

Chapter 2: Literature Review

2.1 Introduction

The research presented here is framed within the context of disease emergence, and the results are presented to help clarify the potential for Chagas disease in the United States. Many interconnected factors can contribute to disease emergence, including: travel, migration, and commerce; deforestation and reforestation; climate change and variability; and deficient public health measures (Haggett 1994; Morse 1995; Patz et al. 2004). By bridging the theoretical frameworks of landscape epidemiology and disease ecology within the context of disease emergence, this study delineates areas within the United States that are at higher risk for the emergence of Chagas disease.

Situated within the sub-discipline of medical geography, this research utilizes the landscape epidemiology approach to analyze characteristics of triatomine biogeography; for example, reports of triatomine domesticity and increased activity in hot temperatures, and their relationship to disease transmission. The aspects associated with landscape epidemiology that are discussed in this literature review relate to the factors that define triatomine domesticity, the characteristics that make the triatomine an effective disease vector, extensive species range, and reports that the triatomine is more active in warmer temperatures. Additionally, these issues are directly linked to the characteristics of human habitation, population, and behavior within the disease ecology approach. By measuring physician awareness along with triatomine biogeography, one can gain a broader understanding of disease ecology which allows for delineation of areas at higher risk for disease emergence.

The connections between landscape epidemiology and disease ecology that are illustrated in this research portray the importance of public health awareness in assisting triatomine control efforts in South America as well as instances where diagnosis of Chagas disease is overlooked by physicians (Betz et al. 1984; Holbert et al. 1995; Ochs et al. 1996; Kirchhoff et al. 2006). As the population which is at higher risk for Chagas disease increases due to an expansion of the vector's range based on the effects of climate change, it becomes more important to explore disease awareness among physicians and

the general population in order to define areas in need of increased public health intervention.

The following schematic is used as a template for this research and for the organization of the thesis (Figure 2.1). The schematic ties together elements of the two theoretical frameworks applied in this study, which are landscape epidemiology and disease ecology. The defined variables are based on what I deemed most important for delineating areas at higher risk for the emergence of Chagas disease after consulting over one hundred-fifty articles, reports, and reviews.

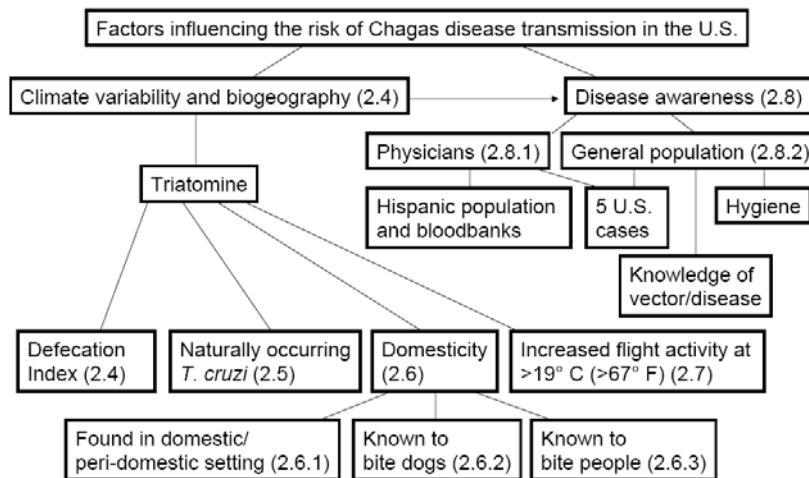


Figure 2.1 Schematic of thesis research. The primary sections discussed in the literature review are in parentheses.

2.2 Medical Geography

The field of geography is broken into two sub-fields called physical geography and human geography. Physical geography involves studying spatial patterns of the physical landscape and the environment; whereas, human geography focuses on spatial patterns created by human activity (Pers. Comm. 2005). Consequently, due to the broad nature of both sub-fields numerous sub-disciplines exist, many of which have components of both sub-fields as well as overlap with other disciplines. For example, the geographical sub-disciplines of biogeography and medical geography both have components of physical and human geography as well as interdisciplinary overlap. One

hundred years prior to Jacques May's founding of the sub-discipline called medical geography, John Snow conducted an experiment to find the source of cholera in London by using a geographical and epidemiological approach (Pers. Comm. 2005). Snow's study is an example of how medical geography utilizes interdisciplinary methods in order to find ways to ameliorate health-related issues (Meade and Erickson 2005).

With the inception of medical geography as a sub-discipline in the 1950s came consideration of how culture and the environment relate to health with a focus on the synthesis of spatial data (Pyle 1983). Presently, medical geography incorporates the study of social health, relating to women and those with disabilities, as well as the status of health in the developing world (Pers. Comm. 2005). Recent technological advancements have increased the capacity for analysis within medical geography. Now, the science of medical geography utilizes the tools of spatial analysis through predictive modeling, GIS, remote sensing, and spatial autocorrelation as well as the processes of interviews and surveys (Gesler 2004).

2.2.1 Geographic methods for delineating disease

The scientific method is used by geographers to perform both quantitative and qualitative analyses of spatial data. As with other scientific disciplines, the geographer first observes, then develops a hypothesis and review, followed by collection and analyzes of data, and finishes with forming conclusions. Geographical tools enable the use of the scientific method in collecting and analyzing data. In the early years, cartography was one of the primary tools used in the field of geography. Cartographic mapping provided a way to visualize spatial data and analyze the clustered or random patterns. Advancements in technology have enhanced the geographer's toolset for quantitative analyses and enable the medical geographer to consider more variables in their research (Pers. Comm. 2005).

The quantitative approach, combined with recent technological advances, allows the medical geographer to conduct complex statistical analyses of spatial data. Medical geographers utilize such tests to measure frequency distributions of disease and relationships among variables (Meade and Erickson 2005). Other commonly-used tools

for studying the spatial aspect of disease are GIS and remote sensing. Medical geographers use GIS to incorporate different layers of disease-related data into maps in order to analyze spatial patterns and relationships among the layers. The layers incorporate point data that represents disease incidence, vector presence, or general sites of interest, as well as polygons to delineate populated areas at risk of disease. In the case of remote sensing, which is landscape data obtained via satellite images and aerial photographs, medical geographers incorporate these data into a GIS layer so as to investigate the patterns and relationships that exist between disease distribution and the climate, landscape, and vegetation (Kitron et al. 2006). The tools of GIS and remote sensing are major components used in predictive habitat mapping and modeling.

The qualitative methods utilized by medical geographers have been used since the sub-discipline began. Qualitative methods require obtaining information from people through the use of interviews, surveys, participant observation, and focus groups. There has been a recent upsurge in the use of these methods, both as a stand alone approach and combined with quantitative techniques for a mixed-methods approach (Gesler 2004). Over the years, medical geographers have increased their use of a mixed-methods approach. An example of this is when data acquired from interviews is incorporated into a GIS for spatial analysis, to more completely address a research problem. In the context of disease ecology, data such as these are necessary in order to investigate patterns of disease mortality, which characterizes the primary focus in the field of medical geography (Gesler 2004).

2.2.2 Predictive habitat mapping/modeling

Today, the use of predictive habitat modeling promotes the use of multiple variables in spatial analyses by providing innovative techniques and tools to delineate species' habitat and range. For example, biogeographers use modeling to predict where an invasive plant species may thrive, or to gauge the potential effects of climate change on vegetation. Likewise, medical geographers use predictive modeling to delineate where disease emergence may occur by utilizing components of landscape epidemiology and disease ecology.

One example of predictive modeling in the context of medical geography is described in a study by Glass et al. (1995), who incorporated remotely sensed data into a GIS along with soils and geological data in order to analyze the risk potential for Lyme disease. The statistical analysis utilized a software program to run multiple iterations of a logistic regression model. Results from this study defined areas where environmental factors increased the risk for transmission of Lyme disease. Another approach to predictive habitat modeling is the genetic algorithm for rule-set prediction (GARP) (Stensgaard et al. 2006). GARP is a new software modeling program that enables the user to predict the distribution of disease vectors and reservoirs by incorporating multiple ecological and environmental variables into a database that then utilizes a genetic algorithm to delineate the potential vector or reservoir range (Stockwell and Peters 1999; Peterson et al. 2002; Peterson et al. 2003; Peterson et al. 2005).

Predictive modeling fits into the theoretical framework of landscape epidemiology and allows medical geographers to predict where disease emergence may occur. The results of predictive modeling methods are illustrated in maps, scatterplots, tables, and graphs thus allowing for more complex statistical analyses of the relationships among variables. For example, a broad-scale example is illustrated in Carbajo et al. (2001), who use multiple maps of Argentina to depict each step in the process of defining the areas at risk for dengue transmission. Additionally, Snow et al. (Snow et al. 1999) outlined the malaria risk on the continent of Africa in tables, through analyses of literature, past surveys and interviews, and hospital records as well as an interpolated map derived from a fuzzy logic climate model.

2.3 Background on Chagas disease

The prevalence of Chagas disease among humans in Central and South America indicates that the population lives in close proximity to the disease vector, which maintains a domestic transmission cycle in this specific region of the world; however, since the vector is sylvatic in the United States, the disease is considered to be zoonotic and the occurrence of human transmission is incidental (Vetter 2001; Dias et al. 2002). An example of a normally sylvatic triatomine species being found in the domestic setting

is described in a 2003 news story from the Centers for Disease Control (CDC) which reports an outbreak of *T. cruzi* infection among dogs in Texas (Beard et al. 2003). This outbreak led to the survey of dwellings in the area and resulted in the discovery of infected triatomines (*T. gerstaeckeri*) at the household where the dogs resided.

The brief CDC article described above reveals the uniqueness of this particular incident which indicates that a normally sylvatic vector in the United States may now have a domestic transmission cycle (Beard et al. 2003). In the context of landscape epidemiology, it is important to monitor changes in the triatomine habitat and range in order to seek areas where vector eradication efforts may be needed. Consequently, in areas susceptible to human Chagas disease transmission, there is a need for increased physician and public risk awareness in order to recognize cases and control infected vectors near the home.

Since the discovery of Chagas disease in 1909, there have only been five autochthonous (locally acquired) cases recorded in the United States (Table 2.1 and Figure 2.2) (Woody and Woody 1955; Anonymous 1956; Betz et al. 1984; Schiffler et al. 1984; Navin et al. 1985; Ochs et al. 1996; Herwaldt et al. 2000). Consequently, Chagas disease in humans is viewed as rare in the United States (CDC 2006). The low incidence of Chagas disease in the United States is attributed to the type of housing (no thatched roofs), weak disease agent pathogenicity (ability to transmit disease), and the vector's inefficiency for transmitting the disease agent (Laranja et al. 1956; Little et al. 1966; Piesman and Sherlock 1983; Zárate et al. 1984; Diotaiuti et al. 1995; Guarneri et al. 2000; Prata 2001). In Latin America, human Chagas disease is endemic and current prevalence of human *T. cruzi* infection is estimated to be between 16-18 million with an annual death rate of 45,000 across the region (TDR 2003).

Table 2.1 Human Chagas Disease in the United States (Woody and Woody 1955; Anonymous 1956; Betz et al. 1984; Schiffler et al. 1984; Navin et al. 1985; Ochs et al. 1996; Herwaldt et al. 2000).

	Case 1-1955	Case 2-1955	Case 3-1982	Case 4-1983	Case 5-1998
Age	10 months	1 month	56 years	7 months	18 months
Sex	female	Male	Female	male	male
Ethnicity	Caucasian	Caucasian	Unknown	Hispanic	unknown
Time of year	July	June-July	August	June	July
Bite marks	No bites found	Unknown	No bites mentioned	no bites mentioned	bites on legs
Location	Corpus Christi, TX	Houston, TX	Lake Don Pedro, CA	Mathis, TX	Rutherford Cty, TN
Home description	newer subdivision	Unknown	modern, well-built	poor repair	27 year old brick home, good condition
Suspected vector	unknown	Unknown	<i>T. protracta</i>	unknown	<i>T. sanguisuga</i>
Vector location	near home	Unknown	near home	unknown	near and inside home
Home setting	near old rangeland overgrown with mesquite and brush	unknown	1100' above sea level, Sierra Nevada foothills, wild grass with scattered oaks, Upper Sonoran Life Zone	Trees and decaying vegetation close to home	Rural, woods on 3-sides

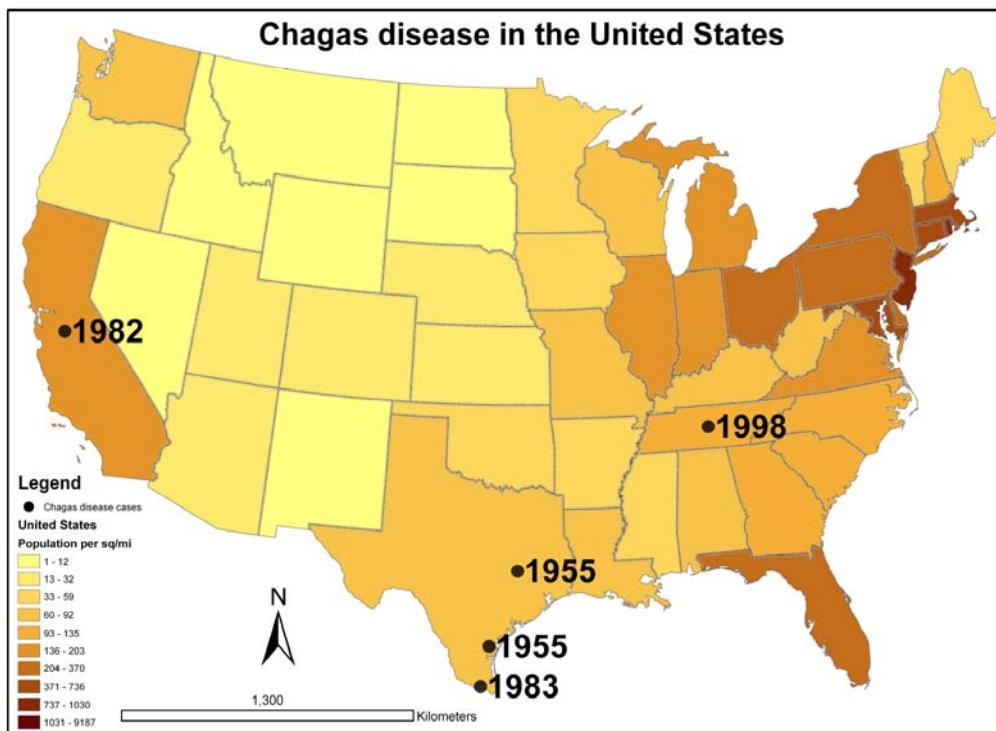


Figure 2.2 Autochthonous Chagas disease in the United States (Woody and Woody 1955; Anonymous 1956; Betz et al. 1984; Schiffler et al. 1984; Navin et al. 1985; Ochs et al. 1996; Herwaldt et al. 2000).

In addition to the five autochthonous cases of Chagas disease in the United States, human *T. cruzi* transmission has also occurred through blood transfusion and organ transplantation (Leiby et al. 2000; CDC 2001; Leiby et al. 2002). Other reports reveal that human *T. cruzi* transmission has taken place via infected needle sticks and through the conjunctiva of the eye (Kagan et al. 1966; Betz et al. 1984; Bradley et al. 2000). Similar to the HIV/AIDS threat to the blood supply, Chagas disease is becoming a growing concern due to the increasing number of Latin American immigrants in the United States. Estimates indicate that the number of Latin American immigrants infected with *T. cruzi* is between 50,000 to 100,000 (Kirchhoff et al. 1987).

In its acute form, Chagas disease lasts from four to six weeks with mild symptoms of fever, depression, and facial edema (CDC 2006). During the acute phase, the disease can be lethal; however, it is during this phase that it is treatable with nifurtimox or benznidazole. Unfortunately, during the acute form it is difficult to detect due to the presentation of unremarkable symptoms that can be misdiagnosed (Holbert et al. 1995; Dias and Schofield 1999; Leiby et al. 2002; CDC 2006; Sánchez-Guillén et al. 2006). The second stage is asymptomatic and is considered the indeterminate phase which can last for decades (Prata 2001; Sánchez-Guillén et al. 2006). The third and final stage has the highest mortality rate and is referred to as the chronic phase. It is during this stage that the heart and the digestive tract experience the negative effects of carrying *T. cruzi* in the blood (Holbert et al. 1995; CDC 2006; Sánchez-Guillén et al. 2006).

The high mortality rate during the chronic stage of Chagas disease has resulted in a considerable economic burden within many Latin American countries (Dias and Schofield 1999; Ramsey et al. 2005). Consequently, most countries in Central and South America have triatomine control measures in place (Dias et al. 2002). These control measures are the result of the World Health Organization/Tropical Disease Research (WHO/TDR) Southern Cone Initiative to eradicate Chagas disease. The initiative consists of increasing public health awareness, eliminating the triatomine vector through insecticide treatment in and around homes, and closely monitoring the blood supply for *T. cruzi* (WHO/TDR 1991).

Dias and Schofield (1999) describe the history of Chagas disease control efforts since its discovery and outline methods of intervention used to ameliorate the spread of Chagas disease. Their review indicates that current control efforts have made a substantial difference in Latin America although the primary issues of a highly adaptive vector and an impoverished population holding little political power still remain (Dias and Schofield 1999). Public health officials must recognize that having a healthy workforce saves money in the long term; however, to achieve this it is necessary to invest in disease eradication and continued surveillance (Dias and Schofield 1999; Ramsey et al. 2005). As the triatomine evolves to changing habitats, it is placed in closer proximity to humans and the lessons learned in Latin America will be valuable in the United States as well.

There is evidence that transmission of *T. cruzi* through blood transfusion and organ transplantation has occurred in the United States as well as growing concerns that the emergence of Chagas disease in Mexico will further increase the risk associated with these modes of transmission (Leiby et al. 2000; CDC 2001; Leiby et al. 2002; CDC 2006). A recent study reveals an increase in human Chagas disease cases in northern Mexico as well as an occurrence of underreporting in other Mexican states (Cruz-Reyes and Pickering-López 2006). Other studies of *T. cruzi* seropositive blood donors in Mexico reveal that 63% have *T. cruzi* parasites circulating in their blood which may result in a recipient acquiring the disease agent (Leiby et al. 2002). Fortunately, recent reports state that blood screening for Chagas disease will begin soon in the United States, which presumably should limit transmission through blood transfusions; however, concerns about the past and current condition of the blood supply should not be discounted (CDC 2006; Lee 2006).

2.4 Landscape epidemiology of the triatomine

Lent and Wygodzinsky (1979) conducted an entomological cataloging of the triatomine, describing nine species and numerous subspecies in the conterminous United States (Table 2.2) (Lent and Wygodzinsky 1979). Of the nine *Triatoma* species catalogued, six are reported to be naturally infected with *T. cruzi*. To be naturally infected

means that the *T. cruzi* disease agent has been found in insects caught during fieldwork as opposed to insects that are experimentally infected with *T. cruzi* in the laboratory (Usinger 1944; Kagan et al. 1966). Triatomine species that are natural carriers of *T. cruzi* are an important concern considering that the range of the triatomine in the United States covers twenty-six states, all of which have at least one species which is found to be naturally infected with *T. cruzi* (Lent and Wygodzinsky 1979).

Table 2.2 United States Summary of Lent and Wygodzinsky's (1979)
Triatoma species.

State	<i>Triatoma</i> species in the United States	Species	Naturally Infected with <i>T. cruzi</i>
New Mexico, Texas		<i>T. gerstaeckeri</i>	X
Arizona		<i>T. incassata</i>	
Arizona, New Mexico, Texas		<i>T. indictiva</i>	
Arizona, California, Florida, Georgia, Illinois, Kansas, Louisiana, Maryland, Missouri, New Mexico, North Carolina, Oklahoma, Pennsylvania, South Carolina, Tennessee, Texas		<i>T. lecticularia</i>	X
Arizona, California, Colorado, Nevada, New Mexico, Texas, Utah		<i>T. protracta</i>	X
Arizona		<i>T. recurva</i>	X
Arizona, California, New Mexico, Texas		<i>T. rubida</i>	X
Florida		<i>T. rubrofasciata</i>	
Alabama, Arizona, Arkansas, Florida, Georgia, Illinois, Indiana, Kansas, Kentucky, Louisiana, Maryland, Mississippi, Missouri, North Carolina, Ohio, Oklahoma, Pennsylvania, South Carolina, Tennessee, Texas, Virginia		<i>T. sanguisuga</i>	X

Archeological and genetic data suggest that triatomines began as a sylvatic (wild) species in Bolivia (Panzera et al. 2004; Noireau et al. 2005). Throughout South America, many triatomine species are now considered domestic and maintain populations inside human dwellings (Lent and Wygodzinsky 1979). This transformation may be a byproduct of deforestation, which is occurring to accommodate timber harvesting, population growth, and agriculture (Patz et al. 2004; Ramsey et al. 2005). As described by Noireau et al. (2005), the triatomine range in Bolivia prior to and since the implementation of control efforts reveals that sylvatic species may fill the niche left open by the eradication efforts of domestic species, especially if control complacency sets in. Similarly, in the United States, the 2003 Texas outbreak of Chagas disease in dogs indicates that the

triatomine is adapting to the domestic setting (Beard et al. 2003). This is further evidence that a landscape epidemiology approach to investigating triatomine biogeography and range must be conducted in order to reveal biological changes in the natural nidus which is an indication of disease emergence (Meade and Earickson 2005).

Exploring the natural nidus of the triatomine requires a look into the South American species' range as well, in spite of the inherent differences between South and North American species. Paruelo et al. (1995) notes that there is considerable similarity between the climate and landscape of the North and South American temperate zones (primarily Chile, Argentina, and Uruguay for South America and from California to Alabama and north into southern Canada for North America). The similarity in climate and landscape along with the Chagas disease threat already present in South America justifies the necessity to seek more information on the potential North American range of the triatomine vector and the *T. cruzi* disease agent.

Wood (1938) provides additional evidence that the potential range of the triatomine in the United States must be analyzed. The study was prompted by the discovery of infected triatomines of the species *T. protracta* in a wood rat nest in California, and the article describes how the known triatomine range in California has expanded, further influencing the potential spread of Chagas disease (Wood 1938). Since Woods' study in 1938, similar research into the expanding range of the triatomine in the United States has been limited. It has only been in the last 15 years that new modeling techniques have been used to analyze the triatomine species' range.

Recent modeling efforts have mapped the triatomine species' range in much of South and Central America as well as in limited parts of North America (Abad-Franch et al. 2001; Costa et al. 2002; Peterson et al. 2002; Guzman-Tapia et al. 2005; López-Cárdenas et al. 2005). Peterson et al. (2002) apply the GARP model to the *T. gerstaeckeri* species in Mexico to uncover the environmental characteristics under which the disease agent and its vector thrive. To date, GARP modeling in the United States has only been applied to parts of the southwest, revealing that the *T. gerstaeckeri* range extends through the western half of Texas to the panhandle and into southeastern New Mexico (Beard et al. 2003). Further investigation into the triatomine range within North America is needed in order to adequately predict the emergence of Chagas disease.

Today in the United States, triatomine species that were once sylvatic are also found more frequently in the peridomestic and domestic settings (Kagan et al. 1966; Sjogren and Ryckman 1966; Ryckman 1984; Herwaldt et al. 2000; Beard et al. 2003). Due to the nocturnal nature of triatomines, they are not normally seen during the day and will remain hidden in dark crevices until coming out at night to feed upon the host (Lent and Wygodzinsky 1979).

The triatomine species that comprise the largest range in the United States are the *T. sanguisuga*, *T. lecticularia*, and the *T. protracta*, all of which have been found to be natural carriers of *T. cruzi* (Table 2.1) (Usinger 1944; Lent and Wygodzinsky 1979). Over the past fifty years, numerous reports of these species in and around human habitations are on record (Sjogren and Ryckman 1966; Lent and Wygodzinsky 1979; Navin et al. 1985; Herwaldt et al. 2000). While the triatomine is most often found in the rural setting, urban occurrences of household infestation by triatomines are found more often in homes where dogs live (Ramsey et al. 2005; Levy et al. 2006). Dogs that are seropositive for *T. cruzi* infection and that are found to have triatomines living in their bedding pose an increased risk of disease transmission to humans (Barr et al. 1995; Bradley et al. 2000; Beard et al. 2003; Enger et al. 2004; Crisante et al. 2006). For more information on the role of dogs in *T. cruzi* transmission, refer to Section 2.6.2.

2.4.1 Uncertainty in triatomine species classification

Uncertainty in data can occur when experts have differing opinions or through unintentional human error (Pers. Comm. 2006). Ryckman (1984) indicates that the lack of taxonomic information on the triatomine has led to differing scientific conclusions about the species' distribution. For example, according to Lent and Wygodzinsky (1979) the most widely distributed triatomine species in the United States are *T. lecticularia* and *T. sanguisuga* whose collective range extends north to south from Illinois to Florida and west to east from California to Maryland. Ryckman (1984) describes a validated report which states that the *T. sanguisuga* species has also been found in New Jersey; however, he discounts invalidated reports that may have mistakenly misidentified the *T. lecticularia* and *T. sanguisuga* species.

Added examples of uncertainty are reports of *T. sanguisuga* in Arizona and New Mexico that have probably been misidentified and are actually *T. indictiva* (Ryckman 1984). The validity of the Texas *T. neotomae* species is not mentioned in the Lent and Wygodzinsky (1979) study; however, it is listed in the Usinger (1944) report along with *T. longpipes* which are mentioned as being in Arizona. The report of *T. longpipes* in Arizona is contested by Lent and Wygodzinsky (1979) and further invalidated by Ryckman (1984).

The range of species that are natural carriers of *T. cruzi* is questionable. For example, in Lent and Wygodzinsky's (1979) study, the authors only listed states in which a valid specimen had been collected, and the state of West Virginia is not included. In a later study, Ryckman (1984) states that the *T. sanguisuga* range most likely extends to Ohio, West Virginia, and Kentucky, but no conclusive evidence is given to support this statement.

For the purpose of this study, the necessary exclusion of one triatomine species that is considered an important vector of Chagas disease may lead to uncertainty. Reports indicate a high *T. cruzi* infection rate among *T. gerstaeckeri* (Usinger 1944); notwithstanding, this species is exempted from the analysis portion of the thesis due to the broad scale of the study (United States) and the reported range as being only in Texas and New Mexico (Usinger 1944; Lent and Wygodzinsky 1979).

2.5 The role of the triatomine as a vector in spreading the *Trypanosoma cruzi* disease agent

All species of triatomine feed on blood and depending on the species are known to feed on the blood of birds, mammals, and reptiles (Usinger 1944; Lent and Wygodzinsky 1979). Triatomine adapt to the available food source and can survive for months without a blood meal (Usinger 1944; Sjogren and Ryckman 1966; Lent and Wygodzinsky 1979; Schofield 1979; Ryckman 1984). Most often, it is during or immediately after the blood meal that the disease agent is transmitted and the triatomine's efficiency for transmitting the disease agent is measured using an "infectivity index." With respect to the triatomine, the primary factor considered in this index is the rate of

defecation (Kagan et al. 1966). The rate of defecation is important given that the mode of disease transmission is via the feces; therefore, if the triatomine defecates while consuming the blood meal or shortly thereafter, the chances of disease transmission are greater (Kagan et al. 1966; Zárate et al. 1984; Yabsley and Noblet 2002).

The life cycle of the triatomine consists of the egg, five nymphal instar stages, and adult (Figure 2.3) (Usinger 1944). During the nymphal stages, the triatomine can hold up to twelve times their body weight in blood due to their naturally more flexible body structure, as opposed to adults who can only hold three times their body weight (Usinger 1944). In the event of domestic colonization, the increased capacity for blood during the nymphal stages creates a higher risk of disease transmission to humans (Vazquez-Prokopec et al. 2004), since there is a strong correlation between the amount of blood ingested and the size of defecation (Piesman and Sherlock 1983).

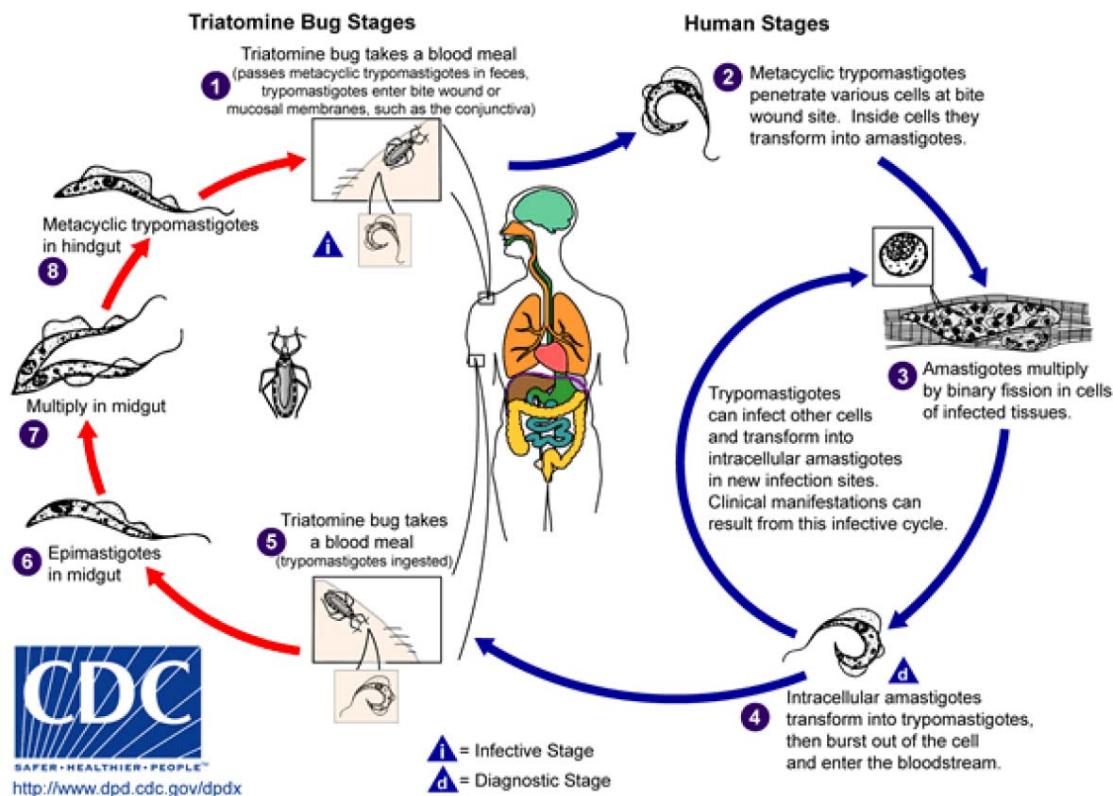


Figure 2.3 Life cycle of the triatomine (CDC image, 2004
www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/TrypanosomiasisAmerican_il.htm).

Since defecation varies among species, the defecation index of each triatomine species is an important factor when determining disease transmission potential (Usinger 1944; Lent and Wygodzinsky 1979; Piesman and Sherlock 1983; Zárate et al. 1984; Diotaiuti et al. 1995; Guarneri et al. 2000). Information on the defecation index of the North American triatomine species is quite limited and reports of delayed defecation in species from the United States are considered in this study (Kagan et al. 1966; Lent and Wygodzinsky 1979).

One Chagas disease case in the United States is believed to have been transmitted through contact with infected triatomine feces because there is no indication that the patient had been bitten (Navin et al. 1985). Reports such as this indicate that research into the possibility of the *T. cruzi* disease agent being introduced to a household through contaminated food and unsanitary habits, as well as during the vector's consumption of the blood meal, should be pursued (Prata 2001; EFE 2005; Benchimol Barbosa 2006).

Studies of *T. protracta* and *T. sanguisuga* isolates (individual samples collected) in the United States reveal a *T. cruzi* infection rate of 20% out of a sample size of 957 and 6% of a sample size of 181, respectively (Usinger 1944; Kagan et al. 1966). Forty years ago, it was reported that the triatomine infection rate for *T. cruzi* was approximately 20% in the United States, nearing the 20-30% infection rates found in South America (Kagan et al. 1966). Furthermore, since the discovery of Chagas disease, a number of non-human reservoirs for *T. cruzi* have been identified in the United States. John and Hoppe (1986) list eighteen reservoirs (mostly rodents) which have been found to carry *T. cruzi*. The geographic range of the reservoirs extends from as far west as California to the eastern half of the United States, and north to Maryland. Other publications have since revealed that domestic dogs (primarily hunting dogs) have been found to be carriers of *T. cruzi* as well (Barr et al. 1995; Meurs et al. 1998; Bradley et al. 2000; Beard et al. 2003).

Despite the sylvatic nature of the triatomine species in the United States (Kagan et al. 1966; Ryckman 1984; Herwaldt et al. 2000; Beard et al. 2003), there are numerous cases of a sylvatic species biting humans when an opportunity is present; for example, in cases where the triatomine enters a dwelling through an open window (Sjogren and Ryckman 1966). Most triatomine feed at night and have been found to be attracted to lights (Usinger 1944; Sjogren and Ryckman 1966; Wood and Wood 1967; Monroy et al.

2003; Vazquez-Prokopec et al. 2004; Vazquez-Prokopec et al. 2006), which may increase the vector's attraction to a domestic dwelling.

When triatomines begin reproducing inside a human dwelling, the home is considered colonized (Lent and Wygodzinsky 1979). The colonization of a home by triatomines is influenced by the materials with which the home is built and access to a host (Lent and Wygodzinsky 1979; Schofield 1979; Dumonteil et al. 2002; Enger et al. 2004; Ceaser 2005). Even without actual colonization of a home, triatomine isolates have been found harbored in shaded crevices behind pictures and curtains, in boxes and furniture, as well as in a basement and a bathroom (Lent and Wygodzinsky 1979; Schofield 1979; Navin et al. 1985; Herwaldt et al. 2000).

2.6 The factors related to triatomine domesticity in the United States

To determine the risk of Chagas disease transmission in the United States it is necessary to delineate characteristics of the triatomine that make it an effective disease vector, the most important of which is domesticity. This thesis highlights isolates of three triatomine species within the United States that are known to harbor *T. cruzi* naturally and that exhibit qualities of domesticity. This approach to defining risk is supported by Lent and Wygodzinsky (1979) who outline the four primary factors that play a role in the transmission of *T. cruzi* to humans via the triatomine vector. The factors used to determine the level of domesticity are: adapting to human habitats; high anthropophily (preference to feed on humans); immediate defecation after blood meal; and broad spatial distribution. It is not necessary for individual triatomine species to meet all four criteria because few species do, and yet the disease transmission cycle is effectively maintained (Lent and Wygodzinsky 1979). Consequently, the defined qualities of domesticity used in this research are based upon whether or not the species is known to bite humans and domestic dogs, and reports indicating that the species has been found in and around the domestic setting.

2.6.1 Triatomine species within the United States that have been found in the domestic and peridomestic setting

Several anecdotes indicate that the behavior of sylvatic triatomine species may increase the risk for human Chagas disease if that behavior places the triatomine in close proximity to people. The four reports presented below illustrate occurrences of human and triatomine contact and serve as an example of increased triatomine domesticity. There are no reports of colonization contained in the three reports presented here; however, the fourth anecdote illustrates triatomine colonization around a home in Texas (Beard et al. 2003).

In the first scenario, the triatomine entered an open window. Sjogren and Ryckman (1966) report that 16 isolates of the *T. protracta* species were found in a Redlands, California home. The residents reported an annual average of 30 *T. protracta* isolates within the home in previous years. These high numbers are attributed to lights located close to the house (Sjogren and Ryckman 1966). The second scenario is attributed to isolates entering via the chimney and sliding doors, and is related to the third autochthonous case of Chagas disease, which occurred in California. Navin et al. (1985) surveyed the patient's home and found a live uninfected *T. protracta* isolate in the bathroom. Neighborhood surveys revealed two of the seven nearby homes also contained a single uninfected isolate each (Navin et al. 1985).

The third report of isolates inside the home does not indicate how they entered the dwellings. Herwaldt et al. (2000) reported the presence of a *T. sanguisuga* isolate in a home, resulting in the fifth reported case of Chagas disease in the United States (Herwaldt et al. 2000). The following year, two more *T. sanguisuga* isolates (no indication of *T. cruzi* infection status) were found inside the victim's home as well as one uninfected isolate in a neighbor's woodpile (Herwaldt et al. 2000). Upon further investigation, *T. cruzi* was found in two raccoons, and one dog tested seropositive in the vicinity of the home (Herwaldt et al. 2000).

The most recent report of triatomines found adapting to the domestic setting is revealed in the fourth scenario that describes an outbreak of *T. cruzi* infection among

dogs in Texas (Beard et al. 2003). This outbreak led to a survey of dwellings in the area that resulted in the discovery of infected *T. gerstaeckeri* isolates around the household where the dogs resided. This report served as the initial catalyst for this thesis and is an example of sylvatic triatomines exhibiting qualities of domesticity.

Reports indicate that isolates from the *T. lecticularia* species were found in human dwellings as well as in beds and hidden in cracks (Lent and Wygodzinsky 1979). This species has been closely tied to and sometimes mislabeled as *T. sanguisuga* (Usinger 1944); however, the range of *T. lecticularia* is one of the three largest in the United States as compared to the range of other triatomine species (Lent and Wygodzinsky 1979).

The anecdotes described above serve to justify using certain triatomine species as focal points in this study. As a result, this analysis focuses on three triatomine species, the *T. protracta*, *T. sanguisuga*, and *T. lecticularia* which all have the ability to serve as natural vectors for *T. cruzi* as well as encompass the widest distribution range in the United States and (Lent and Wygodzinsky 1979). These species have been reported in and around human dwellings and are well documented in numerous entomological reports (Woody and Woody 1955; Anonymous 1956; Betz et al. 1984; Schiffler et al. 1984; Navin et al. 1985; Ochs et al. 1996; Herwaldt et al. 2000).

2.6.2 Triatomines reported living with or biting dogs in the United States

The threat of zoonotic disease transmission to domestic animals is a focal point in landscape epidemiology (Patz et al. 2004). When domestic animals are found to be seropositive for a normally sylvatic disease agent, not only does it indicate human encroachment into the vector habitat but it also places the disease agent in a reservoir that is closely linked to humans (Patz et al. 2004). Examples of this are found in reports that the *T. sanguisuga* and *T. gerstaeckeri* species in the United States have bitten domestic dogs (Bradley et al. 2000; Beard et al. 2003).

When the literature indicates that a certain species feeds on dogs, it is considered to be a quality of domesticity for the purpose of this study. It represents the opportunity of increased proximity between triatomines and humans, therefore resulting in increased risk of disease transmission (Enger et al. 2004; Crisante et al. 2006). Diagnosis of *T. cruzi*

in dogs is complicated (Barr et al. 1995; Meurs et al. 1998), and in the United States limited studies have been conducted looking at the link between infected dogs and the triatomine vector. *T. cruzi* is reportedly more common in dogs that live close to sylvatic reservoir hosts, perhaps due to the consumption of dead reservoir hosts by dogs (Barr et al. 1995), or through their ingestion of infected insects (Barr et al. 1995; Bradley et al. 2000).

A report of seropositive puppies in Virginia states that there were no symptoms or abnormalities to indicate myocardial damage (Barr et al. 1995). This detail illustrates the ability of *T. cruzi* to be maintained in a dog's bloodstream without diagnosis and verifies that dogs may serve as reservoirs (Barr et al. 1995). If dogs are proven to be reservoirs, it is an indication that the disease nidus has changed and may be maintained in closer proximity to humans resulting in an increased risk of Chagas disease emergence. It is hypothesized that the puppies in this study became infected through the placenta or through nursing (Barr et al. 1995).

Furthermore, evidence of increasing triatomine domesticity is apparent in a retrospective study that analyzed the records of 11 seropositive dogs from Texas between 1987 and 1996 (Meurs et al. 1998). Positive *T. cruzi* results in dogs increased from 1.8% in 1987 to 17.1% in 1996 (Meurs et al. 1998). This noticeable rise may be due to increased disease awareness among veterinarians (Meurs et al. 1998), but it does not diminish the fact that the disease exists among domestic dogs in the United States. This particular study exposes the need for more research into the possibility of *T. cruzi* transmission to dogs, and the role they may play in transmission of the disease agent to humans.

2.6.3 Triatomines reported biting humans in the United States

As human populations grow and encroach upon undeveloped areas, there is a greater chance for human contact with disease vectors. The concept of a natural disease nidus in landscape epidemiology describes a zoonotic disease transmission cycle (Meade and Erickson 2005). *T. cruzi* is considered to have a natural disease nidus in the United States because it is maintained between the triatomine vector and sylvatic reservoir host.

The following literature specifies cases where triatomines in the United States have reportedly bitten humans thus creating an opportunity for disease transmission; for the purposes of this thesis, such reports are considered to represent the quality of domesticity.

The first case of Chagas disease in the United States was diagnosed in Corpus Christi, Texas, and an examination did not reveal bites on the patient yet the patient's father reported being bitten frequently at night by triatomines (Woody and Woody 1955). There is no mention of species type in the report. In the fourth case of Chagas disease in the United States, the deceased child's mother stated that there were insect bites on the child in the weeks before he became ill. There is no confirmation that the bites were from a triatomine; however, the home and its surroundings displayed qualities favorable for triatomine habitat (e.g. trees and decaying vegetation) (Betz et al. 1984). The fifth case indicates the presence of insect bites on the patient's legs as well as the discovery of an infected *T. sanguisuga* isolate in the patient's bed (Herwaldt et al. 2000). The isolate was engorged with blood, therefore leading to the assumption that a bite had occurred (Herwaldt et al. 2000).

It is important to note that triatomine bites are often misdiagnosed resulting in underreporting (Vetter 2001). Misdiagnosis may be attributed to the triatomine's nocturnal nature and painless bite (Lent and Wygodzinsky 1979; Vetter 2001). The same protein in the saliva that causes anaphylaxis is also reported as having a numbing effect that allows for blood meal consumption to go undetected (Lent and Wygodzinsky 1979). Accounts of humans being bitten by triatomines are an indicator that there is a present risk of Chagas disease transmission in the United States. Moreover, these accounts illustrate a need to measure the range where triatomine's are found to be most active.

2.7 The role of temperature on triatomine activity

Some triatomine species are more active at higher temperatures (Sjogren and Ryckman 1966; Wood and Wood 1967). Evidence of the relationship between temperature and vector activity is apparent given that all five confirmed cases of Chagas disease in the United States occurred during the hottest months of the year (June, July, and August) (Table 2.1 and Figure 2.2) (Woody and Woody 1955; Anonymous 1956;

Betz et al. 1984; Schiffler et al. 1984; Navin et al. 1985; Ochs et al. 1996; Herwaldt et al. 2000). This section describes reports of triatomines becoming more active in temperatures greater than 19° C (67° F) and illustrates how climate change may affect the potential for disease emergence (Sjogren and Ryckman 1966).

Other supporting evidence of the relationship between triatomine activity and temperature is presented in a study from Redlands, California where *T. protracta* were collected via light traps during a June-October observation period (Sjogren and Ryckman 1966). The greatest number of isolates were captured in evenings following periods of hotter temperatures. The threshold for maximum isolate collection occurred between 19° C (67° F) and 29° C (84° F), with more isolate activity at the higher end of the range. Based on the study, humidity, wind, and precipitation appear to have no correlation with the flight of the *T. protracta*; however, starvation and light intensity do. This conclusion was drawn due to the fact that most isolates collected were in a condition of starvation and within an hour of darkness as well as the discovery of isolates flying to lights near the home (Sjogren and Ryckman 1966). The authors indicate that the *T. protracta*'s increased activity level further supports the assumption that triatomine species are more active in warmer temperatures (Sjogren and Ryckman 1966).

The minimum threshold for transmission of *T. cruzi* is considered 18° C (64° F) and consideration of this, along with the *T. protracta*'s increased activity level at temperatures greater than 19° C (67° F), must be taken into account in order to predict the emergence of Chagas disease (Sjogren and Ryckman 1966; Patz and Olson 2006). Furthermore, the global temperature is predicted to rise as much as 1° C (2° F) by 2030 (IPCC 2001). This temperature increase may result in increased triatomine activity, possibly placing a larger population at increased risk for *T. cruzi* infection. Therefore, modeling the potential triatomine range based on climate conditions and change is useful in illustrating where disease emergence may occur.

2.8 The role of physician and public awareness in the amelioration of Chagas disease

By combining the landscape epidemiology of triatomine with a measurement of physician and public awareness, one can gain a broader understanding of the potential for the emergence of Chagas disease in the United States. The diagnosis of the five human autochthonous Chagas disease cases in the United States corresponds to decades in which there was a considerable increase in Chagas disease research and publication (Table 2.1) (Woody and Woody 1955; Anonymous 1956; Betz et al. 1984; Schiffler et al. 1984; Navin et al. 1985; Ochs et al. 1996; Herwaldt et al. 2000). The link between publication and the cases diagnosed in the United States is the working hypothesis that is set within the context of disease ecology and is the premise for the physician survey conducted as part of this thesis research.

Coutinho's (1999 Figures, Reproduced with permission by Sage Publications) scattergraph illustrates upward trends in Chagas disease publication around the time in which four out of the five diagnosed cases occurred in the United States (Figure 2.4). The fifth case diagnosed in 1998 occurred after a mother recognized a *T. sanguisuga* in her son's bed and realized the potential disease threat after watching a program about parasitic insects (Herwaldt et al. 2000). The link between the dissemination of public health information and disease diagnosis must be studied in order to determine if Chagas disease is perceived to be a threat in the United States. This link supports the notion that the perceived low risk currently associated with Chagas disease in the United States is more a lack of awareness than it is a lack of actual threat.

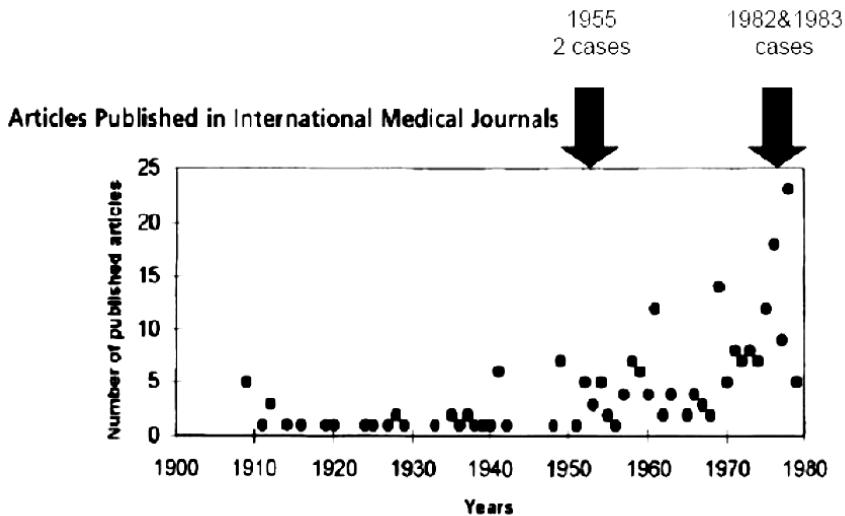


Figure 2.4 International articles published on Chagas disease (Coutinho 1999 Figures, Reproduced with permission by Sage Publications) and the positive correlation with 4 of the 5 diagnosed cases in the United States.

2.8.1 Physician awareness of Chagas disease

In order to eradicate or control established diseases and prevent emergence in new locations, there must be an ongoing dialogue among public health professionals and the general population. First, the health community and the public must recognize that a disease exists before control or eradication can occur. Second, in order to control or eradicate a disease, the routes of disease transmission must be made known to the public.

Deficiencies in Chagas disease awareness is exemplified by a 1992 Mississippi case study of an Hispanic immigrant in the chronic phase of Chagas disease (Holbert et al. 1995). The patient had reported long-term psychiatric treatment for acute depression two years prior to a heart problem; consequently, the physicians evaluated the patient for *T. cruzi* based on the patient's history and origin. The physicians state that the symptoms presented in the acute stage (i.e. acute depression) are often misdiagnosed and that the differential diagnosis does not consider Chagas disease unless there is a strong indication (Holbert et al. 1995). This event illustrates how a misdiagnosis in the acute state of Chagas disease can result in a chronic heart condition years later and indicates a need to explore physician awareness of Chagas disease in the United States.

Another example of misdiagnosis is related to the 1983 case of Chagas disease in the United States. The diagnosis of Chagas disease was not made until almost a year after the victim's death when a physician was preparing to present a viral myocarditis case at a pathology conference (Betz et al. 1984; Ochs et al. 1996). Events such as these support the idea that Chagas disease is commonly misdiagnosed creating an added need for greater physician awareness.

The shared border with Mexico as well as the high emigration from Mexico into the United States has created concern about the status of the blood supply as well. Studies of blood banks in Mexico have revealed a 1 in 133 donor *T. cruzi* prevalence rate (0.75%) (Kirchhoff et al. 2006). Of particular interest in this study is the discovery that 4 recipients of infected blood in Mexico displayed acute symptoms of Chagas disease; however, the physicians failed to make the diagnosis. Kirchhoff et al. (2006) attribute this to the mild symptoms and the physicians' lack of awareness with respect to Chagas disease transmission through blood transfusion, which yields approximately 1,800 new Chagas disease cases each year in Mexico.

2.8.2 Public awareness of Chagas disease

Not only is disease awareness among health professionals crucial in the control and eradication of disease but so is the awareness of the public. Evidence indicates that public knowledge of Chagas disease and its triatomine vector lessens the occurrence of the disease (Ramsey et al. 2005; Sánchez-Guillén et al. 2006). For instance, one study reveals that only 10% of patients that tested positive for *T. cruzi* had any knowledge of Chagas disease (Sánchez-Guillén et al. 2006). Examples illustrating the importance of an informed public can be seen in the case studies of Chagas disease within the United States.

It is suspected that the 1982 case in rural Lake Don Pedro, California occurred when the patient came in contact with infected triatomine feces, but there is no clear indication that a bite occurred. In the vicinity of the home, *T. cruzi* infected *T. protracta* and squirrels were discovered, and a dog tested seropositive (Schiffler et al. 1984; Navin et al. 1985). Interestingly, in a follow-up study, six people residing in the area around the

patient tested seropositive for *T. cruzi* thus indicating disease exposure (Navin et al. 1985). One of the six seropositive patients reported being bitten by a triatomine at some point (Navin et al. 1985). Another example illustrating the importance of the public's awareness of Chagas disease is revealed in the fifth case that was discovered in central Tennessee after a woman watched a program about parasitic insects and later recognized a *T. sanguisuga* in her son's bed (Herwaldt et al. 2000). Having this knowledge prompted her to take her son to see a doctor where he was diagnosed with acute Chagas disease and treated (Herwaldt et al. 2000). The triatomine isolate was sent away for testing and was found to be infected with *T. cruzi* (Herwaldt et al. 2000).

The Tennessee case provides a compelling argument in support of increased public health awareness with respect to Chagas disease. The bite of a triatomine is often misdiagnosed as a spider bite, and can be mistaken as a bite from a number of insects as well (Vetter 2001). This may be due to the triatomine's elusive nocturnal nature and painless bite which allows them to go undetected (Lent and Wygodzinsky 1979; Vetter 2001). Consequently, if the public is not aware that such an insect exists, they will not recognize its presence in their home and therefore may not mention it to their physician if they are bitten.

2.9 Conclusion

The review presented here supports the need for delineating those areas in the United States that are at high risk for the transmission of Chagas disease based upon the range of the triatomine and levels of domesticity expressed by the vector. Furthermore, by analyzing the current triatomine range and the potential range based on warmer temperatures, the potential effect of the triatomine's range expansion on the population can be examined. In addition, the review illustrates the need to survey physicians and the general population in the United States in order to measure their level of Chagas disease awareness.

The theoretical frameworks of landscape epidemiology and disease ecology are applied to this thesis. The landscape epidemiology of the triatomine, which includes the natural disease nidus of the vector and its ability to transmit *T. cruzi*, is combined with

the three factors of disease ecology (population, habitat, and behavior) while evaluating disease awareness. Broadly, combining these approaches allows for a better understanding of the potential for the emergence of Chagas disease in the United States.

In conclusion, this literature review places the thesis in context with the current state of research on the geography of Chagas disease and identifies gaps in the literature that are addressed in this study. The gaps indicate a need to further analyze the current triatomine range in the United States as well as to create models that predict the potential triatomine range based on climate change and other relevant variables, such as changes in landscape and habitat. Furthermore, gaps in the literature reveal a need to explore physician awareness of Chagas disease in the United States. Finally, evaluation of whether or not only Hispanic patients are considered at risk of Chagas disease in a differential diagnosis may be worthwhile.

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Chapter 2 Figures

	Page
Figure 2.1 Schematic of thesis research.....	11
Figure 2.2 Autochthonous Chagas disease in the United States	16
Figure 2.3 Life cycle of the triatomine (CDC image, 2004 www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/TrypanosomiasisAmerican_il.htm)....	23
Figure 2.4 International articles published on Chagas disease (Coutinho 1999 Figures, Reproduced with permission by Sage Publications) and the positive correlation with 4 of the 5 diagnosed cases in the United States	32

Chapter 2 Tables

	Page
Table 2.1 Human Chagas Disease in the United States	16
Table 2.2 United States Summary of Lent and Wygodzinsky's (1979) <i>Triatoma</i> species	19