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# MEDICAL GEOGRAPHY AND ITS CONTRIBUTION TO THE AETIOLOGY OF RARE SYSTEMIC CONNECTIVE TISSUE DISEASES

A Thesis Presented in Partial Fulfilment of the Requirements for the Degree of Master of Arts in

Geography at Massey University

BY

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#### ABSTRACT

This thesis is in two interrelated parts. Part One traced the historical development of medical geography since the idea of applying a geographical perspective to medical problems was first mooted in 4 B.C. The main trends in the evolving philosophy and methodology of this field were noted, and a distinction was made between the Western and Soviet interpretations of the nature and scope of medical geography. The methods available to medical geographers for cartographically portraying medical data were discussed.

Part Two represented the application of geographical principles to the study of rare systemic connective tissue diseases. The inherent problems of collection. and of verification of the medical data used in this study were detailed. Using cartographic and statistical techniques the diseases under study were spatially and temporally defined. It was found that scleroderma had a statistically significantly high incidence in the Taieri Geographic County, and it was this disease and this area which were the principal contributory factors to the statistically significantly high incidence of all connective tissue diseases at the larger scales of areal units in the Otago region.

The structures of the populations affected by these diseases were also studied, with the findings generally confirming the results obtained in overseas surveys. No association was found between the incidence of systemic lupus erythematosus, and high

(i)

sunshine hours, while the disease subsets did not exhibit a rural or urban bias in their incidence. Paucity of cases precluded a study of the possible racial predilection of the diseases or any association of incidence with a patient's occupation.

Suggested avenues for possible actiological research accruing from this analysis were detailed.

#### PREFACE

Despite the long ancestry of medical geography, the field has only recently shown signs of emerging as a distinct speciality (Armstrong, 1965a). The application of geographic techniques to medical problems is frequently viewed with suspicion and scepticism not only by those in medicine, but also by many fellow geographers. This thesis attempts to demonstrate the utility of such an approach to medical research.

Although in two parts, this work should be regarded as a sequential statement on an integrated project. Part One 'The Field of Medical Geography' introduces the concepts of 'health' and 'disease', while also discussing the 'position' of medical geography on the borderline between the two parent disciplines, medicine and geography. The historical development of medical geography is examined in Chapter Two, with a differentiation being made between the respective Western and Soviet interpretations of the nature and scope of the field. While cartography has evolved to become an integral part of contemporary medical geographic research, this situation has not always prevailed. Chapter Three considers the development of medical cartography, and concludes with a discussion and evaluation of the methods available to a medical geographer for portraying health and ill-health data.

Part Two applies a medical geographic methodology to the study of rare connective tissue diseases within the New Zealand environment. The aim of this survey was to provide a perspective

(iii)

on the natural history of the diseases under study, to suggest clues for further investigative research, to test whether the findings of overseas studies are confirmed by New Zealand data, and to provide an illustrative case study in medical geography. As the quality and quantity of the data available determines the extent of a medical geographic study, and the sophistication of the techniques that can be utilised, the data base is extensively discussed in Chapter Two. Cartographic and statistical techniques were employed to test a number of formulated hypotheses aimed at spatially and temporally defining the diseases. Comparison is also made with overseas studies as to the structure of the populations found to be affected by these diseases.

As medical geography is a tool for research and rarely an end in itself (McGlashan, 1972b), this study must be regarded as only a foundation stage of research into the actiology of connective tissue diseases. Therefore, the conclusions that accrue. from this study are offered as tentative hypotheses for subsequent testing.

This thesis provides evidence of the important contribution that geographers have made to medical research. Due to the multiple aetiology of most diseases, prevention or control can only be achieved through inter-disciplinary co-operation. Medical geographers, with their macroscopic perspective of the environment, and their specific geographical competences, should be considered as integral members of future medical research teams.

(iv)

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(v)

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(vi)

(vii)

# TABLE OF CONTENTS

								Page No.
Abstrac	t		••		••	••	••	(i)
Preface	••	••	••				••	(iii)
Acknowl	edgements	••	••	••	••	••	••	(v)
List of	Tables and	Figu	res	••	••	••		(vii)

### PART ONE

# THE FIELD OF MEDICAL GEOGRAPHY

### CHAPTER ONE

ŧ

HEALTH AND DISEASE	••	1
The Role of Geography in Medical Research	••	3
CHAPTER IWO		
THE HISTORICAL DEVELOPMENT OF MEDICAL GEOGRAPHY	••	9
A History of Western Medical Geography	••	9
Classical Medical Geography	••	10
Medical Geography in the Sixteenth and Seventeenth Centuries		12
Medical Geography in the Eighteenth Century		14
Medical Geography in the Nineteenth Century		15
Medical Geography in the Later Nineteenth and Early Twentieth Centuries	••	17
Medical Geography Since 1945	••	20
Medical Geography in the Contemporary Era	••	24
The Evolution of Medical Geography in the U.S.S.R.	••	26
The Late Nineteenth Century	••	27
The Advent of Soviet Medical Geography	••	28
The Emerged Speciality: Soviet Medical Geography Since 1945		29
Centuries in Theory. Decades in Practice!		34

(viii)

### Page No.

### CHAPTER THREE

CARTOGRAPHIC ANALYSIS AS A RESEARCH TOOL IN MEDICAL

GEOGRAPHY		••	••	••	37
The Genesis of Medical Mapping	••	••	••	••	38
Cholera Cartography			••	••	41
Attempts at Global Disease Mappin	ng	••		••	48
The Later Nineteenth and Early T	wentie	th Cent	uries		49
Disease Cartography in the Conter	nporar	y Era	••	••	54
World Atlases		••	••	••	54
Developed Countries		••			58
Underdeveloped Countri	0S		••	••	65
Disease Maps by Computer	••	••		••	70
Methodological Considerations in	the D	isplay	of Heal	.th	
or Ill-Health Data	• •		••		71
Dot Mapping		•••	••	••	72
Rate Mapping	• •		••	••	73
Isolines	••	••	••	••	77
Probability Mapping			••		82
Graphs and Diagrams	••			••	85
Medical Geographic Mode	els		••	••	86

### PART TWO

### THE MEDICAL GEOGRAPHY OF CONNECTIVE TISSUE DISEASES

### CHAPTER ONE

INTRODUCT	TON	••	••	••	89
The Rationale for a Medical Geo	graphi	c Study	of		
Connective Tissue Diseases	••	••	••	••	89
The Aim of the Present Study	••		••	••	90

	- 2	1		- 1
	-	- *	γ.	- 1
- 14.5	<u></u>	. 1	<u>.</u>	- 2
	_		~	

Page No.

The Connective Tissue Diseases	••	••	91
The Principal Clinical Characteristics of th	e Connec	tive	
Tissue Diseases	••	••	92
Systemic lupus erythematosus	••	••	92
Polyarteritis nodosa	••	••	94
Scleroderma	• •	••	95
Polymyositis	••	••	96
Non-specified Connective Tissue Di	sease	••	97
Human Populations Affected by Connective Tis	sue Dise	ases	97
Systemic lupus crythematosus			98
Polyarteritis nodosa		••	99
Scleroderma	••	••	99
Polymyositis and Dermatomyositis	••		101
Causative Hypotheses of Connective Tissue Di	seases		102
Systemic lupus erythematosus		• •	102
Polyarteritis nodosa			103
Scleroderma			104
Polymyositis and Dormatomyositis			104

## CHAPTER TWO

THE DAT	LA BASE	••	••	••	106
Mortality and Morbidity	• ••	••		••	108
Source of Medical Morbidity	Data	••	••	••	109
Collection of Morbidity Data	••				111
Diagnostic Confirmation of I Physician Bias in Recording	Oefinite 	Cases and	the 	Reduction	<u>of</u> 113
Admission and Onset	•••		••		115
Confirmation of Location at	Onset	••	••	••	117
Communication with Patients	••	••	••	••	122
Case Numbers		••	••	••	123

Populatio	n-at-Risk	ç						Page No. 124
	Populati	lon-at	-risk at	the	County Sca	le	••	124
	Populati	on-at	-risk at	the	Hospital B	oard		
	Scale	••	••	••	••	••	• •	125
	Populati	ion-at	-risk at	the	'Regional'	Scale		125
Base Map	••	••		••	••		••	126

### CHAPTER THREE

THE SPACIO-TEMPORAL DEFINITION OF	F CONNECTIVE	TISSUE	DISEASE	127
Method of Analysis		••	••	127
Spatial Analysis				128
Temporal Change		••	••	1 32
Areal Units			••	133
The Spatial and Temporal Definit:	ions of Conn	ective !	lissue	
Disease	•• ••	• •		136
Connoctive tissue disc	asos	••	••	1 36
Systemic lupus erythem	atosus	••		167
Polyarteritis nodosa	•• ••			186
Scleroderma		••		198
Polymyositis and Derma	tomyositis	••	••	216
Possible Bias from the Availabil:	ity of Manpo	wer Res	ources	231
Summary				234

## CHAPTER FOUR

	GEOGRAPHICAL	EVIDER	ICE ON	MEDICAL	HYPOTH	ESIS	••	238
Sex	••	••	••		••			238
Age a	at Onset	••	••		•••	••		239
	Connecti	ve Tis	sue Di	seases	••	••	• •	240

(x)

(xi)

### Page No.

Age at Or	nset cont	inued		4				
	Systemic	o lupu	s erythe	matosus		••	••	241
	Polyarte	eritis	nodosa	••		• •	••	241
	Sclerode	erma	••	••	••	••	••	242
	Polymyos	sitis a	and Derm	atomyos	itis	••		243
Race	••	••	••		••	••	••	244
Rural and	d Urban D:	istribu	itions	• •	••	••	••	245
Occupati	on	••	••		• •	• •	••	247
Connecti	ve Tissue	Disea	ses and	Sunshin	0			250
	Method	••	••		• •		• •	250
	Results	••	••	••	••	••	••	251
Summary					••			254

# CHAPTER FIVE

CONCLUSTON		257
CONCHORTON:	 	 621

### APPENDICES

Appendix	A:	The Scoring Systems used in the Survey	••	261
	B:	The Data Sheet	••	283
	C:	Public Hospitals Visited for Data	••	290
	D:	The Poisson Distribution		291
	E:	Case Numbers for Geographic Counties and Hospital Board Districts		292
	F:	Populations-at-risk for Geographic Count	ies	
		1951, 1961 and 1971 Census		295

BIBLIOGRAPHY .. .. .. .. .. 297

(xii)

Page No.

# LIST OF TABLES

I	Percentage distribution of the total connective tissue disease cases within the main cities of the study area	1 38
II	Percentages of the total cases of connective tissue diseases in each region	140
III	Crude incidence rates of connective tissue diseases per 100,000 population-at-risk (1971) by regions	141
IV	Cases of connective tissue diseases with enset in a specified time period	163
V	The number of cases of connective tissue disease with onset in respective time periods by Hospital Board Districts	166
VI	Ratios of medical staff to the population-at-risk in the principal Hospital Board Districts of the study area	232
VII	Male and female composition of each connective tissue disease subset	239
VIII	Percentages of connective tissue disease patients in different racial groups	245
IX	Percentages of total connective tissue diseases in the urban areas	246
Х	Urban and rural case distribution of each connective tissue disease subset	247
XI	Significance test of the correlation between the spatial distribution of connective tissue diseases and sunshine hours	252
XII	Significance test of the correlation between the spatial distribution of polyarteritis nodosa and surphing hours	253
XIII	Significance test of the correlation between the spatial distribution of scleroderma and sunshine	6JJ
	hours	253

(xiii)

Page No.

XIV	Significance to	est of th	e correlation	between	the	
	spatial distril	oution of	polymyositis	and der	na-	
	tomyositis and	sunshine	hours	••		254

(xiv)

# LIST OF FIGURES

Page No.

# Figure

1	One of the first spot maps used by Seaman (1798, Plate 1) to depict yellow fever in New York in 1796	40
2	Shapter's map (1849) of the deaths from cholera in Exeter in 1832-34	43
3	Petermann's cholera map (1852) of the British Isles showing areas affected in 1831-3	45
24.	Snow's dot map (1855) of cholera mortalities in the Broad Street area of London in September 1854	46
5(A)	Bentley's map (1916) of malaria distribution in the Indian province of Bengal	52
5(B)	Bentley's map (1916) of population change in the Indian province of Bengal which shows the differential effects of malaria on the population	53
6.	Map of S.M.R.'s for males from bronchitis in England and Wales, 1948-57	59
7	Male S.M.R.'s from bronchitis, 1954-8, portrayed on a geographical base map	62
8	Male S.M.R.'s from bronchitic, 1959-63, portrayed on a demographic base map	63
9(A)	A dot distribution map of blind persons in the Luapula province of Zambia	74
9(B)	A 'rate' map of blind persons in the Luapula province of Zambia	75
10	Isopleths of S.M.R.'s for males (1965-66) from pneumonia in Australia	79
11	Areas of high S.M.R.'s for males from pneumonia in Australia in 1959-63 and 1965-66	80
12(A)	A 'rate' map of the occurrence of brain tumours in the counties of the Rzeszow District of Poland	83
12(B)	A map showing areas of the Rzeszow District of Poland with statistically significant divergences of the number of observed cases of brain tumours from expected cases	84

### Page No.

Figure 13 Location of study area 107 Spatial distribution of connective tissue disease cases ... 14 137 Crude incidence rates per 100,000 population (1971 census) 15 of connective tissue disease by Hospital Board Districts 144 16 Significant divergence of observed from expected numbers of cases of connective tissue disease by Hospital Board Districts, 1971 census 145 • • .. . . . . . . 17 Crude incidence rates per 100,000 population (1971 census) of connective tissue disease by Geographic Counties 147 18 Significant divergence of observed from expected numbers of cases of connective tissue disease by Geographic Counties. 1971 census .. 149 . . . . . . . . 'Iso-prob' map of connective tissue disease cases 19 151 . . 20 Crude incidence rates per 100,000 population (1961 census) of connective tissue disease by Hospital Board Districts 154 21 Crude incidence rates per 100,000 population (1951 census) of connective tissue disease by Hospital Board Districts 155 22 Significant divergence of observed from expected numbers of cases of connective tissue disease by Hospital Board Districts, 1961 census 156 .. .. . . Significant divergence of observed from expected numbers of 23 cases of connective tissue disease by Hospital Board Districts, 1951 census 157 .. ... . . . . Crude incidence rates per 100,000 population (1961 census) 24 of connective tissue disease by Geographic Counties 158 25 Crude incidence rates per 100,000 population (1951 census) of connective tissue disease by Geographic Counties 159 . . 26 Significant divergence of observed from expected numbers of cases of connective tissue disease by Geographic Counties. 1961 census .. 161 . . . . • • • • •• 27 Significant divergence of observed from expected numbers of cases of connective tissue disease by Geographic Counties, 1951 census .. 162 . . •• .. .. 28(A) Connective tissue disease - number of case onsets (both sexes) per year of study time period 164 .. .. . .

# (xvi)

Figure

28(B	) Connective tissue disease - cumulative percentage histogram of case onsets per year	164
28(0	) (i) Connective tissue disease - number of male case onsets per year of study time period	165
	(ii) Connective tissue disease - number of female case onsets per year of study time period	165
29	Spatial distribution of systemic lupus erythematosus cases	168
30	Crude incidence rates per 100,000 population (1971 census) of systemic lupus erythematosus by Hospital Board Districts	170
31	Significant divergence of observed from expected numbers of cases of systemic lupus erythematosus by Hospital Board Districts, 1971 census	171
32	Crude incidence rates per 100,000 population (1971 census) of systemic lupus erythematosus by Geographic Counties	173
33	Significant divergence of observed from expected numbers of cases of systemic lupus erythematosus by Geographic Counties, 1971 census	174
34	Crude incidence rates per 100,000 population (1961 census) of systemic lupus erythematosus by Hospital Board Districts	176
35	Crude incidence rates per 100,000 population (1951 census) of systemic lupus erythematosus by Hospital Board Districts	177
36	Crude incidence rates per 100,000 population (1961 census) of systemic lupus erythematosus by Geographic Counties	179
37	Crude incidence rates per 100,000 population (1951 census) of systemic lupus erythematosus by Geographic Counties	180
38	Significant divergence of observed from expected numbers of cases of systemic lupus erythematosus by Geographic Counties, 1961 census	181
39	Significant divergence of observed from expected numbers of cases of systemic lupus erythematosus by Geographic Counties, 1951 census	182
40(A	) Systemic lupus erythematosus - number of case onsets per year of study time period	183
40(B	) Systemic lupus erythematosus - cumulative percentage histogram of case onsets per year	183

# (xvii)

Page No.

Figure		
40(C) /	Systemic lupus erythematosus - number of female case onsets per year of study time period	184
41	Spatial distribution of polyarteritis nodosa cases	187
42	Crude incidence rates per 100,000 population (1971 census) of polyarteritis nodosa by Hospital Board Districts	189
43	Crude incidence rates per 100,000 population (1971 census) of polyarteritis nodosa by Geographic Counties	190
<u>4</u> 4	Crude incidence rates per 100,000 population (1961 census) of polyarteritis nodosa by Hospital Board Districts	192
45	Crudo incidence rates per 100,000 population (1951 census) of polyarteritis nodosa by Hospital Board Districts	193
46	Crude incidence rates per 100,000 population (1961 census) of polyarteritis nodosa by Geographic Counties	194
47	Crude incidence rates per 100,000 population (1951 census) of polyarteritis nodosa by Geographic Counties	195
48. <b>(</b> A)	Polyarteritis nodosa - number of case onsets per year of study time period	197
48(Б)	Polyarteritis nodosa - cumuluative percentage histogram of case onsets per year	197
49	Spatial distribution of scleroderma cases	199
50	Crude incidence rates per 100,000 population (1971 census) of scleroderma by Hospital Board Districts	201
51	Significant divergence of observed from expected numbers of cases of scleroderma by Hospital Board Districts, 1971 census	202
52	Crude incidence rates per 100,000 population (1971 census) of scleroderma by Geographic Counties	204
53	Significant divergence of observed from expected numbers of cases of scleroderma by Geographic Counties, 1971 census	205
54	Crude incidence rates per 100,000 population (1961 census) of scleroderma by Hospital Board Districts	207
55	Crude incidence rates per 100,000 population (1951 census) of scleroderma by Hospital Board Districts	208

# (xviii)

Page No.

Figure		
56	Significant divergence of observed from expected numbers of cases of scleroderma by Hospital Board Districts, 1961 census	209
57	Significant divergence of observed from expected numbers of cases of scleroderma by Hospital Board Districts, 1951	210
	census , , , , , , , , , , , , , , , , , ,	210
58	Crude incidence rates per 100,000 population (1961 census) of scleroderma by Geographic Counties	211
59	Crude incidence rates per 100,000 population (1951 census) of scleroderma by Geographic Counties	212
60(A)	Scleroderma - number of case onsets per year of study time period	214
60(B)	Scleroderma - cumulative percentage histogram of case onsets per year	214
61	Spatial distribution of polymyositis and dermatomyositis cases	217
62	Crude incidence rates per 100,000 population (1971 census) of polymyositis and dermatomyositis by Hospital Board Districts	219
63	Significant divergence of observed from expected numbers of cases of polymyositis and dermatomyositis by Hospital Board Districts, 1971 census	220
64	Crude incidence rates per 100,000 population (1971 census) of polymyositis and dermatomyositis by Geographic Counties	222
65	Significant divergence of observed from expected numbers of cases of polymyositis and dermatomyositis by Geographic Counties, 1971 census	223
66	Crude incidence rates per 100,000 population (1961 census) of polymyositis and dermatomyositis by Hospital Board Districts	225
67	Crude incidence rates per 100,000 population (1951 census) of polymyositis and dermatomy ositis by Hospital Board Districts	226
68	Crude incidence rates per 100,000 population (1961 census) of polymyositis and dermatomyositis by Geographic Counties	227
69	Crude incidence rates per 100,000 population (1951 census) of polymyositis and dermatomyositis by Geographic Counties	228

Pap

Figure		
70(A)	Polymyositis and dermatomyositis - number of case onsets per year of study time period	230
70(B)	Polymyositis and dermatomyositis - cumulative percentage histogram of case onsets per year	230
71	Age-sex structures of connective tissue diseases	240a
72	Significancetest of the correlation between the spatial distribution of systemic lupus erythematosus and sunshine hours	2510

# PART ONE

# The Field of Medical Geography

### CHAPTER ONE

### HEALTH AND DISEASE

The preamble to the World Health Organisation defines health as

"a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity."(1)

To Le Riche and Milner (1971, 81) this statement is

"euphonious, well-meaning and full of splendid idealism, but...it has very little tangible meaning. Perhaps it had better be regarded as a desirable ideal, rather than a definition of a particular condition in mankind."

Health is merely a concept and its standards will vary in different parts of the globe depending upon the availability of medical facilities, the acquisition of knowledge, and the dynamic impact of change in man's environment. Its real measure is the ability of the individual to function in a manner acceptable to himself and in harmony with factors likely to create stress upon his body (Le Riche and Milner, 1971). Health, as May (1958, 1961) suggests, is a complete adjustment of the organs of the body to each other and to environmental conditions. Here environment refers to those forces which act upon the living tissues, namely, both the natural (physical and biological) and socio-cultural realms of man. Conversely, when there is a disruption of this equilibrium disease will manifest itself. Thus disease is

"a maladjustment of the living cells to their environment" (May, 1958, 29).

Disease causation is rarely the consequence of a single, active, harmful factor but rather of a multiple actiology. Of the numerous factors that may influence the occurrence of disease, however, two principal groups can be distinguished: endogenous factors or those which are inside the organism (e.g. the inherited constitution of the organism), and exogenous factors or those which are outside the body.<sup>2</sup> Therefore, if disease is viewed as the result of disruption of a state of balance between organism and environment, it may arise, according to Shoshin (1968, 9), in any of the following situations:

"firstly, when significant endogenous changes take place within the human organism which cannot be compensated by external factors; secondly, when sharp changes of external factors take place and the defensive resources of the organism are unable to ensure the requisite balance; thirdly, when there occur changes of both endogenous and exogenous environmental factors."

In each of these situations there are three basic components which can act in various combinations:

- a) the human organism with its accompanying endogenous factors;
- b) the reactivity and immunity of that organism; and
- c) the exogenous environmental factors.

Disease, or groups of diseases, result from the interaction of these three factors. Endogenous and exogenous factors therefore, will not only determine the patterns of occurrence of disease, or groups of diseases, but also their severity and spacio-temporal extent. Thus it may be better to think, as Banta and Fonaroff (1969, 88) suggest, of

"...degrees of health rather than of disease <u>per se</u>" in which there is a continuum ranging from extreme maladjustment or death through slight illness to perfect adjustment (which would only rarely be attained in most human lives). Among populations, the degree of maladjustment is reflected crudely in morbidity and mortality indices which vary in rate through time and space.

### The Role of Geography in Medical Research

By identifying the factor or group of factors, which, in combination, cause overt disease (or disrupt the balance of the organism with its environment) the first step is taken toward an understanding of the causation of disease. It then becomes possible, in the second step, to remove either that factor or one of those in a combination, and thus hopefully break the causative chain (Muir Grieve and Maytham, 1963). Geography can make an important contribution to the field of medical science, particularly in the first step, the identification of the disease causing factor or factors.

Medical geography may be defined as the study of the spatial variations and temporal changes of health and ill-health and

identifying causal relationships with the geographical environment. As a peripheral area of research, between the fields of geography and medicine, medical geography overlaps research areas of those disciplines within medical science which similarly investigate disease-environment relationships. Each field does, however, have a different emphasis.

Geographical pathology,<sup>3</sup> as defined by Doll (1959, 11), .

"is the comparative study of the incidence of disease and the distribution of physiclegical traits in peoples belonging to different communities throughout the world and the correlation of these data with features of the social and geographical environments."

Avtsyn and Javoronkov (1968) claim that the principal distinguishing feature between medical geography and geographical pathology is that the former studies the total geographical environment whereas the latter investigates the reaction of the organism to that environment.

Epidemiology<sup>4</sup> is a similar search for disease actiology but with emphasis upon the kinds, and structure of the affected populations. Schwabe (1969, 160) succinctly states

"epidemiology is the study of diseases in <u>populations</u> of organisms - often with the object of their prevention or control."

Morris (1967, 275) believes that the utility of this research field derives

"...from the principle that in epidemiology whole 'populations' (or their samples) are studied and compared, and not particular individuals or patients."

Audy (1958, 102) questions the suitability of the term 'medical geography' as a name for the study of the distribution of diseases

over the world and their behaviour in any one community. According

to him

"clear thinking may be hindered by emphasis on geography, which is associated in our minds with large scales and exotic places..."

He, therefore, proposes the use of the term 'medical ecology' to describe

"... the study of populations of man with special reference to environment and to populations of all other organisms as they affect his health and his numbers."

May (1952, 1967b) similarly has urged replacement of the term 'medical geography', with the 'ecology of health and disease'. This latter term he suggests (1952, 2)

"...stresses the fact that this is primarily a study of environmental factors, and that the study of the environment of health cannot be separated from the study of the environment of disease, and that physiology cannot be separated from pathology if the latter is to be understood."

Learmonth (1970, 7) by defining medical ecology as

"the study of the web of relationships of a disease or disease complex in its physical and social environment on ecological sites",

finds the two fields of medical geography and medical ecology complementary though distinguishable. Medical geography in this terminology becomes an extension of medical ecology dealing with larger communities at the macro-geographic scale (Audy, 1958).

In light of the foregoing comments it is apparent, in Banta and Fonaroff's words (1969, 91), that

"disciplinary boundaries, for what they are worth, are hazy here, and hopefully will remain so."

Due to the multiple actiology of most diseases, achieving

"the alleviation of human suffering and the eventual climination of disease" (Muir Grieve and Maytham, 1963, 38),

will involve inter-disciplinary co-operation. McGlashan (1972b, 14) observes that

"collaborative effort as co-members of an inter-disciplinary team is likely to yield best results and even the disciplines represented will vary with the individual problem which requires solution."

Whereas Schwabe (1969, 64) simply states that

"inter-disciplinary co-operation - the team approach - is the keystone of public health practice."

The initiation of any new evidence that may contribute to breaking the disease causative chain and/or prophylactic measures being formulated should be sufficient justification for conducting research whether in medical geography, geographical pathology, epidemiology, or medical ecology. Possibly the only way in which researchers in these fields can be distinguished from each other is by the discipline in which they have received their training. With a medical geographer his trained competence lies in geography and he is first of all a geographer (Learmonth, 1970, 8), whereas a geographical pathologist, according to Avtsyn and Javoronkov. (1968, 278) is first of all a doctor and a pathologist with a wide scope of interests.

The role of the medical geographer is to make the skills and techniques of geography available to medical science, but in no way to usurp the functions of workers in that field. McGlashan (1966a, 1969c, 1972b, 1973) has detailed four tasks which enable the geographer, through his training and experience, to make a valuable contribution to medicine:

a) to prepare and collate disease data and to map them to show their spacio-temporal distributions;

 b) to apply objective statistical tests to these distributions to assess whether or not the pattern is likely to have occurred by chance;

c) to measure the degree of co-extensiveness between disease and other spatially and temporally varying factors. Generally the geographer will utilise medical hypotheses concerning disease actiology as starting points for this further investigative stage; and

d) to test whether the spatial or temporal associations that may have been shown could be causative.

Doll (1959, 1967), Hill (1965), and Hopps and Cuffey (1969) have drawn attention to the difficulties of establishing disease causality. In medical goography this problem assumes a greater complexity due to geography's inevitable generalisations about space and the interrelatedness of variables within that space. Therefore, as McGlashan (1973, 220) has noted, hypothetical relationships formulated in medical geography must also be generalisations. Despite analysing many factors the one critical factor may not be considered in a medical geographic analysis because of data insufficiency or the inherent constraints of the study. For these reasons medical geographic studies may produce inconclusive answers. Nonetheless, the establishment of one new hypothesis or a positive or negative finding for a

current hypothesis for disease actiology will be of value to medical science.

Medical geography is a 'tool for research' (Stamp, 1964a, 1964b) and rarely an end in itself. The consequence of medical geographic studies should be the provision of pointers for further research in other specialists fields, e.g. geobotany, geology and the medical sciences. As McGlashan (1972b, 14) states regarding hypotheses postulated in medical geographic studies

"the confirmation meeded for such hypotheses will lie with a discipline which, rather than the group, studies each individual case."

With the continuing assimilation of quantitative analysis into geography, the increasing availability of the basic data (and refinement into a form applicable for utilisation in medical geographic studies), and the improvement in facilities for storing and processing that data, this tool is likely to become even more useful.

#### CHAPTER TWO

### THE HISTORICAL DEVELOPMENT OF MEDICAL GEOGRAPHY

In this historical survey, Vestern medical geography and Soviet modical geography are considered as separate developing entities. Cognisance may therefore be taken of the respective environments in which the field has evolved, historical trends will be discernible, and a basis provided for a comparative evaluation of the respective contemporary 'positions' of Western and Soviet medical geography.

### A History of Western Medical Geography

As long as man has lived on this earth disease has undoubtedly plagued him. Castiglioni (1958, 13) states this in observing that

"... the investigations of palaeopathology (that is, scrutiny of the history of disease and its norbid manifestations in prehistoric periods) have demonstrated that almost synchronously with the first manifestations of life on the earth there are indubitable evidences of disease."

The earliest references of outbreaks of epidemic diseases known in literature, are probably those relating to the epidemic that made the Philistines return the Ark of the Covenant to Israel about 1100 B.C., the Plagues of Egypt and the Israelites, the various outbreaks of leprosy, and the Plague of Athens in 430 B.C. While supernatural forces and the wrath of God were regarded as causes of diseases,

however, there was little reason to consider the problem of the relation of the environment to disease. •

### Classical Medical Geography

With the advent of scientific medicine in Greece during the fifth and fourth centuries B.C. the geographical distribution of human disease, and, by implication, its association with environmental factors became known to man.

The authorship of the treatise <u>Airs, Maters and Places</u> in the <u>Corpus Hippocraticum</u> has been the subject of much debate.<sup>5</sup> Whether it was written by Hippocrates hinself or. by one of his intimate pupils, this work shows a clear appreciation of the relationship of the geographic environment to disease. A summary of the work is given in the following translation of the first two paragraphs made by Francis Adams for the Sydenham Society (1849):<sup>6</sup>

"Whoever wishes to investigate medicine properly, should proceed thus: In the first place, consider the seasons of the year, and what effect ach of then produces (for they are not all alike, but differ much from themselves in regard to their changes). Then, the winds, the hot and the cold, especially such as are common to all countries, and then such as are peculiar to each locality. We must also consider the qualities of the waters, for, as they differ from one another in taste and weight, so also for they differ much in their qualities. In the same manner, when one comes into a city to which he is a stranger, he ought to consider its situation, but it lies as to the winds and the rising sun, for its influence is not the same, whether it lies to the north or to the south, to the rising or the setting sun. These things one ought to consider nost attentively, and concerning the water which the inhabitants use, whether they be marshy or soft, or hard, and running from elevated and rocky situations, and then if saltish and unfit for cooking. And the ground, whether it be naked and deficient in water, or wooded and well watered, and whether it lies in a hollow,

confined situation or is elevated and cold. And the mode in which the inhabitants live and what are their pursuits, whether they are fond of drinking and eating to excess, and given to indolence, or are fond of exercise and labour, and not given to excess in eating and drinking.

From these things, he must proceed to investigate everything else. For if one knows all things well, or at least the greater part of them, he cannot miss knowing when he comes into a strange city either the diseases peculiar to the place or the particular nature of common diseases, so that he will not be in doubt as to the treatment of the diseases, or commit mistakes, as is likely to be the case, provided one had not previously considered these matters. And in particular, as the season and the year advance, he can tell what epidemic diseases will attack the city, either in summer or in winter, and what each individual will be in danger of experiencing from the change of regimen. For, knowing the change of the seasons, the risings and settings of the stars, how each of them takes place, he will be able to know beforehand, what sort of year is going to ensue. Having nade these investigations, and knowing beforehand the seasons, such a one must be acquainted with each particular and must succeed in the preservation of health, and be, by no means unsuccessful in his art. And. if it shall be thought that these things belong rather to noteorology, it will be admitted, on second thought, that astronomy contributes not a little, but a very great deal, indeed, to medicine. For with the seasons, the digestive organs of men undergo a change."

The author indicated the great complexity of factors relative to disease and recognised that there were diseases which were always present in a population (endenic diseases) and other diseases which were not, but which at particular times and in particular areas became excessively frequent (epidenic diseases). Not only is this the first scientific epidemiological theory (Barkhuus, 1945a, 1988), but it also

"...constitutes the first example...of a rational attempt... to put the phenomena of the macrocosm and the microcosm in direct causal relations." (Castiglioni, 1958, 164). In cities exposed to hot winds and sheltered from northerly winds, it was noted, the inhabitants have heads full of phlegn (one of the four humours), and are poor eaters and drinkers with weak digestions; the women are unhealthy and subject to excessive fluxes. Men suffer from dysentry, diarrhoea, ague, and chronic fevers in winter. In cities exposed to north winds the people are bilious rather than phlegmatic, sinewy and spare, with hard healthy heads, but have a tendency to internal lacerations. Women become barren through the waters being hard and cold and their menstrual discharges are scanty and bad. Marshy drinking water causes phlegmatic diseases, and by contrast, water from snow must produce bilious ones (Jones, 1962).

Although later slightly modified by Sydenham (1624-72), Stoll (1742-87) and others, the thesis of <u>Airs, Waters and Places</u> remained a fundamental epidemiological text until the advent of bacteriology in the mineteenth century with the discoveries of Hemle (1809-85), Koch (1843-1910), and Pasteur (1822-1895). The holistic approach to the disease-environment relationship mooted by the author of this work has, however, remained the ideal of medical geography and for practitioners in this field, their ultimate aim.

### Medical Geography in the Sixteenth and Seventeenth Centuries

As explorations and discoveries opened up new areas for development and exploitation, people in different parts of the world were brought into closer contact. This increased population mobility was, however, frequently accompanied by a similar movement of various types of diseases. To Marti-Ibanez (1958, xi)

"the history of human communication is also the history of transmissible diseases and, often, of their remedies... Death galloped at the heels of the endless processions of pilgrims and nonads, who sandal-footed, slowly plodded across the burning deserts of Asia and Africa."

Contained within the articles, letters, and travel-books of the fifteenth, sixteenth and seventeenth centuries is a wealth of material on medical geography providing examples of the disease-environment relationship. Columbus' account of his travels throughout the 'New World' presents a record of the medical problems of remote areas. In the French <u>Histoire generale des voyages</u>, there is a description of conditions in Bonbay in 1690:

"Before the rains start, the air is extremely dry and hot. When the rain has fallen vapid streams arise of so unhealthy a character that they cause more disease than is present all the rest of the year." (Barkhuus, 1945a, 1993).

In the sixteenth century, Paracelsus attached much importance to the influence of the geographic environment to disease actiology. He stressed that a physician needed to

"...be both a geographer and a cosmographer if he wished to understand the dynamic essence of disease." (Marti-Ibanez, 1958).

Ranazzini, in the seventeenth century, demonstrated the relationship of disease to the environment in his classic medical geographic investigation of malaria around Modena (Markovin, 1962). He later presented the first systematic treatise on occupation and disease and has been credited

"the founder and greatest exponent of a new medical discipline, the study of occupational disease." (Castiglioni, 1958, 565).

### Medical Geography in the Eighteenth Century

In the eighteenth century the first attempts were made to collate the fragmentary material on the global distribution of diseases. One of the earliest, but rather unsuccessful efforts, was by Hoffmann, in a work which he claimed was based on the principles expressed in <u>Airs, Waters and Places</u>. The book is superficial and, according to Barkhuus (1945b, 1997), it is clear that the author was not especially interested in a critical review of his sources.

Friederich Cartheuser, a botanist-pharmacologist, made a similar attempt in a work which is generally credited as being the first attempt at 'geographical medicine'. A British contemporary, James Lind, related diseases in various parts of the world (especially the tropics), which were fatal to Europeans, to the geographical environment (Barkhuus, 1945b; Howe, 1970a).

A German clinician, Finke, endeavoured to collect all the medical geographic material available in the latter eighteenth century. In the introduction to <u>Geographie</u> (1792) the author explained why he chose to title his book a 'Medical Geography':

"...when one brings together all which is worth knowing with regard to the modical status of any country, then no one can deny that such a work deserves the name of a 'Medical Geography'." (Barkhuus, 1945b, 2000).

Whereas Finke was interested in the geographical distribution of disease in his material, Friedrich Schnurrer made an attempt to discover the principles underlying such distributions. His published work (1813) was, however, severely criticised during his life time (Barkhuus, 1945b, 2006). One reviewer wrote that
"...this is only a collection of naterial and that the complete lack of comparative physiology and general pathology does not permit the author to call his book a "nosology'." (Barkhuus, 1945b, 2006).

# Medical Geography in the Nineteenth Century

The first decades of the ninetcenth century have been labelled the 'period of medical topographies' (Barkhuus, 1945b, 2007). In essence these were regional monographs devoted to diseases of particular areas. The ultimate aim of such works, according to Hennen, was

"... to ascertain every circumstance that has an influence upon health, the nature, extent, and variaties of the diseases of the district which he undertakes to describe ..." (Barkhuus, 1945b, 2007).

Medical topographies appeared for many parts of the world. Barkhuus (1945b) records that Huss wrote on Sweden Simonin on France, Rigler on Turkey, Murchison and Webb on the Indian sub-continent, while on the Americas Drake produced

"...by far the finest example of early medical topographics." (Barkhuus, 1945b, 2013).

A considerable number of works on the 'medical climatology' of English towns and districts were also published at this time (Gilbert, 1958).

Up to this stage of medical geography, few attempts had been made to discover the basic principles underlying the geographical distribution of disease. The utility of such an approach at a localised scale in endeavouring to understand disease causation and, hopefully, break the causative chain, was illustrated by Pott,who, in 1775, discovered a relationship between soot and chimney-sweeper's contracting cancer of the scrotum (Winkelstein and French, 1972). Subsequent legislative Acts (e.g. the 1840 Act of Parliament) and improvements in chimney cleaning and the trades hygiene witnessed a decrease in the incidence of this type of cancer.

In 1853 Fuchs published <u>Medicinische Geographie</u> in which he stated

"the knowledge of the laws according to which diseases are distributed and spread over the globe is called geographical medicine..." (Barkhuus, 1945b, 2008).

Barkhuus (1945b, 2010) reviewing the work believes that

"Fuchs represents a type of epidemiological thinking which was very prevalent in the pre-bacteriologic period of the last century. Diseases were caused by the environment, and most of the etiological factors explaining the occurrence of disease were to be found in the science of physical geography. Fuchs' own knowledge of scientific geography was rather mediocre, and it may be seen that his knowledge of natural history was even poorer. He had an almost incredibly naive belief in the power of environmental factors."

Meuhry held a belief that the purely physical environment could no longer be considered as the only factor accounting for the geographical distribution of disease. He was convinced that by arranging his material geographically the main features of the laws governing disease distribution would appear of their own accord. Before this could eventuate, however, Muchry felt **that** a scientific classification of disease was needed. (Howe, 1970a)

Boudin in 1857 presented the theory of a 'kingdom of diseases' similar to that of the animal and plant kingdoms which have their habitats governed chiefly by physical conditions (Howe, 1970a). He believed, therefore, that the scope of medical geography embraced "...neteorology and physical geography, statistical population laws, comparative pathology of different races, the distribution and nigration of disease." (Barkhuus, 1945b, 2013).

Because of the discussion of almost every field within the social and biological sciences, both Barkhuus (1945b, 2013) and Howe (1970a, 11) consider that this work can only partly be labelled a medical geography.

# Medical Geography in the Later Nineteenth and Early Twentieth Centuries

Studies in medical geography were practically neglected after the 'Age of Bacteriology'was ushered in during the later minutcenth century. The gern theory, founded in the discoveries of Pasteur, Koch, and Henle, tended to a belief in a monofactorial pathogenesis of discase in stating that each disease was provoked by a specific microbe with characteristic pathological effects. Little or no importance was now ascribed to the study of the environment as biological explanations could now be made for disease actiology.

It was, however, in this period that the first acknowledged textbook on medical geography was published, and from which, some believe, modern medical geography originates (Mitchell, 1965; Armstrong, 1965a). August Hirsch published a two volume work in 1860 which was republished in three volumes between 1881-6. A second edition was translated into English as the <u>Handbook of</u> <u>Geographical and Historical Pathology</u>. The geographical and temporal occurrence of each disease was discussed and there were attempts to relate these to factors such as location, climate, altitude, soil constitution, season, electrical phenomena, and social conditions. Despite the enthusiasm with which this work was received at the time of publication, it was disappointing

"as a modical geography in the sense of an attempt at elucidating first principles." (Barkhuus, 1945b, 2014). It has continued, however, to be an invaluable source on the geographical distribution of disease.

Earlier (1853) Hirsch had written of an important consideration in undertaking medical geographic studies:

"Modical geography nust not become the playground of learned curiosity or romantic natural philosophy. We must have the facts..." (B-rkhuus, 1945b, 2009).

A useful supplement to Hirsch's '<u>Handbook</u>', but which offers more detailed information about a particular region, was Lombard's work published between 1877 and 1880. In 1880 Lombard also produced an atlas of the geographical distribution of diseases, which represents one of the initial thrusts in medical cartography.

Poincare's work of 1884 contained little new material but it did help to popularise medical geography by its appeal to the practising physician (Barkhuus, 1945b). The previous publications of Hirsch, Boudin, and Lombard generally had contained much detail intended to appeal to a wide range of interests. Poincare, however, who considered a knowledge of the geographical distribution of disease of prime importance for the preventive aspects of hygiene, discussed each disease in a separate chapter illustrating its distribution by a map.

Davidson, in 1892, realised a problem of all medical geographic studies, that accuracy in determining the actual prevalence of a disease depends upon reliable statistical data (Barkhuus, 1945b). While Clenow in 1903 included a post-Pasteur slant to the discussions on unsolved problems like the periodicity of cholera.

In 1932, a German professor, Zeiss, who liked to think of himself as the father of medical geography, coined the term <u>geomedicine</u> (May, 1952). He defined this as that

"... branch of medicine which attempts to clarify and explain the results of medical research by geographical and cartographical treatment." (May, 1952, 1).

Zeiss believed there was a clear distinction between this new field of research and medical geography, which he defined (although May, 1952, disputes this definition) as that

"... branch of geography which attempts to study and explain the effects of geographical space, earth, and its vital forms, on man, animal, and plant." (May, 1952, 1).

Research in the field of geomedicine has since prospered especially through the contributions of the Geomedical Research Unit of the Heidelberg Academy of Sciences in West Germany.

The United States of America, despite providing early examples of disease cartography (Stevenson, 1965; Howe, 1971a) was not especially interested in the field of medical geography until the 1930's. A survey, under the direction of McKinley, was instituted at that time in response to a need for more specific information as to the distribution of tropical and some preventible diseases throughout the world. The subsequent publication is such that Barkhuus (1945b, 2016) doubts whether it should be called a 'Geography of Diseases'.

#### Medical Geography Since 1945

In the years since World War II there has been a considerable upsurge of interest in medical geography and disease cartography. In the previous seventy years micro-organisms were believed to be totally responsible for man's ill-health. Bacteriology had become the centre and goal of medical investigations, or as Bernarde (1972, 22) states

"the germ theory of disease had ascended to centre stage, relegating the environment to the wings."

Subsequent medical research, however, revealed that disease, in most instances, does not represent the response of an individual to a single stimulus (a microbe) but rather results from a multitude of causes, both exogenous and endogenous in character. Consequently, bacterial research was

"...not sufficient to explain the disease picture always and entirely or to illuminate all disease problems..." (Castiglioni, 1958, 987).

The discovery of micro-organisms, and the accruing theory of specific causality did, however, complete the triad of possible causation by adding the agent to the elements of the environment and the host.

In the search for disease actiology attention turned again to the environment in an attempt to relate differences in disease distribution patterns to local environmental factors and afford pointers to possible causal relationships. Ackerknecht (1955, 172) reinforces this return to the environment, noting that

"constitutional, geographical, and social factors, which for decades had been completely neglected because of a blind trust in bacteriology, had to be reconsidered."

The greater complexities of modern life and increased tension of living-conditions (especially in cities) accompanying developments in man's socio-cultural environment, have manifested themselves in the increasing number of persons affected by mental illness in contemporary times. Two concepts, deprivation and stress, introduced into medicine between 1930 and 1950, implied that illness could occur as a result of exposure to sudden or marked changes in the environment which subjected a person to pressures in excess of their ability to tolerate them (Bernarde, 1972).

Two additional factors directed interest back to the environment as holding the possible key in disease causation. First, the two World Wars with their disruption of the environment and the displacement and decimation of millions of persons, both civilian and military, highlighted the disease-environment relationship. The movement of recruits into areas where they had little or no exposure resulted in casualities from disease as well as from bullets.

The second factor, the increasing sophistication of transport technology since the 1950's, has contributed to what Maegraith (1969) calls 'A Jet Age Medical Geography'. The transport systems, especially air transport, have shrunk the world enabling greater numbers of people to travel faster, further, and more often. They have also, as Light (1944, 640) observes,

"...exerted the greatest influence on disease, especially the group of the infectious diseases, those diseases that pass from man to man, either directly or through some intermediate host, To spread widely, they must be transported...by man and man-made transportation, that which moves man himself, his animals, his goods, his foods, and an array of deadly little disease-carrying stowaways about the earth."

The tsetse fly in Liberia, Hughes and Hunter (1970) note, have been attracted and attached itself to, vehicles travelling along roads improved for the economic development of an area. This has frequently resulted in the reintroduction of tryanosomiasis into once cleared areas. Insects and rodents, such as ticks, flies and mice, can propagate disease as quickly as they may be transported by aeroplane, car or ship. The effects of migration on disease have been discussed by Prothero (1965).

Indicative of the renewed interest in medical geography in this \_ period has been the formation of a number of commissions and societies devoted to furthering research in some aspect of the field. The International Society of Geographical Fathology (ISGP) has as its object the study of any relationship that may exist between diseases and the geographical environments in which they occur (Doll, 1959). The International Geographical Union (IGU) created a Commission of Medical Geography<sup>7</sup> in 1949, which provides an international forum for medical geographers. Papers presented at the sessions serve as an introduction to research conducted in the field by member nations.

National medical geographic societies have been formed in the U.S.S.R. (Markovin, 1962), The Netherlands (1955), Belgium, Bulgaria, West Germany, and most recently in the U.S.A. The British Medical Geographic Committee, founded in 1959, has sponsored the publication of the <u>National Atlas of Disease Mortality</u> (Howe, 1963, 1970a). A similar atlas of morbidity has been contemplated.<sup>8</sup> The American Geographical Society established a Medical Research Unit in 1944,

which sponsored May's (1950-55; 1958, 1961a and b) subsequent publications. This unit did, however, cease to function in 1961.

A peripheral field, such as medical geography, must formulate theoretical principles and methods of research to achieve academic respectibility (McGlashan, 1966a). In the most recent decades, modical geographers have attempted a precise determination of the subject and tasks of their field. There are still, however,

"...divergent opinions on the nature of the subject." (McGlashan, 1972b, 5)

The greatest difference in interpretation of the scope and purpose of medical geography exists between the Soviet (U.S.S.R.) medical geographers and their Western counterparts. In the U.S.S.R. the utility of this field is linked to the development of the Soviet economy. Emphasis is upon those factors which

"...either aid in strengthening the health of the population, prolong its labour capacity, and increase the life span of man, or which cause disturbances in man's health, a reduction in working capacity, or the rise of diseases." (Byakov et al, 1962, 250).

In the West medical geography has become principally a research tool for investigating disease actiology with the view to reducing the level of 'diseasedness' in human populations. McGlashan (1972b, 5) notes that

"freedom from centralised direction of research and hence individual choice of topic and scope has resulted in individual contributions..."

# Medical Geography in the Contemporary Era

In contemporary Western medical geography four general research foci are discernible:

a) medical facility locational studies. Due to the increasing
capital expenditure involved in the provision of hospitals and ancillary
equipment and services, health authorities are becoming aware of the
potentialities of this type of study which endeavours to establish the
optimal location of such facilities (Morrill, 1966, 1967; McGlashan,
1968; de Vise et al., 1969; Earickson, 1970; Pyle, 1971; Jackman,
1972; Armstrong, 1972b; Shannon and Skinner, 1972; de Vise, 1973;
Lankford, 1974). A classic in this field is that by Godlund (1961) which
considered transport facilities and population forecasts in Sweden in
relation to the capital expenditure proposed for up-grading facilities
in certain hospitals to make them centres for region-wide medical
networks. He employed a measure of equal travel time ('isochrones')
about possible centres to assess those best placed for future development.

b) the spatial definition of health and ill-health. Examples are provided in McGlashan (1972a), and will be discussed further in Chapter 3.

c) association-in-space studies of disease and environmental factors. Physical factors considered in association with disease include:

(i) soil trace elements (Armstrong, 1964b, 1965b; Carren, 1972, 1973, 1974a, 1974b);

(ii) water resources (Allen-Price, 1960; Schroeder and Brattleboro,
 1960; Armstrong, 1964a; Sauer et al, 1970a; and Ffrench, 1973);

(iii) meteorological factors (Lawrence, 1962; Sakamoto, 1965, 1968; Sakamoto and Katayama, 1966, 1967; Rose, G., 1966; Hopps <u>et al</u>, 1972; Tromp, 1973).

Disease relationship with socio-economic variables have also been considered in a large number of studies throughout the world (Fonaroff and Fonaroff, 1966; Ashley, 1968; Hinkle. <u>et al.</u> 1963; Basu, 1969; Bradshaw and Schonland, 1969; McGlashan, 1969d, 1972e; Choubey, 1971; Griffiths, 1971; Dever, 1972a; Girt, 1972a; Syme<u>et al.</u> 1972a; Bain, 1974; and McGlashan and Gatenby, 1974). While Hughes and Hunter (1970, 1972), Burkitt (1973), and May (1972) have discussed the ramifications of economic development on disease patterns.

d) disease diffusion studies. The ultimate purpose of these studies, McGlashan (1973, 219) believes,

"...is to advise public health authorities regarding appropriate control measures, even when the mechanism causing the speed of spread are not fully understood at a medical level...Such work...is the very body of modern quantitative geography with its emphasis upon flows and networks."

Pyle (1969) has written on the diffusion of cholera throughout the U.S.A. in the nineteenth century, while Hunter and Young (1971) conducted similar research into the spread of the 1957 influenza epidemic throughout England and Wales. Brownlea (1967, 1968, 1972a) and McGlashan (1974b) working respectively in the suburban environment of Wollongong (Australia) and Tasmania, noted the diffusion of infectious hepatitis through the two areas.

Medical geography in the West has not, generally, been accepted as an essential participant of interdisciplinary medical research into aspects of health and ill-health. A principal contributory factor has been the lack of awareness of the practical utility of this field. Medical geography is now, however, beginning to show signs of emerging as a distinct speciality (Armstrong, 1965a).

# The Evolution of Medical Geography in the U.S.S.R."

Up to the eighteenth century Russian medical geography followed, essentially, the same path as that in the Vest. Early descriptions of Russian travels frequently contained medical geographic information concerning local diseases, the status of medicine in countries visited, and epidemics.

The beginning of the eighteenth century, however, marked the initial divergence of Russian medical geography away from that of the West. This period witnessed the genesis of geography as a science in Russia, with the early geographers establishing

"the foundations for medical-geographic study." (Markovin, 1962, 6).

Markovin (1962, 9) concluded that by the 1850's Russian medical geography had

"...become an independent branch of medicine that was being investigated not only in practical (medical-topographic descriptions) but also in theoretical research (work on the effect of geographic factors on man's organism in various climatic zones)."

The development of medical geography was linked, as in the contemporary Soviet period, to the socio-economic conditions and the socio-political philosophy prevailing at the time. Medical geographic studies were further stimulated by the occurrence of major wars in the formulative years of the nineteenth century. Markovin (1962, 8) records an increasing number of studies which he classifies as 'military medical geography'.

### The Late Nincteenth Century

The last fifty years of the nineteenth century has been taken to be the most intensive developmental stage in Russian medical geography.

"Nowhere did medical geography assume the impressive scope, depth and range of subjects that it had achieved in Russia, where, moreover, it played a bold, reformist role." (Markovin, 1962, 13).

It has been estimated that about 1,500 different medical geographic studies were undertaken in this time, many being submitted as requirements for doctoral degrees (Byakov et al, 1962).

Despite the diversity of subjects researched five basic trends were discernible (Markovin, 1952):

a) medical geographic descriptions covering both Russian and foreign territories were the most popular. Produced principally by ships' doctors they thus emphasised the contribution of medical practitioners to medical geography.;

b) the geographic distribution of diseases and their relationships
 with places of occurrence;

c) the influence of the natural environment on public health, the mortality and morbidity rate;

d) there was attention directed to the effect of socio-economic conditions of areas on the health and disease rate of the population.;

e) treatment of the subject and aims of medical geography. Skvortsov (1875) defined this field as being

"...concerned with the study of various areas of the earth from the point of view of the influence of the sum-total of their inherent conditions on the health of their inhabitants." (Markovin, 1962, 13). From this fervour of activity, medical geography in Russia had by the end of the nineteenth century

"...accumulated major theoretical and practical achievements." (Markovin, 1962, 13).

The Advent of Soviet Redical Geography

One consequence of the 'Great October Socialist Revolution' in 1917 was the emergence of a new dimension in the development of medical geography. Man was hereafter viewed as a labour resource and a decisive productive force. To ensure that each individual was capable of working at peak productive capacity and efficiency, public health became a constituent part of the subsequent economic policies of the Soviet government.

It was in the milieu of Socialist order that medical geography was to prosper, for as Shoshin (1964, 68) has stated

"the study of the geographical aspects of public health is the principal task of medical geography."

This theme has been reinforced by Ignat'yev (1967, 495) who believes the most important contribution that a medical geographer can make is

"...taking an active part in the building of models of future complexes, containing the necessary indicators, ensuring the creation of most favourable conditions for the life and work of the population, furthering the preservation and strengthening of public health, physical development and longevity."

The scientific basis of Soviet medical geography is

"the materialistic doctrine of the unity of the external environment and the human organism..." (Byakov <u>et al.</u> 1962, 250). That is, the recognition of the role of the natural and socio-economic environmental factors in the formation and development of the organism. This concept, of the relationship of the environment and the organism, had been expounded by various writers during the late nineteenth century (Byakov <u>et al</u>, 1962). While Pavolov's theory of the role of the external environment in the

"...development of pathological processes in the organism and of the mechanism of actiology of diseases confirms the validity of this theoretical basis..." (Shoshin, 1968, 2).

# The Energed Speciality: Soviet Medical Geography Since 1945

A period of intensive medical geographic development has occurred in the Soviet Union since World War II, similar to that experienced in the West. The direct demands of the national economy and public health has principally promoted this upsurge.

In recent years Soviet medical geographers, like their Western counterparts, have directed much attention toward working out the theoretical problems of medical geography. Despite some progress there still exists a diversity of views on the scope and objectives of this research field. From these various interpretations Ignat'yev and his associates distinguish three basic stands (Gelyakova.et al, 1967):

a) medical geography deals with the geographical distribution of human diseases and the conditions under which it arises;

b) medical geography deals with the effect of natural conditions on the health of man:

c) the object of medical geography is the geographical environment of human society and its influence on the health of man.

Soviet medical geography, therefore, differs from that in the West. It not only studies the geography of disease and the causes of disease but is additionally concerned with

"natural factors that may have a beneficial effect on public health, prolong the work capability of man and extend his life span." (Shoshin, 1964, 71).

Contemporary Soviet medical geography exhibits six main research trends which in turn reflect the underlying philosophy of medical geographic study formulated in the prevailing socio-political-economic conditions (Byakov <u>et al.</u> 1962; Shoshin, 1964):

a) the study of the influence of individual components of the natural and socio-economic conditions on public health. This type of research contributes toward an understanding of each factors' role in the disease causality chain and their effect upon the health of the population of an area. Byakov (1962), for example, has studied the effect of climate solar radiation, soils, waters, plant and animal life on the human organism in mountain landscapes;

b) The investigation of various 'units' of landscape regions endeavouring to detect conditions that adversely affect public health. A medical geographic survey of the European North by Ivanov (1962) showed that precautions had to be taken against the deficiency of ultra-violet radiation and vitamins, frostbite, tick-borne encephalitis and tularemia. He concluded (1962, 56), in a statement illustrating the significance of such medical geographic studies, that

"an absolutely essential condition for the effective organization of all preventive public-health measures in the region...is for public-health workers, especially physicians, to be familiar with all aspects of the adverse effect of local conditions on the health of man, the characteristics of regional pathology and areas of endemic diseases, in short, with the medical geography of the region."

c) the study of individual diseases with a view to discovering patterns in the formation of disease areas and nosocomplexes. From this prophylactic measures may be formulated. Chaklin (1962) found that certain factors in the physical environment and living habits of ethnic groups produce differential incidence rates of some cancers in the Soviet Union. Such information on the geographical distribution of cancers and their relationships to natural and socio-economic conditions, he adds (1962, 68)

"are of definite interest because they indicate a higher incidence of some cancers in various countries or regions of the U.S.S.R. and because they broaden the field of cancer prevention."

d) the elaboration of medical geographic forecasts of those areas intended for future development (the taigs, the arid zone, and the higher mountain areas) and for those where man's economic activity is resulting in an intensive transformation of nature (e.g. virgin lands, areas of industrial construction projects, and new population centers). The aim of forecasting,

"is to predict all possible consequences of the development of production and the transformation of the natural environment with respect to public health." (Ignat'yev 1964, 75).

Emphasis is, thus, on those factors in the environment having a direct or indirect effect on public health, and which are therefore, likely to affect the social and economic conditions of the inhabitants. On this basis, it is not only possible to forecast disruptive effects, but also to take preventive action during the developmental stages of a new area. Khlebovich and Chudnova (1968) studied the consequences for in-migrants to the oil industry in the Middle Ob' valley in Western Siberia, and made recommendations intended to minimise the adaptation problems of the workers;

e) the medical geographic study of foreign countries. This research assists in planning health aid for foreign countries; enables construction of measures to protect the health of Soviet citizens abroad; and insures the sanitation of the Soviet frontier (Shoshin, 1964). A survey of the medical geography of North Vietnam, undertaken by Lysenko and Losev (1966, 52) indicated that

"nosogeographic research of some diseases has proved to be so fruitful that it could be applied in working out a program of eliminating those diseases (for example, malaria and trachoma)."

f) the production of special medical geographic maps reflecting the influence of natural and socio-economic conditions on public health, and from which it may be possible to ascertain the factors of positive and negative influence. Such maps are regarded in the Soviet Union, as the logical culmination of medical geographic research.

Increasing attention is now being directed by Soviet medical geographers to the concepts of 'natural prerequisites of human disease'

(Ignat'yev, 1964; Gelyakova <u>et al</u>, 1966), and the 'natural infection focus of disease' (Voronov, 1967).

The prevailing socio-political philosophy, the demands of the national economy, and the task of preserving public health in the Soviet Union have dictated, the

"necessity of organising a consistent and systematic medicogeographic study of the territory...and composing medicogeographic descriptions on this basis." (Byakov <u>et al</u>, 1962 252).

Through such stimuli, Soviet medical geography has been able to achieve closest parity with the thesis expressed in <u>Airs, Unters and</u> <u>Places</u>. The evolution of medical geographic forecasting, and the concepts of 'natural prerequisities of disease' and 'natural infection foci' have ensured, in part at least, that man

"will not, on arrival at a town with which he is unfomiliar, be ignorant of the diseases, or of the nature of those that commonly prevail." (Jones, trans. <u>Airs, Waters and Places</u>, 1962, 73).

Medical geographic research in the U.S.S.R. is being conducted

"...as a general rule, as part of interdisciplinary field work dealing with the physical environment, population and the economy." (Sochava, 1968b, 300).

Ignat'yev (1964, 77) states that this field creates

"...a bridge between nature and man, and from man to the population as a whole and to production, promotes the development in the full meaning of the word, of an integrated geography...and stimulates an expansion of research now being conducted by physical and economic geography..."

In short, medical geography and medical geographers in the Soviet Union are an integral part of the geographical sciences, the development of the economy and hence, the further advancement of that country.

# Centuries in Theory, Decades in Practice!

Despite medical geography's long ancestry, and some important contributions in the interim, little advance was made in the field until the contemporary period. Ironically, it was the very approach proposed in <u>Airs, Waters and Places</u> that contained the practical development of the field. Prior to the last three decades, knowledge and technology were never sufficient to collect, process and evaluate data on the scale envisaged by the Hippocratic scholars.

Investigations into the spacio-temporal distributions of health and ill-health depend upon availability and reliability of demographic and medical data. The lack of such data has been, in Armstrong's opinion (1965, 62)

"...the most serious handicap of medico-geographical study." Consequently, Rodenwaldt and Jusatz<sup>9</sup> and May (1950-1955) mapped only generalised information on a world-wide basis with their maps containing large areas of incomplete data. Some accord is required throughout the world in the standards of medical diagnosis and recording of information pertinent to medical geographic studies, especially as diseases present various stages in their development in an organism and many diseases have a number of features in common.

To establish relationships or associations between disease patterns and the environment necessitates additional data being available on exogenous factors.

"In many cases it is extremely difficult to find an explanation for the present day distribution of certain diseases because of the lack of relevant data." (Shoshin, 1968,17).

Contributory information is also required from other sciences, such as botany, chemistry, meteorology, sociology and economics. For example, many areas of the world still lack soil survey information.

In areas where the basic data was procurable and sufficiently reliable, its increasing voluminous nature threatened to jeopardise the medical geographer's attempt to consider all possible factors in his analysis. As McGlashan (1973, 206) has observed the researcher

"...had no means of handling the volume of information - a true embarras de richesse."

Two contemporary developments, quantification and computerisation, have, however, provided a means for handling increased spatial knowledge and overcoming the analytic inadequacy. Previous traditional geographic methods were not equipped to undertake a comparative and quantitative analysis of health and ill-health distributions. Techniques, such as regression, correlation, variance, and co-variance, coupled with simpler forms of statistical aids have afforded medical geographers with a method of multi-factorially appraising relationships between the environment and populations. The basic concept here,

"hinges upon the recognition of groups of factors significantly co-extensive with areal patterns of health or ill-health parameters." (McGlashan, 1973, 207).

With the ability to handle diverse data types, results of research may be scientifically tested in different areas, at different times by different researchers. The consistency of any relationship between disease and the environment demands careful consideration and

close scrutiny before one may decide that the most likely interpretation of this association is causation (Hill, 1965).

Thus only since the late 1940's has medical geography been

"equipped to undertake broadly based studies depending upon quantitative assessment of geographical factors and their impact upon human population groups." (McGlashan, 1973, 206).

It has now become feasible to attempt studies on the scope formulated by the Hippocratic scholars.

### Footnotes

- 1. Norld Health Organisation Basic Documents (16th ed.) 1965:1.
- For examples of endogenous and exogenous causes of disease refer to Henschen, 1966, 10-20; May 1958, 1-34; May, 1974.
- For other definitions of geographical pathology see Stewart, 1964; Rao, 1965.
- Refer to Le Riche and Milner, 1971, 1-3 for various definitions of epidemiology.
- Barkhuus, 1945a, 1896; Castiglioni, 1958, 151, 164; Henschen, 1966, 2.
- Adams, Francis (trans.) <u>The Genuine Works of Hippocrates</u>, 2 vols., Sydenham Society, London, Vol. 1 (1849), 179-222. Cited in Barkhuus, 1945a, 1987-1988; Howe, 1970a, 7-0; and Henschen, 1966, 17-18. See also Jones (trans.) 1962.
- This Commission was retitled the 'Standing Commission On Medical Geography' following the I.G.U. conference held in New Delhi, 1968.
- 8. See Stamp, L.D. 'Presidential Address' in <u>Geographical Journal</u>. Vol.131, 1965, 313-317.
- 9. Rodenwaldt, E. and Jusatz, H.J. (1952-61). World Atlas of Epidemic Diseases, Hamburg.

#### CHAPTER THREE

### CARTOGRAPHIC ANALYSIS AS A RESEARCH TOOL

### IN MEDICAL GEOGRAPHY

As a means of portraying, representing, storing and generalising information, maps

"...are dear to the hearts and minds of geographers..." (Harvey, 1969, 369).

While Hartshorne (1939, 249) believed if a geographer's problem

"...cannot be studied fundamentally by maps - usually by a comparison of several maps - then it is questionable whether or not it is within the field of geography."

Although maps are constructed principally to show facts, spatial distributions or temporal changes, with an accuracy not attained by description or statistics, their prime importance is as research tools. Maps are a means of recording observations, analysis, communication and may act as stimulants for hypothesis formulation. As such, cartography has a direct application to medical geography, which studies the spacio-temporal distributions of health and ill-health and their causal relatedness to the environment. Petermann, writing in 1852, clearly explains the advantages of a map for medical purposes:

"The object, therefore, in constructing Cholera Maps is to obtain a view of the Geographical extent of the ravages of this disease, and to discover the local conditions that might influence its progress and its degree of fatality. For such a purpose, Geographical delineation is of the utnost value, and even indispensable; for while the symbols of the masses of statistical data in figures, however clearly they might be arranged in Systematic Tables, present but a uniform appearance, the same data, embodied in a Map, will convey at once, the relative bearing and proportion of the single data together with their position, extent, and distance, and thus, a Map will make visible to the eye the development and nature of any phenomenon in regard to its geographical distribution." (Gilbert, 1958, 178).

Much of the basic work in medical geography, Copperthwaite (1972, 43) states,

"lies in the preparation of maps illustrating areal distributions of various diseases or groups of diseases." McGlashan (1965, 1966a, 1969c, 1972b, 1973) believes mapping disease data is the initial task of the medical geographer, which may in some instances provide quite new information about the spatial variation of 'diseasedness'. From the Soviet Union, Shoshin (1968, 39) writes

"...in our opinion, nosogeographical investigations must be carried out primarily by means of cartographic analysis."

Medical mapping has evolved to become an integral factor in medical geographic studies and there has been an upsurge in the field to

"put it on a map" (Stamp, 1964b, 96).

# The Genesis of Medical Mapping

Disease cartography was born on the eastern seaboard of the United States at the end of the eighteenth century, out of a debate between the contagionist and anticontagionist factions on the nature of yellow fever. It was noted by Spencer (1969, 2) that, "the mapping of disease in America germinated in the virus of yellow fever and blossomed in the cholera vibrio."

The dispute was but five years old when in 1798 Valentine Seaman, a surgeon to the New York Hospital, published a paper on yellow fever mortality and morbidity which presented a

"new method of marshalling and exhibiting the evidence." (Stevenson, 1965, 239)

It was the use of two spot maps (Fig. 1) that distinguished this work from that of contemporaries on the same theme.

A fellow anticontagionist, Pascalis-Ouviere, later included a map in his <u>Statement on the Occurrences during Malignant Yellow Fever</u> in the City of New York (1819) in an effort to establish the causative factors of the disease (Stevenson, 1965).

The spot map was, and generally continued to be, the weapon of the anticontagionist faction, although toward the end of this period (1850's) there was a tendency toward its use by the opposite doctrine (Stevenson, 1965). The spot map was used to show concentrations of cases in a restricted area, characterised by a specific set of environmental factors, thus proving, it was thought, the local origin of yellow fever. The evidence provided by the maps, however, was merely an illustration of a thesis contained in the text. They might enable the reader to form

"a more accurate picture of the spread of the disease but they told him nothing new." (Stevenson, 1965, 261).



FIG. 1 One of the first spot maps used by Seaman (1798, Plate 1) to depict yellow fever in New York in 1796. The numbers 1 to 5 represent fatal cases; ⊙ represents a near-fatal case; ○ a mild case of the fever. From Stevenson, L.G., 1965, 'Putting disease on the map; the early use of spot maps in the study of yellow fever'. J. Hist. Med. vol 20, 226-61.

### Cholera Cartography

While disease mapping may be regarded as the child of yellow fever, it was nutured through the nineteenth century by the cholera epidemics throughout the world, particularly those in England. Gilbert (1958, 173) has asserted, falsely however, that

"the great outbreaks of cholera in the first half of the nineteenth century seem to have been the factor which first stimulated cartographic work of this kind."

The first stage in 'cholera cartography' was Jameson's map in 1820 of the disease in Northern India (Jarcho, 1970).

Within the ensuing years until the 1850's, the mapping of cholera was actively undertaken. Twenty-two maps, heterogenous in scope and technique, were published in 1852, as the disease spread over Eurasia, the British Isles and North America (Jarcho, 1970).

Although these early cholera maps did not exhibit a rigid developmental order, they can be classified into four groups, as maps that show (Jarcho, 1970):

a) places but no indication of disease;

b) places, dates, and lines of spread;

c) lines of spread overwritten in ink;

d) the affected regions in solid colours.

After 1833, the home of disease cartography became principally the cholera ravished milieu of England. Robinson has labelled this period the

"golden age of the development of geographic cartography" (Gilbert, 1958, 173),

as the mapping of disease gained momentum. It would seem, therefore,

that disease cartography owes its birth to the epidemic outbreaks that presented a great challenge to society for their control and eventual elimination. Endemic diseases, generally always active, were not able to stimulate cartography, and therefore,

"plague, yellow fever, and cholera - all exotic accomplised what tuberculosis could not." (Jarcho, 1970, 138).

William Harty (1820) produced the first disease map in the U.K. which depicted cases of 'contagious fever' in Ireland and showed the month, but occasionally only the season, when the epidemic commenced in the named towns (Howe, 1971a).

Baker produced a map in 1833 of the incidence of cholera in the city of Leeds during the 1832 epidemic which showed

"how exceedingly the disease has prevailed in those parts of the town where there is a deficiency, often an entire want of sewcrage, drainage, and paving." (Gilbert, 1958, 175).

In 1849 Shapter drew an "historical" dot map of deaths from cholera in Exeter during 1932-34 utilising the dot technique (Fig.2.). From this it was shown that a large proportion of the cholera mortalities occurred in the lowlying south-eastern sector of the city. Thus, slowly, evidence accumulated about the geographical distribution of cholera incidence which would later be corroborated by the investigations of Snow in 1855.

A German geographer resident in England, Petermann, has been credited by Howe (1971a) as making significant experiments in various techniques of thematic mapping. In 1852 he published a cholera map



FIG. 2 Shapter's map (1849) of the deaths from cholera in Exeter in 1832–34. From Gilbert, E.W., 1958, 'Pioneer maps of health and disease in England'. *Geogr. J.* vol. 124, 176. of the British Isles showing the districts attacked in 1831, 1832, and 1833 (Fig. 3). From this he noted that the first areas where disease struck were situated along the coast line with subsequent penetration into the inland parts of the country. Petermann further observed that the affected cholera areas were predominantly onllower ground or in valleys. Having produced a map with differential shading of population density, Petermann compared this with his disease map, which showed that the more densely populated districts were proportionately the most severely attacked by cholera. He thus concluded

"...with a considerable degree of certainty that these districts were attacked, not so much in consequence of their <u>low situation</u>, as from the <u>great amount of population</u> they contain." (Cilbert, 1958, 179).

Petermann had highlighted the population-at-risk hypothesis that the greater the population-at-risk the higher the incidence of disease, which has become an integral part of medical geographic studies.

It was John Snow (1855) who, through the use of a map as a tool of analysis and not merely as an illustration of the text (Learmonth, 1969) was able to

"strip the veil of mystery...from the disease which had bewildered governments and defeated doctors for a generation." (Longmate, 1966, 204).

On a map employing the dot technique, to pinpoint cholera mortalities (based on direct observation of the deaths) from the 1854 cholera epidemic in the London district of Soho, Snow clearly demonstrated (Fig. 4)



FIG. 3 Petermann's cholera map (1852) of the British Isles showing areas affected in 1831–3. From Gilbert, 1958, 177.



FIG. 4 Snow's dot map (1855) of cholera mortalities in the Broad Street area of London in September, 1854. From Gilbert, 1958, 174.

"...there had been no particular outbreak or increase of cholera, in this part of London, except among the persons who were in the habit of drinking the water of the abovementioned pump-well [the Broad Street pump] ...The deaths either very much diminished, or ceased altogether, at every point where it becomes decidedly nearer to send to another pump than to the one in Broad Street." (Longnate, 1966, 205).

The ramification of this finding was, in Gilbert's (1958, 175) opinion, that

"...on September 8, at Snow's urgent request, the handle of the Broad Street pump was removed and the incidence of new cases in the area ceased almost at once."

The evidence, however, does not support this view and Snow himself is

reported to have stated:

"There is no doubt that the mortality was much diminished ...by the flight of the population, which commenced soon after the outbreak; but the attacks had so far diminished before the use of the water was stopped, that it is impossible to decide whether the well still contained the cholera poison in an active state, or whether, from some cause, the water had become froe from it." (Hill, 1955, 1010).

Hill (1955, 1010) therefore concluded that Snow

"never occupied the flimsy pedestal upon which some would place him."

Through his map, however, Snow (1855) had graphically illustrated an association of cholera deaths with a particular water source and thus reinforced his earlier postulated (1849) theory of the waterborne nature of this disease. By identifying the pump as the proximate cause of the disease and the subsequent request for the removal of the handle, Snow closed down the possible source of further infection. He had interrupted the disease causative chain although unaware of the existence of the cholera pathogen Vibrio Cholerae which was not discovered until 1883 by Koch.

Acland, in 1856, produced maps of the 1832, 1849, and 1854 cholera outbreaks in Oxford. Investigating the relation of cholera mortality to altitude, Acland concluded

"that mortality on our lower level was proportionately three times as great as that of our upper level." (Gilbert, 1958, 182).

The contour correlation may be explained by drainage, as at the lower levels the opportunities for contamination were several times greater than at the higher elevations.

#### Attempts at Global Disease Mapping

While 'local' disease mapping was prospering in England, attempts were being made on the Continent to divide the earth into 'nosozones'. The first atlas of diseases is generally accepted as being in the first edition of Berghaus' <u>Physikalischer Handatlas</u> produced in 1848. It contained, according to Jusatz (1969, 20), a

"planiglobe to give a survey on the geographical spread of the most important diseases to which man is exposed all over the world."

The first German-language textbooks of medical geography containing maps of the world zones, in which particular groups of diseases predominated, were those by Fuchs in 1853 and Muehry in 1856 (Jusatz, 1969). Muehry went a stage further than Fuchs in marking isothermal lines and isocheims on his map, relating the spatial map of diseases to climatic zones, and designating border areas of diseases, e.g. the northern border of malaria, and the southern border of typhoid fever.

### The Late Nineteenth and Early Twentieth Centuries

The development of disease cartography, following the rapid advancements made in the previous cholera era, lost momentum in the later years of the nineteenth century. The principal deceleratory factors were the rise of bacteriology, and improvements in public sanitation. Work in medical mapping, however, did continue.

In England, maps of the distribution of heart disease, cancer (females only), and phthisis (females only) between 1851 and 1860 were produced by Haviland in 1892. The object of the investigation, Haviland wrote, was

"to point out to the medical profession, not only where certain diseases do thrive, but where they do not; with the further object of leading others to inquire why this is the case in their own localities." (Learmonth, 1972d).

He had thus stated an important basic premise of medical geographic studies, that medical geography cannot claim proof of a relationship, but instead attempts to provide fruitful avenues for further intensive research into disease actiology by other specialist disciplines.

Beyond the confines of Europe, medical cartography was continuing to make progress. Disease mapping in East Africa dates back to James Christie's <u>Cholera Epidemics in East Africa</u> published in 1876. This work, Langlands (1969, 9) believes

"may have provided the essential foundation for medical work in East Africa on problems of epidemiology and the adoption of medical mapping as a respectable procedure ...It represents an early extension of the principles of epidemiology and geographic medicine..."

In the United States the peak of cholera mapping was reached in 1875 with the publication of "Woodworth's Tome" and its accompanying fifteen 'progress' and eleven spot maps (Spencer, 1969). This 1061 page volume describing the 1873 cholera epidemic was the consequence of a Congressional resolution (April 8, 1874) which required

"...one medical officer of the Army... [to] collect, so far as possible, all facts of importance with regard to such epidemic and...make a detailed report of the information collected..." (Spencer, 1969, 2).

Back in Britain during the 1880's the British Medical Association sponsored an investigation into the incidence throughout the country of selected diseases with reports being subsequently published (Howe, 1963, 1970a, 1971a). At the turn of the century the publication <u>Survey Gazetteer of the British Isles</u> contained coloured maps, based on the 1901 census, detailing for England and Jales (Howe, 1963, 1970a, 1971a):

a) average total death rate per 1000 population;

b) average death rate of children under one year of age;

c) average death rate from phthisis per million;

d) average death rate from 'zymotic diseases'.

Howe (1970a, 14) has stated that

"no differentiation of the sexes is attempted and the employment of crude death rates inevitably leads to erroneous conclusions."

During the 1930's methods for overcoming the inherent limitations of using crude rates for a study of the spatial distributions of diseases within a country were established.
Generally, a crude death rate will be affected by the age and sex constitution of the population concerned. Stocks produced a number of disease maps employing standardised mortality ratios (S.M.R's) (Howe, 1971a). While Hill (1st ed. 1937) detailed both the direct and indirect methods of using a standard population base in the calculation of death rates for spatial and/or temporal analysis.

Malaria in India became, during the formulative years of the twentieth century, the focus for a number of studies utilizing the advantages of disease cartography (Learmonth, 1957; Stamp, 1964a, 1964b). Each work extended the knowledge about the geographical distribution of this disease and its vector, and thus contributed toward the interruption of the disease causative chain. Bentley, in 1916, for example, used an isopleth map of malaria (based on spleen surveys) to show the prevalence of malaria in western Bengal, north of Calcutta, where many stagnant river channels and cut-off lakes with marshy borders afforded the ideal conditions for malaria-carrying mosquitoes (Stamp, 1964a). This map was correlated with a chloropleth map of population increase or decrease (by census districts for 1901 to 1911) which illustrated (Fig. 5a and b)

"a contrast in population growth or decline between Bast and West Bengal in which differential conditions of malaria play a dominant part." (Learmonth, 1957, 51).

Learmonth (1957) considers this work to be one of the great regional reports on malaria.

Christophers and Sinton, in 1926, prepared the classic map of malaria in Indo-Pakistan (Learmonth, 1957), while Covell mapped the main zones





FIG. 5 Bentley's maps (1916) of (A) malaria distribution and (B) population change in Bengal in which is shown the differential effects of malaria on the population. From Learmonth, A.T.A., 1957, 'Malaria in India and Pakistan'. *Trans. Inst.* Brit. Geogrs. 51, 52.



FIG. 5 (B)

of influence of the seven main species of vector mosquitoes for transmitting the disease through the area.

#### Disease Cartography in the Contemporary Era

The decades following World War II witnessed an intensification of activity in medical cartography, similar to, and for the same reasons, as that experienced in medical geography generally. Learmonth (1972b) has recently reviewed attempts at disease-atlas compilation by geographers since 1950.

Those studies in medical geography which have employed cartography as an analytical research tool will now be considered under three headings: world atlases, works from developed countries, and those from under-developed areas.

## World Atlases

In Germany the monumental three volume <u>Welt-Seuchen-Atlas</u> (World Atlas of Epidemic Diseases) was published between 1951 and 1961, under the direction of Rodenwaldt and Jusatz (Learmonth, 1969; Howe, 1963, 1970a, 1971a). The objective of the editors, Jusatz (1969, 21) states, was

"...to show on one map the correlations of a single [epidemic] disease with one or several geofactors."

Howe (1970a, 15) records that

"this atlas amply demonstrates the possibilities of the graphic recording of epidemic diseases on maps."

The 120 plates contained in this work (many include several maps) are to Learmonth (1969, 35)

"basically simple in technique but full of detailed and painstaking scholarship."

Each plate is accompanied by an exposition in German and English. A number of climate and population distribution maps, on the same scale, were added to the atlas, while further correlations were afforded by the subsequent publishing, in 1966, of <u>Weltkarten zur</u> <u>Klimakunde</u> (World Maps of Climatology) in the same format (Jusatz, 1969).

A further attempt to illustrate the world distribution of major diseases was May's <u>Atlas of Diseases</u> published between 1950-55 in conjunction with the <u>Geographical Review</u>. Although comparable to the larger German work in scholarship and cartography, Learmonth (1972b, 136) notes that

"...May's work is designedly lighter, wholly appropriate to its circulation with the <u>Review</u> to a very wide geographical public throughout the world and to every library of repute."

The seventeen plates of maps in this series follow a flexible mapping scheme, and employ simple cartographic techniques. Correlations are by direct and visual means rather than by sophisticated and statistical procedures (Learmonth, 1969). The poliomyelitis distribution map of plate 1, confirmed the understanding of the mechanism of acquired immunity against this virus infection. It was shown that epidemics are unusual where the virus is rampant and frequent where the virus is rare. Plate 9, concerned with 'Diets and Deficiency', confirms a belief held by a number of people that malnutrition is not common among the very primitive social groups. While each plate is self-explanatory, containing notes on the disease's epidemiology, sources of information and giving full bibliographies, it is May's subsequent volumes (1958, 1961a, 1961b, 1965, 1966, 1967a, 1968, 1970, 1971) that provide the essential commentary.

At the various scales of cartographic analysis, whether global, continental, national, or local, demands are frequently mule upon the data base for which detail is not always available. As Harvey (1969, 376) has succinctly remarked

"a map can be no better than the data that is used as input to it..."

Due to the frequent insufficiency, the doubtful reliability, and non-homogenous nature of portions of the data base, both of these world scale atlases contain areas of incomplete information. Dunham and Bailar (1968), and Verhasselt (1974) were confronted with similar difficulties in mapping at the gross scale. Maps at this scale inevitably are little more than general indicators of the distributions of diseases throughout the world. Nonetheless, world maps may provide some pointer to a relationship of disease to environment which may not be readily apparent at a more restrictive scale. Additionally, such maps highlight those areas where the data falls short of the levels of accuracy and detail required for a comprehensive survey of the global distributions of disease.

#### Developed Countries

Smaller areas (at the regional or national level) generally provide data which is of greater reliability and accuracy than that available for global mapping. Therefore, such areas lend themselves to intensive cartographic analysis, and thus are likely to yield more significant evidence as to possible relationships between factors of the environment and health or ill-health.

The United Kingdom offers

"the best laboratory for those interested in the biostatistical approach to medical geography." (Murray, 1967, 303).

The country contains a population number, and consequently enough deaths and 'diseased' cases to give some significance to the analysis of the spacio-temporal variations of mortality and morbidity. Additionally, Murray (1967, 303) notes that

"the population mobility is contained enough so that relationships between disease and environment may be assessed to some degree."

The existence of a National Health Service enables the operative medical and statistical facilities to penetrate throughout society with some equality. The recording of mortality and morbidity data is of an accuracy and reliability attained by few countries in the world. Finally, the subdivision of the country into administrative units, facilitates the plotting of this data on a base map of considerable detail.

Primarily, two geographers have been responsible for the cartographic portrayal of the United Kingdom's mortality and morbidity statistics. Murray (1962) illustrated, for the period 1948-57, the areal mortality rate variations for total deaths and for a number of categories of causes of death for England and Males. The map of deaths from all causes for both sexes is almost divided into the two-fold division of Highland Britain and Lowland Britain. Two types of area, the older industrial areas (e.g. the towns of Lancashire, and the mining valleys of South Vales), and the remote poorer rural areas (especially the Pennines, the Lake District, and north and west Tales) have death rates well above the national average. The map of deaths from bronchitis (Fig. 6) leaves no doubt that this is a disease of the towns and cities. Where incidence is low it increases with decreasing distance from the city, as seen, for example, with Bristol, Ipswich, Southampton, and especially Hull. Where incidence is high, as in South Wales and Lencashire, it is higher in the towns.

Later, Murray (1967, 301), through the use of the chloropleth technique (as in the earlier work), endeavoured to

"...illustrate the spatial pattern of apparent mortality variations in the conterminous United States and in England and Wales through the medium of maps."

No attempt was made at detailed interpretation of the patterns portrayed as the author deemed it preferable that the reader formulate his own interpretation.

A well-documented work on cancer mortality in Wales for the period 1947-53 was presented by Howe in 1960. Concluding this study,



FIG. 6 Map of S.M.R.'s for males from bronchitis in England and Wales, 1948–57. From Murray, A., 1962, Ann. Assoc. Am. Geogrs., vol 52, 136.

he wrote of the utility of applying geographical techniques to medical

problems:

"the accurate recording of facts on a map undoubtedly facilitates the work of correlation, and it becomes possible to further the statistical analysis by a demonstration of space-relationships. In this respect the geographer's sense of regional variation can often assist in clarifying the problem for the doctor." (Howe, 1960, 212).

In 1963 the first edition of the <u>Mational Atlas of Disease</u> <u>Mortality in the United Kingdom</u> was published with Howe as editor.<sup>2</sup> Prepared under the aegis of the Royal Geographical Society, the stated object of the Atlas was

"to show through the medium of maps the spatial patterns of variations in disease mortality in the United Kingdom... data, embodied in a map, provide an instant visual impression which relates the figures immediately to their appropriate geographical position." (Howe, 1963, 1).

The introduction to this work is cautious, taking full account of the inherent difficulties of disease mapping and acknowledging sources of possible error in the statistics. As appreciable geographical variations exist in the local age-sex structures of the population in the different parts of the country, all the maps, with the exception of the infant mortality rate, are based on a standardised mortality ratio (S.M.R.) (which relates the actual deaths in an area to age-group, sex, population, and the United Kingdom average death rate for that disease).

In addition to total mortality, fourteen classifications of death (based on the International Statistical Classification of Diseases) are cartographically portrayed in 320 administrative units, separately for the sexes, for the period 1954-58. The maps are of the chloropleth type with the symbols for the S.M.R. categories differentiating those administrative units whose mortality ratio is either above or below the national average (Fig. 7). Each set of maps is preceded by a brief text which explains the more salient features of the areal mortality variations.

In 1970 an enlarged and revised edition of this work was published, based on mortality data for the period 1959-63. To those engaged on the project this afforded the opportunity to extend the basic principles of the earlier work by including

"...more up-to-date mortality data, to undertake statistical testing of the computed standardised mortality ratios...and to suggest some reasons for the distributions shown by the maps." (Howe, 1970a, 95).

This latter edition employed a demographic base map for the presentation of areal data. The 1963 atlas utilised geographical base maps which not only gave

"...undue prominence to mortality data of extensive, sparsely and unevenly populated areas of the United Kingdom but provided insufficient weighting in the case of limited and localised areas of dense population associated with towns and cities." (Howe, 1971a, 15).

Sutherland (1962) had experienced this deficiency of the geographical base map in his work on visually representing Scottish statistics. Demographic base maps (Fig. 8) are produced so that

"the area of each administrative unit is made proportional to its population whilst contiguity of geographical positions of the units are maintained as far as is possible." (Forster, 1972, 59).



FIG. 7 Male S.M.R.'s from bronchitis, 1954–8, portrayed on a geographical base map. From Howe, G.M., 1963, 1970a, National Atlas of Disease Mortality in the United Kingdom, 59.



FIG. 8 Male S.M.R.'s from bronchitis, 1959–63, portrayed on a demographic base map. From Howe, G.M., 1970a, 132.

Such maps, therefore, relate disease ratios to both local populationat-risk and to geographical position (Hunter and Young, 1968).

Subsequent research by Howe (1968a, 1968b, 1970b, 1970d, 1970c, 1971b, 1972b) has focused upon cortain problem areas revealed through these two atlases.

In the Soviet Union medical cortography, regarded as an integral part of medical geographic studies, has been extensively developed by the Medical Geography section of the Institute of Geography of Siberia and the Far East of the Siberian Department of the Academy of Sciences U.S.S.R. at Irkutsk. This research unit produced the medical geographic maps for the <u>Atlas of Transbaykalin</u> (Vorob'yev

<u>et al</u>, 1969).

"These maps reflect the medical-geographic character of the natural territorial complexes which are extremely complex in composition and possess a peculiar structure of territory, the Chita region and Buryat ASSR, which includes four physical-geographic regions." (Ignat'yev, 1968, 498).

Learnonth (1972b, 145) in reviewing the contents of this atlas has written:

"It is difficult to think of the application of a similar amount of high quality cartographic and printing skill to a regional atlas elsewhere, or of the allotment of such an important component to medico-geographical maps."

Based upon their experiences in compiling the medical geographic section of this atlas, Vorob'yev <u>et al</u> (1969) produced an important methodological work entitled <u>Principles and Methods of Medical</u> Geographic Mapping.

#### Underdeveloped Countries

Underdeveloped countries, rather against expectation Learnonth (1972b, 151) notes.

"have provided studies which show how atlas-based studies can be analytical and hypothesis-finding, without...outrunning the content proper to an atlas or the competence of an atlasmaker or atlas-making tean."

Learnonth has extensively researched the medical geography of the Indian sub-continent (1952, 1957, 1958). He evolved a chloroploth method of plotting on the same map health and disease data concerning both intensity and variability of incidence (1954). Closeness of shading increased for higher incidence, while direction of shading was altered for three grades of variability - vertical for high variability, obligue for medium, and horizontal for low variability. The same author used the isopleth technique to show urban infant mortality rates for India (1965). More detailed mapping (1961, 10) illustrated

"that there are differing patterns of disease-association in different types of human settlement and in differing environments within even a part of the sub-continent."

Despite problems of data reliability and sufficiency, various areas of Africa have become the milicu for some excellent cartographicbased investigations in medical geography.

The maps in the regional geo-modical memoirs on Libya and on Ethiopia (Learmonth, 1972b) serve

"...not only as an illustration of the interdependence of the occurrence of diseases and the character of the region ...but also as a prognosis of the development of the occurrence or the absence of certain diseases for the tegion." (Jusatz, 1969, 22). Brown (1955) used proportional circles to demonstrate the spatial distribution of various diseases (e.g. cerebrospinal meningitis, sleeping sickness, relapsing, and leprosy) in Nigeria during the late 1940's and early 1950's. While in some instances these maps show a marked regional localisation of certain diseases, frequently case numbers have not been 'rated' to the population-atrisk in a particular area. Consequently, possible meaningful spatial distributions may have been masked with the incidence of apecific diseases perhaps being no more than a more 'shadow' of the population distribution.

In Uganda, medical men, statisticians, and geographers collaborated in producing the <u>Uganda Atlas of Disease Distribution</u>. Edited by Hall and Langlands (1968) this work treats selected diseases or topics covering groups of diseases in order according to the International Classification (1965 revision). Although restricted by imperfect data, the atlas does contain as much information as was available about the distribution of each disease (or groups of diseases) in Uganda. Wherever possible these distributions have been set against the relevant environmental and vector factors. The fifty maps are accompanied by short analytical commentaries written by an authority in the field, and a bibliography.

A variety of cartographic techniques were employed to portray the basic information. The spatial distribution of yellow fever cases was plotted using the dot technique, while a chloropleth map highlighted the differential incidence rates (per 100,000 population

aged 0-15 ye rs) of Burkitt's tunour. Flow lines give the directional spread of trypanosomiasis and highlight the diffusion of the disease from source areas along the northeastern shore of Lake Victoria and in the northwest sector of the country. Bar graphs illustrate and emphasise not only the spatial distribution but also, in some instances, temporal changes in the incidence of policyelitis, cormon helminths in children, pulmonary tuberculosis, and meningococcal meningitis. The cartography, however, is uneven reflecting the participation of a large number of individual contributors to the project. Nonetheless, the atlas is

"of considerable value in demonstrating the importance of human disease as a factor of the environment as a better approach to regional geography and to the biogeographer." (Langlands, 1969, 13).

In Central Africa, McGlashan's (1968a) doctoral thesis was based on an atlas of disease distribution. It also included analytical work into factors which may influence disease, with any new associations energing from the geographical comparisons being offered as tentative hypotheses for subsequent testing in other disciplines.

After this survey, individual topics have been further examined, some with significant ranifications. For several years it had been recognised that desophageal cancer had a remarkable geographical distribution in Africa. Reports by Ahmed (1966) and McGlashan (1967c) emphasised the difference of incidence in qualitative terms. Using cartographic and simple statistical correlation, McGlashan (1969d,1972e) found a significant order of spatial correlation between

the geographical pattern of this disease in Central Africa and the drinking of sugar-based alcoholic spirit. Through this McGlashan has been credited with having

"...solved the problem of differential incidence of cancer of the oesophagus in East Africa." (Learnonth, 1970, 13). Research, however, is continuing throughout Africa into the causal relatedness of oesophageal cancer to the environment (Bradshaw and Schonland, 1969; Ahmed and Cook, 1969; Cook, 1971; McGlasham and Harington, 1973). The Transkei region of South Africa,with the second highest incidence of oesophageal cancer in the world, has become a specific rea of concentration for such studies (Rose, 1967, 1968, 1973; Harington and McGlashan, 1973; Warwick and Harington, 1973; Rose and McGlashan, 1974; Harington and McGlashan <u>et al</u>, 1974).

The exceptionally high incidence of blindness in the Luapula province of Zambia has stimulated a number of medical geographic studies employing cartographic analysis (Awdry <u>et al</u>, 1967; Anderson, 1971). McGlashan (1966b, 1972c) mapped out the distribution of the disease and investigated (1969a) the association of blindness to measles and malnutrition.

In 1959, Burkitt, a surgeon in Uganda, noted a large number of cases of children with malignant tunours of the jaw. He then toured eastern and central Africa, plotting the incidence of the disease. The research showed that the tunour did not occur above a height of 5,000 feet near the equator in East Africa, and Burkitt (1962b) suggested that this critical altitude lowered as latitude increased. He also suggested that altitude was important because it reflected air temperature conditions and that the minimum temperatures of the coldest seasons were of special significance. By comparing maps of the disease's incidence with other geographical distributions, it was shown that the lymphoma distribution was closely similar to that of mosquitoes and tsetse-flies. From this, an association was inferred between the lymphoma and an anthropod-borne virus. McGlashan (1965, 38) has concluded of this work that

"amongst medical-geographical studies in Africa those of Burkitt should perhaps take price of place."

Haddow (1963) postulated a 'temperature gradient' whereby the tumour was absent above a critical height, which was placed at 5,000 feet on the equator, but fell steadily northward and southward from the equator at a rate of  $\pm$  1,000 feet per 5° of latitude. The critical temperature it scemed was a minimum mean temperature of  $60^{\circ}F$  (15°C) in the coldest month.

McGlashan (1969b, 113) attempted

"... to examine Burkitt's conclusions by a geographical approach to the same hypotheses in certain regions of African distant from his Uganda study area."

From the resultant cartographic analysis, McGlashan (1969b) confirmed an inverse association of the tumour with altitude but found the tumour incidence tended not to vary significantly with the mean minimum temperature of the coldest month. This latter evidence provided

"...strong, but not compelling, evidence against the hypothesis of a totally virus-borne causation of the African lymphoma." (McGlashan, 1969b, 118).

The map work, therefore, provided a basis for this analysis, partly to reassess, and urge subsequent reappraisal of the existing hypotheses, and partly to provide, through new hypotheses, a starting point for future investigations. This is the contribution that medical geographic studies can make to disease aetiological investigations.

Thus, through the application of geographical concepts and techniques, the study of the African lymphoma has been greatly advanced. Cook and Burkitt (1971, 20) have summed up the role of geography in the study of this disease:

"the wide implications of this tumour, which now impinge on many cancer problems, all stem from studies in geographical distributions and help to illustrate the significance of examining the geographical patterns of disease."

#### Disease Maps by Computer

One of the most promising developments in medical cartography in recent years has been the advent of computer graphics, or the construction of maps and diagrams by electronic computer. Its principal advantages are the speed, efficiency and reliability with which the computer can process, store and map the medical data. Armstrong (1966, 1972a), Howe (1969a), McGlashan and Bond (1970), and Monmonier (1970) have discussed the application of the computer to medical cartography and the increased utility of the ensuing maps. A major project in the U.S. employed the computer in the production of disease maps (Hopps, 1969). A report was subsequently produced (Hopps <u>et al</u>, 1968) detailing the objectives, methodology, and results of this research.

# Methodological Considerations in the Display of Health and Ill-Health Data

The methods of portraying spacio-temporal variations of mortality or morbidity on maps are the same as utilised for other geographic phenomena. Medical geographic maps, however,

"are often for the instruction or action of physicians untrained in any cartographic awareness. It is therefore more than ever important that the quality of data utilised and the limitations of mapping conventions be absolutely explicit. To non-geographers a printed map assumes canonical authority! We must ourselves beware of conveying spurious reliability." (McGlashan, 1973, 210-11).

Generally, the cartographic technique employed in seeking a definition of distributions, whether in space or time, is dependent on the nature of the data to be portrayed. For example, sophisticated mapping techniques are appropriate only for higher quality data.

With due consideration to the data base, the medical geographer has, broadly, four types of mapping available to him: dot, 'rate', isopleth, and probability mapping.

## Dot Mapping

The simplest method for showing general spatial distributions involves the use of dots. As this technique graphically represents the non-uniform distribution of the phenomena being mapped it is appropriate to define the distributional density of mortality and/or morbidity.

Although the underlying principle of the dot map is simple, a number of ancillary problems must be considered. As a dot represents a definite number of a mapped phenomena, not only must the size of a dot be determined, but also its 'weight'. The value for which the dot stands is dependent on the degree of development of the phenomena and their geographical distribution. The greater the number of dots on a map the more expressive becomes the distribution portrayed on that map. Therefore, the aggregated 'super-dot' has little distributional meaning, as it may mask small-scale variations in the mapped phenomena.

Applying this technique to medical geography requires that the dots be correctly placed according to the object of the study. For example, in investigating a disease-environment relationship, the dot needs to be placed at the 'site-of-risk'; that is, at the site where a patient was initially at risk to contract the disease. Incorrect dot location may distort further associative analysis of the disease with the environment. The data collected, however, may not yield a precise locational factor which will partly dictate the accuracy of the placement of the dot.

Early medical cartographers demonstrated the utility of this technique for medical geographic studies (Seaman, 1798; Shapter, 1849; Snow, 1855). Stevenson (1965, 260) claims that the

"anticontagionists probably invented it." More recently dot distribution maps have been used as the initial stage of cartographically defining spatial variations of diseases (Harington and McGlashan, 1973; Borman, 1974). Such a map does, however, have the disadvantage of 'mirroring' the total (statistical) population distribution as those areas with larger populations will, generally, provide a greater population-at-risk. To avoid this weakness, the absolute case numbers (whether for health morbidity, or mortality) can be related to the total population-at-risk within a . specific unit of area to produce a 'rate'.

#### Rate Mapping

A rate map is basically a chloropleth map, constructed to show any spatial variations or temporal changes in the 'density' of mortality or morbidity cases that may exist between areas. Gradient patterns of these phenomena may, as a consequence, be detected (Borman, 1974). The effect of transforming a dot map into a rate map has been demonstrated for oesophageal cancer in West Kenya (Ahmed, 1966), and for blindness in Luapula province (McGlashan, 1972c) (Fig. 9a and b).

Two avenues are available for the conversion of a dot map into a rate map:



FIG. 9 (A) A dot distribution map of blind persons in the Luapula Province of Zambia. From McGlashan, N.D., 1972c, 'Blindness in Luapula Province, Zambia', in McGlashan, N.D. (ed), 1972a, Medical Geography: Techniques and Field Studies, 160.



FIG. 9 (B) The basic disease data used in Fig. 9 (A) portrayed as a 'rate' map. From McGlashan, N.D., 1972c, 161.

a) the researcher may accept predefined units of area and calculate a rate for each area. Administrative, and not geographical, divisions are commonly used as ancillary data (e.g. age and sex breakdowns of a population) are often procurable for such areas.
Copperthwaite (1972) used the administrative commune districts of Yugoslav Macedonia; Murray (1967) counties in the U.S.; McGlashan (1972c) census enumeration areas; and White (1972) the county divisions of England and Wales;

b) the alternative method involves superimposition of an artificial grid system over the mapped area. From a count of the population-at-risk and the mortality or morbidity cases within each grid square a rate may be calculated for each quadrat.

Relating case numbers to the absolute (total) population-at-risk produces a 'crude rate'. Such a rate is, therefore, likely to be affected by the age and sex constitution of the population concerned. For example, the greater the proportion of old persons in an area the higher the crude mortality figure will generally be, compared with that figure produced in an area of predominantly younger persons. Depending on the nature of the data available, refinements of this crude rate may be carried out which make due allowance for structural variations of a population. Howe (1963, 1970a) mapped chloropleths of death based upon S.M.R.'s, as did Bako (1973), while Sauer (1962, 1970a), Sauer <u>et al</u> (1970b), Sauer and Parke (1972) used age-sex adjusted and specific rates for mapping.

Determination of class intervals requires consideration so that

the finished map effectively illustrates the most important areal variations. Armstrong (1969) has urged medical geographers to use the standard deviation of S.M.R.'s from the norm (which is 100) as the method of selecting class intervals and assessing significance. McGlashan (1972d) has mapped S.M.R's of stomach cancer in South Africa in classes determined by standard deviation from the norm, and alternatively by scatter diagram.

The construction of chloropleth maps implies two conditions, neither of which is actually true in reality. Firstly, there is an implied presupposition that no variations in the distribution occur within the boundaries of the individual areal units. Secondly, abrupt changes in the distribution may occur along the boundaries between areas belonging to different classes. Disease distribution, however, rarely conforms to administrative boundaries, and changes are most likely to be gradual. Therefore, the boundaries on such a map assume a degree of significance out of proportion to their true importance.

These disadvantages may be overcome by treating the area to be mapped as a continuous surface and employing isopleths of disease or death - what McGlashan (1965) has tormed 'isomorbs' or 'isomorts'.

## Tsolines

Isolines, or contours, are constructed as contrived cartographic devices to connect data points of equal value (McGlashan, 1972b), Learmonth and Nichols (1965) and later Learmonth and Grau (1969) used

this technique in illustrating S.N.R.'s of selected diseases in Australia. Based on sixty-five data points distributed throughout the continent, the maps were valuable

"in bringing out any spatial trends - hills and valleys as it were - from the data. In this respect they are easier to read than the chloropleth maps." (Learmonth and Nichols, 1965, 4).

Isoline maps showing male deaths from pneumonia (1965-66) and those areas with high S.M.R.'s (for both 1959-63 and 1965-66) are examples of this technique as employed in these Australian atlases. (Figs.10 and 11). The maps exhibit a marked inland and rural bias which

"is surely significant, but not surprising, since this is the one important cause of mortality mapped which fairly clearly and generally involves a pathogen or pathogens." (Learmonth and Grau, 1969, 11).

The maps of mortality from cancer of the lung, bronchus, and trachea show a concentration of high values in inland areas (where the population is sparse), although high ratios are discernible in the more densely populated and more urbanised areas (e.g. Melbourne and Sydney).

Through 'isoplenic' maps (isolines of spleen values) Fontaroff (1968) displayed the declining rates of malaria in Trinidad over the period 1945 to 1955. McGlashan (1969d, 1972e) used an isopleth technique for part of his work into the relationship of oesophageal cancer and alcoholic spirits. The <u>Geographical Pathology</u> atlas of Iran (1966) contained a number of such maps, while the <u>Mapping of</u> <u>Disease</u> (M.O.D.) project placed major emphasis on mapping by the contour technique (Hopps, 1969; Hopps et al., 1968).



FIG. 10 Isopleths of S.M.R.'s for males (1965–66) from pneumonia in Australia. From Learmonth, A.T.A., and Grau, R., 1969, Maps of Some Standardised Mortality Ratios for Australia for 1965–66 Compared with 1959–63, Fig. 25.



FIG. 11 Areas of high S.M.R.'s for males from pneumonia in Australia in 1959–63 & 1965-66. From Learmonth, A.T.A., and Grau, R., 1969, Fig. 27.

This form of mapping requires that there be available a large number of points with numerical data on the basis of which the corresponding isoline systems will be drawn. As these points have different numerical indices and the isolines must be drawn using a definite scale of quantitative differences this technique makes extensive use of the interpolation method. Hopps and Cartwright (1972) have discussed the problems of this method, and that of extrapolation in the production of isopleth disease maps. The isoline method can only be used when there is a gradual areal change in the indices. If the data has a random character the isomorts or isomorbs become chaotic in arrungement in order to accoundate the data points and thus cease to be meaningful.

By selecting from the methods described above, the medical geographer can produce maps portraying the spatial patterns or temporal changes of health or ill-health. Under real world conditions, however, diseased or healthy cases will not be evenly distributed across the landscape <u>pro\_rata</u> to population (i.e. at a constant rate of incidence). The operation of random chance will ensure that any patterning of incidence will have inherent variations and thus some irregularity will occur (McGlashan, 1972a, 1974d). Therefore, until the case numbers can be shown to deviate at a <u>statistically</u> <u>significant</u> level from those attributable to the overall 'norm' of cases expected in the general population, local case variations may be put down to the operation of chance factors.

#### Probability Mapping

In 1959 Choynowski presented a paper applying probability testing to maps of brain tumours in parts of southern Poland. Although there were wide variations in the rate of incidence of this disease, only two administrative counties reached the 95 per cent level of significance by Poisson's distribution (Fig. 12a and b). A similar work by McGlashan (1974d), also using Poisson's distribution, was based on incidence rate maps of oesophageal cancer compiled in two earlier South African studies (Burrell, 1969; von Zeynek, 1973). He concluded (1974d, 1623) that

"far from the rates for oesophageal carcinoma in the Glen Grey district differing widely between locations, most do <u>not</u> in fact vary significantly from the district norm. This map based on probability locates the three areas whose case numbers differ at significant levels from those of the district."

The same test has been applied to male stomach cancer deaths among Europeans in South Africa (McGlashan, 1972d); ischnemic heart disease in Tasmania (McGlashan, 1972f); leukaemia deaths in England and Wales (White, 1972); oesophageal cancer (Rose and McGlashan, 1974; Harington and McGlashan, 1973) and three other cancers in South Africa (Harington <u>et al</u>, 1974); and connective tissue di seases in New Zealand (Borman, 1974).

While tests based on the Poisson distribution are the most commonly used in medical geography, other spatial tests of non-random occurrence have also been utilised, especially when larger numbers of cases are involved. For example, the chi-squared test has been



FIG. 12 (A)

FIG. 12 The same base data on the occurrence of brain tumours in the counties of the Rzeszow District of Poland expressed by different techniques: (A) as rates per 100,000 population-at-risk; (B) showing areas with statistically significant divergences of the number of observed cases from expected cases. From Choynowski, Mieczyslaw, 1959, 'Maps based on probabilities'. J. Amer. Stat. Assoc., vol 54, 385–388.



FIG. 12 (B)

applied to assess spatial links of acsociation or causation between the environment and the diseases of diabetes mellitus (McGlashan, 1967a; McGlashan and Bond, 1970), oesophageal cancer (McGlashan, 1969d, 1972e), and the African lymphoma (McGlashan, 1969b). Armstrong (1969)has advocated the useof a further means of assessing significance, that of the standard deviation from the 'norm'. Little use has, however, been made of this technique (McGlashan, 1972f).

## Graphs and Diagrams

Increasingly medical geographers are utilising a variety of other cartographic and statistical techniques, in addition to the map forms discussed, to portray health or ill-health data in a visual form. Reference has been made to the use of bar graphs, proportional circles and flow lines in the <u>Uganda Atlas of Disease Distribution</u> (Hall and Langlands, ed., 1968). McClashan (1967b), like Brown (1955), produced proportional circles to illustrate the distribution of specific diseases in Zambia. Graphs have been chosen principally to show temporal variations of certain factors, or as a presentation of regression lines with significantly varying limits, high and low on each side (Girt, 1972a). Sakamoto (1965, 1968), and Sakamoto and Katayama (1966, 1967) developed line and bar graphs to highlight the seasonal variations of mortality and morbidity in the U.S. from selected causes.

#### Medical Geographic Models

The application of the model typology of Ackoff <u>et al</u><sup>3</sup> to medical geography demonstrates that models have long been used by medical geographers, and the nineteenth century medical topographers (Learmonth, 1968b). In a medical geographical context, iconic models would date at least from Snow's mapping of the 1854 Soho cholera epidemic as related to the water supply; analogue models since Petermann shaded a contour map of cholera in the British Isles in 1852; while Howe's atlas of mortality (1963), and especially the latter edition (1970a) may be regarded as employing symbolic models (Learmonth, 1968b).

Learmonth (1962b) has experimented in building models of a malarial continent (further developed in 1972c), of lung cancer in Victoria (Australia), and

"a simulation model of the movement of infective hepatitis from a Sydney-like capital of a New South Wales like State, and subsequent incidence at its destinations." (Learmonth, 1968b, 6).

While Brownlea (1967, 1968, 1972a) endeavoured to construct a

"...model to simulate a range of spatial and temporal features of infectious hepatitis incidence in the Wollongong system of settlements between 1954 and 1970..." (Brownlea, 1972a, 279).

The task of medical cartography has evolved from the production of maps as mere illustrations of a text, to the contemporary use of a map as a method for suggesting correlations between disease occurrence and environmental factors. Correlations in space, however,
may be as misleading as correlations in time, and the data provided by maps will usually be of this character (Doll, 1959). Therefore, although an apparently adequate hypothesis may accrue from such cartography, maps only offer pointers to possible answers that must be tested in subsequent research. Proof of causation requires strict criteria to be fulfilled (Hill, 1965) and also detailed evidence of the conjunction of the cause and effect in the individual as well as in the community. Medical mapping, as has been shown, can make a vital contribution to the former, but inter-disciplinary co-operation is essential to break a disease causative chain which will lead to the eventual elimination of that disease, and the alleviation of human suffering.

#### Footnotes

1. The following abbreviated table shows the sequence of events as determined by Snow's inquiry (from Hill, 1955, 1009).

Date	No. of fatal attacks commencing on each day
August 26 27	1 1
28 29 30	1 1
31 September 1	5 <b>6</b> 143
2	116 54
4 5	46 36
67	20 28
8 ≠ 9	12
11	5
13 14-30	3 18
Date unknown	45

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Pump handle removed

- Reviews of this atlas are given by Murray, N.A., <u>Geogr. Rev.</u> 1964, vol. 54, 582-4; and May, J.N., <u>Geogr. Journ</u>. 1964, vol. 130, 268-70
- Ackoff, R.L., with Gupta, S.K., and Minas, J.S., 1962, <u>Scientific method: optimizing applied research decisions</u>. New York.

PART TWO

# The Medical Geography of

**Rare Systemic Connective Tissue Diseases** 

#### CHAPTER ONE

#### INTRODUCTION\*

Despite extensive study and clinical description of rare systemic connective tissue diseases during recent years, this group of disorders remain of obscure aetiology (Siegel <u>et al</u>, 1962; Pearson, 1962; Dubois and Tuffanelli, 1964; Logan <u>et al</u>, 1966; Masi and D'Angelo, 1967; Kurland <u>et al</u>, 1969; Wigley, 1970; Medsger <u>et al</u>, 1970; Medsger and Masi, 1971; Winkelmann, 1971; Wallace <u>et al</u>, 1972; Hahn <u>et al</u>, 1973; Siegel and Lee, 1973; Dubois, 1974a; Dubois <u>et al</u>, 1974).

# The Rationals for a Medical Geographic Study of Connective Tissue Diseases

A medical geographic study of these diseases may provide new information resulting from a spatial and temporal definition of the disease distributions, which may subsequently be used as a foundation for disease-environment associative studies. Until it is known with confidence the location, in space and time, of these diseases it is meaningless to try to ascertain what other factors occur in similar patterns (McGlashan, 1974a). Through the employment of the macroscopic techniques of medical geography, specialists trained in the use of

<sup>\*</sup> The Clinical aspects of this Chapter were written with the assistance of Dr R.A.D. Wigley, Palmerston North Medical Research Laboratory.

microscopic techniques, will be able to focus their research resources upon those environmental factors revealed as being associated with one or all of the diseases.

The utility of a medical geographic approach to these diseases will not diminish if negative findings are produced in the resultant analysis. Such results will establish that there does not seem to be a relationship evident between the studied environmental factor, or factors, and the incidence of connective tissue diseases in New Zealand. Future research can therefore, concentrate on other avenues of possible association or causation, or on re-examination of the current hypotheses under different conditions.

In either instance, the medical geographer has a responsible and positive contribution to make to research into the actiology of rare connective tissue diseases.

#### The Aim of the Present Study

The intent of this research project is to provide a perspective on the natural history of connective tissue diseases, collectively and severally, through the employment of medical geographic techniques, with a view to furnishing clues to their actiology or to aid in focusing future investigation.

## The Connective Tissue Diseases

The diseases involved in this medical geographic study are dermatomyositis and polymyositis (International Classification (eighth revision) of Disease (I.C.D.) categories 716.0 and 716.1), polyarteritis nodosa (I.C.D. 446.0), scleroderma (I.C.D. 734.0), and systemic lupus erythematosus (I.C.D. 734.1). All are chronic diseases with an episodic course, and have a number of features in common which may make it difficult to separate them in some patients. Until effective treatment was available (Dubois, 1974a) these diseases were considered to be uniformly fatal, but increased awareness of them. together with improved laboratory methods for diagnosis, particularly with respect to systemic lupus erythematosus (SLE), has lead to prolonged survival in many cases. Seventy to one hundred years ago these entities were separated out from the other chronic skin and rheumatic diseases, as it was increasingly recognised that almost every organ system in the body could be affected by them, hence the title systemic and the term multiple system disease sometimes used in the U.S.A.

Pathologists regarded these diseases as low grade inflammatory disorders of the connective tissue and though other tissues are frequently involved the general term of connective tissue disease has now been used to describe these complaints collectively. Collagen, which forms the basic building material of connective tissue, was suspected (in the 1950's) of bearing the brunt of the attack and the term collagen disease was introduced. Subsequent research has

revealed however, that collagen itself does not appear to be abnormal in these diseases with the exception of scleroderma, in which there is an increase of apparently normal collagen in the deeper layers of the skin. Therefore, the term collagen disease has been discarded.

The common connective tissue disease which has been excluded from this study is rheumatoid arthritis. This disease, chiefly affecting the synovial tissue of tendons and joints, is generally not fatal, but causes immense disability and pain. As it is closely related to the connective tissue diseases of this survey, it is believed that the discovery of the cause of, or the detection or interruption of some part of the cause of the other diseases of this group. There is a variant of rheumatoid arthritis called Sjögrens syndrome which affects the lachrimal and salivary glands in addition to the joints and this can also be difficult to distinguish from SLE. Some of the patients categorised in the present study as having SLE also have features of this syndrome, but cases primarily diagnosed as having Sjogrens syndrome were not included.

# The Principal Clinical Characteristics of the Connective Tissue Diseases

#### Systemic lupus erythematosus

The most distinctive feature of this disease is reddening of the skin of the cheeks, forehead and other parts of the skin exposed to the sunlight. In the acuto form, which may be precipitated by

sunburn, the skin blisters, weeps and fails to heal as ordinary sunburn does. In a chronic form, which may be an isolated complaint (discoid lupus erythematosus), this discolouration of the skin may be more or less permanent though varying in degree. Sir William Osler early this century first noted that this complaint could also affect other parts of the body. An acute inflammatory arthritis affects the joints and a nephritis affects the kidneys so that protein and red cells appear in the urine. Since then it has come to be realised that the heart. lung, brain, bowel and bones can be affected together with various abnormalities in the white cells, platelets and red cells of the blood. Apart from the rash, and the kidney disease, involvement of the other organs has no characteristic pattern to distinguish it from other disease of the same organ. Each of these justifies a diagnostic label itself, so that a number of organs become involved at the same time or sequentially in separate episodes of the disease suggests a diagnosis of SLE. The same is true of the other diseases in this group to a lesser extent and the term multiple system disease is some times used as a general term for these complaints. In 1948-49 it was found that sixty to seventy per cent of patients with this disease had abnormal blood cells called LE cells (Dubois, 1974a). These are white blood cells which are in the process of engulfing the degenerate nuclei of other blood cells. It has subsequently been shown that these cells have been damaged by antibodies to nuclear material. These are called anti-nuclear antibodies (ANF) and this discovery has lead to the general introduction of laboratory tests for these antibodies facilitating diagnosis. Therefore, a rise in incidence since the general

availability of these tests between 1958 and 1966 would be expected. Difficulties in the precise classification of this disease have been partly resolved by the American Rheumatism Association scoring system (<u>Bull. Rheum. Dis</u>. 1971) which requires a score of at least four to make a definite diagnosis out of a possible of fourteen features (Appendix A).

### Polyarteritis nodosa

This disease may, like SLE, affect any organ in the body. It does this primarily by producing an inflammatory process in the walls of arteries which may become blocked and this in turn produces the symptoms. Like SLE, this disease may be present as a multiple system disease, initially difficult to classify, with a fever responding at least temporarily to steroid treatment. Again like SLE, involvement initially of one organ only may simulate another disease entity so that lesser degrees of polyarteritis may escape detection. Polyarteritis nodosa often presents with a fever not otherwise explained, frequently with an inflammatory arthritis or involvement of the kidney evidenced by red cells and protein in the urine. Sometimes involvement of the small vessels to the peripheral nerves leads to patchy paralysis. The small vessels to the skin may be blocked producing patchy areas of inadequate circulation which may slough to form chronic ulcers. These are usually on the lower leg. Any other organ in the body may be involved in this vascular blockage, particularly the brain, heart, or bowel. In a small proportion of cases there is an increase in eosinophil cells in the blood with asthma and in a few cases the inner part of

the nose is destroyed (Wegener's disease). This rare sub-variety has been included in this study as polyarteritis nodosa. The diagnosis of polyarteritis nodosa is established by removing an affected piece of tissue and demonstrating the damage to the vessels walls with surrounding infiltration of inflammatory cells which are small round cells in a low grade process and in an acute phase polymorphs and eosinophils. The actiology of this disease has been reviewed by Wigley (1970).

### Sclerodorma

This disease may have a very gradual onset. The patient may have noted changes many years before requesting advice. Characteristically the skin of the finger tips thickens and no longer wrinkles easily when pinched up. Eventually the increased collagen in the dermis (the deeper layer of the skin) leads to stiffness of the fingers which become susceptible to minor injuries and do not heal readily. There is usually Raynaud's phenomenon in which the circulation to the fingers is interrupted causing bluish discolouration, which is worse in the cold. Later, deposits of calcium may form under the skin, and these may be shed from time to time. In the more generalised form of this disease the skin may be thickened over the forearm, of the face, and eventually the whole surface causing increasing discomfort and invalidity. The musculature of the oesophagus becomes involved causing difficulty in swallowing. The small bowel may be affected so that food is not absorbed properly with resulting loss of weight. The

heart may also be affected and death frequently ensues when the kidney becomes involved with a consequent rise in blood pressure. This is the most clearly defined of all the connective tissue diseases in this study.

# Polynyositis

The low grade chronic inflammatory process of this disease has its major effect on muscle, producing progressive loss of muscle power, wasting, and tenderness of muscles. This can lead to general paralysis and a fatal outcome, but if appropriately treated with cortico-steriods partial or complete recovery results.

If the skin is involved in this complaint it is called dermatomyositis. With this disease, the skin becomes reddened, thickened, and a bluish discolouration appears below the eyes while the skin over the knuckles develops a characteristic tissue paper appearance referred to as 'collodion patches'. In children this occurs as an isolated disorder which is usually fatal with an indifferent response to steroids. In adults it has been frequently claimed that dermatomyositis is associated with cancers, and that the cancer is the cause of the disease. Not all studies, however, have supported this contention. A subsidiary analysis to the present study has been instituted to test the validity of this hypothesis.

#### Non-specified Connective Tissue Disease

Following classification of the diseases in this general group of connective tissue disease into one of the above categories, a group of patients remain who cannot clearly be diagnosed into a specific category, but who have many of the relevant features of connective tissue disease. It is this group and the patients, which show features predominantly of one disorder with some features of one or more other disorders that has lead some researchers (Klemperer <u>et al</u>, 1942) to view these diseases as a spectrum of the same disease with no clear distinction between each category. In the present study allowance has been made in the scoring system for inclusion of such cases, and they contribute to the number of cases in the category labelled 'connective tissue disease'. This is not to be confused with the recently described mixed connective tissue disease syndrome (MCTD) in which similar clinical features are associated with an RNAas sensitive antinuclear antibody (Dubois, 1974a).

# Human Populations Affected by Connective Tissue Disease

To establish a comparative framework within which the findings of the present study, with regard to the population affected, may be evaluated, necessitates a detailing of the structure of populations previously found to be affected by these diseases.

# Systemic Lupus Erythematosus (SLE)

The mean age at onset of symptoms has generally been placed in a range from 26 to 30 years of age (Dubois and Tuffanelli, 1964; Maddock, 1965; Estes and Christian, 1971). Kurland <u>et al</u>,(1969) placed the mean age at onset at forty years of age, while the oldest age of onset recorded has been eighty-three years of age (Dubois, 1974b). Approximately sixty per cent of cases are in the age group twenty to fifty at onset. Both Dubois and Tuffanelli (1964) and Maddock (1965) noted respectively fifty-six and sixty-one per cent of their cases being thirty years of age or younger at onset of symptoms. Siegel and Lee (1973) observed a maximum incidence rate for females in the age group fifteen to forty-four years.

A distinct sex bias has been recorded in previous studies, with approximately eighty to ninety per cent of recorded cases being female (Siegel <u>et al</u>, 1962; Siegel and Lee, 1973; Dubois, 1974b; Dubois <u>et al</u>, 1974).

A differential attack rate on various races has been documented (Siegel and Lee, 1973). Siegel <u>et al</u>,(1962) found in New York city a higher incidence, prevalence, and mortality SLE rates in non-white and Puerto Rican populations than in the white population. Dubois and Tuffanelli (1964), Dubois (1974b) and Dubois <u>et al</u>,(1974) did not observe a similar racial predilection.

Dubois <u>et al</u> (1974) have recorded that the median time from diagnosis of SLE to death is 3.5 years. The same survey also showed

that at successive decades the median age at death had increased from thirty years of age to forty-five. Improved methods of diagnosis can lead to inclusion of less severely affected cases and no apparent decrease in mortality.

# Polyartaritis Nodosa (PN)

This disease may occur at all ages, but the majority of patients are in the fourth and fifth decades of life (Kurland ... <u>et al</u>, 1969). While the disease is rare in ages under twenty and over sixty-five cases have been recorded in the aged and in the first year (Benyo, 1968).

Unlike the other diseases in this study, polyarteritis nodosa frequently predominates in males (Kurland <u>et al</u>, 1969; digley, 1970). The sex ratio of males to females has been placed as high as 4 : 1 (American Rheumatism Ass. 1959).

Masi (1967) studying fatal polyarteritis nodosa in Baltimore (U.S.) found a mortality rate twice as high for Negroes as for whites, and a higher incidence in female Negroes than in the males of the same race.

# Scleroderma (SCL)

Tuffanelli and Winkelmann (1961) have reported that only 8.8 percent of their patients had onset of symptoms in the first two decades of life. Onset age ranged from five to eighty-six years, with a median of forty years. Medsger and Masi (1971) corrobrated this finding, with 8.1 per cent of their patients showing symptoms of onset of the disease in the first two decades. There were few childhood cases recorded compared with adult cases, and no male patient under age twenty-five was identified. Therefore, unlike SLE, which has its highest incidence and mortality in the childbearing ages and up to the age of fifty, scleroderma shows increasing incidence with age, peaking in the oldest age groups (Medsger and Masi, 1971). The median interval from onset of first symptoms to diagnosis has been found to be about seventeen months (Medsger and Masi, 1971).

Fenales have been recorded as predominating uniformly in all reported series of scleroderma patients, comprising 58 to 90 per cent of cases (Medsger and Masi, 1971). Masi and D'Angelo (1967) reported a sex ratio of two or three females to one male, and a similar ratio has been found by Tuffanelli and Winkelmann (1961), and hedsger and Masi (1971).

Initially, Masi and D'angelo (1967) revealed a higher mortality rate for negro females when compared with white females. Subsequent research has not, however, indicated a differential attack rate between races (Medsger and Masi, 1971). Other reports have shown no accord with respect to the varying incidence of scleroderma on different racial groups.

## Polymyositis and Dermatomyositis (PMS/DMS)

Pearson (1966) has commented that these diseases occur about as commonly as progressive systemic sclerosis (scleroderma), half as frequently as SLE, and twice as frequently as polyarteritis nodosa. Although the age of onset varies widely, the largest number of cases begin in the fifth and sixth decades of life (Pearson, 1962; Kurland <u>et al</u>, 1969). Winkelmann <u>et al</u> (1968) reported a binodal distribution of the onset ages of their patients with peaks at the first decade and in middle age, and trough in the third and fourth decade. A similar bimodal distribution has been noted by Logan <u>et al</u> (1966) and Medsger <u>et al</u> (1970). Death has been found to occur most frequently in the first two years of disease (Wallace <u>et al</u>, 1972).

Females are generally affected nearly twice as often as males (Pearson, 1962, 1966; Logan <u>et al</u>, 1966; Kurland <u>et al</u>, 1969), although Medsger <u>et al</u> (1970) observed a smaller sex ratio of females to males of 1.5 : 1. Where malignancy is associated, however, males have a 3 : 1 predominance (Pearson, 1966).

The general susceptibility of female Negroes to connective tissue diseases is again evident with polymyositis. Cobbhas shown that age-adjusted U.S. mortality data for dermatomyositis demonstrates a non-white female to white female ratio of 2 : 1 (Medsger <u>et al</u>, 1970). Medsger <u>et al</u> (1970) observed an incidence in Negro females significantly different from that in white females and four times greater. It was also found that the incidence in Negroes of both sexes was

earlier and higher than in whites of both sexes, while in Negro females the peak occurred at older ages (fifty-five to sixty-five age group, compared with the forty-five to fifty-four age group peak for white male, white female, and Negro male patients).

# Causative Hypotheses of Connective Tissue Diseases

In selecting parameters for testing for association with the distribution of the disease or diseases, under study, a medical geographer utilises aetiological hypotheses postulated by medical researchers. Therefore, a medical geographer considers the geographical evidence in relation to medical hypotheses (McGlashan, 1973).

#### SLE

The role of sunlight in precipitating and aggravating skin lesions of SLE has been well documented (Epstein and Tuffanelli, 1974). Onset and progression of the disease frequently follow excessive sun exposure, and the incidence of the disease has been found to be significantly higher in the spring and summer than in the winter. It is not clear, however, whether this is a basic cause of the disease or merely a triggering factor. Areas of the body not exposed to sunlight are sometimes involved and the process rarely clears with simple elimination of sun exposure. Development in complete independence of the effects of sunlight has been recorded (Epstein and Tuffanelli, 1974). Nonetheless, there is a suggestion from animal work that exposure to ultra-violet light causes the release of altered nuclear material which in turn results in the production of antibodies to this material and so to an illness not unlike SLE.

The relationships of SLE to sex, to certain ethnic groups (Siegel <u>et al</u>, 1962; Siegel and Lee, 1973; Dubois, 1974b; Dubois <u>et al</u>, 1974) and to familial occurrences of the disease (Dubois, 1974b) have suggested environmental or genetically determined factors in this disorder. Studies of the NZB x NZU hybrid mice which developed a very similar disease suggests a complex pattern of inheritance as neither parent develops the florid disease, yet this occurs consistently in all the hybrids (Helyer and Howie, 1963).

#### Polyarteritis Nodosa

Inappropriate immune response has been postulated as the cause for this disease. Usually an allergic response sometimes with an increase in esoimophil cells in the blood and a generalised damage to the blood vessels is assumed in the allergic angiitis of Zeek (1953). The commonest variety has a more chronic relapsing course in which there is no specific evidence of allergy and this is the largest sub-group and the most difficult to distinguish from SLE. The same aetiological possibilities arise from this disease as SLE.

The possibility of a virus, and emotional and physical stress contributing to the actiology of this disease has been mooted (Wigley, 1970).

# Sclerodorma

Information on the causation of this disease is very meagre. Occupational exposure to silica dust has been postulated as a possible contributory cause of seleroderma. Erasmus (1957) drew attention to the increased incidence of this disease among gold miners in South Africa, while also noting a report by Bramwell (1914) of seleroderma among Scottish stonemasons. Rodnan <u>et al</u> (1967) found that twenty-six of the sixty men in their survey with seleroderma had been coal miners or engaged for long periods of time in other occupations in which there was prolonged and heavy exposure to silicious dust. Freneaux <u>et al</u> (1973) also observed a similar association. Masi and D'Angelo (1967) however, have argued against silica exposure as a principal factor in causation. This study found no association of the disease with socio-accommic or occupational factors.

# Polymyositis and Dermatomyositis

These discusses have not been extensively studied from the point of view of actiology. During the collection of data for the present study if was found that a number of polymyositis patients had also been admitted to hospital with alcoholism. Alcohol causes a muscle damage which may be difficult to distinguish microscopically from polymyositis so that the possibility that this is an error of classification arises (Pollock, 1974). This problem is being studied further. The alleged association with malignant disease is referred to above.

No epidemiologic evidence of a direct infectious agent or communicable disease actiology was found in the patients surveyed by Medsger <u>et al</u> (1970). Despite differential racial incidence of the disease, no socio-economic or other environmental associations were established.

Although a few reports of multiple occurrence of the disease in the same family and in twins (Lambie and Duff, 1963) have been made, in two large series family aggregation was not found (Barwick and Walton, 1963; Pearson, 1966).

Exposure to sunlight has been postulated as a precipitating factor in the occurrence of this disease (Barwick and Walton, 1963).

The purpose of this research was to test a number of hypotheses, and where applicable compare the results with those obtained in overseas studies. The scope of the consequent analysis was determined by the nature and reliability of the data available. It is therefore, important to take cognisance of the data base used in this medical geographic study of connective tissue diseases within the New Zealand environment.

#### CHLIPTER TWO

#### THE DATA BASE

Due to the nature of the data available, the methods employed for collection and verification of data, and the subsequent refinement of the data into a form suitable for a medical geographic analysis, a New Zealand wide survey could not be conducted.

The area of study, therefore became (Fig. 13):

a) that area of the North Island of New Zealand south of, but including, Dannevirke County to Cook Strait;

b) and the total area of the South Island of New Zealand excluding the provinces of Nelson and West Coast.

This area contained, at the 1971 New Zealand population census, 42.8% of the total New Zealand population.

The study was a retrospective survey covering the time period from January 1, 1950 to Lugust 31, 1973 (inclusive).



#### Mortality and Morbidity

Two types of basic medical diagnostic information are available to the medical geographer for analysis. These are:

a) data pertaining to deaths from a disease or other cause called mortality data;

b) and morbidity data which is concerned with illness or sickness suffered from a disease or some other cause. This may be expressed in two ways: either by incidence, which is a measure of the attack rate of a disease or some other cause, representing the number of new cases of a condition or disease in a given population during a stated period of time; or by prevalence of a disease or condition, which is the total number of existing cases, old and new, in a defined population at a stated time or over a stated period of time (Hill, 1966).

This present survey was concerned with morbidity rather than mortality data. The factors influencing this decision were that:

a) the uncommon occurrence of connective tissue diseases in populations would result in a diminished number of cases in the survey if only mortality figures were included;

b) in view of the chronic nature of the diseases involved, mortality data would not furnish information pertaining to the spacio-temporal location and ancillary data of patients when they were exposed to the risk of contracting connective tissue diseases; c) these diseases affect more than one part of the body so they may mimic other diseases. Therefore a death certificate may not specify that a patient was suffering from connective tissue disease, and thus an 'under-recording' of this type of disease would occur if mortality data was used as the base information for this study;

d) the laboratory and clinical information necessary for constructing the scoring systems, used to confirm or reject the diagnosis of connective tissue disease for a patient, could not be obtained from mortality data.

#### Source of Medical Morbidity Data

The rarity of connective tissue diseases, and the lack of a practical mass-screening test precluded direct population sampling for suspected cases. A sample size for such a survey may be as large as half a million individuals. If all patients with requisite symptoms sought medical attention and all were appropriately classified the ideal would be achieved. The nature of these diseases presents some difficulty for precise classification and, therefore, until connective tissue diseases are fully developed they may escape appropriate classification.

Since the diseases are chronic and in general progressive, almost all patients with overt disease will, at some stage of the disease development, be admitted to a hospital to be fully studied and eventually classified as having definite or possible disease in one of

these categories. Therefore, the search for cases depended on a review of clinical and laboratory reports from all available sources. For connective tissue diseases these problems have been reviewed by Medsger <u>et al</u> (1970).

It is estimated that at least 81.1 per cent of patients treated in New Zealand hospitals are treated in a public hospital (<u>Medical</u> <u>Statistics Report, 1969 and 1970, Part III</u>). The remaining patients are treated within the private hospital system, which has a strong bias toward surgical and short term medical cases. The majority of the most fully developed cases of connective tissue diseases, therefore, are treated within the New Zealand public hospital system.

It was believed that almost all patients admitted to private hospitals in the first episode of their disease would be admitted at some stage to a public hospital as the disease became chronic. Principally this would be due to the long duration of treatment involved with these diseases, and the consequent financial expense required to sustain a patient in a private hospital. Some patients, however, would never be admitted to a public hospital. While no follow-up or assessment was made to ascertain the exact case total of those patients admitted to private hospitals with connective tissue diseases, in preference to a public hospital, it was believed that the total would be minimal.

Thus, it was deemed justifiable to use as the primary medical data source a patient's hospital case history available in the public

104

hospitals medical records department. Therefore, case history records of patients admitted to the public hospitals within the defined study area, and during the designated time period, and showing a diagnosis at admission of systemic connective tissue diseases, including SLE (I.C.D. 734.1), polyarteritis nodosa (I.C.D. 446.0), polymyositis (I.C.D. 716.1) and dermatomyositis (I.C.D. 716.0), and scleroderma (I.C.D. 734.0), were retrieved and examined.

Generally, retrospective studies of medical records are unsatisfactory (Doll, 1959; Case and Davies, 1964), but the prolonged course, high mortality, and complexity of these diseases present a challenge to the physician in diagnosis and management. This results in unusually full records being kept over long time periods, availing more complete case histories to the researcher than is general with studies of this nature.

### Collection of Morbidity Data

A special data sheet was constructed to facilitate the transferrence of data pertinent to the study from an individual's case history to computer cards for use in the later analytical stage. Provision was made on the data sheets for inclusion of selected 'medical geographic' parameters. The results of laboratory tests, and patients' symptoms were to be recorded on a coded checklist. The patient's disease diagnosis on discharge from the public hospitals was also to be noted (Appendix B).

To obtain the requisite information each principal public hospital in the study area was visited (Appendix C).

Gleaning the 'medical' data necessitated the reading of each case history by a qualified physician<sup>1</sup>, while the 'geographic' data was obtained from the admission form, and the discharge or death certificates of each patient.

The medical geographer's ubiquitous problem of data insufficiency and the inherent inaccuracies of recorded data were confronted. The information that could be obtained concerning a patient was limited to that which had been requested on the admission form. The parameters of place of birth (whether in New Zealand or outside of this country), how long in New Zealand (if a patient had not been born in this country, or was a New Zealander returning 'home'), and occupation were frequently not filled out on the form. Although provision was made for a patient's 'race' to be included on the admission form, there was no definition given as to what criteria a patient must fulfil in belonging to a particular racial group. Thus, patients were at liberty to state what 'race' they considered themselves to be part of. The non-inclusion of a females 'maiden' name proved to an especially burdensome emission in the subsequent research.

Whether a patient was dead or alive at the last entry in a case history could not be relied upon as a true assessment of the mortality of the diseases. This entry may have been placed some years prior to this survey, and a patient may have died in the interim.

# Diagnostic Confirmation of Definite Cases and the Reduction of Physician Bias in Recording

Generally, all medical diagnoses contain a subjective element, and there are nearly always some cases which will be classified differently by different observers. Since the specific actiology and pathogenesis of connective tissue diseases are not known, and since they have such protean clinical and laboratory manifestations, the identification and diagnosis of these diseases are not always made ... with the same criteria by physicians with varying frames of reference (American Rheumatism Association, 1971). It was, therefore, essential in the present study to attempt to reduce the possibility of observer error to a minimum and thereby lower the risk of introducing bias into the results.

To achieve a uniform classification of patients through the study area, a single physician<sup>2</sup> produced a second diagnosis based on his interpretation of the medical evidence as presented in a patient's case history. This reduced, somewhat, bias prevailing in the classification of the initial diagnosis, by applying uniform critical criteria for definite case identification to all cases discharged from a public hospital with a diagnosis of connective tissue disease. Cases other than those pronounced 'possible' or 'definite' from this method were eliminated from further analysis in this study. These comprised 26 per cent of the initial number of cases in the survey.

A second technique was instituted to reduce any local or subjective bias that may have permeated into the former stage, as well

as to lessen still further any diagnostic bias in the initial recording. In this phase, the stringency of the criteria employed were such, that the critical level for achieving a 'definite' (that is, a 'positive') classification was that which would have the greatest accord amongst diagnosing physicians.

An objective analysis of the clinical data incorporated into the data sheet leading to a precise classification of the diseases was accomplished through the employment of scoring systems (see appendix A). For SLE the system utilised was that which had been developed by the American Rheumatism Association (1971) in which a definite diagnosis is made if a patient scores four or more of fourteen manifestations. Similar systems were developed for the other connective tissue diseases so they could be categorised in the same manner. The scoring is not used as a measure of degree of severity, as almost invariably once a patient has accumulated a score of four steriods, or other effective medication has been used the score may not increase further and may decrease.

The respective scoring systems were programmed for the computer<sup>2</sup>. The punch cards containing clinical data were thereby able to be analysed with scores being allocated with regard to the number of positive criteria exhibited by a patient.

The resultant 'computer diagnosis' categorised positive diagnosis into one of five disease groups classified as follows:

- 1 for SLE;
- 2 for polyarteritis nodosa (PN);
- 3 for scleroderma (SCL);
- 4 for dermatomyositis (DMS), and
- 5 for polymyositis (PMS).

These scores were then compared to the original physicians diagnosis and the scores adjusted until, by trial and error, the best fit was achieved (degree of fit).

A number of cases presented positive features of one or more of the diseases, but did not score (four or more) sufficiently to be included as a positive case in one disease category. Where this occurred and the combined total score from features in all diseases was five or higher, these cases were included into a category 6 labelled 'combination'. This group was not considered separately in the analysis, but was included as part of the total connective tissue disease classification.

Cases that did not score the requisite number of positive features by this analysis were considered other than 'definite' cases and were, therefore, excluded from the study at this point.

## Admission and Onset

Due to the insidious beginnings and ill-defined early course of connective tissue diseases, previous studies investigating epidemiological aspects of these diseases have utilised the spacio-temporal distributions and ancillary data, as at a patient's date of definite diagnosis (Siegel, <u>et al</u>, 1962). In the New Zealand study, date of definite diagnosis was marked at the time of admission to hospital.

This approach presupposes, however, that the spacio-temporal definitions of patients at diagnosis and onset of symptoms are the same. The chronic nature of these diseases, and the fact that they can mimic other diseases until fully developed, may mean that connective tissue diseases can remain undetected until definite diagnosis is made; nonetheless, the patient is presumed to be suffering from such a disease from the time of first symptoms.

Within the context and aims of this study it was of critical importance that the medical geographic data utilised be only that which pertained to the onset of symptoms of the disease. If the incidence of a disease is in some way co-related with the environment, it will have been prior to, and at onset, that a patient was at greatest risk to contracting the disease. Similarly, the appropriate environmental factor or factors is/are presumed to have been at maximum operational effect at the same time, either as causative agents or as precipitative factors. Due to the chronic nature of connective tissue diseases, these exogenous factors may no longer be of aetiological importance or relevance at the date of definite diagnosis. Spurious findings as to a disease-environment relationship may result from an analysis taken only at date of definite diagnosis.

Establishing time of onset of symptoms for connective tissue diseases can be a difficult problem. In this study, time of onset for

all patients was determined by the reading (by a single physician) of each individual case history. This reduced any bias that would have occurred from a number of physicians placing time of onset; in this study uniform criteria were applied to all cases. The designated time of onset was considered to be when the first symptoms, which the physician considered could be due to connective tissue disease, occurred.

Therefore, in this present study, some patients with connective tissue disease, who were admitted to public hospitals within the study area and time period, may have had their first symptoms prior to January 1, 1950.

#### Confirmation of Location at Onset

To confirm a patients spatial location at the time of onset of symptoms was, therefore, an essential factor in this research. The address provided on the hospital admission form was that from which a patient had entered the hospital. It was not valid, however, in the context of investigating causal relationships between the environment and disease, to assume that it was at this location that a patient was exposed to risk of contracting a disease.

Verification of a patients address at onset was a principal difficulty confronting this survey. Two sources were utilised to establish the spatial location of a patient at time of onset:

a) telephone directories which are, generally, produced annually by the New Zealand Post Office;

b) and the general electoral rolls which are published every three years. Although in a constant process of compilation, this source material remains unpublished in the interim, except for a supplement issued for the period between the closing of the general roll and the time of a general election.

These sources were consulted for those years in which onset had been taken to have occurred. Neither would, however, enable complete confirmation of all patients residence at onset.

Assumptions had to be made in the consultation of this material:

a) youthful patients (those under the age of registering on the general electoral rolls, or those who did not have a listing in a telephone directory) were assumed to be living with parents. Therefore, if a patient of this age stated a particular address from where admitted to hospital, and at time of onset a person of similar surname was listed as residing at this same address, either in a telephone directory or on the general electoral rolls, the address of the patient was assumed to be the same. The patients location at onset was, thus, deemed to be confirmed;

b) married women, whose admission address correlated with a listing (presumably the male head of household) of the same surname at the time of the patients onset were therefore, considered to have had their onset address confirmed.

118.

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Despite these assumptions, a patient's address at onset could still be unconfirmed. This may arise in the following situations:

a) where onset went further back in time than 1950. Tracing addresses by telephone directories would be hazardous because of the lesser numbers of households, at that time, with a telephone connection;

b) a patient living with other persons in a flat, which did have a telephone connection, may not be 'confirmed' as the listing was in the name of a 'flat-mate'.

Verification of those patients whose onset address remained unconfirmed from consultation of telephone directories, was attempted through reference to the general electoral rolls and supplements.

To be eligible for enrolment on the general electoral rolls of New Zealand a person must fulfil the following criteria:

a) they must be a British subject;

b) they must have resided continuously in New Zealand for a period of one year or more;

c) they must have resided in an electorate in which a vote may be cast for a period of three months or more 5

d) have attained the requisite age qualification, which during the period of this survey has been lowered from twenty-one years to eighteen years of age.

The assumptions taken in regard to telephone directories were held to apply to the general electoral rolls, especially to those patients under the age of registration for enrolment.

No confirmation of onset from consulting this source would be attained in the following circumstances:

a) although enrolment is a legal requirement in New Zealand, it is in fact not compulsory to do so. Few convictions are made of persons fulfilling the criteria, but neglecting to enrol<sup>6</sup>. Therefore, it is feasible for the names of patients in this survey not to appear on the electoral rolls, and thus remain with an unconfirmed onset address;

b) those patients, under the age of registration, and who were living away from their 'home' address. This situation would apply especially to tertiary education students.

'Migrant' patients were a special case. If it was established, from the case history, that such a patient had not been resident in New Zealand for at least two years prior to onset, they were excluded from the survey. It would be possible for British 'migrant' patients, who, although not fulfilling this criteria, would be included in the survey, because there was no evidence to suggest they were from the country other than New Zealand. 'Non-British' migrant patients, although living in New Zealand at least two years before onset, were most likely to have onset address unconfirmed. Such patients would not be eligible to register on the electoral rolls unless they became 'naturalised' New Zealanders. The frequent non-recording of a females' 'maiden' name on the hospital admission forms (although provision was made for this) was an especially prohibitive factor in verifying onset address. This applied to women who were married at diagnosis but who, at onset, were single. The requisite information could not be obtained from the utilised data sources. The ramification of this lack of basic data was increased as connective tissue diseases have been found to be female predominant. Therefore, a number of females in this category would remain with an 'unconfirmed' onset address.

Using telephone directories and the general electoral rolls, the spatial location at onset was found for 87 per cent of the patients.

Residential mobility was considered as a possible factor in making the confirmed onset address inaccurate. For example, a patient may have resided at the confirmed onset address only a short time and lived for the majority of the prior period in an area removed from that site. The problem, therefore, is this: when a **patient** becomes overtly ill is this from a factor at influence in the present environment, or was it from something acquired at the prior residence? Thus, such a patient may not have been at risk at the onset address, but at the earlier address. It is feasible, however, that the conditions dominant in the new locality may be sufficiently diverse from those prevailing at the previous address that they precipitated disease onset.

The data on 'how long at present address' was not obtainable from the hospital admission form or the case record. The supplementary
rolls were consulted in an endeavour to lessen the effects of patients changing address. But it was impractical to delve retrospectively into the telephone directories and general electoral rolls in order to establish the duration of a patient at onset address. One could not, therefore, distinguish between a patient who had lived at an address for four months, and one who had lived at an address for ten years. Two assumptions were made: firstly, it was assumed that a patient's confirmed address at onset was the address at which that patient was exposed to greatest risk of contracting connective tissue disease; and secondly, if a patient had not previously been located in the study area at the time of onset, it was assumed that there had been no change in residence if time of onset was within one year (twelve months) of the time of diagnosis. These patients were, therefore, included into the total case numbers.

All patients who were not located within the study area at the time of onset and who had a time difference between onset and diagnosis greater than one year, were excluded from the survey. Those cases comprised 5% of the case numbers remaining in the survey after the physician had eliminated those cases which were not 'possible' or 'definites'.

# Communication with Patients

Personal contact with individual patients may have alleviated some of the data insufficiencies confronting this survey. For example, a patient may have provided information concerning the duration of

resident at place on onset. Such an approach, however, was not considered to be practical. A number of the case histories contained information which had been compiled some time prior to the institution of this study and would, therefore, be out of date. Contact with patients was not always guaranteed as some had died at last recording, while others would have died since the last recording in the case history.

Communication with physicians would not always lead to requested information being provided. In some instances case records may have been destroyed or were out of date.

### Case Numbers

With regard to the methods employed in redefining the number of cases to be handled in the analytical stage, the following patient case numbers were enumerated:

- (a) the total number of cases attaining a 'score' sufficient to allow a 'computer diagnosis' of connective tissue disease, with address at onset established, was 266;
- (b) of this total, the individual case numbers with the respective disease subsets were:
  - (i) SLE ninety-eight (98)
  - (ii) polyarteritis nodosa (PN) fifty-four (54)
  - (iii) scleroderma (SCL) fifty (50)
  - (iv) polymyositis and dermatomyositis (PMS/DMS) forty-seven (47)
    - (v) and a group of seventeen (17) who did not score

sufficiently to be diagnosed in one individual disease category, but which could be regarded as belonging to the general connective tissue disease.

#### Population-at-risk

A population-at-risk is defined as the aggregation of those individuals who are either potentially subject to, and thereby 'at risk' of contracting, the pathologic or disease phenomenon under consideration, or those who are exposed to the salient actiological factor being considered (Banta and Fonaroff, 1969). In the present study this term refers to an enumeration of the 'healthy' population at risk to contracting a disease resident within a specified areal unit.

The population-at-risk statistics utilised in this study were obtained from the successive <u>New Zealand Census of Population and</u> <u>Dwellings reports</u> (vol. 1), published every five years.

# Population-at-risk at the County level

Since 1950 a number of counties have changed their boundaries, while others have amalgamated with adjacent counties. To establish a uniformity of areal units and county identification throughout the time span of this survey, the following procedure was adopted:

a) the names of counties as at the 1971 census were maintained throughout the time covered by this survey;

b) allowance was made in the number of the population-at-risk where a county was amalgamated, or where county boundaries were altered. The census data of the year of the census was used as the base population, and by adding or subtracting the proportion of change in the population of a county shown in the successive census, the original population-at-risk could be adjusted. Therefore, for the purpose of this study, the county boundaries did not change during the time span of twenty-three years covered.

Population-at-risk at the Hospital Board Scale

Although the population-at-risk for each Hospital Board in the study area was available (Department of Health, <u>Medical</u> <u>Statistics Report. Part III</u>), it was decided that the county populations-at-risk within a Hospital Board District would be aggregated to achieve the Hospital Board population-at-risk. For example, the population-at-risk of the Otago Hospital Board District in this study was the combined population-at-risk of the Waihemo, Waikouaiti, Taieri, and Tuapeka Geographic Counties. This would mean that the study area population-at-risk would be constant at all areal scales.

Population-at-risk at the regional scale

The population-at-risk of the largest areal unit in this study, was obtained by aggregating the population-at-risk of each of the Hospital Board Districts within that 'region'.

## Base Map and Sources of Maps

The base map for this survey was that drawn by the Department of Statistics and included with the report <u>N.Z. Census of Population</u> and <u>Dwellings</u>, 1971, Vol. 1.

The source for figures 14 to 72 and all tables, except Table VI, was the Field Survey of 1975. Figure 13 was adapted from the Department of Health's publication <u>Hospital Statistics of N.Z</u>. (1972) and the Department of Statistics report <u>N.Z</u>. Census of Population and <u>Dwellings</u>, 1971, Vol. I.

The data base was therefore formed with a number of in-built assumptions. In the context of this study and the uncommonness of the diseases each of these were considered valid and justifiable. Every attempt was made to reduce to a minimum the possibility of spurious results accruing from biased data. The analysis, however, had to be conducted with due regard to the knowledge that bias may still be or have been present which could not be reduced by the methods employed.

#### Footnotes

- 1. & 2. Dr R.A.D. Wigley assisted by Sister Fowles, of the Palmerston North Medical Research Laboratory.
- 3. These were written by B. Reay and P. Hill of the Palmerston North Medical Research Laboratory.
- Dr R.A.D. Wigley assisted by Sister Fowles.
- 5. This has since been altered to one month or more residency period in an electoral district.
- 6. Personal communication with the Registrar of Electors, Palmerston North.

#### CHAPTER THREE

# THE SPACIO-TEMPORAL DEFINITION OF CONNECTIVE TISSUE DISEASE

The principal tasks of the medical geographer are to determine where diseases are located and to relate these distributions to other spatially varying factors in the environment (McGlashan, 1969c,1972b,1973). It is of fundamental importance that the location of ill-health is known with confidence before embarking on either associative or diffusion studies.

The aim of this chapter is to define the temporal changes and spatial variations in the occurrence of connective tissue disease (CTD), collectively and severally; and to distinguish those areal units or time periods which experienced either statistically significantly high or statistically significantly low numbers of morbid cases compared with the rest of the study area or the total time duration of the survey.

### Method of Analysis

The analytical methodology of this survey has been employed elsewhere in medical geography (Harrington and McGlashan,1973; Harington <u>et al</u> 1974; McGlashan,1972f,1974d; McGlashan and Gatenby,1974; Rose and McGlashan,1974) and broadly introduced above in Part One, Chapter Three of this study.

### Spatial Analysis

A three level method of analysis was used to define the spatial distributions of these diseases. The foundation stage incorporates dot distribution maps illustrating the exact spatial location, at onset, of the morbid cases recorded in this survey.

To avoid the inherent deficiencies of such a technique, the numbers of morbid cases occurring within a specified areal unit have been 'rated' against a population-at-risk living within that spatial unit at the time of the taking of the 1971 N.Z. census.<sup>1</sup> Several methods have been used in medical geography to minimise the possible effects of the age and sex constitution of areas on the resultant mortality or morbidity rates. Standardisation is generally carried out by mathematical comparison with a selected wider population group as a standard (Hill, 1937, 1966). While the present study does not utilise these procedures, full allowance is made for local population age structures through the use, at the next stage, of the Poisson distribution in which the population structure for the total study area has been accepted as the 'standard' or 'norm'. This standard is used as a comparative basis upon which to calculate how many morbid cases would be expected in each lesser-sized population unit (McGlashan and Chick, 1974). Therefore, only crude incidence rates (the number of morbid cases per 100,000 population-at-risk within a specified area) were calculated. Class intervals were selected by scatter diagram (or dispersal graph) to emphasise distributional discontinuities in space. Any gradient patterns of morbidity within the study area may, thus, be discernible. As diseases are not limited in their occurrence

to administrative boundaries these have not been drawn in.

It is, however, inadequate to use only variations of incidence rates as an analytical method in medical geography (McGlashan, 1974d). Widely differing population-at-risk sizes produce incidence rates that are not of comparable reliability and therefore do not present a valid comparison. Rarely will disease cases be evenly distributed across a landscape at a constant rate of incidence. A degree of 'random chance' will prevail and lead to some irregularity in the distribution for which no 'explanation' should be sought. A high rate of disease incidence in a specific area or time period does not presuppose that a possible relationship with 'causative' or 'precipitative' factors will be discovered in consequent research; all that has been established is that such a rate is present in that particular area or time. Until the absolute case numbers can be shown to deviate at a statistically significant level from those attributable to the overall 'norm' of cases expected in the general population, local case variations may be put down to the operation of chance factors (McGlashan, 1972a).

Armstrong (1969) has urged medical geographers to use the standard deviation (s.d.) of standardised mortality ratios (S.M.R.'s) from the selected norm (which is 100) as a method for assessing significance. This measure has, however, been found to be unsuitable for use with small numbers of cases (McGlashan and Chick, 1974), and S.M.R.'s cannot be computed for areal units which record nil mortalities or morbidities. As the case numbers in the present study were small, with some areal units recording no cases, this method was

not employed.

The test of statistical significance used in this study for recognising areal units and time periods with a number of cases observed statistically significant above or below that which could reasonably have occurred by chance is the Poisson distribution. The method for employing this technique in medical geography has been documented by Choynowski (1959), White (1972), McGlashan (1974c, 1974d), and McGlashan and Chick (1974). This distribution is used to compare the number of cases 'observed' against the number of cases that would be 'expected' in order to test whether any significant local variations from the overall rate are occurring (Appendix D). Unless otherwise specified all tests for significance in this work have been by use of the Poisson distribution. The present cartography for the 'significance' maps was designed to emphasise only statistical significance, whether 'high' or 'low', with the near-to-normal areas ('norm') left plain.

Once areas of significant statistical variations have been established, attention should focus upon those areas which have extremely dissimilar levels of statistical significance. That is, further research is upon the tails of the distribution. The rationale for this is that it should be within these such defined areas that potentially the greatest contrast in possible associative factors with disease occurrence will be found. Further analysis of areas which have disease incidence close to the norm can thus be eliminated and resources concentrated upon the statistically significant areas.

There existed a possibility that this analysis may yield spurious findings resulting from the effects of random factors associated with the selection of one specific population-at-risk, that of 1971 (Appendix F), as the base for rate computations. To lessen the effect of 'chance' results accruing, assessment was made of the consistency of the spatial variations, arising from the initial analysis, through the duration of the study time period. This was accomplished by re-analysing the data at the second and third stages of the methodology, but with calculations based on the population-atrisk of the areal units as at the time of the 1951 and 1961 N.Z. census (Appendix F).<sup>2</sup> The total number of diseased cases in the survey were used at each time point for reckoning incidence rates and 'expected' numbers of cases, thereby achieving a measure of standardisation throughout the analysis. Too few cases would have occurred prior to the two earlier time points for these to be used in the calculations with the population-at-risk at the same points.

As incidence rates will be influenced by the size and/or fluctuations in the population-at-risk, these could not adequately be used for an assessment of the spatial consistency of disease variations in time. A more meaningful approach, and one which takes account of such fluctuations over time, was to statistically determine the degree of correlation between the rank orders of areal units at the three time points of 1951, 1961, and 1971. Spearman's rank order correlation test (Conover, 1971), denoted by  $r_{\rm g}$ , was used in preference to Kendall's rank order correlation test because of the fewer and less difficult computational steps involved. Throughout,

 $r_s$  was used to test the null hypothesis (H<sub>0</sub>) of no significant correlation between the rank orders of areal units at the 1951, 1961, and 1971 time points. The alternative hypothesis (H<sub>1</sub>) formulated was that there existed a significant correlation between the rank orders at the three time points. The rejection level for H<sub>0</sub> was set at the 5% confidence level.

#### Temporal Change

Due to the unavailability of population census data for all scales of areal unit, it was not possible to compute and graph the incidence rates for all years of the designated time period. Instead, the occurrence of the absolute case numbers in specific years of the study period were calculated and graphed, as were the cumulative case totals with time.

A second analysis was conducted. Two time periods, with the 1956 and 1966 population census as the respective mid points, were designated:

 (a) the first to include all cases which had onset of symptoms in the years up to, and including, December 31, 1961. This period included those cases with onset prior to 1950;

(b) the second period covered the years from January 1,1962 to August 31, 1973.

The null hypothesis  $(H_0)$  formulated for testing was that the occurrence of a disease did not differ statistically significantly between the respective time periods. The alternative hypothesis  $(H_1)$  was that the occurrence was statistically significantly different between the time periods. This  $H_0$  was tested for each disease subset using the chi-square distribution test (Conover, 1971). The region of rejection for  $H_0$  was at the 5% confidence level with one degree of freedom (df = 1).

A further null hypothesis  $(H_0)$  was formulated for testing at the Hospital Board District (HBD) scale of areal unit - that there was no statistically significant deviation of observed case numbers in HBD's than those expected, if the morbidity rate for the study area in the respective time periods was applied ubquitously. This was tested using the Poisson distribution test (McGlashan, 1974c).

# Areal Units

Three scales of areal units were utilised for the spatial and temporal analysis of the collected data.

The smallest units were the 'Geographic Counties' (Fig. 13) used by the N.Z. Statistics Department, (N.Z. Census 1971, <u>Increase</u> and Location of Population, Vol 1), to cover

> "both the county and any city, borough, or town district which may be geographically within or adjacent to that county."

These vary considerably both in areal extent and in population-atrisk within their boundaries. The populations are such, that chance variations in the occurrence of one or two cases may make a difference to local incidence rates, with the consequence that cartographic portrayal may become meaningless.

The fourteen Hospital Board Districts (HBD) (Fig. 13) were the second type of areal unit used in the survey. These had populations-at-risk ranging from 2737 (Maniototo) to 320,915 (Wellington) with a mean of 86,432, which greatly lessens the effect of random noise when seeking spatial differentiation.

A third areal unit of groupings of specific HBD's was contrived purely for this analysis, and labelled 'regions'. These regions were

I. which includes the combined area of Palmerston North HBD, the Dannevirke HBD, and the Wairarapa HBD;

II. which includes the areas of the Wellington HBD and Marlborough HBD;

III. which covers the combined areas of the North Canterbury HBD, the Ashburton HBD, and the South Canterbury HBD;

IV. which includes the HBD's of Maitaki, Otago, Maniototo, Vincent, South Otago, and Southland;

V. which is all of that area of 'region' IV, except for the Southland HBD. This differentiation was conducted because few cases were recorded in · Southland prior to 1960, and various staffing problems at that time were experienced by that HBD. Therefore, it was justified to consider the 'Otago region' without Southland.

Designation of these regions was based on the location of the five principal public hospitals (Palmerston North, Wellington-Hutt, Christchurch, Dunedin, and Invercargill) and an assessment of the disease 'drainage'<sup>3</sup> for each hospital.

By using three scales of areal unit, greater statistical significance may attach to the larger areas with the aggregation of data, but the smaller units may be employed more precisely, through disaggregation of data to locate deviations from the study area norm. In this latter instance it should be possible to determine, for example, which Geographic County within a HBD is most contributory to that HBD's significance level.

### The Spatial and Temporal Definitions of Connective Tissue Disease

A total of 266 cases of connective tissue disease (CTD) were included in this survey for medical geographic analysis. Of this number, systemic lupus erythematosus (SLE) cases comprised 36.8%, polyarteritis nodosa (PN) cases 20.3%, scleroderma (SCL) cases 18.8%, and polymyositis and dermatomyositis (PMS/DMS) cases 17.7%. A further group, defined as combination, contributed 6.4% of the total case number. While these cases  $\omega_{\rm crc}$  not studied as a separate group, they are included in the absolute case total of all CTD's.

In this analytical stage of the research, various hypotheses were formulated and tested, by initially considering all CTD, and subsequently focusing on the specific individual disease subsets of SLE, PN, SCL, and PMS/DMS. The prime hypothesis under test was that there is a statistically significant spatial variation and temporal change in the occurrence of connective tissue disease, collectively and severally, within the defined study area and time period. Subsequent hypotheses were subsumed from this initial hypothesis.

## CTD

The spatial location of patients at time of onset of symptoms generally upholds the population-at-risk hypothesis, i.e., the greater the population-at-risk in an area the larger will be the number of cases of the disease occurring within that area (Fig. 14). A hierarchy of total case numbers by location was discernible which



corresponds to a similar hierarchy of the population-at-risk.

The six cities of the study area, with 58.86% (1971 census) of the total population-at-risk, had 63.16% (168 cases) of the cases residing within their boundaries at disease onset (Table I).

TABLE I. Percentage distribution of total connective tissue disease<sup>#</sup> cases within the main cities of the Study Area.

City	% of population of study	SLE	PN	SCL	PMS/DES	CTD
	area (1971)					
Palmerston North	4.29	8.16	1.85	4.00	10.64	7.14
Wellington Hutt Porirua	21.93	15.31	29.63	20.00	8.51	17.67
Christchurch	18.57	20.41	20.37	14.00	17.02	18.42
Timaru	2.34	3.06	3.70	2.00	4.26	3.38
Dunedin	7.84	13.26	7.41	18.00	14.89	13.53
Invercargill	3.89	2.04	3.70	2.00	4.26	3.00
Total	58.86	62.24	66.67	60.00	59.58	63.16

\* disease abbreviations are those used in the text.

Only Palmerston North and Dunedin recorded a substantially higher percentage of CTD cases within their area than their respective percentages of the population-at-risk of the study area.

Immediately below this level in the hierarchy are the secondary population centers of which Timaru registered 3.38% of the total cases, Blenheim-Picton 3.38%, Levin 3.01%, Oamaru 1.88%, and Ashburton 1.50%. Less than 1% of the cases resided in Masterton at the time of onset of symptoms. At the final disaggregated level in the hierarchy, the minor population areas generally registered no more than one case occurring in their areas.

There was evidence of locational clustering of cases at time on onset about the major population centres, which serve as the location of the principal public hospitals in the study area. Approximately 82% of the total number of recorded cases of CTD were located at onset within a radius of 56 kms of such centres. Palmerston North's 'diseased hinterland' extends to Feilding, Sanson, Shannon, and Levin, with the complete area containing 12.41% of the total cases. An area about the Wellington-Hutt Valley-Porirua Basin urban area, including Paekakariki and Raumati, registered 20.67% of the patients. The Christchurch sphere of disease incidence, which recorded 19.92% of the cases, included Rangiora, Kaiapoi and Darfield. Smaller clusters were observed about Invercargill (5.26% of the total cases), and Timaru (4.88%). Ninor concentrations of disease cases occurred in the areas of Balclutha-Kaitangata, Roxburgh-Oturehua-Ranfurly (2.63% of total cases resided within this area at time of onset), and Dannevirke-Woodville-Pahiatua.

### Regional Units

Aggregation of the data into the contrived regions showed that there exists a distinct spatial bias in the location of CTD cases at the time of onset (Table II). Only three regions recorded percentages of the total CTD cases in excess of the percentage of the total population-at-risk of the study area in the region. For region I this difference in percentage was 2.07%, while for

Region	% total population (1971)	SLE	PN	SCL	PMS/DMS	CTD
I	14.13	19.39	9.26	16.00	17.02	16.16
II	28.89	20.41	38.89	24.00	17.02	24.44
III	33.12	28.57	31.48	20.00	25.53	27.07
IV	23.86	31.63	20.37	40,00	40.43	32.33
V	14.66	25.51	16.67	32,00	27.65	25.19

region IV it was 8.47%, and region V 10.53%.

TABLE II. Percentages of the total cases of connective tissue

Although the Otago-Southland region (IV) contained only 23.8% of the total study area population-at-risk (1971 census), approximately one-third of all CTD cases of the study area were located at onset within this region. SCL and PMS/DMS cases respectively comprised 23.26% and 22.09% of all CTD cases in this region, but 40.00% of the total number of cases of these diseases in the study area were resident at time of onset within the region. Consideration of the figures for region V (Otago) suggests that it is this area which is the contributory factor for creating the intense concentration of cases in region IV. Region V recorded 14.66% of the total population-at-risk of the study area (1971 census), but 32% of SCL cases in the study area and 27.65% of PMS/DMS cases were resident in the region at onset. The case numbers of these two diseases, however, made up only 23.88% and 19.40% of all CTD cases in the region, while SLE cases were 37.43% of the total number of CTD cases. Overall region V contained approximately one-quarter of

diseases in each region.

all CTD cases involved in this study.

While no emphasis could be placed on such an examination of percentage figures it did, however, suggest that CTD and specifically SCL and PMS/DMS have a spatial bias in their incidence.

Calculations of crude incidence rates corroborates this suggestion of a regional differentiation of case incidence (Table III). These rates, however, should be compared to the rates for the total study area in order to assess the true importance of any divergence from the study area norm.

TABLE III. Crude Incidence Rates of connective tissue diseases per 100,000 population-at-risk (1971) by Regions

Region	SLE	$\mathbb{PN}$	SCL	FNS/DNS	CTD
I	11.12	2.93	4.68	4.68	25.16
II	5.72	6.01	3.43	2.29	18.59
III	6.99	4.24	2.50	3.49	17.96
IV	10.74	3.81	6.93	6.58	29.78
V	14.10	5.08	9.02	7.33	37.78
For study area	8.10	4.46	4.13	3.88	21.98

A gradient of incidence may be noted, emanating from the lowest figure in region III, and extending north through regions II and I. An abrupt change in crude incidence rates existed between regions III and IV, in the order of 11.82 cases per 100,000 populationat-risk This difference became larger with regard to region V (19.82 cases per 100,000 population-at-risk). While regions I, II, and III had small divergences from the study area norm (of crude incidence rate), for region IV the divergence was 7.8 cases per 100,000 population-at-risk, and for region V, 15.80 cases per 100,000 population-at-risk.

Applying the Poisson distribution test to these rates, only regions IV and V were found to have a statistically significant divergence of 'observed' cases from those 'expected'. Region IV, with 86 cases observed and 63.48 cases expected, was significant at the 99% confidence level. Similarly, region V, with 67 cases observed and 38.98 cases expected, was statistically significant at the 99% confidence level. Region I recorded a higher, but not statistically significant, number of observed cases (43) than expected cases (37.57), while both regions II and III recorded fewer, but not statistically significant numbers of observed cases (65 and 72 respectively) than expected cases (76.85 and 88.10 respectively).

Hospital Board Districts (HBD's)

Disaggregating the basic data allows one to be more specific in assessing whether the spatial variation of CTD incidence at the regional level is consistent at the lower scale of areal unit. It further affords an opportunity to determine which HBD may be a contributory factor in the spatial bias of CTD case location at onset, which was evident at the larger scale areal unit.

Reinforcing the earlier finding of case groupings about the locations of the principal public hospitals in the study area, 80.45% of all CTD cases were found to be resident at onset within the HBD's of Palmerston North, Wellington, North Canterbury, Otago

and Southland (Appendix E). The combined populations of these HBD's represented 81.96% of the total population-at-risk of the study area (1971 census). The Otago HBD, with 10.45% of the total study area population-at-risk, had 18.79% of all CTD cases resident: within its boundary at the time of a patient's disease onset. Only Palmerston North, of the remaining principal HBD's, exhibited a divergence of the percentage of cases in the area above the percentage of population-at-risk of the study area in that HBD.

Radiating out from the Maniototo HBD (with the highest crude incidence rate of the HBD's) was a gradient pattern of incidence rates (Fig.15). This gradient became especially marked north from the high incidence area, through the successive HED's of Waitaki, South Canterbury, Ashburton and North Canterbury. The HBD's of the Otago region (V) form a distinctive high incidence area. The North Island HBD's, while exhibiting no gradient of incidence, did show an indistinct pattern with high incidence areas (Palmerston North HBD and Dannevirk HBD) in close proximity to low incidence areas. The Wellington HBD was bordered in the north by the higher incidence HBD, while across Cook Strait the Marlborough HBD had a similar incidence rate to the Palmerston North HBD.

After testing for statistical significance only the Otago HBD, with 50 observed cases and 27.79 expected cases, reached a statistically significant level ( $p \neq 99\%$ ) (Fig. 16).

Geographic Counties (GC's)

The GC's of Kairanga, Hutt, Heathcote, Taieri and





Southland had 65.78% of all CTD cases resident at onset within their boundaries, while their combined populations (1971 census) accounted for 62.60% of the total population-at-risk of the study area (Appendix F).

The outstanding feature of the distribution of the crude rates of incidence was the very high incidence recorded in the Central Otago and Otago GC's (Fig. 17). The Maniototo GC registered the highest incidence rate of the study area, while the GC's bordering it (Vincent, Waihemo, Taieri, and Tuapeka) also had high or moderately high incidence rates. With the exception of the Taieri GC, which includes Dunedin, and which recorded a moderately high incidence rate, all GC's, within which main cities are located, registered low incidence rates.

The GC's which comprise the Marlborough HBD recorded moderately high to high incidence rates, especially the GC of Awatere. Although the GC (Amuri) immediately south of these GC's also recorded a relatively high incidence rate, the Kaikoura GC on the coast had a very low incidence rate. Generally in the South Island there was no abrupt change of incidence rates between GC's but rather a gradual rise or fall of rates.

This situation did not, however, appear to exist between the GC's in the North Island area of the study. The GC's of Kairanga and Horowhenua had moderately high incidence rates, while the adjoining Oroua, Manawatu, and Hutt GC's recorded low incidence rates. A gradient of incidence rates, therefore, was discernible



between the GC's of the Palmerston North HBD, with low rates in the north and higher rates in the south. A similar trend was exhibited between the GC's on the eastern side of the Tararua-Ruahine ranges, with the highest rates recorded in the Woodville and Pahiatua GC's.

After testing for statistical significance, higher case numbers came from Taieri GC (p > 99%), and Horowhenua GC (p > 95%). The two adjacent GC's of Paparua and Waimari had statistically significantly fewer observed case numbers than expected (p > 95%) (Fig. 18).

From the above analysis it has been shown that CTD incidence varies in space. By employing a consistent methodology at three different scales of areal unit, it has been shown that the incidence of this disease is significantly (statistically) greater in the southern regions (IV and V). Refinement of the scale of areal unit highlighted that it is specifically the Otago HBD and within that, the Taieri GC, that have the highest statistically significant (p > 99%) deviation of the number of observed cases of CTD from the number that could reasonably be expected to have occurred due to chance factors.

Although statistically significant divergences of observed cases from those expected occurred in the Horowhenua, Paparua, and Waimari GC's this finding was not supported by the analysis of data at the more aggregated areal units.

Spatial trends in the distribution of diseases may be further highlighted through the construction of an isopleth map.



Usually, rates or S.M.R.'s have been employed as the data for drawing such maps in medical geography. The accompanying map (Fig. 19), however, was an experiment in the use of 'iso-probs', or isolines of confidence or probability levels. Following computation of Poisson percentage probability integrals (McGlashan and Chick, 1974) for each GC (using the 1971 census population-at-risk),<sup>5</sup> the principal population centres for each GC were used as the data points, and the 'iso-probs' drawn. Therefore, for this map only, the lows (troughs) signify areas where statistically significantly fewer cases were observed than expected while the highs (hills or ridges) are areas where the number of observed cases are statistically signifibantly higher than expected.

Two outs tanding features of this map are the high areas focusing on Levin, Palmerston North, and Dunedin, and the opposed statistically significant levels of the two adjacent GC's of Waimari and Heathcote. A gradient is evident across the Otago region with a low on the western coast (an area where statistically significantly fewer cases were observed than expected) and an increasing high toward the east coast. The summit of the high statistical significance area is the Taieri GC (p > 99.84%). A low trough of statistical significance occurs in Southland, and continues north through the inland GC's of South Canterbury end on to the GC's about Christchurch city.

Generally, the pattern surrounding Christchurch is one of low statistical significance with Waimari recording only 6 observed cases but having an expected number of 15 ( $p \neq 98.56\%$ L). The



adjoining Heathcote GC, however, registered a Poisson percentage probability integral of +45.90.

A gradient of increasing high statistical significance is discernible from those GC's around Christchurch city northward to Cook Strait. This pattern is broadly similar to that existing between the Southland and Otago HBD's.

In the North Island two distinctive features stand out. A very high hill of statistical significance in the Levin-Palmorston North area which rises steeply to the +90% level of statistical significance. To the north-west, south, and east of this summit exist areas of low statistical significance.

Areas of high statistical significance were, therefore, located in the Taieri, Horowhenua and Kairanga GC's, while Southland, Wellington-Hutt, and the Wairarapa were areas of low statistical significance. Canterbury exhibits increasing low statistical significance towards Christchurch, but there exists the extreme juxtaposition of the two adjacent counties of Waimari and Heathcote.

Spatial Consistency Through Time

Rates of incidence increased for all regions with rating against the respective populations-at-risk in 1961 and 1951. A null hypothesis ( $H_0$ ) that the rank orders of regions (by incidence rates) at the three time points (1971, 1961, and 1951) were independent was tested.  $H_0$  was rejected and the alternative hypothesis - that the ranks at the time points were positively correlated - accepted.  $(1971-1951, r_s = 1.00; 1971-1961, r_s = 1.00; 1961-1951, r_s = 1.00).$ 

Testing for statistical significance revealed that for region IV, although the number of observed cases always exceeded the number of expected cases, there was a diminishing level of statistical significance. In 1971 this region was highly statistically significant (p > 9%), but with the 1961 population-at-risk it was only moderately statistically significant (p > 95%). In 1951 there was no statistically significant divergence of observed cases from those expected. The Otago region (V), however, was highly statistically significant (p > 9%) at all three time points.

With the exception of the Maniototo HBD, which showed a reverse trend, all other HBD's registered successively decreasing rates of incidence with time from 1951 (Figs. 15, 20, 21). Correlation of HBD's rank order between these time periods was, however, very high (1971-1951,  $r_s = 0.92$ ; 1971-1961,  $r_s = 0.97$ ; 1961-1951,  $r_s = 0.97$ ).

The Otago HBD remained a consistently statistically significant area throughout the study time (1951 p > 95%; 1961 p > 99%) (Figs. 16, 22, 23). The only other HBD that had a statistically significant divergence of observed cases from those expected was the Palmerston North HBD (p > 95%) with the 1961 population-at-risk.

Declining incidence rates over the time period were recorded in 60% of those GC's which recorded cases of CTD (Figs. 17, 24, 25). These were, generally, GC's within which the main population












centres are located. The largest changes in GC rank order (1971-1951,  $r_s = 0.89$ ; 1971-1961,  $r_s = 0.95$ ; 1961-1951,  $r_s = 0.97$ ) were those by Horowhenua, from rank 1 (1951) to rank 6 (1971), and Lake, from rank 2 (1951) to rank 10 (1971). Approximately 8.00% of the GC's showed a rise in incidence rates with time, while the remaining exhibited fluctuations in rates, with a trough of low incidence rate generally occurring with the 1961 population-at-risk.

After statistical significance testing, Taieri GC was shown to have remained statistically significant at each time point although with decreasing statistical significance levels (Figs. 18, 26, 27). The GC's of Paparua and Waimari were significant (p > 95%) only with the 1971 population-at-risk, but the Horowhenua GC had a decreasing statistical significance level through time (1951, p > 99%; 1961, p > 95%). With the 1951 population-at-risk Kairanga GC was statistically significant (p > 95%), thus creating a statistically significant concentration in the North Island with the adjacent Horowhenua GC.

## Temporal Change

Patients who had onset of symptoms prior to January 1, 1950 comprised 8.27% of the total CTD case numbers. Although the earliest established data of onset was 1925, 54.55% of these cases had onset during the period 1945-49.

It was initially believed that fewer case onsets would be recorded in the period up to and including 1961 than in the latter period of 1962-1973. The rationale was that there would be some





patients with onset in the latter period, who would not have been admitted to a public hospital by August 31, 1973. Conversely, there would exist a greater likelihood for patients with onset in the earlier period to be admitted to a public hospital, and thereby be included in this survey. Therefore the null hypothesis  $(H_0)$ formulated was that there was no statistically significant variation in the number of case onsets between the two time periods. Generally, there has been a trend for an increasing onset of CTD with increasing time (Figs. 28a, 28b), with the majority of CTD cases (55.64%) having onset in the period 1962-1973 (Table IV). The H<sub>0</sub> was tested using the chi-square test, with one degree of freedom (df = 1). Thus it was rejected at the 95% significance level.

Disease	prior 1950-1961	1962-73		
SLE	43	55		
PN	25	29		
SCL	31	19		
PMS/DMS	11	36		
CTD	118	148		

TABLE IV. Cases of connective tissue diseases with onset in a

Disaggregation of the data into sexes showed that 59.29% of all the male cases had onset during the later period, compared with 53.93% of the female cases (Fig. 28c). This distribution was not, however, statistically significant at the 5% confidence level.

specified time period

A null hypothesis  $(H_0)$  was formulated for testing at the HBD areal scale - that there was no statistically significant



(A) CONNECTIVE TISSUE DISEASE - NUMBER OF CASE ONSETS PER YEAR OF STUDY PERIOD

FIGURE 28



# (i) CONNECTIVE TISSUE DISEASE - NUMBER OF MALE CASE ONSETS PER YEAR OF STUDY TIME PERIOD

FIGURE 28C

deviations of observed case numbers in HEDsthan those expected, if the morbidity rate for the study area in the respective time periods was applied ubquitously. In the first period Palmerston North was the only HED reaching a statistically significant level (p > 95%) with significantly more cases than expected (Table V). In the second, and more recent period, the Wellington HED had statistically significantly fewer observed cases than expected (p > 95%), while in the Otago HED statistically significantly more cases (p > 95%) were observed than expected. H<sub>o</sub> was therefore rejected.

TABLE V. The number of cases of connective tissue disease with onset in respective time periods by Hospital Board Districts.

HBD	before 1950-1961	1962-73
Palmerston North	18	17
Dannevirke	1	2
Wairarapa	3	2
Wellington	30	25
Marlborough	-	10
North Canterbury	28	27
Ashburton	2	2
South Canterbury	λ.	9
Waitaki	_	6
Vincent	2	2
Maniototo	2	-
Otago	17	33
South Otago	3	2
Southland	8	11
Total	118	148

The spatial distribution of SLE cases, the largest numerical subset of CTD in this survey, generally follows the same pattern as that of CTD, with the heaviest concentrations of cases in the cities (Fig. 29: Table I).

## Regional Units

Although 23.86% of the total population-at-risk (1971 census) resided within region IV, 31.63% of all SLE patients were resident in this region at the time of disease onset (Table II). The Otago region (V), however, with only 14.66% of the study area's total population-at-risk, had about one quarter of the SLE patients in its area at onset of symptoms. Approximately one fifth of SLE patients were in either region I or II at onset, although the latter had more than double the population-at-risk of the former. The Canterbury region (III) recorded a percentage of SLE patients closely similar to the percentage of the total population-at-risk in the area.

Examination of the crude incidence rates verifies this apparent spatial variation in SLE incidence (Table III). With the rate for the study area at 8.10 per 100,000 population-at-risk, the highest regional rates were recorded in regions V and I. The gradient of incidence rates, therefore, differs from that for CTD, with the lowest rate recorded for SLE in region II. Region V, however, was the only region with a statistically significant

167.

## SLE



(p > 95%) divergence of observed cases, 25, from expected cases, 14.37. Hospital Board Districts

Although the majority (79.59%) of SLE cases were resident in the five principal HBD's at onset, the HBD's of South Canterbury, Waitaki, and Maniototo combined, recorded 11.23% of the total cases (these HBD's had 6.76% of the total population-at-risk at 1971 census). Vincent was the only HBD not to register any cases of SLE (Appendix E).

Generally, all HBD's had a low incidence rate of SLE (Fig. 30). Maniototo, however, recorded an incidence rate eight times greater than the norm for the study area, and 300% higher than the second highest rate (Waitaki HBD). There was a very sharp change from low incidence rate areas around Maniototo to the high incidence rate area, with a notable contrast between the adjoining HBD's of Vincent and Maniototo. These HBD's respectively recorded rates at the tails of the distribution. Overall the study area, the higher incidence rates occurred in the northornmost HBD's (Palmerston North and Dannevirke) and the most southern HBD's (Waitaki, Otago, Maniototo, South Otago, and Southland). The HBD's between these two areas, those of Canterbury, Marlborough, Wellington, and Wairarapa, recorded low incidence rates.

When these rates were checked against the Poisson distribution (Fig. 31) only Maniototo and Otago case numbers were shown to be statistically significantly higher (p > 95%). No HBD's recorded statistically significantly fewer cases than those expected.





## Geographic Counties

The outstanding feature accruing from calculation of incidence rates was the rate of the Maniototo GC (Fig. 32). This rate is approximately 100% greater than the second highest rate of 36.96 cases per 100,000 population-at-risk (Amuri GC). Adjacent GC's of Vincent and Waihemo, however, did not register any SLE cases (Appendix E). There was a broad band of moderately high incidence surrounding this area and including the GC's of Lake, Tuapeka, Bruce, Taieri, Waikouaiti, and Waitaki.

All GC's around Christchurch registered low incidence rates, but the Amuri GC recorded the second highest incidence rate for the total study area. Generally, the incidence rates of SLE in the South Island GC's became increasingly higher from north to south.

A definite gradient pattern exists on the western side of the Tararua-Ruahine Ranges. With the highest incidence rate of this area recorded in the Horowhenua GC, incidence fell away north and south. Although the Woodville GC recorded the highest rate of those GC's of the east coast of the North Island, no consistent pattern of incidence was observed.

Maniototo was the only GC statistically significant (p > 95%) after testing (Fig. 33).

#### Spatial Consistency Through Time

Although the incidence rates for all regions increased





retrospectively from 1971, the rank orders were perfectly correlated (1971-1951,  $r_s = 1.00$ ; 1971-1961,  $r_s = 1.00$ ; 1961-1951,  $r_s = 1.00$ ).

Testing for statistical significance showed that only region V was statistically significant (p > 95%) with the 1971 and 1961 populations-at-risk. Despite this region recording more observed cases than expected with the 1951 population-at-risk, this was not a statistically significant divergence.

Except for the Dannevirke and Maniototo HBD's, all HBD's had higher incidence rates with the 1951 and 1961 populations-at-risk than with that of 1971 (Figs. 30, 34, 35). Dannevirke HBD had a higher rate in 1971 than for 1961, but it was lower than that for 1951. Maniototo, however, recorded a greater incidence rate with the 1971 population-at-risk than with either the 1961 or 1951 populations-at-risk. Correlation between the rank order of HBD's by incidence rates at the three time points was very high (1971-1961,  $r_s = 0.96$ ; 1971-1961,  $r_s = 0.98$ ; 1961-1951,  $r_s = 0.98$ ).

While both the Maniototo and Otago HBD's were statistically significant (p > 95%) with the 1971 population-at-risk, this was not sustained with either of the two earlier populations-at-risk. Thus, no HBD at the 1961 or 1951 time points had a statistically significant divergence of observed cases of SLE from the number of cases expected.

Of the total number of GC's recording the occurrence of this disease, only the Maniototo and Taieri GC's registered higher incidence rates for the populations-at-risk after that of 1951





(Figs. 32, 36, 37). Rating against the 1961 population-at-risk produced the lowest incidence rate of the three time points for six of the GC's, three of which were the adjacent GC's of Dannevirke, Woodville, and Pahiatua. The rank order of GC's (by incidence rates) was virtually unchanged throughout the time period, and the null hypothesis of independence between the ranks of 1971, 1961, and 1951 was rejected (1971-1961,  $r_s = 1.00$ ; 1971-1951,  $r_s = 0.99$ ; 1961-1951,  $r_s = 1.00$ ).

The Maniototo GC was statistically significant (p > 95%) with the 1971 population-at-risk, but this was not sustained with the analysis using either the 1961 or 1951 populations-at-risk (Figs. 33, 38, 39). The Horowhenua GC had statistically significantly (p > 95%) more observed cases than expected with both the 1951 and 1961 populations-at-risk. No other GC reached a statistically significant level.

### Temporal Change

Six SLE patients (6.12%) had a date of onset prior to January 1, 1950, of which 66.67% had onset in the decade 1940-49.

From the data there appears to be a regular pattern in the years with heaviest onset of SLE symptoms (Figs. 40a, 40b). Generally there is a four year cycle discernible, with the first and second years the highs, and the third and fourth years the lows. The small number of cases (21) in this survey, precluded a similar trend being observed for males, but the female figures reinforced this cyclic suggestion (Fig. 40c).











## (A) SYSTEMIC LUPUS ERYTHEMATOSUS - NUMBER OF CASE ONSETS PER YEAR OF STUDY TIME PERIOD

FIGURE 40





FIGURE 40C

The majority (56.12%) of all cases had onset in the period 1962-1973. Of the female cases 54.55% had onset in this period, while for males the figure was 61.90%. A null hypothesis  $(H_0)$  was formulated: that the occurrence of SLE did not differ statistically significantly between time periods. The rejection level was set at the 5% confidence level with one degree of freedom.  $H_0$  was accepted at the 95% confidence level using the chi-square distribution test. Therefore the proportion in which the disease occurred over time did not differ statistically significantly.

At the HBD level the null hypothesis that cases of SLE occurred evenly throughout the HBD's of the study area in each period was tested. That is that HBD's showed only chance fluctuations above or below the onset case numbers that would have occurred locally had the study area rate been experienced by all HBD's. After testing,  $H_0$ was accepted for the period to 1961. In the second period, however, the Otago HBD was highly statistically significant (p > 99%) with 14 observed cases and an expected case number of 5.96 cases.  $H_0$  was rejected for this period.

Although the cities in the study area had 66.67% of the total PN patients resident within them at disease onset (Table I), 50% of the cases were located in either Christchurch or Wellington (Fig. 41). Almost 70% of the total number of North Island cases were in the Wellington-Hutt Valley-Porirua area at disease onset, while 35.48% of the South Island cases were in Christchurch city.

#### Regional Units

Region II had the highest percentage (38.89%) of PN cases within it at disease onset (Table II), and was the only region which recorded a substantially greater percentage of PN cases than its percentage of the study area's total population-at-risk. The difference for region II was 10%, while for region V (Otago) it was just 2.01%. FN was the only disease subset for which region II registered a higher percentage of the total case number than its percentage of the total study area population-at-risk. The incidence rates for the regions (Table III) reinforces the initial impression of an increased concentration in the number of disease cases in region II. After testing for statistical significance, however, no region had a statistically significant divergence in the number of observed cases from those expected.

Hospital Board Districts (HBD's)

The Wellington and North Canterbury HBD's combined had 55.56% of all PN cases resident within them at the time of disease

186.

PN



onset. The Wellington HBD alone had one third of all the cases. Four HBD's registered no cases within their areas at onset of PN symptoms (Appendix E).

The Marlborough HBD, however, recorded the highest incidence rate (Fig. 42), with a high rate also registered in the Ashburton HBD. Despite its large absolute numbers, the North Canterbury HBD showed as a low incidence trough between these two high incidence areas. No HBD was found from testing to have statistically significantly more or fewer cases than the number of cases expected to occur.

Geographic Counties

PN occurred in only 30% of the total number of GC's, with two counties, Hutt and Heathcote, recording 64.82% of the total number of cases (Appendix E).

Three high incidence rate areas were discernible (Fig. 43), with Waihemo GC having the highest rate. This area, although with only one case, had a rate thirteen times greater than the norm for the study area. This illustrates the effect that the size of the population-at-risk may have on the calculation of incidence rates, and thus, rendering it important that some 'significance' test be instituted to assess whether this distribution is due to chance factors or not. Pahiatua and Waipara GC's were the other high incidence rate areas, which, like Waihemo, are surrounded by very low incidence rate areas. The GC's which include the main cities,





excluding Southland, recorded similar. but low incidence rates.

When these rates were compared to the Poisson distribution, no GC's recorded an observed case number statistically significantly different from the expected case number.

#### Spatial Consistency Through Time

Although the incidence rates increased retrospectively, the rank order of the regions remained constant (1971-1951,  $r_s =$ 1.00; 1971-1961,  $r_s = 1.00$ ; 1961-1951,  $r_s = 1.00$ ). While the Otago region (V) was the only statistically significant area with both the 1971 and 1961 populations-at-risk (p > 95%), no region was statistically significant with the 1951 population-at-risk.

All HBD's showed lower incidence rates for 1971 than for 1961 or 1951 (Figs. 42, 44, 45). The null hypothesis that the ranks were of HBD's / independent for the three time periods was tested and rejected (1971-1951,  $r_s = 0.99$ ; 1971-1961,  $r_s = 0.98$ ; 1961-1951,  $r_s = 0.99$ ). No HBD was statistically significant throughout the time of the study.

Of the fifteen GC's recording at least a case of PN, only Waihemo and Waimate GC's had a higher incidence rate with the 1971 population-at-risk, than with the 1951 population-at-risk (Figs. 43, 46, 47). Waihemo's incidence rate increased with each successive time point from 1951, while Waimate recorded a trough of lower incidence in 1961 between the peaks of 1951 and 1971. The null hypothesis that the rank order of the GC's at each time period was








not significantly correlated was rejected (1971-1951,  $r_s = 1.00$ ; 1971-1961,  $r_s = 1.00$ ; 1961-1951,  $r_g = 1.00$ ).

Comparison of the distribution of the absolute case numbers with the Poisson distribution revealed that no GC had a statistically significant divergence of observed cases from those expected.

Temporal Change

Only two patients (3.70%) had onset of symptoms prior to January 1, 1950 (in 1941, and 1949). Since 1950 a small yearly increase in the number of cases was observed (Figs. 48a, 48b).

The null hypothesis  $(H_0)$  for testing was that the occurrence of the disease did not differ statistically significantly between the respective time periods. Using the chi-squared distribution test the region of rejection was set at the 95% confidence level with one degree of freedom. H<sub>0</sub> was accepted.

Analysis of the respective dates of onset for males and females revealed that no year was statistically significant for onset for males, but 1966 was for the onset of female cases (p > 95%). Generally, however, the onset of cases of both sexes was evenly distributed in each time period.

No HBD in either period showed a significant divergence in the number of case onsets observed from those expected. Thus, the null hypothesis  $(H_0)$  that the number of case onsets diverging above or below those expected to have occurred, may be attributed to chance factors, was accepted.



## (A) POLYARTERITIS NODOSA - NUMBER OF CASE ONSETS PER YEAR OF STUDY TIME PERIOD

(B) POLYARTERITIS NODOSA - CUMULATIVE PERCENTAGE HISTOGRAM OF CASE ONSETS PER YEAR



FIGURE 48

While 60% of all SCL cases were located in the main cities at the time of onset, all of these areas except Dunedin recorded a lower percentage of the absolute case number than their percentage of the study area's population-at-risk (Table I). Dunedin, with only 7.84% of the study area population-at-risk, had 18% of the SCL cases resident within its boundary at the time of disease onset. The cases of this disease comprised 25% of the total CTD case number in Dunedin city. Within a twenty-five mile radius of Dunedin city, 24% of the total study area case numbers and 38.71% of the South Island total were located at onset of symptoms (Fig. 49).

## Regional Units

The outstanding feature of the distribution of case numbers by regional units (Table II) was that 40% of all 3CL cases were in the Otago-Southland region (IV) at onset. This is 67.65% greater than the percentage of the study area population-at-risk (1971 census). But, SCL cases were only 23.26% of the total number of CTD diseases of this region. It is, thus, suggested that region V (Otago) may be contributing to the high occurrence of SCL in region IV. While region V had 14.66% of the population-at-risk (1971 census), just under one third of all SCL cases were in this region at time of disease onset. As with region IV the case numbers of this disease were 23.88% of the total CTD case numbers.

Examination of the incidence rates by regions (Table III) reinforced the seemingly spatial disparity in the occurrence of SCL.

198.

## SCL



The Otago region (V) had an incidence rate double that of the study area norm, and which was higher than the rate for the combined region (IV) of Otago-Southland. The northern adjacent region of Canterbury (III), on the other hand, showed a very low rate when compared to the study area norm.

Following testing for statistical significance only two regions were found to have a statistically significant divergence of observed cases from those expected. Region IV was statistically significant at the 95% confidence level, while the Otago region (V) was very statistically significant (p > 99%).

Hospital Board Districts (HBD's)

The Otago HBD had 26% of all SCL cases in its area at the time of disease onset, but the highest incidence rate in the study area was that of the adjacent Vincent HBD (which had only two cases). These two HBD's, however, comprised the centre of a gradient which radiates out to the coastal areas (Fig. 50). Elsewhere in the study area, the incidence rates for HBD's were generally low, with the Waitaki and Maniototo HBD's registering no cases of SCL (Appendix E).

Otago was the only HBD that had a statistically significant (p > 99%) divergence of observed cases, 13, from those expected, 5.22 (Fig. 51).

Geographic Counties (GC's)

The Taieri GC, with 9.20% of the study area's total





population-at-risk, had 20% of all the SCL cases resident within its boundary at the time of disease onset. Awatere GC, however, with one case, recorded the highest incidence rate for the GC in the study area (Fig. 52).

The adjacent GC's of Marlborough and Awatere produced incidence rates at either tail of the incidence rate scale, while the GC's north and south of Taieri had higher incidence rates than the GC with the greatest absolute number of cases in the area. Over much of the study area, low incidence rates prevailed with only 36% of the GC's recording occurrence of SCL (Appendix E).

When the distribution was checked for statistical significance only Taieri GC was statistically significant at the 95% confidence level (Fig. 53).

## Spatial Consistency Through Time

Although the incidence rates did increase retrospectively, the rank order of the regions was found to be perfectly correlated between the three time points (1971-1951,  $r_s = 1.00$ ; 1971-1961,  $r_s = 1.00$ ; 1961-1951,  $r_s = 1.00$ ). Changes, however, did occur when testing for statistical significance at the three time points. Whereas with the 1971 population-at-risk region IV was statistically significant (p > 95%), it was not with either the 1961 or 1951 populations-at-risk. Region V (Otago) did, however, remain a statistically significant area throughout the study time period. In 1971 this region was very statistically significant (p > 99%), but with the 1961 and 1951 populations-at-risk only moderately





statistically significant (p > 95%). It was, nonetheless, the only region at these two earlier time points to reach a statistically significant level.

While all HBD's recorded lower incidence rates with the 1971 population-at-risk than with the 1951 population-at-risk, there was not a consistent decline in all areas. The Dannevirke and South Otago HBD's recorded a higher incidence rate with the 1971 populationat-risk than with the 1961 population-at-risk (Figs. 50, 54, 55). Correlation between the rank orders of the HBD's at the three time points was very high (1971-1951,  $r_s = 0.98$ ; 1971-1961,  $r_s = 0.98$ ; 1961-1951,  $r_s = 0.99$ ).

Otago was the only HED to record a statistically significant divergence of observed cases from those expected, but with a lower level of statistical significance at the 1951 and 1961 time points than at the 1971 point (Figs. 51, 56, 57).

While the majority of GC's (77.78%) with SCL cases had lower incidence rates with the 1971 population-at-risk than with the 1961 population-at-risk, the GC's of Dannevirke, Awatere, Waikouaiti (Figs. 52, 58, 59) recorded the highest incidence rate with the 1951 population-at-risk. Tuapeka GC registered a rise in incidence rate from the time point of 1951, and thus exhibited a reverse trend to the other GC's. The null hypothesis of no independence between the rank orders of the GC's at the three time points was tested and rejected (1971-1951,  $r_s = 0.99$ ; 1971-1961,  $r_s = 1.00$ ; 1961-1951,  $r_s = 1.00$ ).

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	17.0 - 28.9
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25	FIGURE 54
	FIGURE 54











Taieri was the only GC to reach a statistically significant level and this was just with the 1971 population-at-risk (p > 95%) (Fig. 53).

#### Temporal Change

Analysis of the data of this disease revealed that 24% of the total SCL cases had onset prior to January 1, 1950. Despite 1925 being the earliest onset date, 50% of these cases had onset of symptoms during the period 1946-49. This was the only disease subset of CTD to have more cases (62%) with onset before 1961 than after that date. Although only 38% of SCL cases had onset after 1962, 63.16% of these cases had onset in either 1965, 1966, or 1967 (Figs. 60a, 60b). The null hypothesis ( $H_{o}$ ) for testing was that the occurrence of this disease did not differ statistically significantly between the respective time periods. The region of rejection was at the 5% confidence level with one degree of freedom. Using the chi-square distribution test,  $H_{o}$  was accepted.

For 72.73% of the total number of male cases, onset occurred in the years up to and including 1961, with 36.36% of the total cases having onset prior to 1950. While the respective figures for females were less than those for males, a similar trend was observed: 58.97% of the total female cases with onset in the period to 1961, and 20.51% with onset prior to 1950.

A null hypothesis  $(H_0)$  was formulated for testing in each time period at the HBD scale: that the study area rate of onset applied evenly to all HBD's, and therefore any divergence from this



# (A) SCLERODERMA - NUMBER OF CASE ONSETS PER YEAR OF STUDY TIME PERIOD





FIGURE 60

number would be due to the influence of chance factors. For the first period (up to and including 1961) Vincent was the only statistically significant HBD (p > 95%) with more observed cases than expected. H<sub>o</sub> was not accepted for this period. In the second period Otago HBD was highly statistically significant (p > 99%) with 8 observed cases and an expected case number of 2.06. H<sub>o</sub> was also not accepted for this period.

# PMS/DMS

This disease subset of CTD, with 59.58% of the cases in cities (Table I) would seem to have a greater number of rurally located cases at onset than the other subsets (Fig. 61). Both Palmerston North city and Dunedin city had a higher percentage of cases than their percentage of the population-at-risk, while the Wellington-Hutt Valley-Porirua city area recorded a substantially lower percentage of cases than the percentage of population-at-risk. Within an area around Palmerston North, extending to include Feilding, Sanson, Shannon, and Levin, 12.77% of all PMS/DMS cases were located at the time of disease onset.

### Regional Units

Despite region II containing twice the population-at-risk (1971 census) of region I, both recorded a similar percentage of the total numbers of cases within their respective areas.(Table II). Conversely; regions IV and V registered very much higher percentages of the total case numbers than the percentage of the study area population-at-risk within the area. The figures in these two regions for PMS/DMS were very similar to those for SCL in terms of percentage of cases.

Examination of the incidence rates (Table III) highlighted a distinct increasing gradient emanating north and south from the low rate of region II. The Palmerston North-Wairarapa region (I) recorded an incidence rate double that of the adjacent region to the



south, thus showing the differential incidence of this disease subset. Although region IV had a rate nearly 70% higher than the study area norm, excluding Southland (Region V) from the calculation increased the rate to 88.92% above the norm.

After testing for statistical significance, only regions IV and V were statistically significant, both at the 95% confidence level.

Hospital Board Districts (HBD'S)

Four HBD's did not record any cases of PMS/DMS as being located within their areas at the time of disease onset (Appendix E). The highest rate was in the Central Otago HBD of Vincent (Fig. 62) but, apart from the Marlborough HBD, low rates of incidence generally prevailed throughout the study area HBD's.

Testing for statistical significance, however, revealed that the only statistically significant HBD was that of Wellington (p > 95%) where fewer cases were observed than expected (Fig. 63).

Geographic Counties (GC'S)

Only one third of all GC's in the study area recorded the occurrence of this disease subset (Appendix E). Although 57.45% of the cases were located at disease onset in GC's around the cities, the more rural counties recorded a substantially higher incidence for this subset than for other CTD's.

The highest incidence rates were recorded in the adjacent

	7
CRUDE INCIDENCE RATES PER 100,000 POPULATION (1971 CENSUS)	$\sim n$
OF POLYMYOSITIS AND DERMATOMYOSITIS BY HOSPITAL BOARD DISTRICTS	$\gamma \gamma \gamma$
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	FIGURE 62

SIGNIFICANT DIVERGENCE OF OBSERVED FROM EXPECTED NUMBERS OF CASES OF POLYMYOSITIS AND DERMATOMYOSITIS BY HOSPITAL BOARD DISTRICTS 1971 CENSUS	my >
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Central Otago GC's of Vincent and Lake (Fig. 64). A gradient of diminishing incidence was evident from these areas to the coast. Smaller gradients were observed through the GC's comprising the Palmerston North HBD and the South Canterbury HBD. Very low incidence rates were recorded throughout the Wairarapa and Canterbury GC's, as well as the Hutt GC.

While Hutt was the only GC to be statistically significant (Fig. 65), recording fewer cases than expected, this may in fact be a spurious result. At the time of the data collection it was known that the case records of three PNS/DMS patients, held at a public hospital in this GC, had been destroyed. As no confirmation could therefore be made as to address at onset and diagnosis, these patients were excluded from the analysis. If, however, such cases were included as being resident within the Hutt GC at the time of disease onset, and from the altered rate for the study area, a new expected case number was computed, the Hutt GC would not be statistically significant.

#### Spatial Consistency Through Time

In accord with the other disease subsets, the regions exhibited decreasing rates with increasing time from 1951, but the rank order did not alter (1971-1951,  $r_s = 1.00$ ; 1971-1961,  $r_s =$ 1.00; 1961-1951,  $r_s = 1.00$ ). The statistical significance level reached by both regions IV and V (p > 95%) with the 1971 populationat-risk was not achieved with the earlier populations-at-risk.





Despite a tendency for lower incidence rates to be recorded with the 1971 population-at-risk than with either the 1951 or 1961 populations-at-risk, the Waitaki HBD registered a higher rate in 1971 than for 1961 (Figs. 62, 66, 67). The difference, however, was 0.47 cases per 100,000 population-at-risk. The rank orders of the HBD's at the respective time points were tested for independence, but were found to have a high correlation (1971-1951,  $r_s = 0.99$ ; 1971-1961,  $r_s = 1.00$ ; 1961-1951,  $r_s = 1.00$ ).

Testing for statistical significance with the earlier populations-at-risk revealed that no HBD had statistically significantly more or fewer observed cases than expected. The statistical significance level of the Wellington HBD with the 1971 population-at-risk (p > 95%) was, therefore, not sustained through time.

Contrary to a trend of GC's having decreasing rates with increasing time from 1951, the GC's of Waimate and Tuapeka exhibited increasing rates with increasing time (Figs. 64, 68, 69). While the Manawatu and Waitaki GC's had a rate with the 1971 population-at-risk higher than with the 1961 population-at-risk, but lower than the rate with the 1951 population-at-risk. The rank orders of the GC's at the three time points showed a high correlation (1971-1951,  $r_s = 0.99$ ; 1971-1961,  $r_s = 1.00$ ; 1961-1951,  $r_s = 1.00$ ).

Apart from the Hutt GC, with the 1971 population-at-risk (p > 95%) (Fig. 65), no other GC was found to have a statistically significant divergence in the number of observed cases from those

CRUDE INCIDENCE RATES PER 100,000 POPULATION (1961 CENSUS) OF POLYMYOSITIS AND DERMATOMYOSITIS BY HOSPITAL BOARD DISTRICTS	
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CRUDE INCIDENCE RATES PER 100,000 POPULATION (1951 CENSUS) OF POLYMYOSITIS AND DERMATOMYOSITIS BY HOSPITAL BOARD DISTRICTS	
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e service and a service of the servi	26.0 - 35.9
	FIGURE 67





expected at any of the time points.

Temporal Change

The data exhibits a strong asymmetrical distribution with regard to the time of onset of disease symptoms. One patient had onset prior to January 1, 1950, and only 23.40% of the total case numbers had onset in the period up to and including 1961 (Figs. 70a, 70b). During the period 1962-1973, 95.45% of the male patients and 60% of the female patients had onset. For male cases approximately 52% had onset in either 1968, 1969, or 1970, while for females no such concentrated onset period was discernible.

The null hypothesis  $(H_0)$  under test was that the study area rate of onset applied evenly to all HBD's, and therefore any divergence from this number would be due to the influence of chance factors. No HBD was statistically significant for the first period (up to and including 1961) while the Wellington HBD was the only statistically significant (p > 95%) HBD in the second period. Fewer cases of PMS/DMS were observed than expected in this HBD.




FIGURE 70

230

# Possible Bias From the Availability of Manpower Resources

That this distinct spatial pattern in the incidence of CTD's may be due to a variation in the medical facilities of the study area was considered. Specifically, is the consistent statistically significant level reached at all scales of areal units by the Taieri area, the result of the location of the Otago Medical School and ancillary medical services in Dunedin?

By using the number of medical personnel in each HBD (N.Z. Department of Health, <u>Hospital Management Data, Year Ended 31</u> <u>March, 1972</u>), and the population-at-risk (1971 census) of the HBD's, a ratio of medical staff to population was computed (Table VI). The highest ratio (of medical staff to population) was reckoned for the Otago HBD. This is consistent with the possibility that the increased incidence in this area may be attributable to more assiduous search for these diseases. The higher frequencies in region V (Otago) also fits this hypothesis. Differentiation of Dunedin city from both the remainder of region V and the Otago HBD further emphasises the high frequencies of the city.

Less severe city cases, however, might be treated as outpatients and, thus, be less likely to be admitted to hospital. The scoring systems adopted for this survey were constructed so that only the most 'obvious' cases would be included for final analysis. Almost all these would be severe enough to warrant admission to hospital. Physicians taking a special interest in these diseases would have included more cases with a score of less than four (4) than other

TABLE VI. Ratios of medical staff to the population-at-risk in

HBD	Medical Staff (1972)	Population-at- risk (1971 census	Ratio medical staff : population
Palmerston North	51.8	113,319	1 : 2187.6
Wellington	175.9	320,915	1 : 1824.4
Christchurch	151.5	319,690	1 : 2110.2
Otago	123.3	126,442	1 : 1025.5
Invercargill	49.9	111,409	1:2232.7

the principal Hospital Board Districts of the study area.

Source: Medical staff statistics from Department of Health, <u>Hospital</u> Statistics of New Zealand, Year ended <u>31 March 1972</u>, N.Z. Population Census 1971, Volume 1.

physicians, but it was considered unlikely that an increased number of overt cases of the diseases would be detected. By applying a uniform cut off point for achieving a definite diagnosis any bias due to local enthusiasm by physicians would be minimised, although not completely eliminated.

A further and most important consideration, however, is that the incidence of scleroderma, of all the disease subsets, was consistently and statistically significantly increased. In the analysis at various levels it could be noted that this disease was the principal contributory factor to the high statistically significant level for CTD reached by the Otago area. Rarely, did either SLE, PN, or PMS/DMS have a statistically significant level sustained at all scales of area, or at the three time points. Physicians generally consider that SCL is the most obvious CTD to diagnose because the manifestations of the disease are fewer and less variable than the other CTD subsets. Therefore, physicians are less likely to disagree over a diagnosis of SCL than the other CTD's. With regard to this present study, it was noted that the lowest percentage of the total diagnostic exclusions (either by the physician or the computer) were those cases diagnosed on discharge from hospital with SCL (13.22%). Exclusions of the other diseases were SLE 35.54%, PN 33.06%, PMS/DMS 14.05%, and others (this included connective tissue disease as a group) 4.13%.

Thus, although some initial diagnostic under-recording at the individual public hospitals may have occurred, it was believed that if any resulting bias had permeated this survey it would be minimal. The measures taken to confirm a diagnosis were such that only the most obvious disease classifications would be included in the survey. Further, the statistically significant levels attained in the Dunedin area were much higher than one would have expected for the manpower resources available. The consequent findings, therefore, were considered to give as accurate as possible an estimate of the true spatial and temporal variations in CTD incidence throughout the study area. However, because of the availability of expertise and manpower in the Dunedin area further research may thus be needed to verify these findings.

#### Summary

The spacio-temporal analysis of the data has revealed the following:

(a) that region V (Otago) had statistically significantly more observed cases of CTD's than expected with each time point population-at-risk;

 (b) region V was consistently statistically significant throughout the study time period with regard to the disease subset
SLE, but especially SCL;

(c) at the HBD areal scale and with CTD, Otago was statistically significant with the 1951, 1961, and 1971 populationsat-risk. Palmerston North HBD had a statistically significant divergence of observed CTD cases from those expected with the 1961 population-at-risk;

(d) with regard to SLE both the Maniototo HBD and the
Otago HBD were statistically significant, but only with the 1971
population-at-risk;

(e) the Otago HBD had statistically significantly more observed cases of SCL than expected with the three time point populations-at-risk. No other HBD was statistically significant;

(f) Taieri and Horowhenua were the only GC's to have statistically significantly more observed cases of CTD's than expected with each time point population-at-risk. Paparua and Waimari GC's were statistically significant in 1971, with fewer observed cases of CTD than expected; (g) there were statistically significantly more SLE cases observed than expected in the Maniototo GC with the 1971 populationat-risk, while Horowhenua GC was statistically significant with both the 1951 and 1961 populations-at-risk;

(h) Taieri GC was statistically significant in 1971 with more SCL cases observed than expected;

(i) at no scale of areal unit, and at no time point were there statistically significant divergences of observed cases of PN from those expected;

(j) statistically significantly more cases of PMS/DMS were observed in regions IV (Otago-Southland) and V (Otago) than expected with the 1971 population-at-risk. No region was statistically significant with either the 1951 or 1961 population-at-risk;

(k) both the Wellington HBD and the Hutt GC had statistically significantly fewer cases of PMS/DMS observed than expected, but only with the 1971 population-at-risk. This was probably an artefact of some case notes being destroyed at one of the public hospitals in this area. If a new 'expected' frequency figure were computed, including these additional cases, these two areal units would not be statistically significant.

By successive disaggregations of the data through the areal scales it was possible to 'locate' the principal area that was contributing to the statistical significance of region V. This area, Taieri GC (and especially Dunedin city) was consistently statistically significant at all areal scales and time points. Subsequent research into the spatial and temporal distributions of

each disease subset revealed that it was SCL that was contributing to the statistically significantly more cases of CTD observed in this area than expected.

Temporal changes in the incidence of CTD's were found to have occurred. Otago HBD had statistically significantly more observed cases of all CTD's, but specifically both SLE and SCL cases, in the latter period than expected. Wellington HBD was also statistically significant in the latter period.

No HBD had statistically significantly more or fewer observed cases of SLE than expected in the first time period. No statistically significant temporal change in the occurence of PN in the respective HBD's was noted. Vincent HBD was statistically significant in the first period with more observed cases of SCL than expected.

Therefore, the principal hypothesis that there were statistically significant spatial variations in the incidence of CTD's, collectively, was supported. The subsumed hypotheses that the individual disease subsets had statistically significant spatial variations were not supported for PN and PMS/DMS. The hypotheses were supported with respect to SLE, and SCL.

The hypothesis of statistically significant temporal changes in the occurrence of CTD's, collectively and severally, was not supported with analysis over the study area. At the HBD scale this hypothesis was supported. The findings of this analysis, therefore, have implications with regard to both actiology and prevention.

### FOOTNOTES

- 1. The 1971 N.Z. census was taken on March 23rd, 1971.
- 2. The 1951 N.Z. consus was taken on April 17th, 1951. The 1961 N.Z. consus was taken on April 18th, 1961.
- 3. 'Disease drainage' areas may be likened to river catchment areas with the principal public hospitals of a region acting as the 'main rivers'. The territory covered by a region, therefore, would be that in which almost all patients would go to a principal public hospital of that region.

## CHAPTER FOUR

# GEOGRAPHICAL EVIDENCE ON MEDICAL HYPOTHESES<sup>1</sup>

In this chapter the populations with connective tissue diseases (CTD's) will be analysed in terms of the following parameters:

- (a) sex;
- (b) age at onset;
- (c) race;
- (d) rural and urban distributions;
- (e) occupation.

These results may therefore be compared to the findings of overseas studies which were detailed earlier.

It was outside the scope of this thesis to investigate a number of possible relationships that may exist between the environment and the occurrence of CTD, in the statistically significantly defined areas. Examination was made, however, of one specific medical hypothesis, that of the possible relationship between sunlight and the incidence of CTD, especially systemic lupus erythematosus (SLE). This is used principally as an illustrative case study of the application of a medical geographic methodology to further aetiological researeh.

### Sex

The hypothesis under test was that in accordance with overseas studies there is a female dominance in the numbers of cases of CTD's, but a male dominance in the cases of the subset disease polyarteritis nodosa (PN).

From the analysis of the data this hypothesis was supported (Table VII). For all CTD's females comprised 66.92% of the morbid cases, while for three of the individual disease subsets females predominated. The female to male ratio was 3.6:1 for SLE and scleroderma (SCL), and 1.14:1 for polymyositis (PMS) and dermatomyositis (DMS). Although the difference between the sexes in absolute case numbers for PN was only two, a male dominance (51.85%) in total cases was recorded.

TABLE VII. Male and Female composition of each connective tissue

Disease	Male	Female	Total
SLE	21	77	98
PN	28	26	54
SCL	11	39	50
PMS/DMS	22	25	2+7
CTD	88	178	266

disease.

# Age at Onset

Due to the small numbers of cases involved in this study it was not practical to analyse the parameter of age at onset by the more generally used method of five year intervals. Therefore, the data was aggregated into the following larger, but mutually exclusive, age decades:

- (a) up to 19 years of age;
- (b) 20 years to 29 years of age;

- (c) 30 years to 39 years of age;
- (d) 40 years to 49 years of age;
- (e) 50 years to 59 years of age;
- (f) 60 years to 69 years of age;
- (g) 70 years and all ages older than this.

#### CTD

Ages at onset of disease symptoms ranged from 1 year old to 78 years of age, with a mean onset age of 41.15 years of age (standard deviation (s.d.) = 19.00). The larger percentage (44.36%) of the total cases had onset during the age range 15 to 44 years, with a slightly smaller number (31.96%) with onset during the years 45 to 64 years of age. Approximately 45% of all cases had onset during the third, fourth, and fifth decades of life, while 27.82% had onset in the first two decades of life. Almost 36% of the patients, however, had onset when fifty years of age and older.

From the data females are at greatest risk to contracting these diseases at younger ages than males (Fig. 71c). The mean age of onset for males was 47.59 years of age (s.d. = 17.40), while for females, the mean onset age was 37.96 years of age (s.d. = 18.99). The reversed polarity of the age-sex structure supports this contention. Whereas 17.77% of the male cases had onset before the age of 30, onset for 34.27% of the female cases occurred in the first three decades of life. The majority of males (51.14%) had onset after the age of 50, but for females most had onset (49.44%) between the ages of 20 and 49.



#### AGE-SEX STRUCTURES OF CONNECTIVE TISSUE DISEASES







c) connective tissue disease



e) polymyositis and dermatomyositis

241.

#### SLE

The mean age of onset of SLE in this survey, 34.02 years of age, was older than that found by Dubois and Tuffanelli (1964), Maddock (1965), and Estes and Christian (1971), but younger than the mean age of the patients in the Kurland <u>et al</u> (1969) survey. In concert with overseas studies (Dubois and Tuffanelli, 1964; Maddock;, 1965), the greatest percentage of cases (63.27%) had onset of symptoms prior to 30 years of age. In 26.53% of the total cases, onset occurred in the first two decades of life. Onset of this disease therefore occurrs at a younger age than for the other CTD subsets.

From the data it would seem that females are at greatest risk of contracting SLE at a much earlier age than males (Fig. 71a). The mean age of onset for females, 30.85 years of age (s.d. = 16.62), was 14.82 years earlier than that for males (45.67 years of age, s.d. = 16.24). As Siegel and Lee (1973) had previously observed, the highest percentage (63.64%) of females had onset in the age group 15 to 44 years. Almost 50% of female SLE cases recorded onset as occurring prior to their thirtieth year, whereas the figure for males was only 14.29%. For males, 76.19% of the cases had onset after age 40.

PN

Ages at which onset occurred ranged from 8 to 75 years of age, with a mean age of onset of 47.28 (s.d. = 20.08) years. The majority (55.56%) of patients had onset after their fiftieth year which suggests that this disease may not be contracted until later in life. Only 20.37% of the total cases recorded onset prior to 30 years of age, while 38.89% contracted the disease within the first four decades of life.

The mean age of onset for females was 44.81 years (s.d. = 22.59), with a range of ages from 8 to 74 years. Although 23.08% of the female patients had onset in the first two decades of life, 53.85% had onset after the fourth decade (Fig. 71b). The male age distribution at onset exhibits a similar trend. With a mean onset age of 49.57 years (s.d. = 17.55), 57.14% of the total male number of cases had onset after their fiftieth year, while 39.29% had onset after their sixtieth year.

#### SCL

Onset age ranged from 7 to 78 years with a median of 45.98 years (s.d. = 16.52). Analysis of the data from this survey confirmed the findings from other studies (Tuffanelli and Winkelmann, 1961; Medsger and Masi, 1971). Only 10% of the SCL cases had onset of symptoms during the first two decades of life, but 68% had onset in, or after their fortieth year.

The female mean age of onset was 45.64 years (s.d. = 17.13), with a range from 7 to 78 years. Most females (43.59%) had onset between their fifteenth and fortieth years (Fig. 71d), but 52% had onset after this latter age. For males the median age for onset was 47.18 years (s.d. = 14.83) with onset ages ranging from 17 to 73 years. Males comprised only 18.75% of all cases with onset during the first three decades of life, and 21.74% of those cases with onset after age 50. Onset for males generally seemed to occur in the age group 30 to 50 years (45.45%). The low numbers of males in this survey with SCL (11) necessitates that caution be taken in considering these figures.

# PMS/DMS

The median age of onset of this disease was 40.51 years (s.d. = 21.08) with a range from 1 year old to 77 years. The data of this survey does not confirm the results of previous studies as to the population affected (Pearson, 1962; Kurland <u>et al</u>, 1969). Although the age at onset varies widely, the largest number of cases had onset in the fourth and fifth decades of life, with a high onset rate also in the first two decades. There is, therefore, a bimodal distribution of onset ages, as noted by Winkelmann <u>et al</u> (1968), but with the peaks and troughs occurring in different decades from those of the earlier study.

For females, the bimodal distribution is more marked, with a similar number of cases having disease onset in the first two, fourthand fifth decades of life (Fig. 71e). The mean onset age was 36.48 years (s.d. = 20.34) with a range from 2 years old to 77 years. Males, however, exhibited a reverse trend with peaks of onset occurring in the third, fourth, and sixth decades of life. With a mean onset age of 45 years (s.d. = 21.43), 50% of all male cases had onset after their fiftieth year, while 22.7% had onset prior to age 30.

244.

#### Race

The hypothesis for testing was that there exists a differential incidence of CTD between various races, specifically between Maoris and Europeans.

Siegel <u>et al</u> (1962) studying SLE; Masi and D'Angelo (1967) studying fatal SCL and Masi (1967) studying fatal PN in Baltimore; and Medsger <u>et al</u> (1970) studying PMS all found a higher incidence of these diseases in Negro women than Negro men or Europeans. Not all studies, however, found a racial predilection in the incidence of CTD's (Medsger and Masi, 1967; Dubois et al, 1970).

In the present study it was believed that consideration of this hypothesis would yield only spurious and meaningless results. The following factors would play a determining role in the analysis:

(a) The greater proportion of races other than European reside outside the defined study area. At the 1971 census only
16.96% of the total N.Z. Maori population were living in the study area;

(b) Approximately 31% of the total number of cases in this study did not have the answer to the question 'what race' included on their hospital admission form.

Thus, between 61.70% (PMS/DMS) and 74.07% (PN) of the total cases in each disease subset were European (Table VIII). Four Maori cases were observed in the survey, of which three had SLE, and one PN. Three of the four patients classed as 'other races' were Chinese (two had SLE, and one SCL).

Race	SLE	PN	SCL	FMS/DMS	CTD
Maori	3.06	1.86	-	-	-
European	64.29	74.07	66.00	61.70	76.47
Other	3.06	-	2.00	-	-
Not given	29.59	24.07	32.00	38.30	23.53

TABLE VIII. Percentages of connective tissue disease in different

racial groups.

Support or rejection of this hypothesis was, therefore, left in abeyance for this study.

#### Rural and Urban Distribution

An earlier study of hospital admission statistics suggested that SCL and PMS/DMS are predominantly urban diseases, while SLE and PN are rural in distribution (Couchman and Wigley, 1971).

Due to the large urban concentration of the N.Z. population (70.2% - 1971 census), and the small number of cases involved in this study, the definition of 'urban' is that used by the N.Z. Statistics Department (N.Z. Census 1971, <u>Increase and Location of Population</u>, Vol. 1,13) to define 'urban areas':

"In addition to the central city or borough, urban areas (non-administrative) include neighbouring boroughs, town districts, and parts of counties which are regarded as suburban and as belonging to that centre of population, irrespective of their being under different local administration."

There are seven urban areas in the study area comprising 70.38% of the total study area population-at-risk: Palmerston North, Wellington-Hutt Valley-Porirua, Masterton, Christchurch, Timaru, Dunedin and Invercargill (Table IX). All other areas were classed as rural.

						and the second second second second
Urban % poj area stud	pulation of y area (1971 census)	SLE	PN	SCL	PMS/DMS	CTD
Palmerston North	4.72	8.16	1.85	4.00	10.64	7.14
Wellington- Hutt-Porirua	25.42	17.35	31 .48	22.00	10.64	19.92
Masterton	1.67	1.02	-	2.00	-	0.75
Christchurch	22.81	21.43	20.37	16.00	17.02	19.17
Timaru	2.39	3.06	3.70	2.00	4.26	3.38
Dunedin	9.18	16.33	12.96	22.00	14.89	16.54
Invercargill	4.19	3.06	3.70	2.00	4.26	3.38
Total	70.38	70.41	74.06	70.00	61.71	70.28

TABLE IX. Percentages of total connective tissue diseases in the

urban areas.

SLE and PN recorded the lowest percentages of cases in rural areas, while SCL and PMS/DMS had the highest percentages of rural cases (Table X). PMS/DMS registered the lowest urban to rural ratio (1.6:1), with PN recording the highest (2.86:1). Thus, except for PMS/DMS, the urban/rural distributions of the disease subsets seem to show little departure from the study area norm. The null hypothesis  $(H_0)$  under test therefore, was that there were no statistically significant differences between the urban and rural occurrences of the diseases. The chi-square distribution test was used with three degrees of freedom, and the level of statistical significance set at the 5% confidence level. After testing, H<sub>0</sub> was accepted.

At the regional level the null hypothesis for testing was that the rate for the study area occurred evenly in all urban areas -

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	Urban		Rur	al
	No.	%	No.	%
SLE	69	70.41	29	29.59
PN	40	74.06	14	25.94
SCL	35	70.00	15	30.00
PMS/DMS	29	61.71	18	38.29
CTD	187	70.28	79	29.72

TABLE X. Urban and rural cases distribution of each connective

tissue disease.

that is, that urban areas showed only chance fluctuations above or below the number of cases that would have occurred had the study area rate been experienced ubiquitously. Region II had statistically significantly (p > 95%) less cases observed, 5, than expected, 11.95, while region V had statistically significantly (p > 95%) more cases of SLE and SCL than expected.

Therefore, while no statistically significant distributional differences between urban and rural areas were evident for each disease over the whole study area, there were statistically significant distributional irregularities within individual regions.

# Occupation

Except for SCL, no studies have revealed a possible association between occupations of patients and the incidence of CTD's. Bramwell (1914), Erasmus (1967), Rodnan <u>et al</u> (1967), and Freneaux <u>et al</u> (1973) have drawn attention to the increased incidence of SCL among miners. The occupational groups used for this study were those of the N.Z. Statistics Department (1971 census - <u>Increase and Location</u> of Population, Vol. 6):

(a) professional, technical, and related workers;

(b) administrative, executive, and managerial workers;

(c) clerical workers;

(d) sales workers;

(e) farmers, fishermen, hunters, loggers, and related workers;

(f) miners, quarrymen, and related workers;

(g) workers in transport and communications;

(h) craftsmen, production process workers, and labourers not elsewhore classified;

(i) service, sport, and recreation workers.

Three further groups were constructed for this study, as some patients would not be included into the above categories:

(j) students which included all those persons attending some form of educational institution as pupils;

(k) housewives;

(1) retired persons, invalids,

(m) other, which includes children not of an age to be in the category of a student (e.g. a kindergarten child).

The difficulties in determining a patient's occupation at the time of onset necessitated that this survey use for analysis occupation as at the time of diagnosis. Caution, therefore, had to be exercised in drawing any conclusions from this part of the study as any occupational association with a disease may be spurious. The occupation of the patient may not be that of the time of onset of first symptoms.

While 42.48% of the total number of CTD cases were housewives, it must be noted that 66.93% of the total cases were females, and 51.68% of those were married at time of diagnosis. In each disease subset at least 50% of the total female cases were housewives.

Persons in occupational category (h) comprised 10.53% of the total cases, but were male dominated (92.86%), and evenly distributed in all disease subsets.

The age differential between males and females at the time of onset was emphasised with reference to categories (j) and (l). Males comprise only 15.88% of the students with CTD, but are 72% of those persons classed as retired or invalids. The younger age of onset for patients with SLE is indicated by these figures. Although students were 7.14% of the total case number, the majority (52.6%) were SLE patients, who comprised 10.20% of all SLE cases.

No association was noted between SCL and patients with silicosis. The only miner recorded in the study was a PN patient, who worked in the non-silica Kaitangata mine. The contention, however, that alcoholism may be causally related to PMS, did receive some support from this analysis. Five PMS patients (two females, and three males) had also been admitted to a public hospital with alcoholism.

Therefore, while no positive associations appeared to exist

exist between the incidence of CTD's and patients' occupations, a final assessment was precluded because:

(a) occupations of patients given were not those at the time of enset;

(b) non specific nature of a patients occupation if provided on the hospital admission form;

(c) relatively small numbers involved in the study.

# Connective Tissue Diseases and Sunshine

The detrimental effect of sunlight on SLE is well documented (Dubois, 1974a). Onset and progression of the disease frequently follow excessive sun exposure, but it is also clear that photosensitivity is not a consistent or essential part of the disease.

The principal aim of this section was to establish and evaluate a methodology which would enable a specific medical hypothesis to be tested employing geographical and statistical techniques. The method could subsequently be applied to the examination, at the wider scale, of possible relationships between the occurrence of CTD's and various environmental factors.

The hypothesis for testing was that the occurrence of SLE is related to areas with high sunshine hours rather than low sunshine hours.

#### Method

The method of analysis was an extension of a technique employed in earlier studies (McGlashan, 1969b; Borman, 1974).

Cases of SLE were plotted (by the dot distribution technique) on a chloropleth base map of four divisions of mean annual hours of bright sunshine.<sup>2</sup> Overlaying of a dot distribution map of total population in the study area, gave the divisions of population resident within each sunshine hour division. In a simple manner this allows one to assess whether or not statistically significantly different incidence rates or statisticially significant deviations from expected cases occur in different sunshine areas (McGlashan, 1974a). Therefore, statistically significant levels of association-in-space may (or may not) be illustrated. The total population of a district can be brought to account in the calculations of statistically significant correspondence in space.

#### Results

When the incidence rates of SLE in each sunshine hour region were compared to the Poisson distribution it was found that no area had a statistically significant divergence of observed cases from those expected (Fig. 72). Analysis of the data suggests that, <sup>.</sup> contrary to the findings of some overseas studies, the incidence of SLE in the study area is not in a statistically significant relationship with sunshine hours. The hypothesis therefore, was not supported.

This same method was applied to the occurrence of all CTD's as a group, and to the other subsets of CTD, PN, SCL, and PMS/DMS.

When the distribution of CTD's in each sunshine region were checked for statistical significance, it was found that areas with 1800 or less sunshine hours had statistically significantly (p > 99%)



251a

more observed cases than expected (Table XI).

TABLE XI. Significance test of the correlation between the spatial distribution of connective tissue diseases and sunshine hours.<sup>#</sup>

Mean annual hours of bright sunshine	Population 1971	Observed cases	Expected cases	Poisson probability
2200 and over	21,981	5	4.83	norm
2000 - 2200	392,544	74	86.29	norm
1800 - 2000	602,998	120	1 32.56	norm
1800 and less	192,523	67	42.32	99% high
Total	1,210,046	266	266.00	

\* after Garnier, B.J., 1958, The Climate of New Zealand, Arnold.

There were no statis tically significant divergences of observed PN cases from those expected in any of the sunshine regions (Table XII), but with regard to SCL (Table XIII) the areas receiving 1800 or less hours were statistically significant (p > 95%). Testing the distribution of PMS/DMS (Table XIV) for statistical significance revealed that those areas receiving 2000 to 2200 mean sunshine hours had statistically significantly (p > 95%) fewer observed cases than expected. While areas with 1800 or less mean sunshine hours had statistically significantly (p > 95%) more cases than expected. Therefore this PMS/DMS data does not support the contention that this disease may be associated with high sunshine hours.

This method can be of use principally against physical variables, in any situations where total population dot maps allow both the cases and the population-at-risk to be divided into separate

Mean annual hours of bright sunshine	Population 1971	Observed cases	Expected cases	Poisson probability
2200 and over	21,981	2	0,98	norm
2000 - 2200	392,544	20	17.52	norm
1800 - 2000	602,998	23	26.91	norm
1800 and less	192,523	9	8,59	norm
Total	1,210,046	54	54.00	

TABLE XII. Significance test of the correlation between the spatial distribution of polyarteritis nodosa and sunshine hours."

\* after Garnier, B.J., 1958, The Climate of New Zealand, Arnold,

TABLE XIII. Significance test of the correlation between the spatial distribution of scleroderma and sunshine hours.<sup> $\pi$ </sup>

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Mean annual hours of bright sunshine	Population 1971	Observed cases	Expected cases	Poisson probability
2200 and over	21,981	1	0.91	norm
2000 - 2200	392,544	15	16.22	norm
1800 - 2000	602,998	19	24.92	norm
1800 and less	192,523	15	7.95	95% high
Total	1,210,046	50	50.00	

\* after Garnier, B.J., 1958, The Climate of New Zealand, Arnold.

TABLE XIV. Significance test of the correlation between the spatial distribution of polymyositis and dermatomyositis and sunshine hours.\*

Mean annual hours of bright sunshine	Population 1971	Observed cases	Expected cases	Poi <b>sso</b> n probability
2200 and over	21,981	2	0.85	norm
2000 - 2200	392,544	6	15.25	95% low
1800 - 2000	602,998	25	23.41	norm
1800 and less	192,523	14	7.48	95% high
Total	1,210,046	47	47.00	

\* after Garnier, B.J., 1958, The Climate of New Zealand, Arnold.

areas on the basis of any relevant set of isopleth lines. This test can be applied <u>seriatim</u> against any number of isoplethed parameters. As the result is a one-to-one relationship, no difficulty of interpreation can occur, as it often does with instances of multiple causation or non-linear relationships (McGlashan, 1974a).

# Summary

From the analysis of the data in this chapter the following were found to apply to the incidence of CTD, collectively and severally:

(a) that females are at greatest risk to contracting SLE,SCL, PMS/DMS, whereas males are the dominant sex of PN cases;

(b) females are at greatest risk to contracting all subsets of CTD's at an earlier age than males. Usually onset occurs during the first four decades of life. Males, however, are at greatest risk in their fifth and later decades of life; (c) onset of the first symptoms of SLE occurs at an earlier age for both sexes than does onset for the other disease subsets;

 (d) there appears to be no association of CTD incidence and occupations of the patients, but further testing is required for more specific information to be gained;

(e) the incidence of the diseases does not exhibit a significant urban or rural bias over the whole study area, but in the urban area of region V (Otago) statistically significantly more cases were observed than expected for SLE and SCL. Statistically significantly fewer cases were observed in the urban area of region II (Wellington-Marlborough);

(f) No correlation was shown between the incidence of SLE and areas of high sunshine hours. PMS/DMS incidence was found to be statistically significant in the low sunshine areas, which was further supported by the statistically significantly fewer observed cases recorded in the second to highest sunshine area than were expected. The low sunshine area also showed statistically significantly more observed SCL cases than expected. This sunshine region does, however, include the Dunedin area which was consistently statistically significant throughout the spatial analysis.

With regard to age at disease onset the results of this survey generally confirm the findings of overseas research. Lack of data and when available, its unrealiability, precluded the application of rigorous statistical tests to determine the possible associations of the diseases with race and occupation. The conclusive findings of no association between the incidence of SLE and areas of high

sunshine hours further confuses the actiological 'picture' of SLE. It also suggests that other environmental variables should be considered as being possibly associated with SLE.

# Footnotes

-			1050	-				
2.	Garnier,	B.J.,	1958,	The	Climate	e of New Ze	ealand,	Arnold.

# CHAPTER FIVE

#### CONCLUSION

The analysis of the data of this survey highlighted two important features which have implication for medical geography and research into the actiology of connective tissue diseases.

Firstly, through the methodology employed, it was shown that spurious results may accrue from aetiological research based solely on the calculation of mortality or incidence rates. Although crude rates were used in this survey, refinement of these with regard to the age and sex of the population-at-risk will not overcome all size variations in the population structures of the various areal units. Thus, the consequent incidence rates will not be of compatible reliability. In this survey, it was shown that the Maniototo Geographic County (and Hospital Board District) recorded an exceptionally high incidence rate for all connective tissue diseases (CTD) and systemic lupus erythematosus (SLE), but it had only two cases (both SLE) located within its boundaries at the time of onset. The population (1971 census) was 2,737. Conversely, the large population area of the Hutt Geographic Country, with fifty-five CTD cases, recorded low incidence rates. Therefore, from such rates one may be lead to believe that further actiological research should focus on these two 'tails of the distributions'. The rationale would be that it was within these areas that the greatest contrast in possible associative factors of disease incidence will be found. The spatial

variations and temporal changes in the incidence rates could have been the product of chance factors, and thus there becomes no need in seeking explanation of such patterns.

Probability mapping, however, enables the researcher to consider the influence of chance, and so define meaningful spatial and temporal variations. The significance of medical distributions may thus be assessed. If a distribution is found not to be the result of chance, then, and only then, is it appropriate to seek explanation. In the present study, although with only moderate incidence rates for the disease subsets, the Otago area was found to be consistently statistically significant at three areal scales, and through time. Whereas when the rates for the very high incidence areas were compared to the Poisson distribution it was generally found that they were not statistically significant.

Therefore, it is important for actiological studies to test disease distributions for statistical significance, and not to rely on variations in incidence rates as the basis for further investigative research. In medical geography this step to probability mapping is even more important. As geography must generalise about an area, its hypothetical relationships are also generalisation (McGlashan, 1972b). Correlations in space can be as misleading as correlations in time (Doll, 1959) and thus it is vital that associations that may have occurred by chance not be considered further. An association may seem to exist, but until it reaches a statistically significant level no attempt should be made to explain it. By its very scope medical geography cannot provide proof but it can postulate

hypotheses that may lead to the breaking of a disease causative chain. Confirmation of these will lie with specialists trained in the 'microscopic' investigative technique.

Secondly, the spacio-temporal definition of the disease data in this survey indicated that CTD's do have a statistically significant spatial variation in occurrence. The Otago area was found to be highly statistically significant, through time and space. While some measure of recording bias may have occurred due to the location of prominent medical facilities in the area, further research revealed that a single disease, SCL, was the principal contributory factor to this high statistically significant level. The Horowhenua area in the North Island was also found to be a statistically significant area. Further research into the actiology of connective tissue diseases should, therefore, focus on these two areas. Initially emphasis needs to be on establishing if any similar environmental factors exist in both areas.

The structure of the populations affected by these diseases was also researched. Generally, there was accord with the findings of earlier studies. In view of the racial differentiation of connective tissue disease incidence found elsewhere, this parameter should be investigated in areas where there are appreciable numbers of races other than European. Males seem to be at risk at a later age than females for all diseases, while for both sexes age at onset of SLE occurs earlier than for the other disease subsets. The small number of cases involved precluded a consideration of an association

of the diseases with a patient's occupation, and from the data no distinctive urban or rural distributional bias in the incidence of the disease was found.

Ancillary research is now being conducted on the data collected for this study. Dr Kinlen of Oxford University, England, is working on a cluster analysis (Knox, 1963, 1964a, 1964b, 1971) as a test of the hypothesis that this is a transmissible disease. A possible association of patients with polymysoitis who had been admitted to hospital with alcoholism is also being investigated.

It was the purpose of this thesis to demonstrate the application and utility of a geographical approach to medical research, while at the same time providing a perspective on the natural history of connective dissue diseases. As the spatial and temporal definition of diseases is the base upon which either associative or diffusion studies must rest, this study however, should only be regarded as the first stage in continuing research into the acticlogy of these rare diseases.

# APPENDIX A: THE SCORING SYSTEM USED IN THE SURVEY

by Dr R.D. Wigley, Director, Palmerston North Medical Research Laboratory, Palmerston North Public Hospital.

The connective tissue diseases are complex disorders which are readily recognised in their florid form, but episodes of illness contributing to the complete pattern may occur at different points of time so that there is usually a period of illness when definite distinction from other diseases is difficult or not possible. For studies of the epidemiology of these diseases and for comparison of treatments used in different centres a standardised, reproducible method for categorising these diseases is required. The American Rheumatism Association (1971) has published a scoring system for the definition of SLE. A list of 57 variables proved too large to classify by cluster analysis. The list was reduced to fourteen and the sensitivity and specificity of only selected combinations were studied. These 14 (Table one) form the preliminary criteria for the classification of SLE. This system was used in the present study with the addition of a significant anti-nuclear antibody titre (more than one in ten) as equivalent to positive LE cells, as recommended by Fries (1974). An additional point was allowed for definite histological evidence of SLE as the specificty is high, though the sensitivity of this feature is low.

Similar scores have not till now been published for the other connective tissue diseases so that these have been developed by the authors of this study. The various features recorded were weighted according to the emphasis given in the literature. All data sheets were then classified into definite probable and

possible cases in a normal clinical manner (R.D.W.). The possible cases were excluded and the remainder tested in the computer for agreement between the clinical and score diagnosis. The score was then adjusted by trial and error till the best fit was achieved, a score of four or more allowing a definite classification (Table twe). The remaining cases were excluded from further analysis except where five or more points were recorded towards any of the categories. These cases (CTD) were included with the analysis of all the connective tissue diseases only. As all the diseases have features in common this grouping was justified by the assumption that they may have a common causation, and so distribution, in relation to the geographical variables studied.

The level of agreement achieved for PN, SCE and DMS/PMS compared favourably with that of the modified American Rheumatism Association score used. Except for PN specificity exceeded sensitivity, so that more cases were lost from an insufficient score (34) than were gained from a positive score with only a probable clinical diagnosis (14). This tendency was considered desirable in this study where doubtful cases are best excluded. Seventeen cases not scoring four in the specific categories scored five or more in any category and so were included in the general analysis as having connective tissue disease (CTD). 266 of the original 292 remained in the combined analysis. The clinical diagnoses that were positive with a score below four usually depended on rare but specific features not occurring frequently enough for inclusion in the score. Clinical diagnosis depends on appreciation of the whole pattern of detailed observations over a period of time and only a simplified version of this can be handled by computer. The advantage of computer diagnosis is that it can be applied without bias to data collected by physicians other than the one responsible for the scoring system, though bearing the imprint of the particular physician's concept of the various diagnoses. The objectively applied score also allows elimination of cases in which the diagnosis is less certain at a uniform cut off point so that only cases on which most physicians would agree on diagnosis are included. This minimises inter-district differences due to different degrees of assiduity in identifying these diseases.

Table three shows the details of cases remaining in the analysis in this category. Table four shows the frequency of the recorded features in relation to the diagnosis by score and in those scoring five or more points in any category (CTD). Table five shows the sensitivities and specificities for each feature recorded in relation to disease category. Table six shows the final scores attributed to the features used in scores for polyarteritis nodosa, scleroderma, polymyositis and dermatomyositis.

# Bibliography

- American Rheumatism Association, 1971, Preliminary Criteria for the classification of systemic lupus erythematosus, <u>Bulletin on the</u> <u>Rheumatic Diseases</u>, Vol. 21, No. 9, 643-648
- Fries, James F., and Siegel, Robert C., 1973, Testing the 'Preliminary Criteria for classification of SLE', <u>Annals of Rheumatic Diseases</u>, Vol. 32, 171-177.
### Acknowledgement

The author wishes to acknowledge the work of Mr Brian Reay, of the Palmerston North Medical Research Laboratory, in the compilation of these tables and the computer analysis.

### TABLE ONE

### Preliminary Criteria for Classification of SLE

The proposed criteria are based on 14 manifestations which include 21 items, as follows. For the purposes of classifying patients in clinical trials, population surveys and other such studies, a person shall be said to have systemic lupus erythematosus (SLE) if any 4 or more of the following 14 manifestations are present, serially or simultaneously, during any interval of observation.

264.

- Facial Erythema (Butterfly Rash).
  Diffuse erythema, flat or raised, over the malar eminence(s) and/or bridge of the nose; may be unilateral.
- 2. Discoid Lupus.

Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions; may be present anywhere on the body.

3. Raynaud's Phenomenon.

Requires a two-phase colour reaction, by patient's history or physician's observation.

4. Alopecia.

Rapid loss of large amount of the scalp hair, by patient's history or physician's observation.

5. Photosensitivity.

Unusual skin reaction from exposure to sunlight, by patient's history or physician's observation.

- 6. Oral or Nasopharyngeal Ulceration.
- 7. Arthritis without Deformity.

One or more peripheral joints involved with any of the following in the absence of deformity:

- (a) Pain on motion,
- (b) Tenderness,
- (c) Effusion or periarticular soft tissue swelling.

(Peripheral joints are defined for this purpose as feet, ankles, knees, hips, shoulders, elbows, wrists, metacarpophalangeal, proximal interphalangeal, terminal interphalangeal and temporomandibular joints.)

8. L.E. Cells.

Two or more classical L.E. cells seen on one occasion or one cell seen on two or more occasions, using an accepted published method.

9. Chronic False-Positive STS.

Known to be present for at least six months and confirmed by TPI or Reiter's tests.

- 10. Profuse Proteinuria. Greater than 3.5 gm per day.
- 11. Cellular Casts.

May be red cell, hemoglobin, granular, tubular or mixed.

- 12. One or both of the following:
  - (a) <u>Pleuritis</u>, good history of pleuritic pain; or rub heard by a physician; or x-ray evidence of both pleural thickening and fluid.
  - (b) Pericarditis, documented by EKG or rub.
- 13. One or both of the following:
  - (a) Psychosis,
  - (b) <u>Convulsions</u>, by patient's history or physician's observation in the absence of uremia and offending drugs.
- 14. One or more of the following:
  - (a) <u>Leukopenia</u>, WBC less than 4,000 per cu mm on two or more occasions,
  - (b) Hemolytic anemia,
  - (c) <u>Thrombocytopenia</u>, platelet count less than 100,000 per cu mm.

TABLE TWO

All definite and probable clinical diagnoses are shown in this Table which shows the interrelationships of clinical diagnoses and score diagnoses and the percentage in which the two were in agreement.

	SLE	PN	SCL	PMS DHS	CTD	REMAINDER	Total	% Agreement
1	4	4	4.	2 <sub>F</sub>	5			
SLE	89	3	1	2	3	13	111	80
PN	1	47	-	-	1	24-	53	89
SD	1	-	2-7	-	3	6	5 <b>7</b>	82
PMS DMS	-	1	-	43	1	3	48	90
All Probable Cases	7	3	2	2	9	_	23	
Total	98	54	50	47	17	26	292	
% Agreement	91	87	94	91				

## SCORING SYSTEM

## TABLE THREE (A)

Shows the clinical features contributing to the scores of cases with five or more points but not satisfying the criteria for individual diseases. These are defined as having connective tissue disease (CTD).

No. of case	Score	
59	7	Eosinophilia, peripheral neuritis, pericarditis, myositis, and asthma.
83	5	Pleuritis, hypertension, erythema with skin oedema, and a biopsy positive for SLE.
91	5	Hypertension, Raynaud's phenomenon, arthritis without deformity, and red cell casts in the urine.
111	6	LE cells, red cells in the urine, hypertension, and biopsy positive for PN.
187	12	Pleuritis, Raynaud's phenomenon, arthritis without deformity, skin thickening, muscle weakness, muscle tenderness, erythema, lung fibrosis, and biopsy positive for PN.
201	5	Peripheral neuritis, hypertension, erythema, asthma, and testicular pain.
242	5	Proteinuria and casts, pleuritis, wasting and erythema with skin oedema.
266	6	Eosinophilia, pleuritis, Raynaud's phenomenon, arthritis without deformity, erythema, and testicular pain.
276	7	Pericarditis, skin thickening, lung fibrosis, and biopsy positive for PN.
343	6	Pleuritis, arthritis without deformity, skin thickening, muscle weakness, and erythema.
407	5	LE cells, red cells in the urine, pleuritis, skin oedema, and a necrotic ulcer.
436	6	Proteinuria with pus and red cells, thrombocytopenia, hypertension, facial erythema, muscle weakness and wasting.
472	5	Red cells and casts in the urine, Raynaud's phenomenon, and necrotic ulcer, and positive LE cells.
485	10	Proteinuria with white and red cells and casts, muscle weakness and wasting, and biopsies consistent with DMS and PN

No. of case	Score	
489	5	Urinary pus cells, pleuritis, arthritis without deformity, skin oedema, and positive ANF.
502	13	ANF positive, proteinuria, leucopenia, telang- iectases, Psychosis, convulsions, facial erythema, Raynaud's phenomenon, photosensitivity, skin thickening, ulceration and calcification of fingers.
564	6	LE cells, hypertension, arthritis without deformity, muscle weaking, muscle tenderness, and erythema.

## TABLE THREE (B)

Shows details of the patients scoring three or four points but not fitting any of the individual disease scores.

No. of Case	Score	
48	3	Urinary casts, hypertension, and arthritis without deformity.
54	4	Pleuritis, pericarditis, hypertension, Raynaud's phenomenon, and arthritis without deformity.
72	24	Facial erythema, photosensitivity, arthritis without deformity, and skin oedema.
77	2+-	Urinary casts, skin thickening of fingers, and lung fibrosis.
118	24-	Arthritis without deformity, and biopsy positive for DMS.
119	24	Urinary casts, arthritis without deformity, muscle weakness and tenderness.
126	24	Pleuritis and pericarditis, arthritis without deformity, erythema, and positive LE cells.
1 30	$l_{\rm F}$	Leucopenia, arthritis without deformity, erythema, and positive LE cells.
245	3	Pleuritis, Raynaud's phenomenon, and arthritis without deformity.
287	2+	Pleuritis, arthritis without deformity, testicular pain and positive LE cells.
321	λ_+	Proteinuria, eosinophilia, and biopsy positive for SLE.
368	4	Hypertension, arthritis without deformity, large artery occlusion, and a necrotic ulcer.
393	4	Hypertension, arthritis without deformity, erythema, and asthma.
415	4	Eosinophilia, arthritis without deformity, erythema, and asthma.
419	4	Hypertension, facial erythema, arthritis without deformity, and positive LE cells.
422	24-	Pleuritis, arthritis without deformity, skin oedema, and positive LE cells.
461	4	Pus and red cells and casts in the wrine, facial ervthema and discoid lumus ervthematosus.

No. of case	Score	
480	14	Pus cells and casts in the urine, and arthritis without deformity.
491	24-	Psychosis, arthritis without deformity, erythema and skin oedema, and positive LE cells.
497	24-	Arthritis without deformity, erthyma, positive LE cells, and EMG for myositis.
530	3	Proteinuria with pus and red cells and casts, and arthritis without deformity.
531	24	Proteinuria, Raynaud's phenomenon, muscle weakness and wasting.
556	<i>l</i> <sub>+</sub>	Arthritis without deformity, muscle weakness, muscle tenderness, and erythema.
561	4	Photosensitivity, arthritis without deformity, erythema, and positive LE cells.

## TABLE FOUR

The frequency of features contributing to the scores in each disease category studied by score diagnosis.

(A)

SLE	PN	Combination N SCL DMA PMS (>4 points) T		Total	Feature		
8	6	3	1	0	2	20	Nodules
0	0	0	0	0	· 0	0	Nil
3	1	0	1	0	1	6	Nailfold erythema
7	1	0	0	0	0	8	Non blanching focal erythema
9	10	7	0	3	1	30	Myocarditis
1	0	0	0	0	0	1	Cytoid bodies
7	0	1	0	0	0	8	Endocarditis
13	3	1	0	0	1	18	Oedema, generalised
24	7	1	0	0	2	1 <i>L</i> <sub>F</sub>	Peripheral neuritis
3	24-	0	1	0	0	8	Peritonitis
16	1	3	0	2	1	23	Splenomegaly
21	16	3	3	3	6	52	Pneumonitis
0	0	0	0	0	0	0	Nyasthenia gravis
2424	9	9	1	2	7	72	Pleuritis
27	7	7	0	1	2	44	Pericarditis
52	18	4.	7	2	6	89	Fever
25	17	10	3	2	6	63	Hypertension, degree
38	1	0	0	0	1	40	Biopsy (SLE)
10	1	1	0	0	0	12	Palmar erythema
10	0	0	2	1	0	13	Fingertip erythema
61	1	1	7	1	2	73	Facial erythema
12	0	0	1	0	0	13	Discoid lupus
23	3	33	4	24-	5	72	Raynauds
5	0	0	1	0	0	6	Alopecia
25	0	1	5	0	1	32	Photosensitivity
11	5	0	4	0	0	20	Oral/naso ulcer
51	18	2	2	3	6	82	Arthritis with-

SLE	PN	SCL	DMA	PMS	Combination $(>4 \text{ points})$	Total	Feature
64	20	5	4	7	12	112	Pain on motion
51	17	4	3	5	9	89	Tenderness
43	14	2	3	4	6	72	Effusion or per- articular soft tissue swelling
14	5	2	1	1	1	24	Psychosis
10	3	1	1	0	1	16	Convulsions
7	3	3	1	0	1	15	Drug sensitivity
5	2	2	1	0	1	11	Allergy

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(B)

SLE	PN	SCL	DMS	PMS	Combination $(>4 \text{ points})$	Total	Features
0	0	24	2	0	0	26	Biopsy (SCL)
1	1	45	0	0	Δ <sub>1</sub>	51	Skin thickening (finger)
0	1	14	0	0	1	16	Finger ulcers
0	0	19	0	0	1	20	Face
0	0	18	0	0	O	18	General
0	1	22	2.	3	0	30	Oesophagus
0	0	2	0	0	0	2	Morphoea
0	0	11	0	0	1	12	Calcinosis fingers
0	0	2 <sub>F</sub>	1	0	0	5	Calcinosis muscle
1	1	3	22	18	1	46	Biopsy (DMS)
0	1	2	15	20	1	39	Myositis
3	8	3	11	15	5	45	Muscle weakness
3	2+	2	11	17	3	2+2	Wasting
3	4	0	8	13	2	30	Muscle tenderness
0	0	0	3	2	0	5	E.M.G.
31	12	1	19	0	7	70	Erythema
0	1	0	9	0	0	10	Violaceous colour under eyes
0	0	1	5	0	0	6	Collodian patches
1	3	5	12	0	24-	25	Skin oedema
3	51	2	0	0	2+	60	Biopsy (PN)
3	8	13	0	2	2	28	Lung fibrosis
1	6	0	0	0	2	9	Asthma
0	0	0	0	0	0	0	Myelitis
2	9	1	0	0	0	12	Mononeuritis
1	6	1	0	0	0	8	Nasal granuloma
0	3	0	0	0	0	3	Encephalitis
1	8	0	2	0	0	11	Large artery occlusion
9	9	10	5	0	2	35	Necrotic ulcer
0	5	0	0	0	0	5	Livedo reticularis
2	1	0	0	0	1	4	Digital arteritis
0	2	0	0	0	1	3	Testicular pain and/or swelling

(C) Laboratory Features

SLE	PN	SCL	DMS	PMS	Combination $(>4 \text{ points})$	Total	Features
15	1	0	0	0	4	20	ANF $1/10$ - heat stable
5	3	0	0	1	1	10	ANF $1/10$ - granular
71	0	2	1	0	24-	78	LE cells
6	2	1	1	0	1	11	Coombs - direct
6	0	0	0	1	0	7	Coombs - indirect
57	15	5	1	0	4.	82	Proteinuria
41	15	4-	24.	3	3	70	Pus cells
40	19	5	4	3	6.	77	Red cells
39	10	2	3	1	24-	59	Casts - plain
17	5	0	1	0	1	24	Casts - cellular
0	0	0	2	0	0	2	False positive W.R.
22	1	1	0	1	1	26	Thrombocytopaenia
3	0	0	0	0	0	3	Hemolytic anaemia
31	3	5	0	1	1	41	Leucopenia 74000
24	18	1	0	4	3	30	Eosinophilia
1	0	7	0	0	0	8	Telangiectasis
75	24	2	1	1	6	89	At least one of: LE cell, ANF titre
56	11	13	1	3	9	93	At least one of: Pleuritis, peri- carditis
21	8	3	2	1	1	36	At least one of: Psychosis, convulsions
43	3	6	0	2	2	56	Thrombocytopaenia, Haemolytic anaemia, leucopenia
5	14	2	0	0	2	23	Mononeuritis, peripheral neuritis
21	10	3	2	1	1	38	Psychosis, convul- sions, myelitis, encephalitis
69	27	11	6	3	9	125	Proteinuria, red cells, pus cells
1	1	24.	25	22	2	55	Biopsy (DMS), Myositis

SLE	PN	SCL	DMS	PMS	Combination (>4 points)	Total	Features				
32	14	6	23	0	9	84	At least one of: Erythema, Skin oedema				
17	4	0	Ũ	1	4	26	ANF heat stable, ANF granular				
41	11	2	3	1	4	62	Casts - plain, Casts - cellular				

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## TABLE FIVE

This shows the sensitivity and the specificity of each of the features contributing to the scores for the different clinical diagnoses.

(A) SLE

Features	n =	%	%	n =	%	%	n =	%	%	n =	%	%	n =	%	%	n =	%	%		a. 1.	
	98	Sen	Spe	54	Sen	spe	20	Sen	spe	25	sen	spe	22	ben	spe	41	Sen	spe	ALL	Combi	nations
	SLE			PN			SCL			DMS			PMS		5	DNS DNS	)			n =	266
Facial Ervthema	61	62	84	1	2	1	1	2	1	7	28	10	1	5	1	8	17	11		7	3
Discoid lupus	12	12	92	0	0	0	0	0	0	1	4	8	0	0	0	1	2	8		1	3
Raymauds	23	23	32	3	6	1.	33	66	46	2	16	6	L.	18	5	8	17	11		7	2
Alopecia	5	5	83	õ	0	Ó	0	0	0	1	h	17	0	0	õ	1	2	17		1	5
Photosensitivity	25	26	78	0	õ	Õ	1	2	3	5	20	16	0	õ	õ	5	11	16		3	2
Oral or nasal																-				-	
ulceration	11	11	55	5	9	25	0	0.	0	4	16	20	0	0	0	4	9	20		2	0
Arthritis without																					
deformity	51	52	62	18	33	22	2	4	2	2	8	2	3	14	2+	5	11	6		8	2
LE cells or if																					
ANF 1/10	75	77	84	4	4-	24	2	4	2	1	4	1	1	5	1	2	4	2		8	9
Chronic false																					
positive STS	0	0	0	0	0	0	0	0	0	2	8 -	100	0	0	0	2	4	100		3	2
Profuse																					23
proteinuria	57	58	70	15	28	18	5	10	6	1	4	1	0	0	0	1	2	1		8	2
Cellular casts	41	42	66	11	20	1.8	2	4	3	3	12	5	1	44	2	4	9	6		6:	2
At leas one of:																	0.84				
Pleuritis																					
Pericarditis	56	57	60	11	20	12	13	26	14	1	4	1	3	14	3	4	9	4		9	3
At least one of:																					
Psychosis																					
Convulsions	21	21	58	8	15	22	3	6	8	12	8	6	1	5	3	3.	6	8		30	5
At least one of:										20 A											
Haemolytic anaemia																			÷.		
Leucopenia																					
Thrombocytopaenia	43	44	77	3	6	5	6	12	11	0	0	0	2	9	4	2	4	4		56	5
Positive Histology																					
Biopsy = SLE	38	39	95	1	2	3	0	0	0	0	0	0	0	0	0	0	0	0		4	C

Features	n = 98 SLE	· % Sen	% Spe	n = 54 PN	% Sen	% Spe	n = 50 SCL	% S <b>o</b> n	% Spe	n = 25 DMS	% Sen	% Spe	n = 22 PMS	% Sen	% Spe	n = 47 DMS (PMS	% Ser	% Spe	All	Com n	bina =	ations 266
At least one of:																						
Peripheral neuritis	5	5	22	14	26	61	2	4	9	0	0	0	0	0	0	0	0	0			23	
Arthritis without	-	-							1				100	Ĩ.			0	×.			£)	
deformity	51	52	62	18	33	22	2	4	2	2	8	2	3	14	4	5	11	6			82	
At least one of:																						
Psychosis																						
Encephalitis																						
Myelitis	24	04	<b>FF</b>	10	4.0	01	7	r	0	0	0	<b>F</b>		-	-7	-	1	0				
Asthma	21	1	22	6	19	67	0	0	0	2	0	5	1	50	2	2	6	8			38	
Nasal Granuloma	1	1	13	6	11	75	1	2	13	0	0	0	0	0	0	0	0	0			Z	
Large Artery				9	6.0	12	0	Are.	1.2	0	0	0	Ŭ	0	<u> </u>	0	~	<sup>o</sup>			U	
Occlusion	1	1	9	8	15	73	0	0	0	2	8	18	0	0	0	2	24	18			11	
Necrotic ulcer																						
or Gangrene	9	9	26	9	17	26	10	20	29	5	20	14	0	0	0	5	11	14			35	
Livedo				-							1.20											
Reticularis	0	0	0	5	9	100	0	0	0	0	0	0	0	0	0	0	0	0			5	
Digital Arteritis	2	2	50	1	2	25	0	0	0	0	0	0	0	0	0	0	0	С			4	
Arteritis	0	0	0	2	2.	67	0	0	0	0	0	0	0	0	0	0	0	0			Z	
At least one of:	0	0	0	6	4	01	U	0	0	0	0	0	0	U	0	U	U	U			2	
Red Cell																						
Pus Cell																						
Proteinuria	69	70	55	27	50	22	11	22	9	6	24	5	3	14	2	9	19	7		1	25	
Urinary Casts	41	42	66	11	20	18	2	4	3	3	12	5	1	5	2	4	9	6			62	
Eosinophilia	4	4	13	18	33	60	1	2	3	0	0	0	4	18	13	4	9	13			30	
(Piercer) DN	z	Z	E	<b>C</b> 4	01	QE	2	,	z	0	0	0	0	0	0	0	0	0			(0	
(Proba) M	2	2	2	51	74	09	2	4	2	0	0	0	0	0	0	0	0	0			60	

(B) PN

(C)	DMS	AND	PMS

Features	n = 98 SLE	% Sen	% Spe	n = 54 PN	% Sen	% Spe	n = 50 SCL	% Sen	% Spe	n = 25 DMS	sen	% Spe	n = 22 PMS	= % Sen	% Spe	n = 47 DMS	= % Ser	% n Spe	All	Com n	bina =	tions 266
POLYMYOSITIS																(PMS	5)					
At least one of: Biopsy (PMS)																						
Myositis	1	1	2	1	2	2	4	8	7	25	100	45	22	100	40	47	100	85			55	
Muscle Weakness	3	3	7	8	15	18	3	6	7	11	44	24	15	68	33	26	55	58			45	
Muscle Wasting	3	3	7	4	7	10	4	8	19	11	44	26	17	77	40	28	60	67			42	
Muscle Tenderness	3	3	10	4	7	23	0	0	0	8	32	27	13	59	43	21	45	70			30	
E.N.G. Positive	0	0	0	0	0	0	0	0	0	3	12	60	2	4	40	5	11	100			5	
DERMATOMYOSITIS																						
At least one of: Ervthema																						
Skin Oedema	32	33	38	14	26	17	6	12	7	23	92	27	0	0	0	23	49	27			84	
Violaceo us colour	0	0	0	1	2	10	0	0	0	9	36	90	0	0	0	9	19	90			10	
Collodian Patches Calcinosis of	0	0	0	0	0	0	1	2	17	5	20	83	0	0	0	5	11	83			6	
Muscle	0	0	0	0	0	0	4	8	80	1	2+	20	0	0	0	1	2	20			5	

(D) SCL

Features	n = 98 SLE	% Sen	% Spe	n = 54 PN	: % Sen	% Spe	n = 50 SCL	% Sen	% Spe	n = 25 DMS	% Sen	% Spe	n = 22 PMS	% Sen	% Spe	n = 47 DMS (PMS	% Sen	% Spe	All (	ombina n =	tions 266
Raynauds	23	23	32	3	6	4	33	66	46	4	16	6	4	18	6	8	17	11		72	
Skin Thickening -													<u>e</u> 2				2			1-	
Fingers	1	1	2	1	2	2	45 :	90	88	0	0	0	0	0	0	0	0	0		51	
Skin Thickening -																					
Face	0	0	0	0	0	0	19	38	95	0	0	0	0	0	0	0	0	0		20	
Skin Thickening -																					
General	0	0	0	0	0	0	18	36	100	Q	0	0	0	0	0	0	0	0		18	
Skin Thickening -																					
Morphoea	0	0	0	0	0	0	2	4-	100	0	0	0	0	0	0	0	0	O		2	
Finger Ulcers	0	0	0	1	2	6	14	28	88	0	0	0	0	0	0	0	0	0		16	
Oesophagus	0	0	0	1	2	3	22	44	73	4	16	13	3	14	10	7	15	23		30	
Calcinosis of																					
Fingers	0	0	0	0	0	0	11	22	92	0	0	0	0	0	0	0	0	0		12	
Telangiectasis	1	1	13	0	0	0	7	14	88	0	0	0	0	0	0	0	0	0		8	
Biopsy (SCL)	0	0	0	0	0	0	24	48	92	2	8	8	0	0	0	2	4	8		26	
Lung Fibrosis	3	3	11	8	15	29	13	26	46	0	0	0	2	9	7	2	4	7		28	
Hypertension	25	26	40	17	31	27	10	20	16	3	12	5	2	9	3	5	11	8		63	

The scores allocated to the clinical features for each disease category studied.

# (A) SLE

As in ARA system but add 2 for positive histology or PM and one for ANF 1/10 or greater unless LE cells positive. (see text)

## (B) POLYARTFRITIS NODOSA

Nononeuritis Peripheral n	s neuritis	2	maximum
Serositis:	Peritonitis Pericarditis Pleuritis, pleural effusion	) ) 1 )	
Arthritis w:	ithout deformity	1	
Psychosis Encephalitis Myelitis Convulsions	5	1	
Asthma		1	
Nasal granu	loma	1	
Large arter	y occlusion	1	
Necrotic ul	cer or gangrene	1	
Livedo retio	cularis	1	
Digital art	eritis	1	
Testicular atrophy)	arteritis (pain, swelling,	1	
Proteinuria	red cells or white cells	1/2	
Urinary cas	ts	<u>1</u> 2	
Eosinophilia	a	1	
Positive his	stology or PM	3	
Pneumonitis		1/2	
Myocarditis		<u>1</u> 2	
Hypertension	n	12	
Fever		-	
Raynauds		-	

2

# (C) SCLERODERMA

Raynauds		1
Skin Thickening:	Fingers	2
	Face Ceneral	2
	Morphoea	1
Finger ulcers		1
Oesophagus (Dysphe positive)	agia and/or x-ray	1
Calcinosis of find	gers	1
Telangiectasis, f:	ingers	1
Histology positive PM positive	e )	2
Lung Fibrosis		1
Proteinuria, cells Raised urea or cre hypertension	s or casts ) patinine ) )	1
(D) POLYMYOSITIS		
Biopsy and/or P.M.	. = Myositis	3
Muscle weakness		1
Muscle wasting		1
Muscle tenderness		1
EMG Positive		1
Mononeuritis or po	olyneuritis, subtract	- 3
(A) DEREATOTATOST	rin hiongy pogitive	1
Enverthema	avin probað þosiðiðe	
Skin Oedema)		1
Violaceous colour	r	1
Collodion patches		1
Calcinosis of mus	cle	1
	2	

PMS/DMS = sums of scores in (c)

-q

### APPENDIX B

### CONNECTIVE TISSUE DISEASE

Hospital	Patient No.	
Hospital No.		
Surname		
1st		
2nd		
Maiden Name		
Sex		
Marital Status		
Birthdate		
Age		
Address: Name of Town or Rural Delivery		





Splenomegaly		a	Pain on motion	
Pneumonitis		Ъ	Tenderness	
Myasthenia Gravis		С	Effusion or Periarticular soft tissue swelling	
Plouritis		a	Psychosis	
Pericarditis		Ъ	Convulsions	
Fever			Drug Sensitivity (names of drugs)	
Hypertension, degree		Al	lergy	
Family History same disea	250		Y. Yes N. No	
Other				
SCLERODERMA		PO	LYARTERITIS	
Biopsy (site)		Bi	cpsy (site)	
Skin thickening (Fingers	)	Lu	ng Fibrosis	
Finger Ulcers		As	thma	
Face .		My	elitis	

SCLERODERMA continued		POLYARTERITIS continued	
General		Mononeuritis	
Oesophagus		Nasal Granuloma	
Morphoea		Encephalitis	
(Fingers Calcinosis ( (Muscle		Large artery Occlusion	
(MUBOLO	]	Necrotic Ulcer	
DERMATOMYOSITIS Biopsy (site)		Livedo Reticularis	
Myositis		Digital Arteritis	
Muscle Weakness		Testicular pain and/or swelling	
Wasting			
Muscle Tenderness			
E.M.G.			
Erythema			
Violaceous colour under eyes			
Collodian patches			
Skin oedema			

### LABORATORY



Haemolytic anaemia		
Leucopenia 4,000		
E.S.R.		
Globulin (Gms/100ml)		
Gamma Globulin		
Hb		
Eosinophilia (degree)		
Other findings	an ar 1 na marana ann anns an	1997 - Marina Moray, - 11, 18, 18, 1972
	A.J. S. B. M.	

### APPENDIX C

The following public hospitals in the study area were visited to gather the basic medical data for this survey.

Hospital Board District	Public Hospital
Palmerston North	Palmerston North
Dannevirke	Dannevirke
Wairarapa	Masterton
Wellington	Hutt Wellington
Marlborough	Wairau
North Canterbury	Burwood Christchurch Princess Margaret
Ashburton	Ashburton
South Canterbury	Timaru
Waitaki	Oamaru
Otago	Dunedin

Those public hospitals in HBD's not visited were contacted to supply, for inclusion in the study, case records of patients whose diagnosis on discharge was a connective tissue disease.

### APPENDIX D

The use of the Poisson distribution in this survey to consider the question of random variations in disease occurrence was as follows:

(a) The incidence rate for the total study area was calculated, i.e. the total number of cases in a specified areal unit was divided by the population at risk (per 100,000) of that areal unit.

(b) Upon a null hypothesis that the rate of the study area applied evenly to all areal units an 'expected' number of cases was computed. For example, if the rate for the study area was 21.98 cases per 100,000 population-at-risk, and a Geographic County had a population-at-risk of 82,600 the 'expected' number of cases would be 18.16.

(c) Pre-calculated Poisson probability tables (Diem and Lentner, 1970) were then consulted. The 'observed' frequency (or the number of cases that did in reality occur in the areal unit) was located and if the calculated 'expected' frequency was either above or below the range of values shown the area had statistically significantly more or less observed cases than expected. The confidence limits of 95% and 99% were used.

## APPENDIX E

The absolute case distribution of connective tissue disease subsets in the Geographic Counties of the study area:

Geographic County	SLE	PN	SCL	PMS/DMS	COMB	TOTAL
	1	2	3	4/5	6	
Kiwitea	-			-	-	0
Pohangina			-	-	-	0
Oroua	-	-	1	1	-	2
Manawatu	-	-	-	1	-	1
Kairanga	8	2	2	4	3	19
Horowhenua	6	2	3	2	-	13
Dannevirke	1	-	1	-	-	2
Woodville	1	-	-	-	+	1
Pahiatua	1	1	-	-	-	2
Akitio	-	-	-	-	-	0
Eketahuna	-	-	-	. <del></del>	-	0
Masterton	1	-	1	-	-	2
Wairarapa South	-	a <b>-</b> 0	-	-	-	0
Featherston	1		-	-	-	1
Hutt	18	18	11	5	3	55
Marlborough	2	3	-	3	1	9
Awatere	-	-	1	-	-	1
Kaikoura	_	-	<u> </u>	-	÷.	0
Amuri	1	-	-	-	-	1
Cheviot	-	-	-	-	-	0
Waipara	-	1	-	-	-	1
Malvern	-	-	1	-	-	1
Oxford	-	-	-	-	-	0
Ashley	-	-	-	-	-	0
Rangiora	-	-	1	1	-	2
Eyre	-	-	-	-	-,	0
Paparua	1	-	-	-	-	1

Geographic County	SLE	PN	SCL	PMS/DMS	COMB	TOTAL
	1	2	3	4/5	6	
Waimairi	3	1	-	2	-	6
Heathcote	17	10	7	6	3	43
Mt Herbert	-	-	-	-	-	0
Ellesmere		-	-	-	-	0
Wairewa	-	-	-	-	-	0
Akaroa	-	-	-	÷	-	0
Ashburton	1	2	-	<del></del>	1	4
Geraldine	2	-	-	-	-	2
MacKenzie	-	-	-	-	-	0
Levels	3	2	1	2	1	9
Waimate	-	1	-	1	-	2
Waitaki	24	-	-	2	-	6
Vincent	-	-	2	2	-	4
Maniototo	2	-	-	-	-	2
Waihemo	-	1	-	-		1
Waikouaiti	2	-	2	-	-	2,
Taieri	15	7	10	7	3	42
Tuapeka	1	-	1	1	-	3
Bruce	1	1	-	1	-	3
Clutha	-	-	1	-	1	2
Lake	1	-	-	1	-	2
Fiord	-	-	-	-	-	0
Wallace	-	-	1	-	-	1
Southland	5	2	3	5	1	16
Stewart Island	-	-	-	-	-	0
Chatham Islands	-	-	-	-	-	0
Totals	98	54	50	47	17	266

The absolute case distribution of connective tissue disease subsets in the Hospital Board Districts of the study area were as follows:

0	0	3		
1	ч	z	٤.	
-	1	-	-	٠

HBD	SLE	PN	SCL	PMS/DMS	COMB	TOTAL
	1	2	3	4/5	6	
Palmerston North	14	4	6	8	3	35
Dannevirke	2	-	1	-	-	3
Wairarapa	3	1	1	-	-	5
Wellington	18	18	11	5	3	55
Marlborough	2	3	1	3	1	10
North Canterbury	22	12	9	9	3	55
Ashburton	1	2	-		1	4
South Canterbury	5	3	1	3	1	13
Waitaki	24	_	-	2	-	6
Maniototo	2	-	-	-	-	2
Vincent	-		2	2	2. <del></del> 6	4
Otago	18	8	13	8	3	50
South Otago	1	1	1	1	1	5
Southland	6	2	24	6	1	19
Totals	98	54	50	47	17	266

This table also gives the 'regional' breakdown of absolute case number distribution by the demarcation of HBD's within each 'region'.

### APPENDIX F

The populations-at-risk of the Geographic Counties of the study area at the taking of the 1951, 1961 and 1971 census. Hospital Board District populations-at-risk are achieved by summing the respective populations-at-risk of the Geographic Counties within such areas.

Geographic County	1951	1961	1971	
Kiwitea	2,298	2,298 2,339		
Pohangina	1,318	1,199	924	
Oroua	9,821	12,731	14,543	
Manawatu	8,340	9,916	9,278	
Kairanga	36,197	47,174	57,640	
Horowhenua	16,957	22,866	29,061	
Dannevirke	9,027	10,105	9,496	
Woodville	3,092	3,265	3,014	
Pahiatua	4,824	5,318	4,848	
Akitio	1,237	1,189	940	
Eketahuna	2,546	2,590	2,159	
Masterton	15,855	19,775	22,586	
Wairarapa South	5,200	6,115	6,306	
Featherston	7,039	8,154	8,237	
Hutt	214,943	260,313	320,915	
Marlborough	18,396	23,086	26,999	
Awatere	1,566	1,740	1,669	
Kaikoura	3,159	3,132	3,070	
Amuri	2,643	2,940	2,706	
Cheviot	1,354	1,532	1,520	
Waipara	2,476		2,724	
Ashley	2,592	2,885	2,913	
Rangiora	8,463	10,435	12,836	
Eyre	1,812	1,876	2,524	

Geographic County	1951	1961	1971	
Oxford	1,580	1,586	1,561	
Malvern	4,894	6,106	6,413	
Paparua	11,334	18,761	27,147	
Waimari	33,488	46,982	68,626	
Heathcote	1 34, 321	161,141	176,500	
Mt Herbert	581	627	683	
Akaroa	2,051	1,827	1,552	
Wairewa	900	798	687	
Ellesmere	6,082	6,624	7,512	
Chatham Islands	471	487	716	
Ashburton	19,788	23,512	24,521	
Geraldine	8,828	9,411	9,722	
Levels	26,445	30,552	33,130	
MacKenzie	4,033	3,310	5,159	
Waimate	8,907	9,368	8,574	
Waitaki	18,525	23,753	22,503	
Waihemo	2,015	1,871	1,714	
Waikouaiti	6,915	7,405	7,036	
Taieri	96,293	105,282	111,354	
Tuapeka	7,764	6,879	6,338	
Bruce	6,749	7,152	6,837	
Clutha	8,449	10,053	10,314	
Maniototo	2,865	2,949	2,737	
Vincent	6,450	7,250	8,520	
Lake	2,857	3,332	5,404	
Southland	65,269	80,094	91,173	
Wallace	11,565	12,816	14,283	
Fiord	29	51	1 35	
Stewart Island	576	542	414	
Totals for Study Area 881,179		1,054,123	1,210,046	

Source: N.Z. Census, <u>Increase and Location of Population</u>, Vol. I, for 1951, 1961, 1971

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