Cerebro Vascular Accident.
FIGURE 4

Total population
Median: 35%
Mean: 38%
S.D.: 19%

Proportion of fat calories (%)

Category: b
Median: 28%

Areas with concentration of population
groups of categories a and b

Category: a
Median: 40%

Proportion of subjects in the
population groups of categories
(a) (%) (b)

Urban
Rural
Socio Economic level
High
Intermediate
Low
Physical Activity Level
High
Intermediate
Low
Smokers: severe
Intermediate
Low
Level of Personal Stress
High
Intermediate
Low

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