THE HISTORICAL DEVELOPMENT OF MULTI DRUG THERAPY FOR THE TREATMENT OF HANSEN'S DISEASE

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To the Associate Vice President of Research and
Dean of the Graduate School:

I am submitting herewith a dissertation written by Jody A.C. Terrell entitled "The Historical Development of Multi Drug Therapy for the Treatment of Hansen's Disease." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy with a major in Health Education.

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And Dean of the Graduate School

DEDICATION

This dissertation is dedicated to Dr. Ruth "Betsy" Tandy, my instructor, advisor and mentor. Dr. Tandy instilled in me a love for learning and a desire to search for the truth. She challenged me to strive for excellence in all things. She encouraged me to learn from the past, live in the present and look to the future. Her strength, support and understanding will always be with me.

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ABSTRACT

COMPLETED RESEARCH IN HEALTH STUDIES
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Hansen's disease carries many fears because of how it has been portrayed. Since Biblical times as a curse from God, a sentence of living death, and a life away from family and friends in isolation and seclusion. Patients today continue to live in isolation; they live with fear and depression. This is brought about as a result of persistent attitudes of the community members toward Hansen's disease.

Hansen's disease when diagnosed and treated is not contagious. It can be treated and cured and the devastating effects of it can be avoided if medication is taken for the prescribed time. Patient education, compliance with treatment, and family and community support are necessary to eradicate this devastating disease along with its stigma.

Through the years, treatment of Hansen's disease has evolved from the earliest treatments of isolation to the present and effective treatment of multi drug therapy. Major steps to achieve this treatment came about by isolating the bacteria that causes Hansen's disease known as *Microbacterium leprae* and finding the right combination of drugs that can effectively destroy the *Microbacterium* yet be safe for the patient.

The number of cases of Hansen's disease as decreased somewhat, although many patients fail to get early treatment. In addition to receiving better health care and more advanced drug treatments, people must also be educated about the reality of the disease. Knowledge takes away fear and by learning about Hansen's disease and the treatments available, the goals of the World Health Organization to eliminate the threat and fear of Hansen's disease by the year 2000 can be achieved.

TABLE OF CONTENTS

DEDICATION. iii

ACKNOWLEDGEMENTS iv

ABSTRACT vi

CHAPTER

I. INTRODUCTION. 1

Statement of the Purpose 3

Research Question 3

Definition of Terms 3

Limitations and Delimitations 6

II. REVIEW OF LITERATURE 7

Biblical references to Leprosy 8

Medieval Period 10

The Classical World 11

Early Christian Europe 13

History in the United States 16

Hansen's Disease Center 20

Drug Treatments 26

III. DESIGN AND METHODOLOGY 35

Procedure 35

Human Subjects 38

Instrumentation 38

Treatment of Data 39

IV. FINDINGS 42

HistoricalReview 42
The Stigma 50
The Patient 57
The Treatment 59
Sulfone therapy of Leprosy 66
Promin 67
Rifampicin 78
Clofazimine 87
Multi drug therapy 89
V. DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS. 93
REFERENCES 112
APPENDICES 118
Appendix A - Skin Smear/Biopsy Charts. 119
Appendix B - Questionnaire sent to Experts 122
Appendix C - List of Experts Consulted 126
Appendix D - Patient Interview Questions 130
Appendix E - List of Terms specific to Hansen's disease 135
Appendix F - Patient and Expert Consent Forms 140
Appendix G - Cover Letter to experts 145
Appendix H - Institution permission letter 147
Appendix I - Milestones in the History of Leprosy Timeline 149

CHAPTER I

INTRODUCTION

Diseases have been with the human population since the beginning of pre-recorded history. It was thought in the past that diseases were a curse from God. The 'miasma theory' presented the idea that when the air was of a "bad quality" the person breathing the bad air would become ill (Lilienfield, 1980). After the invention of the microscope by Leuwenhook (Lilienfeld, 1980), microorganisms were discovered. This discovery helped to provide answers for questions concerning the causes of illness and death. After pathogens were identified using the microscope, scientists were able to develop "miracle" drugs such as penicillin, which led to the treatment and cure for some diseases that previously plagued the population. Penicillin and other drugs have become common treatments for illnesses caused by bacteria. Today, , however, one single antibiotic can no longer be the sole treatment for many diseases. Pathogens are mutating and requiring multi drug therapies. Because of the mutating pathogens and the wide variety of diseases diverse treatments are often necessary.

This study focuses on the treatment of Hansen's disease from a historical vantage point. Hansen's disease is one of the oldest diseases

known to man and has had a variety of treatments. This study will investigate the different treatments from the earliest known therapies through the development of multi drug therapy which, according to the World Health Organization, will eradicate Hansen's disease in the future.

Multi drug therapy is not the only treatment for Hansen's disease and it may or may not be the most effective treatment. The historical documentation of treatments for Hansen's disease may help one understand the development and treatments for other diseases, some of which may not have manifested today. The understanding of the disease and its treatments are necessary for patient compliance, family and community education, and physician success in curing or eradicating the disease.

Health educators are presently confronted with answering many questions about the various drug treatments prescribed by doctors. Because of the great scientific advances of the microscope and the identification of a wide variety of pathogens and illnesses, health educators play an important role in public awareness and promoting patient compliance with their treatments. Knowledge of medical advancements among both health educators and the public is essential if

chronic diseases like Hansen's disease and tuberculosis are to be eradicated.

Statement of the Purpose

A historical investigation will describe the evolution of therapy for Hansen's disease from the first treatment to the sophisticated multi drug therapy of today. The implications of multi drug therapy upon various social parameters will be studied using a review of specific sources of medical and related information. An analysis of data obtained through interviews with Hansen's disease patients, and an analysis of survey data from experts involved in the development and implementation of multi drug therapy.

Research Question

The study addressed the following research question.

1. How did multi drug therapy evolve through history to become an effective treatment today for Hansen's disease patients?

Definition of Terms

For the purpose of this study, the terms listed below are defined as follows:

1. Hansen's disease - A chronic infectious disease caused by Mycobacterium leprae, an acid-fast, rod-shaped bacillus (Yoder, 1991). Previously, the term leprosy was commonly used.

2. Multi drug therapy - A drug treatment plan to treat Hansen's disease patients usually consisting of three main drugs: dapsone, clofazimine, and rifampin (Yoder, 1991).

3. Multibacillary - A diagnostic skin smear with any number of *Mycrobacterium leprae* present.

4. Pausabacillary - Bacteria are absent in a skin scraping. (See Appendix A)

5. Borderline (dimorphous) lepromatous leprosy- A type of leprosy which spans the spectrum between the lepromatous and tuberculoid poles. It is the most important part of the spectrum in terms of numbers of patients and of severity of nerve damage. It causes most of the disability and deformity seen in Hansen's disease. It is possible to find features suggestive of both forms of Hansen's disease in a single patient (Hastings, 1989).

6. Indeterminate leprosy - The stage in which early lesions, usually hypopigmented macules, without developed tuberculoid or lepromatous features (CDC, 1990).

7. Tuberculoid - one or a few well-demarcated, hypopigmented, and anesthetic skin lesions, frequently with active, spreading edges and clearing center; peripheral nerve swelling or thickening may also occur (CDC, 1990).

8. Laboratory criteria for diagnosis - The demonstration of acid-fast bacilli in skin or dermal nerve, obtained from the full-thickness skin biopsy of a lepromatous lesion (CDC, 1990).

9. Downgrading - This occurs when a patient downgrades then they arrive at a secondary position of sub-polar LL (LLs), which is not quite the same as that of the patient who originates as LL, i.e. primary, polar LL (LLs) (Hastings, 1989) "The existence of subgroups needs to be recognized, but for routine classification they may not be important" (Hastings, 1989, pg. 107).

10. Lesions - The areas on the patient where the M. leprae are discharged. These areas are located on the skin, nose, and eyes. Closed lesions are located on the epidermis and remain intact, while open lesions, usually present in the lungs of the patient with pulmonary tuberculosis (Hastings, 1989).

11. Nodules - A small node or rounded projection which is solid and can be detected by touch (Dorland, 1997).

Limitations and Delimitations

This historical investigation will include a study of the development of other drug therapies for Hansen's disease only to the degree that they contribute directly to the evolution of the multi drug therapy used today.

The study was limited by the following factors:

1. The availability of primary data collection sources.
2. The validity of the evidence obtained from secondary sources.
3. The legal restraint of access to documents from private and third party investigators.
4. The availability of the direct providers of multi drug therapy.

CHAPTER II

REVIEW OF LITERATURE

This review of literature will provide historical information about Hansen's disease, the patients, the stigma and events which lead to the development of multi drug therapy. The following review of literature consists of these sections: Medieval period, Biblical references to Leprosy, the Classical world, Early Christian Europe, History in the United States, Hansen's disease Center, and Drug Treatment.

Hansen's disease, historically referred to as leprosy, is a chronic infectious disease caused by *Mycobacterium leprae*, an acid-fast, rod-shaped bacillus. The disease mainly affects the skin, the peripheral nerves, mucosa of the upper respiratory tract, the eyes, and other areas of the body (Yoder, 1991). The disease has been known and described for several thousand years with the earliest descriptions recorded about 600 BC in India (Yoder, 1991). "Historically, persons with the disease were isolated, ostracized and the disease was considered a mysterious incurable sentence to isolation and death" (Yoder, 1991, p.347). Since ancient times, leprosy has been regarded by the community as a contagious, multi-acting, and incurable disease. Leprosy has afflicted humanity since ancient time (Noordeen, 1994).

Biblical references to Leprosy

Leprosy has been written about since biblical times. These writings have shown an ignorance of this disease by the general public.

Some biblical references to leprosy are probably the most well known negative references to leprosy. Some of these quotations follow:

> "The leper who has the disease shall wear torn clothes and let the hair of his head hang loose, and he shall cry, 'unclean, unclean.' He shall remain unclean as long as he has the disease; he is unclean. he shall dwell alone in a habitation outside the camp" (Leviticus 12:45, Revised standard version).
>
> ...and behold, a leper came to him and knelt before him, saying, 'Lord, if you will, you can make me clean.' And he stretched out his hand and touched him, saying, 'I will; be clean.' And immediately his leprosy was cleansed. (Matthew 8:2,3)
>
> And a leper came to him, beseeching him, and kneeling said to him, 'If you will, you can make me clean.' Moved with pity, he stretched out his hand and touched him, and said to him, 'I will; be clean.' And immediately the leprosy left him, and he was made clean." (Mark, 1:40-42)

"While he was in one of the cities, there came a man full of leprosy; and when he saw Jesus, he fell on his face and besought him, 'Lord, if you will, you can make me clean.' And he stretched out his hand, and touch him saying, 'I will; be clean.' And immediately the leprosy left him." (Luke 5: 12, 13)

"And as he entered a village, he was met by ten lepers, who stood at a distance and lifted up their voices and said, 'Jesus, Master, have mercy on us.' When he saw them he said to them, 'Go and show yourselves to the priest.' And as they went they were cleansed. Then one of them, when he saw that he was healed, turned back, praising God with a loud voice" (Luke 17:12-15)

Some experts believe that the disease described in these passages was not leprosy in many cases, but several different skin diseases. Many chronic, incurable and dreaded diseases have been confused with leprosy over time. Regardless of whether or not these biblical references dealt with actual leprosy, the disease today, known as Hansen's disease, has been perceived as that disease. Peoples' beliefs about leprosy have been negatively influenced because of the writings of early times (Davis, 1989).

Medieval Period

The early medieval period (c.300-1000 AD) was characterized by a Neo-Platonic world view, a decline of competent government, and the loss of much classical knowledge. Nonetheless, the early medieval period saw the rise of the Roman Catholic Church as the only significant institution common to society. According to Levitical law, the leper was considered dead to the world, without rights to marriage or property, and required to live apart. This exacerbated the idea of leprosy as a disease of profound religious significance and the treatment of its victims was isolation (Ell, 1994). During the Middle Ages, lepers were separated from the rest of the population by a requirement of church law. A decree of the Lateran Council in 1179 required lepers to be buried in separate graveyards (Thomsen, 1991). Diagnosis in medieval times began with public inspection so that the people in the community could decide whether the person was leprous or whether they needed to remain under observation. In order to become free of the disease, the patient had to get a medical certificate of freedom from the disease, according to the best medieval practice (Thomsen, 1991). During the high and later Middle Ages (c.1000 - 1500 AD), abundant evidence of the presence of leprosy as we know it today existed (Ell, 1994).

As in the case with other cultures, medieval western society treated leprosy patients very harshly, considering them legally dead and segregating them in every way from the unaffected. While this approach may have had an influence on the decline and eventual disappearance of leprosy from Western Europe, the imagery of leprosy was extremely powerful and continues to influence popular attitudes even today (Bragg, 1995). There is some very sketchy evidence regarding the incidence of leprosy in parts of medieval Europe that suggests the area experienced a very high incidence of the disease (Ell, 1994).

The Classical World

The most important contribution of the classical great age was a view of leprosy that came not from the works of the great classical physicians, but rather from mistranslation of the documents passed down (Ell, 1994). As early as 300 BC, Hellenistic culture, created by the conquests of Alexander the Great, had impressed itself upon the eastern Mediterranean. Alexandria became the seat of learning, with a famous library said to contain 50,000 books which provided the milieu for the great scholars of the age (Cochran, 1963).

Although little reliable information exists, when the Hebrew Bible was translated into Greek, the phrase, *lingua franca* came from the

Hellenistic world. During this process, one Hebrew word was translated as *isaraath* and *lepra* (Cochran 1963). It is quite clear that both words were generic terms for essentially any disease producing scaly lesions on the skin.

There is no clear evidence that the ancient Hebrews suffered from leprosy as it is seen today (Cochran, 1963). This translation had immense consequences; however, for it was the basis for applying the strict ritual of cleanliness and the laws of exclusion described in the Book of Leviticus, to leprosy patients in Christian Europe (Davis, 1989). At some point, the word lepra came to refer to leprosy. It remained a mistranslation throughout time. In addition, this act of mistranslation also added a moral judgment regarding victims of the disease described. That judgment was ambiguous; it assigned a state of sin to the leprosy patient and at the same time considered him/her blessed by being able to atone for at least part of that sin while still in this life (Brody, 1974).

There are many ancient writings which may contain at least partial descriptions of leprosy, but scholars generally consider that the first recognizable description of leprosy was written by Aretaeus of Cappadocia in the middle of the second century AD (Cochran, 1963;

Adams, 1856). He referred to the disease in question, however, as elephantiasis.

The presence or absence of a leprosy source and the prevalence of leprosy in the classical world are matters simply beyond the limits of current knowledge. Whether Alexander brought leprosy to Europe and the Near East from India or whether the Persians introduced it to Europe during their invasions are questions with no present hope of answer. Given fragmented descriptions partly compatible with leprosy and the work of Aretaeus, one can assume that leprosy was known in the Roman Empire by the second century, but beyond that, a swamp of pure speculation is all that exists (Cochran, 1963; Adams,1856).

Early Christian Europe (300-1000 AD)

The idea of the Roman Empire was so pervasive that the last Roman Emperor was disposed only in 1806. However, the political reality of the Roman Empire disintegrated in the West. At that time Western Europe became a mixture of petty principalities. During this time it is believed that the feudal system was beginning, although its primary features were more often the exception rather than the rule. It seemed that effective government operated only at a very local level. The

combination of barbarian invasions and epidemic disease resulted in the sharp decline of cities (Richards, 1990).

It is worth noting that the very word "civilization" is derived from the word for city. The inhabitants of some French (Frankish) cities were so decimated in the fifth and sixth centuries that they all lived in the cities' amphitheaters (Gregory of Tours, 1964). The history of disease is a relatively new concept. It would have more value if there were a way to accurately document the whole series of epidemic diseases. The death of the Roman Empire took with it the very concept of the state (Thomson, 1991). Government, among the Franks and all the barbarian tribes, was inseparable from the designated ruler. Roman law of government was far too complex and foreign for the barbarian tribes to adopt in a meaningful way. The households of Frankish kings eventually started to evolve. The Franks used Roman tax rolls that were sometime centuries out of date, to set their land and tax laws. They would assume because the writing impressed them, that if a 200-year-old document stated that someone lived on a certain farm and paid a certain tax, that individual was still there. One king burned the tax rolls when his children were ill, believing God was punishing him for taxing his people (Thomson, 1991).

The only remaining platform of learning was the Catholic Church (Ell, 1978). The Rule of St. Benedict, which dominated the monastic life of this period, also subsumed medicine on religious grounds. Because the monks took great pride in documenting and preserving the manuscripts entrusted to them, historical records have been passed down but with their interpretations. The early translators of the Bible held many of the rules that people of this era lived by, one of the rules stated, above all care for the sick... for Christ said, "I was sick and you visited me" (Davis, 1989)

Other writings about leprosy in the Bible show an ignorance of the disease by the general public. This ignorance was passed from generation to generation by folktales and beliefs about how the disease is transmitted, and the prevailing attitudes toward people with leprosy.

Leprosy, whether correctly or incorrectly identified, was the subject of a number of restrictive laws. This was; however, a period in which laws were more often curiosities rather than principles to be observed. Nonetheless, the seeds of the future were sown, for the intellectual dominance of the Church proved critical when leprosy was accurately diagnosed, at least in its more serious forms, because of the recognized death sentence or a sentence of exile (Ell, 1978).

History in the United States

Although leprosy is not predominately a problem in the United States, the local history of the disease worth noting. Leprosy was introduced to the United States by many immigrants, entering the country, starting in the 1700s (Hudson, 1982). Although the disease has been reported in most states at one time or another, there have been only seven centers of infection present in the country. The centers are Louisiana, Texas, Florida, California, Hawaii, and New York. These centers account for an overwhelming majority (80.5%) of all leprosy cases reported in the United States, although the Mississippi River Valley was once a center of infection, it is no longer considered a major concentration (Jacobson, 1998).

One of the earliest centers of leprosy infection that developed was in French Louisiana. Although leprosy is believed to have been present in Louisiana prior to 1755, the arrival of the Arcadian population from Canada beginning that year appears to have substantially increased to the infected population (Jacobson, 1990). Affected by immigration from all parts of Louisiana, New Orleans has experienced an increase in its relative incidence rate during the past twenty years. The highest incidence rates among blacks in Louisiana occur in the French parishes

rather than in the traditional slave-holding regions (Jacobson, 1990). This fact lends acceptance to the argument that no evidence has been forthcoming which would link the importation of slaves to the United States to an increase in the rate of leprosy. Nonetheless, Louisiana has remained one of the truly endemic areas of infection in the United States with 76% of its cases occurring in persons born in that state (Jacobson, 1990).

Texas also has a significant population of leprosy sufferers, with the population predominately of Spanish decent. Four major areas of infection have been identified within the state of Texas. The first is in the south and is centered in the Rio Grande Valley (Hudons, 1982). The second major focus is in the Corpus Christie area. San Antonio is the third concentration of leprosy infection. The fourth and largest center of infection is in the southeastern part of the state near the Louisiana border which is centered in the Houston-Galveston complex. Contributing to over 33% of the state's cases, the concentration is apparently the result of contact with the French Louisiana in that the majority of the cases are found in people with non-Spanish surnames (Hudson, 1982). Texas is the only other state besides Louisiana in which most of the leprosy cases occurring in the state are found in the native-

born state population. Texas also contains over one half of all native-born cases in the United States (Hudson, 1982).

Over the past several decades, the major concentration of leprosy in Florida has shifted from Key West to Miami. In all likelihood, this is due to Miami superseding Key West as a port of entry to the United States. Leprosy was initially brought to Florida from the West Indies and the Caribbean, and this area remains the principle source region for the 86% of Florida's cases that are foreign born (Jacobson, 1990). Within the last two decades, the Cuban population has contributed substantially to the number of leprosy cases reported in the United States (Jacobson, 1990). Most Cubans who are victims of leprosy are found in Florida, with the majority in Miami. Currently, a controversy exists over allowing Cuban refugees and immigrants who may have either had leprosy or been in contact with sufferers to let enter the United States (Mastro, 1992).

Since the middle of the last century, California has experienced a relatively high incidence rate of leprosy. Its first cases were imported from both Mexico and China. Later, cases began to arrive from other parts of Oceania, most notably the Philippines (Mastro, 1992). Today, over 90% of California's cases are found in foreign born patients, with the

Mexican and Filipino populations accounting for the majority of these cases (Mastro, 1992). Most of the leprosy present in California is found in the large population centers, particularly San Francisco, Los Angeles, and San Diego. Currently, California is the largest contributor to the total leprosy population in the United States (Mastro, 1992).

The Hawaiian Islands appear to have had a long history of leprosy, with a substantial infected population in existence in the mid-19th century (Mastro, 1992). As the percentage of Hawaii's foreign-born population has increased, the percentage of foreign-born cases of leprosy, has also increased. Over 80% of the state's total number of cases came from the Filipino population (Mastro, 1992). The Philippines, in general, have contributed substantially to the number of leprosy sufferers in the United States, accounting for over one-fifth of all cases reported since 1967 (Mastro, 1992).

Historically, New York City has been the major port of entry to the United States for most of the country's immigrant population. Nearly all cases reported in that area were found in individuals born outside the U.S. The primary source area for these cases was the Caribbean, with Puerto Rico accounting for an overwhelming majority of all cases reported in New York (Mastro, 1992).

The increase in leprosy incidence since 1942 has been slight and erratic. Today, it is estimated that there are approximately 4000 leprosy cases in the United States (Jacobson, 1990).

Hansen's Disease Center

The Hansen's Disease Center began as the Louisiana Leper Home at Carville in 1894 (Furman, 1988). In 1921, the Public Health Service assumed responsibility for the treatment of Hansen's disease (Furman, 1988). The purpose of the home was to take care of the people with Hansen's disease and to keep them away from the general public. Quarantine was previously believed to be an effective way to end the spread of the disease. Homes and centers similar to the one in Carville were set up all over the world. From 1921 until 1960, most newly diagnosed patients with Hansen's disease in the continental United States were admitted to Carville, often under compulsion (Furman, 1988).

The cost of providing care for the center's residents has been climbing steeply since about 1988, due to the decreasing number residents and cost to maintain the property. Presently, only about 75 patients reside at Carville. The cost to maintain these patients at a large institution is approximately $44,000 per year (Yoder, 1991). Due to large

costs, the Public Health Service has agreed to let the Bureau of Prisons gradually take over the center if they provide care that is equal to or better than the immediate past. Eventually, when only a few patients remain, they will be discharged to suitable nursing homes and the Hansen's disease center at Carville will be closed (Yoder, 1991).

Despite the advances of modern technology, people continue to hold outdated beliefs about Hansen's disease. These beliefs contribute to the stigma that is attached to the disease and prevent its timely treatment in some cases (McConnaughey, 1994). The disease is not highly communicable and is slow to develop. Most people are even resistant to the disease (Yoder, 1991). Leprosy is very curable with a long-term treatment regimen of various drugs. Nevertheless, many misconceptions are passed on, even in the United States where Hansen's disease is not a significant problem. Folklore, customs, and practices related to people with Hansen's disease around the globe are diverse. Quarantine was frequent and believed to be necessary in the past (McConnaughey, 1994). A number of Hansen's disease facilities or villages still exist including the Hansen's Disease Center in Louisiana. There are other forms of ostracism and isolation all over the world that

also exists today. Even today in communities all over the world, people believe some of the myths about leprosy.

Since 1995, approximately 2,400,000 people lived in countries where the prevalence of Hansen's disease was more than one case per 10,000 in the population. There are many countries in Asia, Africa, and Latin America with a significant number of Hansen's disease cases. It is estimated that, in 1995, there were between one and two million people visibly and irreversibly disabled due to Hansen's disease, who required care which was provided by the community in which they lived (Noordeen, 1994).

In a number of ways, Hansen's Disease remains a mystery today. When Hansen discovered the leprosy bacillus in 1873, he opened the door to experimental leprosy (Yoder, 1991). In common with most revolutionizing events in medical science, Hansen's discovery did not happen in an intellectual vacuum. The hypotheses and findings of earlier investigators, particularly those of Danielssen, had created the scientific environment for Hansen's systematic inquiries into the epidmiology and etiology of leprosy (Troutman, 1989). "It was, above all, Hansen's epidemiological studies on leprosy in Norway that convinced him of the infectious etiology of leprosy" (Troutman, 1989, p 4). "This conviction led

to his landmark observations that set the course for the comprehension of the pathogenesis of leprosy" (Troutman, 1989, p. 4). To satisfy his own intellectual curiosity and prove to his many critics that the rods he had seen repeatedly in tissue fluid from lepromatous patients were the cause of leprosy, Hansen attempted in vitro cultivation and began the quest for animal models.

In Rees' review (1973) of the first century of experimental leprosy, 1873-1973, includes a chronicle of Hansen's trials and triumphs in gaining acceptance of the infectious etiology of leprosy. Johnstone (1987) summarized the pursuit of suitable animal models for leprosy, and estimated that Hansen probably inoculated only 12 rabbits, rather than monkeys, cats and rabbits as noted by Jeanselme (1934). Approximately 30 species of animals have been inoculated with leprosy bacilli, exploring a wide variety of methods. At best, several investigators obtained limited or evanescent disease. Successful transmission claims were frequently only misinterpretations. For example, Soule & McKinley (1932) seem to have induced lepromin reactions in monkeys and believed them to be active lesions. However, Burnet (1938) apparently did not appreciate the long persistence of carcasses of M. *leprae* in inoculated hamsters and reported, ' a decisive first step in the experimental reproduction of

leprosy in a laboratory animal.' The first adequately documented instance of disseminated experimental leprosy was in a chimpanzee inoculated in the skin, nerve peritoneal space, and bloodstream (Gunders, 1958). A biopsy specimen from this animal on file at the Armed Forces Institute of Pathology (AFIP), shows active borderline (BB-BL) disease.

Generally, there was no underlying rational for the earlier attempts to infect animals. At the First Carville Conference on 'Progress and Potentials in Leprosy Research', Binford (1956) offered a hypothesis on the pathogenesis of leprosy, developed from his own clinical observations and interpretation of a comment made by Virchow in 1863. Virchow noted that the distribution of lesions in leprosy patients favored sites exposed to air, such as the anterior segment of the eye and the ear. Binford presumed that the selective distribution of lesions was not related to exposure to air but rather to the cooler temperature of those body sites. In 1958, at the 7th International Leprosy Congress in Tokyo, Brand reported an association between cool body sites and tissue damage in leprosy patients, particularly in superficial nerves. In a follow-up of his own hypothesis, Binford during a 3-year period inoculated over 1500 hamsters, mice, rats, and guinea pigs, and in 1959

reported the successful transmission of leprosy to the ears and testes of hamsters. Waters & Niven (1965) confirmed Binford's essential findings in hamsters. These findings were the initial steps in finding a potential host for the bacilli. Until this point no animal hosts were favorable for the bacilli to grow.

The transmission of leprosy to the mouse footpad (Shepard, 1960) and the inoculation of armadillo with *M.Leprae* (Kirchheimer & Storrs, 1971, Storrs, et al., 1974) were based directly on the hypothesis of selective growth of M. leprae in cooler anatomic sites. "Extensive utilization of these two animal models has made possible many of the remarkable advances in recent years in leprosy research and patient management" (Storrs, 1974, p. 89). Shepard (1985) has reported a detailed account of the development and uses of the mouse footpad model. The use of animal models in evaluating the chemotherapy of leprosy was extensively reviewed by Walsh et al (1986b), and Rees reviewed the general status of animal models in leprosy (1988, 1991).

Since the causative agent, *Mycobacterium leprae*, was described by Armauer G. Hansen in Norway in 1873, the bacterium still has not been cultured *in vitro*. The source of infection and mode of transmission are still being debated by experts. Some researchers believe there may be a

genetic defect in susceptible individuals. The nature of the immune defect in susceptible individuals is still unknown. The cause of the nerve damage and the immunologic reactions that occur in some cases are still misunderstood (Yoder, 1991).

Drug Treatments

Because Hansen's disease still remains a mystery, finding an effective combination of chemicals was elusive. The sulfones were first used to treat leprosy in the 1940's. Dapsone has been the mainstay treatment and has had a significant impact on the disease worldwide (Trautman, 1990). This drug was inexpensive, effective, and the side effects were minimal. The treatment period was long, patient compliance was often poor and, in the 1970's primary and secondary resistance began to appear. By the late 1970's, leaders within the World Health Organization (WHO) and other concerned scientists recommended urgent steps be taken to avert a disaster in the treatment of leprosy (Yoder, 1991).

In 1981, a World Health Organization Study Group recommended that Hansen's disease be treated with short-term multi drug treatments. There were only four generally acceptable anti-leprosy drugs: dapsone,

rifampin, clofazimine, and ethionamide (or prothionamide). Ethionamide -prothionamides tend to be toxic to the liver and are relatively expensive. Unfortunately, the available evidence suggests the efficacy of these drugs is compromised if they are taken at irregular intervals (Yoder, 1991). Thus, only the first three drugs were considered suitable for routine use (Yoder, 1991). Rifampin is the only rapid bactericidal drug in this group and was considered to be effective when given as a single dose on a monthly basis (Vanderveken, 1989).

In the United States, multi drug therapy for multibacillary cases had already been instituted prior to the World Health Organization recommendations (Yoder, 1991). Because of the relatively small number of patients and because cost was not a major consideration, patients in the United States have been treated for considerably longer periods than recommended by the World Health Organization protocols. The protocols used in the United States have been effective and have resulted in few complications (Yoder, 1991). However, based on experience in the United States and elsewhere shorter treatment periods are now also being initiated in the United States under investigative protocols (Yoder, 1991).

Multi drug therapy (MDT), consisting of dapsone, rifampicine (Rimactane), and clofazimine (Lamprene), is able to change the course of the disease dramatically. This combination has been the cornerstone of the World Health Organization's leprosy control policy since 1982 (WHO, 1998). MDT kills the bacilli which interrupts the chain of transmission, and a rapid cure prevents mutilations and deformities. The 70-80% of cases with paucibacillary leprosy (PB) are noninfectious and can be cured within six months. The remaining 20-30% that have the multibacillary form (MB) are curable within one year. In most cases, visible improvements can be observed at the onset of MDT, encouraging patients to comply with the treatments (WHO, 1998). The drug company, Novartis, developed two of the three drugs currently used in MDT. A calendar pack simplifies dispensing the medicines, which improves patient compliance and protects the tablets against heat and moisture (Bryceson & Pfaltzgraff, 1990).

There is still a need for new drugs, however, with the possible exception of clofazimine, drug resistance has been reported for all of the afore mentioned drugs. It has been a major problem only with dapsone (Yoder, 1991). Clofazimine produces an objectionable skin discoloration in many light-skinned persons and the treatment period is still long for

multibacillary patients. It would be very useful to find new bacterial drugs to shorten the treatment time and provide alternative drug combinations for cases of drug resistance or toxicity (Grosset, Ji B, Guelpa-Lauras, Perani, & N'Deli, 1990). Several potentially new anti leprosy drugs are being investigated. "The flurooquinolones, pefloxacin and ofloxacin, have already undergone limited clinical trials"(N'Deli, Guelpa-Lauras, Perani, Grosset, 1990, p. 284).

> "In 1995, there were an estimated 2 million cases in the world, most of them concentrated in South-East Asia, Africa and the Americas. Among them 1.3 million patients are registered for treatment of whom 1 million are treated with Multi drug therapy (MDT)." "The number of new cases detected worldwide each year is about half a million" (WHO, 1996, p. 3).

The WHO/PAHO regional plan of action for the elimination of Hansen's disease with MDT in Americas is as follows:

> "* improve the stratification process through the elaboration and implementation of plans for elimination at the different levels of the national health system.

* promote the involvement of the peripheral level of the health care systems (municipalities, local health units) in the control/elimination activities;

strengthen management capacity of intermediate level managers of the health care system;

* support special action projects in areas with limited MDT access, high prevalence, and urban and peripheral areas of metropolitan cities;

* "improve leprosy information system at national and district level, including the use of computer-based systems such as geographical information system" (http://www.paho.org.english/hctcp01.htm#case)

The goal of multi drug therapy is to sterilize the *Mycobacterium leprae* agent in the human body through treatment of all infectious cases with an effective, potent drug regimen. The three basic requirements are as follows: first, early diagnosis and complete treatment in order to reduce the duration of the spread of bacilli from untreated patients and complete treatment (Desai,1955). Second, also an important requirement, is an effective multi drug regime in which patients can comply with the treatment for the designated duration. The third key factor in the elimination and control of Hansen's disease is health

education. Prejudice against Hansen's disease is one of the most important obstacles or barriers to overcome to successfully controlling Hansen's. The best way to combat prejudice against Hansen's disease is to demonstrate that it can be cured. Health educators should promote early detection and adequate treatment. Education should enlist the participation and cooperation of all concerned which include public authorities, population, patients, and health personnel (Brandsma, Heerkens, Lakerveld-Heyl, & Mischner-Van-Ravensberg, 1992).

The disfiguration and deformities caused by Hansen's disease force sufferers and their families into extreme psychological, social, and economic distress. More than that, they reinforce the stigmatizing image of what leprosy represented in ancient times. This adds greatly to the difficulty of detection and treatment of the individual at the early stages of the disease.

The introduction of multi drug therapeutic regimens contributed major changes in control of Hansen's disease during the last decade. For the first time since statistics have been collected, declining trends in the prevalence of the Hansen's disease have been observed at the global level (World Health Organization, 1993). In countries where multi drug therapy has been introduced on a large scale, decreases in prevalence up

to 80% or more over a five year period have been observed. This is partially due to the shorter duration of treatment, and also to the new attention given to the programs addressing all aspects of Hansen's disease (Brandsma, Heerkens, Lakerveld-Heyl, & Mischner-Van-Ravensberg, 1992). Patients who have been registered for years are systematically reviewed and possibly discharged. Also uniform protocols of treatment and self-reporting of new cases are enhanced since multi drug therapy has a strong bactericidal effect. Researchers have been able to predict, at least in theory, a sharper than ever decline of the incidence of Hansen's Disease (Brandsma, et al., 1992,).

In 1991, the World Health Assembly formulated a new objective: to attain the global elimination of Hansen's disease as a public health problem by the year 2000 (WHO, 1992). Elimination of the disease is defined as the reduction of prevalence to a level below one case per 10,000 population (WHO, 1992). "This is a formidable challenge" (Brandsma, et al., 1992, p. 344).

The advent of multi drug therapy (MDT), recommended by the World Health Organization (WHO), has dramatically changed the leprosy situation. MDT cures the disease in a relatively short time, interrupts the chain of transmission, and thus holds out the possibility of

eliminating Hansen's disease for good. Thanks to the widespread use of multi drug therapy, millions of people have already been cured. The estimated number of registered Hansen's disease cases fell from 5.5 million in 1991 to 1.8 million in 1995 (a 67% reduction). Yet, because many cases go undiagnosed, the actual number of cases far exceed cured estimates. If the WHO goal of eliminating Hansen's disease by the end of the century, defined as only one case per 10,000 inhabitants, it is to be achieved, an estimated 6 - 7 million cases will have to be detected and treated. The 1997 prevalence rates in the 16 most endemic countries were 3.3 cases per 10,000. Whether the goal of eliminating leprosy will be reached depends primarily on whether the national political support and the necessary resources can be mobilized. The problems that must be overcome are huge: the low priority given to Hansen's disease control, poor infrastructure of health care systems, shortage of adequately trained personnel, the stigma attached to Hansen's disease, and unfamiliarity of general health care providers with early symptoms of the disease and more.

Although Hansen's disease has lost some of its terror since the introduction of MDT, the image of unarrestable and irreversible deformities that it has conjured from ancient time will not go away. Two

to three million people are branded by the stigma of the disease and require urgent medical attention to prevent a worsening of their condition. These numbers will continue to swell with delays in patients seeking or receiving adequate and timely treatment (Ells, 1994)

The number of cases of leprosy has decreased somewhat although many patients fail to get early treatment. The World Health Organization has a goal to reduce the prevalence of leprosy by the year 2000 to less than one case per ten thousand people (WHO, 1998). In addition to receiving better health care and more advanced drug treatments, people must also be educated about the reality of the disease.

CHAPTER III

DESIGN AND METHODOLOGY

Procedure

This is a descriptive and exploratory study using a historical research method, which is a retrospective approach that seeks to illuminate a question, problem, or issue by an intensive study of materials that already exist (Kesling, 1987). In this study data will be gathered via face to face patient interviews, journal article reviews, examination of patient files, and a written questionnaire sent to experts in the field of Hansen's disease. Fox (1969) identified nine major steps in the process of historical research. The nine steps and their application in this study follow.

1. Determination that the problem selected is appropriate for study through the historical method. Although multi drug therapy for Hansen's disease is a relatively new procedure, in existence since the 1960's, enough time has elapsed to make it appropriate for historical research.

2. Specification of the type of data needed. Data were collected through journal articles, patient interviews, questionnaire, and other historical documents such as letters.

3. Initial determination that sufficient data are available. Conversations were held with health care specialists such as nurses, physicians, public health officials, to document sufficiency in data to warrant beginning the process. It was necessary to collect available data and begin analyzing it. Then it was necessary to re-state the question, return to the field for more data, analyze, and once again restate the question in order to achieve the whole historical picture of multi drug therapy.

4. Begin data collection through a consideration of known data. The known available data was primarily secondary in nature including journal articles, historical papers, patient files, and notes on conferences held on multi drug therapy.

5. Begin to write the report. Initial review of the literature was improved. Data from historical documents, patient files, interviews, questionnaires, and other notes were analyzed via HyperResearch (see treatment of data) and an initial report was written.

6. Interaction of writing and additional search for data or examination of data. After examining the secondary data, names of experts in the development of multi drug therapy emerged. A questionnaire, (see Appendix B), was sent to these experts for additional

input from this primary source. The questionnaire was mailed to 30 experts engaged in the study of Hansen's disease. Among those experts were medical doctors, nurses, patients, researcher's, administrators, and educators who presented at the Hansen's disease Conference on Multi drug therapy (MDT) in San Antonio, Texas, 1996. A list of these individuals are found in Appendix C.

Interviews with two Hansen's disease patients living at Carville, LA, were conducted to gain knowledge from this primary source. The questions focused on their personal experiences with early treatment to the development of multi drug therapy including the effects of multi drug therapy on their case (see Appendix D). Two patients, living in Dallas County, were interviewed to obtain information on patients living outside an institution. Their questions also focused on their personal experiences with early treatment and their use of multi drug therapy.

7. Completion of descriptive phase. This phase of the study considered a list of words and their definitions specific to Hansen's disease. A list of words that emerged see Appendix E.

8. Completion of the interpretative phase. During this phase interpretation of the interviews and other data were used to create a

chronological listing of events which brought about and/or contributed to the development of the multi-drug therapy.

9. Application of data to present. In this phase the data were applied to health education and health care workers who work with Hansen's disease patients, their families, and community.

The historical method involves a clearly defined problem, in this case "What was the development of multi drug therapy?" The final objectives were to put events that lead to the development of multi drug therapy in chronological order. "It requires expert and imaginative planning, careful analysis and interpretation of the data gathered, and logical and skillful reporting of the findings" (Kesling, 1987, p.38).

Human Subjects

The rights of human subjects were protected by following the procedures set forth by Texas Woman's University Human Subjects Committee. See Appendix F for a copy of the signature form used for the interview. Patient rights were respected throughout this study.

Instrumentation

The format for the questionnaire was developed from the questions used by Dr. William Cissell (1976) in his dissertation "A History of the Organization and Development of the Society for Public Health

Education, Inc." The focus of the questionnaire was to determine individual perspectives of the development of multi drug therapy used in the treatment of Hansen's disease. The questions were reviewed by a panel of experts consisting of two medical doctors, a nurse, and three university professors, one in the field of qualitative research, one in the field of health education, and one in the field of biology.

Treatment of Data

The information gathered from the questionnaire was analyzed through the HyperRESEARCH program developed by Dr. Sharlene Hesse-Biber. HyperRESEARCH is a "software program which aids the qualitative researcher not only in handling the coding of the large quantities of data involved in a research project, but also in analyzing the data to reach reliable, verifiable conclusions" (Hesse-Biber, 1993 p. 1).

The data collected by patient interviews were transcribed from audio cassettes. The transcription took approximately 14 hours. The transcriptions were set up in an ascii file and coded using HyperResearch. Thematic analysis of key words and themes were used to identify categories. Constructs were used. Based on the transcriptions, particular words and phrases used by the patients and

experts on the questionnaires from the experts were recorded. They were then listed and grouped together to look for recurrent themes. Thirty-six key words and phrases were identified. Because HyperResearch was available on a limited basis much of the data was analyzed by manual methods of coding and then re-checked with HyperResearch.

Some of the key words and phrases which emerged from the data included: humiliation, shame, disgust, isolation, stigma, therapy, family, identity, leprosy, Hansen's disease, bacilli, contagious, sulfones, drug resistance, adverse reactions, toxicity, hypersensitivity, leision, blindness, pain, Carville, beliefs, infectious, patients, treatment period, treatment, clinical trails, regimens, prevalence, health education, detection, diagnosis, cure, prejudice, cases. After the above words were coded, the phrases were grouped by similar words, for example: stigma and prejudice. These words could mean the same and, in this context, they were related to each other. This process helped narrow the categories but did not compromise the coding process. This grouping also encompassed the relationship to each word and how they would relate to the general theme. For example when the word "stigma" emerged, it was

usually related to isolation, shame and humiliation. When the word toxicity emerged it was occasionally related to adverse reactions.

A chronological listing of the events and other treatments which contributed to the development of the multi drug therapy for Hansen's disease was created. Applications of this information for health educators are discussed in Chapters IV and V.

CHAPTER IV

Qualitative methods were used to analyze the data generated by the patient interviews, questionnaires, journal articles, and the library archives from the Gillis W. Long Hansen's Disease Center in Carville, LA. This chapter will present the themes that emerged from the data regarding the development of multi drug treatment for Hansen's disease. The data analyses will be presented in the following sequences: historical review, the stigma, the patient, the treatment, Promin, Sulfone therapy, Rifampicin and Clofazimine.

HISTORICAL REVIEW

Leprosy has imprinted itself on our collective memory as a terrifying disease, physically mutilating and socially and mentally isolating its victim. At one time, it was an affliction on every continent, and always and everywhere it has been looked on as a particularly repulsive disease (WHO, 1998).

There is no real certainty as to where leprosy first began. Archeologists have produced little evidence, except for some skeletal remains showing an erosion of the nasal bones, characteristic of lepromatous leprosy along with arthritic-like deformities of the finger and toe bones. In India, as far back as 1400 B.C., leprosy was referred to as "Kushta" in the sacred vedic scriptures. Also, there is a mention of the disease made by the renowned Indian physician, Sushruta, in his

book Sushruta Samhita" as early as 600 B.C. However, there is some doubt as to whether "Kushtha" meant leprosy (Hansen's disease) as we know it today. Similarly, "leprosy" in the Bible (the Hebrew "Tzaraath") probably covered a whole range of horrible skin conditions just as the Greek "Lepra" did in the New Testament (The Leprosy Mission, 1998).

So acute were the sufferings of those infected with leprosy that it was thought to be highly contagious. This necessitated the isolation of its victims from the rest of society. Patients were segregated and "cast out" from their cities and villages. Leprosaria's started to appear and, throughout Europe during the Middle Ages, there were virtually thousands of them (The Leprosy Mission). Leprosy came to be referred to as "the living death" and its victims were actually treated as though they had already died. Funeral services were conducted to actually declare their "death" to society. Other cruel practices required the patient to walk on a particular side of the road, according to the direction from which the wind was blowing. In some areas, they were required by law to dress in special garb, wear a declaration sign around their neck, and to ring a warning bell announcing to all who were in shouting distance that they were "lepers". When the people would hear the word "leper," they would flee (The Leprosy Mission, 1998).

In Norway, a young physician, Armauer Hansen, working in his Bergen laboratory was meticulously examining under the microscope

material obtained from skin lesions of patients diagnosed with leprosy. Appointed medical officer to a leprosy hospital in 1866, G.H. Armauer Hansen (1841 - 1912) probably first saw and isolated the leprosy bacilli in 1872 (Hastings, 1987).

Hansen mentioned his recognition of these organisms on February 28, 1872, in his 1872 Annual Report. The following year, he published his tentative conclusions, that the rod-shaped bodies he consistently observed in his material, were probably the cause of leprosy (Hansen, 1875). The primitive staining methods at his disposal had to wait for the better aniline dyes that were introduced and popularized by Neisser, before the morphology of the organisms could meet the criteria of his critics (Hastings, 1987).

> The hospital at Carville came in to being in 1894 by the State of Louisiana by Dr. Isadore Dyer. There were seven Hansen's disease patients in different hospitals in New Orleans and in those times people knew very little about the dreaded old disease. Most everyone believed it to be highly contagious, which it is not. None of the hospitals wanted to have anything to do with the "Lepers" so the state bought a plantation about 60 miles up the Mississippi River from New Orleans and moved the small group to their new home under the cover of darkness. The patients were housed in the old slave cabins at the plantation.

> The place could hardly qualify as a hospital. Nurses were needed and the state asked for volunteers. Over a hundred sisters sent in applications. More were needed. The Sisters of Charity came in April of 1896. The Sisters were tireless, dedicated workers and changed a hideous existence into a paradise on earth for a group of unfortunate abandoned souls (Harmon, 1995, p.17).

Hansen's disease is a chronic infectious disease caused by mycobacterium leprae, which is also related to the causative organism of tuberculosis. The exact incubation period is not known today. It can vary from three months to 40 years. The disease strikes mainly young people between 10 and 20 years of age, males more often than females (WHO, 1998).

> It is believed that Hansen's disease is usually acquired in childhood through prolonged and intimate contact with someone who has it. When a new patient discovers that in Carville there are number of examples of more than one member of a family coming there as patients, he, or she begins fearing for the other members of their family - a fear which may continue through the rest of his or her lifetime. This fear had grown to intense proportions with me, and to my daily prayers to get well, and away from Carville I would always add, "But, God, keep me here rather than give this cross to any other member of my family". I

> think every other patient offered a similar prayer, for it was the greatest fear we knew and the deepest hurt when occasionally the fear seemed justified by the arrival of a patient's child, sister, aunt, brother, or cousin. So often in my laboratory work had I observed such tragic arrivals. The family susceptibility follows strange patterns and seems to defy its secret being traced. There is one case where mother and father were both healthy and lived to be old but where all five of their five children were stricken, one by one, over a period of twenty-five years. In another case one child was stricken out of the ten children of healthy parents. In other cases no immediate member of a patient's family circle might acquire the disease but an aunt, uncle or cousin would appear at Carville. In other cases one parent might be ill but all the children healthy. And so on, and the fear is undying (Martin, 1950, pp. 102).

It was one of the first human bacterial pathogens to be described (McDougall, & Ulrich, 1993). This organism is an obligate intercellular pathogen which means that it replicates only within the cells of the host. It reproduces very slowly and affects the skin, nerves, and mucous membranes. M. Leprae is the only bacterial pathogen capable of entering peripheral nerves (McDougall, et al., 1993). It can cause permanent and extensive deformities of the skin and the peripheral

nerves resulting in physical disabilities of many types. Until the 1940s, Hansen's disease was regarded as incurable, but with the development of the drug dapsone, Hansen's disease became curable (McDugall, et al., 1993).

Hansen's disease takes various clinical forms, depending on the immune system of the patient. Patients without any defenses whatever against the bacilli develop multibacillary form of Hansen's disease, while those with a stronger immune system come down with paucibacillary form of Hansen's disease. The latter form is relatively harmless and as a rule is not infectious (WHO, 1998).

The typical signs are flat or slightly raised patches on the skin, usually single but at most three, well defined, non-itching, and hypopigmented or reddish. The patient will feel nothing in the affected area even when pricked with a pin. The sensory loss is very important for diagnosis because bacilli are often undetectable in the skin smears (WHO, 1998).

The damage that the bacilli cause to the peripheral nerves leads to numbness, muscle weakness, or even paralysis. The consequent claw hand or foot drop will soon develop. Dry skin is also a characteristic of the bacilli attack on a person's body. Because of the loss of sensation the patient fails to notice any injury or potential dangers, for example a hot pan or sharp knife. Injuries easily result in

infection, which will lead to ulcers and can damage the dermal tissues, joints, and bones. This happens in an estimated 25% of the cases that are not treated at an early stage of the disease (WHO, 1998).

Stanley Stein writes in his book "*Alone no Longer*" about the disfigurement and disabilities Hansen's disease will cause if left untreated. He states: In some cases unnoticed infections become so advanced that amputation is necessary. And absence of feeling can be so profound that amputation has on rare occasions been performed without even a local anesthetic (Stein, 1974. p. 46).

Transmission of the bacilli is still a mystery. Hansen's disease is still classified as a communicable disease and the human being is the only known source for infecting other human beings. It is thought that the bacilli are passed from one person to another through the skin and upper respiratory tract. Persons with untreated Multibacillary types of the disease which include Lepromatous and Borderline, are the main sources of infections. The theory of transmission through the respiratory tract, which may house millions of Hansen's bacilli, is based on:

1. The inability of the organism to be found on the surface of the skin.

2. The demonstration of a large number of organisms in the nasal discharge.

3. The high proportion of intact bacilli in the nasal secretion.

4. The evidence that the *M. Leprae* can survive outside the human host for several days or even weeks (Bryceson & Pfaltzgraff 1990). Also, with each cough or sneeze, the bacilli are discharged on droplets or dust particles that healthy individuals can then inhale. However, the transmission through skin contact can not be ruled out. The people who work with Hansen's patients, have by far, a much greater chance of acquiring the disease, however, there are no known cases of health care workers at Carville who have contracted the disease in the history of the Gillis W. Long Hansen's Disease Center (Trautman, 1989).

> Stanley Stein writes: The isolation which follows diagnosis-the cruelest feature of the patients' suffering-is founded upon a misconception as to its communicability. When I tell you, Dr. Frisch, that during the forty-five years that the hospital has been at Carville, not a single case of leprosy has developed in that neighborhood, you will realize how groundless is the fear of contagion...I stress this one point because it is at the root of the leprosy problem. We do hope in time to enlighten the public to the extent that the patients will no longer have to carry a burden bequeathed to them by six thousand years of misunderstanding (Stein, 1974, p. 193).

Even today, there is not a lot known about Hansen's disease. It is caused by a bacterium, but the organisms have never been cultured. They grow only in intact animals and it is impossible to prove what mode of transmission or what level of exposure is required to transmit the disease. If left untreated, the disease will become quite serious. It is a common cause of blindness and outside of the United States it is the leading cause of severe deformities (Nalick, 1997).

Some people are naturally resistant to the bacilli and their bodies can destroy the infection without any medical assistance. Today patients become unable to transmit the disease after taking only a few doses of medication so there is no need to quarantine them. Further, they can generally continue their normal work and other activities uninterrupted during the treatment that may last several years (Nalick, 1997).

The Stigma

Even though the disease is treatable, the stigma attached to it remains. Often, people are fearful that they will be shunned if others discover their condition (Natlick, 1997). Some of the patients at Carville have told stories of the stigma and how it has effected their lives and the lives of other Hansen's disease patients. Stanley Stein recalls when the doctor diagnosed his condition as leprosy:

"Well", the doctor said, "I have a report from the laboratory, and while it is not exactly cheerful news, I don't want you to go into a blue swivet. You see...." "What is it, Doctor?" I blurted. "Have I got cancer?" "No no. Nothing like that." The doctor smiled reassuringly and I immediately grew more apprehensive. "You have leprosy." He said. "Leprosy! The room started spinning on its axis and I closed my eyes to shut out the dizzy motion. That was a mistake, for I immediately saw the mysterious siren in the black veil of the leper woman of Boerne who I had not thought in years. My nostrils quivered again to the nauseous smell of chaulmoogra oil, and I could feel my insides slowly turning over. I opened my eyes quickly. "We've had pretty good results with chaulmoogra oil therapy, and if you come to me twice a week for treatment...." I scarcely heard what he had said. Leprosy! The word was not a diagnosis, it was a pronouncement of doom. My hopes and ambitions were collapsing about me. My future was in ruins. My present? A great cold emptiness...Leprosy was not just a disease- it was a stigma, a disgrace, a visitation from on high, a punishment for some dreadful sin. What had I done to bring down the wrath of God upon my head? My panicking mind tried to review my life of depravity. I was disappointingly meager. I was not much of a man, "I'm afraid. (Stein, 1974, p.18)

Johnny Harmon a current resident at Carville stated "A word that scares the living daylights out of almost everyone. LEPROSY" (Harmon, 1999). Johnny's brother, Elmo, contracted Hansen's disease first in his family and Johnny remembers the time when his father pleaded with the family doctor not to tell anyone that leprosy was in their family. Johnny stated: "The public did not have long to wonder. Our good family doctor told everyone what Elmo had. Elmo and I used to double date but after the publicity we stayed away from daylight events and our main entertainment was picture shows at night."

Stanley Stein writes "I was still in mortal fear of being found out; the stigma was far more terrifying to me than the progress of the disease" (Stein, 1974, p. 47).

Dr. Kellersberger wrote about an experience he had with a woman who had a tremendous fear of the word leprosy and the leprosy germ. He wrote, One usually finds two extreme attitudes expressed. A

> woman called my office, in a very much disturbed state of mind. She stated that she had heard over the radio that there are cases of leprosy in New York City; that she had not been able to sleep since that time, and that she became frightened when she even saw a person with a bandage on any part of their body! She wanted to know how long the 'leper germs' stay on money, and

finally confided in me that when she had been in Chinatown a short time before, a Chinese had handed her some change. 'What makes you think the Chinese had leprosy?' I asked. 'I thought, ' she replied, 'that all Chinese had leprosy! (Kellersberger, 1945, p. 1.)

Carville was home to Betty Martin, who at the age of 19 fell victim to the bacilli that changed her life. While she battled the disease she wrote of many accounts of patients that shared her life and trials, she tells the story of a patient friend who didn't die from the bacilli but from the stigma.

"She was a well-to-do widow in her sixties with two married daughters. Although she had been diagnosed in the early stages of the disease and was told she had every chance to recover, she had chosen to believe otherwise. The terrible word 'leprosy' convinced her that she had come to the end, therefore she disposed of all her property and other valuables and divided her money between her daughters. After seven unhappy years in Carville she got the required number of negative tests and passed her physical. The doctors told her she was free-free to return to her daughters, to the easy aristocratic world she had loved. She was like a woman reborn, and the dark past began to blur before

a bright future. She hurried to write her daughters the joyous news that she could return to them, and began packing." "But when she postponed that date and set another one, I wondered a little. Mrs. Jewel postponed that date and set a third, and still stayed on. One morning she was found dead fully clothed, across her bed. Her hand had dropped a letter from her daughter that read they didn't have room for her to return to them." "Here she lay, exposed to scalpel and knife. It did not take long at the autopsy to discover the cause of death, for the doctor who examined her heart found the aorta, the blood vessel that leads directly from the heart, was badly ruptured, heartbreak, not from the disease she overcame, but from the dread label- one her daughters had not been able to face." (Martin, 1950, p. 103)

The stigma stays with the patient through out one's life. When they live in the confines of Carville or other Hansen's disease centers they are protected in some ways. However, if they are in the "other world" as the patients call it, they fall victim to the stigma that surrounds them. Betty Martin and her male friend escaped Carville to live on the outside world. She wanted to be at home with her parents and family. After escaping through the "hole in the fence," she was able

to find work as a stenographer. She gives this account in her book "Miracle at Carville" about the fear she had to endure on the outside world.

> The fear of stigma kept us in a prison. The stigma was always before me. A friend introduced me to one of the social leaders of New Orleans. She met me graciously and calmly, with no hint of the many times we had met when she was visiting her two relatives who are Carville patients. Like me, she lived in dread, in her case with the knowledge of family susceptibility. One morning before the office opened for business we stenographers were chatting, and the girl at the next desk to mine tuned to me. She was an intelligent person and unusually well informed on medical matters. "Say, did you listen to the March of Time last night?" she asked. "It told about a girl leper in Carville who is going to have a baby, and the minute it is born it's going to be taken from her; she'll never see it." Then, as I sat stunned, she added her own quota of misinformation: "Leprosy is so contagious that no one is allowed even to go anywhere near that hospital." Several of the girls had never heard of Carville. "Have you, Betty?" one wanted to know. My knees were shaking and my insides turning over, but outwardly I stayed calm. "Never heard of it," I said, and strolled off to the water cooler. It was cowardly

but the easiest way. I did not have the courage to correct the girl (Martin, 1950, pg. 125).

The victory over the stigma and the ability to mainstream with society, will be of little help to some of the surviving victims of Hansen's disease. Their average age is 71, and 60%, suffer from physical disabilities (Satsuki, 1996). The majority have no jobs and no relatives willing to support them. Even today, a lingering prejudice makes them unwelcome at ordinary nursing homes. Although the victims will soon become legally free to leave the leprosarium, they have nowhere to go. The government has agreed to support them for the remainder of their life by turning the leprosarium into state-run homes, but many consider that scant compensation for their ordeal" (Satsuki, 1996, p 46).

Betty Martin, describes her feelings when she was told she had leprosy as: Mind and ears-were playing tricks, was the word real? "Leprosy!" It spread like a stain in my mind. Oh no, not in this day and place." "Its horror belonged to Christ's time, to draped forms and warning bells and perpetual banishment. Some cases might exist in lands far away, in India perhaps, or China, but surely leprosy could not exist here, in our own United States, and surely not in me. Not to a high-spirited girl of nineteen (Martin,1950. Pg. 9).

The Patient

Many of the patients, before being diagnosed with Hansen's disease, are diagnosed and treated for a variety of ailments from dermatitis, serosis, even acne. But when the diagnosis of "leprosy" is given, the patients feel punished for some dreadful sin. Hansen's disease is not defined along racial, gender or age lines. Hansen's disease was endemic throughout the world until the late 19th century. A drop in its incidence became evident in Northern Europe and North America, so that the tropical areas are the currently endemic areas (Ramarathnam, 1999). The lepromatous form of Hansen's disease is more prevalent in Africa while the tuberculoid form is more frequent in Asia (Ramarathnam, 1999).

Males are affected more frequently than females, with the exception in some areas of Africa, where the prevalence in females is equal or higher than males. Hansen's disease is known to occur at all ages ranging from early infancy to the very old. It is extremely rare in infants, but about 20% of cases occur in children below the age of 10 years (Ramaratnam, 1999).

An 18-year-old engineering student in Nagoya, Japan, found dark spots appearing on his body and face. Doctors diagnosed one of the most feared diseases ever to strike humanity: leprosy. At the time, more than 50 years ago, leprosy was mistakenly believed to be highly

contagious. Many people shared the sentiments of a 17th century Japanese physician who wrote that leprosy victims had been "abandoned by heaven" (McDougall, et.al. 1993, p. 2396). For a few years this young man's family kept his affliction a secret, but as the symptoms progressed, there was no evading the Leprosy Prevention Law. Today, at the age of 70, this man's face still clouds with sadness when he recalls his mother's words during her visit more than 40 years ago: "Die here on the island. Don't ever come home"(McDougall, et al. 1993, p. 2396).

He never did go home and at the age of 70. He still lived at the leprosarium in Aiseien. Promin, a drug used to treat and often to cure Hansen's disease became widely available in Japan in the 1950's. The young engineer was treated and became free of the disease before it could disfigure him in any obvious way. In 1956, international medical experts declared that Hansen's disease, caused by prolonged exposure to lepra bacilli, was in fact rarely contagious and called for an end to quarantine. However, for decades this engineer and thousands of other Japanese victims remained in confinement. "At the insistence of deeply conservative medical authorities and leprosarium directors, the law was never changed"(McDougall, et al.1993, p. 2397).

About 90% of the population are not susceptible to Hansen's disease. Children are more susceptible than are adults. Immunological

and epidemiological studies suggest that only 10-20% of those exposed to *M.Leprae* will develop signs of indeterminate Hansen's and only 50% of those with indeterminate disease will develop full blown clinical Hansen's disease (Ramarathnam, 1999).

The Treatment

It took many centuries for the treatment of leprosy to pass from the horrific to the scientific, from the commonly accepted bathings in the blood of infants under two years of age to the administration of synthetic mycobacteriostatic drugs (Hastings, 1987). In China and in India they used the oil expressed from the ripe seeds of Hydnocarpus wightiana. This oil, also called chaulmoogra oil or Flacourtiaceae, comes from the chaulmoogra and is expressed from the seeds of the Indian tree of the hydnocarpus genus is found in tropical Asia. The seeds were discovered by a Burmese prince who contracted leprosy and withdrew into the depths of the jungle to contemplate the evils of the world. Here, an occult message led him to eat the seed-laden fruit of a certain tree. As a result he was cured (Stein, 1974). It is a velvety brown fruit the size of a large orange that was thereafter given as a treatment for leprosy. The Burmese of the later part of this era, were also thought to have used this treatment.

"Historically, the first mention of chaulmoogra oil as a treatment for Hansen's disease was made by a British Civil Surgeon, Dr. F.J.

Mouat, on the west coast of India in 1853" (Stein, 1974, p. 38.) As early as the turn of the 19th century, the ethyl esters of hydnocarpic acid, the therapeutic principle of the oil were being tested alone and in combination with other drugs (Stein, 1974). Chaulmoogra oil was later replaced by more effective synthetic substances.

Chaulmoogra oil was given in two ways, and the patients at Carville had a choice which way they would like to take the Chaulmoogra oil treatments. "They could take the oil externally, internally, or - as some of the patients would say eternally" (Stein, 1974, p 38). "The technique for both shots was the same - a sharp jab into the gluteal muscles. The after effects were sometimes frightfully painful, suppurating abcesses which the chaulmoogra oil would generate in the patient's backside. The sight of a man with a pillow under his arm, on his way to sit down somewhere, was quite common" (Stein, 1974, p39). Stanley Stein was hospitalized several times with a chaulmoogra-induced, rear-end ulceration (Stein,1978).

One of the major problems with chaulmoogra oil treatment was the tendency toward relapse following arrest of lepromatous leprosy, which was very disappointingly high (Cochran, 1947). F.J. Mouat of the Indian Medical Service did an intense investigation on chaulmoogra oil and reported his findings in 1854. Leonard Rogers continued the research of the derivatives of the oil, despite many publicized positive

claims, the general consensus was that while it may have had slight mycobacteriostatic properities it did little more than stimulate fibrosis when injected intradermally and intralesionally (Hastings, 1987).

Stanley Stein in his book "Alone no Longer" described his experience with chaulmoogra oil. He states, Dr. McGlasson was

> injecting me with the ethyl esters of chaulmoogra which at least were less vile smelling than the oil itself. He held out no great promise of results. He knew chaulmoogra was not a cure for leprosy, but he hoped it might stay its spread. At any rate there was no other treatment available. He held the extremely unorthodox view, since widely adopted, the state of mind was an important weapon against the bacillus. In 1923, therefore, when I was invited to Detroit for the wedding of my cousin, he urged me to go (Stein, 1974, p. 46.).

Much research continued to improve the chaulmoogra Oil treatment, which was anything but the ideal therapy. Orally taken, it had the most nauseating side effects and, by injection, it was the most painful experience a patient could go through, being thick oil (The Leprosy Mission, 1998).

There was usually an experimental treatment being investigated by some medical teams or individuals. Johnny Harmon, one of the patients interviewed, remembers one group of patients who, for some

reason, decided that the willow tree bark tea would cure Hansen's. "A lot of willow trees lost their bark, but I don't believe any Hansen's Disease germs got hurt in the experiment" (Harmon, 1999, p. 85). Most patients were eager to try anything promoted by the doctors in the hopes of finding a cure (Harmon, 1999).

At another time, the government was experimenting with a fever machine treatment. Someone had suggested or had reason to believe that the Hansen's bacilli were encased in a wax like coating, therefore, no drug would penetrate the coating and kill the bacteria. The researchers reasoned that, if the coating was destroyed, they would then be able to attack the bacilli. The researchers needed volunteers to take part in the experiment. Johnny Harmon thought this would be a good idea to try, especially since the chagmoogra oil was not working. The researchers also reasoned that fever therapy was an answer because almost all diseases produce a fever in order to help kill the organisms. Hansen's disease does not make one sick enough to cause a fever, so the bacilli can keep right on working.

The fever machine sounded like a good idea to Johnny and he was eager to get started with the treatments as soon as possible. The following is his experience with the fever treatment:

> I packed my bags. Six patients at a time would go to the U.S. Marine Hospital in New Orleans where the experiment would

be conducted. Each patient would take one treatment a week for six weeks. Several of the patients had taken the treatment before me and said it was not too bad. I was asleep and had my head partly covered when my day arrived. A nurse came to get me. When she threw back my covers, she was startled. I was young and the disease had not yet damaged me, except for a couple of small spots on my body. The nurse and orderly escorted me to the treatment room, where I was introduced to the fever machine. It looked a lot like an iron lung. It was a cylinder approximately, thirty inches in diameter by six or more feet long, mounted on four legs, at a height convenient for the nurse or attendant, to work with the patient. I was put on a tray like bed, and shoved into the cylinder, with only my head remaining outside. A sliding door was lowered around my neck to prevent the heat from escaping. There were doors on the sides of the cylinder. My flimsy gown was removed leaving me in the nude except over my pubic area, which a small towel was placed. A thermometer was placed in my mouth and my rectum. There was a small fan on the front of the machine to cool my face. There was a mirror arranged so I could see the nurse, who sat in a chair, and keep a constant vigil on my temperature. With the patient in place and all systems checked out, the heat was turned on. Hot air blows

over your body. They must have given me some kind of tranquilizer to sleep. The treatment lasted probably four to six hours. My first three treatments were uneventful and I had no trouble at all (Harmon, 1999)

"Ah...but the fourth treatment was a different story. I marched proudly to the treatment room and was proud of my super strength. I had not let the machine get the best of me. It had caused some of the other patients problems. Everything was O.K. in the beginning and I drifted off into my usual tranquilized sleep. I know not what happened but when I woke up, I was completely disoriented, and totally confused. I went hog-wild crazy, and demanded that they let me out of the infernal machine promptly. I was as uncontrollable as a west Texas Mustang. It took three or four men to hold me down and keep me on the bed or maybe it was a table. They were really worried about me. I could hear them trying to call my family, in Texas. Then I began to come down to earth, and I too began to worry. My God, I said. They must have over done it, and I may die. Then I passed out. Quite sometime later, I awoke in my bed with an upset stomach, but otherwise normal. I ate nothing but tomato juice for the next twenty four hours. I completely recovered from the ordeal but I took no more fever treatments. It may have been a good thing to

do because in March, 1937, I ran my first negative test. I do not have documented proof, but I am told, my fever went up to 106.8 degree F. That was the highest they had induced into any patient. I was young and strong and they believed I could take it. They were wrong. I believe, that of all the patients, who took part in the fever machine experiment, I am the only survivor." (Harmon, 1999)

This was the state of leprosy treatment until the early 1940's. At the Second International Leprosy Congress held in Bergen, Norway, in 1909, it was left to a layman, Wellesley Bailey, to suggest that an effective medical treatment for leprosy would eventually be found. A few months before, two German chemists, Fromm and Wittman, had actually synthesized a compound that would, some three decades later, introduce the concept of chemotherapy into leprosy treatment. But, diaminodiphenylsulfone lay unused on the shelves of the research chemists for 30 years longer (Hastings, 1987). Researchers did not recognize the potential of the drug.

Isolating the bacteria or the causative agent was a milestone in the treatment for Leprosy. In the constant search for a medical treatment for leprosy, many products created a hope that it would be the cure, but nothing would free the patients from the curse that had been bestowed on them. In addition to chaulmoogra oil, other

treatments included gurjan oil, methylene blue, various aniline dyes, diphtheria toxoid, etc. The theraputic pathway of leprosy is littered with many rapidly discarded nostrums. Similarly, the association of leprosy with articles of diet (tubers, palm oil, dried fish, fresh salmon, etc.) and its transmission by cockroaches have long since been forgotten (Hastings, 1987).

In the 1950's, the questions raised were whether serological differences between the different antigenic constituents of culture filtrates of the tubercle bacillus were of any specific significance in relation to tuberculous disease (Chang, Wolcott, & Doull, 1950). In addition, they were trying to understand the effects of cortisone on the monocyte cells and its power to inhibit multiplication of bacilli, without inhibiting phagocytic power. These questions raised about the bacilli and it ability to grow were, according to what type of leprosy, BB, LL, etc., was influenced or if it was influenced by the endocrine system (Chang, Wolcott & Doull, 1950).

Sulfone Therapy of Leprosy

In 1941, the American physician, Dr. Faget, was courageous enough to use the parent sulphone drug with encouraging results on the Hansen's disease patients at Carville, according to Dr. Hastings. This was the beginning of sulfone therapy. Three years later, in April 1944 the first sulfone-treated patient fulfilled the criteria for arrest of

the disease. From April, 1944 until 1950, a total of 77 patients who had active disease when treatment was begun experienced the disease arrested with the use of sulfone drugs. Up to July 1, 1949, it had been possible to keep only 33 of the patients under observation with routine clinical and laboratory examinations. The patients under observation were all of the lepromatous type. The follow-up varied from 6 months to 5 years (Cochran, 1947)

In 1950, the discovery of reactivation of the disease in six patients in whom the disease was supposedly arrested by sulfone treatment was made at Carville. Three of these patients showed a reappearance of leprosy bacilli in the skin without any other manifestations of the disease. They were termed subclinical relapses. The other three patients presented, in addition unquestionable leprous skin lesions, or what they called a true clinical relapse of the disease.

Promin

A search for a related compound of lower toxicity led to the discovery of Promin. This drug significantly delayed deaths from experimental tuberculosis and caused resolution of lesions in the guinea pig (Cowdry & Ruangsiri, 1941). It was tried on a few patients at the U.S. Public Health Service Hospital (National Leprosarium), Carville, Louisianna, in 1941 (Chang, Wolcott, & Doull, 1954). Sulfonamide derivatives (sulfanilamike, sulfathiazole, sulfapyridine and sulfadiazine)

had previously been shown to be ineffective (Chang, Wolcott & Doull, 1954).

Initially, Promin was administered orally to 10 patients in doses of 0.5 to 1 gram daily. Due to the high toxicity, Promin was abandoned in favor of Promacetin, then called Internal Antiseptic No. 307 (Chang, et al., 1954). Twenty patients were given Promacetin in oral dosages of 0.3 to 1 gram daily. Another group of 20 patients, who were matched as to type and stage of disease, were given a placebo by mouth. After eight months, the condition of the Promacetin group was superior, especially in regard to such complications as ulceration, rhinitis and laryngitis.

Meanwhile a preparation of Promin suitable for intravenous use had been perfected. This was well tolerated by most patients in doses of five grams, six days weekly, for months with only short intervals of rest of one to two weeks three times a year. Administrative disadvantages of intravenous therapy led to a search for similar drugs which could be given orally with minimal toxic effects (Chang, et al.,1954).

With all sulfones, a period of rest was advisable several times a year. Thus,patients would return to Carville for a period of two weeks, every three months with oral compounds prescribed. Patients whose diseases were arrested were advised to continue taking small daily doses of sulfone for life. This recommendation came about because of

the recurrence of the disease among patients who had discontinued treatment (Chang, et al.,1954).

Periodic medical tests such as urinalysis, hemoglobin estimations, and red cell counts are necessary while on any medication, but, especially for those on sulfone therapy. Studies of renal and liver function should be performed if indicated, although sulfones have a high safety record. At Carville more than 1,100 patients have taken one or another compound for prolonged periods without a single instance of fatality or serious illness attributable to the drug (Barnes & Barnes, 1951). This does not mean that sulfones and, particularly, DDS are used indiscriminately without institutional supervision. It means the treatment complications in Nigeria, where seven cases of jaundice and one death in 153 patients treated with DDS, were all associated with exfoliate (a condition where the skin is falling off in layers) had dermatitis before treatment (Barnes & Barnes, 1951).

Sulfone therapy, 4'-diaminodiphenyl sulfone, (DDS) was synthesized by Fromm and Wittmann in 1908, but, it was not until 1937 that this compound was tried in infections of laboratory animals. Activity against tuberculosis in guinea pigs was demonstrated but the drug was considered too toxic for clinical use (Chang, Wolcott, & Doull, 1954). It was difficult to create experimental leprosy in animal models

and scientists searched to find an animal that would be able to support the M. Lepra sufficiently for the various treatments to react.

Sulphones were first used in treating leprosy in 1941, and they still remain the most useful drugs. Dapsone has proved to be cost effective, safe and effective, and eminently suitable for outpatient care. "Since 1965 two major problems have emerged: dapsone resistance and microbial persistence" (Bryceson, & Pfaltzraff, p. 79).

Dapsone is bacteristatic but its exact mode of action is unknown. "It is a competitive inhibitor of para-aminobenzoic acid and interferes with folate metabolism, but the unique sensitivity of M. leprae to dapsone suggests that some other mechanism may also be involved" (Bryceson & Pfaltzgraff, p. 79). "The morphological index (see Appendix G) of bacilli from smears of patients with lepromatous leprosy treated with dapsone falls to zero in five to eight months" (Bryceson, & Pfaltzgraff, p. 79).

In 1950, a derivative of the sulfones emerged, and by 1952, Burroughs Wellcome & Company of London stated "Sulphetrone is the drug of choice. Its proved efficiency and low toxicity place it in a class of its own. In addition to its therapeutic advantages, sulphetrone is water-soluble; thus, injections are simpler, and more economical than with oil-suspended sulphones" (Bowersock, 1995, p. 311). The sulfonamides are the distinguished group of antimicrobials that started

the antibacterial revolution in 1935 (Bowersock, 1995). The older sulfonamides did not survive because of their poor water solubility which led to problems in preparing acceptable dose forms. The crystallization in renal tubules are frequent because of the water solubility problem, made them a feared medication.

Another problem in producing the sulfonamides was the pure water supply that was needed to produce this group of antimicrobials. In addition to correcting these deficiencies, modern derivatives also tend to require less frequent administration which improved convenience and patient compliance (Bowersock, 1995). Although the specific agents have changed completely, they are still in use today. Many derivatives were created by modifying the sulfanilamide structure and the list of clinically used sulfonamides were extensive (Bowersock, 1995).

Sulfonamides are used in a wide range of infectious diseases because of their broad spectrum of activity, which rivals that of the tetracyclines. Alone and in combination with trimethoprim, sulfonamides are used as first-line drugs in a wide variety of bacterial diseases including Hansen's disease, pneumonia, bacterial meningitis, and urinary tract infections. Sulfonamide plus trimethoprim may be used intravenously for HIV infected patients suffering from Pneumocystis carinii pneumonia. Some sulfonamides have effectively

inhibited the activity against intestinal coccidia. "Sulfisoxazole has been recommended for treatment of chloroquine-resistant malaria in conjunction with chloroquine and/or other agents" (Pearson, 1983, 88s). "Sulfadoxine (a rapidly absorbed, but slowly eliminated sulfonamide, and has a half-life 100 to 230 hours) plus pyrimethamine is recommended particularly in cases where chloroquine resistance is expected or proven" (Pearson, 1983, p.88s).

Together sulfonomides and trimethoprin are synergistic and bactericidal. This reactant has made the combination extremely popular in both veterinary and human medicine (Bowersock, 1995). "Sulfonamides and trimethoprim, alone and in combination, demonstrate three important modes of drug action; competition, false synthesis, and sequential blockade or inhibition. Both drugs acting individually are competitive inhibitors of specific enzyme reactions" (Bowersock, 1995 p. 315). "False synthesis contributes to the effectiveness of some sulfonamides. Combinations of the two drugs result in a synergistic sequential blockade" (Bowersock, 1995, p. 315).

"Specificity of these actions is due to unique and pharmacologic differences. Vertebrates do not have dihydropteroate synthase and, therefore, cannot synthesize folic acid. It must be supplied as part of their diet. Conversely, many bacteria and protozoans must form their own folic acid, thereby becoming susceptible to the action of the

sulfonamides" (Bowersock, 1995p. 315). "The difference in binding attraction between bacteria and vertebrates accounts for the specific characteristics of trimethoprim" (Bowersock, 1995, p. 316).

However, resistance to sulfonamides is fairly common. Individual sulfonamides generally reflect the activity of the group so switching among sulfonamides for reasons other than toxicity or pharmacokinetics is not rational (Pearson, 1983). Resistance may be chromosomal, in which case it is familiar to the organism. Clinical problems are more often related to plasmid, DNA related and produced, borne resistance. "Transferred (plasmid) resistance does not result in altered drug or accumulation of drug in the organism. Therefore, it must result from a change in the organism's dihydropteroate synthase (DHPtS) to alter drug binding, or development of the organism's ability to use preformed folic acid" (Bowersock, 1995, p. 317).

In the past 25 years, dapsone resistance has become an increasing problem around the world. Most resistance has been secondary, appearing in multibacillary patients after 10 - 20 years of treatment with dapsone alone. "The delay in the appearance of resistance from 1945 to 1965 may have been due to the weak bactericidal levels produced by conventional dosage of dapsone" (Bryceson & Pfaltzgraff, p. 81). Primary resistance began to appear in the late 1970's and is becoming less frequent. It results in individuals

with dapsone resistant *M. leprae* and may be present in patients with any type of Hansen's disease. The degree of resistance may be low, intermediate, or high, as measured by the dietary dose of dapsone needed (Bryceson & Pfaltzgraff). Combinations of trimethoprim and sulfonamide overcome some of the problems with resistance,mentioned above, but organisms do become resistant to the combination of dapsone and trimethoprim (Bowersock, 1995).

Today, sulfonamides and trimethoprim are probably more commonly used in combination than separately (Bowersock, 1995). Combinations of these sulfonamides with trimethoprim are synergistic and bactericidal whereas sulfonamides alone are static (Bowersock, 1995). Sulfonamides are recommended and available in ophthalmic, oral, and parenteral dose forms. Ophthalmic forms; are obviously intended to be used topically. Vaginal sulfonamides exist, but in the United States Pharmacedial Directory (USPDI10th90) it states that they have no proven efficacy and most authorities advise against their use. (Booth & McDonald, 1985).

"Sulfonamide solutions that have not been buffered are strongly alkaline and cause tissue necrosis and sterile abscess formation when injected intramuscular (IM) or perivascularly. These strongly alkaline solutions should not be injected intraperitoneally. Intrauterine dose forms of sulfonamides alone and in combination with urea are

available"(Booth & McDonald, 1985, p. 1029). The true benefit of adding urea to the intrauterine sulfonamide has been questioned, but it is claimed to increase the concentration of free sulfa and enhance its activity (Booth, McDonald 1985). "Drug residues in breast milk constitute a frequent and important hazard of intrauterine sulfonamides. Because of the strong tissue binding for which sulfas are known, there is reason to doubt their efficacy in topical applications to abscesses as well as for the intrauterine applications" (Booth, McDonald, 1985, p. 1031).

Sulfonamides, produce reactions in all three categories: biological, direct toxicity, and hyersensitivity. The biological reaction, although not a prominent adverse effect, can produce disturbances in gastrointestinal flora because of its broad spectrum of activity. This would be more pronounced with the older drugs that are less well absorbed from the gastrointestinal tract. This would manifest initially as diarrhea (Booth, & McDonald,1985, p. 1038). "With hypersensitivity, sulfonamides are too small to be immunogenic and require metabolic activation to a reactive intermediate before they function as haptens (partial antigens). Nevertheless, a review of the literature would reveal that nearly every conceivable type of hypersensitivity reaction has been associated with sulfonamides" (Booth & McDonald, 1985). "Hypersensitivity is still one of the more frequent

adverse reactions with the sulfonamides, but it is rarely serious. It may occur in up to three percent of patients and may manifest as fever, itching, or skin rash" (Booth & McDonald, 1985, p.1039). The third reaction, sometimes called Stevens-Johnson syndrome, (arthralgia and myalgia, redness to blistering of skin, and weakness) is also a form of hypersensitivity reaction, but is less frequent (Booth & McDonald 1985). Other toxicity consists of direct miscellaneous toxicities that are seen more frequently and include dizziness, headache, and gastrointestinal disturbances such as diarrhea, anorexia, nausea, and/or vomiting (Booth & McDonald 1985).

Other side effects of sulfonamides are renal crystalluria which are crystals in the urine. This is classically associated with the older sulfonamides, and rarely observed with newer derivatives because copious quantities of water dilute it and decreases the urine crystallization. With the older compounds it was also advised to alkalinize the urine to increase the solubility of the drug and its metabolites (Booth & McDonald 1985).

Photosensitivity is another side effect, so patients should minimize exposure to sunlight while taking sulfonamides. "Cardiovascular collapse leading to death has been noted on too rapid administration of intravenous forms of these drugs. It is not due to the alkalinity"(Booth & McDonald 1985, p.1033). "Tissue necrosis can be

expected if solutions not intended for IM administration are accidentally injected into the tissues. This is because the strongly alkaline solutions required to mix with most of the sulfonamides" (Booth & McDonald 1985, p.1033). Blood dyscrasias, has been reported in association with the newer sulfonamides. USPDI indicates that these occur more often than rarely! Significant warnings associated with new drugs, include fever, paleness, sore throat, unusual bleeding or bruising, and unusual tiredness and weakness (Booth & McDonald, 1985).

Some older sulfonamides were known to cause blood in the urine but, with newer derivatives, this condition is rare. This hemolysis may be more likely in patients with reduced glucose-6-phosphate dehydrogenase however, some races are genetically predisposed to this condition. The tendency for hemolysis follows the sickle cell trait in Blacks, and also people from the Eastern Mediterranean. Approximately 10% of US blacks have the trait (Booth & McDonald, 1985).

Drug interactions should be a concern because most sulfonamides are highly protein bound which makes them a substance that can displace substances making those substances toxic or be themselves displaced and produce toxicity. The other source of drug interaction is their nature as sulfonamides (Booth & McDonald, 1985). They could also enhance the action of furosemide, thiazide diuretics, sulfonylureas (antidiabetics), or carbonic anhydrase (enzyme)

inhibitors"(Booth, McDonald 1985. 1040). This is important for patients taking a diuretic, because of the danger of dehydration or cardiac arrhythmia's.

Rifampicin

"Rifampicin is the most effective anti-leprosy drug and brings down the morphological index in lepromatous leprosy to zero in about five weeks" (Bryceson & Pfaltzgraff, p. 82). "Rifampicin is an exceptionally potent bactericidal agent against M. leprae. "A single dose of 600 mg is capable of killing 99.9% or more of viable organisms" (Bryceson & Pfaltzgraff, p. 82). However, the rate of killing is not proportionately enhanced by subsequent doses. It is also possible that rifampicin exerts a delayed antibiotic effect for several days, during which the organism is incapable of multiplying. The high bactericidal activity of rifampicin makes a once a month application of the drug feasible and cost-effective for leprosy control programs (Yoder & Ross, 1998).

Although bacteria are rapidly killed, the rate of fall of the bacterial indexes, the speed of the clinical improvements and the incidence of type 2 reaction in lepromatous patients are the same as with dapsone (Bryceson & Pfaltzgraff). Rifampicin has two drawbacks. It is very expensive, and it may produce toxic syndromes. Its toxicity depends both on the dosage (renal failure and hepatitis being more frequent with

large doses) and on the interval between doses (fever, heamolytic anemia and thrombocytopenia being more frequent when the drug is given at weekly intervals). No toxic effects have been reported with monthly administration (Bryceson & Pfaltzgraff).

Rifampin is active against microorganisms of the genus Mycobacterium, including M. tuberculosis, M. kansasii, M. marinum, M. avium complex, and M. leprae. Rifampin is also active against some gram negative bacteria including N. meningitidis and H. influenzae type b, in addition to some gram positive bacteria including S. aureus and S. epidermidis (Bryceson & Pfaltzgraff). Because of rapid emergence of resistant strains, rifampin's use is generally recommended in combination with other antibacterial agents. Rifampin inhibits DNA dependent RNA polymerase activity in susceptible cells" (Bryceson & Pfaltzgraff, 1990, p. 78). Specifically, rifampin interacts with bacterial RNA polymerase. This is the probable mechanism of action by which rifampin exerts its therapeutic effect. Pharmacokinetics: Rifampin is readily absorbed and peak blood concentrations are reached between two and four hours following the oral administration of a 600 mg. dose (Bryceson & Pfaltzgraff, 1990). Absorption of rifampin tends to be delayed if the drug is taken after food (Bryceson & Pfaltzgraff, 1990). Rifampin is distributed throughout the body and is detectable in many organs and body fluids, including the cerebrospinal fluid, where

concentrations are also increased if the meninges are inflamed. High concentrations are found in the liver, bile and urine (Pattyn, 1984).

Approximately 80% of rifampin in the blood serum is bound to protein. Rifampin crosses the placenta and is excreted in breast milk, and is contraindicated for pregnancy and breast feeding mothers (Bryceson & Pfaltzgraff, 1990). In normal subjects the serum half-life of rifampin is approximately three hours with variations from one to five hours. Neither the peak concentration nor the half-life of rifampin in the blood is significantly altered in patients with impaired or absent renal function. These parameters are, however, increased in patients with impaired liver function or bile flow obstruction. The principal metabolite of rifampin, desacetylated rifampin. "Desacetylated rifampin retains to a large extent the antimycobacterial properties of rifampin, and is detectable in the blood, bile and urine following an oral dose of rifampin"(Bryceson & Pfaltzgraff, p.78). Rifampin and its metabolized factor are excreted principally by the liver into the bile; however, the maximum excretory capacity of the liver is surpassed at doses larger than 5 mg/kg (Bryceson & Pfaltzgraff, 1990). In contrast, the amount of rifampin excreted by the kidney in the urine is proportional to the concentration of the drug in the blood and high urinary concentrations result with recommended dosages (Bryceson & Pfaltzgraff, 1990). Other

indications for rifampin are for active cases of tuberculosis, whether it is in the primary or chronic phase (Bryceson & Pfaltzgraff, 1990).

"To prevent or delay the emergence of drug resistance, rifampin must be used in combination with at least one other effective antitubercular drug" (Pattyn, 1984, p.6). "Choice of appropriate drug combinations should be based on in vitro sensitivity studies, comparative safety as well as the patient's previous clinical history" (Pattyn, 1984, p.6). Also used for prophylaxis of selected individuals exposed to persons with invasive disease due to N. meningitidis and H. influenzae type b (Bryceson & Pfaltzgraff, 1990, p. 78).

The contraindications for refampin are usually jaundice (Baohong, 1984). Also, hypersensitivity to rifamycins is common. "Premature and newborn infants, in whom the liver is not yet capable of functioning with full efficiency, will usually experience jaundice. Rifampin has been shown to produce hepatic dysfunction in both the newborn and adult patients" (Baohong, 1984, p. 287). There have been fatalities associated with jaundice in patients with preexisting liver disease or in patients receiving rifampin in combination with other hepatotoxic agents (Pattyn, 1984). Predisposing factors include chronic liver disease and alcoholism. Therefore, the benefits, must be weighed carefully against the risk in individuals with impaired liver function.

For this reason, it is essential that liver function be regularly assessed, in patients, with impaired liver function.

"Rifampin may precipitate acute adrenal crisis in persons with adrenal insufficiency, possibly resulting from increased cortisol metabolism secondary to hepatic microsomal enzyme induction" (Pattyn, 1984, p123). In pregnancy rifampin crosses the placenta so the unborn fetus must be considered and its stages of development. Reproductive and fetal toxicity studies in rats and mice with rifampin alone, have indicated teratogenic (deformity in the developing embronic stage) effects. The most common is known as spina bifida and cleft palate at rifampin doses of 100 mg/kg and above. Although the effect of rifampin alone or in combination with other antitubercular drugs on the human fetus is not known, the drug has been used (combined with isoniazid and/or ethambutol) to treat clinical tuberculosis in pregnant women (Pattyn, 1984). Generally, rifampin should not be used in pregnant women. However, if rifampin therapy is judged to be essential, such treatment should be implemented, only after carefully weighing the potential benefits of therapy against the risks which may be involved, particularly from use during the first three months of pregnancy (Pattyn, 1984).

In women with childbearing potential, treatment with rifampin should be undertaken only when the possibility of pregnancy during

therapy is judged to be remote. Oral contraceptive therapy has have not proven to be effective at times so alternative or additional contraceptive measures are essential in women who are receiving rifampin (Pattyn, 1984). When administered during the last few weeks of pregnancy, rifampin has been shown to cause post-natal hemorrhage in the mother and infant, therefore vitamin K should be given during labor to mothers receiving rifampin and to their offspring immediately after birth. In the newborn, careful surveillance for bleeding symptoms and decrease of coagulation factors is mandatory (Merek, 199). During lactation, rifampin transfers into breast milk in limited amounts, but is considered to represent a low risk to the nursing infant (Bryceson & Pfaltzgraff, 1990).

Some precautions are the urine, feces, saliva, sputum, sweat and tears may be colored reddish orange by rifampin and its metabolites. To prevent undue anxiety, patients should be made aware of this possibility. Soft contact lenses should not be worn during rifampin therapy as they may become permanently stained (Bryceson & Pfaltzgraff).

"Daily treatment with rifampin is often better tolerated than intermittent therapy, since rare hypersensitivity reactions may occur" (Bryceson & Pfaltzgraff, p. 77). Resumption of treatment after termination of a course of long-term therapy with the drug involves

risks and therefore, should if possible, be avoided (Bryceson & Pfaltzgraff). If unavoidable, possible adverse reactions may be minimized if the drug-free interval or rest period is less than or closely resembles the interval of the previous drug treatment period. "When resuming treatment with rifampin, the drug should be re-introduced gradually, beginning with a daily dose of 75 mg and increasing the dose by 75 mg daily until the required dosage is reached" (Bryceson & Pfaltzgraff, p.78). During the transitional period, renal and hepatic function should be closely monitored.

Corticosteroids may be useful in preventing adverse reactions since antigen-antibody complexes are suspected causes (Bryceson & Pfaltzgraff,1990). If as may happen in exceptional cases, the patient develops thrombocytopenia, purpura (a group of disorders characterised by brownish or purplish coloration), hemolytic anemia, or renal failure, treatment should be stopped at once and not re-instituted at a later date. Rifampin should be used with caution in patients with porphyria as it could induce delta-aminolaevulinic acid synthetase activity (Pattyn, 1984).

The drug interactions since the multi drug therapy of Hansen's disease involves the use of at least two drugs, the possible adverse reactions of each drug should be considered as well as a possible interaction of the drugs when used in combination of the other drugs.

Caution is recommended when instituting therapeutic regimens, in which isoniazid is to be used concurrently with rifampin, in patients with impaired liver function, the elderly and malnourished. Hepatotoxicity has been reported to occur more frequently when rifampin and isoniazid are given concurrently. The incidence may be higher in slow isoniazid acetylators, those receiving high doses of isoniazid, prior general anesthesia and those with pre-existing liver disease. Rifampin is a potent inducer of hepatic drug metabolism (cytochrome P-450). As a consequence, the rate of metabolism of numerous drugs can be accelerated, which can result in reduced pharmacological effects of the drugs involved or toxicity when rifampin is discontinued.

Adjustments in the dosage and monitoring of the effects of these drugs is therefore necessary when used concomitantly with rifampin. This is particularly important when rifampin administration is either initiated or withdrawn. The effect on enzyme induction may develop gradually over several days after starting rifampin and may take even longer to dissipate after withdrawal of rifampin (Bryceson & Pfaltzgraff, 1990).

Some adverse side effects that may occur when taking rifampin are: sore mouth, sore tongue, dyspepsia, epigastric distress, anorexia, nausea, vomiting, gas, cramps and diarrhea have been noted. There

have been isolated cases of pseudomembranous colitis have been reported. Also headache, drowsiness, fatigue, ataxia, dizziness, inability to concentrate, mental confusion, visual disturbances. Dermatological side effects include ururitus, urticaria, skin rashes, have occasionally been encountered. Hepatic side effects usually are transient abnormalities in liver function tests (elevations of serum bilirubin, alkaline phosphatase and serum aminotransferases) have been observed. In isolated cases, induction of porphyria has been noted. A few cases of jaundice with evidence of hepatocellular damage have been reported in some patients receiving rifampin (Pattyn, 1984). In some of them it was possible, to resume rifampin treatment without recurrence of abnormalities.

Hypersensitivity reactions include a flu-like syndrome (fever, chills, dizziness, pain in extremities, dyspnea), have been noted. Hematuria, renal insufficiency and acute renal failure have also occurred infrequently. These hypersensitivity reactions are usually associated with high-dose intermittent rifampin therapy (900 to 1 200 mg twice weekly) or resumption of treatment after termination of a course of long-term therapy (Pattyn, 1984). Some miscellaneous disturbances of menstruation including breakthrough bleeding, spotting, amenorrhea (stopping of menstral periods), and prolongation of both the menstrual interval and menses have been reported in

women taking rifampin either alone or in conjunction with oral contraceptives. Elevations in serum urea and serum uric acid have been reported (Pattyn, 1984).

Rifampin objective dosage is to ensure optimal absorption, rifampin should be taken on an empty stomach (1 hour before a meal). Should intolerance occur, the daily dosage may be taken after meals and/or reduced. In general, therapy should be continued until at least bacterial conversion has been established and maximum clinical improvement has occurred. Rifampin may also be administered twice weekly at the above doses as part of a directly observed therapy program following an initial phase of daily treatment during the first one to two months. Rifampin when used for the treatment of Hansen's disease is in combination with at least one other antileprosy agent. The adult required dose is 600 mg once daily or once monthly for a minimum of 6 months (for paucibacillary leprosy) to 2 years (for multibacillary leprosy) or until smear is negative (Merck Index, 1989).

Clofazimine

Clofazimine, one of the drugs used in WHO MDT is virtually nontoxic in the dosage used for MDT but the drug causes brownish-black discoloration and dryness of the skin, nevertheless, this disappears several months after stopping treatment (Cunha, 1999).

Clofazimine is unique in the treatment of Hansen's disease, as it has an action equal to that of dapsone, and also acts as an anti-inflammatory effect which is of value in reactional states of the disease. Clofazimine is a red crystalline substance in which is suspended in an oil/wax base and marketed in gelatin capsules of 50 to 100 mg (Cunha, 1999).

The drug is best absorbed after food and is distributed unevenly in tissues, high concentrations being reached in intestinal mucosa, lymph nodes and fatty tissue. The serum half-life is about ten days but the tissue half-life may be as long as 70 days. A steady state is reached after about six weeks. Because of the uneven distribution its MIC (minimum inhibitory concentration) cannot be calculated (Bryceson, Pfaltzgraff, 1990). Resistance to clofazimine is very rare. The drug was used on its own for many years to treat dapsone resistant patients. Its precise mode of action is not known, but it probably interferes with the mycobacterial DNA (Bryceson & Pfaltzgraff, 1990).

Clofazimine is used in treatment of lepromatous leprosy, including dapsone-resistant lepromatous leprosy and lepromatous leprosy complicated by erythema nodosum leprosum, and for treatment of other leprosy-associated inflammatory reactions (Merek, 1989). Clofazimine does not show cross-resistance with dapsone or rifampin; preliminary data which suggest that dapsone may inhibit the anti-inflammatory activity of clofazimine have not been confirmed. (PDR,

1993). Generally, clofazimine is well tolerated when doses not exceeding 100 mg/day are used. Clofazimine may cause skin pigmentation (pink to brownish-black) in 75 - 100 percent of the patients within a few weeks of treatment. Other adverse reactions may include ichthyosis and dryness, rash and pruritus (itching), abdominal and epigastric pain, diarrhea, nausea, vomiting, gastrointestinal intolerance, conjunctival and corneal pigmentation (due to Clofazimine crystal deposits)(Merek, 1989).

Multi drug therapy (MDT)

"Multiple drug therapy (MDT), consisting of dapsone, rifampicine (Rimactane®) and clofazimine (Lamprene®) is able to change the course of the disease dramatically" (Ellard, 1984, p. 394). It has been the cornerstone of the World Health Organization's leprosy control policy since 1982. By killing the bacilli MDT interrupts the chain of transmission, and by curing very rapidly it prevents mutilations and deformities (WHO Expert Committee, 1988). The 70-80% of cases who have paucibacillary leprosy (PB), i.e. are non infectious, and can be cured within six months. The remaining 20-30% who have the multibacillary form (MB), are curable within one year. "In most cases visible improvements can already be observed at the outset of MDT, encouraging patients to comply with the treatment" (Ellard, 1984, p. 394).

Novartis developed two of the three drugs used in multiple drug therapy. A calendar pack simplifies dispensing of the medicines, improves patient compliance, and protects the tablets against heat and moisture (Bryceson, Pfaltzgraff, 1990). It is the best combination available today, and has proven by its successful application, in leprosy control under varying conditions since 1982. The combination not only cures leprosy but is also highly cost-effective (Ellard, 1984). The recommended standard regimen for multibacillary (MB) leprosy are: Rifampicin: 600 mg. once a month Dapsone: 100 mg. daily Clofazimine: 300 mg. once a month, and 50 mg. daily. The duration for this treatment is 12 months. The recommended standard regimen for paucibacillary (PB) leprosy is: Rifampicin: 600 mg. once a month Dapsone: 100 mg. daily and the duration for this treatment is six months. Children should receive appropriately reduced doses of the above drugs.

In developing the WHO MDT regimens, three main principles were adhered to: rifampicin should be one of the components of MDT rifampicin 600 mg. should be given at least once a month to all patients. At least two anti-leprosy drugs should be used in the MB regimen and one anti-leprosy drug should be used in the PB regimen, in addition to rifampicin, this would prevent the occurrence of rifampicin-resistant M. leprae (WHO Study Group, 1982).

Treatment is given for two years or 24 months in a 36 months period, or until the skin smear become negative. Treatment should never be less than 24 months. The thioamides are used if drug intolerance develops or if clofazimine is refused because of the discoloration of the skin.

When MDT has been completed, the patients with paucibacillary disease are seen every six months for two years and with multibacillary disease for at least five years. Patients are questioned and examined for evidence of activity or reactivity, and slit skin smears are carried out on multibacillary patients (McDougall, 1988). The average patient has one serology examination of the blood, during the year, and at the rate for the year will have his next spinal fluid serologic test at that time. His blood, will be examined, specifically for malaria once in 2 1/2 years, and the parasites will be found if present in once in 50 years (Fite, 1945).

The benefits of MDT if properly implemented would be to prevent drug resistance, treat pre-existing dapsone resistant infections, and eliminate the need to determine the sensitivity of M. Leprae before starting the treatment. Another benefit of MDT is to shift the concept of treatment from prolonged treatment that merely arrests the disease, to a short course of treatment that cures the disease. By boosting morale and making treatment regiments compatible with the patient, patient

compliance can and will be achieved. Other benefits are the prevention of deformities, the patients before non-infectious more quickly and long-term costs of the control programs are reduced. (Bryceson, & Pfaltzgraff, 1990).

The development of multi drug therapy has taken many years and has overcome many obstacles. Treatment for any disease is not just prescribing drugs or placing a patient on a special diet. Treatment is any act or care, method or manner given to someone or something (Watson, 1978). With Hansen's disease patients, their treatment throughout the ages has been of isolation, torment and even death. Their families have also suffered with them, in some cases their houses were burned with all their belongings. Patients have been forced to divorce their spouses and give up their children. Other married patients were told if they had children they would be taken from them at birth and turned over to the state.

Only since the 1940's has the hope for a cure become a reality. This study has tried to research the various methods of treatment and various drugs which has brought about the development of multi drug therapy. By reviewing what has been done in the past and the treatment patients have endured it may help in discovering what successful combination of drugs along with health education and patient support can eradicate Hansen's disease.

CHAPTER V

DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

This chapter will present a general summary of the study, the themes that emerged, summary of the treatments, a conclusion, and recommendations for future research. In addition, a section on how health educators can become involved in the care and treatment of the Hansen's disease patient, their families, and the community.

Patients and doctors have struggled to find a cure for Hansen's disease, hoping to stop it's ugly deformities. As Hastings describes, "it took many centuries for the treatment of Hansen's disease to pass from the horrific to the scientific, from the repeatedly efficacious bathings in the blood of infants under two years to the administration of synthetic mycrobacteriostic drugs" (Hastings, p.9). Many "cures" have been tried with disappointing effects.

Experimental treatments were not new in Carville. Since there was no specific treatments or guidelines for the disease, many patients were eager to try anything. For example, in 1933, a young Mexican girl who lived in Cottage Thirty-one was deported to Mexico, and from a leprosarium there, wrote back about some patented Mexican preparation that was bringing about wonderful "cures." A

group of Carville patients, without the doctors knowledge, sent for the drug. A patient who had some infirmary experience gave the injections. The treatment was not only a failure, but it had aggravated the disease.

Another example came in 1935, when fever therapy was a fad as a cure-all. The doctors reasoned that since patients seemed to improve after severe reactions, the high fever these reactions caused might be the thing that helped destroy the bacilli. Spurred on by this theory, plus the patients' eagerness to try it out, an experiment was launched. Seventeen patients were carefully selected from the volunteers and taken to the Marine Hospital in New Orleans where the experiments were carefully conducted. Out of the seventeen patient volunteers, thirteen got worse, two died of other causes, two remained stationary, and one was later discharged (Harmon, 1999).

> The Willow-Bark Era came when an elderly patient who had been in Carville for some years hit upon the idea that tea made from the willow bark would be helpful in treating the disease. He tried some himself and improved a little, and when word got around, the place there was a rush to the woods where the patients skinned clean every

willow tree within a half-mile radius. As the originator of the idea stopped improving and began to worsen, other experimenters lost their enthusiasm and the willow bark cure died with the hopes of the patients that tried it (Stein, 1963).

Alophan, a carotene preparation, was yet another experiment. Alophan, produced by a South American pharmaceutical house, it was used extensively in a leprosarium in Brazil. It was given intramuscularly daily. The South American workers reported favorable results in the clearing up of lesions and sent a large supply for experimental use to Carville. Evidently a handful of patients tried this treatment but without satisfactory results; it was soon discontinued (Martin, 1951).

Some leprosariums claimed remarkable results from chaumooan, a proprietary preparation of the ethyl esters of chaulmoogra oil. That too had failed the victims of Hansen's disease.

Then came the new sulfa experiments and that was met with mixed emotions. When Dr. G.H. Faget arrived at Carville,

he authorized the use of the sulfa drugs. In response, a group of nine Hansen's disease patients began using the new drug called sulfanilamide. The treatment was strenuous and several patients showed temporary improvement. During this study only two of the nine patients were able to complete the study because the drugs were too toxic for the others to continue (Martin, 1951).

Soon after the sulfa treatments were implemented at Carville, Dr. D.R. Collier's diphtheria toxoid treatment for leprosy was given wide publicity. Dr. Collier believed that there was a close biologic relationship between leprosy and diphtheria. He hypothesized that diphtheria toxoid injections would stimulate the production of diphtheria antitoxins in the patient, which would react by neutralizing leprosy toxin. A small group of Carville patients were started on the treatment. The experiments continued, but hope was still with the sulfa drugs in spite of their toxic effects (Martin, 1951).

The World Health Organization was excited about the success of the sulfa drugs but had reservations on the long term effects and their toxicity.

> While progress had been made in expanding leprosy control programmes, the twin constraints of dapsone resistance and bacterial persistence were causing serious operational problems and a feeling of uncertainty regarding the future of leprosy control programmes. There was therefore an urgent and imperative need for recommendations on globally applicable therapeutic regimens based on research efforts from all over the world and on the operational and logistic constraints in the field" (WHO, 1982, p.7).

Stanley Stein, a patient at Carville and editor of the Star Magazine realized in order to have an effective cure drug therapy and health education, along with an informed public needs to be in place. He stated: "In order that leprosy may be dealt with successfully on a

> comprehensive scale and before any large proportion of early cases will come voluntarily for examination, there must be a change in the attitude of the public towards the disease. Any scheme for the control of leprosy will depend for its success on an educated public opinion" (Stein, 1950, p.126).

The Star published the Recommendation of the World Conference on Leprosy, Cairo, Egypt, March 1938. It stated "the medical world

> classes Hansen's disease as 'feebly communicable,' but susceptibility is much greater in infants and young children, and decreases with age. It is also probably that in most cases the susceptibility is familiar. In the United States, endemic foci are limited to Louisiana, Texas, and Florida. Outside of these states, Hansen's disease is so rarely communicated to contrasts that from the public-health standpoint it might be considered as practically a non-communicable disease. The hospital at Carville was founded fifty-four years ago. To date not a single member of the medical or nursing staff has contracted the disease.
>
> Doctors and nurses take very simple precautions, not comparable with those they would take in dealing with diphtheria, typhoid, and other communicable disease.
>
> Visitors are admitted freely, nor are they required to take any special precautions. Children under ten are not

admitted. Patients are permitted to visit their homes semi-annually for periods of a month.

Facts, based on actual experience over a long period of years (the most valid scientific yardstick), furnish indubitable proof of the remoteness of the communicability of Hansen's disease.

Since Hansen's isolation of the bacillus, hundreds of attempts have been made to grow it in artificial media, but to date none of these have successfully met the requirements for proof, and all attempts for inoculations of animals have been unsuccessful to the same extent. No scientist in more than 145 recorded cases have been able to infect him or other human volunteers by attempted inoculation of the germ. THE TRANSMISSION OF THE DISEASE IS THE BIG PROBLEM in Hansen's. Once that is determined, the 6,000-year-old practice of imprisoning a person for life because he happens to be sick will be done away with.

This paper and all outgoing mail are sterilized before leaving the hospital. This is done only as a gesture

> of respect to the unconvinced and not because there is any scientific necessity for it. (The Star, 1950).

In the above quote, the doctors and patients knew Hansen's disease could not be transmitted through the casual contact with newsprint but they still thought it was necessary to remind their readers the magazine was sterilized. They did this for the consideration of their readers but this was contradictory to the cause to educate the public about the susceptibility and transmission of Hansen's disease.

Hansen's disease still remains a public health problem in thirty-two countries, although just sixteen of these account for 92% of the Hansen's disease cases in the world (WHO, 1998). Hansen's disease afflicts the poorest strata of the population most of all; approximately 600,000 new cases are detected each year, all of whom must be treated if we are to stop the disease from continuing on its destructive course (Novartis Foundation for Sustainable Development, (1999).

Dapsone seemed to be the cure but after many year of treatment Hansen's disease patients were developing a drug resistance. This became a global threat. Many prominent leprologists started looking for alternatives. After extensive tests in the mouse

foot pad in the early 1970's quite a few therapeutic trials were launched in the late 1970's.

> Dr. Groenen wrote: "I was fortunate to be able to collaborate with Professor Pattyn of the Tropical Institute, Antwerp, Belgium. We know, that we had to give combined therapy, and we wanted it to be as short as possible, because, one of the reasons why Dapsone had led to problems, was its extremely long therapy duration, from five years for TT and ten years for BT, to life long for others. We had at our disposal four drugs: Dapsone, Clofazimine, Rifampicin and Ethionamide. The first regimens were tested were 1 year for PB (two drugs) and also one year for MB (four drugs). Patients were very closely monitored clinically, bacteriologically an anatomopathologically. When a problem of hepatotoxicity was discovered with our MB regimen, we right away changed to Prothionamide and reduced the dosage. We found that our regimens worked. The next step: let's reduce more. We gave 10 weeks to PB and 3 months to MB. Again, it worked. Then we gave single dose Rifampicin to PB and one month to MB. The one-month did not work the

single dose PB worked well for patients with only one or two lesions."

In the meantime, WHO MDT had been launched by Geneva. The doctors in Zaire, were very much into their rigorous therapeutic trials, and were not happy about the WHO just moving in and prescribing a treatment which had little testing. Dr. Groenen states: The WHO just moved in, with all

> its authority, to say: 'this is the answer to all our problems.' However, we asked: How do you know? All the regimens we were testing were based on initial mouse foot pad tests, a strict protocol was developed, totally randomized, and we followed up on our patients very regularly and for many years. We thus felt we could tell a thing or two about new treatment regimens.

According to Dr. Groenen, the "WHO had locked up a few wise men in a room and let them out only when they had come up with an answer to the threat of spreading Dapsone resistance." It was frustrating for the doctors in the field who had been testing different theories and treatments with scientific procedures and not to be consulted on a new therapy which was to change the treatment of

Hansen's disease patients. It turned out the WHO was correct in their assumptions and multi drug therapy was the answer to drug resistance and drug tolerance. Even though the drug regime was correct the doctors in the field still had doubts about the testing of the drugs and whether there was sufficient field study before this was implemented. Dr. Groenen continues, In Zaire, we felt we could not

> just start an untested regimen because some big shot in Geneva told us to. We thought this was unethical, and potentially dangerous. We thus decided to subject the WHO MDT regimens to the same rigorous protocol as the other regimens we were testing. We randomly allocated patients to one of our regimens or to MDT. We found that MDT was well tolerated and was able to cure the patients, but we also found it was difficult to ensure monthly rendezvous, and we also found that the MB regimen, then given until smear negativity, was way too long. Our conclusion was: the MDT regimens are therapeutically OK, but there are operational problems. It is thus necessary to continue to look to better alternatives, i.e. the shortest possible effective combined regimens. But this was not accepted by WHO, who, using all kinds of pressure, made us stop our trials.

With the advent of multiple drug therapy (MDT), recommended by the World Health Organization (WHO), the Hansen's disease situation has changed dramatically. MDT cures the disease in a short time, interrupts the chain of transmission, and thus holds out the possibility of eliminating Hansen's disease for good. The widespread use of MDT already has cured millions of people. The estimated number of registered Hansen's disease cases fell from 5.5 million in 1991 to 1.8 million in 1995 (a 67% reduction). There is still a number of cases that are undiscovered so the actual number is thought to be very much higher (WHO,1998).

The World Health Organization's goal to eliminate Hansen's disease by the year 2000 is defined as only one case per 10,000 inhabitants. If this goal is to be achieved, an estimate 6-7 million cases will have to be detected and treated. The 1997 prevalence rate in the 16 most endemic countries was 3.3 cases per 10,000.

Whether the goal of eliminating Hansen's disease will be reached depends first and foremost on whether national political support and the resources required can be mobilized. The following barriers must be addressed:

- The low priority given to Hansen's disease control

- The poor infrastructure of health care system
- The shortage of adequately trained personnel
- The stigma of Hansen's disease is still attached to leprosy
- The unfamiliarity of general health cares providers with early symptoms of the disease and more.

Dr. S.K. Noordeen, Retired Director of the Action Program for the Elimination of Leprosy (LEP) said in New York: "Time is short. If the goal is to be reached on time, there can be no slackening on the part of governments, ministries of health and health workers in the field of leprosy everywhere. The world cannot afford to miss the present window of opportunity to put paid to this centuries-old disease and the unjust stigma that is attached to it" (WHO 1997, Press Release).

MDT does not work when only one drug is used because of development of drug resistance to that drug. This is why Rifampicin, Clofazamine, and Dapsone are used together. Rifampicin is used once a month and has no toxic effects; however, urine will be slightly colored red after the first treatment. Clofazamine is most active when given daily and is well tolerated and virtually nontoxic in the correct dosage for MDT. The drug has a side effect; it causes brownish, black

discoloration and dryness of the skin. Dapsone, given orally, is the safest drug and has very few side effects, except for allergic reactions. Dapsone was the main anti-leprosy drug, but in the 1960's Clofazamine became available. This duo of Dapsone and Clofazamine proved to be invaluable in treatment of Hansen's disease patients. Once again a new drug was introduced, this time it was Rifampicin, in the 1970's Rifampicin is now the main bacterial drug used in MDT (Novartis Foundation for Sustainable Development, 1999).

MDT kills bacilli, which interrupts the chain of transmission, and cures the disease before any serious nerve damage happens. Because of the danger of emergence of drug-resistance microbacteria lepra bacilli, treatment must be given regularly. Although MDT sounds very expensive, it is the most cost-effective form for preventing disabilities due to Hansen's disease.

MDT works so well and fast that 70-80% of those who have Paucibacillary Hansen's disease and are noninfectious can be cured in six months. The remaining 20-30% who has Multibacillary Hansen's disease can be cured in two years. The fast action of MDT shows immediate improvements, encouraging the patient to go on with the treatment (Novartis Foundation for Sustainable Development, (1999).

Dr. Grosset stated since MDT was introduced at the WHO Study Group on chemotherapy of leprosy for control programms that was convened in Geneva on 12 - 6 October, 1981. "Those who convened the study group in Geneva were Dr. H. Snasarricq, Director of the WHO leprosy unit and Dr. Louis Levy, Chairman of THELEP steering committee". "The recommendation was based on the following points: 1.) Leprosy like tuberculosis is an infectious disease due to mycrobacteria. 2.) In lepromatous leprosy as in pulmonary cavitary tuberculosis, the size of the microbial population is large: 10^8 organisms or more. 4.) Mono therapy of lepromatous (multibacillary) leprosy results in the development of drug resistance.

"By analogy with tuberculosis, the members of the WHO study Group considered that multi drug therapy of lepromatous leprosy would prevent the selection of drug resistant mutants. Because their reasoning was right, their recommendation was right: my only contribution was to be one of these members. Of course, the recommended duration of therapies and the recommended rhythm of drug administration were based on the

research conducted by C.C. Shepard and Rees, and on the field experience of many doctors" Dr. Grosset.

Millions are in need of effective MDT chemotherapy. Scientists hypothesize that between now and the year 2000, a total of 7 million people will need to receive MDT (Novartis Foundation for Sustainable Development, (1999).

There are several other possible treatments under study, but none has been approved for generalized use as of yet. These all involve the use of rifampin and one or more of three other drugs, which are very active against this disease: minocyclin, clarithromycin, and ofloxacin. According to Dr. Robert Jacobson, "only the combination of rifampin, ofloxacin and minocycline (ROM) as a single dose for the treatment of single lesion paucibacillary leprosy has been approved for use by WHO to date."

Major challenges to eliminate leprosy as a public health problem, include the following: up to 50% of patients are not receiving any drug therapy. Too many patients are escaping early detection, too many countries lack adequate basic health resources, and many patients disabled by leprosy are still not receiving adequate care. With the United Nations commitment to resources to provide adequate

care, much of the problem will be solved. Some solutions given by various experts to decrease the stigma towards Hansen's disease patients is to stop using the word "Leprosy" and use "Hansen's disease" instead. Another suggestion is education about the disease for the general population.

Despite the advances of modern technology, many people continue to hold old and outdated belief about Hansen's disease. Many still believe that Hansen's disease is not curable and the only way to protect the public is by quarantine and isolation.

The treatment of people with Hansen's disease is similar to the treatment of those affected by other epidemics. An example today is AIDS. Society perceives transmission and risk of both diseases, in many cases, incorrectly, which gives rise to stigma in both cases. The solution in is better education. Today, Hansen's disease as a public health problem is well on the way to being controlled. According to some experts, the disease remains not only the subject of misunderstanding, but at times mishandling. "MDT needs supervision and public health field workers willing to go to the patients to make sure they are taking the antibiotics," said Hansen's Hospital's Wexler, adding that Hansen's disease patients are no longer

hospitalized because there is no need. (The only patients who stay permanently at Hansen's Hospital are those who have been there many years and would have trouble moving).

Another reason the disease hasn't been eradicated is that the treatment programs are not always managed well, said Dr. Hillel Bercovier. According to Dr. Bercovier, a professor of micro and molecular biology at the Hebrew University of Hadassah Medical School in Jerusalem, the MDT regime is so efficient-both in treating and preventing Hansen's disease- that he strongly endorses the WHO's disease elimination policy. He also believes that through MDT, and not continued scientific research, leprosy can be eradicated and relegated to medical textbook history"(Bercovier, 1999).

Recommendations

This study identified the development of multi drug therapy for the treatment of Hansen's disease. In the research and literature there is an overwhelming fact that Hansen's disease has a stigma which instills fear in the patient, the patients family, and the community. Hansen's disease is not easily transmitted as is syphilis. Hansen's disease is not deadly as is some form of cancers. Hansen's disease is not caused because the patient committed a sin. Hansen's

disease is curable, most people are immune to it and it is not a curse from God, however, the Hansen's disease patients are isolated, shunned and discriminated against. Health educators have an opportunity and responsibility to educate the public about Hansen's disease. The stigma needs to be erased from this disease. Patients not only suffer from the drugs, the bacilli they have to face their families and communities that do not understand. If more communities knew the truth about Hansen's disease, more cases would be detected. Many patients hide because of the fear of the disease, and the stigma attached to it. Health educators need to get the word out this is a curable disease when diagnosed and treated, and if caught in the early stages no visible signs of deformities may result.

A better understanding is required of the economic, social and cultural factors which influence MDT coverage, case finding, compliance, and other aspects which may promote or impede the Hansen's disease programs. The treatments the Hansen's disease patient had to endure to arrive at one effective treatment has been horrendous. Early diagnosis, early treatment, and patient compliance are needed to eradicate this disease from this earth.

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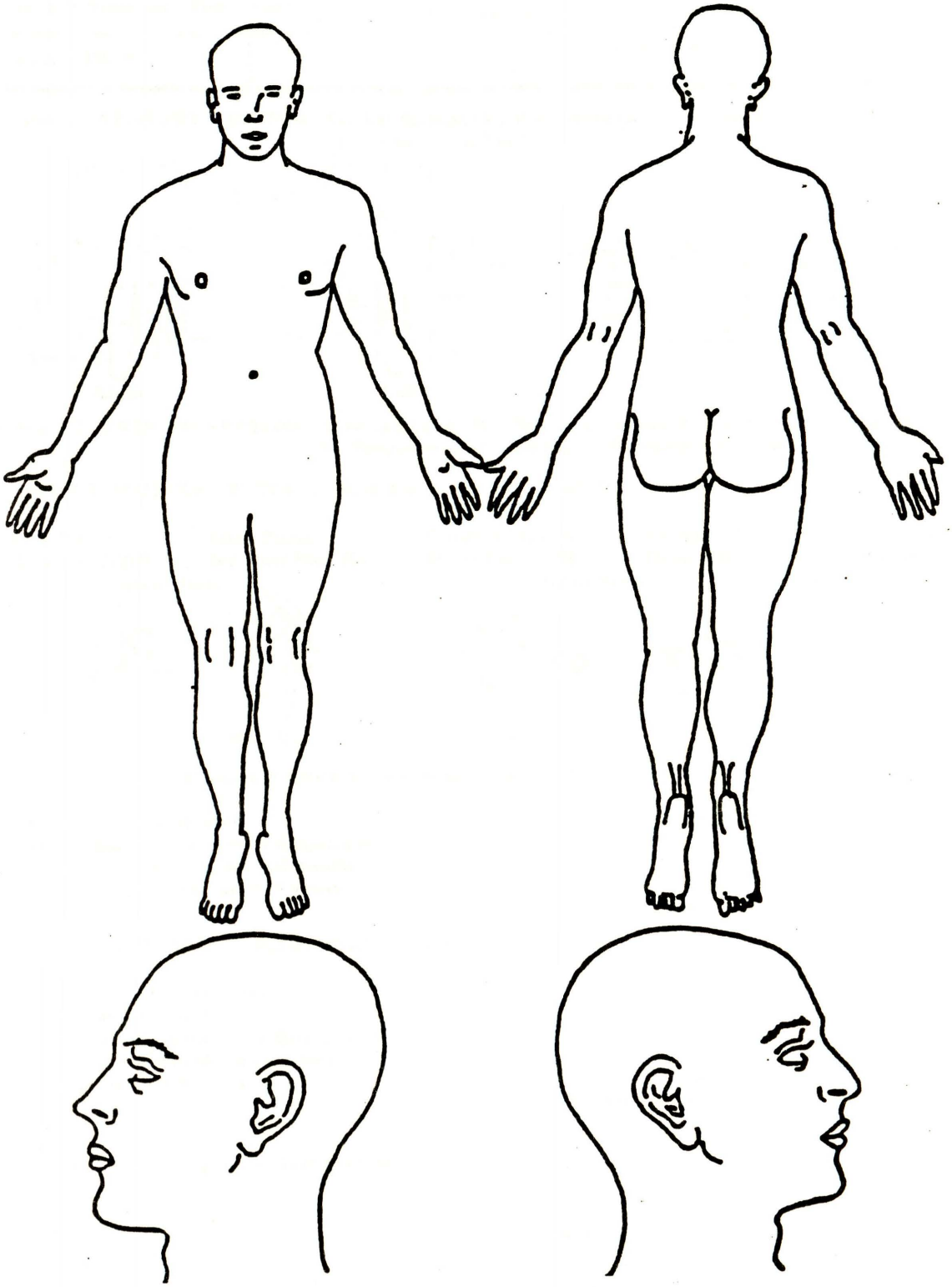
APPENDIX A

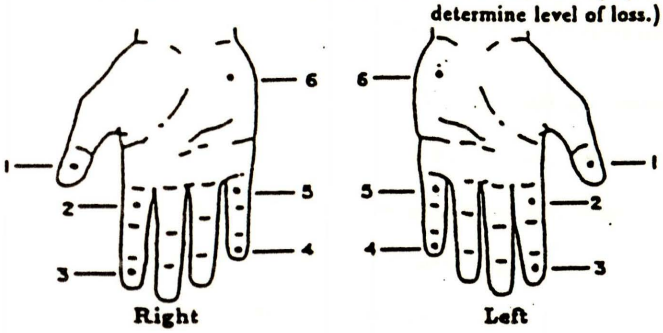
Skin Smear/Biopsy Charts

27. Patient's Name:_____ Date of Examination _____



REGIONAL HD CENTER		HAND SCREEN RECORD	Date:
Patient's Name(Last, First, Middle)_____			HD ID No:
Patient's File No:	Medications:	Date of Disease Onset:	Initial_____ F/U_____

Section I. SENSORY TESTING: Use first filament (A) at site indicated. (If no response, use next heavier to determine level of loss.)



Filament	Force, gms	Interpretation
A (Green)	0.05	(normal)
B (Blue)	0.20	(residual texture)
C (Purple)	2.00	(residual protective sensation)
D (Red)	4.00	(loss of protective sensation)
E (Orange)	300.00	(residual deep pressure)

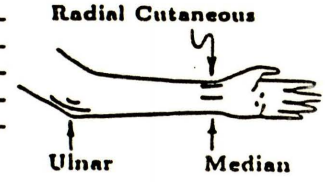
Section II. SKIN INSPECTION: Draw and Label: W - Wound, C - Callus, S - Swelling, R - Redness, D - Dryness T - Temperature, M - Missing, J - Contracture, O - Other

Section III. MUSCLE TESTING: (Mark S = Strong, W = Weak, P = Paralysis)

Index Finger Abduction (FDI)	Little Finger MP Joint Flex. (L)	Thumb Abduction Out of Palm (APB)	Thumb to Little Finger (OP)	Radial Wrist Extension (ECR)
Ulnar Nerve		Median Nerve		Radial Nerve
R__ L__	R__ L__	R__ L__	R__ L__	R__ L__

Section IV. PERIPHERAL NERVE RISK: (Mark U, M, or UM)

1. Enlarged or swollen nerve	R__ L__
2. Tender/painful on stretch or compression	R__ L__
3. Sensory change in the last 6-12 months	R__ L__
4. Muscle change in the last 6-12 months	R__ L__
High Risk:	Yes__ No__



Section V. DEFORMITY RISK: (Check if present)

1. Loss of Protective Sensation	R__ L__
2. Clawed but Mobile Hand	R__ L__
3. Fingertip Absorption (check Mild__ Severe__)	R__ L__
4. Injuries (open wounds, blisters, etc.)	R__ L__
5. Contracted or Stiff Joints	R__ L__
High Risk:	Yes__ No__

Has there been a change in the hand since the last exam? Yes__ No__

Examined by: _____

Rev. 11/15/80

REGIONAL HD CENTER	FOOT SCREEN RECORD	Date:
Patient's Name(Last, First, Middle)_____		IID ID No:
Patient's File No:	Social Security No:	Initial_____ F/U_____

Fill in the following blanks with an R, L, or B to indicate positive findings on the right, left or both feet.

Has there been a change in the foot since last evaluation? Yes__ No__ N/A__

Is there a foot ulcer now or history of foot ulcer? Yes__ No__

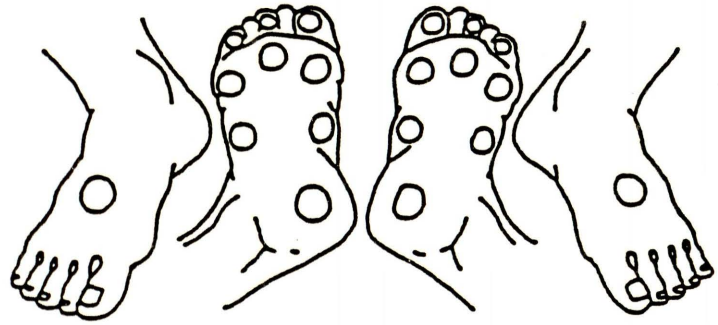
Does the foot have an abnormal shape? Yes__ No__

Is there weakness in the ankle or foot? Yes__ No__

Are the nails thick, too long or ingrown? Yes__ No__

Label: Sensory Level with a "+" in the circled areas of the foot if the patient can feel the 10 gram (5.07 Semmes-Weinstein) nylon filament and "-" if he/she can not feel the 10 gram filament.

RIGHT



LEFT

Draw in and Label: Callus ▨, Pre-ulcer ▩, Ulcer ■ (Note width/depth in cm.)
Skin Condition with R - Redness, S - Swelling, W - Warmth, D - Dryness, M - Maceration

Does the patient use footwear appropriate for his/her category? Yes__ No__

RISK CATEGORY:	__ 0 No loss of protective sensation.			
	__ 1 Loss of protective sensation (no weakness, deformity, callus, pre-ulcer or Hx. ulceration.)			
	__ 2 Loss of protective sensation with weakness, deformity, pre-ulcer or callus but no Hx. ulceration within last 2 years.			
	__ 3 History of plantar ulceration within last 2 years.			
	__ 4 Charcot foot			
Date of Next Evaluation: (Guidelines)	Category 0	One Year _____	Category 2	Six Months _____
	Category 1	One Year _____	Category 3	One to Three Months _____

Rev. 07/19/89

APPENDIX B
Questionnaire sent to Experts

Expert Questionnaire

Directions: Please answer the following questions to the best of your ability. I am looking for your honest and candid answers. If you do not want your name printed with the answers please leave your name off the sheet. I would like to use your name as a reference but would respect your rights and privacy if you choose. If you need more space please feel free to use extra sheets of paper. The answers to your questionnaire will be analyzed through HyperResearch and cited with the correct reference. Also is you would include a vita or short Bio on yourself I will include it in my dissertation.
Note: I understand you have a busy schedule and this will take time I appreciate any effort you can give. Thank you.

1. What contributions did you make in the development of the multi drug therapy in the treatment of Hansen's disease?

2. When were these contributions made?

3. Which aspects of multi drug therapy were most important?

4. Was there a national or international event during the time that promoted more concentration on finding a treatment, which would make patients more compliant?

5. What were some major setbacks or milestones you had to overcome when working with multi drug therapy?

6. Has patient compliance been effected with the new regimes of multi drug therapy compared with the old treatments of Hansen's disease?

7. Do you see any positive aspects of multi drug therapy?

8. Do you see any negative aspects of multi drug therapy?

9. What are other treatments of Hansen's disease that you use if not multi drug therapy?

10. In your opinion do you think multi drug therapy was researched and tested sufficiently before it went on the market? Why? Why not?

11. What are the drawbacks of multi drug therapy?

12. In your opinion what is the patient compliance rate for patients using multi drug therapy?

APPENDIX C
List of Experts Consulted

List of Experts Consulted

Name	Position	Location
Marijke	Nederlandse Stichting Voor Leprabestrijding	Amsterdam, Netherlands
Ken Brown	Group Director of Regulatory Affairs	West Point, PA
Bruce Clements	Medical Director,	Carville. LA
Jacinto Convit	Director, Instituto de Bio Medicina	Caracas, Venezula
Maria Da Graca	Medical Doctor	Manaus Brazil
Emanuel Faria	Editor, The Star	Carville, La
Pieter Feenstra	Head of Leprosy Unit	The Netherlands
Paul Fine	London School of Hygiene And Tropical Medicine	Great Britain
Irma Guera	Chief, Ambulatory Care	Carville, LA
S. Groenen	Medical Doctor	Zaire
Jacques Grosset	Service de Bacteriologie Hospital Pitie-Salpetriere	France
Darrel Gwin	National Institute of Health	Bethesda, MD.
M.I. Gunzareth	Ministry of Health	Tanzania
Nancy Goldstein	Nurse	Dallas, TX
Robert Hastings	Staff Physician & Deputy Chief	Carville, LA
Johnny Harmon	Patient	Carville, LA

Kumar Jesudasan	The Leprosy Mission	Singapore
Judith Justice	Medical Doctor	Berkeley, CA
Robert Jacobson	Chief, Clinical Branch	Carville, LA
Richard Keeler	Attending Physician	Fisherville, VA
Carolyn Lyde	Medical Doctor	Dallas, Texas
Lechat, M.F.,	Professor	Brussels, Belgium
Michael Lavender	The Save the Children fund	Khatmandu, Napal
Wayne Meyers	Chief, Mycrobacteriology Branch	Washington, DC
S.K. Norrdeen	Retired	Geneva Switzerland
Deltor Opromolla	Hospital Lauro de Souza Lima	Baura SP Brazil
"Pete" Pederson	Patient	Carville, LA
S.R. Pattyn	Medical Doctor	Belgium
N.B.B. Reddy	Director of Training	Addis Ababa Ehiopia
W. Felton Ross	Medical Director	Greenville, SC
Thomas Shinnick	Chief, Hansen's. Disease Lab	Atlanta GA
Cairns Smith	The Leprosy Mission	Katong Singapore
Dixie Snider	Director of Division of Tuberculosis Control	CDC - Atlanta, GA
Gerald Stoner	National Institute of Health	Bethesda, MD

Luc van Parijs	Medical Doctor	Brussels, Belgium
Gerald Walsh	Medical Doctor	Rockvilke, MD
M.F.R. Waters	Medical Doctor	Great Britain
Li Huan Ying	Medical Doctor	Beijing, China
Yo Yuasa	Medical Director	Tokyo, Japan

APPENDIX D
Patient Interview Questions

Patient Information

Name or identification for research only: _____
Interview date_____ Time: _____
Interview location_____
M/FM_____ Age_____ Time at Carville _____

Interview Questions

1. When were you diagnosed with Hansen's disease?

2. What age were you when you were diagnosed?

3. Did you know what Hansen's disease was?

4. What were your symptoms that brought you to the doctor?

5. Did your doctor diagnose Hansen's disease in the early stages?

6. What did your doctor tell you about Hansen's disease when you were first diagnosed?

7. How did you feel when you were diagnosed with Hansen's disease?

8. How did it change you life?

9. How did your family and friends treat you after you were diagnosed?

10. What was your response to your family and friends after your diagnosis?

11. What was the first treatment you remember?

12. Was it hard to follow the directions for the treatment?

13. How many different treatments have you gone through with Hansen's disease?

14. What were the treatments that you had to go through?

15. What was the most effective for you?

16. What made it more effective than the other treatments?

17. Have you had Multi drug therapy?

18. What was good about multi drug therapy?

19. What didn't you like about multi drug therapy?

20. How long have you been on multi drug therapy?

21. What do you think of the name Hansen's disease instead of leprosy?

22. What is the extent of your disease?

23. Any comments you would like to add?

24. What is your opinion of Hansen's disease?

25. What would you like people to know about Hansen's disease?

APPENDIX E
List of terms specific to Hansen's Disease

List of terms specific to Hansen's Disease

1. Acetylators - Individuals who differ in their inherited ability to metabolize certain drugs.
2. Bioavailability - The degree to which a drug or other substance
3. Borderline (dimorphous) lepromatous leprosy- A type of leprosy which spans the spectrum between the lepromatous and tuberculoid poles. It is the most important part of the spectrum in terms of numbers of patients and of severity of nerve damage. It causes most of the disability and deformity seen in Hansen's disease. It is possible to find features suggestive of both forms of Hansen's disease in a single patient (Hastings, 1989).
4. Downgrading - This occurs when a patient downgrades then they arrive at a secondary position of sub-polar LL (LLs), which is not quite the same as that of the patient who originates as LL, i.e. primary, polar LL (LLs) (Hastings, 1989) "The existence of subgroups needs to be recognized, but for routine classification they may not be important" (Hastings, 1989, pg. 107).
4. Carbonic anhydrase inhibitors - A substance that interferes with the enzyme that catalyzes the decomposition of carbonic acid into carbon dioxide and water, facilitating the transfer of carbon dioxide from tissues to the blood and from the blood to the alveolar air (Doland, 1987).
5. Drug resistance - The ability of a individual to remain unaffected by

the drug.

6. Dyscrasis is an abnormal or pathologic condition of the blood.

7. Hansen's disease - A chronic infectious disease caused by Mycobacterium leprae, an acid-fast, rod-shaped bacillus (Yoder, 1991). Previously, the term leprosy was commonly used.

8. Immunogenic - The bacilli is eliciting an immune response with genetic factors controlling the individual's immune response which are the transmission factors from generation to generation.

9. Indeterminate leprosy - The stage in which early lesions, usually hypopigmented macules, without developed tuberculoid or lepromatous features (CDC, 1990).

10. Laboratory criteria for diagnosis - The demonstration of acid-fast bacilli in skin or dermal nerve, obtained from the full-thickness skin biopsy of a lepromatous lesion (CDC, 1990).

11. Lesions - The areas on the patient where the M. leprae are discharged. These areas are located on the skin, nose, and eyes. Closed lesions are located on the epidermis and remain intact, while open lesions, usually present in the lungs of the patient with pulmonary tuberculosis (Hastings, 1989).

12. Multibacillary - A diagnostic skin smear with any number of *Mycrobacterium leprae* present.

13. Multi drug therapy - A drug treatment plan to treat Hansen's

disease patients usually consisting of three main drugs: dapsone, clofazimine, and rifampin (Yoder, 1991).

14. Nodules - A small node or rounded projection which is solid and can be detected by touch (Dorland, 1997).

15. Pausabacillary - Bacteria are absent in a skin scraping. (See Appendix A)

16. Photosensitivity - A condition exhibiting abnormally heightened

17. Polymerase - An enzyme that catalyzes the combining of several simpler compounds, to form another compound, usually of high molecular weight (Dorland, 1987)

18. Purpura - A group of disorders characterized by purplish or brownish red discoloration, this is easily visible through the epidermis (Dorland, 1987).

19. Relapse - The return of a disease after its apparent cessation (Dorland, 1987).

20. Skin Smear - A technique used to determine the level of bacilli present in the body. Usually performed in six routine sites, the B.I. and M.I. help determine the type of disease and progress of treatment.

21. Systemically active - The organism is active throughout the whole Body.

22. Tuberculoid - one or a few well-demarcated, hypopigmented, and

anesthetic skin lesions, frequently with active, spreading edges and clearing center; peripheral nerve swelling or thickening may also occur (CDC, 1990).

23. Thrombocytopenia - A decrease in the number of platelets in the circulating blood that is associated with the presence of an anti-platelet antibody (Dorland, 1987).

24. Hemolytic - A complement of the erythocytes which are sensitize as a consequence of interaction with a specific antibody to them (Dorland, 1987).

becomes available to the target tissue after adinistration.

25. Dyspepsia - An impairment of the function of the digestion system, this usually causes discomfort after meals.

26. Ururitus - An inflammation to the prostatic utricle of the ear (Dorland, 1987).

27. Urticaria - This is an reaction of the skin marked by the appearance of slightly elevated patches, which are redder or paler than the surrounding skin. This condition is often attended by severe itching, the exciting cause may be certain foods or drugs, infection or emotional stress (Dorland, 1987)

APPENDIX F
Patient and Expert Consent Forms

TEXAS WOMAN'S UNIVERSITY
SUBJECT CONSENT TO PARTICIPATE IN RESEARCH

Title of Study: The Historical Development of Multi-drug therapy in the Treatment of Hansen's Disease

Name of Investigator: Jody A.C. Terrell, M.Ed. Phone Number: (972) 420-7149

Advisor: Susan Ward, Ph.D. Phone Number: (940) 898-2843

I am volunteering to participate in a research study on the historical development of the multi-drug therapy used today to treat Hansen's Disease. I will be asked to fill out a questionnaire using my expertise in Hansen's disease. The questionnaire will take approximately one hour depending on the amount of involvement I have with multi drug therapy. The questionnaire will be analyzed with the assistance of HyperResearch software and the data will be combined with approximately 50 other questionnaires to compile a time line sequence of multi drug therapy.

The foreseeable risks or discomforts are the time it would take to complete the questionnaire. I have will have approximately three weeks to complete the questionnaire but if more time is required it will be granted. The data will be stored in a locked cabinet for a period of five years and then destroyed.

The possible benefits to all that participate will be to be cited in the dissertation. Also all parts of the dissertation will be publishable and all contributors will have their input cited. Another benefit is the more information published on Hansen's disease, its treatment and cure will help inform the public that this disease is curable and not life threatening. To help dispel the stigma of Hansen's disease con only be done through information about Hansen's disease.

I understand that my participation is voluntary and that I may withdraw from the study at any time. My refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled.

An offer has been made to answer all my questions and concerns about the study. I will be given a copy of the dated and signed consent form to keep.

If I have questions about the research or about my rights as a subject, I should ask the researchers: their phone numbers are at the top of this form. If I have questions later, or if wish to report a problem, I may call the researchers or the Office of Research & Grants Administration at 817-898-3377.

The researchers will try to prevent any problem that could happen because of this research. I should let the researchers know at once if there is a problem and they will

help me. I understand, however, that TWU does not provide medical services or financial assistance for injuries that might happen because I am taking part in this research.

Signature of Participant	Date

TEXAS WOMAN'S UNIVERSITY
SUBJECT CONSENT TO PARTICIPATE IN RESEARCH

Title of Study: The Historical Development of Multi-drug therapy in the Treatment of Hansen's Disease

Name of Investigator: Jody A.C. Terrell, M.Ed. Phone Number:(972) 420-7149

Advisor: Susan Ward, Ph.D. Phone Number: (940) 898-2843

I am volunteering to participate in a research study on the historical development of the multi-drug therapy used today to treat Hansen's Disease. I will be participating in an interview with the researcher and will be asked questions concerning the treatments I have been exposed to since my diagnosis of Hansen's Disease. The interview will take anywhere from one to two hours. This interview will be audio-taped and transcribed and then analyzed by the HyperResearch software.

The foreseeable risks or discomforts would be to recall all the treatments both positive and negative. Since Hansen's Disease is a disease with a stigma this interview may bring up some uncomfortable times. A copy of the questions asked will be given before the interview and any question can be changed or deleted at my request. The interview will be stored in a locked cabinet for a period of five years and then destroyed.

The possible benefits to all who participate will be given the opportunity to be represented or they may remain anonymous. Any information published about Hansen's Disease may help to remove the stigma that has plagued this disease for centuries.

I understand that my participation is voluntary and that I may withdraw from the study at any time. My refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled.

An offer has been made to answer all my questions and concerns about the study. I will be given a copy of the dated and signed consent form to keep.

If I have questions about the research or about my rights as a subject, I should ask the researchers: their phone numbers are at the top of this form. If I have questions later, or if wish to report a problem, I may call the researchers or the Office of Research & Grants Administration at 817-898-3377.

The researchers will try to prevent any problem that could happen because of this research. I should let the researchers know at once if there is a problem and they will help me. I understand, however, that TWU does not provide medical services or

financial assistance for injuries that might happen because I am taking part in this research.

I do hereby consent to the recording of my voice and/or images by Jody A.C. Terrell, M.Ed. and Susan Ward, Ph.D. acting on this date under the authority of the Texas Woman's University. I understand that the material recorded today is for the purpose of this study which is to fulfill the requirements for a doctoral degree. The people who will hear the tapes will be the primary researcher, advisor and possibly other committee members. The tapes will be kept in a locked cabinet at the home of the primary researcher and destroyed in five years.

I hereby release the Texas Woman's University from any and all claims arising out of such taping, recording, reproducing, transmitting, or exhibiting as is authorized by the Texas Woman's University.

_____ _____

Signature of Participant Date

I understand my name and identity will be kept confidential unless signed below.

_____ _____

Name to use Signature of Participant

APPENDIX G

Cover Letter to Experts

April 1, 1999

Dear :

I am a doctoral student at Texas Woman's University working on my dissertation. I am doing a historical study on the development of multi drug therapy for the treatment of Hansen's disease. I selected your name because of the extensive work you have done with Hansen's disease patients I would like to illicit your help with this project.

Enclosed is a questionnaire that I would like you to complete about multi drug therapy or other treatments for the treatment of Hansen's disease. I will compile this information and put it in a chronological sequence to establish the development of multi drug therapy. I realize that not everyone is using MDT or even agrees with the treatment and I want that information to be included. Also, any other information on Hansen's disease and the treatments that have been given to patients through history would be extremely helpful.

A consent form is enclosed for you to read and sign and if you have any questions please don't hesitate to call me at my home phone: (972) 420-7149 or e-mail me at:: jterrell3@aol.com. I will be happy to answer any questions.

I will be compiling this information in January and February so if I could receive your information as soon as possible that would be greatly appreciated. I would also like to cite you in my dissertation and if you have a short vita or information sheet I would like to include it with the others that are participating.

After you have completed the questionnaire and gathered any information on yourself and Hansen's disease and multi drug therapy then please enclose it in the stamped enclosed envelope. Again, thank you for your help and input on this project.

Sincerely,

Jody A.C. Terrell, M.Ed.

1325 JUNIPER LANE • LEWISVILLE, TEXAS • 75067
PHONE: 972-420-7149 • E-MAIL: JTERRELL3@AOL.COM

APPENDIX H

Institution Permission Letter

Texas Woman's University

Health Studies Program
Permission for Conducting Patient Interviews

The G. W. Long Hansen's Disease Center grants to Jody A.C. Terrell, M.Ed., a doctoral candidate in the department of Health Studies at Texas Woman's University, the privilege of its facilities in order study the following:

> The Historical Development of Multi-drug Therapy in the Treatment of Hansen's Disease.

This study involves interviewing patient patients living with Hansen's Diseases. The qualifications for this study is the patients must have lived with Hansen's Disease for more than 10 years and that have had more than one type of treatment for the disease. Each patient interviewed will be given a consent form that they must sign before the interview. The patients chosen for the interview study will be on a voluntary basis.

Please, read each item below and circle and initial the appropriate choice in parenthesis. You may fill in additional conditions if you wish. The conditions mutually agreed upon are as follows:

1. The institution (may) (may not) be identified by name in the final report.

2. The names of consultative or administrative personnel in the institution (may) (may not) be identified in the final.

3. The institution (wants) (does not want) a conference with the student when the report is completed.

4. Other (please fill in): _____

_____

_____ _____

Agency representative Date

_____ _____

Student Signature/Date Doctoral Committee Chairperson

APPENDIX I

Milestones in the History of Leprosy
Timeline

Milestones in the History of Leprosy

600 BC	An Indian document describes an "eating disease" called Kushta - still the name for leprosy in Hindi
400 BC	Chinese medical text Nei Jing describes the disease as Da Feng
1200 AD	An estimated 19,000 leprosaria exist all over Europe
1873	Armauer Hansen identifies the bacillus *Mycobacterium leprae*
1897	International Leprosy Conference in Berlin agrees that leprosy is "incurable"
1905	Five acres were roped off and declared the "Massachusetts State Leper Colony" - the only state-controlled isolation area for the disease in the United States
1921	The USPHS (United States Public Health Service) took over Carville from the State of Louisiana, eleven men and two women patients were transferred from Penikese Island to Carville (the last of them died in 1950.
1931	May 16, 1931 the first issue of the *Sixty-Six Star* was published (this is the Hansen's disease magazine now called *The Star*
1932	Efforts were made by the Star to eliminate the word "leper" in writings and conversations regarding the disease
1947	Abott laboratories developed Diasone to be taken orally, also oral Promizole was introduced, thus ending the chaulmoogra oil therapy
1949	The drug dapsone comes into use and proves effective against leprosy
1964	First reports of resistance to dapsone, from Malaysia, arouse fears that the only known cure for the disease might become worthless

1964-1966	Early trials of Clofazimine
1970's	Extensive tests in the mouse foot pads
1970-1976	Clofazimine for treatment for cases not responding to DDS monotherapy
1973	A century after Armauer's discovery, the groundwork is laid for the formation of the immunology of Leprosy Committee (IMMLEP - now IMMYC) and the Chemotherapy of Leprosy Committee (THELEP - now THEMYC), which begin to recruit the best scientists available in the quest for a solution to the leprosy problem
1981	A WHO study Group recommends treatment with a "Cocktail" of dapsone, rifampicin, and clofazimine - multi-drug therapy (MDT)
1984	WHO estimates that there are 12 million leprosy sufferers in the world
1991	World Health Assembly adopts Resolution WHA 44.9 setting the goal of elimination of leprosy as a public health problem by the year 2000
1992	Ofloxacin Multicentric Trail in MB and PB Hansen's Disease cases; a multicentric trial coordinated by WHO - as principal investigtor of the Manaus project
1994	First International Conference on Elimination of Leprosy, held in Viet Nam, reaffirms commitment to the goal, of eliminating Hansen's Disease, in the Hanoi Declaration.
1995	Total registered leprosy cases in the world falls below one million for the first time
1996	Second International Conference on the Elimination of Leprosy held in New Delhi on October 11-13, 1996 with the theme "Reaching every patient in every village
2000	WHO declares December 31, 2000 is the target date for leprosy elimination