

13

PROGRESS IN CARDIOLOGY

Edited by

PAUL N. YU, M.D., F.A.C.C.

JOHN F. GOODWIN, M.D., F.R.C.P., F.A.C.C., F.A.C.P.

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PREFACE

Volume 13 continues the editorial policy of surveying aspects of importance in cardiovascular disease on a worldwide basis and includes two chapters from Australasia, the Pacific Islands, and Japan, respectively.

Ian Prior gives a searching account of the work done by himself and others on hypertension in the Pacific. He comments on studies in migrant population and on the effects of urbanization in Samoa, Japan, Hawaii, and California. Based on the data that has been collected, he makes a strong appeal for a coordinated community control approach emphasizing measures of hygiene before pharmacologic therapy is instituted. The importance of weight gain and body mass, especially in groups that are migrating or becoming urbanized is stressed. Prior emphasizes that the place of sodium and potassium intake in the control of hypertension requires more research, and indeed these matters will be discussed in Volume 14 of *Progress in Cardiology*. Prior's chapter shows how lessons learned from populations across the world can have an important bearing on the identification of problems and of research at home.

Sekiguchi and his colleagues give in depth treatment to the mucocutaneous lymph node syndrome (MCL), otherwise known as Kawa-

saki disease, based on extensive experience and much original work. Between 1968 and 1982, 47,000 cases were diagnosed in Japan. As a strong data base on this disease these figures are second to none. The authors survey all the features of the disease thoroughly, and it is likely that this chapter will become a standard up-to-date work on the subject. The mucocutaneous lymph node syndrome is a disorder of increasing importance and interest to pediatricians, pediatric cardiologists, cardiologists, and primary health-care workers that cases are being increasingly recognized in the United States and elsewhere. This chapter also emphasizes the useful role that geographic reporting of a disease plays in its management at home.

The remaining four chapters deal with current aspects important to the diagnosis and treatment of other forms of cardiovascular disease. Doppler echocardiography is of increasing interest and importance to the diagnosis of both congenital and acquired heart disease. The latest aspects are covered in an exhaustive, scholarly, and illuminating chapter by Navin Nanda, a well-known expert, who comments on the new fields of color flow mapping, fetal Doppler echocardiography, and Doppler examination of the coronary arteries.

Ischemic heart and cerebral vascular disease are the topics of the other three chapters.

FitzGerald and Friesinger deal with the relevance of the products of arachadonic acid to ischemic heart disease. They point out the limitations of current methodology in many of the tests and conclude that there is little to implicate a critical thromboxane A₂-prostacycline balance in specific cardiovascular syndromes, although admitting that either or both might play a critical role if specific methodology was introduced. They also quote data suggesting that promotion of local endothelial synthesis of prostacycline may be important. They also discuss selective inhibitors of thromboxane synthase that have potential advantages over cyclo-oxygenase inhibitors. The platelet story is continued by Gent and colleagues who analyse the available drugs that inhibit platelet function. As a result of their critical analysis, they conclude that dipyridamole alone has not been shown to be of any value in preventing cerebral or cardiac vascular events, but it is of value in combination with anticoagulants in preventing embolism from prosthetic heart valves, and in combination with aspirin in maintaining patency of coronary artery bypass grafts. Gent and colleagues suggest that there is little evidence to support the value of dipyridamole alone, and that aspirin emerges

the most valuable of the antiplatelet drugs at the moment. This challenging and exciting chapter will undoubtedly invite discussion and perhaps contention.

The chapter by McLeod and Chamberlain surveys in depth and at length all that is known and can be concluded about beta-adrenergic antagonists and their pharmacology and place in therapy. The authors' analysis of the place of beta-adrenergic antagonists in the secondary prevention of myocardial infarction is masterly, and will be of great interest to all practicing physicians who will find useful guidance on which trials to believe, which patients to treat, and which drug to use and for how long after myocardial infarction. The authors wisely point out the pitfalls of a blanket policy of treating all patients who do not have definite contraindications. While by no means all the problems in this area are solved, McLeod and Chamberlain have provided all the answers possible on present evidence to the questions that still remain.

We hope that our readers will find the chapters in Volume 13 up-to-date, useful, challenging, and of current relevance and interest.

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Chapter 1

EPIDEMIOLOGY OF HYPERTENSION

Ian Prior, M.D.

In the past twenty years, the epidemiology of hypertension has greatly contributed to our knowledge of the varying distribution, causation, recognition, and management of the disorder. Studies in populations of similar ethnic origin living in contrasting environments have raised a number of research questions and hypotheses to be tested.

The Pacific nations, including those on the Pacific rim, provide a unique range of opportunities for such research.

This chapter will present some of these data and explore how it has helped give leads to concepts of prevention. At the same time, the realities and difficulties of the prevention of hypertension will be considered.

The World Health Organization's definition of prevention includes primordial, primary, secondary, and tertiary prevention. Primordial prevention, a new term, refers to measures that can be introduced to a community to prevent a risk factor, occurring at a low rate, from increasing and becoming an important contributor to particular disorders. This applies to low-risk populations in countries and communities undergoing changes, such as modernization and migration, which could be expected to lead to an increased level of risk factors. Primary prevention is a more widely understood concept and involves measures to lessen the development of risk factors in individuals and communities.

Coronary heart disease (CHD) is a condition that has commanded the most attention for both

primordial and primary prevention. Hypertension, however, is one of the key risk factors for CHD along with smoking and cholesterol levels.

Pacific studies will be used to illustrate various aspects of the global study of hypertension. The transition from descriptive epidemiological studies to experimental studies testing hypotheses particularly relevant to the possibilities of prevention will be detailed. These aspects include the relationship between blood pressure and body weight and Body Mass Index (BMI) (wt/ht^2); the relationships between blood pressure and dietary factors, including habitual sodium and potassium intake; and those relationships related to life-style factors including alcohol intake. Of particular relevance to the Pacific studies are the effects of urbanization and migration, and the way psychosocial and cultural factors influence blood pressure levels.

Intervention studies, such as the Australia Blood Pressure Trial, which tested the influence of treatment on mild hypertension, represent an important contribution from the Pacific region with results that are relevant on the world scene.^{31,32}

The epidemiology of hypertension must continue to be viewed on a wide perspective in the eighties. It is important to recognize that conditions such as diabetes and gout are associated with hypertension, and that these conditions are of increasing importance in the Pacific, particularly in Polynesians and some of the Micronesian groups including Nauru.^{44,70}

Within the Pacific rim and basin lies the Peo-

ple's Republic of China (population 900 million) and Japan (population 114 million). While information from Japan concerning hypertension and stroke has been available, it is only in recent years that results of epidemiological surveys of blood pressure from the People's Republic of China have become available.⁶⁵ These surveys show some remarkable gradients with low blood pressures and little increase in blood pressure with age in the South around Guangdong, where the age adjusted prevalence of significant hypertension 160/95 and above was 2.44%. Notably higher blood pressure levels and rates of hypertension were found in the northern and northeastern provinces, and the national minority groups such as Tibetians in Lahsa, in whom the age adjusted prevalence of significant hypertension was 17.6%. Higher hypertension rates were found in the urban populations of all regions—the higher the stage of industrialization, the greater the urban rural difference. In the period from 1959 to 1979, there had been a 50% increase in definite and borderline hypertension in areas such as Beijing, where the prevalence rate was 7.44% in 1959 and 13.66% in 1979. In contrast, Southern China, with its millions of people and yet low blood pressures, and its small Pacific atolls such as Pukapuka, typified by low blood pressures among its total population of 900, or the three small atolls that comprise Tokelau, with a population of 1,560, indicates the exciting opportunities and challenges of epidemiology in the Pacific.

THE PACIFIC: ITS PEOPLE AND SOME NATIONAL MORTALITY STATISTICS

The Pacific Ocean is the largest ocean in the world. It is inhabited by continents such as Australia, islands such as Japan and New Zealand, high islands such as Rarotonga and Ponape, and atolls such as Pukapuka and Tokelau. Flanking it lie the Pacific rim countries, including the People's Republic of China, California, British Columbia, Peru, Chile, and others. The wide range of countries and peoples offers a greater contrast of environment, living patterns, cus-

toms, and material resources than exist in any other part of the world. For the epidemiologist, geneticist, demographer, cultural anthropologist, biostatistician, and biochemist involved in multidisciplinary epidemiological studies, this contrast becomes an exciting and central part of work in this region. The map of the Pacific and surrounding Pacific rim countries is set out in Figure 1.

Philosopher Karl Popper, who worked in New Zealand from 1937 to 1945 as senior lecturer in Psychology at Canterbury University said, "Find out where difficulties arise and take an interest in disagreement. These are the questions you should take up." This is certainly relevant for some of the scientific opportunities found within the Pacific.

An estimate of the populations of certain Pacific and Pacific rim countries and smaller territories are illustrated in Table 1. Epidemiological studies of hypertension have been carried out in many of these countries and are referred to throughout this chapter. The wide range of studies in which standard blood pressure measurements have been part of the survey procedure represent a valuable resource and data base as the process and tempo of change extends to all corners of the Pacific. The independence gained by many of the smaller Pacific countries and the growing sense of nationalism that is a necessary part of their growth now make it essential that local people, including medical staff, have a responsible role in such studies. They should help in the collection and interpretation of data, and also in the writing of reports and articles for the scientific literature. They must also take the major responsibility of developing follow-up procedures and interventions that may be considered.

National Mortality Statistics

Mortality statistics provide an important area of base-line knowledge when an epidemiological investigation is being considered and planned. In many of the more traditional areas in the Pacific, health statistics are inadequate, particularly those areas short of doctors where deaths are certified by nurses or the heads of

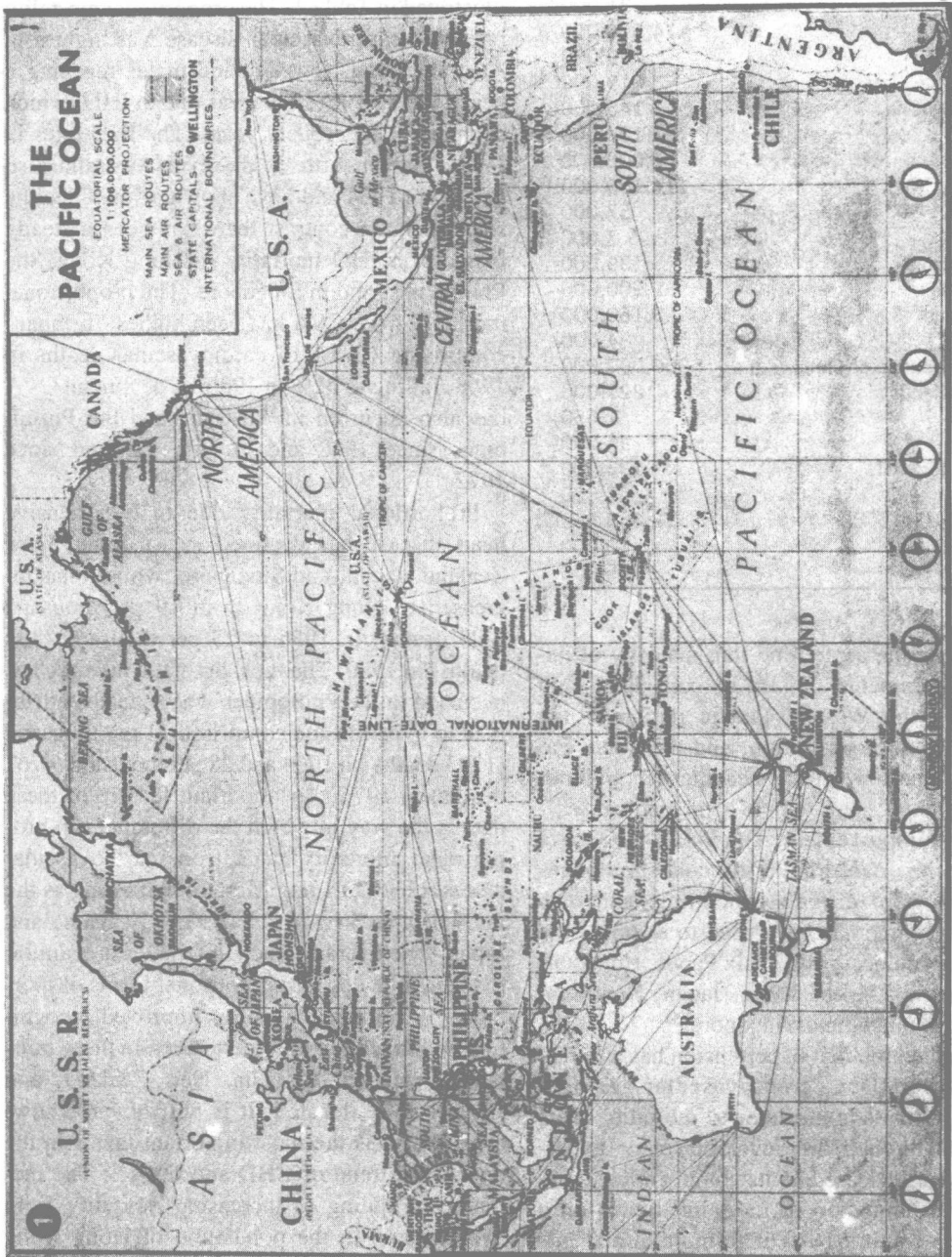


Fig. 1. Map of Pacific and Pacific Basin countries.

Table 1. Estimated Population in Certain Pacific and Pacific Basin Countries

Countries	1979
American Samoa	31,000
Australia	14,516,000
Cook Islands	19,000
Fiji	619,000
French Polynesia	145,000
Guam	100,000
Hawaii	1,000,000
Japan	114,150,000
Kiribati	57,000
Nauru	7,000
New Caledonia	139,000
New Guinea	2,900,000
New Zealand	3,150,000
Nuie	4,000
People's Republic of China	900,000,000
Solomon Islands	221,000
Tokelau	1,650
Tonga	96,000
Trust Territory P.T	133,000
Tuvalu	7,000
California (USA)	23,668,562
Wallis & Futuna	10,000
Western Samoa	155,000

villages. At the same time, the majority of national governments assisted by consultants and staff from the Western Pacific region of the World Health Organization, and the South Pacific Commission with its headquarters in Noumea, are taking steps to help local medical services effect improvement. The WHO in Geneva plays an important role in the collection of information from different countries, and data from this source has been used to examine the trends that are occurring in six Pacific rim countries: Australia, Hong Kong, Japan, New Zealand, Philippines, and Singapore.⁵⁴

The contention that hypertension has as a risk factor for CHD,* cerebrovascular accident (CVA), and as a contributor to mortality in its own right through the development of hypertensive heart disease and its complications, justifies an examination of mortality trends on a country-to-country basis if primordial and primary prevention are to be considered.

The total deaths and proportional mortality

rate per 1000 from different forms of cardiovascular diseases in males of all ages by country for the years 1961, 1968, 1976, and 1980 are illustrated in Table 2. The proportional mortality rate from cardiovascular disease was highest in Australian and New Zealand males reaching a peak level in 1968. This was due to IHD, which declined in subsequent years. The IHD rates in Japan, only a fifth of those in Australia also peaked in 1964 and have shown a small decline since then. In contrast there has been a steady increase in IHD mortality in Hong Kong, the Philippines, and in Singapore. The proportional mortality from CVA has been highest in Japan, comprising 63.5% of cardiovascular deaths in 1968, falling to 52% in 1980. A decline in CVA has also occurred in Australia and the Philippines since 1968 and in New Zealand since 1972.

Proportional mortality due to hypertensive heart disease has declined in Australia, New Zealand, Japan, and Singapore, while it has increased in Hong Kong from 19 per thousand (203 deaths) in 1956 to 23 per thousand (334 deaths) in 1980. The most dramatic increase has occurred in the Philippines where deaths attributed to hypertension comprised 11 per thousand (1293 deaths) in 1964 and 28 per thousand (4767 deaths) in 1976. An important feature of these data is the way in which the differences in proportional mortality rates from cardiovascular diseases between countries are narrowing as the rates decline in Australia, New Zealand, and Japan. The overall trends in females are similar to those in males for proportional forms of mortality.⁵⁴ The part played by improved recognition and treatment of hypertension in these mortality trends in Australia, New Zealand, and Japan can be debated. It is put forward, however, that it is the most important factor in the downward trend of CHD and CVA.⁵⁴ The factors contributing to increasing mortality from hypertension in the population of Hong Kong and the Philippines are likely to include an increase in urbanization, crowding, and changes in life-style, including diet. This hypothesis is being tested in several studies in the Philippines.¹⁸

*Synonymous with ischemic heart disease (IHD) in tables.

Table 2. Number of Total Deaths and Proportional Mortality Rate per 1000 in Different Forms of Cardiovascular Diseases in Males of All Ages by Year and Country

	1961	1968	1976	1980
Australia				
Total deaths	50,248	61,061	62,527	60,518
Proportion of all CVD	519	533	507	483
RHD	7	7	7	3
HPN	21	13	10	10
IHD	327	333	325	303
OHD	28	37	34	45
CVA	104	109	100	94
Hong Kong				
Total deaths	10,294	10,567	12,881	14,522
Proportion of all CVD	172	219	268	263
RHD	7	10	8	6
HPN	23	33	35	23
IHD	40	56	66	76
OHD	25	35	56	39
CVA	69	78	84	114
Japan				
Total deaths	371,858	372,931	378,630	390,644
Proportion of all CVD	343	395	407	401
RHD	6	5	4	2
HPN	21	23	23	17
IHD	66	56	65	69
OHD	21	51	70	94
CVA	223	251	236	209
New Zealand				
Total deaths	11,899	13,508	13,970	
Proportion of all CVD	487	512	481	
RHD	8	11	9	
HPN	17	12	11	
IHD	308	324	318	
OHD	32	42	24	
CVA	94	94	90	
Philippines				
Total deaths		141,730	170,278	
Proportion of all CVD		95	134	
RHD		6	6	
HPN		16	28	
IHD		22	48	
OHD		15	27	
CVA		28	17	
Singapore				
Total deaths		6,625	6,889	7,165
Proportion of all CVD		226	315	333
RHD		5	6	4
HPN		50	16	16
IHD		83	144	178
OHD		33	38	32
CVA		48	101	95

RHD = Rheumatic fever & Rheumatic heart disease

HPN = Hypertension

IHD = Ischaemic heart disease

OHD = Other heart disease

CVA = Cerebrovascular disease

Standardization of Measurements

The World Health Organization has played an active role in the Western Pacific region to encourage standardization of the methods of measuring blood pressure and also improve comparability between different study groups. The wide distribution of the Rose and Blackburn manual when it became available in 1968 has helped in this process.⁵¹ In addition, there have been WHO meetings reviewing cardiovascular epidemiology in the Pacific in Wellington, New Zealand (1970),⁶¹ and Manila (1975)⁶² which have included emphasis on the standardization of methods, including blood pressure measurement. Randon zero sphygmomanometers were tested in 1968¹⁵ and are widely used in the Pacific region.

WHAT ARE THE IMPORTANT QUESTIONS IN THE 1980'S?

Where are the Difficulties and the Areas of Disagreement?

The epidemiology of hypertension in the 1980s includes a number of areas in which our knowledge is inadequate and yet provide important insights into the determinants that influence blood pressure levels in individuals within a community. They hold an important position as we move toward prevention and community control of hypertension. These questions are:

- 1) Why does blood pressure increase with age in the majority of populations but not in low blood pressure populations, now identified in many parts of the world? What are the characteristics of these populations?
- 2) What is the contribution of habitual sodium and potassium intake in the diet to blood pressure levels?
- 3) What are the factors that distinguish low blood pressure populations when they occur in crowded, densely populated cities such as Guang-dong?
- 4) What part does weight, body mass, and weight gain play in setting the blood pressure growth and track?

- 5) What are the effects of urbanization and migration? Is there evidence of a difference in response of systolic and diastolic pressures? Is there a difference in response between males and females?
- 6) To what extent does decreased distensibility and increased rigidity of the aorta and larger arteries play a role in producing elevation of systolic pressures leading to systolic hypertension? Do these vessel wall changes contribute to both systolic and diastolic pressures? What part does cholesterol in the vessel wall play in this?
- 7) How can genetic factors be best identified, and how can genetic versus environmental contributions be characterized?

Some of these issues are discussed below, using work carried out in the Pacific Basin or Pacific rim countries. An historical approach is used when it is appropriate and when it illustrates the progress of knowledge in the area being considered.

Why does Blood Pressure Increase with Age in the Majority of Populations but not in Low Blood Pressure Populations?

Sir George Pickering, in the 1964 St. Cyres Lecture entitled "Hyperpiesis: high blood pressure without evident cause: essential hypertension," stressed the special importance of environmental factors.³⁹ He suggested that the nature and size of the environmental factors determining the rise of blood pressure with age provided a rewarding field for research. He suggested that repeated observations on individuals over 20 to 30 years of age would be particularly instructive. His advice is still very relevant and is encouraging to those working on the problem.

The identification of populations living in a wide range of different climates, with different diets and life-styles, showing little or no increase of blood pressure with age, has been a critical factor in the recognition that hypertension and its sequelae could be prevented if more could be learned about these societies and the determinants of blood pressure within them.

PONAPE

In the Pacific, the first such group studied was the population of Ponape, part of the Eastern Caroline Islands, by R. I. Murrill in 1947.³⁶ He visited villages and recorded blood pressure and weight in adult males and females. Blood pressures were low even in older people and showed little or no increase with age. In 1953, Navy personnel on a health mission to the Eastern Carolines on the U.S. Whitby recorded blood pressures in Ponape and found that blood pressures were again low.⁶

Historically, Ponapeans have a hierarchial society, with traditional classes of leaders, which has survived conquest and occupation by the colonial empires of Spain, Germany, and Japan over a period of 60 years. In 1945, following the defeat of Japan in WWII, the United States took over Ponape as part of a United Nations Trust Territory. The cultural and social changes related to the modernization of Ponape that followed U.S. occupancy, particularly in Kolonia the capital, were the stimulus for another study in 1971.^{8,38}

PUKAPUKA

In 1951, the survey team of the Medical Research Council of New Zealand carried out a general health survey on Pukapuka in the Northern Cook Islands. Pukapuka is a small, isolated traditional Polynesian atoll with a total population of 900. They had a subsistent atoll economy with a low per capita income of approximately 20 dollars per head in 1951 and boat contacts with Rarotonga, the capital of the Cook Islands, three or four times per year. The blood pressures were low in both sexes, with systolic pressures of 110 mm Hg in those men in their twenties, increasing to 114 mm Hg in those men aged 60 to 65 years. The older females showed a greater increase with age than the males, reaching 126 mm Hg in those aged 60 to 65 years. The 1951 team also recorded their own blood pressures at intervals and showed some decline which they attributed to the higher ambient temperatures. No mention was made of the consumption of salt by the Pukapukans, but

they recorded weights and noted that obesity was extremely uncommon.³⁵

PUKAPUKA AND RAROTONGA

In 1964, another visit confirmed the low blood pressures in Pukapuka with little increase with age. This presented a contrast to the blood pressures in Rarotonga which showed similar patterns to those recorded in western societies.^{47,48} The fact that systolic pressures in women in both groups became higher than men in the 35 to 45 age group demonstrated another feature that has been widely described but inadequately understood. It can be seen that the crossover, with the blood pressure levels of females rising above males, occurs around 35 years of age in Rarotonga, but in Pukapuka it occurs around 45 years of age. This clearly relates to the greater rate of rise occurring in the Rarotongan females. The mean systolic and diastolic pressures by age, sex, and island are illustrated in Figure 2.

The traditional life-style of the Pukapukans, the limited resources and reliance on a subsistent economy to produce fish and certain local foods grown with considerable labor costs in areas where there was almost no soil, contrasted with the cash economy, diet patterns and life-style of those in Rarotonga. Rarotonga is a lush, high island with fertile soil and a variety of food imported from New Zealand. There is ready access to canned corned beef, frozen mutton flaps, rice, flour, bread, and local foods such as taro, bread fruit cassava, and fruit that grows readily on the rich soil. The considerable differences in weight between the two groups was expected and is illustrated in Figure 3.

The Rarotongans tended to be taller as well as heavier than the Pukapukans, and in both populations, blood pressure was positively correlated with body weight. Analyses showed that the differences in blood pressure were usually not attributable to differences in body weight. This raised the question of other factors that might influence blood pressure levels, including the habitual use of salt.⁴⁷

Three measures of salt intake were used in this 1964 survey. First, the nutritionist collected information on dietary salt use. Second, casual