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A FIELD TRIAL OF AMANTADINE CHEMOPROPHYLAXIS IN ACUTE RESPIRATORY DISEASE

by
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A dissertation submitted in partial fulfillment
of the requirements for the degree of
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ABSTRACT

A FIELD TRIAL OF AMANTADINE CHEMOPROPHYLAXIS IN ACUTE RESPIRATORY DISEASE

By John F. Finklea, M.D.

Amantadine, or adamantanamine 1 hydrochloride, was found to have in vitro antiviral activity against A influenzas in the early 1960's. Prophylactic, but not therapeutic, antiviral activity in vivo was subsequently demonstrated in experimental A_2 influenza infections among laboratory animals and human volunteers. Orally administered amantadine was well tolerated and not metabolized in human beings. Laboratory study suggested that the antiviral activity of amantadine encompassed viruses other than the A influenzas.

The field trial here reported used a modified double blind design and was conducted among 299 boarding student volunteers at a school for retarded but educable children, the Wayne County Training School. Volunteers were assigned either to the amantadine or the placebo group by randomization with restrictions for housing unit and length of residence in the school. Volunteers received an oral dose of amantadine (1.0-2.5 mgm per Kg.) or placebo twice daily during an initial loading period of one week and once daily throughout the remainder of the four month trial. Medication administration was monitored by capsule counts, dose calendars, and assay of biological materials. Sick volunteers were referred daily for clinical observations and specimen collection. Throat swabs for bacteriologic studies, throat washings for viral isolations, and paired sera were collected from each trial illness. Illness was clinically diagnosed according to predetermined criteria.

Analysis of demographic characteristics and medical histories indicated that the placebo and amantadine groups were not significantly different. Amantadine was well tolerated and no side effects occurred that could not be due to chance alone. Both amantadine and placebo groups correctly ingested over 97 per cent of the prescribed medication doses.

During three weeks of pretrial observations the trial groups did not differ significantly in total illness experience or experience with any of the subgroupings of illness. Illnesses were grouped first into streptococcal illness and nonstreptococcal illness and then nonstreptococcal illnesses were subgrouped into "other" illnesses (see page 33 of text) and nonstreptococcal respiratory illness.

During the trial proper the placebo group experienced significantly more total illness, nonstreptococcal illness, acute nonrespiratory illness, and nonstreptococcal respiratory illness. Trial groups did not differ significantly in streptococcal illness. By dividing the trial proper into three six week time periods, the difference between trial groups was found to occur only during the first twelve weeks of the trial.

Virus isolation and serological study associated a portion of trial illness with A_2 or B influenza. Serological study associated another portion of trial illness with one or another of the following agents: Mycoplasma pneumoniae; parainfluenza 1, 2, 3; respiratory syncitial virus; influenza C; or members of the adenovirus group. Significantly less A_2 influenza illness occurred in the amantadine group. The number of illnesses associated with any one of the other agents was too

small to permit statistical testing; but collectively these illnesses did not differ significantly between trial groups.

When all identified illnesses were excluded from the analyses of the entire trial, the placebo group still experienced more nonstreptococcal illness. This difference between trial groups was found to be significant only during the second six weeks of the trial and was caused by an increase in upper respiratory illness of unknown etiology in four housing units. The previously described illness difference between trial groups during the first six weeks of the trial could be ascribed to A_2 influenza alone.

Length of illness did not differ between trial groups in any time division or any illness subgrouping.

Thus amantadine had a significant prophylactic effect against naturally occurring A_2 influenza and this trial suggests an additional prophylactic effect against another respiratory agent which is not currently identified.

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CHAPTER I

INTRODUCTION

Acute respiratory disease ranks first among the causes of morbidity in the United States. This statement is valid whether one considers incidence rates, restricted activity days, bed disability days, school loss days, or work loss days. That mythical average American suffered 1.2 such illnesses each year during the last three years. This represents an annual individual burden of 1.8 bed disability days, 6.9 additional restricted activity days, and 2.4 school loss days or 1.5 work loss days. These losses constitute 30 to 55 per cent of the total in each of these morbidity categories.[1]

This morbidity burden, being greatest in preschool children, school children, and mothers, is unequally distributed. The seasonal fluctuation results in 80 per cent of these illnesses occurring during the fall and winter quarters of the year. An additional striking feature is the year to year fluctuation, which is primarily caused by epidemics of influenza A and influenza B. Thus, if other time periods with epidemic influenza had been chosen as a basis for the morbidity burden, this burden would appear even heavier.

The term acute respiratory disease embraces influenza-pneumonia and other bronchopneumonias. The former consistently ranks fifth and the latter usually tenth among the causes of mortality in the United

States. Together they accounted for 5.2 per cent of total mortality in 1963. Admittedly, many of these deaths occurred in the very young and the very old where they were associated with other disorders. Nevertheless, acute respiratory disease remains an important cause of death, direct or contributory.

The etiologic considerations in acute respiratory disease are complex and confusing. We can easily tally 120 microbiological agents which may be involved. Of these we can clinically diagnose but a few and then only with reservation. The usually available laboratory services are of limited utility and specialized laboratory procedures are expensive, time consuming, rarely available, and at best provide only retrospective etiologic identification.

Etiology is no more of a problem than control. We seem to live in a miasma of these agents. We know little of monitoring this miasma and can only speculate about removing it. Immunization is complicated by the number of agents and problems of vaccine development, production, and administration. Our treatment measures are limited to sympathy, support, and antibacterials. As applied, antibacterials are restricted in efficacy, expensive, and even potentially harmful. Physicians have had no chemotherapeutic or chemoprophylatic substance effective against the viral agents which undoubtedly are the cause of most of these disorders.

When a potential chemoprophylactic drug of demonstrated safety became available, it was important to conduct a clinical trial to begin to answer questions about efficacy and practicability. The study here reported describes the planning, organization, conduct and evaluation of

such a trial in children resident in a training school for the educable but mentally retarded.

CHAPTER II

HISTORICAL REVIEW OF AMANTADINE

A. Physical Properties: Amantadine hydrochloride (Figure II.1) is a synthetic organic compound described by Setter in 1960.[2] This salt of a symmetrical C-10 primary amine has a molecular weight of 187. The amine is a somewhat volatile, thermally stable solid with a pKa of 9.0. Vapor phase chromatography, yielding a single peak, provides a sensitive and specific method for quantitative assay of amantadine in body fluids or tissue.[3]

B. Pharmacology[3,4]

1. Absorption: Amantadine given orally is well absorbed in all species studied, namely, man, mouse, rat, dog, rabbit and monkey. This is shown within a species by a low level of the compound in the feces and a regularity of urinary excretion over a wide range of doses. Further evidence for excellent oral absorption is that blood levels after intraperitoneal (mouse) or intravenous (dog, monkey) injection are no higher than after ingestion.

2. Distribution: Blood and tissue distribution of amantadine has been studied in the mouse, rat and dog. In each species drug levels were highest in the kidney, liver and lung; intermediate in the heart

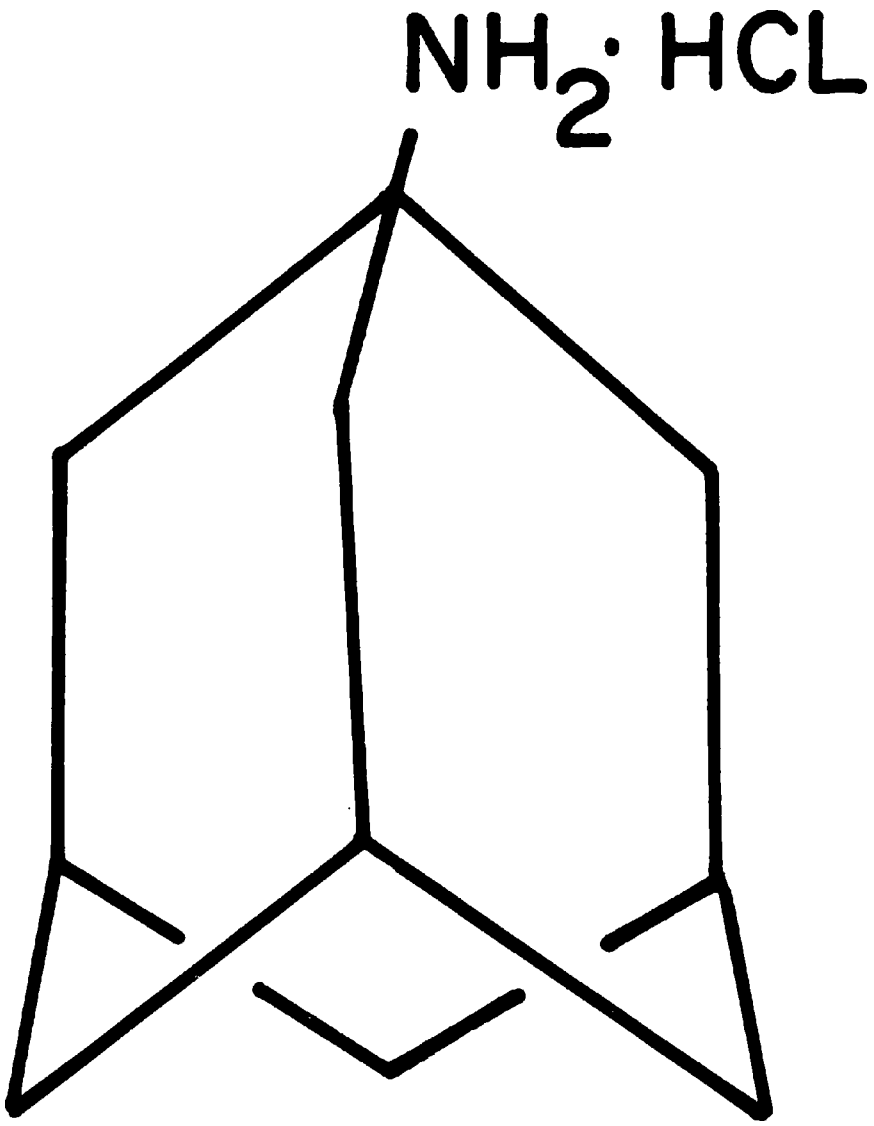


Figure II.1

Amantadine Hydrochloride

and brain; and lowest in the blood. After the drug is discontinued, there is no significant tissue retention of amantadine in the dog. Lack of retention is shown by the presence of less than one part per million of amantadine in eight selected tissues of a dog autopsied 24 hours after the last of thirty successive daily doses.

3. Metabolism: All laboratory animals studied, but not man, metabolize amantadine to some extent. Metabolism is demonstrated by extraneous peaks on vapor phase chromatography of urine and a significant deficit in the amount of drug which can be recovered unchanged in the urine. N-Methylamantadine has been identified in the dog but not in any other species. Unknown metabolites are present in the urine of the mouse, rat, rabbit and monkey. In man amantadine is not metabolized because it is excreted quantitatively and unchanged.

4. Excretion: The only significant route of amantadine excretion is renal. In man an average of 86 per cent of the drug is recovered unchanged in the urine. Other species show less recovery of unchanged drug because of metabolism. Recovery values range from 70 per cent for the mouse to about 20 per cent in the rat and dog. Over all species studied, less than 3 per cent of the drug was found in feces. No drug was seen in expired air of amantadine treated mice. Human saliva exhibits levels of amantadine which reflect blood concentration but this is a closed circuit because swallowed drug is reabsorbed.

Half life of amantadine varies with species, being two hours in the mouse and about twenty hours in man. Half life determinations for the rat, dog and monkey are more difficult because of extensive metabolism of the drug.

A half life of 20 hours in a well absorbed drug could mean that amantadine would accumulate to high levels in man. However, the rate of amantadine excretion is seen to be dependent on the amount of drug in the body, i.e., first order kinetics. Drill has said that such a drug will accumulate in the body until the rate of excretion approaches the rate of administration.[5] This has been shown to be true for man.

5. Toxicology: In laboratory animals toxic signs are referable to the nervous and cardiovascular systems. As dosages are increased, animals experience hyperkinesis and hyperirritability, followed by tremors and clonic seizures and ending in respiratory paralysis. Cardiac arrhythmias may be induced in dogs by large intravenous doses of amantadine. No sedative, anti-convulsant, or analgesic properties have been noted in animals. However, there is a weak local anesthetic effect. Wendel has noted insomnia when adult humans are given 400 mgm of amantadine for several days.[6] No other toxic signs or symptoms have been reported in man.

C. Antiviral Spectrum

1. Systems Used: A variety of systems have been used by a number of investigators to explore the antiviral activity of amantadine. These systems include many different cell types in tissue culture, organ cultures, chick embryos, mice, ferrets and man. A number of different methods may be applied to each system to deflect antiorial activity. Moreover, virus strains, virus dose, amantadine dose and a host of other variables are present. Thus, it is expected that the antiviral spectrum of amantadine will vary from study to study.

2. Viruses Generally Inhibited: Complete suppression of virus production by amantadine has not been observed in any system with any virus.[4] Influenza type A is generally inhibited by amantadine, but groups of type A vary greatly in their degree of susceptibility. Among the human groups of influenza, A_2 strains are most susceptible. The susceptibility gradient continues downward with A_1 strains, A_0 strains and A_{porci}. Among animal influenzas, A_{Duck} and A/Equi/Miami/65 are equally susceptible (but A/Equi/Prague/56 is less susceptible than A/Equi/Miami/63). Within groups there is strain variation in susceptibility. For example, the PR8 strain of A_0 is less susceptible than the WSN strain.[4,7,8,9,10]

This picture is further complicated when other variables are considered. The system used is important. Influenza A strains are inhibited in tissue culture monolayers, chick embryos and mice, but not in ferrets. Indeed, influenza A infection in ferrets is "aggravated rather than alleviated by amantadine."[8] In organ cultures of human foetal nasal or tracheal epithelium A_2 influenza affects on ciliary activity are delayed by amantadine; but virus production after the first replicative cycle actually is enhanced.[9] The time of drug treatment is crucial. In most type A infections amantadine must be used prophylactically. However, mice with A_2 infections have responded to therapeutic amantadine begun as late as 72 hours after the infecting dose.[4] Likewise, the dose of infecting virus and the dose of drug have an influence. The degree of amantadine inhibition of mouse influenza A varies directly with the drug dose and inversely with the dose of infecting virus.[4] Lastly, the route of infection affects inhibition. A_{WSN} infections of

mice are inhibited if the infecting dose is administered intranasally but not with intracerebral infection.

3. Viruses Sometimes Inhibited: Other myxoviruses, pseudorabies and rubella, are sometimes inhibited by amantadine. Cochran et al. have shown inhibition of respiratory syncitial virus, parainfluenza 2, and parainfluenza 3.[8] This inhibition of cytopathogenic effect and virus production was observed in tissue culture after a low infecting dose of virus and high doses of amantadine. The same investigators observed a moderation of mouse influenza B infection. Other investigators have found influenza C, parainfluenza 1/Sendai, and pseudorabies/Aujesky to be inhibited in tissue culture.[12] Maassab discovered that amantadine would inhibit rubella in tissue culture infected acutely but not chronically.[11]

These studies showing amantadine inhibition are opposed by other studies which show no inhibition. Several workers have found all three parainfluenza types and respiratory syncitial virus insensitive to amantadine inhibition in tissue culture.[7,12] The results need not be contradictory as the studies utilized different culture systems, infecting doses and drug doses. Amantadine does not inhibit several strains of influenza B in chick embryos or in tissue culture.[12] Again, the apparent contradiction may be caused by the different systems used.

4. Viruses Not Inhibited: Amantadine inhibition has not been demonstrated with other viruses which cause respiratory symptoms in man. At least five strains of M and H rhinoviruses are not inhibited in tissue cultures. Likewise, adenoviruses (2, 4, 7), representative

enteroviruses and herpes simplex are not inhibited by amantadine.[7,9,12] For other nonrespiratory viruses not inhibited the reader may consult the review of T. R. Wood.[4]

D. Mode of Action: Hoffman et al. using influenza A_2 in tissue cultures have shown that amantadine probably acts by preventing penetration of the cell by virus.[13] Apparently, virus is not directly inactivated by concentrations of the drug used in tissue culture. Neither virus adsorption to the cell or virus neuraminidase is detectably altered; and infective adsorbed virus may be recovered from adamantine treated systems.[13] Other workers have demonstrated that specific immunity and amantadine are additive. Inhibition of influenza A by aminophenylmethane sulfonic acid which blocks cell penetration and amantadine inhibition are quite similar but not additive.[8,10] Moreover, addition of the aromatic amino acids tyrosine, phenylalanine and proline do not alter amantadine inhibition of influenza in tissue culture. This suggests that competitive inhibition in the metabolism of structurally similar amino acids is not involved in the antiviral activity of amantadine.[10] Influenza A_2 has developed resistance to amantadine in one tissue culture system but not in mice. The mechanism of this resistance is unknown.[8]

E. Prior Human Trials: At this time there have been five human trials reported. There are others in progress or completed but unreported.[14] Three of these trials have been in volunteers experimentally challenged with influenza A_2 virus.[9,15,16] The other two have been

field trials, of which one involved naturally occurring A_2 influenza[6] and the other naturally occurring influenza and rubella.[17]

One group of investigators conducted two double-blind experimental challenge trials of amantadine prophylaxis or therapeusis by instilling live attenuated influenza A_2 virus intranasally. In each case they divided several hundred college students into placebo and drug groups on the basis of pretrial hemagglutination inhibition antibody titers. Trial results were assessed in terms of clinical illness and four fold hemagglutination inhibition antibody titer rises. In the 1962 trial significantly fewer rises occurred in the low antibody, amantadine pretreated group when compared to a similar placebo group. In those with high antibody titer fewer rises occurred in the amantadine pretreated group than in a similar placebo group but the difference was not statistically significant. However, no beneficial effect was observed in either high or low antibody groups when amantadine was given therapeutically. There were few clinical illnesses in either group. These results were extended and confirmed in the second trial in 1964.[15,16]

In 1964 another group of investigators pretreated volunteers with amantadine or a placebo and subjected them to intranasal instillation of unattenuated influenza A_2 virus. There was no difference between amantadine and placebo groups in serological response or clinical illness in this trial. However, the subjects were only twenty in number and prechallenge antibody titers are not known.[9]

A field trial of amantadine prophylaxis and therapeusis in 850 prisoner volunteers was undertaken by Wendel during an epidemic of A_2

influenza in 1963. In this double blind study, prophylactic amantadine exhibited a significant protective effect by reducing both clinical illness and serological rises. Therapeutic amantadine did not alter the serologic response or duration of illness; but clinical symptoms were ameliorated by the drug. In this study no virus was isolated and there were design difficulties, in that the populations may not have been exposed equally to risk.[6]

In another field trial, 1964, Quilligan studied amantadine prophylaxis in volunteers from a California state hospital for mentally retarded children. Some 125 children were divided into one placebo and four drug groups after matching groups for age, sex and influenza vaccine status. Volunteers were bled prior to the study and at monthly intervals thereafter. The investigators believed they demonstrated that prophylactic amantadine significantly reduced clinical and serological influenza. Prophylaxis was most effective in individuals with high antibody titers. Attempted amantadine prophylaxis of rubella was not successful.[17]

CHAPTER III

MATERIALS AND METHODS

A. Goals: The study was designed to answer four questions about amantadine prophylaxis in acute respiratory disease. First, does amantadine prophylaxis lower the incidence of acute respiratory disease? Second, does amantadine prophylaxis alter the length of illness in acute respiratory disease? Third, what microbiological agents, if any, are inhibited by amantadine prophylaxis? Fourth, is it possible to administer daily prophylactic medication in a school population?

B. Field Methods

1. Site

a. Location, Time: The study was carried out at a facility for mentally retarded, but educable children, the Wayne County Training School (WCTS). This school is located near Northville, Michigan, and has a population of about 500 boarding students who range in age from 8 to 20 years.

Preparatory study began at WCTS in October 1964. Pretrial observations commenced in January 1965, and the trial proper lasted for four months, from February 10 to June 10, 1965.

b. Housing: WCTS students live in sixteen housing units, called cottages (Figure III.1). Each cottage usually shelters from 20

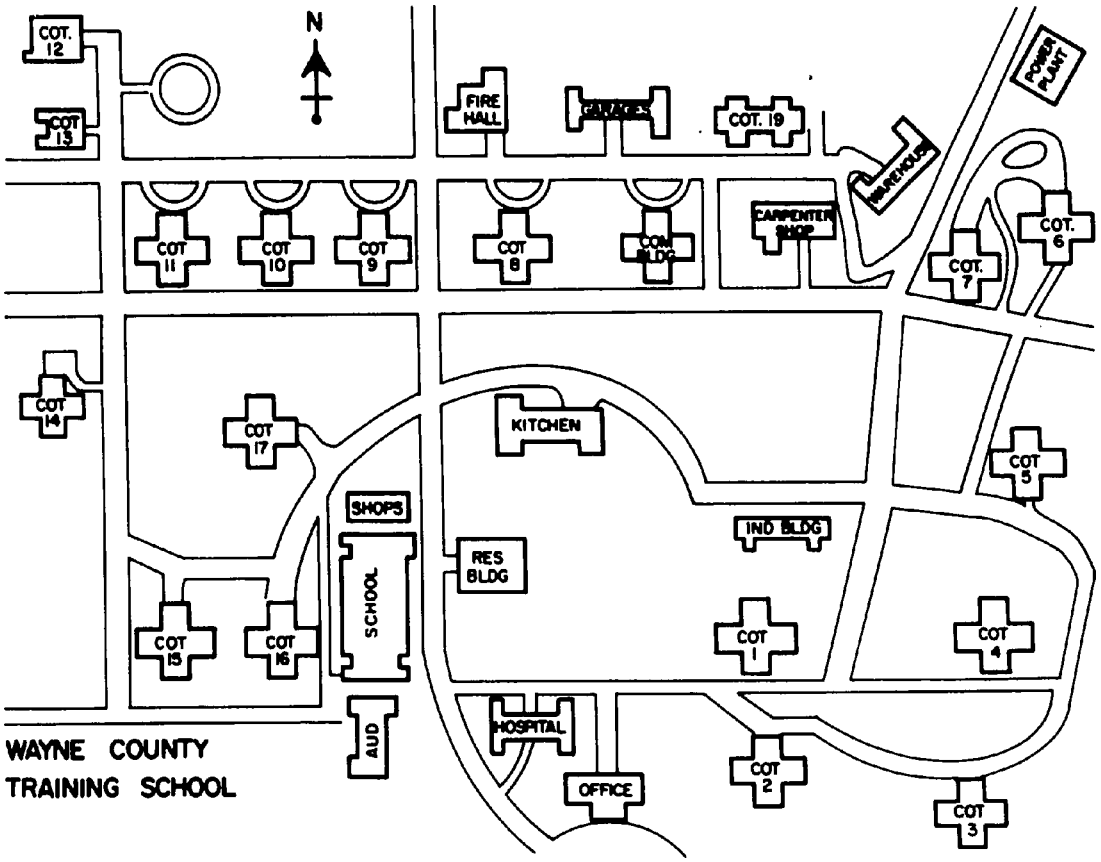


Figure III.1

Map of the Wayne County Training School

to 40 students of the same sex and a similar age. Students sleep, eat and have their recreational activities in cottage groups. Cottage groups intermingle in classes in the academic program of the school. In addition, students from several cottages mix with school employees and the general public in student vocational assignments.

c. Cottage Parents: Within each cottage there are school employees who are called "cottage parents." One or two of these employees are on duty at all times during any 24-hour period. Generally, an employee will be assigned to a single cottage for several months or more. These employees minister to the children and dispense needed medications much like parents in a home.

d. Regular Medical Care: Each student has a medical history form, which is completed by a physician prior to WCTS admission. Shortly after admission, a pediatrician performs a complete physical examination, a routine urinalysis and a hemoglobin determination.

Cottage parents observe children for illness and refer those who are ill to the medical clinic. The medical clinic divides this illness burden among four daily sick calls. Staff nurses screen complaints during sick calls and schedule selected children for consultation with a visiting physician. One of the two visiting physicians conducts a daily clinic at the school. If necessary, a child may be referred to the University of Michigan Medical Center for special medical care.

There are two WCTS infirmary units, one for each sex. Children are admitted to the infirmary if their oral temperature exceeds 101°F on a sick call visit or if some other condition requires bed rest.

One or two nurses are on duty in the infirmary units at all times.

e. Academic School: Students may attend the academic school full time or may combine a vocational assignment with academic pursuits. A few students are on full time vocational assignment, usually in preparation for discharge. The academic school is generally staffed by teachers with special education training and offers a wide range of activities.

f. Other Facilities: WCTS has a resident dentist to care for students. A staff of social workers compiles a social history for each student and works with the student and his family. Two psychologists carry out intelligence testing. Three visiting psychiatrists are involved with selected groups of children in psychotherapy. Lastly, there is an active organization of the parents of the students.

2. Estimates of Illness

a. WCTS Records: The WCTS medical staff estimated that about 40 per cent of sick call visits were caused by acute respiratory illness and that each illness required four to five clinic visits. The total number of WCTS clinic visits for the period July 1963 to August 1964 was available during the planning phase of the study. Thus, an estimated number of past WCTS student respiratory illnesses for the preceding fourteen months could be computed as follows:

$$\text{Estimated number respiratory illness} = \frac{.4(\text{Total Number of Clinic Visits})}{5(\text{Visits per Illness})} =$$

.08 of total number of clinic visits.

Estimated incidence rates can be obtained from such estimates by dividing the number of respiratory illnesses during a time period by the population at risk during that time period. Table III.1 shows an actual count of clinic visits, the estimated number of respiratory illnesses, and estimated respiratory illness incidence rates for the period from July 1963 to August 1964. The mean estimated monthly number of respiratory illnesses is 213. The mean estimated monthly respiratory illness incidence rate is 38.7 per hundred of population.

TABLE III.1

WCTS, ESTIMATES OF PREVIOUS RESPIRATORY ILLNESS INCIDENCE RATES PER HUNDRED OF POPULATION

Year	Month	Total Number of Clinic Visits	Estimated Number of Respiratory Illnesses*	Estimated Monthly Incidence per 100 of Population**
1963	July	2343	187.4	34.1
1963	August	2610	208.8	38.0
1963	Sept.	2574	206.3	37.5
1963	Oct.	3172	253.7	46.2
1963	Nov.	2698	215.8	39.3
1963	Dec.	2332	186.6	34.0
1964	Jan.	3236	258.8	47.1
1964	Feb.	2663	210.6	38.3
1964	March	2909	232.7	42.4
1964	April	2778	222.2	40.4
1964	May	2862	229.0	41.7
1964	June	1942	153.3	27.9
1964	July	2755	222.0	40.4
1964	August	2382	190.6	34.7
Mean		2663	213.0	38.7

*.08 times the total number of clinic visits

**$\frac{\text{Estimated number of respiratory illness per month}}{\text{Average number of students during the month}} \times 100.$

This estimate disagreed with monthly incidence rates computed from the records of individual students. Three hundred such records showed a mean monthly respiratory illness incidence rate of only 17.6 per hundred of population.

Both estimates were within incidence rate ranges reported by other observers in various populations.[18,19,20] However, both exceeded the 6 to 16 year age group rate of 11.2 respiratory illnesses per hundred of population per month computed from National Health Survey figures for the years 1963 and 1964.[1]

The number of expected respiratory illnesses during the four month period of the study could be computed for study groups of various sizes by using both sets of WCTS estimates. This is shown in Table III.2.

TABLE III.2

WCTS EXPECTED RESPIRATORY ILLNESSES DURING A FOUR MONTH PERIOD, DISTRIBUTION ACCORDING TO SIZE OF STUDY GROUP AND METHOD OF ESTIMATION

Number in Study Group	Expected Respiratory Illnesses	
	Using Total Clinic Visit Estimate	Using Individuals' Record Estimate
50	77.4	35.2
100	154.8	70.4
150	222.2	105.6
200	309.6	140.8
300	464.4	151.2

WCTS infirmary records revealed that there were 12 to 15 monthly admissions of students with febrile respiratory illness during 1964, a noninfluenza year. The WCTS student incidence rate for febrile respiratory illness was 2.55 per hundred of population per month during 1964. Similar incidence rates were noted in the pre-influenza period in 1952.[21] Table III.3 presents the expected number of febrile respiratory illnesses for study groups of various sizes during a four month trial.

TABLE III.3

WCTS EXPECTED NUMBER OF FEBRILE (>101°F) RESPIRATORY ILLNESSES DURING A FOUR MONTH TRIAL. DISTRIBUTION BY STUDY GROUP SIZE

Study Group Size	Expected* Number of Febrile Respiratory Illnesses
50	5.1
100	10.2
150	15.3
200	20.4
300	30.6

*Expected number of illness = $\frac{2.55 \text{ cases} \times 4 \text{ months}}{100 \text{ person-months}} \times$ number of persons in group

It was expected that influenza A_2, if it should occur, would have an attack rate of 5 to 15 per cent in this population with previous A_2 antigenic experience.[21,22]

b. Expected Respiratory Illness and Observable Protection: If one is to observe protection, there must be sufficient illness of the appropriate type during the trial period. The maxim is more simply stated, "No illness, no trial."

The number of expected illnesses necessary for a trial varies inversely with the assumed protective effect of the procedure which is being investigated. That is, only a few illnesses are required to evaluate a highly protective procedure; but many illnesses must be observed to evaluate a procedure with little protective effect. Table III.4 relates the number of needed respiratory illnesses in a placebo group to assumed protective effect in a treated group, and a "chance" p value of .05.

TABLE III.4

RELATIONSHIP BETWEEN NEEDED RESPIRATORY ILLNESSES IN THE PLACEBO GROUP AND ASSUMED PROTECTIVE EFFECT OF TREATMENT, GIVEN p = .05

Assumed Protective Effect of Treatment	Number of Needed Respiratory Illnesses in Placebo Group
.1	> 75 <100
.2	> 30 < 50
.3	> 25 < 30
.4	> 15 < 20
.5	> 10 < 15

Two trial groups of 100 to 150 volunteers would be needed to detect a 10 per cent overall protective effect of amantadine prophylaxis. This conclusion can be drawn by consulting Table III.5. Only larger protective effects might be observed when specific etiologic agents are

considered, because any agent would produce only a portion of the expected respiratory illness. For example, a 50 per cent level of effectiveness could be detected if ten to fifteen cases of influenza A_2 were present in the placebo group. This number of A_2 influenza cases could be expected in trial groups of 100 to 150 each.

TABLE III.5

RELATIONSHIP BETWEEN NECESSARY TRIAL GROUP SIZE AND ASSUMED PROTECTIVE EFFECT, GIVEN p = .05

Assumed Protective Effect	Necessary Trial Group Size	
	Total Clinic Visit Record Estimate	Individual Record Record Estimate
.1	> 50 <100	>100 <150
.2	> 20 < 40	> 50 < 75
.3	> 16 < 20	> 30 < 50
.4	> 10 < 16	> 20 < 30
.5	< 10	> 15 < 25

3. Study Population

a. Study Eligible WCTS Population: Only a portion of WCTS students was eligible to become volunteers. Children were not eligible when they received tranquilizers, amphetamines, anticonvulsants, or other sympathomimetic amines. Fifty-three of the 490 children in residence during study planning were not eligible for these reasons.

Table III.6 summarizes the total and study eligible populations. The noneligible students were distributed over all ages and both sexes. Both the total and study eligible populations contain about 30 per cent females and 70 per cent males. Prepubertal children comprised one-third and pubertal or post pubertal students two-thirds of the eligible population.

TABLE III.6

WCTS TOTAL AND STUDY ELIGIBLE POPULATIONS
DISTRIBUTION BY AGE AND SEX

Age (Yrs)	Total Population			Study Eligible Population		
	Males	Females	Subtotal	Males	Females	Subtotal
8-13	113	35	148	103	32	135
13-15	110	55	165	105	48	153
> 15	125	52	177	109	50	159
Total	348	142	490	317	130	447

b. Volunteers, Call and Response: An attempt was made on two occasions to contact the family of each WCTS student. Appendix A-1 contains the letters, information sheet, and permission card which were enclosed in these mailings. Requests for participation were sent to families of study eligible and noneligible students. The families of noneligible students were queried so that no family would feel slighted.

Table III.7 reveals the response to this call for volunteers. Ninety-four per cent of families were contacted; but only 70 per cent of those contacted responded. Of the responders, 90.2 per cent

volunteered their children. Of the volunteers, 90.6 per cent were study eligible. Eligible volunteers accounted for 53.9 per cent of the total population.

TABLE III.7

WCTS CALL FOR VOLUNTEERS AND RESPONSE

Factor	Number	Per Cent of Total Mailing	Per Cent of Families Contacted	Per Cent of Families Replying	Per Cent of Volunteers
Total mailed	555	--	--	--	--
Not contacted	32	5.8	--	--	--
Contacted	523	94.2	--	--	--
Contacted					
No reply	157	28.3	30.0	--	--
Reply	366	65.9	70.0	--	--
Reply					
Not volunteering	36	6.5	6.9	9.8	--
Volunteering	330	59.4	63.1	90.2	--
Volunteer					
Not eligible	31	5.6	5.9	8.5	9.4
Eligible	299	53.9	57.2	81.7	90.6

The total mailing of 555 exceeds the previously mentioned population total of 490 because of school admissions after the planning survey and during the period when volunteers could be admitted to the study.

c. Assignment of Volunteers to Trial Groups: Eligible volunteers were assigned to an amantadine group or a placebo group. First, the eligible volunteers were divided into groups by cottage

residence. Then, eligible volunteers within a cottage were divided into two groups, depending on length of residence at WCTS. Eligible volunteers of less than one year's residence composed one group, and eligible volunteers of more than one year's residence composed the other group. Volunteers in each of these groups were listed alphabetically and numbered. This list was partitioned into amantadine and placebo groups by assigning odd numbers to the amantadine group and even numbers to the placebo group.

Blocking for cottage and length of school residence had been shown advisable in a previous study.[21] Unless acute respiratory illness is dependent on alphabetical order, the sample should be random with an excess of about sixteen volunteers in the amantadine group.

d. Entrance, Exit, and Cottage Transfers: The WCTS amantadine trial was open-ended in that study eligible volunteers could enter up to April 10, 1964. New volunteers were assigned the next listed number and placed in the appropriate trial group.

Exits or removals from the study could be occasioned by discharge from the school, suspected pregnancy, treatment with tranquilizers or anticonvulsants, or an expressed desire of a volunteer to cease participation.

If a child were transferred from one cottage to another, the child would continue in the same trial group, i.e., "once placebo, always placebo" or "once amantadine, always amantadine." WCTS record study revealed that 30 to 40 transfers could be expected in a study population of 300 students during a four month trial.

4. Drug Dosage

a. DuPont Recommendations: The DuPont Company, producers of the drug, recommended that 3 mgm per Kg. be given to adults for several days followed by 1.5 mgm per Kg. for several weeks.[23] Since amantadine has a half-life of twenty hours and is excreted by first order kinetics in the human (see Chapter II), the initial higher dose loads the body and the lower dose maintains recommended levels of drug in the tissues.

b. Expected Volunteer Dose: Cottage drug dosage had to be standardized so that each cottage parent could readily administer medication to as many as thirty children daily. A standard dose would be feasible if there were not a great variation in volunteer weights. The possibility of using one standard dose for prepubertal volunteers and another for pubertal and postpubertal volunteers was suggested by WCTS policy. This policy assigned children to cottages on the basis of sex and puberty.

The author examined weight distribution of both sexes for the ages in residence at the School. The ages with the greatest variation in weight were the pubertal years. The decision could then be made to give 60 mgm of amantadine to prepubertal volunteers and 100 mgm to pubertal and postpubertal volunteers. Table III.8 shows the distribution of the portion of the population by sex and age which would receive an acceptable daily dose of amantadine, 1.0-2.5 mgm/Kg, if a 60 mgm or 100 mgm capsule were ingested once daily.

TABLE III.8

PROPORTION OF VOLUNTEERS OF VARIOUS AGES AND BOTH SEXES EXPECTED TO RECEIVE ACCEPTABLE DAILY DOSE OF AMANTADINE UNDER THE 60 mgm OR 100 mgm DAILY DOSE SCHEDULE

Age in Years	Sex	Daily Drug Dose/mgm	Percentage of Population Expected to Receive 1.0 to 2.5 mgm/Kg/Day
8	Female	60	81.0
8	Male	60	82.1
9	Female	60	89.0
9	Male	60	92.4
10	Female	60	95.5
10	Male	60	94.3
11	Female	60	97.9
11	Male	60	97.7
12	Female	60	95.1
		100	74.2
12	Male	60	96.7
		100	64.4
13	Female	60	87.6
		100	88.3
13	Male	60	89.2
		100	79.7
14	Female	100	95.8
14	Male	100	91.8
15	Female	100	98.2
15	Male	100	98.0
16	Female	100	99.0
16	Male	100	99.6
17	Female	100	99.0
17	Male	100	99.9

5. Medication Control

a. Dispensing Capsules: The DuPont Company furnished color coded capsules, containing either drug or placebo. Placebo capsules were green or yellow. Amantadine 60 mgm capsules were dark red; and 100 mgm capsules were light red. Within each cottage, only one color placebo capsule and one color amantadine capsule were dispensed. A week's supply of medication was kept in each cottage. In addition to color coded capsules, each supply bottle was letter coded with A, representing amantadine, or B, representing placebo. Each volunteer knew what color medication he would take throughout the trial.

Separate medication lists for drug and placebo were furnished each month to each cottage. Each list contained the names of all children in one group in that cottage. Lists were related to appropriate capsules by the same letter and color code which was used with capsules and capsule bottles.

Cottage parents were consulted about the best time and method of dispensing capsules to their volunteers. During an initial loading period of one week, both placebo and amantadine capsules were given twice daily. Following this period, all capsules were given once daily throughout the trial. Generally, cottage parents used one of two methods of dispensing. Volunteers were seated at the supper table and each given one capsule to take with a liquid prior to their meal. Alternatively, each child was called up after the evening meal and given a capsule. The child then ingested the capsule with water in the presence of the cottage parent.

If a child was transferred to the infirmary, to a discipline unit, or to another cottage, the remainder of a week's supply of capsules went with him. The study team daily recorded and adjusted cottage and central rosters for these transfers.

b. Test for Color Blindness: Red-green color blindness in cottage parents was a potential source of dispensing error. Study design compensated for this by volunteer awareness of the appropriate capsule color and letter coding of medication lists and bottles. Nevertheless, the study team sought by color vision screening to alert any color blind cottage parents to this potential hazard. A clear plastic box was layered with white cotton; and the four different colored capsules were placed between cotton and plastic. Each employee was asked to identify the color of each capsule.

Table III.9 presents the results of this color vision screening. This shows that two of 51 males (3.9 per cent) and none of 41 females had red-green color blindness. These results agree well with the expected 3 per cent in males and 0.2 per cent in females.[24] Both of the affected males customarily worked at a time when medications were not dispensed.

TABLE III.9

COLOR VISION SCREENING OF COTTAGE PARENTS
DISTRIBUTION OF RESULTS BY SEX

Sex	No Red Green Color Blindness	Red Green Color Blindness
Male	49	2
Female	41	0

c. Weekly Cottage Capsule Count-in and Count-out: The exact capsule requirement for each cottage was computed from a central roster. The required capsules were placed in appropriately labeled bottles and dispensed once weekly to the cottage parents. At that time cottage parents returned the unused portion of the previous week's supply. If a cottage returned a large number of capsules, the study team could immediately review medication procedures. If a cottage consistently returned no capsules, the study team could purposefully place extra capsules in another week's supply. Thus, there could be continual monitoring of capsule dispensing in each cottage. The count-in, count-out form may be found in Appendix A-2.

d. Cottage Dose Calendars: Each list of volunteers in each cottage was constructed with a calendar feature. There was thus a block of space in which each volunteer's daily dose of medication could be indicated. This form is found in Appendix A-3.

From this calendar-dose form the number of missed capsules for each child could be counted. These counts could be correlated with the weekly cottage count-in and count-out forms to further monitor the dispensing of capsules.

e. Week End Slips: About once monthly, volunteers would leave WCTS to visit their families for a weekend. The study team would obtain a leave list and fill out a weekend slip for each child. The weekend slips and envelopes for medication would be delivered to the cottages and appropriate capsules inserted. This packet would be given to the child just prior to departure for home. Children would receive

the departure day dose at WCTS prior to leaving. Since leaves generally began late Friday afternoon and were over Sunday afternoon, only one capsule was usually included. If leaves were to last longer, the appropriate number of capsules were dispensed.

Children were to return the marked weekend slips to their cottage parents who then forwarded these slips to the study clinic. The weekend slip form may be found in Appendix A-d.

f. Drug Assays

1) Goal: The previously described control measures are all designed to answer the question, "Are capsules properly dispensed?" Drug assay of materials from study subjects was designed to answer the questions, "Do volunteers ingest capsules?" and "Do volunteers exchange drug and placebo capsules?" The assay program was begun during the sixth week of the trial. Assays were performed by the DuPont Company who did not know an individual's trial group.

2) Blood Assays: Every third new illness had blood drawn for amantadine determination at the time of acute sera collection. On the same day, a control was randomly chosen from the same cottage and same trial group and bled for amantadine determination. This allowed the control to be matched for age, sex, time, drug group, and cottage of residence.

At the time convalescent sera were obtained most of the amantadine group gave specimens for amantadine blood levels. All bloods were collected in glass B-D vacutubes with lithium oxalate as a preservative and refrigerated at 4°C until shipment to the DuPont Company.

3) Urine Assays: Once or twice weekly the author would arise at 0400 and present himself to a cottage before the students awakened. The morning visit would not be announced to a cottage parent until after midnight. Thus, cottage parents could not know of impending specimen collection until long after all children were asleep.

Cottages and children to be sampled were chosen in a random manner. Children were awakened and escorted to the bathroom where the author or a female employee watched the specimen being collected. These early morning urines are called casual urines.

In selected cases 24 hour urines were collected to confirm drug balance studies. These children were already in the school infirmary and the collection was supervised by infirmary nurses. A child was asked to discard his first morning urine on the day of collection. Then all urine, through the next morning's first voiding, was collected. A blood amantadine level was obtained on the first morning of collection.

All urines were frozen in polyethylene bottles at -20°C while awaiting shipment to the DuPont Company.

6. Clinical Study

a. Cottage Observers: Cottage parents ascertained the fact of illness in volunteers. These observers were not aware of capsule content. Prior to the study, cottage parents were impressed with the necessity of referring to the medical clinic all children with complaints or signs of illness. These employees were accustomed to referring minor illness to the medical clinic, as can be seen from an average of four monthly clinic visits per child in 1964.

b. Regular Medical Clinic: Volunteers were seen as usual at the medical sick calls. The clinic nurses could identify immediately which patients should also be seen in the study clinic because the regular clinic card of each volunteer had been tagged with an indelible green "S.C." for study clinic. These clinic cards are kept in a child's cottage but brought to the medical clinic with each visit.

Each day the nurses were furnished a list of volunteers who were to be seen as study clinic follow-ups. This list was checked after the last sick call and errant patients were contacted.

The study clinic had the opportunity of seeing over 99 per cent of sick children prior to the visiting school physician. Thus, studies could be carried out before any chemotherapy was instituted. The visiting physicians were most cooperative and in no case asked that trial capsules be discontinued. The study clinic provided the visiting physicians with results of routine laboratory work and throat cultures.

c. Study Clinic

1) Location and Facilities: The study clinic was located in small rooms adjacent to the large sick call room. An interview room, three examining rooms, and a laboratory were available. The laboratory was equipped with a centrifuge, a microscope, and a small incubator.

2) Interviewer: Upon entering the study clinic, the newly ill volunteer was greeted by an interviewer. This lady was a former elementary school teacher and an interested worker in civic programs directed toward the mentally retarded. The interviewer questioned the child and filled out the study history form. A copy of the

interviewer instructions and the study history form may be found in Appendix A-6. The interviewer also collected throat washings and prepared the child for physical examination by the physician.

On follow-up visits the interviewer continued to inquire about symptoms and consulted the physician about repeat physical examinations or discharge.

The interviewer assisted in many other ways. She kept the central roster up to date, participated in medication control tasks, filled out daily and weekly prevalence and incidence tallies, and was invaluable in maintaining good relations with the cottage parents, children and nursing staff.. The incidence and/or prevalence tally form may be found in Appendix A-13.

3) Study Physician: The study physician performed a physical examination on each child with a new respiratory illness. Repeat physical examination was performed if a new symptom occurred or old symptom persisted for longer than one week. Within 48 hours after the patient was seen in the study clinic, the physician had to make a clinical diagnosis. In practice, diagnosis was made immediately after the physical examination and routine laboratory work were completed. The physical examination form may be found in Appendix A-7.

The physician performed white blood counts, differential counts, and routine urinalysis on as many febrile patients as was possible. On each new patient the physician collected acute sera on the initial visit. A convalescent sera was obtained about three weeks later. During clinical study, the physician did not know which particular trial group contained any individual child.

d. Criteria for Clinical Classification

1) General: As mentioned, the fact of illness was established by referral to the study clinic. It was decided prior to the trial that there should be a symptom free period of four days before a second episode of illness was counted as a separate new illness.

2) Clinical Syndromes: Prior to the study criteria were established for seven respiratory disease syndromes.[25,26] These were called coryzal, pharyngeal, laryngeal, bronchitis, pneumonitis, herpangina, and acute undifferentiated respiratory disease. An "other" category was added. This included "other, no illness," "other, nonrespiratory" (e.g., diarrhea) and "other, respiratory." "Other, respiratory" included otitis externa and isolated otitis media. The diagnostic criteria for the respiratory syndromes may be found in Appendix A-8.

7. Other Population Observations During Trial

a. Employee Absentee Records: WCTS maintains a time sheet which includes all employees and covers a two week interval. The personnel officer, who keeps these records, is also responsible for hospitalization insurance. From these records it was possible to count the number of illnesses and the number of sick days for WCTS employees. Since the number of employees in each of several employee groups was precisely known, incidence rates could be computed. Long term illness was excluded from consideration by consultation with the personnel officer. Appendix A-9 displays a WCTS employee absentee form.

b. Academic School Absentee Records: The academic school keeps a daily record of whether each pupil was present or absent. There

is a separate monthly record for each classroom. The central roster in the study clinic allowed the author to ascertain which children were in discipline units and which were admitted to the infirmary. An "episode" of absence was defined as absence from school for an entire day or more, not caused by disciplinary confinement or nonrespiratory infirmary admission. With this information, weekly absentee "episode" rates and absentee day rates could be computed.

c. Total Medical Clinic Visits: WCTS records list the outpatient medical clinic visits by day and sex. Since the central study roster contained the school population for each week, it was possible to compute medical clinic visit rates for the total population and for each sex.

d. Sick Ward Admission Records: From study clinic records and sick ward admission records, it was possible to compute total and respiratory sick ward admission rates.

C. Laboratory Methods

1. Specimens

a. Throat Washings: Throat washings were obtained on the initial visit for each illness. The sick volunteer gargled 30 ml of beef heart infusion broth (Difco) and expectorated into a paper cup. The washing, with 0.2 per cent gelatin (Coignet Chemical Company), was poured into a sterile lusteroid tube and frozen at -70°C. A delay of up to ten hours could occur between collection and freezing. During this period specimens were stored at 4°C.

b. Throat Swabs: Throat swabs were obtained on the initial visit for each illness. Calcium alginate swabs (Colab Laboratories, Inc.) were rubbed over the tonsilar pillars and posterior pharynx.

c. Acute and Convalescent Sera: Blood was collected in 30 ml vacutubes (Scientific Glass Instrument Company) and allowed to stand at room temperature until clot retraction occurred. Sera was separated by centrifugation and stored at 4°C for several months prior to serological testing.

2. Clinical: Routine urinalysis and blood counts were performed in the customary manner.

3. Drug Assay: The DuPont Company performed amantadine determinations, using the vapor phase chromatography method described by Bleidner.[3]

4. Bacteriology: Routine throat culture swabs were streaked on sheep blood agar plates (Difco) after collection. Plates were inspected at 24 and 48 hours for the presence of beta hemolytic colonies. Plates with beta hemolytic colonies were stored at 4°C for as long as three months and subcultured into broth. After 12 to 24 hours, the broth subcultures were smeared on slides to prepare for streptococcal grouping by a standard direct immuno fluorescent technique. Dr. Warren Eveland performed the grouping using the Difco antiserum.

5. Virus

a. Isolation

1) Specimens Selected: Throat washings were selected on the basis of clinical data which had been coded and punched into cards.

In the first isolation attempts, fourteen throat washings obtained on the first or second day of febrile illness were randomly selected. In the second series, isolations were attempted from ten throat washings obtained from patients in the first or second day of nonstreptococcal respiratory illness during weeks 7 to 13 of the trial. Additional washings were chosen for attempted influenza virus isolation if the corresponding paired sera showed a four-fold antibody rise against influenza A_2 or B.

2) Isolation Systems

a) Chick Embryos: Influenza isolations from throat washings were attempted by amniotic inoculation of ten or eleven day old embryonated White Leghorn eggs, using 0.1 cc amounts of throat washing fluid. Three amniotic passes were made before a specimen was declared negative. Once isolated and egg adapted, influenza viruses were inoculated allantoically.

b) Tissue Culture: Four tissue culture systems were used in isolation attempts: (1) HL cells, a continuous human epithelial line, were obtained from Dr. H. F. Maassab. These cells were placed in a growth medium of x2 Eagles with 5 per cent inactivated calf serum (Microbiological Associates) and later, in a maintenance medium of x2 Eagles with 2 per cent inactivated horse serum (Microbiological Associates). (2) WI38 cells were obtained from Flow Laboratories and a maintenance medium of Eagle's minimal essential medium (MEM) with 2 per cent inactivated calf serum was used. (3) Primary chick kidney m nolayers were obtained from three day old Leghorn chicks. A growth medium

of Eagle's MEM with 10 per cent inactivated calf serum and a maintenance medium of x2 Eagles was used. (4) Primary monkey kidney monolayers were obtained from rhesus monkeys, grown in Melnick's A medium and maintained in Melnick's B medium.

In each cell system the inoculate was 0.2 cc of throat washing. Three blind passages were carried out in all systems, save the WI38 cells, where only two blind passages were used.

c) Identification of Isolates: A daily search for CPE was made in tissue cultures. Each tissue culture passage was checked for hemadsorption with guinea pig cells.[27] Hemadsorption neutralization was used to type influenza virus growing in primary chick kidney menolayers.[28] Hemagglutination was used to detect influenza virus in egg materials.[29]

b. Serology

1) Specimens Selected: Sera were indexed in such a fashion that each individual's bleedings were in chronological sequence and all specimens from a cottage were grouped together. All sera pairs in the study were tested by hemagglutination inhibition and complement fixation against influenza A_2/AA/1/65 and B/Md/1/59. All sera pairs from all illnesses during weeks 7 to 13 of the trial were tested by complement fixation against an adenovirus group antigen. All sera pairs from nonstreptococcal respiratory illnesses during weeks 7 to 13 of the trial were tested by complement fixation against respiratory syncitial virus, parainfluenza (1, 2, 3) viruses, influenza C virus, and Mycoplasma pneumoniae.

2) Serologic Tests

a) Hemagglutination Inhibition: Hemagglutination inhibition tests were performed with the reagents outlined by Davenport and Minuse.[30] The test was modified in that Perspex plastic trays were used instead of tubes. Serial dilutions were performed with a 0.2 ml Takatsy diluting loop. Volumes were modified for the plate method. Thus, 0.2 ml of diluted serum, 0.2 ml of diluted virus, and 0.4 ml of 0.5 per cent rooster red blood cells were used in the modified test.

Antigens used in hemagglutination inhibition testing were A_2/AA/1/65 (AE 6-E4*) and B/Md/1/59 (Mk2-E1-Mk1-E1a). These antigens were produced by allantoic inoculation of 11 day old chick embryos. Allantoic fluids were harvested after 72 hours of incubation at 35°C.

Known human and ferret antisera were furnished by Miss Elva Minuse.

Sera to be tested against A_2/AA/1/65 were trypsin-periodate treated; while wera to be tested against B/Md/1/59 were heat treated at 56°C for 30 minutes.

b) Complement Fixation: Complement fixation testing was carried out by the method of Dr. Stewart-Harris as modified in the Virus Laboratory, University of Michigan. This test was performed in Perspex plastic plates. Complement was obtained by bleeding adult guinea pigs and was preserved at 4°C by the method of Richardson.[31] Antisheep hemolysin was obtained from the Baltimore Biological Laboratory. Sheep erythrocytes were obtained from adult sheep and preserved in Alsever's solution.

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*Six amniotic and four allantoic passages in eggs.

Dr. Arnold S. Monto of the Virus Laboratory, University of Michigan, furnished parainfluenza 1 (2/27/63-MK11), parainfluenza 2 (9/27/63 $Mk5\text{-}MH_3\text{-}Mk_2$), parainfluenza 3 (Mk2), and respiratory syncitial (Long, LID strain, KB6-L2-HEP2-HL3) viruses. Adenovirus group complement fixation antigen was obtained from the Communicable Disease Center, Atlanta, Georgia. Influenza C/Jamaica/64 amniotic fluid was donated by Miss Minuse.

Parainfluenza 1, 2, 3 normal and immune guinea pig sera were purchased from Flow Laboratories. Ferret normal and immune respiratory syncitial virus antisera was given by Dr. Monto. Human adenovirus and influenza immune sera were furnished by Miss Minuse.

Influenza S antigens were prepared from A_2/AA/1/65 and B/Md/1/59 infected embryonated eggs by the method described in the WHO monograph series.[32]

Sera were heat treated at 56°C for 30 minutes prior to testing.

6. Mycoplasma

a. Isolation Attempts: Five throat washings from individuals with nonstreptococcal respiratory disease during trial weeks 7 to 13 were selected for isolation attempts. Isolation attempts were performed as suggested by Chanock.[33]

b. Serology: All sera pairs from nonstreptococcal respiratory illness during weeks 7 to 13 of the trial were tested against Mycoplasma pneumoniae by the complement fixation technique previously described. Mycoplasma pneumoniae antigen was obtained from Robbin Laboratories as was mycoplasma pneumoniae immune rabbit serum.

CHAPTER IV

COMPARISON OF THE AMANTADINE AND PLACEBO GROUPS

A. Introduction: Treatment (Amantadine) and control (placebo) groups must be comparable before any acceptable trial can take place. Some form of randomization is the best method of obtaining comparable treatment and control groups. Blocking, i.e., restriction, prior to randomization assures that the variables, judged most important, will not differ significantly between groups. However, randomization is difficult or impossible when blocking is done for more than a few variables. Patently, it is most advantageous to block for a few important variables and use randomization thereafter. After randomization has been completed, it is wise to search for differences between treatment and control groups in the distributions of important variables.

This study blocked for cottage residence and length of WCTS residence prior to randomization. Blocking for cottage residence was necessary because of WCTS living patterns. Blocking for length of WCTS residence was necessary because of the "seasoning effect." "Seasoning effect" simply means that new arrivals are more likely to become ill with a variety of acute disorders than are veterans. This effect is observed in military encampments, boarding schools, and mental institutions.

B. Demographic Characteristics

1. Participant Age at Study Midpoint: Acute respiratory disease incidence generally decreases significantly after the sixth year of life.[34] This decline is rapid for two years and then more gradual through adolescence.[34] The WCTS study population contained those ages where the incidence decline is gradual. Thus, age would influence incidence less in the WCTS population than in the general population.

Table IV.1 presents the age distributions of the trial groups. A chi square test shows that there was no significant difference in age distribution between the trial groups. This is expected because blocking for cottage residence also blocks for a 2 to 3 year age span.

TABLE IV.1

PARTICIPANT AGE AT STUDY MIDPOINT
DISTRIBUTION BY TRIAL GROUP

Age in Years	Group	
	Amantadine	Placebo
<9	2	1
9	2	3
10	12	11
11	19	16
12	19	12
13	26	21
14	24	31
15	26	17
16	14	11
>16	13	19
All Ages	157	142

$\chi^2_{(8)} = 5.72564$

$.75 > p > .50$

2. Sex of Participants: Females have been found to have a somewhat higher incidence of respiratory disease during the school years.[34,1]

Table IV.2 presents the sex distribution of the trial groups. A chi square test shows that the sex distribution of trial groups did not differ significantly. Actually, blocking for cottage residence also blocks for sex, since students within any cottage are all male or all female.

TABLE IV.2

SEX OF PARTICIPANTS
DISTRIBUTION BY TRIAL GROUP

Sex	Group	
	Amantadine	Placebo
Male	110	97
Female	47	45
Both sexes	157	142

$\chi^2_{(1)} = .07043$

$.90 > p > .75$

3. Race of Participants: Little information is available on the influence of race, if any, on acute respiratory illness. Table IV.3 presents the racial distributions of trial groups. A chi square test of significance reveals no significant difference in racial distribution between trial groups. The racial distribution of study participants simply reflected the race distribution of the entire WCTS study body.

TABLE IV.3

RACE OF PARTICIPANTS
DISTRIBUTION BY TRIAL GROUP

Race	Group	
	Amantadine	Placebo
White	86	85
Non-white	71	57
All races	157	142

$\chi^2_{(1)} = .87641$

$.50 > p > .25$

4. Cottage Residence of Participants on Entrace to the Study: Cottage residence was the single most important variable in the trial design. The chapter on methods describes how WCTS living patterns made cottage residence the principal factor in exposure to respiratory illness. In addition, the cottage groups were similar in demographic characteristics and were served by the same observers of illness and dispensers of medication, the cottage parents.

Table IV.4 presents the distribution of the WCTS population at the study midpoint according to cottage residence and study participation. The proportion of participants within a cottage varied from 40 to 70 per cent.

Table IV.5 presents cottage residence of participants on entrance to the study, distributed according to trial group.

TABLE IV.4

PARTICIPANTS AND NONPARTICIPANTS DISTRIBUTION BY COTTAGE OF RESIDENCE AT STUDY MIDPOINT

Cottage	Total Cottage Population	Group		Per Cent Participants
		Participants	Nonparticipants	
1	36	20	16	55.6
2	36	21	15	58.3
4	15	9	6	60.0
5	34	24	10	70.6
6	27	14	13	51.8
7	38	24	14	63.2
Fire Hall	10	7	3	70.0
9	33	21	12	63.6
10	37	19	18	51.4
11	38	15	23	39.5
12	40	20	20	50.0
13	33	13	20	39.4
14	38	22	16	57.9
15	38	23	15	60.5
16	40	28	12	70.0
19	24	11	13	45.8
Total	531*	291	240*	54.8

*14 individuals were in discipline, sickward, or on leave.

TABLE IV.5

COTTAGE RESIDENCE OF PARTICIPANTS ON ENTRANCE TO STUDY
DISTRIBUTION BY TRIAL GROUP

Cottage	Group	
	Amantadine	Placebo
1	11	10
2	11	11
4	6	5
5	13	12
6	6	7
7	14*	10*
Fire Hall	3	2
9	12	11
10	11	10
11	8	6
12	12	10
13	7	6
14	12	11
15	11	11
16	14	14
19	6	6
All Cottages	157	142

*One individual who should have been assigned to the placebo group was mistakenly assigned the amantadine group.

5. Participant Length of WCTS Residence Prior to Beginning of Trial: As previously described this variable is the key to compensating for any "seasoning effect." Table IV.6 presents the distribution of WCTS stay of the trial groups. As expected from the design, there is no significant difference in length of residence between the trial groups. Incidentally, this table also shows that fully one-third of participants had not been at WCTS for a full respiratory season prior to the study.

TABLE IV.6

PARTICIPANT LENGTH OF WCTS RESIDENCE PRIOR TO BEGINNING OF TRIAL DISTRIBUTION BY TRIAL GROUP

Length of Residence (years)	Group	
	Amantadine	Placebo
< 1/2	26	26
1/2 to 1	24	15
1 to 2	27	22
2 to 3	23	18
> 3	57	61
Total	157	142

$\chi^2_{(4)} = 2.74881$

$.75 > p > .50$

6. Time of Participant Entrance Into the Study: This trial allowed volunteers to enter after the trial began. In such a trial, a significant bias might be introduced if all the late entries were in one trial group. As previously described, trial group assignments were made in a fashion that should have prevented grossly unequal distribution of late entries. Table IV.7 shows that late entries were not significantly

different in the trial groups. These late entries were also similarly distributed as to elapsed time from start of study to entry.

TABLE IV.7

TIME OF PARTICIPANT ENTRANCE INTO STUDY
DISTRIBUTION BY TRIAL GROUP

Time of Entrance	Group	
	Amantadine	Placebo
Pretrial	151	134
During trial	6	8
Total	157	142

$\chi^2_{(1)} = .29980$

$.75 > p > .50$

7. Withdrawal of Participants from the Study: A significant bias may be introduced into the trial by unequal participant withdrawal from the trial groups. Table IV.8 shows that participant withdrawal was not significantly different between trial groups.

TABLE IV.8

WITHDRAWAL OF PARTICIPANTS FROM STUDY
DISTRIBUTION BY TRIAL GROUP

Withdrew	Group	
	Amantadine	Placebo
Yes	11	11
No	146	132
Total	157	142

$\chi^2_{(1)} = 0$

$p > .995$

8. Cottage Transfer of Participants During the Trial: Conceivably, blocking for cottage residence could be disturbed by a different transfer experience in the trial groups. Table IV.9 shows that the transfer experience of the trial groups was not significantly different. In no case did transfers significantly alter the basic block design.

TABLE IV.9

COTTAGE TRANSFER OF PARTICIPANTS DURING TRIAL
DISTRIBUTION BY TRIAL GROUP

Transferred	Group	
	Amantadine	Placebo
Yes	24	19
No	133	123
Total	157	142

$\chi^2_{(1)} = .10900$

$.75 > p > .50$

9. Participant Vocational Assignment: Vocational assignment implies more contact with the world outside WCTS and less contact within WCTS. Trial group vocational assignment distribution also implies trial group academic school distribution because a child is in academic school if he is not assigned vocationally. Table IV.10 reveals the distribution by trial group of participant vocational assignment. The chi square test shows there is no significant difference in vocational assignment between trial groups.

TABLE IV.10

PARTICIPANT VOCATIONAL ASSIGNMENT
DISTRIBUTION BY TRIAL GROUP

Vocational Assignment	Group	
	Amantadine	Placebo
Yes	118	101
No	39	41
Total	157	142

$\chi^2_{(1)} = .61592$

$.50 > p > .25$

10. Participant Intelligence Quotient: If trial groups differ significantly in intelligence, there could be a number of difficulties with assessing the reliability of the histories and with syndrome classifications. Table IV.11 shows that the trial groups did not differ significantly in intelligence quotient.

TABLE IV.11

PARTICIPANT INTELLIGENCE QUOTIENT
DISTRIBUTION BY TRIAL GROUP

Intelligence Quotient (%)	Group	
	Amantadine	Placebo
< 46	4	2
46-55	12	9
56-65	23	31
66-75	50	43
76-85	54	39
86-95	13	17
96-105	0	1
106-115	1	0
> 115	0	0

$\chi^2_{(5)} = 3.92766$

$.70 > p > .50$

The Wechsler-Bellvue test was used to measure full scale intelligence quotient. These tests are performed shortly after entrance to the school and every two years thereafter. Table IV.11 also shows that the majority of the study participants were in the 65 to 85 per cent range with respect to intelligence quotient.

C. Medical History of Participants

1. Past Respiratory Disease Experience

a. Prior Respiratory Illness Attack Rates of Participants: Other investigators have shown that individuals differ markedly in respiratory illness experience.[34] A given individual will usually blend his personal pattern with the expected age pattern. Thus an individual who is prone to respiratory illness will have more illness than his peers at any given age, but will have the expected decreasing incidence during later childhood and adolescence.

Table IV.12 presents the prior respiratory illness yearly attack rates of participants. There is no significant difference between trial groups in the distribution of attack rates.

An individual's attack rate was computed from his WCTS clinic card. In this calculation several conventions were used. First, any illness recorded as streptococcal was not counted. Second, two illness episodes had to be separated by at least one week of discharge from the WCTS medical clinic. Lastly, yearly attack rates were based on illness experience during WCTS residence for any length of time up to three years before the beginning of the trial.

TABLE IV.12

PRIOR RESPIRATORY ILLNESS ATTACK
RATES OF PARTICIPANTS
DISTRIBUTION BY TRIAL GROUP

Prior Attack Rate Illness per Year	Group	
	Amantadine	Placebo
< 1	54	51
1-2	28	27
2-3	38	19
3-4	10	14
4-5	13	17
> 5	14	14
Total	157	142

$\chi^2_{(5)} = 7.47426$

$.20 > p > .10$

Table IV.13 shows that the mean annual respiratory illness attack rate was 2.13 for amantadine and 2.22 for placebo. This compares with a national mean annual respiratory disease attack rate of 1.37 for

TABLE IV.13

MEAN ANNUAL NUMBER OF PRIOR RESPIRATORY ILLNESSES
DISTRIBUTION BY TRIAL GROUP

Trial Group	Mean Annual Number of Respiratory Illnesses
Amantadine	2.13
Placebo	2.22

the age group 6 to 16 years during the three years ending July 1965.[1] Thus, WCTS volunteers had about 50 per cent more respiratory illness during pretrial years than the general 6 to 16 year old population. This is not an excessive increase in a boarding school population.

b. Participant Past History of WCTS Infirmary Admission with Respiratory Illness: Trial groups might have differed in the severity but not the number of respiratory illnesses. Pyrexia greater than 101°F per os at the time of a WCTS medical clinic visit results in infirmary admission. Thus, infirmary admissions reflect febrile respiratory disease. Admissions, diagnosed as streptococcal, were excluded from the tally because the trial was primarily concerned with nonstreptotoccal respiratory illness. In addition, only infirmary admissions during the three years preceding the trial were considered.

Table IV.14 reveals the distributions of past WCTS infirmary admissions in the two trial groups. These distributions do not differ significantly in the chi square test.

TABLE IV.14

PARTICIPANT PAST HISTORY OF INFIRMARY ADMISSION WITH RESPIRATORY ILLNESS DISTRIBUTION BY TRIAL GROUP

Number of Infirmary Admissions	Group	
	Amantadine	Placebo
0	101	85
1	34	31
2	14	14
3	7	8
> 4	1	4
Total	157	142

$\chi^2_{(4)} = 3.8310$

$.50 > p > .30$

c. Participant Prior History of Pneumonia: Another index of past respiratory disease severity is a history of pneumonia. Table IV.15 shows that the trial groups do not differ significantly in past pneumonia history.

TABLE IV.15

PARTICIPANT PRIOR HISTORY OF PNEUMONIA
DISTRIBUTION BY TRIAL GROUP

Prior History of Pneumonia	Group	
	Amantadine	Placebo
Yes	14	20
No	143	122
Total	157	142

$\chi^2_{(1)} = 1.90406$

$.20 > p > .10$

2. Prior History of Allergies: Individuals with allergic disorders, particularly hay fever and asthma, seem to shoulder a heavier burden of respiratory symptoms. The complexities of this problem are many but it is apparent that these disorders could cause diagnostic difficulty in this trial.

Table IV.16a shows the distributions of allergic disorders in the trial groups and shows that only a few individuals in either group have a history of asthma or hay fever. Table IV.16b shows that the past allergic history of the trial groups does not differ significantly.

TABLE IV.16a

PARTICIPANT PRIOR HISTORY OF ALLERGIES
DISTRIBUTION BY TRIAL GROUP

Allergy	Group	
	Amantadine	Placebo
None	139	123
Asthma	6	7
Hay Fever	2	2
Eczema	4	4
Hives	3	1
Drug Allergy	0	2
More than one allergy	3	3
Total	157	142

TABLE IV.16b

2 x 2 TABLE SHOWING ALLERGIC PARTICIPANTS
DISTRIBUTION BY TRIAL GROUP

Allergy	Group	
	Amantadine	Placebo
Yes	18	19
No	139	123
Total	157	142

$\chi^2_{(1)} = .12350$

$.80 > p > .70$

3. Participant Past History of Cardiac, Renal, or Convulsive Disorder: Past history of heart disease or convulsive disorder might be related to adverse effects of amantadine (see pharmacology in Chapter II). In addition, it is well to ascertain history of renal disease in any new drug trial. Moreover, certain types of heart disease are associated with a larger number of severe respiratory illnesses. In this study individuals having heart murmurs, described as functional, were considered to be free of heart disease.

Table IV.17 shows that the trial groups did not differ significantly in the history of heart disease. The observed 2 per cent prevalence of heart disease is somewhat higher than in a general population of children.[35]

Table IV.18 shows that the trial groups did not differ significantly in the history of renal disease.

TABLE IV.17

PARTICIPANT PAST HISTORY OF HEART DISEASE
DISTRIBUTION BY TRIAL GROUP

Heart Disease History	Group	
	Amantadine	Placebo
Yes	2	4
No	155	138
Total	157	142

p = .296 (Fisher Exact Probability Test).

TABLE IV.18

PARTICIPANT PAST HISTORY OF RENAL DISEASE
DISTRIBUTION BY TRIAL GROUP

Renal Disease History	Group	
	Amantadine	Placebo
Yes	7	6
No	150	136
Total	157	142

$\chi^2_{(1)} = .0000$

$p > .995$

Table IV.19 shows that the past history of convulsions was not statistically different between the trial groups. Children with seizures during the three years prior to the study and any other children receiving anticonvulsants had already been excluded from participation.

TABLE IV.19

PARTICIPANT PAST HISTORY OF CONVULSIVE DISORDER
DISTRIBUTION BY TRIAL GROUP

Convulsive Disorder History	Group	
	Amantadine	Placebo
Yes	14	5
No	143	137
Total	157	142

$\chi^2_{(1)} = 3.60692$

$.10 > p > .05$

4. Participant Past History of Influenza Immunization: Amantadine antiviral activity in previous studies (see Chapter II) was primarily against type A influenza. Thus, immunization against influenza at some time in the past is an important variable. Influenza vaccine had not been given by the WCTS during the past decade. A record search was made to ascertain which individuals were said to have received vaccine.

Table IV.20 shows that only 1.3 per cent of the study population were said to have received influenza vaccine and that these immunizations were at least three years prior to the trial. The Fisher exact probability test shows that the trial groups do not differ in past history of influenza immunization.

TABLE IV.20

PARTICIPANT PAST HISTORY OF INFLUENZA IMMUNIZATION
DISTRIBUTION BY TRIAL GROUP

Influenza Immunization	Group	
	Amantadine	Placebo
Yes	1*	3*
No	156	139
Total	157	142

p = .274 (Fisher Exact Probability Test)

*Immunizations in two placebos and one amantadine were prior to 1958; the other placebo was immunized in 1962.

D. Medication Control

1. Drug Dose: Dose of amantadine within the amantadine group was a variable of fundamental importance. Less obvious was the concept of "placebo dose." Placebo capsules were considered to be "60 mgm" or

"100 mgm." The "60 mgm" placebo capsules and 60 mgm amantadine capsule were given in some cottages, while the "100 mgm" placebo capsule and the 100 mgm amantadine capsule were given in other cottages. Thus, we can consider a drug dose distribution for each population. This is a useful concept since it will answer questions about weight distributions in the two populations and about how well predicted doses compared with observed doses.

Table IV.21 shows the drug dosage distribution for the two trial groups. The chi square test shows that drug dose distribution does not significantly differ between trial groups. This also means that weight distributions do not differ significantly between trial groups.

TABLE IV.21

PARTICIPANT DRUG DOSE*
DISTRIBUTION BY TRIAL GROUP

Maintenance Dose mgm per kg per day	Group	
	Amantadine	Placebo
< 1	1	0
1.0-1.5	24	24
1.5-2.0	79	63
2.0-2.5	41	49
2.5-3.0	11	4
3.0-3.5	1	2
> 3.5	0	0
Total	157	142

$\chi^2_{(1)} = 4.13724$

$.30 > p > .20$

*Placebo dose is computed by considering placebos given in prepubertal children to be 60 mgm and placebos given in other children 100 mgm.

Table IV.22 shows the expected and observed proportions of children included in two acceptable dose ranges for the amantadine group. The expected and observed agree quite well. This simply indicates that WCTS children have weights which are distributed much like the general population of the same age.

TABLE IV.22

PARTICIPANT DRUG DOSE, EXPECTED AND OBSERVED PROPORTION OF AMANTADINE GROUP IN ACCEPTABLE DOSE RANGES

Acceptable Dose Ranges (per kg per day)	Acceptable Dose Range	
	Per Cent Expected	Per Cent Observed
1.5-2.0 mgm	55.2	50.3
1.0-2.5 mgm	93.4	91.7

2. Dispensing Capsules

a. Participant Missed Medication Doses per Month: Each individual was listed on a dose calendar in his cottage (see Chapter II). This allowed for the calculation of the number of missed doses per month for each individual. Now a missed dose would mean either that the cottage parent failed to dispense a capsule to a child who was present or that a child was not available to receive medication. In either case the child could not ingest his medication. There is no reason to believe that capsules would be differentially dispensed to children present. Thus, any differences should be caused by availability of the child.

Table IV.23 presents the distributions of missed medication doses per month in the two trial groups. The amantadine group missed significantly more medication doses than did the placebo group. This difference is caused by the larger number of amantadine subjects who missed one to three doses per month. If we considered only those individuals who missed more than three doses per month, there would be no significant difference between the trial groups.

TABLE IV.23

PARTICIPANT MISSED MEDICATION PER MONTH
DISTRIBUTION BY TRIAL GROUP

Mean Number of Missed Medication per Month	Group	
	Amantadine	Placebo
1	107	112
1-3	45	22
4-6	3	8
7-9	2	0
9	0	0
Total	157	142

$\chi^2_{(1)} = 4.37992$

$.05 > p > .01$

Figure IV.1 shows the participant missed medication dose distribution by trial group and week of trial. The curves are remarkably similar and both show more missed doses during the eleventh week of the trial. This was the week of spring vacation for many of the students. The table from which this figure was drawn may be found in Appendix B-1.

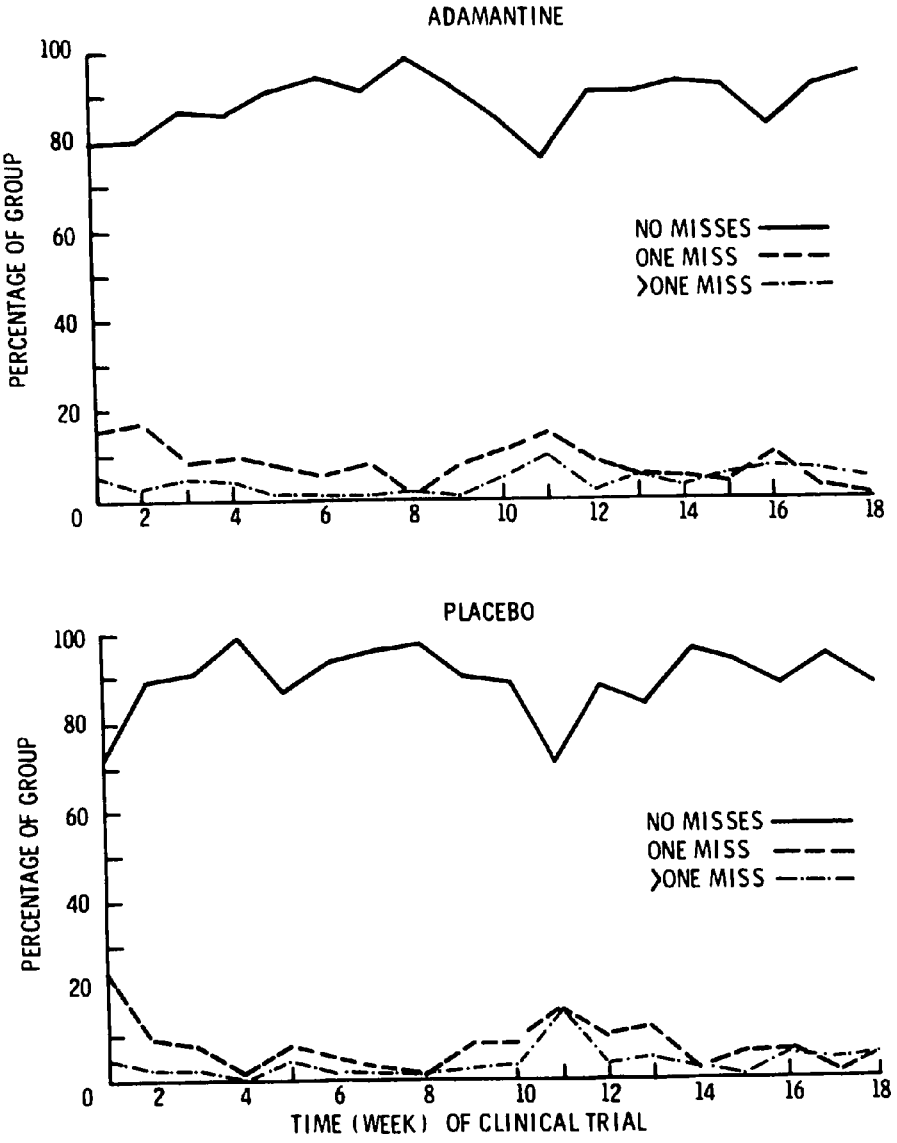


Figure IV.1

Participant Missed Medications
Distribution by Trial Group and Week of Trial

b. In and Out Capsule Count: Each cottage returned the unused portion of the previous week's capsule supply before obtaining the next week's supply (see Chapter II). Figure IV.2 shows the capsule return rate per 100 capsules counted out. This return rate is distributed by trial group and week of trial. The curves for amantadine and placebo groups are quite similar and both show a peak of returns coinciding with spring vacation for many of the children.

The peak at week one is exaggerated because an extra dose of medication for each child was dispensed during this week. This chart also ignores another error. When a child entered the study, a full week's complement of loading capsules was provided. Should these not be exhausted before the next week's capsule issue, they would be counted as returned and thus considered improperly dispensed. The table from which this figure was derived may be found in Appendix B-2.

Table IV.24 compares the results of the dose calendar and count in-out procedures. Adjustment in the count in-out procedure has

TABLE IV.24

MEDICATION DOSES INCORRECTLY DISPENSED
DISTRIBUTION BY TRIAL GROUP AND
MEDICATION CONTROL METHOD

Trial Group	Total Doses	Doses Not Dispensed			
		Count In and Out Method		Dose Calendar Method	
		Number	Per Cent	Number	Per Cent
Placebo	17,359	492	2.83	473	2.72
Amantadine	19,366	494	2.55	515	2.66
Total	36,725	986	2.68	988	2.69

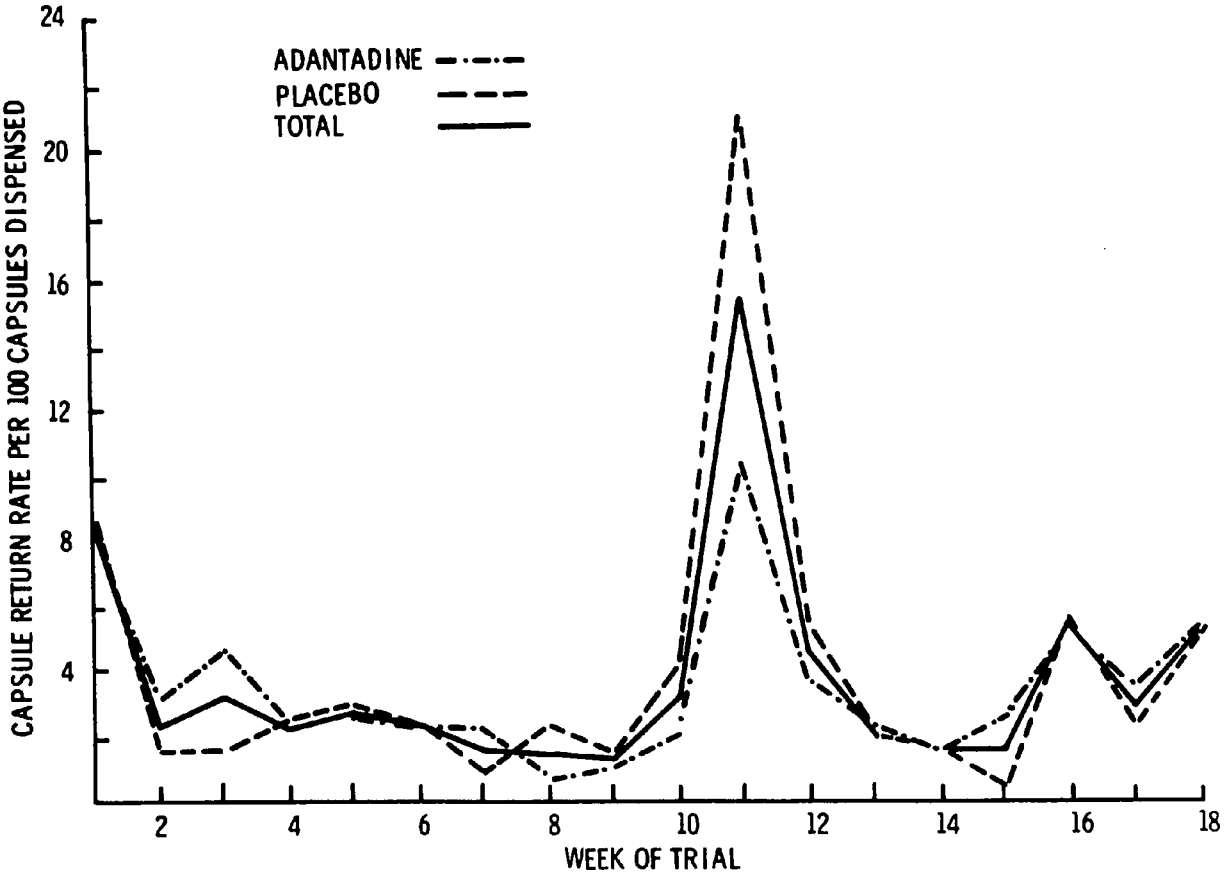


Figure IV.2

Capsule Return Rate per 100 Counted Out
Distribution by Trial Group and Week of Trial

been made to exclude the extra doses dispensed in the first week of the trial and to exclude capsules counted in because of volunteer entrance and withdrawal. This table shows the two procedures to yield remarkably similar results. The overall discrepancy between the two methods is only 40 capsules out of 36,725 total prescribed doses. Both amantadine and placebo groups have received over 97 per cent of the capsules prescribed.

c. Week End Slips: Trial participants, like other WCTS students, could visit their homes about once monthly. Weekend slips were given to participants who were leaving for a home visit (see Chapter III). Table IV.25 reveals that the placebo group averages 1.9 leaves per person and the amantadine group 2.2 leaves per person during the trial period.

TABLE IV.25

PARTICIPANT WEEKEND LEAVE DURING TRIAL
DISTRIBUTION BY TRIAL GROUP

Trial Group	Population	Total Number of Trial Weekend Leaves	Mean Number of Trial Weekend Leaves
Placebo	142	268	1.9
Amantadine	157	348	2.2
Total	299	616	2.0

Table IV.26 shows that the trial groups did not differ significantly in the return of weekend slips. Table IV.26 also shows that the trial groups did not differ significantly in the returned slips which indicated that the capsule(s) were taken. Overall 57.5 per cent

TABLE IV.26

PARTICIPANT WEEKEND SLIPS--NUMBER ISSUED, NUMBER RETURNED, AND NUMBER RETURNED AND MARKED TO INDICATE CAPSULE HAD BEEN TAKEN DISTRIBUTION BY TRIAL GROUP

Trial Group	Number Slips Issued	Number of Slips Returned	
		Total*	Marked to Indicate Capsule Had Been Taken**
Placebo	268	159	154
Amantadine	348	195	186
Total	616	354	340

* $\chi^2_{(1)} = .67556$

$.50 > p > .30$

** $\chi^2_{(1)} = .30356$

$.70 > p > .50$

of slips issued were returned and 55.2 per cent of slips issued were returned and marked capsule taken. The table from which these numbers were extracted will be found in Appendix B-3.

3. Drug Assay

a. Questions Asked: Chapter III described the procedures used in obtaining specimens for drug assay and the method of assay. Drug assay was intended to answer several questions: Are there errors in capsule ingestion? Does the drug equilibrium concept hold true? Do blood levels of amantadine differ significantly between groups receiving 60 mgm and 100 mgm and between different groups sampled (ill, ill control, convalescent)?

b. Errors in Capsule Ingestion: Two kinds of capsule ingestion error are possible, omissions of capsules and mixing capsules. Drug assay will neither detect all errors nor separate type of error. Lack of amantadine in an amantadine group specimen could indicate either mixing or omission of capsules. There was no method to detect omissions in the placebo group but mixing could be detected by the presence of amantadine. If a placebo subject had taken amantadine in the preceding 72 hours, the substance can definitely be detected in urine Similarly, an amantadine subject would have to omit three days of medication before a casual urine specimen would be amantadine negative.

Table IV.27 shows the distribution of drug assays which might indicate errors in capsule ingestion. The overall error detected

TABLE IV.27

ERRORS IN CAPSULE INGESTION AS INDICATED BY DRUG ASSAY
DISTRIBUTION BY TRIAL GROUP AND GROUP ASSAYED

Type of Assay	Group				Total Assays	
	Amantadine		Placebo			
	Correct	Error	Correct	Error	Correct	Error
Casual urine	53	0	64*	3	117	3
Convalescent blood	35	2	--	--	35	2
Acute illness blood	18	0	21	1	39	1
Acute illness control	15	0	17	2	32	2
Total	121	2	102	6	223	8

*During second assay period five urine specimens with trace of amantadine were reported. This was thought to be caused by trouble with specimen bottle washing and never occurred again. They are counted as correct.

was 3.6 per cent. More errors were detected in the placebo group. This was expected as the assay procedure here would detect a single error of mixing for at least three days prior to the day of the specimen. Whereas, an error of omission in the amantadine group would have to occur continuously for at least three days before detection would be possible.

Table IV.28 shows that the distribution of error in the two trial groups does not differ significantly, but approaches significance.

TABLE IV.28

ERROR IN CAPSULE INGESTION
DISTRIBUTION BY TRIAL GROUP

Error Detected in Assay	Group	
	Amantadine	Placebo
Yes	2	6
No	122	102
Total	124	108

p = .0967 (Fisher Exact Probability Test)

c. Drug Equilibrium Concept: As stated in Chapter II, the drug equilibrium concept predicted that amantadine would accumulate in the body until excretion balanced ingestion. Fifteen 24-hour urines were collected to test this hypothesis. Unfortunately, a collection error occurred in two specimens. In each case the first voided specimen of the morning was not discarded before collection began. Substantial assay error is introduced because the early morning specimen contains up to 50 per cent of the previous evening's dose of amantadine.

Table IV.29 summarizes 24-hour urine studies of drug equilibrium. The two specimens, where collection error occurred, are included

TABLE IV.29

TESTING DRUG EQUILIBRIUM CONCEPT WITH
24 HOUR URINE AMANTADINE ASSAY
DISTRIBUTION BY INGESTED DOSE

	Dose		
	60 mgm	100 mgm	
Number of specimens	8	5	(7)*
Mean number of mgm in specimens	55	96.25	(112.4)*
Standard error of mean	2.63	9.79	(16.16)*
95% Confidence Interval of mean (mgm)	49.7 to 60.3	76.7 to 115.8	(80.1 to 144.7)*
99% Confidence Interval of mean (mgm)	47.1 to 62.9	66.9 to 125.6	(63.9 to 160.9)*

*Includes two specimens where collection error occurred.

only in the calculations enclosed in parentheses. This table shows that participants had essentially quantitative excretion of ingested amantadine.

d. Blood Amantadine Levels, Differences Between Dose Groups and Between Groups Sampled: Table IV.30 shows that blood levels of amantadine were significantly higher in participants receiving 100 mgm per day. This higher level is not surprising because these children received a slightly higher milligram per kg. dose.

TABLE IV.30

BLOOD AMANTADINE LEVELS
DISTRIBUTION BY DOSE GROUP

Factor	Group	
	60 mgm	100 mgm
Number of observations	30	54
Mean amantadine level (gamma per ml)	.086	.128
Standard error of mean	.0356	.0620

$$\text{Test } z = \frac{\bar{x}_{100} - x_{60}}{\left(\frac{Sp^2}{30} + \frac{Sp^2}{54}\right)^{1/2}}$$

$z = 3.48$

$p < .002$

Table IV.31 summarizes the findings in the different groups sampled for blood amantadine levels. Comparison over the four groups is made after dividing each group into those receiving 60 mgm daily and those receiving 100 mgm daily. If this daily dose effect is eliminated, the four groups sampled do not differ significantly when Duncan's Multiple Range Test is applied. Thus blood amantadine levels were not dependent on whether an individual was acutely ill, convalescent, well, or hospitalized.

TABLE IV.31

BLOOD AMANTADINE LEVELS
DISTRIBUTION BY GROUP SAMPLED AND DOSE

Factor	Group Sampled							
	24 Hour Urine		Acutely Ill		Control for III		Convalescent	
	60	100	60	100	60	100	60	100
Number sampled	8	8	4	14	4	11	14	21
Mean amantadine level (gamma per ml)	.101	.171	.080	.120	.070	.115	.085	.123
Standard error of sample mean	.0167	.0094	.0002	.0034	.0015	.0068	.0012	.0055

Duncan's Multiple Range Test. No significant difference between sample groups receiving same drug dose.

E. Adverse Effect in Trial Groups

1. Drug Reactions: Table IV.32 presents the distribution of possible drug reactions in the two trial groups. Adverse effects are infrequent in either group and adverse effects did not differ

TABLE IV.32

POSSIBLE DRUG REACTIONS AMONG PARTICIPANTS
DISTRIBUTION BY TRIAL GROUP

Possible Reaction	Group	
	Amantadine	Placebo
No reaction	150	135
Rash	2	5
Insomnia	1	0
Eneuresis increased	1	0
Syncope	2	1
Abdominal pain	1	1
Total	157	142

$\chi^2_{(1)} = .05640$

$.90 > p > .80$

significantly between trial groups. No individual with a possible reaction had more than one reaction. The effects observed are probably not related to medication.

2. Seclusion and Discipline Episodes: Punishment at WCTS was synonymous with a seclusion or discipline episode. If amantadine were having an adverse effect on behavior, more such episodes would be expected to occur among the amantadine group. Table IV.33 presents the punishment experience of the trial groups. The distributions in Table IV.33 did not differ significantly.

TABLE IV.33

SECLUSION OR DISCIPLINE EPISODES AMONG PARTICIPANTS DISTRIBUTION BY TRIAL GROUP

Number of Seclusion or Discipline Episodes	Group	
	Amantadine	Placebo
None	130	110
1	17	27
2	7	5
3	2	0
4	1	0
> 4	0	0
Total	157	142

$\chi^2_{(2)} = 4.61826$

$.10 > p > .05$

3. Psychiatric Therapy Groups: Psychiatrists, who were seeing children in group therapy, might be a more sensitive indicator of behavioral effects of amantadine. Table IV.34 shows that the trial groups were not significantly different in psychiatric group therapy participation. The psychiatrists involved in the therapy programs could offer no observations on the effect, if any, of either amantadine or placebo.

TABLE IV.34

TRIAL PARTICIPANTS IN PSYCHIATRIC GROUP THERAPY*
DISTRIBUTION BY TRIAL GROUP

Psychiatric Group Therapy	Group	
	Amantadine	Placebo
No	143	126
Yes	14	16
Total	157	142

$\chi^2_{(1)} = .59533$

$.50 > p > .30$

*Study participants comprised 55.6 per cent of therapy group populations.

CHAPTER V

RESULTS

A. Observations Reflecting Total WCTS Morbidity

1. Medical Clinic Visits: Medical clinic visits should reflect WCTS student morbidity. Figure V.1 presents WCTS medical clinic visit rates for the total population and for both sexes during the first 23 weeks of 1965. The visit rates in week eight have been adjusted to compensate for the loss of two days of clinics during a blizzard. Similarly, the rates in weeks 15 and 16 have been adjusted to compensate for population loss during the spring vacation.

This figure reveals several interesting features. First, the medical clinic is visited often. The number of visits for the total population ranged between 1.4 and 2.1 per person per week. Second, females visit the medical clinic much more often than males, even though females in this age group would be expected to experience only slightly more acute illness than males.[36] Third, there are four peaks of clinic visits during the period of observation: the first peak occurred during the January pretrial period; the second and largest peak occurred early in the trial in February; the third peak appears bimodal and occurred during April; and the fourth peak appeared during June. Females appeared to contribute more to the first two peaks than did males; but

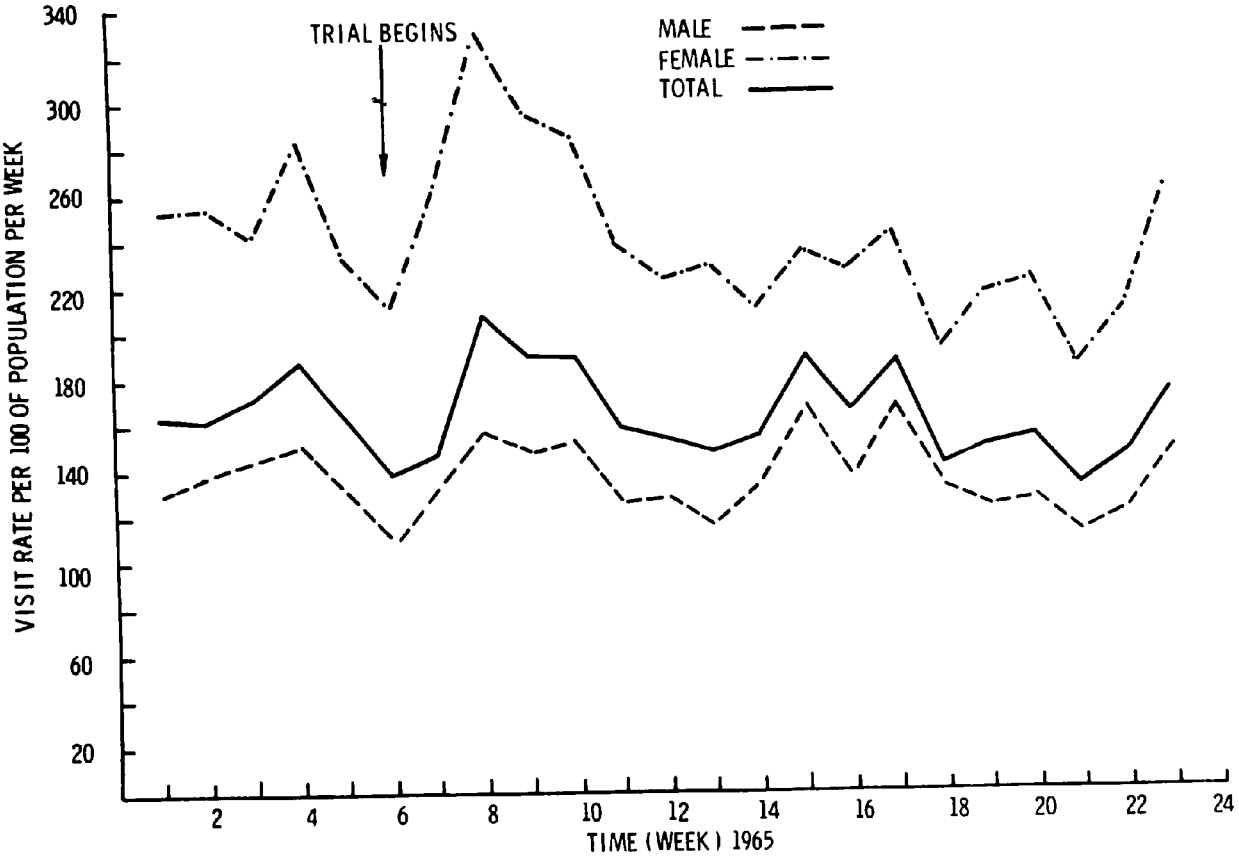


Figure V.1

Medical Clinic Visits by All WCTS Students
Distribution of Rates by Sex and Time

males contributed more than usual to the third peak. Both groups contributed equally to the fourth peak. The first three peaks coincided with periods of increased prevalence of respiratory illness. The fourth peak coincided with a school immunization program.

Appendix B.4 contains the source table for Figure V.1.

2. Infirmary Admissions

a. Among Trial and Nontrial Populations: Figure V.2 presents respiratory illness infirmary admission rates during the third through twenty-third week of 1965 for both trial and nontrial populations. This figure is drawn from the table in Appendix B.5 and includes admissions with streptococcal and nonstreptococcal illness. The rates have been adjusted to reflect population loss during spring vacation.

The admission rates exhibit a jerky course because of the relatively small number of admissions in any one week. Trial population admission rates have two distinct peaks, of which the first is bimodal. These admission peaks coincide with the previously described February and April peaks in medical clinic visits.

b. Among Trial Groups: Figure V.3 plots infirmary respiratory illness admission rates for amantadine and placebo groups. The source table may be found in Appendix B.5 and an adjustment for spring vacation population loss has been made. This figure shows that the placebo group contributes excessively to the bimodal February admission peak and both trial groups contribute to the April admission peak.

If each week is considered to be a separate trial with amantadine and placebo groups, there should be no significant excess in

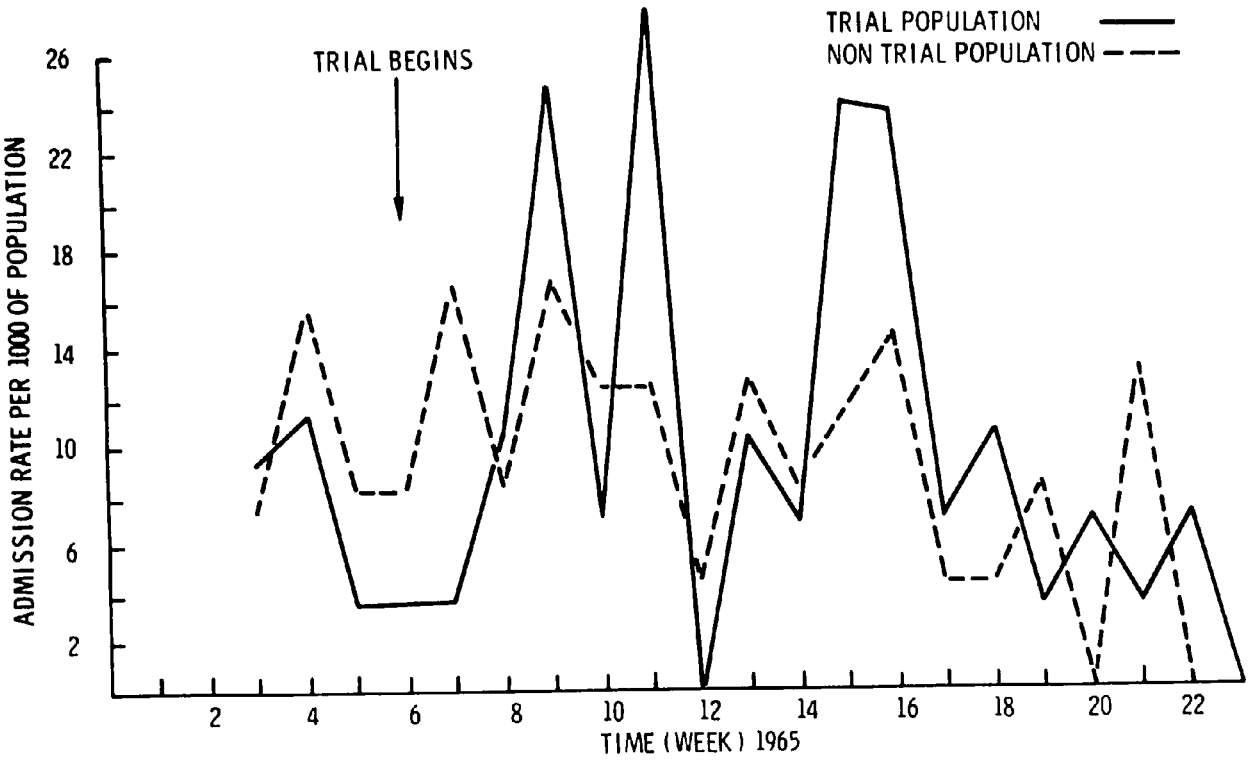


Figure V.2

WCTS Infirmary Admissions with Respiratory Illness
Distribution by Trial Participation and Time

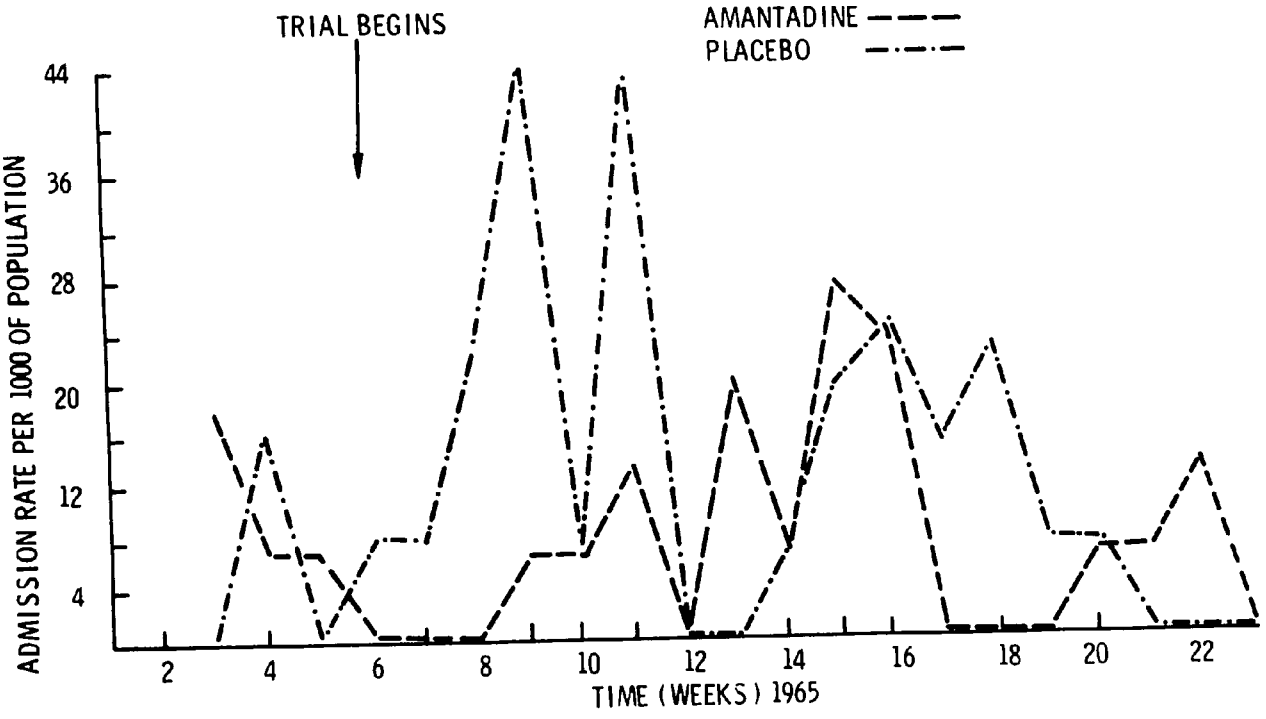


Figure V.3

Infirmary Admissions Among Trial Participants with Respiratory Illness
Distribution by Trial Group and Time

admission rates of either trial group over the 17 week trial period under the hypothesis that amantadine has no effect on infirmary admission. The sign test may be applied to these 17 pairs of rates and a "p" value of .059 results. Thus, the difference between rates borders on statistical significance with a lower admission rate more frequently found in the amantadine group.

Infirmary admissions may be analyzed using the experience of individual trial participants. Table V.1 shows that placebo individuals experience significantly more infirmary admissions during the trial than did amantadine individuals. Table V.2 reveals that admissions with streptococcal illness did not differ between the trial groups. Table V.3 shows that admissions occasioned by all nonstreptococcal illness were greater in the placebo group. Table V.4 indicates that admissions with illness diagnosed as "other" were increased in the placebo group, but not significantly so. Table V.5 shows that, having removed the "other" illnesses, admissions with nonstreptococcal respiratory illness were significantly increased in the placebo group.

TABLE V.1

ALL PARTICIPANT INFIRMARY ADMISSIONS*
DISTRIBUTION BY NUMBER OF ADMISSIONS AND TRIAL GROUP

Trial Group	Number of Admissions per Participant				Number of Admissions	All Participants
	0	1	2	3 or more		
Placebo	115	24	3	0	30	142
Amantadine	141	15	1	0	17	157
Total	256	39	4	0	47	299

$\chi^2_{(1)} = 5.3476$

$.05 > p > .02$

*Excluding trauma, surgery and skin disorders.

TABLE V.2

PARTICIPANT INFIRMARY ADMISSIONS WITH STREPTOCOCCAL ILLNESS
DISTRIBUTION BY NUMBER OF ADMISSIONS AND TRIAL GROUP

Trial Group	Number of Admissions per Participant			Number of Admissions	All Participants
	0	1	2 or more		
Placebo	132	10	0	10	142
Amantadine	146	11	0	11	157
Total	278	21	0	21	299

$\chi^2_{(1)} = .00204$

$.98 > p > .95$

TABLE V.3

PARTICIPANT INFIRMARY ADMISSIONS
WITH NONSTREPTOCOCCAL ILLNESS
DISTRIBUTION BY TRIAL GROUP AND NUMBER OF ADMISSIONS

Trial Group	Number of Admissions per Participant				Number of Admissions	All Participants
	0	1	2	3 or more		
Placebo	124	16	2	0	20	142
Amantadine	151	6	0	0	6	157
Total	275	22	2	0	26	299

$\chi^2_{(1)} = 8.9381$

$.01 > p > .001$

TABLE V.4

PARTICIPANT INFIRMARY ADMISSIONS WITH
ILLNESS DIAGNOSED AS "OTHER"
DISTRIBUTION BY TRIAL GROUP AND NUMBER OF ADMISSIONS

Trial Group	Number of Admissions per Participant			Number of Admissions	All Participants
	0	1	2 or more		
Placebo	137	5	0	5	142
Amantadine	155	2	0	2	157
Total	292	7	0	7	299

p = .18 (Fisher Exact Probability Test)

TABLE V.5

PARTICIPANT INFIRMARY ADMISSIONS WITH
NONSTREPTOCOCCAL RESPIRATORY ILLNESS
DISTRIBUTION BY TRIAL GROUP AND NUMBER OF ADMISSIONS

Trial Group	Number of Admissions per Participant				Number of Admissions	All Participants
	0	1	2	3 or more		
Placebo	129	11	2	0	15	142
Amantadine	153	4	0	0	4	157
Total	282	15	2	0	19	299

$\chi^2_{(1)} = 6.2583$

$.02 > p > .01$

3. Academic School Absentees

a. Days of Absence

1) Among Trial and Nontrial Participants: Figure V.4 plots days of absence rates for trial and nontrial students. Generally, the rates for these groups are similar. Three peaks of absence are present in both groups. Two of these peaks are in January and one is in February. The peaks for trial students were higher in January and the peak for nontrial students was higher in February. The first January peak is probably related to students who returned late from the Christmas holiday. The second January peak relates to a quarrantine imposed upon two cottages because of a high prevalence of streptococcal disease in those cottages. The February peak coincides with previously observed peaks in medical clinic visits and sick ward admissions. An April peak is missing and this may be related to the closing of school during the spring vacation.

2) Among Trial Groups: Figure V.5 presents days of absence rate for amantadine and placebo groups. This figure appears similar to Figure V.4 in the presence of three peaks of absence. The trial groups have a similar absence experience through February. During the last three and one half months of the trial there may be a slight excess in the placebo group. Applying the sign test to weekly pairs of days of absence rates, there is no significant difference between trial groups over the fourteen weeks of trial ($p = .395$).

The source table for Figures V.4 and V.5 may be found in Appendix B.6.

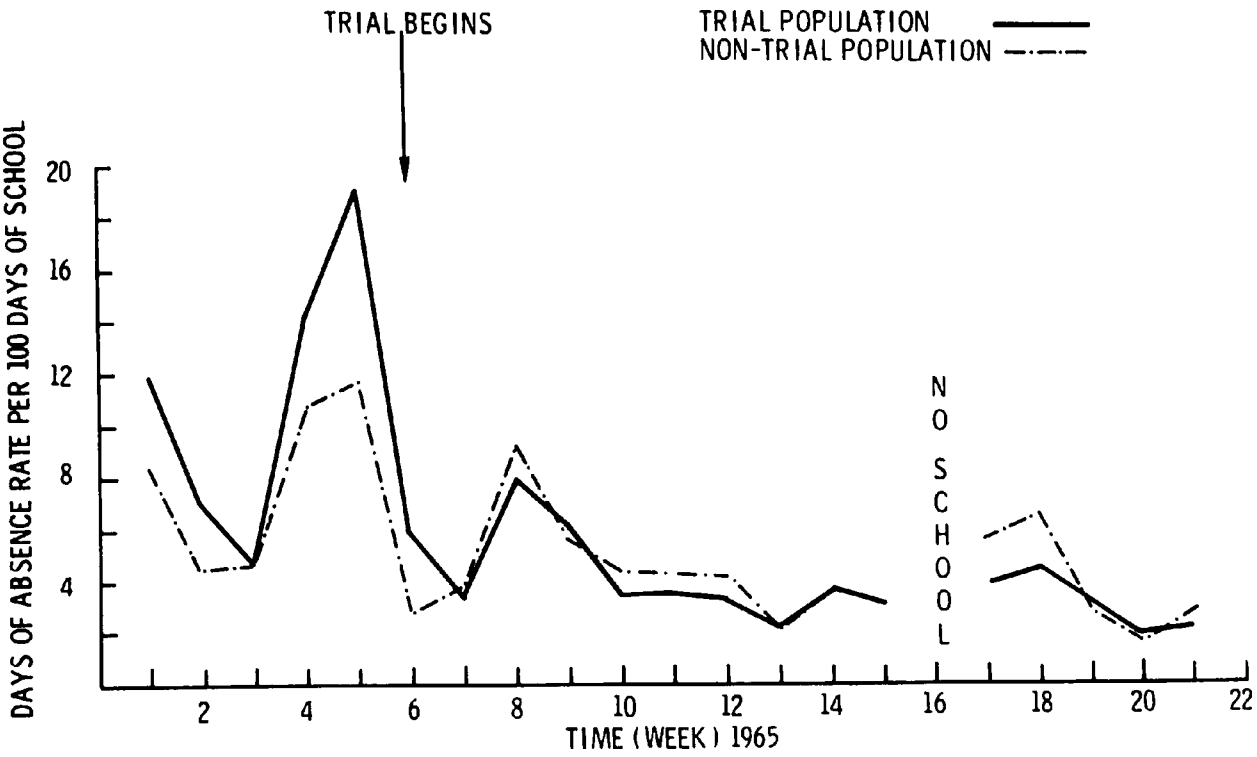


Figure V.4

Absentee Rates of WCTS Academic School
Distribution by Trial Participation and Time

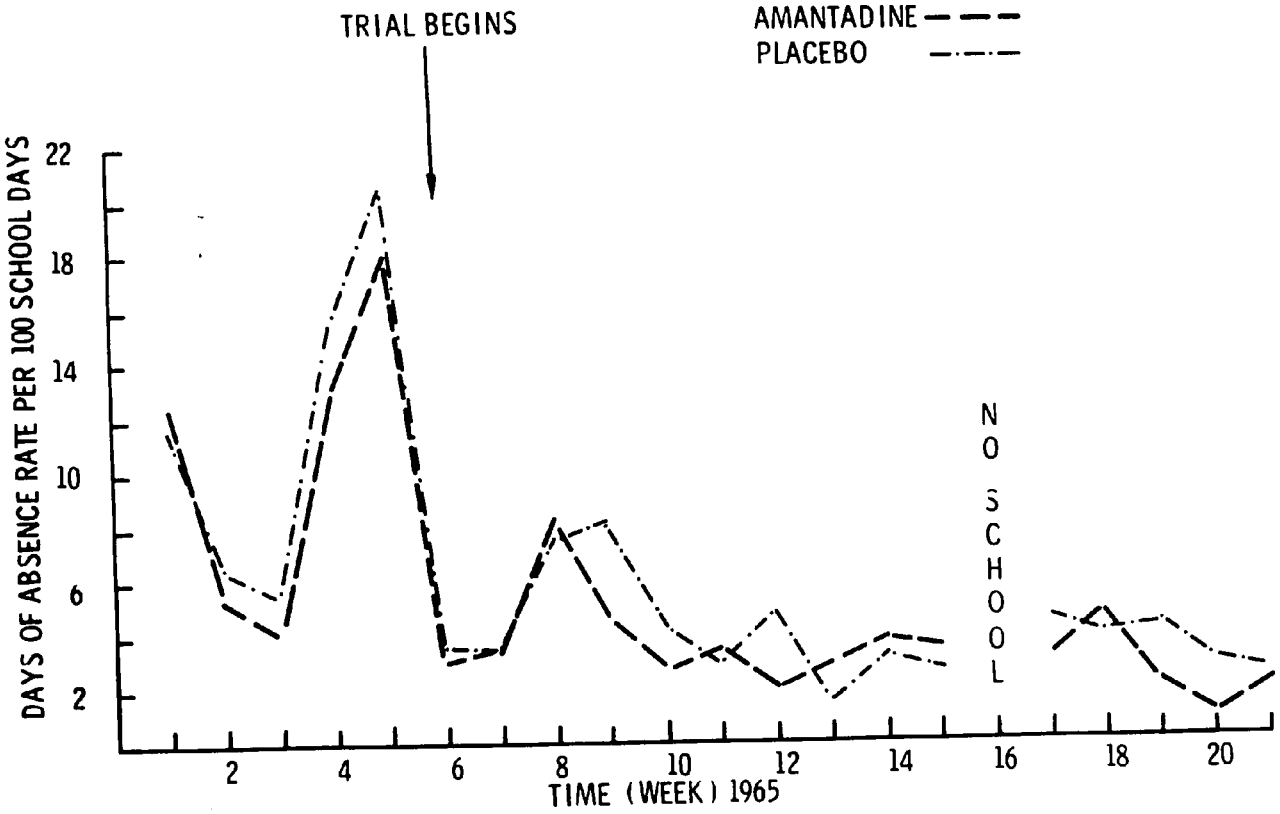


Figure V.5

Academic School Absentee Rates Among Trial Participants
Distribution by Trial Group and Time

b. Episodes of Absence

1) Among Trial and Nontrial Populations: An individual experienced an episode of absence if he missed one or more days of school during a school week. The same individual would have to miss all five days of school to be counted ill for an entire week in the days of absence analysis. Thus, days of absence rates give increased weight to length of illness and episodes of absence reflect the numbers of individual illnesses.

Figure V.6 shows three peaks of absence. The first peak embraces the entire month of January. A second small peak occurs in February and a third peak in April. The plots for trial and nontrial groups are similar but the trial group exhibits a higher late January peak and the nontrial group a higher April peak. Part of the January peak may be explained by the previously mentioned quarrantine and late returns from Christmas vacations. The February and April peaks coincide with peaks in infirmary admissions and medical clinic visits and are thought to be related to respiratory illness.

2) Among Trial Groups: Figure V.7 presents episodes of absence rates for amantadine and placebo groups. The plots of these rates are similar to those seen in Figure V.6. One notable difference between the trial group rates is an excess in the placebo group during February and March. Applying the sign test to weekly pairs of absentee episode rates, there is a significant ($p = .046$) excess in placebo rates over the fourteen weeks of the trial.

The source table for Figures V.6 and V.7 may be found in Appendix B.7.

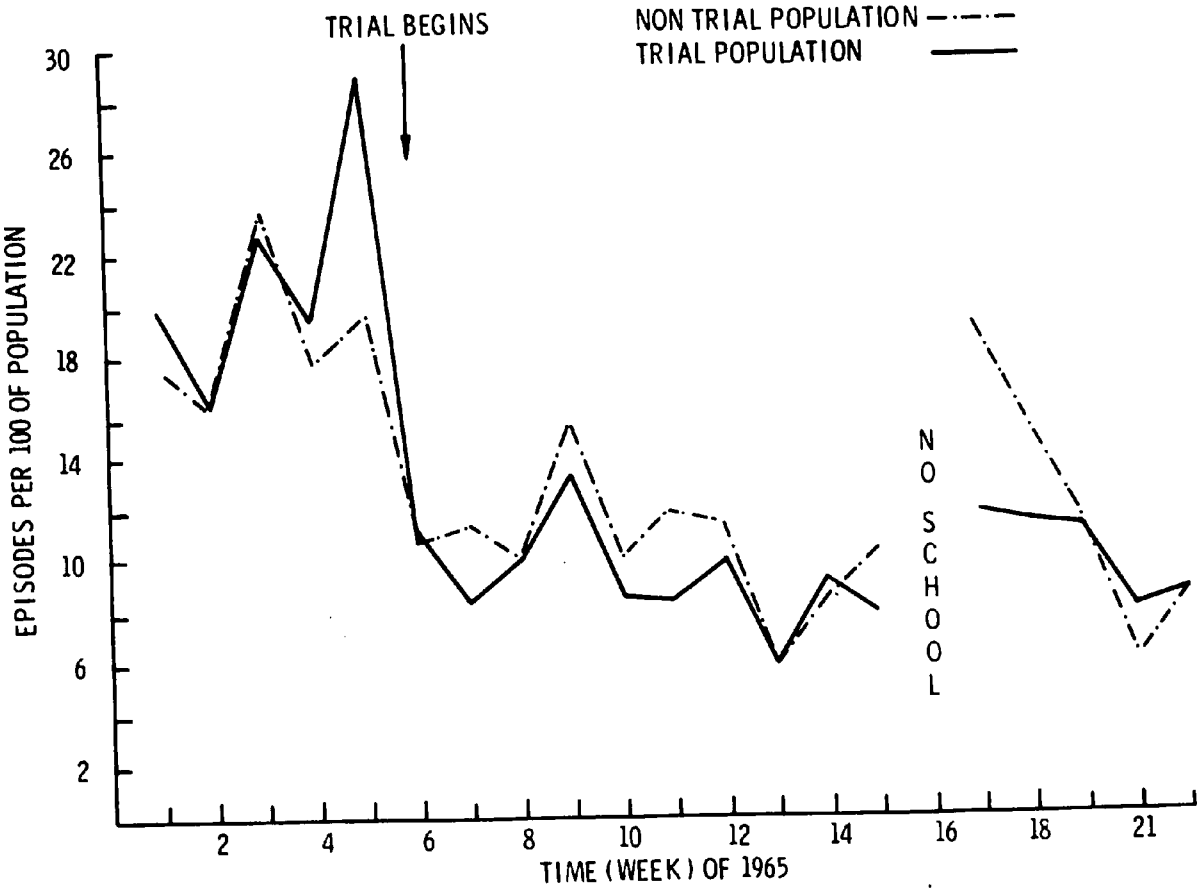


Figure V.6

Episodes of Absence from Academic School Among All Students
Distribution by Trial Participation and Time

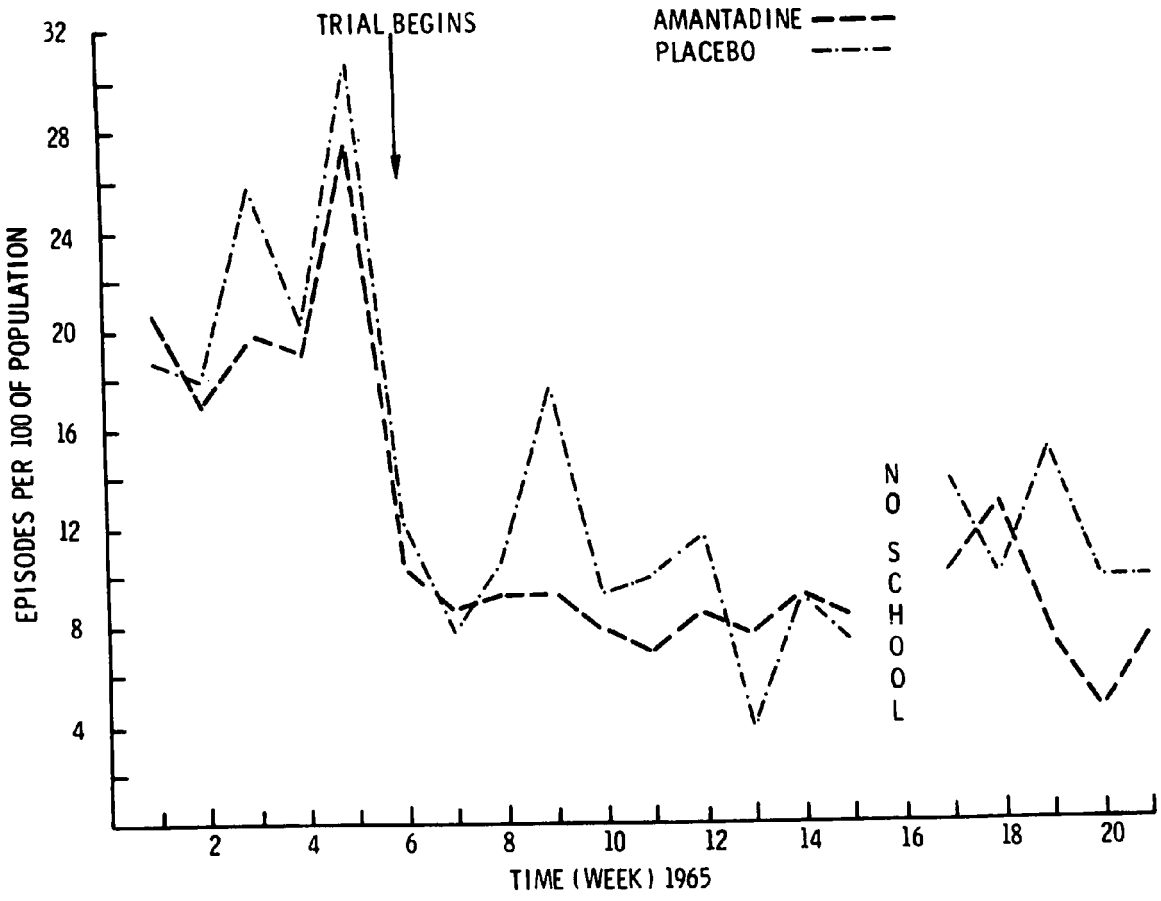


Figure V.7

Trial Participant Episodes of Absence from Academic School
Distribution by Trial Group and Time

4. Employee Absentees

a. Days of Absence: Figure V.8 presents days of absence rates for all WCTS employees and for cottage employees. Cottage employee absentee rates are generally somewhat higher than employees as a whole. Both rates are somewhat erratic in behavior and lower than school absentee rates. Employee absence rates were highest in late January and early February. The upturn at the end of the observation period is probably caused by employees using sick days to lengthen the Memorial Day weekend.

The source table for Figure V.8 may be found in Appendix B.8. This table also presents academic school employee absentee rates which show some peaking in February.

b. Episodes of Absence: Figure V.9 presents episodes of absence rates for all WCTS employees and for cottage employees. Cottage employees again exhibit a higher rate than do all employees. There now appear to be definite peaks of illness in January, February, and late March. These peaks are more pronounced in cottage employees. The source table for Figure V.9 is in Appendix B.9. This table also presents academic school employee episode of illness rates which have definite peaks in February and March. Among employees most intimately associated with students, namely teachers and cottage parents, there is evidence of increased illness during those periods when student illness was highest.

B. Study Population Morbidity

1. Clinical Diagnoses: Table V.6 presents the clinical diagnoses associated with illness during the trial. Upper respiratory

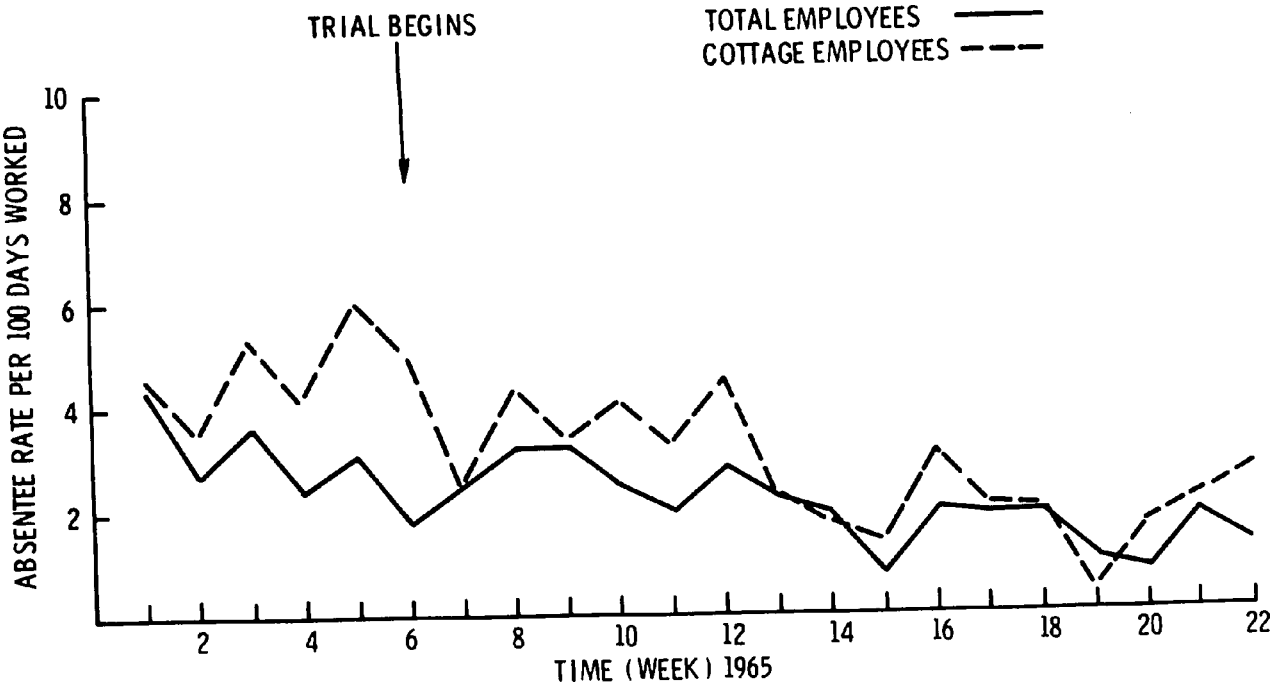


Figure V.8

WCTS Employee Absentee Rates
Distribution by Employee Group and Time

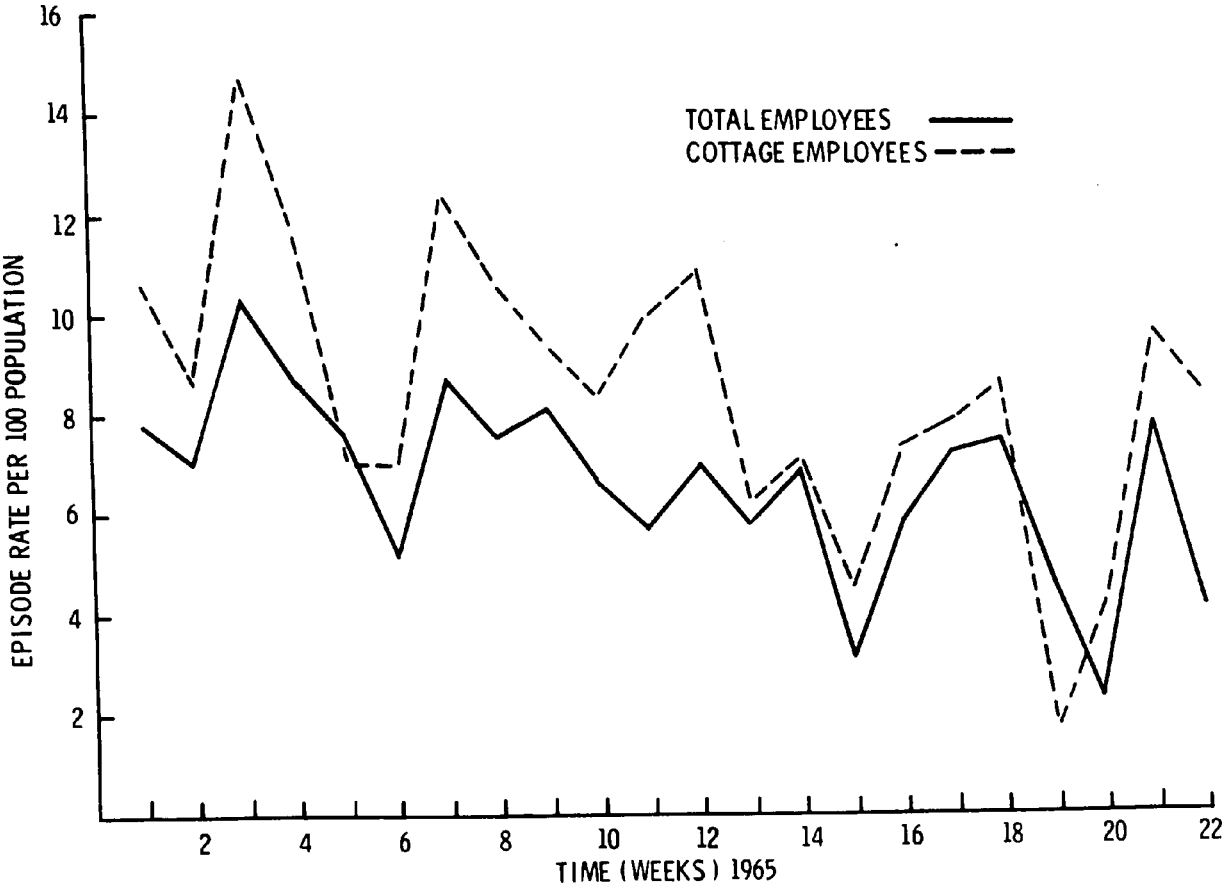


Figure V.9

Episodes of Absence Among WCTS Employees
Distribution by Selected Groups and Time

illness accounted for about 60 per cent of observed illness. This proportion agrees well with the proportion of all respiratory illness classed as upper respiratory in the National Health Survey.[36] All diagnostic categories, save the "other, nonrespiratory" which is increased in the placebo group, are similarly distributed in both trial groups.

TABLE V.6

CLINICAL DIAGNOSES AMONG TRIAL PARTICIPANTS
DURING ENTIRE TRIAL
DISTRIBUTION BY TRIAL GROUP

Diagnosis (Respiratory Syndrome)	Total Trial Group		Amantadine		Placebo	
	Cases	Per Cent of Total Cases	Cases	Per Cent of Total Amantadine Cases	Cases	Per Cent of Total Placebo Cases
Coryzal	72	30.4	32	30.8	40	30.1
Pharyngeal	80	33.8	40	38.4	40	30.1
Acute Undifferentiated Respiratory Disease	21	8.9	7	6.7	14	10.5
Laryngeal	8	3.3	3	2.9	5	3.75
Bronchitis	10	4.2	6	5.8	4	3.0
Pneumonitis	3	1.3	1	1.0	2	1.5
Other, Respiratory	6	2.5	4	3.8	2	1.5
Other, Nonrespiratory	27	11.4	6	5.8	21	15.8
Other, No Illness	10	4.2	5	4.8	5	3.75
Total	237	100.0	104	100.0	133	100.0

2. Effects of Blocking: Before proceeding with the analysis of trial illness, one can consider whether blocking for cottage residence and length of school residence was justified. Table V.7 presents the trial participant attack rates for various classes of illness distributed over the sixteen cottage units. Attack rates may be seen to vary greatly among cottages. Thus, blocking for cottage was justified.

TABLE V.7

PARTICIPANT TRIAL ILLNESS, ATTACK RATE
PER 100 PERSON WEEKS AT RISK
DISTRIBUTION BY COTTAGE RESIDENCE AND TYPE OF ILLNESS

Cottage Residence	Person Weeks at Risk	All Trial Illness		Streptococcal Illness		Nonstreptococcal Illness		"Other" Illness		Nonstreptococcal Respiratory Illness	
		Number	Attack Rate/100 Weeks at Risk	Number	Attack Rate/100 Weeks at Risk	Number	Attack Rate/100 Weeks at Risk	Number	Attack Rate/100 Weeks at Risk	Number	Attack Rate/100 Weeks at Risk
1	347	24	6.92	6	1.73	18	5.19	5	1.44	13	3.75
2	379	20	5.28	2	0.53	18	4.75	3	0.79	15	3.96
4	165	9	5.45	0	0.00	9	5.45	2	1.21	7	4.24
5	419	23	5.49	3	0.72	20	4.77	7	1.67	13	3.10
6	245	19	7.76	1	0.41	18	7.35	3	1.22	15	6.12
7	429	22	5.13	13	3.03	9	2.10	0	0.00	9	2.10
Fire Hall	117	6	5.13	2	1.71	4	3.42	2	1.71	2	1.71
9	381	11	2.89	6	1.57	5	1.31	0	0.00	5	1.32
10	325	6	1.85	1	0.31	5	1.54	1	0.31	4	1.23
11	272	10	3.68	4	1.47	6	2.20	0	0.00	6	2.20
12	371	8	2.16	1	0.27	7	1.89	2	0.54	5	1.35
13	238	13	5.46	2	0.84	11	4.62	3	1.26	8	3.85
14	371	20	5.39	5	1.35	15	4.04	4	1.08	11	2.96
15	401	8	2.00	4	1.00	4	1.00	0	0.00	4	1.00
16	494	30	6.07	13	2.63	17	3.44	4	0.81	13	2.63
19	196	8	4.08	1	0.51	7	3.57	4	2.04	3	1.53
Total	5150	237	4.60	64	1.24	173	3.36	40	0.78	133	2.58

Table V.8 presents participant trial illness distributed by length of residence prior to the trial and number of illnesses. The distribution for those in residence less than one year does not differ significantly from those in residence more than one year. Thus, blocking for length of residence was justified but did not appear to have been necessary.

TABLE V.8

PARTICIPANT TRIAL ILLNESS
DISTRIBUTION BY LENGTH OF WCTS RESIDENCE

Number of Illnesses During Trial	Length of WCTS Residence	
	Less Than One Year	Greater Than One Year
0	37	85
1	29	61
2	15	36
3	6	18
4	3	5
5	0	3
6	1	0
7 or more	0	0
Total	91	208

$\chi^2_{(4)} = .50439$

$.98 > p > .95$

C. Analysis of Incidence of Illness

1. Conventions

a. Grouping Illness: Illnesses were grouped for analysis. No referred child is excluded from the analysis. First, those illnesses associated with throat cultures which grew beta hemolytic streptococci

were grouped together, prior to any grouping based on clinical diagnosis. This partition produced two subgroups of illness called "streptococcal" and "all nonstreptococcal." Next, those nonstreptococcal illnesses clinically diagnosed as "other" were grouped. This partition resulted in two further subgroups of illness called "other" and "nonstreptococcal respiratory."

b. Time Periods: Following an initial period of 23 days of pretrial observation, the trial proper began and is first considered as a whole and then was subdivided into three six week time periods called Period I, Period II, and Period III. Period I refers to the first 46 days; Period II refers to days 47 through 88; and Period III refers to days 89 through 121.

c. Eligible Participants: Entry of volunteers into the trial and exit from the trial did not differ significantly between trial groups (see Chapter III). Thus, no great error should occur if entrance and exit were ignored. Actually, analysis of total trial experience was made under three different eligibility assumptions. The first analysis assumed that entrance and exit have no effect and treats the data as if all subjects were in constant residence. The second analysis assumed eligibility for those individuals who entered the trial not later than two weeks after the trial began or who exited not earlier than two weeks before the trial ended. These are called "16 week" participants. The third analysis utilized only the experience of the participants who were constantly present during the whole trial.

An individual was eligible for consideration in any trial subdivision if he were in residence for four of the six weeks.

d. Ways of Analyzing Incidence: Incidence of illness can be analyzed by one or more of three methods. First, the illness experience of individuals within each trial group may be considered. Second, the illness experience of each trial group among cottages can be examined. Finally, the illness experience of each trial group among the weeks of the trial can be considered.

The most important approach considers individual experience within each trial group. This method may be applied to the entire trial or any trial subdivision. The other two approaches are only useful when total trial experience is examined.

2. Pretrial Illness: During the pretrial period the illness experience of the two trial groups should not differ significantly.

Table V.9 presents the clinical diagnoses of pretrial illness in both trial groups. Both the numbers of cases and the clinical diagnoses appear similar.

TABLE V.9

PARTICIPANT PRETRIAL ILLNESS
DISTRIBUTION BY TRIAL GROUP AND CLINICAL SYNDROME

Clinical Syndrome	Total Trial Group		Amantadine		Placebo	
	Cases	Per Cent of Total Cases	Cases	Per Cent of Amantadine Cases	Cases	Per Cent of Placebo Cases
Coryzal	37	46.2	19	47.5	18	45.0
Pharyngeal	26	32.5	11	27.5	15	37.5
Acute Undifferentiated Respiratory Disease	5	6.3	2	5.0	3	7.5
Laryngeal	1	1.2	1	2.5	0	0.0
Bronchitis	0	0.0	0	0.0	0	0.0
Pneumonitis	0	0.0	0	0.0	0	0.0
Other, Respiratory	2	2.5	1	2.5	1	2.5
Other, Nonrespiratory	4	5.0	3	7.5	1	2.5
Other, No Illness	5	6.3	3	7.5	2	5.0
Total	80	100.0	40	100.0	40	100.0

Table V.10 presents the distributions of all pretrial illnesses in amantadine and placebo individuals. These distributions did not differ significantly ($.50 > p > .30$).

TABLE V.10

ALL PRETRIAL ILLNESS AMONG PARTICIPANTS
DISTRIBUTION BY NUMBER OF ILLNESSES
AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant				Total Number of Illnesses	Pretrial Participants
	0	1	2	3 or more		
Placebo	96	36	2	0	40	134
Amantadine	115	32	4	0	40	151
Total	211	68	6	0	80	285

$\chi^2_{(1)} = .65918$

$.50 > p > .30$

Table V.11 presents the distributions of all pretrial streptococcal illnesses. Streptococcal illness experience did not differ significantly between amantadine and placebo groups ($.50 > p > .30$).

TABLE V.11

PARTICIPANT PRETRIAL STREPTOCOCCAL ILLNESS
DISTRIBUTION BY NUMBER OF ILLNESSES
AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant				Total Number of Illnesses	Pretrial Participants
	0	1	2	3 or more		
Placebo	124	10	0	0	10	134
Amantadine	144	6	1	0	8	151
Total	268	16	1	0	18	285

$\chi^2_{(1)} = 1.00397$

$.50 > p > .30$

Table V.12 presents the distributions of all pretrial nonstreptococcal illnesses. Nonstreptococcal illness did not iffer significantly between the trial groups ($.80 > p > .70$).

TABLE V.12

PARTICIPANT PRETRIAL NONSTREPTOCOCCAL ILLNESS DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant				Total Number of Illnesses	Pretrial Participants
	0	1	2	3 or more		
Placebo	105	28	1	0	30	134
Amantadine	121	28	2	0	32	151
Total	226	56	3	0	62	285

$\chi^2_{(1)} = .0856$

$.80 > p > .70$

Table V.13 presents the distributions of pretrial illnesses diagnosed as "other." These distributions did not differ significantly between trial groups ($.90 > p > .80$).

TABLE V.13

PARTICIPANT PRETRIAL ILLNESS DIAGNOSED AS "OTHER" DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant			Total Number of Illnesses	Pretrial Participants
	0	1	2 or more		
Placebo	130	4	0	4	134
Amantadine	145	6	0	6	151
Total	275	10	0	10	285

$\chi^2_{(1)} = .04146$

$.90 > p > .80$

Table V.14 presents the distributions of pretrial nonstreptococcal respiratory illnesses. Nonstreptococcal respiratory illness did not differ significantly between trial groups ($.70 > p > .50$).

TABLE V.14

PRETRIAL NONSTREPTOCOCCAL RESPIRATORY ILLNESS AMONG PARTICIPANTS DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant				Total Number of Illnesses	Pretrial Participants
	0	1	2	3 or more		
Placebo	108	26	0	0	26	134
Amantadine	126	24	1	0	26	151
Total	234	50	1	0	52	285

$\chi^2_{(1)} = .3832$

$.70 > p > .50$

3. All Trial Illness

a. All Illness: Figure V.10 plots the weekly incidence rates of all illness among participants over the pretrial and trial periods. The high rates during the first week of pretrial observations were in part artifact because these incidence rates contain illness beginning prior to the period of observation. Thus, the rates for the initial week are, in part, prevalence rates. After the trial began there was more illness in the placebo group during Period I (mid-February) and Period II (late April). When the sign test is applied to weekly pairs of incidence rates during the trial, the placebo group had the higher rate more frequently than would be expected on a chance basis ($p = .038$). The source table for Figure V.10 and this sign test may be found in Appendix B.10.

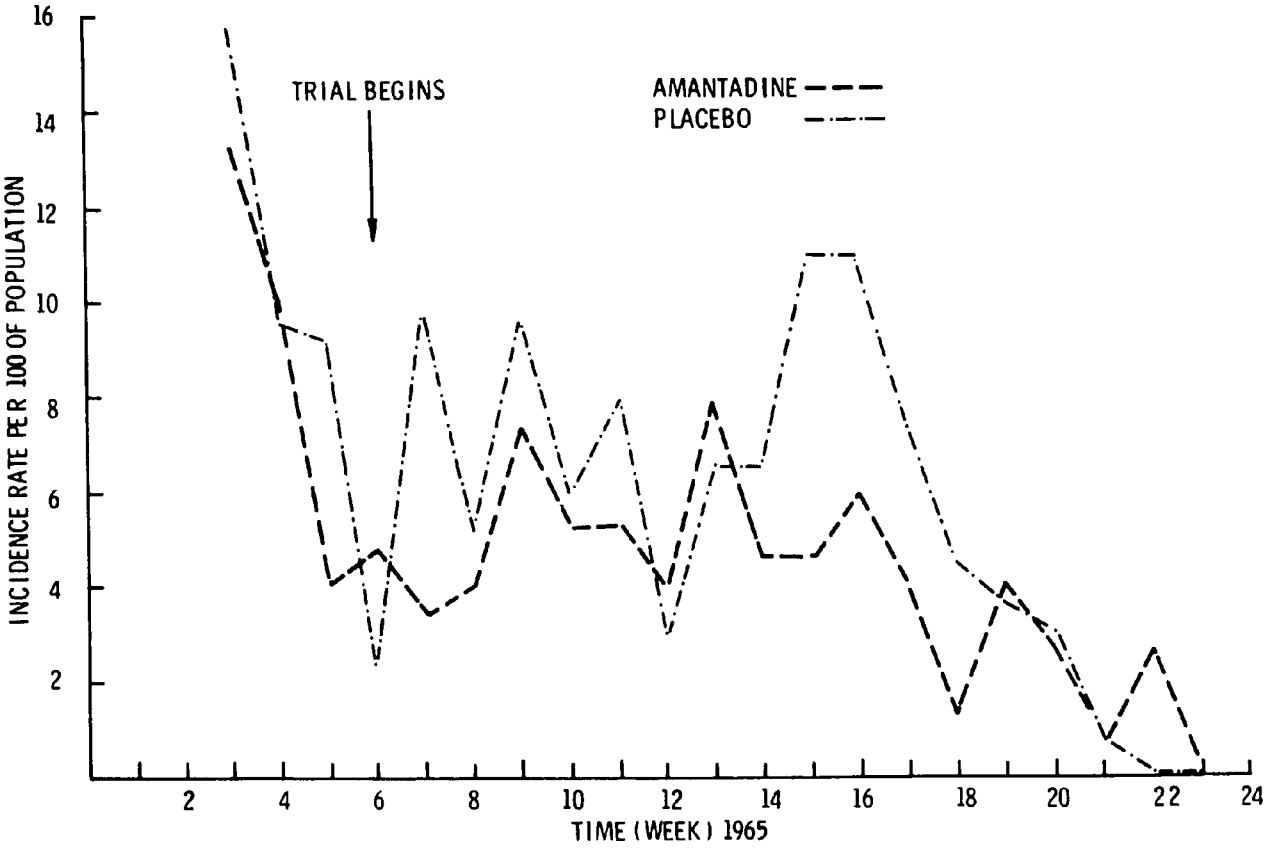


Figure V.10

Incidence of All Illness, Excluding Trauma, Among Participants
Distribution by Trial Group and Time

Table V.15 distributes all trial illness attack rates by treatment group and cottage. In this presentation we have, in effect, sixteen different trials in the sixteen different cottages. Attack rates were higher in the placebo group in 13 of the 16 cottages. The sign test shows that placebo attack rates among cottages exceeded amantadine attack rates more frequently than would be expected on a chance basis ($p = .011$).

TABLE V.15

ALL TRIAL ILLNESS
ATTACK RATE PER 100 PERSON WEEKS AT RISK
DISTRIBUTION BY TRIAL GROUP AND COTTAGE

Cottage Residence	Amantadine			Placebo		
	Weeks of Risk	Number of Illnesses	Attack Rate/100 Weeks at Risk	Weeks of Risk	Number of Illnesses	Attack Rate/100 Weeks at Risk
1	160	9	5.62	187	15	8.02
2	196	9	4.59	183	11	6.01
4	77	2	2.60	88	7	7.95
5	228	12	5.24	191	11	5.76
6	132	9	6.82	113	10	8.85
7	231	14	6.06	198	8	4.04
Fire Hall	72	3	4.17	45	3	6.67
9	205	4	1.95	176	7	3.98
10	188	1	0.53	137	5	3.65
11	150	4	2.67	122	6	4.92
12	203	5	2.46	168	3	1.78
13	126	3	2.38	112	10	8.93
14	207	11	5.31	164	9	5.49
15	180	4	2.22	221	4	1.81
16	249	13	5.22	245	17	6.94
19	102	1	0.98	94	7	7.45
Total	2706	104	3.84	2444	133	5.44

$p = .011$ (Sign Test)

Table V.16 distributes all trial participants by treatment group and number of illnesses during the trial. The placebo individuals experienced more illness but the difference between trial groups did not attain significance ($.10 > p > .05$).

TABLE V.16

ALL TRIAL ILLNESS AMONG ALL PARTICIPANTS
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant							Total Number of Illnesses	All Participants
	0	1	2	3	4	5	6 or more		
Placebo	59	48	23	9	3	0	0	133	142
Amantadine	87	45	19	4	1	1	0	104	157
Total	146	93	42	13	4	1	0	237	299

$\chi^2_{(3)} = 6.2972$

$.10 > p > .05$

Table V.17 distributes trial participants who were in residence for all but two weeks of the trial, i.e., 16 week participants, by treatment group and number of trial illnesses. Placebo individuals experienced more illness but the difference between trial groups was not significant ($.20 > p > .10$). Thus it appears that participants from both groups may have entered and exited in a similar fashion but more participants with illness exited from the placebo group.

Table V.18 distributes all trial illness among constant participants by treatment group and number of illnesses. As in Table V.17, the placebo group had more illness but the difference between trial groups was not significant ($.20 > p > .10$).

TABLE V.17

ALL TRIAL ILLNESS AMONG 16 WEEK PARTICIPANTS*
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant							Total Number of Illnesses	22 Week Participants
	0	1	2	3	4	5	6 or more		
Placebo	54	41	23	8	3	0	0	123	129
Amantadine	80	44	18	4	1	1	0	101	148
Total	134	85	41	12	4	1	0	224	277

$\chi^2_{(3)} = 5.2865$

$.20 > p > .10$

*In residence at least 16 of the 18 trial weeks.

TABLE V.18

ALL TRIAL ILLNESS AMONG CONSTANT* PARTICIPANTS
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant							Total Number of Illnesses	Constant Participants
	0	1	2	3	4	5	6 or more		
Placebo	51	40	23	7	3	0	0	119	124
Amantadine	76	40	18	4	1	1	0	97	140
Total	127	80	41	11	4	1	0	216	264

$\chi^2_{(3)} = 4.76015$

$.20 > p > .10$

*In residence all 18 of the 18 trial weeks.

b. Streptococcal Illness: Figure V.11 plots the weekly incidence rates of streptococcal illness in the two trial groups. Streptococcal illness was present throughout the trial. The highest incidence occurred during Period I (late February). Rates appear to be somewhat higher in the amantadine group. The sign test may be applied to weekly pairs of incidence rates during the trial and shows that streptococcal weekly incidence rates in the amantadine group did not exceed placebo rates more frequently than could be expected on a chance basis ($p = .151$). Appendix B.11 contains the source table for this sign test and Figure V.11.

Table V.19 presents streptococcal attack rates for both trial groups in the sixteen cottage units studied. A sign test may be applied to these pairs of rates. This test shows that amantadine streptococcal attack rates did not exceed placebo rates more frequently than expected on a chance basis ($p = .227$).

Table V.20 distributes all participant streptococcal illness by number of illnesses and trial group. Trial groups did not differ significantly ($.50 > p > .30$).

Table V.21 distributes streptococcal illness among "16 week" participants by number of illnesses and trial group. Trial groups did not differ significantly ($.50 > p > .30$).

Table V.22 distributes streptococcal illness among constant participants by number of illnesses and trial group. Trial groups did not differ significantly ($.80 > p > .70$).

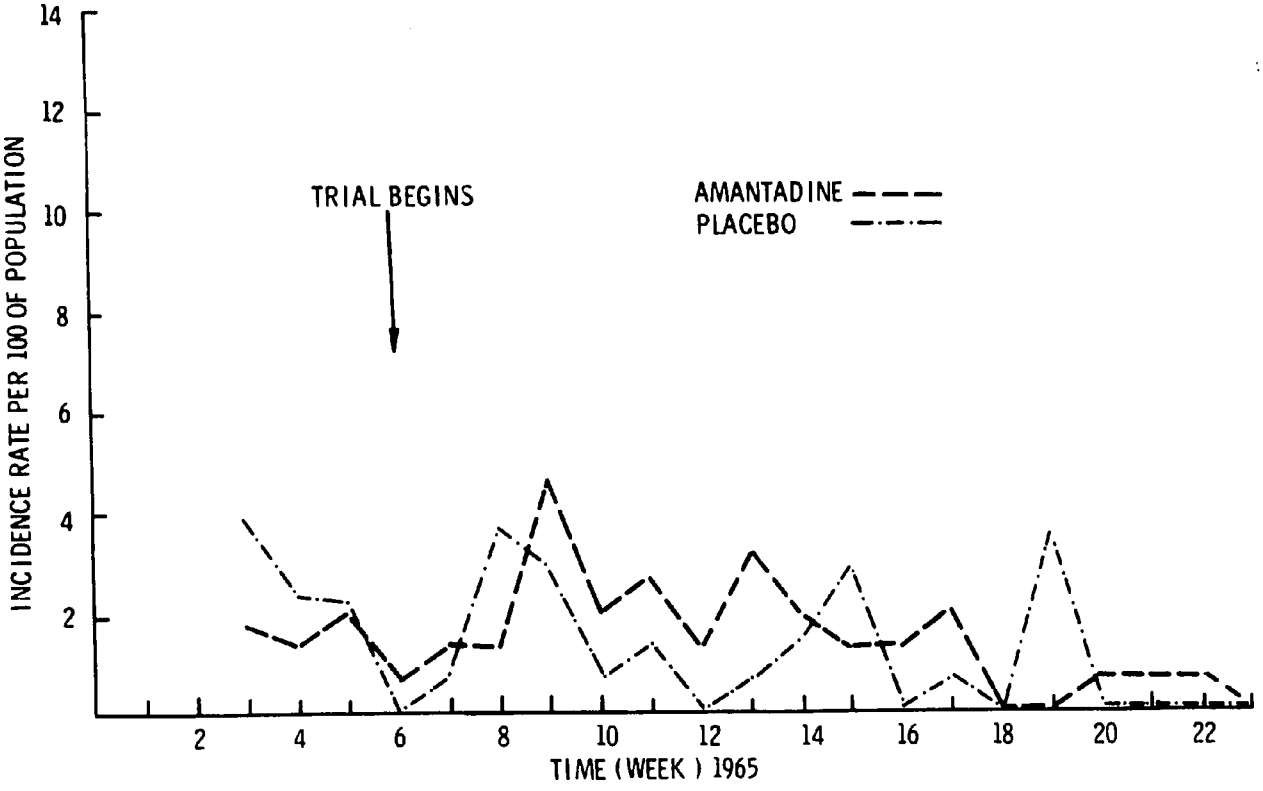


Figure V.11

Incidence of Streptococcal Illness Among Participants
Distribution by Trial Group and Time

TABLE V.19

STREPTOCOCCAL ILLNESS
ATTACK RATE PER 100 PERSON WEEKS AT RISK
DISTRIBUTION BY TRIAL GROUP AND COTTAGE RESIDENCE

Cottage Residence	Amantadine			Placebo		
	Weeks of Risk	Number of Illnesses	Attack Rate/100 Weeks at Risk	Weeks of Risk	Number of Illnesses	Attack Rate/100 Weeks of Risk
1	160	3	1.88	187	3	1.60
2	196	2	1.02	183	0	0.00
4	77	0	0.00	88	0	0.00
5	228	2	0.88	191	1	0.52
6	132	1	0.76	113	0	0.00
7	231	9	3.90	198	4	2.02
Fire Hall	72	1	1.39	45	1	2.22
9	205	3	1.46	176	3	1.70
10	188	0	0.00	137	1	0.73
11	150	1	0.67	122	3	2.46
12	203	1	0.49	168	0	0.00
13	126	0	0.00	112	2	1.78
14	207	2	0.97	164	3	1.83
15	180	3	1.67	221	1	0.45
16	249	8	3.21	245	5	2.04
19	102	1	0.98	94	0	0.00
Total	2706	37	1.37	2444	27	1.10

p = .227 (Sign Test)

TABLE V.20

TRIAL STREPTOCOCCAL ILLNESS AMONG ALL PARTICIPANTS
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant					Total Number of Illnesses	All Participants
	0	1	2	3	4 or more		
Placebo	118	21	3	0	0	27	142
Amantadine	124	30	2	1	0	37	157
Total	242	51	5	1	0	64	299

$\chi^2_{(1)} = .7824$

$.50 > p > .30$

TABLE V.21

TRIAL STREPTOCOCCAL ILLNESS AMONG
16 WEEK PARTICIPANTS*
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant					Total Number of Illnesses	22 Week Participants
	0	1	2	3	4 or more		
Placebo	106	20	3	0	0	26	129
Amantadine	116	29	2	1	0	36	148
Total	222	49	5	1	0	62	277

$\chi^2_{(1)} = .8195$

$.50 > p > .30$

*In residence at least 16 of the 18 trial weeks.

TABLE V.22

TRIAL STREPTOCOCCAL ILLNESS AMONG
CONSTANT* PARTICIPANTS
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant					Total Number of Illnesses	Constant Participants
	0	1	2	3	4 or more		
Placebo	102	19	3	0	0	25	124
Amantadine	109	28	2	1	0	35	140
Total	211	47	5	1	0	60	264

$\chi^2_{(1)} = .8527$

$.50 > p > .30$

*In residence all 18 of the 18 trial weeks.

c. All Nonstreptococcal Illness: Figure V.12 depicts the weekly incidence rates of all nonstreptococcal illness among trial groups. This figure shows three distinct trial peaks. The first two peaks are in Period I (February and March) and the third and largest peak is in Period II (April). During each peak period there is more illness in the placebo group. When the sign test is applied to weekly pairs of rates during the trial, the placebo group had the higher rate more frequently than expected on a chance basis ($p = .011$). Appendix B.12 contains the source table for this sign test and Figure V.12.

Table V.23 presents cottage attack rates for trial nonstreptococcal illness. The sign test shows that the placebo group had the higher attack rate more frequently than would be expected on a chance basis ($p = .011$).

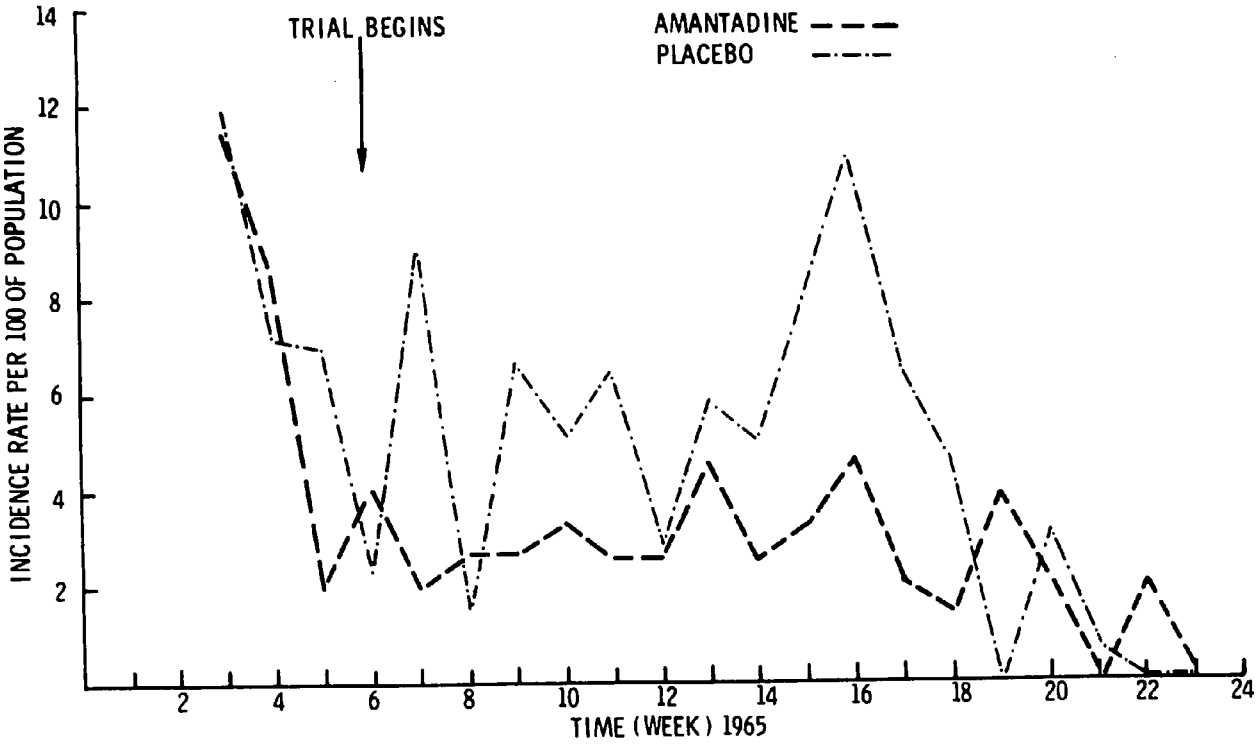


Figure V.12

Incidence of All Nonstreptococcal Illness Among Participants
Distribution by Trial Group and Time

TABLE V.23

TRIAL NONSTREPTOCOCCAL ILLNESS, ATTACK RATE
PER 100 PERSON WEEKS AT RISK
DISTRIBUTION BY TRIAL GROUP AND COTTAGE OF RESIDENCE

Cottage Residence	Amantadine			Placebo		
	Weeks of Risk	Number of Illnesses	Attack Rate/100 Weeks at Risk	Weeks of Risk	Number of Illnesses	Attack Rate/100 Weeks At Risk
1	160	6	3.75	187	12	6.42
2	196	7	3.57	183	11	6.01
4	77	2	2.60	88	7	7.95
5	228	10	4.38	191	10	5.24
6	132	8	6.06	113	10	8.85
7	231	5	2.16	198	4	2.02
Fire Hall	72	2	2.78	45	2	4.44
9	205	1	0.49	176	4	2.27
10	188	1	0.53	137	4	2.92
11	150	3	2.00	122	3	2.46
12	203	4	1.97	168	3	1.78
13	126	3	2.38	112	8	7.14
14	207	9	4.35	164	6	3.66
15	180	1	0.56	221	3	1.36
16	249	5	2.01	245	12	4.90
19	102	0	0.00	94	7	7.45
Total	2706	67	2.48	2444	106	4.34

$p = .011$ (Sign Test)

Table V.24 distributes nonstreptococcal illnesses of all participants by trial group and number of illnesses. The placebo group had significantly more illness than the amantadine group ($.01 > p > .001$).

TABLE V.24

TRIAL NONSTREPTOCOCCAL ILLNESS AMONG
ALL PARTICIPANTS
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant							Total Number of Illnesses	All Participants
	0	1	2	3	4	5	6 or more		
Placebo	73	42	20	4	3	0	0	106	142
Amantadine	112	30	11	2	1	1	0	67	157
Total	185	72	31	6	4	1	0	163	299

$\chi^2_{(3)} = 13.13877$

$.01 > p > .001$

Table V.25 distributes nonstreptococcal illnesses of 16 week participants by trial group and number of illnesses. The placebo group had significantly more such illness than the amantadine group ($.01 > p > .01$).

TABLE V.25

TRIAL NONSTREPTOCOCCAL ILLNESS AMONG
16 WEEK PARTICIPANTS*
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant							Total Number of Illnesses	22 Week Participants
	0	1	2	3	4	5	6 or more		
Placebo	67	36	20	3	3	0	0	97	129
Amantadine	104	30	10	2	1	1	0	65	148
Total	171	66	30	5	4	1	0	162	277

$\chi^2_{(3)} = 10.7118$

$.02 > p > .01$

*In residence at least 16 of the 18 trial weeks.

Table V.26 distributes nonstreptococcal illnesses of constant trial participants. The placebo group experienced significantly more such illness than did the amantadine group ($.02 > p > .01$).

TABLE V.26

TRIAL NONSTREPTOCOCCAL ILLNESS AMONG CONSTANT* PARTICIPANTS DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant							Total Number of Illnesses	Constant Participants
	0	1	2	3	4	5	6 or more		
Placebo	64	35	19	3	3	0	0	94	124
Amantadine	99	27	10	2	1	1	0	62	140
Total	163	62	29	5	4	1	0	156	264

$\chi^2_{(3)} = 10.3446$

$.02 > p > .01$

*In residence all 18 of the 18 trial weeks.

d. "Other" Illness: Figure V.13 depicts the weekly incidence rates of illnesses diagnosed as "other." These illnesses occurred at a low rate throughout the trial and rates in the placebo group are generally higher than rates in the amantadine group. The sign test may be applied to weekly pairs of rates during the trial and shows that placebo rates exceeded amantadine rates more frequently than would have been expected on a chance basis ($p = .011$). Appendix B.13 contains the source table for Figure V.13 and this sign test.

Table V.27 presents the attack rates of "other" illnesses in the sixteen cottage units. The sign test may be applied to pairs of

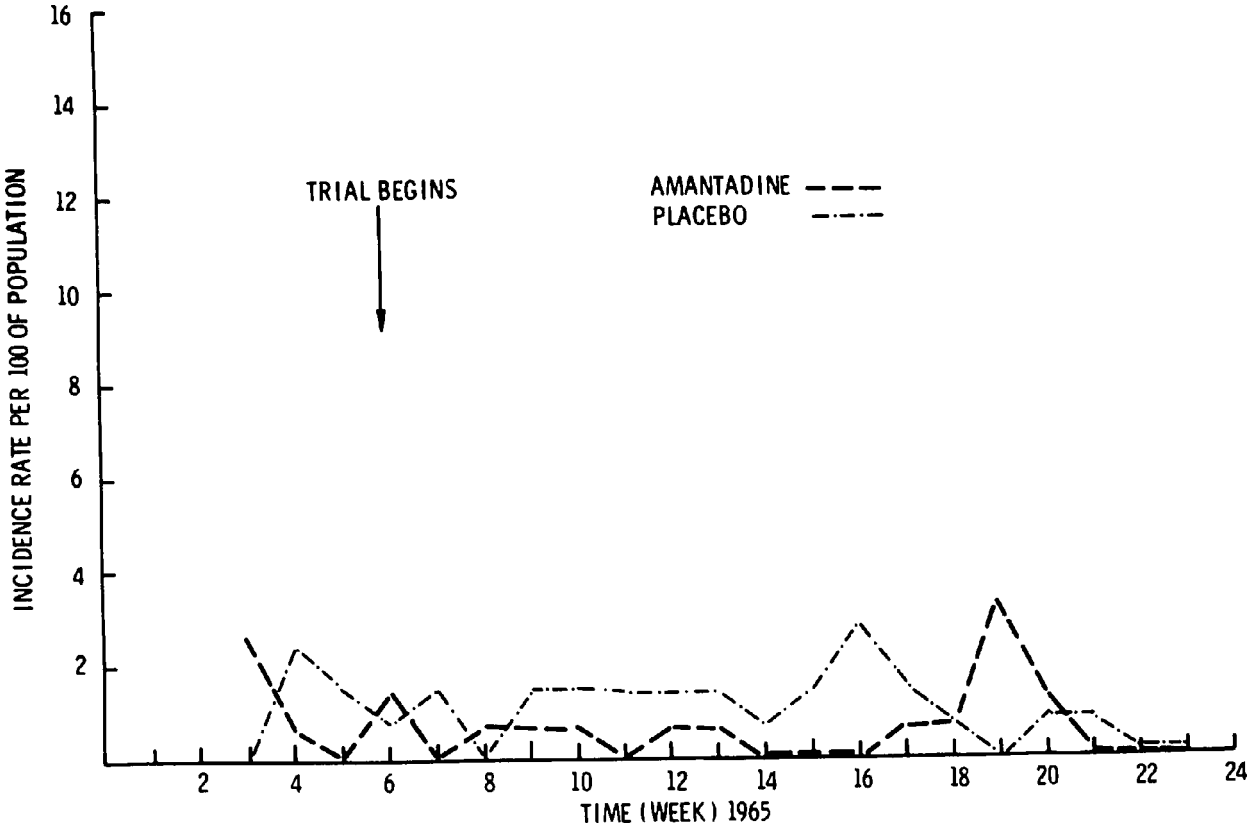


Figure V.13

Incidence of Illness, Diagnosed as "Other," Among Participants
Distribution by Trial Group and Time

attack rates and shows that placebo cottage attack rates did not exceed amantadine attack rates more frequently than expected on a chance basis ($p = .113$).

TABLE V.27

ALL TRIAL ILLNESS DIAGNOSED AS "OTHER"
ATTACK RATE PER 100 PERSON WEEKS AT RISK
DISTRIBUTION BY TRIAL GROUP AND COTTAGE RESIDENCE

Cottage Residence	Amantadine			Placebo		
	Weeks of Risk	Number of Illnesses	Attack Rate/100 Weeks at Risk	Weeks of Risk	Number of Illnesses	Attack Rate/100 Weeks at Risk
1	160	3	1.88	187	2	1.07
2	196	2	1.02	183	1	0.55
4	77	0	0.00	88	2	2.27
5	228	3	1.32	191	4	2.09
6	132	0	0.00	113	3	2.65
7	231	0	0.00	198	0	0.00
Fire Hall	72	1	1.39	45	1	2.22
9	205	0	0.00	176	0	0.00
10	188	0	0.00	137	1	0.73
11	150	0	0.00	122	0	0.00
12	203	0	0.00	168	2	1.19
13	126	0	0.00	112	3	2.68
14	207	4	1.93	164	0	0.00
15	180	0	0.00	221	0	0.00
16	249	1	0.40	245	3	1.22
19	102	0	0.00	94	4	4.26
Total	2706	14	0.82	2444	26	1.06

$p = .113$ (Sign Test)

Table V.28 distributes all participant illness diagnosed as "other" by number of illnesses and trial group. The placebo individuals experienced significantly more "other" illness than did the amantadine ($.02 > p > .01$).

TABLE V.28

TRIAL ILLNESS, DIAGNOSED AS "OTHER" AMONG
ALL PARTICIPANTS
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant				Total Number of Illnesses	All Participants
	0	1	2	3 or more		
Placebo	119	20	3	0	26	142
Amantadine	147	6	4	0	14	157
Total	266	26	7	0	40	299

$\chi^2_{(1)} = 6.6837$

$.02 > p > .01$

Table V.29 distributes illness diagnosed as "other" among "16 week" participants by number of illnesses and trial groups. Placebo individuals experienced significantly more "other" illness than did the amantadine ($.01 > p > .001$).

TABLE V.29

ALL TRIAL ILLNESS DIAGNOSED AS "OTHER" AMONG
16 WEEK PARTICIPANTS*
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant				Total Number of Illnesses	22 Week Participants
	0	1	2	3 or more		
Placebo	108	18	3	0	24	129
Amantadine	138	6	4	0	14	148
Total	246	24	7	0	38	277

$\chi^2_{(1)} = 7.14823$

$.01 > p > .001$

*In residence at least 16 of the 18 trial weeks.

Table V.30 distributes "other" illness among constant participants by number of illnesses and trial group. Placebo individuals experienced significantly more "other" illness than did the amantadine ($.02 > p > .01$).

TABLE V.30

TRIAL ILLNESS DIAGNOSED AS "OTHER" AMONG CONSTANT* PARTICIPANTS DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant				Total Number of Illnesses	Constant Participants
	0	1	2	3 or more		
Placebo	103	18	3	0	24	124
Amantadine	130	6	4	0	14	140
Total	233	24	7	0	38	264

$\chi^2_{(1)} = 6.0143$

$.02 > p > .01$

*In residence all 18 of the 18 trial weeks.

e. Nonstreptococcal Respiratory Illness: Figure V.14 depicts the weekly incidence rates of nonstreptococcal respiratory disease. Nonstreptococcal respiratory disease incidence for both groups appears similar during the pretrial period and during Period III (May and June). In both trial groups incidence rates are high during the pretrial period and low during Period III. During the first twelve weeks of the trial incidence rates appear higher for the placebo group. The placebo group experienced three peaks of incidence. Two of these peaks occurred during Period I (one in February and one in March) and one peak occurred during Period II (April). The amantadine group also

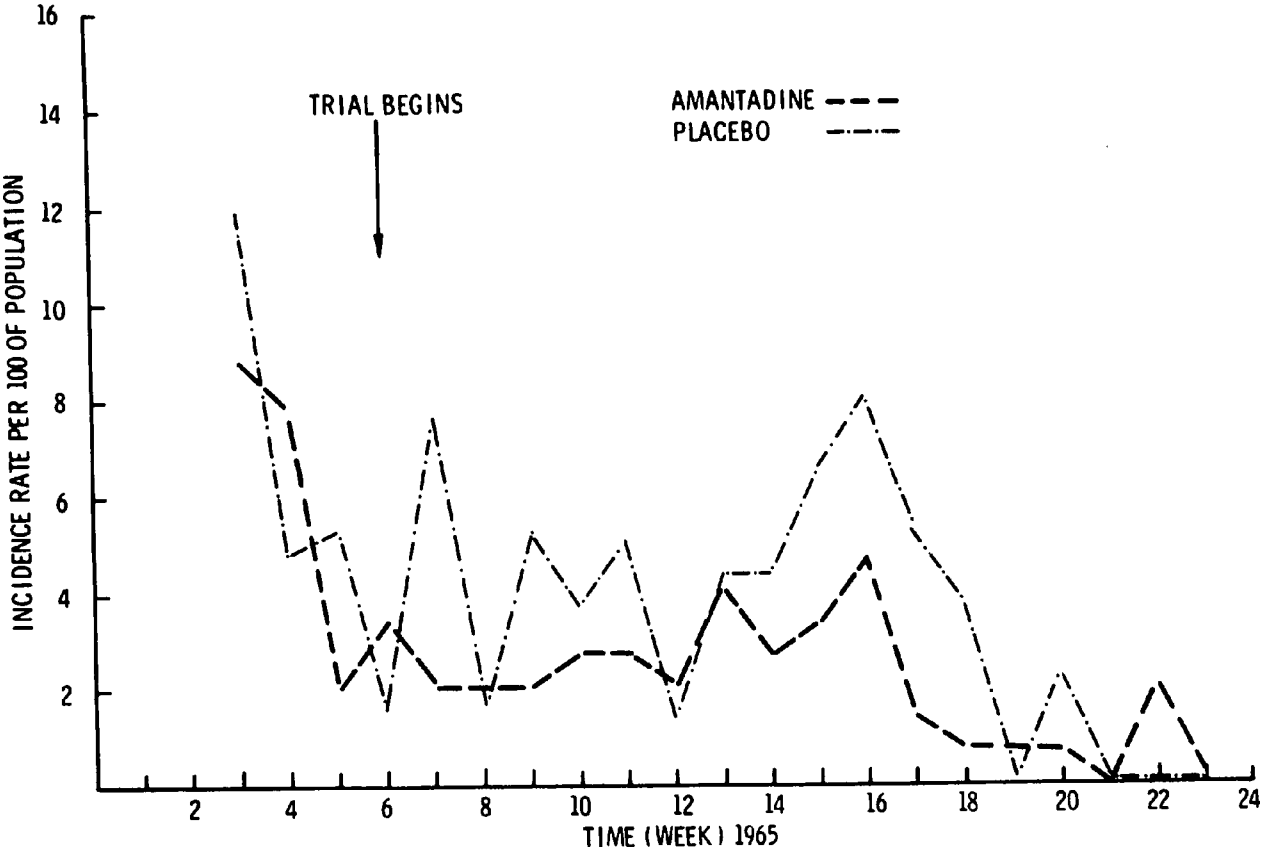


Figure V.14

Incidence of Nonstreptococcal Respiratory Illness Among Participants
Distribution by Trial Group and Time

experienced increased incidence during Period II (April). When the sign test is applied to weekly pairs of incidence rates during the trial, the placebo rates are more frequently increased; but this may have occurred on a chance basis ($p = .059$). Appendix B.14 contains the source table for Figure V.14 and this sign test.

Table V.31 distributes attack rates for nonstreptococcal respiratory disease by cottage and trial group. When the sign test is applied to each cottage pair of rates, placebo rates are higher more frequently than would be expected on a chance basis ($p = .002$).

TABLE V.31

TRIAL NONSTREPTOCOCCAL RESPIRATORY ILLNESS, ATTACK RATE PER 100 PERSON WEEKS AT RISK DISTRIBUTION BY TRIAL GROUP AND COTTAGE RESIDENCE

Cottage Residence	Amantadine			Placebo		
	Weeks of Risk	Number of Illnesses	Attack Rate/100 Weeks at Risk	Weeks of Risk	Number of Illnesses	Attack Rate/100 Weeks at Risk
1	160	3	1.88	187	10	5.35
2	196	5	2.55	183	10	5.46
4	77	2	2.60	88	5	5.68
5	77	2	2.60	88	5	5.68
6	132	8	6.06	113	7	6.19
7	231	5	2.16	198	4	2.02
Fire Hall	72	1	1.39	45	1	2.22
9	205	1	0.49	176	4	2.27
10	188	1	0.53	137	3	2.19
11	150	3	2.00	122	3	2.46
12	203	4	1.97	168	1	0.60
13	126	3	2.38	112	5	4.46
14	207	5	2.42	164	6	3.66
15	180	1	0.56	221	3	1.36
16	249	4	1.61	245	9	3.67
19	102	0	0.00	94	3	3.19
Total	2706	53	1.96	2444	80	3.27

$p = .002$ (Sign Test)

Table V.32 distributes all trial participants by number of nonstreptococcal respiratory illnesses and trial group. Individuals in the placebo group experienced significantly more illness than did amantadine individuals ($.02 > p > .01$).

TABLE V.32

TRIAL NONSTREPTOCOCCAL RESPIRATORY ILLNESS
AMONG ALL TRIAL PARTICIPANTS
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant					Total Number of Illnesses	All Participants
	0	1	2	3	4 or more		
Placebo	83	42	13	4	0	80	142
Amantadine	117	29	9	2	0	53	157
Total	200	71	22	6	0	133	299

$\chi^2_{(2)} = 8.7967$

$.02 > p > .01$

Table V.33 considers nonstreptococcal respiratory illness in "16 week" participants. Individuals in the placebo group experienced significantly more illness than individuals in the amantadine group ($.01 > p > .001$).

Table V.34 considers nonstreptococcal respiratory illness in constant trial participants. The placebo group experienced significantly more illness than did the amantadine group ($.05 > p > .02$).

4. Subdivisions of Trial

a. Period I (10 February to 27 March)

1) Clinical Diagnoses: Table V.35 presents the clinical diagnoses of illnesses observed during Period I. More acute

TABLE V.33

TRIAL NONSTREPTOCOCCAL RESPIRATORY ILLNESS
AMONG 16 WEEK PARTICIPANTS*
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant					Total Number of Illnesses	22 Week Participants
	0	1	2	3	4 or more		
Placebo	76	37	12	4	0	73	129
Amantadine	109	29	8	2	0	51	148
Total	175	66	20	6	0	124	277

$\chi^2_{(2)} = 7.1913$

$.01 > p > .001$

*In residence at least 16 of the 18 trial weeks.

TABLE V.34

TRIAL NONSTREPTOCOCCAL RESPIRATORY ILLNESS
AMONG CONSTANT* PARTICIPANTS
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant					Total Number of Illnesses	Constant Participants
	0	1	2	3	4 or more		
Placebo	73	36	11	4	0	70	124
Amantadine	104	26	8	2	0	48	140
Total	177	62	19	6	0	118	264

$\chi^2_{(2)} = 6.24618$

$.05 > p > .02$

*Resident during all 18 of the 18 trial weeks.

TABLE V.35

CLINICAL DIAGNOSES OF ILLNESS OCCURRING DURING PERIOD I
DISTRIBUTION BY CLINICAL SYNDROME AND TRIAL GROUP

Clinical Syndrome	Total Period I		Amantadine		Placebo	
	Number of Illnesses	Per Cent of Total Period I Illness	Number of Illnesses	Per Cent of Amantadine Illness	Number of Illnesses	Per Cent of Placebo Illness
Coryzal	27	25.7	15	32.6	12	20.3
Pharyngeal	35	33.3	18	39.1	17	28.8
Acute undifferentiated respiratory disease	18	17.1	6	13.1	12	20.3
Laryngeal	3	2.9	2	4.3	1	
Bronchitis	2	1.9	1	2.2	1	1.7
Pneumonitis	2	1.9	0	0.0	2	3.4
Other, respiratory	2	1.9	1	2.2	1	1.7
Other, nonrespiratory	11	10.5	1	2.2	10	17.0
Other, no illness	5	4.8	2	4.3	3	5.1
Total	105	100.0	46	100.0	59*	100.0

*One illness occurred in a participant who was not eligible for the remaining Period I analysis.

undifferentiated respiratory illness was observed during this period than during other trial periods. Upper respiratory disorders account for about 60 per cent of all illness. When the trial groups are compared, the placebo group appears to have "other" illness and acute undifferentiated respiratory disease diagnosed more often than did the amantadine group.

2) All Illness: Table V.36 distributes eligible Period I participants by number of illnesses and trial group. The distributions of the two trial groups did not differ significantly ($.30 > p > .20$).

TABLE V.36

ALL ILLNESS AMONG ELIGIBLE* PARTICIPANTS
DURING PERIOD I
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant					Total Number of Illnesses	Eligible Participants
	0	1	2	3	4 or more		
Placebo	90	43	6	1	0	58	140
Amantadine	113	35	4	1	0	46	153
Total	203	78	10	2	0	104	293

$\chi^2_{(3)} = 3.1517$

$.30 > p > .20$

*Eligible participants were in residence at least four of the six weeks.

3) Streptococcal Illness: Table V.37 distributes Period I participants by number of streptococcal illnesses and trial group. The distributions for the trial groups did not differ significantly ($.30 > p > .10$).

4) Nonstreptococcal Illness: Table V.38 distributes eligible Period I participants by number of nonstreptococcal illnesses and trial group. The placebo group experienced significantly more nonstreptococcal illness than did the amantadine group ($.01 > p > .001$).

5) "Other" Illness: Table V.39 distributes eligible Period I participants by number of "other" illnesses and trial group.

TABLE V.37

STREPTOCOCCAL ILLNESS AMONG ELIGIBLE*
PARTICIPANTS DURING PERIOD I
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant				Total Number of Illnesses	Eligible Participants
	0	1	2	3 or more		
Placebo	127	13	0	0	13	140
Amantadine	133	19	1	0	21	153
Total	260	32	1	0	34	293

$\chi^2_{(1)} = 1.2307$

$.30 > p > .20$

*Eligible participants were in residence at least four of the six weeks.

TABLE V.38

NONSTREPTOCOCCAL ILLNESS AMONG ELIGIBLE*
PARTICIPANTS DURING PERIOD I
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant					Total Number of Illnesses	Eligible Participants
	0	1	2	3	4 or more		
Placebo	101	34	4	1	0	45	140
Amantadine	133	16	3	1	0	25	153
Total	234	50	7	2	0	70	293

$\chi^2_{(2)} = 10.5348$

$.01 > p > .001$

*Eligible participants were in residence at least four of the six weeks.

TABLE V.39

ILLNESS, DIAGNOSED AS "OTHER" AMONG ELIGIBLE* PARTICIPANTS DURING PERIOD I DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant				Total Number of Illnesses	Eligible Participants
	0	1	2	3 or more		
Placebo	129	10	1	0	12	140
Amantadine	149	4	0	0	4	153
Total	278	14	1	0	16	293

$\chi^2_{(10} = 4.5164$

$.05 > p > .02$

*Eligible participants were in residence at least four of the six weeks.

6) Nonstreptococcal Respiratory Illness: Table V.40 distributes eligible Period I participants by number of nonstreptococcal respiratory illnesses and trial group. The placebo group experienced significantly more nonstreptococcal respiratory illness than did the amantadine group ($.05 > p > .02$).

TABLE V.40

NONSTREPTOCOCCAL RESPIRATORY ILLNESS AMONG ELIGIBLE PARTICIPANTS DURING PERIOD I DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant				Total Number of Illnesses	Eligible Participants
	0	1	2	3 or more		
Placebo	109	29	2	0	33	140
Amantadine	134	17	2	0	21	153
Total	243	46	4	0	54	293

$\chi^2_{(1)} = 4.7344$

$.05 > p > .02$

*Eligible participants were in residence during at least four of the six weeks.

b. Period II (28 March to 8 May)

1) Clinical Diagnoses: Table V.41 presents the clinical diagnoses of illnesses observed during Period II. Upper respiratory illness accounts for 70 per cent of all observed illness. Trial groups appear to have similar patterns of diagnoses.

TABLE V.41

CLINICAL DIAGNOSES OF ILLNESS OCCURRING DURING PERIOD II
DISTRIBUTION BY CLINICAL SYNDROME AND TRIAL GROUP

Clinical Syndrome	Total Period II		Amantadine		Placebo	
	Number of Ill-nesses	Per Cent of Total Period II Illness	Number of Ill-nesses	Per Cent of Amantadine Illness	Number of Ill-nesses	Per Cent of Placebo Illness
Coryzal	44	41.1	16	37.3	28	43.7
Pharyngeal	32	29.9	15	34.9	17	26.6
Acute undifferentiated respiratory disease	3	2.8	1	2.3	2	3.1
Laryngeal	3	2.8	1	2.3	2	3.1
Bronchitis	8	7.5	5	11.6	3	4.7
Pneumonitis	1	0.9	1	2.3	0	0.0
Other, respiratory	2	1.9	1	2.3	1	1.6
Other, nonrespiratory	13	12.2	3	7.0	10	15.6
Other, no illness	1	0.9	0	0.0	1	1.6
Total	107	100.0	43	100.0	64	100.0

2) All Illness: Table V.42 distributes eligible Period II participants by number of illnesses and trial group. The

TABLE V.42

ALL ILLNESS AMONG ELIGIBLE* PARTICIPANTS
DURING PERIOD II
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant					Total Number of Illnesses	Eligible Participants
	0	1	2	3	4 or more		
Placebo	84	43	9	1	0	64	137
Amantadine	115	35	4	0	0	43	154
Total	199	78	13	1	0	107	291

$\chi^2_{(2)} = 6.4386$

$.05 > p > .02$

*Eligible participants were in residence during at least four of the six weeks.

placebo group experienced significantly more illness during Period II than did the amantadine group ($.05 > p > .02$).

3) Streptococcal Illness: Table V.43 distributes eligible Period II participants by number of streptococcal illnesses and trial group. The distributions of the trial groups do not differ significantly ($.50 > p > .30$).

4) Nonstreptococcal Illness: Table V.44 distributes eligible Period II participants by number of nonstreptococcal illness and trial group. The placebo group experienced significantly more such illness than did the amantadine group ($.02 > p > .01$).

5) "Other" Illness: Table V.45 distributes eligible Period II participants by number of "other" illnesses and trial group. The placebo group experienced significantly more such illness than did the amantadine group ($.01 > p > .001$).

TABLE V.43

STREPTOCOCCAL ILLNESS AMONG ELIGIBLE*
PARTICIPANTS DURING PERIOD II
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant				Total Number of Illnesses	Eligible Participants
	0	1	2	3 or more		
Placebo	129	7	1	0	9	137
Amantadine	140	14	0	0	14	154
Total	269	21	1	0	23	291

$\chi^2_{(1)} = .7293$

$.50 > p > .30$

*Eligible participants were in residence at least four of the six weeks.

TABLE V.44

NONSTREPTOCOCCAL ILLNESS AMONG ELIGIBLE*
PARTICIPANTS DURING PERIOD II
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant					Total Number of Illnesses	Eligible Participants
	0	1	2	3	4 or more		
Placebo	92	36	8	1	0	55	137
Amantadine	128	23	3	0	0	29	154
Total	220	59	11	1	0	84	291

$\chi^2_{(2)} = 9.9762$

$.02 > p > .01$

*Eligible participants were in residence at least four of the six weeks.

TABLE V.45

ILLNESS, DIAGNOSED AS "OTHER" AMONG ELIGIBLE* PARTICIPANTS DURING PERIOD II DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant			Total Number of Illnesses	Eligible Participants
	0	1	2 or more		
Placebo	125	12	0	12	137
Amantadine	151	3	0	3	154
Total	276	15	0	15	291

$\chi^2_{(1)} = 7.05997$

$.01 > p > .001$

*Eligible participants were in residence at least four of the six weeks.

6) Nonstreptococcal Respiratory Illness: Table V.46 distributes eligible Period II participants by number of nonstreptococcal illnesses and trial group. The placebo group experienced significantly more such illness than did the amantadine group ($.05 > p > .02$).

TABLE V.46

NONSTREPTOCOCCAL RESPIRATORY ILLNESS AMONG ELIGIBLE* PARTICIPANTS DURING PERIOD II DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant				Total Number of Illnesses	Eligible Participants
	0	1	2	3 or more		
Placebo	101	29	7	0	43	137
Amantadine	130	22	2	0	26	154
Total	231	51	9	0	69	291

$\chi^2_{(1)} = 4.1784$

$.05 > p > .02$

*Eligible participants were in residence at least four of the six weeks.

c. Period III (9 May to 10 June)

1) Clinical Diagnoses: Table V.47 presents the clinical diagnoses of illnesses observed during Period III. Few illnesses occurred and the pharyngeal syndrome accounted for the largest portion of diagnoses. Trial groups appear to have similar patterns of diagnoses.

TABLE V.47

CLINICAL DIAGNOSES OF ILLNESSES OCCURRING DURING PERIOD III
DISTRIBUTION BY CLINICAL SYNDROME AND TRIAL GROUP

Clinical Syndrome	Total Period III		Amantadine		Placebo	
	Number of Illnesses	Per Cent of Total Period III Illnesses	Number of Illnesses	Per Cent of Amantadine Illness	Number of Illnesses	Per Cent of Placebo Illness
Coryzal	1	4.0	1	6.7	0	0.0
Pharyngeal	13	52.0	7	46.6	6	60.0
Acute undifferentiated respiratory disease	0	0.0	0	0.0	0	0.0
Laryngeal	2	8.0	0	0.0	2	20.0
Bronchitis	0	0.0	0	0.0	0	0.0
Pneumonitis	0	0.0	0	0.0	0	0.0
Other, respiratory	1	4.0	1	6.7	0	0.0
Other, nonrespiratory	3	12.0	3	20.0	0	0.0
Other, no illness	5	20.0	3	20.0	2	20.0
Total	25	100.0	15	100.0	10	100.0

2) All Illness: Table V.48 distributes eligible Period III participants by number of illnesses and trial group. The

TABLE V.48

ALL ILLNESSES AMONG ELIGIBLE* PARTICIPANTS
DURING PERIOD III
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant			Total Number of Illnesses	Eligible Participants
	0	1	2 or more		
Placebo	123	10	0	10	133
Amantadine	136	15	0	15	151
Total	259	25	0	25	284

$\chi^2_{(1)} = .70306$

$.50 > p > .30$

*Eligible participants were in residence at least four weeks of the six week period.

distributions of the trial groups did not differ significantly ($.50 > p > .30$).

3) Streptococcal Illness: Table V.49 distributes eligible Period III participants by number of streptococcal illnesses and trial group. The distributions of the trial groups did not differ significantly ($p = .28$).

4) Nonstreptococcal Illness: Table V.50 distributes eligible Period III participants by number of nonstreptococcal illnesses and trial group. The distributions of the trial groups did not differ significantly ($.20 > p > .10$).

5) "Other" Illness: Table V.51 distributes eligible Period III participants by number of "other" illnesses and trial group. The distributions of trial groups did not differ significantly ($p = .12$).

TABLE V.49

STREPTOCOCCAL ILLNESS AMONG ELIGIBLE*
PARTICIPANTS DURING PERIOD III
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant			Total Number of Illnesses	Eligible Participants
	0	1	2 or more		
Placebo	128	5	0	5	133
Amantadine	148	3	0	3	151
Total	276	8	0	8	284

$p = .28$ (Fisher's Exact Probability Test)

*Eligible participants were in residence at least four of the six weeks.

TABLE V.50

NONSTREPTOCOCCAL ILLNESS AMONG ELIGIBLE*
PARTICIPANTS DURING PERIOD III
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant			Total Number of Illnesses	Eligible Participants
	0	1	2 or more		
Placebo	128	5	0	5	133
Amantadine	139	12	0	12	151
Total	267	17	0	17	284

$\chi^2_{(1)} = 2.2603$

$.20 > p > .10$

*Eligible participants were in residence at least four of the six weeks.

TABLE V.51

ILLNESS DIAGNOSED AS "OTHER" AMONG ELIGIBLE* PARTICIPANTS DURING PERIOD III DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant			Total Number of Illnesses	Eligible Participants
	0	1	2 or more		
Placebo	131	2	0	2	133
Amantadine	144	7	0	7	151
Total	275	9	0	9	284

p = .12 (Fisher Exact Probability Test)

*Eligible participants were in residence at least four of the six weeks.

6) Nonstreptococcal Respiratory Illness: Table V.52 distributes eligible Period III participants by number of nonstreptococcal respiratory illnesses and trial group. The distributions of trial groups did not differ significantly (p = .43).

TABLE V.52

NONSTREPTOCOCCAL RESPIRATORY ILLNESS AMONG ELIGIBLE* PARTICIPANTS DURING PERIOD III DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant			Total Number of Illnesses	Eligible Participants
	0	1	2 or more		
Placebo	130	3	0	3	133
Amantadine	146	5	0	5	151
Total	276	8	0	8	284

p = .43 (Fisher Exact Probability Test)

*Eligible participants are in residence at least four of the six weeks.

D. Length of Illness Analysis

1. Conventions: Illnesses were grouped and time periods were defined as described in the analysis of incidence. All illnesses observed were considered in this analysis.

2. Pretrial: Table V.53 analyzes length of illness during the pretrial period. Illnesses averaged about a week in length except for "other" illnesses which appeared shorter. Mean length of illness did not differ significantly between trial groups in any of the illness categories.

3. All Trial: Table V.54 analyzes length of illness during the trial proper. Illnesses averaged about a week in length except for "other" illnesses which appeared shorter. Mean length of illness did not differ significantly between trial groups in any of the illness categories.

4. Period I: Table V.55 analyzes length of illness during Period I. Illness again averaged about a week in length and "other" illnesses were somewhat shorter. Again, the mean length of illness did not differ significantly between trial groups in any of the categories of illness.

5. Period II: Table V.56 analyzes length of illness during Period II. Illnesses continued to average about a week in length. The amantadine group appeared to have slightly greater mean illness length in each of the disease categories; but in no category did the mean length of illness differ significantly between trial groups.

6. Period III: Few illnesses occurred during Period III. Table V.57 analyzes length of illness during Period III. Mean length of illness did not differ significantly between trial groups in any category of illness.

TABLE V.53

LENGTH OF ILLNESS
ANALYSIS OF PRETRIAL PERIOD

Measurement	Illness Group									
	All Illness		Streptococcal Illness		Nonstreptococcal Illness		"Other" Illness		Nonstreptococcal Respiratory Illness	
	Amantadine	Placebo	Amantadine	Placebo	Amantadine	Placebo	Amantadine	Placebo	Amantadine	Placebo
Number of Illnesses	40	40	8	10	32	30	6	4	24	26
Days of Illness	257	300	60	71	197	229	15	8	172	221
Mean Length of Illness (days)	6.425	7.50	7.50	7.10	6.16	7.63	2.50	2.00	7.17	8.50
Pooled Variance	22.07		35.81		24.37		1.75		23.77	
Test of Significance of Difference Between Means	$z = 1.02$ $p = .30$		$t_{(14)} = .14084$ $p > .50$		$z = 1.17$ $p = .24$		$t_{(8)} = .58520$ $p > .50$		$t_{(48)} = .9649$ $p > .50$	

TABLE V.54

LENGTH OF ILLNESS
ANALYSIS OF ENTIRE TRIAL

Measurement	Illness Group									
	All Illness		Streptococcal Illness		Nonstreptococcal Illness		"Other" Illness		Nonstreptococcal Respiratory Illness	
	Amantadine	Placebo	Amantadine	Placebo	Amantadine	Placebo	Amantadine	Placebo	Amantadine	Placebo
Number of Illnesses	104	133	37	27	67	106	14	26	54	80
Days of Illness	751	884	258	154	493	730	51	106	442	624
Mean Length of Illness (days)	7.22	6.65	6.97	5.70	7.36	6.89	3.64	4.08	8.34	7.80
Pooled Variance	19.07		13.90		21.66		11.34		18.13	
Test of Significance of Difference Between Means	$z = .997$ $p = .32$		$z = 1.35$ $p = .177$		$z = .65$ $p = .516$		$t_{(38)} = .3936$ $p > .50$		$z = .72$ $p = .472$	

TABLE V.55

LENGTH OF ILLNESS
ANALYSIS OF PERIOD I

Measurement	Illness Group									
	All Illness		Streptococcal Illness		Nonstreptococcal Illness		"Other" Illness		Nonstreptococcal Respiratory Illness	
	Amantadine	Placebo	Amantadine	Placebo	Amantadine	Placebo	Amantadine	Placebo	Amantadine	Placebo
Number of Illnesses	46	59	20	13	26	46	4	12	22	34
Days of Illness	308	381	139	76	169	305	16	48	153	257
Mean Length of Illness (days)	6.52	6.46	6.95	5.85	6.50	6.63	4.00	4.00	6.95	7.56
Pooled Variance	15.30		11.31		17.39		12.00		16.80	
Test of Significance of Difference Between Means	$z = .08$ $p = .94$		$t_{(31)} = .9667$ $.50 > p > .25$		$z = .13$ $p = .90$		No difference between means		$t_{(54)} = .5434$ $p > .50$	

TABLE V.56

LENGTH OF ILLNESS
ANALYSIS OF PERIOD II

Measurement	Illness Group									
	All Illness		Streptococcal Illness		Nonstreptococcal Illness		"Other" Illness		Nonstreptococcal Respiratory Illness	
	Amantadine	Placebo	Amantadine	Placebo	Amantadine	Placebo	Amantadine	Placebo	Amantadine	Placebo
Number of Illnesses	43	64	14	9	29	55	4	12	25	43
Days of Illness	354	443	95	54	259	389	25	41	234	348
Mean Length of Illness (days)	8.23	6.92	6.79	6.00	8.93	7.07	6.25	3.42	9.36	8.09
Pooled Variance	23.18		16.88		24.73		20.33		22.78	
Test of Significance of Difference Between Means	$z = .33$ $p = .641$		$t_{(21)} = .4501$ $p > .50$		$z = 1.63$ $p = .102$		$t_{(14)} = 1.0869$ $.50 > p > .25$		$z = 1.06$ $p = .289$	

TABLE V.57

LENGTH OF ILLNESS
ANALYSIS OF PERIOD III

Measurement	Illness Group									
	All Illness		Streptococcal Illness		Nonstreptococcal Illness		"Other" Illness		Nonstreptococcal Respiratory Illness	
	Amantadine	Placebo	Amantadine	Placebo	Amantadine	Placebo	Amantadine	Placebo	Amantadine	Placebo
Number of Illnesses	15	10	3	5	12	5	8	2	4	3
Days of Illnesses	79	60	24	24	55	36	36	17	19	19
Mean Length of Illness (days)	5.27	6.00	8.00	4.80	4.58	7.20	4.50	8.50	4.75	6.33
Pooled Variance	9.06		4.80		15.85		22.44		10.28	
Test of Significance of Difference Between Means	$t_{(23)} = .5941$ $p > .50$		$t_{(6)} = 1.9883$ $.10 > p > .05$		$t_{(15)} = 1.2364$ $.25 > p > .10$		$t_{(8)} = 1.0690$ $.50 > p > .25$		$t_{(5)} = .6450$ $p > .50$	

E. Laboratory Results

1. Serology

a. All Trial Illness: All pairs of sera from trial illnesses were titered by hemagglutination inhibition and complement fixation against A_2/AA/1/65 and B/Md/1/59 influenza viruses.

1) A_2/AA/1/65: Table V.58 presents fourfold rises in titer against A_2/AA/1/65. In the placebo group 11 of 139 individuals, 7.91 per cent, and 11 of 133 illnesses, 8.27 per cent, were associated with a fourfold rise in titer against A_2/AA/1/65. In the amantadine group one of 154 individuals, 0.65 per cent, and one of 104 illnesses, 0.96 per cent, were associated with a fourfold rise in titer against A_2/AA/1/65. No individual experienced more than one illness associated with a fourfold rise in titer against A_2/AA/1/65. The amantadine group experienced significantly less clinical illness associated with a fourfold rise in titer against A_2/AA/1/65 ($p = .0016$).

TABLE V.58

FOURFOLD RISES IN CF AND/OR HI TITER AGAINST A_2/AA/1/65 AMONG ALL TRIAL ILLNESSES DISTRIBUTION BY TRIAL GROUP

Trial Group	Group* Population	Fourfold Rises	Sera Pairs Tested
Placebo	139	11**	133
Amantadine	154	1**	104
Total	293	12	237

** $p = .0016$ (Fisher Exact Probability)

*Must have participated during 10 of 12 weeks in Period I and Period II.

2) B/Md/1/59: Table V.59 presents fourfold rises in titer against B/Md/1/59. Only three of 237 trial illnesses, 1.26 per cent, were associated with such a rise. Two of these were in the amantadine group and one in the placebo group. All of these rises occurred during Period II (April). The number of rises is too small for statistical testing.

TABLE V.59

FOURFOLD RISES IN CF AND/OR HI TITER AGAINST B/Md/1/59 AMONG ALL TRIAL ILLNESSES DISTRIBUTION BY TRIAL GROUP

Trial Group	Group* Population	Fourfold Rises	Sera Pairs Tested
Placebo	136	1	133
Amantadine	151	2	104
Total	287	3	237

*Must have participated 10 of 12 weeks during Period II and Period III.

b. Period II

1) All Period II Illness: All pairs of sera from individuals who experienced an illness during Period II were titered by complement fixation against an adenovirus group antigen prepared from adenovirus 4. Table V.60 distributes the results of this testing by trial group. Only four individuals had fourfold rises in titer associated with illness and all of these were in the placebo group. These rises were associated with 2.92 per cent of placebo individuals and 5.40 per cent of tested placebo illnesses. The numbers are too small to permit statistical testing.

TABLE V.60

FOURFOLD RISES IN CF TITER AGAINST ADENOVIRUS GROUP AMONG SERA FROM PARTICIPANTS WITH ANY ILLNESS DURING PERIOD II DISTRIBUTION BY TRIAL GROUP

Trial Group	Group* Population	Fourfold Rises	Sera Pairs Tested
Placebo	137	4	74
Amantadine	154	0	55
Total	291	4	129

*Must have participated during four of six weeks in Period II.

2) Nonstreptococcal Respiratory Illness: Sera pairs from individuals with nonstreptococcal respiratory disease during Period II were titered by complement fixation against six antigens. These antigens were parainfluenza 1, 2, 3; influenza C/Jamaica/64; respiratory syncitial virus; and Mycoplasma pneumoniae. Table V.61 distributes the results of such testing by trial group. At least one fourfold rise in titer against each antigen occurred. Two individuals had an illness associated with a fourfold rise in titer against more than one antigen. The fourfold rises associated with individual antigens were too few in number to allow statistical testing. Seventeen illness of 88 tested, 18.18 per cent, were associated with a significant titer rise against at least one antigen. Fourfold rises in complement fixation titer against at least one antigen were associated with 7 illnesses of 54 tested in the placebo group or 12.96 per cent, and with 10 illnesses of 34 tested in the amantadine group or 29.41 per cent.

TABLE V.61

FOURFOLD RISES IN CF TITER AMONG SERA FROM PARTICIPANTS WITH NONSTREPTOCOCCAL RESPIRATORY ILLNESSES DURING PERIOD II DISTRIBUTION BY TRIAL GROUP AND ANTIGEN

Trial Group	Group* Population	Antigens: Parainfluenza 1	Parainfluenza 2	Parainfluenza 3	Influenza C/Jamaica/64	Respiratory Syncitial Virus	Mycoplasma Pneumonia	Sera Pairs Tested
Placebo	137	0	0	2***	0	1	3***	54
Amantadine	154	1**	2**	0	2	2	4	34
Total	291	1	2	2	2	3	7	88

*Must have participated 4 of 6 weeks during Period II.

**One patient had fourfold rise to both parainfluenza 1 and 2.

***One patient had fourfold rise to parainfluenza 3, M. pneumoniae and adenovirus.

Not all of the illnesses thus associated and identified were nonstreptococcal respiratory illnesses occurring during Period II. A portion of the sera pairs were from illnesses of another grouping or another time period because all sera from an individual having a nonstreptococcal respiratory illness during Period II were titered; and some of these individuals experienced illness of another group or during another time period. Thus 88 sera pairs were tested but only 69 of these sera pairs were obtained from nonstreptococcal respiratory illness during Period II.

Table V.62 distributes Period II participants by number of identified Period II nonstreptococcal respiratory illness and trial group. Trial groups do not differ significantly in identified nonstreptococcal respiratory illness ($.50 > p > .30$).

TABLE V.62

SEROLOGICALLY IDENTIFIED* NONSTREPTOCOCCAL
RESPIRATORY DISEASE DURING PERIOD II
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Identified Illnesses per Participant			Total Identified Illnesses	Total Eligible Participants
	0	1	2		
Placebo	127	9	1	11	137
Amantadine	146	8	0	8	154
Total	273	17	1	19	291

$\chi^2_{(1)} = .5346$

$.50 > p > .30$

*Includes illnesses associated with fourfold serological titer rise against any of nine antigens tested.

2. Virus Isolations: Only influenza A, A_2/WCTS/65, and influenza B, B/WCTS/65, were isolated from throat washings. Influenza A_2 was isolated from throat washings of two patients and influenza B was isolated from one patient. Isolates were typed against known ferret sera.

Despite the persistent attempts outlined in Chapter III, no other agents were isolated either in tissue culture or in PPLO broth and PPLO agar.

F. Analysis of Incidence of Illness, Excluding Identified Illness

1. Entire Trial

a. All Illness: Table V.63 distributes participant illness during the entire trial, excluding serologically identified illness, by number of illnesses per participant and trial group. The overall illness

experience of the trial groups did not differ significantly though somewhat more illness occurred in the placebo group ($.30 > p > .20$).

TABLE V.63

PARTICIPANT ILLNESS DURING ENTIRE TRIAL, EXCLUDING SEROLOGICALLY IDENTIFIED ILLNESS DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant						Total Illnesses	Total Participants
	0	1	2	3	4	5 or more		
Placebo	70	46	15	8	3	0	112	142
Amantadine	93	43	16	3	2	0	92	157
Total	163	89	31	11	5	0	204	299

$\chi^2_{(3)} = 4.5457$

$.30 > p > .20$

b. Streptococcal Illness: Table V.64 distributes participant streptococcal illness, excluding serologically identified illness, by number of illnesses per participant and trial group. Streptococcal illness does not differ significantly between the trial groups though somewhat more such illness occurred in the amantadine group ($.30 > p > .20$).

TABLE V.64

STREPTOCOCCAL ILLNESS AMONG PARTICIPANTS DURING ENTIRE TRIAL, EXCLUDING SEROLOGICALLY IDENTIFIED ILLNESS DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant					Total Illnesses	Total Participants
	0	1	2	3	4 or more		
Placebo	121	18	3	0	0	24	142
Amantadine	125	29	2	1	0	36	157
Total	246	47	5	1	0	60	299

$\chi^2_{(1)} = 1.5229$

$.30 > p > .20$

c. Nonstreptococcal Illness: Table V.65 distributes participant nonstreptococcal illness, excluding serologically identified illness, by number of illnesses per participant and trial group. The placebo group experienced significantly more nonstreptococcal illness than did the amantadine group ($.05 > p > .02$).

TABLE V.65

NONSTREPTOCOCCAL ILLNESS AMONG PARTICIPANTS DURING ENTIRE TRIAL, EXCLUDING SEROLOGICALLY IDENTIFIED ILLNESS DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant						Total Illnesses	Total Participants
	0	1	2	3	4	5 or more		
Placebo	87	34	13	4	4	0	88	142
Amantadine	118	27	9	1	2	0	56	157
Total	205	61	22	5	6	0	144	299

$\chi^2_{(3)} = 8.5502$

$.05 > p > .02$

d. "Other" Illness: Table V.66 distributes participant "other" illness, excluding serologically identified illness, by number of illnesses per participant and trial group. The placebo group

TABLE V.66

"OTHER" ILLNESS AMONG PARTICIPANTS DURING ENTIRE TRIAL, EXCLUDING SEROLOGICALLY IDENTIFIED ILLNESS DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant				Total Illnesses	Total Participants
	0	1	2	3 or more		
Placebo	120	20	1	0	23	142
Amantadine	146	9	2	0	13	157
Total	266	29	3	0	36	299

$\chi^2_{(1)} = 4.9105$

$.05 > p > .02$

experienced significantly more illness diagnosed as "other" than did the amantadine group ($.05 > p > .02$).

e. Nonstreptococcal Respiratory Illness: Table V.67 distributes participant nonstreptococcal respiratory illness, excluding serologically identified illness, by number of illnesses per participant and trial group. The placebo group experienced more such illness than did the amantadine group; however, the observed difference approaches but does not attain statistical significance ($.10 > p > .05$).

TABLE V.67

NONSTREPTOCOCCAL RESPIRATORY ILLNESS AMONG PARTICIPANTS DURING ENTIRE TRIAL, EXCLUDING SEROLOGICALLY IDENTIFIED ILLNESS DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant						Total Illnesses	Total Participants
	0	1	2	3	4	5 or more		
Placebo	95	35	7	4	1	0	65	142
Amantadine	123	26	7	1	0	0	43	157
Total	218	61	14	5	1	0	108	299

$\chi^2_{(2)} = 4.9799$

$.10 > p > .05$

2. Period I: Previous analysis of Period I showed that the trial groups differed significantly in incidence of illness. This period is now analyzed excluding A_2 influenza illnesses, serologically identified.

a. All Illness: Table V.68 considers all illness among eligible participants during Period I, excluding A_2 influenza illness, and distributes participants by number of illnesses and trial group.

TABLE V.68

ELIGIBLE* PARTICIPANT ILLNESS DURING PERIOD I, EXCLUDING ILLNESS IDENTIFIED AS A_2 INFLUENZA DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant					Total Illnesses	Total Eligible Participants
	0	1	2	3	4 or more		
Placebo	100	34	5	1	0	47	140
Amantadine	113	35	4	1	0	46	153
Total	213	69	9	2	0	93	293

$\chi^2_{(2)} = .4998$

$.80 > p > .70$

*Must have participated 4 of 6 weeks during Period I.

Trial groups did not differ significantly in such illness during Period I ($.80 > p > .70$).

b. Streptococcal Illness: Table V.69 considers streptococcal illness among eligible participants during Period I, excluding A_2 influenza illness, and distributes participants by number of illnesses and trial group. The amantadine group experienced somewhat more

TABLE V.69

STREPTOCOCCAL ILLNESS AMONG ELIGIBLE* PARTICIPANTS DURING PERIOD I, EXCLUDING ILLNESS IDENTIFIED AS A_2 INFLUENZA, DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant				Total Illnesses	Total Eligible Participants
	0	1	2	3 or more		
Placebo	130	10	0	0	10	140
Amantadine	134	18	1	0	20	153
Total	264	28	1	0	30	293

$\chi^2_{(1)} = 2.4524$

$.20 > p > .10$

*Must have participated 4 of 6 weeks during Period I.

streptococcal illness but the difference between trial groups is not significant ($.20 > p > .10$).

c. Nonstreptococcal Illness: Table V.70 considers nonstreptococcal illness, excluding A_2 influenza illness, among eligible participants during Period I and distributes participants by number of illnesses and trial group. The placebo group experienced somewhat more such illness than did the amantadine group but the difference is not significant ($.20 > p > .10$).

TABLE V.70

NONSTREPTOCOCCAL ILLNESS AMONG ELIGIBLE* PARTICIPANTS DURING PERIOD I, EXCLUDING ILLNESS IDENTIFIED AS A_2 INFLUENZA, DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant					Total Illnesses	Total Eligible Participants
	0	1	2	3	4 or more		
Placebo	108	28	3	1	0	37	140
Amantadine	132	17	3	1	0	26	153
Total	240	45	6	2	0	63	293

$\chi^2_{(2)} = 4.0195$

$.20 > p > .10$

*Must have participated 4 of 6 weeks during Period I.

d. "Other" Illness: Table V.71 considers participant illness diagnosed as "other," excluding A_2 influenza illness, during Period I and distributes eligible participants by number of illnesses and trial group. The placebo group experienced somewhat more "other" illness than did the amantadine group but the difference between groups is not significant ($.20 > p > .10$).

TABLE V.71

"OTHER" ILLNESS AMONG ELIGIBLE* PARTICIPANTS DURING PERIOD I
EXCLUDING ILLNESS IDENTIFIED AS A_2 INFLUENZA
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant				Total Number of Illnesses	Total Eligible Participants
	0	1	2	3 or more		
Placebo	130	9	1	0	11	140
Amantadine	149	4	0	0	4	153
Total	279	13	1	0	15	293

$\chi^2_{(1)} = 2.7007$

$.20 > p > .10$

*Must have participated 4 of 6 weeks during Period I.

e. Nonstreptococcal Respiratory Illness: Table V.72 considers nonstreptococcal respiratory illness, excluding A_2 influenza illness, among eligible participants during Period I and distributes participants by number of illnesses and trial group. The trial groups did not differ significantly in nonstreptococcal respiratory illness during Period I ($.50 > p > .30$).

TABLE V.72

NONSTREPTOCOCCAL RESPIRATORY ILLNESS AMONG ELIGIBLE*
PARTICIPANTS DURING PERIOD I, EXCLUDING A_2 INFLUENZA
DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant				Total Illnesses	Total Eligible Participants
	0	1	2	3 or more		
Placebo	116	22	2	0	26	140
Amantadine	133	18	2	0	22	153
Total	249	40	4	0	48	293

$\chi^2_{(1)} = .9646$

$.50 > p > .30$

*Must have participated 4 of 6 weeks during Period I.

3. Period II Nonstreptococcal Respiratory Illness: Table V.73 considers nonstreptococcal respiratory illness, excluding serologically identified illnesses, among eligible participants during Period II and distributes participants by number of illnesses and trial group. The placebo group experienced significantly more such illness than did the amantadine group ($.02 > p > .01$).

TABLE V.73

NONSTREPTOCOCCAL RESPIRATORY ILLNESS AMONG ELIGIBLE* PARTICIPANTS DURING PERIOD II, EXCLUDING SEROLOGICALLY IDENTIFIED ILLNESS, DISTRIBUTION BY NUMBER OF ILLNESSES AND TRIAL GROUP

Trial Group	Number of Illnesses per Participant				Total Illnesses	Total Eligible Participants
	0	1	2	3 or more		
Placebo	111	19	7	0	33	137
Amantadine	136	18	0	0	18	154
Total	247	37	7	0	51	291

$\chi^2_{(2)} = 8.5826$

$.02 > p > .01$

*Must have participated 4 of 6 weeks during Period II.

G. Residual Period II Nonstreptococcal Respiratory Illness

1. Clinical Diagnoses: Nonstreptococcal respiratory illness during Period II which was not serologically identified is hereafter referred to as residual Period II nonstreptococcal respiratory illness. Table V.74 presents the clinical diagnoses of such illnesses. Upper respiratory illnesses comprise over 80 per cent of total illness in each trial group. The distribution of diagnoses within trial groups appear similar.

TABLE V.74

CLINICAL DIAGNOSES OF RESIDUAL NONSTREPTOCOCCAL RESPIRATORY ILLNESSES DURING PERIOD II, DISTRIBUTION BY CLINICAL SYNDROME AND TRIAL GROUP

Clinical Syndrome	Total Residual		Amantadine		Placebo	
	Number of Illnesses	Per Cent of Total	Number of Illnesses	Per Cent of Total	Number of Illnesses	Per Cent of Total
Coryzal	29	56.86	11	61.11	18	55.5
Pharyngeal	14	27.45	4	22.22	10	30.30
Acute Undifferentiated Respiratory Disease	1	1.96	0	0.00	1	3.03
Laryngeal	3	5.88	1	5.56	2	6.06
Bronchitis	4	7.85	2	11.11	2	6.06
Pneumonitis	0	0.00	0	0.00	0	0.00
Total	51	100.00	18	100.00	33	100.00

2. Cottage Attack Rate: Table V.75 presents residual Period II nonstreptococcal respiratory illness attack rates per 100 person weeks at risk and distributes these rates by cottage units. Attack rates appear similar except in cottages 1 and 16 where the placebo group had a much higher attack rate and in cottages 13, 14 and 19 where placebo attack rates are somewhat higher. The observed difference between total trial groups resulted from illness experience in these five cottages.

TABLE V.75

RESIDUAL PERIOD II NONSTREPTOCOCCAL RESPIRATORY ILLNESS ATTACK
RATE PER 100 PERSON WEEKS AT RISK
DISTRIBUTION BY COTTAGE UNIT AND TRIAL GROUP

Cottage	Total			Amantadine			Placebo		
	Person Weeks of Risk	Number of Illnesses	Rate/100 Weeks at Risk	Person Weeks of Risk	Number of Illnesses	Rate/100 Weeks at Risk	Person Weeks of Risk	Number of Illnesses	Rate/100 Weeks at Risk
1	124	7	5.65	54	0	0.00	70	6	8.57
2	119	2	1.68	63	1	1.59	56	1	1.78
4	53	3	5.66	23	1	4.35	30	2	6.67
5	135	7	5.18	75	4	5.33	60	3	5.00
6	78	7	8.97	42	4	9.52	36	3	8.33
7	141	1	0.71	75	1	1.33	66	0	0.00
Fire Hall	41	2	4.88	28	1	3.57	13	1	7.69
9	124	2	1.61	70	1	1.43	54	1	1.85
10	108	0	0.00	63	0	0.00	45	0	0.00
11	85	1	1.18	45	1	2.22	40	0	0.00
12	121	2	1.65	67	1	1.49	54	1	1.85
13	91	4	4.40	56	1	1.78	35	3	8.57
14	123	4	3.25	69	1	1.45	54	3	5.56
15	138	1	0.72	60	0	0.00	78	1	1.28
16	162	5	3.09	84	0	0.00	78	5	6.41
19	64	4	6.25	30	1	3.33	34	3	8.82
Total	1707	52	3.05	904	18	1.99	803	33	4.11

3. Length of Illness: Table V.76 considers length of residual nonstreptococcal respiratory illness during Period II. There is no significant difference between trial groups in length of illness ($p > .50$).

TABLE V.76

ANALYSIS OF LENGTH OF RESIDUAL NONSTREPTOCOCCAL RESPIRATORY ILLNESS DURING PERIOD II

Measurement	Group	
	Amantadine	Placebo
Number of Illnesses	18	33
Days of Illness	164	275
Mean Length of Illness (days)	9.11	8.33
Pooled Variance	25.73	
Test of Significance of Difference Between Two Means	$t_{49} = .5644$ $p > .50$	

4. Profile of Clinical Symptoms and Signs: Table V.77 considers the occurrence of 13 selected symptoms associated with residual Period II nonstreptococcal respiratory disease and distributes symptom occurrence by trial group. The symptom profiles of the trial groups appear similar except for greater prevalence of sudden onset, aching, and vomiting in the placebo group.

TABLE V.77

PROFILE OF CLINICAL SYMPTOMS ACCOMPANYING RESIDUAL NONSTREPTOCOCCAL RESPIRATORY ILLNESS DURING PERIOD II DISTRIBUTION BY TRIAL GROUP

Symptom	Total Residual (51 Illnesses)		Amantadine (18 Illnesses)		Placebo (33 Illnesses)	
	Number of Illnesses with Symptom	Per Cent of Total Illnesses with Symptom	Number of Illnesses with Symptom	Per Cent of Amantadine Illnesses with Symptom	Number of Illnesses with Symptom	Per Cent of Placebo Illnesses with Symptom
Sudden onset	16	31.4	3	16.7	13	39.4
Aching	11	21.6	0	0.0	11	33.3
Chills	11	21.6	3	16.7	8	24.2
Anorexia	24	47.0	9	50.0	15	45.4
Headache	18	35.3	8	44.4	10	30.3
Vomiting	3	5.9	0	0.0	3	9.1
Abdominal pain	11	21.6	3	16.7	8	24.2
Diarrhea	6	11.8	2	11.1	4	12.1
Rhinorrhea	38	74.5	14	77.8	24	72.7
Sore throat	43	84.3	15	83.3	28	84.8
Hoarseness	26	51.0	9	50.0	17	51.5
Cough	38	74.5	16	88.9	22	66.7
Burning eyes	9	17.6	2	11.1	7	21.2

Table V.78 considers eight selected clinical signs associated with residual Period II nonstreptococcal respiratory disease and distributes the occurrence of these signs by trial group. Except or pyrexia which is somewhat more frequent in the placebo group, the clinical sign profile did not differ between trial groups.

TABLE V.78

PROFILE OF CLINICAL SIGNS ACCOMPANYING RESIDUAL NONSTREPTOCOCCAL RESPIRATORY ILLNESS DURING PERIOD II DISTRIBUTION BY TRIAL GROUP

Sign	Total Residual (51 Illnesses)		Amantadine (18 Illnesses)		Placebo (33 Illnesses)	
	Number of Illnesses with Sign	Per Cent of Total with Sign	Number of Illnesses with Sign	Per Cent of Amantadine with Sign	Number of Illnesses with Sign	Per Cent of Placebo with Sign
Oral temperature > 99° F	13	25.5	3	16.7	10	30.3
Rash	1	2.0	1	5.6	0	0.0
Conjunctivitis	3	5.9	1	5.6	2	6.1
Nasal discharge	46	90.2	17	94.4	29	87.9
Pharyngeal erythema	36	70.6	12	66.7	24	72.7
Pharyngeal exudate	8	15.7	3	16.7	5	15.2
Cervical adenopathy	30	58.8	11	61.1	19	57.6
Râles or rhonchi	4	7.8	1	5.6	3	9.1

The overall clinical pattern is that of an upper respiratory illness characterized by nasal discharge, pharyngitis, hoarseness, cough, and mild pyrexia.

CHAPTER VI

DISCUSSION

A. Critique of Study Design and Methods

1. Natural Disease and Experimental Infections: Field trials of chemoprophylaxis in natural respiratory disease are a difficult undertaking at best. One difficulty is the large number of known etiologic agents. Another problem is the significant portion of acute respiratory illness not associated with any presently known etiologic agent. Thus, a large number of illnesses may be observed and yet only a few will be associated with any particular agent. Chemoprophylactic agents must be administered repeatedly over a relatively long period of time. Failure to dispense or to ingest medication results in a bias against the prophylactic agent on trial. The importance of any such failure will vary with the nature of the prophylactic agent, with host resistance, and with exposure to infectious agents at the time of failure.

Experimental infections in human volunteers largely avoid the difficulties of trials in a natural population. In experimental infections a known agent may be used to infect a defined population of known immune status and the chemoprophylactic drug may be given for only a short period of time. Experimental infections are a most useful tool

in evaluating potential chemoprophylactic agents. Evaluating chemoprophylactic activity by experimental infections produces other problems. The infectious agent must often be attenuated; and the more the agent is attenuated, the less the agent resembles its counterpart in nature. Inducing illness with experimental infections is not always easy and large numbers of suitable volunteers may be difficult to find. Certainly, transmission in experimental infections is not equivalent to natural transmission, e.g., the usual infecting dose for A_2 influenza exceeds 10^5 $TCID_{50}$.

Both trials in experimental human infections and trials in natural populations are necessary steps to evaluate chemoprophylaxis in acute respiratory illness.

2. Population and Setting: Conducting the present trial in this boarding school population of retarded but educable children afforded several advantages. Essential information about the population was readily available. This information included a social history and a medical history with individual records of previous respiratory disease. The school did not offer influenza immunizations to the students. Procedures necessary for medication administration and clinical observation were easily superimposed on the usual routine of the school. The boarding student population had many more opportunities for contact with the outside world than is usual in an institution. These contacts occurred in vocational assignments and on weekend leaves. The populations of the various housing units had greater opportunity to intermingle than is found in most institutions.

There are several limitations inherent in a population of this type. The age span of the trial groups is restricted to school age youths. The intelligence level of the population is low and the population is housed in large units, which resemble families of thirty to forty people. The use of concurrent medications could have been a problem but was avoided by excluding volunteers who received other medications.

3. Immune Status of Volunteers: Knowing the immune status of volunteers prior to study would have been helpful. However, the necessary pretrial bleedings would have caused difficulty in this population. Moreover, even if one had known each individual's immune status against all the known respiratory agents, the randomization scheme could have been restricted to assure equal immune status against only one or two agents. This restriction would have made further restriction on the basis of cottage residence difficult, if not impossible, thus risking differential exposure to infection among trial groups. Restricted randomization, as applied in the present study, should have resulted in trial groups with comparable immune status.

4. Investigator Bias: The fact that the investigator knew the contents of the capsules could result in serious bias. In practice the investigator did not know the trial group of a sick volunteer. In addition, volunteers were designated well or ill by cottage observers who could not know capsule content. Therefore, the investigator was forced to classify all referred children.

Investigator bias in favor of the drug would be revealed by a

greater than expected number of amantadine illnesses in the "other" categories. "Other nonrespiratory" illnesses could be atypical illnesses associated with respiratory agents but differences in the "other, no illness" category could only be due to chance or bias. Investigator bias against the drug would be revealed in a greater than expected number of placebo illnesses in the "other" categories. If the investigator was biased in this study, he was biased against the drug as more "other, nonrespiratory" illnesses occurred in the placebo group. However, there was no difference between trial groups in the "other, no illness" category.

B. Comparison of Amantadine and Placebo Groups: Chapter IV has shown that the trial groups did not differ significantly in any of the examined demographic or medical history variables. Thus groups appeared to be comparable.

C. Medication Control: The various medication control procedures indicated an overall failure rate of about 3 per cent. Medication failure would result most frequently in a bias against the drug. The failure bias could favor the drug only if the drug enhanced the development or persistence of illness.

The dose calendar and capsule count methods of monitoring medication dispensing yielded remarkably similar results with both trial groups receiving over 97 per cent of prescribed doses. The distributions of individual missed monthly doses of medication differed significantly between the trial groups. This difference resulted from more amantadine individuals missing one to three doses per month and more

placebo individuals missing more than three doses per month. However, when each trial week is considered, individuals in the two trial groups did not differ in the number of missed medication doses.

Weekend leaves could have been a point of medication failure. If all weekend leave doses had been omitted, this omission would have been an important source of error only during the spring holiday. The usual weekend leave required only one dose of medication at home but the spring holiday leave required seven home doses. An individual previously loaded with amantadine may miss one day's dose and still retain significant tissue and blood levels of the drug. However, if that individual should omit three to seven consecutive doses, tissue and blood levels would fall rapidly to trace or nondetectable levels. During the spring holiday leave the trial groups did not differ significantly in the proportion of participants on leave, in the return of weekend slips or in the returned slips marked "capsule taken."

Twenty-four hour urine studies indicated an equilibrium is reached between ingested and excreted amantadine. Thus amantadine accumulates in the body only to the point where excretion balances continued ingestion.

Blood amantadine levels differed significantly between groups receiving 60 mgm per day and groups receiving 100 mgm per day. The 100 mgm group received a daily average of .13 mgm per Kg more amantadine than did the 60 mgm group. However, blood amantadine levels did not differ significantly between individuals whether they were well, acutely ill, or convalescent. If medication failure or low amantadine dosage were the crucial factor in illness, these groups might be expected to

differ. A dosage effect could also be investigated by computing attack rates for the different dosage levels, but this approach is not possible due to the small numbers of illness in each dosage category and the differences between cottages.

Amantadine was well tolerated in the doses given and no side effects occurred that could not be ascribed to chance alone.

D. General Measurements of Morbidity: WCTS medical clinic visits, infirmary admissions, and school absence reports revealed three peaks which coincided with periods of increased respiratory illness that were observed clinically. One of these peaks occurred during the pretrial observation period in January and the other two peaks occurred during the trial proper, in February and April. The choice of time periods for subdivisions of the trial was primarily dictated by observations on population morbidity and clinical illness. Fortunately, these observations permitted a subdivision of the trial into three equal time periods of six weeks each. The first time period, Period I, included the February peak of illness, while Period II included the April peak. There was a rapid fall off in all respiratory illness during Period III. An abrupt decline in incidence and prevalence of respiratory illness occurred with the onset of balmy spring weather during the fourteenth week of the trial.

Infirmary admissions during the trial were increased significantly in the placebo group. This increase was caused by marked increase in admissions of individuals with nonstreptococcal respiratory illness.

During the trial placebo individuals experienced significantly

higher episodes of absence rates from academic school than did amantadine individuals but the days lost from school did not differ significantly between trial groups. This was explained by two WCTS policies: the first policy was to allow children not admitted to the infirmary to go to school if at all possible. The second policy was to treat each streptococcal illness with seven to ten days of intramuscular penicillin in the infirmary. Thus, a streptococcal illness would contribute five or more days of absence but a nonstreptococcal respiratory illness would contribute two or less days of absence.

E. Incidence of Illness: The trial groups did not differ significantly in incidence of any of the groups of illness in the pretrial period.

During the entire trial the placebo individuals experienced more total illness but the difference between trial groups was not statistically significant ($.20 > p > .10$). Streptococcal illness did not differ significantly between trial groups. Nonstreptococcal illness was increased significantly in the placebo group ($.02 > p > .001$). Part of this difference rests with a significant increase in "other" illness among placebo individuals ($.02 > p > .001$). When "other" illness is further partitioned, the trial groups did not differ in the "other, no illness" and "other, respiratory illness" categories. The difference between trial groups is found in the "other, nonrespiratory illness" (see Table V.6). Other, nonrespiratory illness individuals were those with acute illness but without respiratory symptoms. Many of these could represent atypical illnesses caused by respiratory agents. The

remaining group of illness, nonstreptococcal respiratory illness, was significantly more frequent in the placebo group ($.05 > p > .001$).

Subdivision of the trial into three time periods facilitates the search for any chemoprophylactic effects. During Period I the placebo group experienced significantly more nonstreptococcal illness, nonstreptococcal respiratory illness, and "other" illness. During Period II the placebo group experienced significantly more total illness, nonstreptococcal illness, nonstreptococcal respiratory illness, and "other illness." During Period III the trial groups did not differ significantly in any of the illness groupings. Thus, any difference in illness between trial groups occurred during the first twelve weeks of the trial.

F. Serologically Identified Illness: Ten of the twelve illnesses serologically identified as A_2 influenza occurred during Period I. All of these illnesses were in placebo individuals and these individuals were residents of eight different cottages. The other two cases of A_2 influenza occurred during Period II. One of these cases was in each trial group and the onset of both cases was shortly after spring vacation.

All sera pairs from all trial illnesses were titered against A_2 and B influenza by both hemagglutination inhibition and complement fixation.

All sera pairs from individuals with nonstreptococcal respiratory illness during Period II were titered against the following additional antigens: influenza C; adenovirus; parainfluenza 1, 2, 3; respiratory syncitial virus; and Mycoplasma pneumoniae. Small numbers

of illnesses were serologically identified with each of these agents. Three additional illnesses identified as B influenza occurred during Period II. When all serologically identified illnesses were partitioned by the trial group there was no significant difference between trial groups.

Thus, influenza A_2 was significantly decreased in the amantadine group but trial groups did not differ in experience with other serologically identified illness.

G. Residual Illness: When all serologically identified illnesses were removed from total trial incidence of illness analyses, the placebo group continued to experience significantly more nonstreptococcal and "other" illness. In addition, nonstreptococcal respiratory illness was increased in the placebo group by an amount that approached statistical significance ($.10 > p > .05$).

When Period I is reanalyzed after exclusion of influenza A_2 illness, there is no significant difference between the illness experience of trial groups in any illness category. Illness experience of the amantadine and placebo groups did not differ in the original Period III analysis. Thus any residual difference in trial groups must have occurred during a limited period of time, Period II.

Serologically identified nonstreptococcal respiratory illness did not differ between trial groups during Period II but residual nonstreptococcal respiratory illness and "other" illness is significantly increased in the placebo group during Period II.

The residual nonstreptococcal respiratory illnesses during Period II had similar diagnoses in both trial groups. These residual

illnesses occurred in fourteen of the sixteen cottages. Placebo individuals experienced markedly more illness in two of these cottages. Clinical sign and symptom patterns in these residual illnesses were similar in both trial groups except for the symptoms of vomiting, sudden onset, and aching which were more frequent in the placebo group.

Thus the trial groups differed in illness experience during Period I and Period II but not during pretrial or Period III. The significant increase in placebo illness during Period I was caused by A_2 influenza. A significant increase in Period II nonstreptococcal respiratory illness occurred among placebo individuals but was not identified etiologically. These residual Period II placebo illnesses appeared clustered in time and place but were not clinically different from illnesses occurring in the amantadine group.

The present trial indicates that amantadine is an effective agent in preventing clinical illness with A_2 influenza and strongly suggests the drug may be at least partially effective in preventing clinical illness caused by another respiratory agent, currently unidentified.

H. Length of Illness: Length of illness in trial groups did not differ significantly in any of the illness groups during any time period. Neither did trial groups differ in length of residual Period II nonstreptococcal respiratory illness. This indicates that amantadine does not alter the length of illness once illness develops.

CHAPTER VII

CONCLUSIONS

1. Field trials of chemoprophylactic drugs in acute respiratory disease are feasible.

2. Repeated medication dosing may be monitored by counting doses in and out, by keeping a dose calendar, and by assaying biological substances for drug.

3. The drug equilibrium concept, postulated for amantadine, is valid.

4. Amantadine was well tolerated and no side effects were observed that could not be ascribed to chance alone.

5. Amantadine significantly reduced the incidence of clinical illness associated with A_2 influenza.

6. Trial results strongly suggest amantadine prevents at least a portion of clinical illness associated with another agent(s) which is not thought to be a parainfluenza virus, respiratory syncitial virus, an adenovirus, influenza B, influenza C, or Mycoplasma pneumoniae.

7. Amantadine did not alter the length of illness in any of the illness groups during any period of the trial.

8. Further field trials of this and other antiviral agents are needed.

APPENDIX A

Study Forms

APPENDIX A.1a

THE UNIVERSITY OF MICHIGAN
School of Public Health
Ann Arbor, Michigan

Dear

I am writing to ask your permission for _____, who is a student at the Wayne County Training School, to participate in a study of the prevention of respiratory illness. These illnesses include colds, influenza, and viral sore throats. As you know they are a troublesome health problem in school children.

Until recently there was no medication that promised to prevent these diseases. A safe drug, tested in laboratories and in several hundred volunteers, has recently become available. It may now be possible to prevent this kind of illness by taking one capsule of this drug with one or two of the daily meals.

This research has been discussed with and approved by the superintendent, Dr. Bouniconto, and the staff of the Wayne County Training School.

If you wish _____ to be included in this study, please sign the enclosed stamped self-addressed card and return it.

Also enclosed is a pamphlet that may answer your questions about this work. If you have any additional questions you may write or call

John F. Finklea, M.D.
School of Public Health
The University of Michigan
Ann Arbor, Michigan
Telephone: 764-5487

Sincerely yours,

John F. Finklea, M.D.
Department of Epidemiology

JFF
Enclosure

APPENDIX A.1b

THE UNIVERSITY OF MICHIGAN
School of Public Health
Ann Arbor, Michigan

Dear

We still need your help in studying the prevention of respiratory disease. Since the original letters asking your permission were sent during a busy time of year we are reforwarding the information about this work.

If you have already replied, we have not received your card at the time of this mailing.

Thank you.

Sincerely.

John F. Finklea, M.D.

JFF
Enclosure

APPENDIX A.1c

I hereby grant the request that my child _____
(last name) (first name)
be included in the Respiratory Disease Study at the Wayne County Training School.

I understand that either capsules containing a protective drug or capsules without any protective effect will be given.

_____
Parents Signature

_____
Address

_____
Phone Number

NOTE: If you do not wish your child to be included in the study, state so on this line.

_____

_____
Parents Signature

APPENDIX A.1d

Questions and Answers About This Study

1. Question: Who will be included in this study? Answer: Wayne County Training School children whose parents give their permission.

2. Question: Where will the study work be done? Answer: The giving of the drug and all examinations will be done at the Wayne County Training School.

3. Question: Will studies like this be done elsewhere? Answer: This is the first school study but more such studies will be needed.

4. Question: Will the study interfere with the children's school or play? Answer: No.

5. Question: Will the study change children's weekends at home or holidays? Answer: No.

6. Question: Will the study prevent my child from receiving any other medicine or treatment he or she might need? Answer: Absolutely not.

7. Question: Are the drugs safe? Answer: Yes, they have been found safe by testing in the laboratory and testing in humans.

8. Question: How long will the study last? Answer: It is planned for January to May 1965.

9. Question: Where will the medicine be given? Answer: In the child's cottage at the school.

10. Question: How will the medicine be given? Answer: In a capsule by mouth before one or two meals each day.

11. Question: Will the medicine be given by "shot"? Answer: No.

12. Question: Who will see my child if he or she gets a cold? Answer: The regular training school staff and a specially trained children's doctor from the University.

13. Question: Will all the children get the same medicine? Answer: No. If they did, the doctors could not tell how much sickness the medicine was preventing. That is, the doctors could not compare the medicines' effect to any control group.

14. Question: What medicines will be given? Answer: The doctors plan to give two kinds of medicine. One kind will be a medicine containing a common substance with no protective effect. The other will be the medicine which may prevent colds. This way the doctors can see how effective the medicine is.

WCTS - RDS Weekly Medication Control Sheet

Week of _____

Cottage	Population	Capsules Dispensed		Capsules Returned		Capsules Taken	
		Drug A	Drug B	Drug A	Drug B	Drug A	Drug B
2	( )						
7	( )						
9	( )						
16	( )						
Subtotal	( )						
1	( )						
4	( )						
5	( )						
6	( )						
F.H.	( )						
10	( )						
11	( )						
12	( )						
13	( )						
14	( )						
15	( )						
19	( )						
Subtotal	( )						

Accumulative Totals	Light Red	Yellow	Dark Red	Green
Capsules in Cottage				
Capsules in Drug Room				
Capsules Taken				
Total Capsules				
Bottle Errors				
Damaged				

Drug A is light red and dark red. Drug B is yellow and green. Dark red and green are used in cottages 2, 7, 9 and 16. Light red and yellow are used in the other cottages.

WCTS Respiratory Disease Study Medication Record

Cottage Number _____ Month _____ Drug A ☐ B ☐ (check one) Color of Drug _____

Day of Month

Name	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
1.																															
2.																															
3.																															
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REMARKS:

APPENDIX A.4

THE UNIVERSITY OF MICHIGAN
School of Public Health
Ann Arbor, Michigan

Dear Parent:

Enclosed in this envelope is one dose of the medication your child is taking in the study of the prevention of respiratory disease.

During weekend leave your child should take this capsule at suppertime on Saturday. When the medication is taken, check this box. ☐

Have your child return this slip to the cottage at the school.

Thank you.

Sincerely yours,

John F. Finklea, M.D.

APPENDIX A.5

A Letter to Cottage Parents

Dear Cottage Parents:

We need you to help study the prevention of viral respiratory disease. These illnesses are familiar to you as colds, sore throats and "flu."

You are vital to this work. Unless children take the correct medication and are properly referred to the medical clinic, all the other work will be useless. The study team is interested in your problems and your suggestions. We will always be available to discuss these with you.

There are several questions which we will attempt to answer for you. If these answers are not clear or if you have additional questions, please contact us.

Question: Who will receive the medications?
Answer: Children whose parents have given permission for study participation. Naturally for various medical reasons some of the volunteers have been excluded from the study. Each cottage will obtain from the medical clinic a medication sheet with a list of children that are to receive each drug.

Question: How will the cottage get the medication and what will it be?
Answer: The medications will be capsules and will be obtained in the same fashion as the medications presently used in the cottage, i.e., from the medical clinic.

Question: How many different medications will be given in each cottage?
Answer: Two medications will be given in each cottage, however, an individual child will receive only one of them during the study.

Question: When, how often, and how long will the medications be given?
Answer: The medications will be given during the months of February, March, April, and May. During the first week of administration each child will receive two capsules daily, one before breakfast and one before supper. After the first week each child will receive one capsule daily, before supper.

Question: How will the capsules be passed out to the children?
Answer: It is the suggestion of the study team that children who are to receive one drug be seated at tables which are separate from children receiving the other drug. After they are seated they may each

be given one appropriate capsule. They may then take this capsule in your presence with any liquid of your choice prior to beginning the meal. Perhaps you have other ideas. If you do, please discuss them with us.

Question: What will be done about weekend leaves?
Answer: Prior to leaving the cottage for leave, a child should receive one dose of the appropriate medication. Another dose should be given to the child upon return on Sunday evening. These capsules should be taken in your presence.

Before leaving the school each child should go to the medical clinic to pick up a dose of medication for the Saturday the child will be away. The parent of the child will be asked to mark a slip and the child should bring the slip to the cottage on return to the school. These slips should be sent to the clinic on the next Monday.

Question: What about children who are transferred to the sick ward or to the discipline cottage?
Answer: These children should continue on their appropriate medication unless the physician decides to discontinue it.

Question: What sort of change in cottage to clinic referral will be necessary?
Answer: Little if any change will be necessary. The study team would like to see any study child with a complaint. You will be given copies of the interview form which will give a good idea of the things in which we are interested. Generally these are fevers, aches, coughs, running noses, sore throats, hoarseness, earaches, rashes and diarrhea.

Question: Suppose an error of medication administration or referral occurs?
Answer: Errors will occur. We would hope to gain from them. The regular school error forms should be filled out forwarded to the study team at the medical clinic.

Question: What other studies will the study team do?
Answer: If there is increased respiratory illness in the school or in the individual cottage, the study team may take specimens for laboratory study. These would be blood specimens and throat washings. As a check on medication the study team will from time to time take early morning urine specimens on children in the cottage.

Thank you for your time and cooperation.

Sincerely yours,

John F. Finklea, M.D.

APPENDIX A.6a

WCTS Respiratory Disease Study
Interviewer Instructions

Background: Pretesting of a symptom questionnaire showed that children in this population would give a positive answer to direct questions about symptoms in the absence of these symptoms. The following procedure is intended to allow the child to volunteer as much information as possible and yet preserve as much uniformity as possible.

First Visit:

1. When the child enters the interview room, introduce yourself and state that you wish to ask a few questions about his illness.
2. Record identifying information, name, age, date and cottage on both the symptom questionnaire and physical exam form.
3. Ask, "When did you become sick?" Circle the day of illness on the questionnaire and record interview data in this column.
4. Ask, "What is bothering you?" When the child answers you should then ask those questions under the appropriate questionnaire head such as eyes, chest, etc.
5. Ask, "Is there anything else bothering you?" If another complaint is elicited, you should ask the questions under the appropriate subhead.
6. Ask, "Are you having any trouble with. . . .?" Substituting the remaining headings not covered in previous questioning.
7. Always ask the questions under the heading "general."
8. List any additional information under remarks. This would include any additional complaints and your estimate of any subject lack of comprehension or cooperation.
9. Make a parting statement that the doctor wants to "check you over" and direct the child to an examining room.

Follow Up Visit:

1. Identify the child.
2. Inquire about those symptoms previously present.
3. Ask if there are any new complaints. If there are new complaints, ask the questions under the appropriate heading.
4. The follow up patient should see the study physician if there is a new complaint or if the child has an oral temperature over 100°F.

Symptom Form, Respiratory Disease Study -- Name:_____ Age:_____ Sex: M☐ F☐

WCTS Cottage:_____ Date of Initial Interview:_____

	Day of Illness														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Remarks
Eyes: Are your eyes watery or red?															
Do you hurt behind your eyes?															
Does the light in this room hurt your eyes?															
Ears: Do you have trouble hearing?															
Are your ears popping or stopped up?															
Do your ears hurt?															
Do you have running ears?															
Nose: Are you sneezing?															
Is your nose stuffy?															
How many times did you blow your nose yesterday? 1 = <5; 2 = >5															
Do you have trouble smelling things?															
Throat & Larynx: Have you lost your voice or has your voice changed?															
Do you have sore spots in your mouth?															
Is your throat sore?															
Does it hurt to swallow your food?															
Chest: Do you cough?															
Do you wake up at night coughing?															
Do you cough up something or either spit it out or swallow it?															
Does it hurt you to breathe in?															
Does your chest or breathing feel tight?															
General: Did you get sick quickly?															
Do you feel achey?															
Do you have chills?															
Have you felt hot or feverish?															
Have you stopped wanting to eat?															
Does your head ache?															
Have you vomited?															
Does your stomach hurt?															
Have you had three sit downs in one day since you got sick?															
Do you have trouble passing your water?															

Physical Examination Form -- Name:_____ Age:_____ Sex: M☐ F☐

WCTS Cottage:_____ Date of Initial Exam:_____

Sign	Day of Illness					Remarks
Temperature (oral°)						
Rash						
Eyes: Overflow tearing						
Mucoid discharge						
Conjunctival congestion						
Ears: 1. Otorrhea						
2. Tympanic Membrans -- N = Normal, E = Erythema, F = Fluid, B = Bulging						
3. Positive Rinne Test -- R = Right, L = Left						
Nose: 1. Discharge -- P = Profuse, S = Scanty, M = Mucoid, W = Watery						
2. Mucosa -- N = Normal, E = Erythematous, Ed = Edematous						
3. Occlusion to air passage						
Mouth & Pharynx: 1. Faucial Hyperermia (Grade 0 to 4)						
2. Vesicles -- B = Buccal, P = Palatine						
3. Petechiae						
4. Faucial exudate						
Cervical Adenopathy: Location -- P = Posterior chain, A = Anterior chain, T = Tonsilar group						
Size -- 1 = 1 cm, 2 = 1-2 cm, 3 = 2 cm						
Other -- T = Tender, M = Mobile, Fx = Fixed, S = Soft, D = Discrete, H = Firm						
Salivary gland swelling: P = Parotid, S = Submaxillary						
Hoarseness						
Chest: 1. Coughing -- H = Hacking or D = Deep						
2. Rhonchi						
3. Rales -- L = Localized, G = Generalized						
4. Wheezing						
5. Limitation of expansion						
6. Dullness (note location)						
Other:						
Impression (syndrome Name)						

APPENDIX A.8

Respiratory Syndrome Criteria

Syndrome	Cardinal Sign(s) and Symptom(s)	Commonly associated sign(s) and symptom(s)
Coryzal	Nasal symptoms of discharge, sneezing, and occlusion.	1. Nasal signs of mucous membrane edema and/or erythema. 2. Complaints of dry scratchy throat, watery burning eyes, and cough. 3. Constitutional symptoms of malaise, anorexia, fever, aching.
Pharyngeal	1. Pain on swallowing. 2. Pharyngeal erythema or exudate.	1. Nasal symptoms and cough. 2. Cervical adenopathy. 3. Constitutional symptoms of fever, malaise, aching, anorexia and chilliness.
Laryngeal	Hoarseness.	1. Constitutional symptoms as previously outlined. 2. Cough which may be barking. 3. Pharyngeal erythema.
Bronchitis	Persistent deep cough with nocturnal component.	1. Wheezing, rhonchi, sputum. 2. Constitutional symptoms as previously outlined.
Pneumonitis	Fine rales or signs of consolidation.	1. Constitutional symptoms. 2. Cough, sputum. 3. Pleural chest pain.
Herpangina (special case of pharyngeal)	1. Pharyngeal or palatal vesicles and/or ulcers. 2. Pain on swallowing.	1. Constitutional symptoms. 2. Cervical adenopathy.
Acute Undifferentiated Respiratory Disease	1. Sudden onset of febrile illness with constitutional symptoms of malaise, chilliness, aching. 2. Cough	1. Nasal stuffiness. 2. Sore throat. 3. Hoarseness.

WCTS - RDS Employee Absentee Sheet

Pay Period of _____

Employee Group	Group Population	Number Sick Days Taken	Number of Illnesses	Sick Days per Illness	Illnesses Rate per 100 Individuals per Pay Period	Remarks
Total						

APPENDIX A.10

WCTS - Population Movement

Type of Movement (circle):
1. Admission
2. Discharge
3. Transfer to another cottage
4. Transfer to sick ward
5. Transfer to discipline cottage

Name	Date	Cottage of Origin	Place Transferred
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			
11.			
12.			
13.			
14.			
15.			
16.			
17.			

APPENDIX A.11

Identification and History Form
Respiratory Disease Study

Wayne County Training School Number: _____

Name: _____

Address: St. & No. _____ State: _____

City _____ Race: White ☐ Non-white ☐

Birth Date: _____

Admission (WCTS) Date: _____ Cottage Number: _____

Next of Kin:

Name _____	Name _____
St. & No. _____	St. & No. _____
City _____	City _____
State _____	State _____
Phone No. _____	Phone No. _____

Allergic History:

Medical History	Yes	No
Asthma	___	___
Allergic rhinitis (hay fever)	___	___
Eczema	___	___
Hives	___	___
Drug Allergy	___	___

a) If yes, what allergens? _____

b) If yes, what drugs? _____

Previous Respiratory Disease:

1. Average number respiratory infections per year during one or more of the preceding three years:
   Number _____ Number of Years 1 ☐ 2 ☐ 3 ☐
2. Pneumonia: Number of Times _____ Years _____

Immunization: Influenza Yes ☐ No ☐ If Yes, when (year) _____

Other Illness:	Yes	No	Unknown	If Yes, when (year)
Rheumatic Fever	___	___	_____	_____
Glomerulonephritis	___	___	_____	_____
Heart Disease	___	___	_____	_____
Convulsive Disorder	___	___	_____	_____
Eneuresis	___	___	_____	_____
Otitis Media	___	___	_____	If Yes, otorrhea Yes__ No__

Chronic Disease, if any ___ ___ If yes, what _____

Recent Weight: Weight _____ lbs., (date) _____

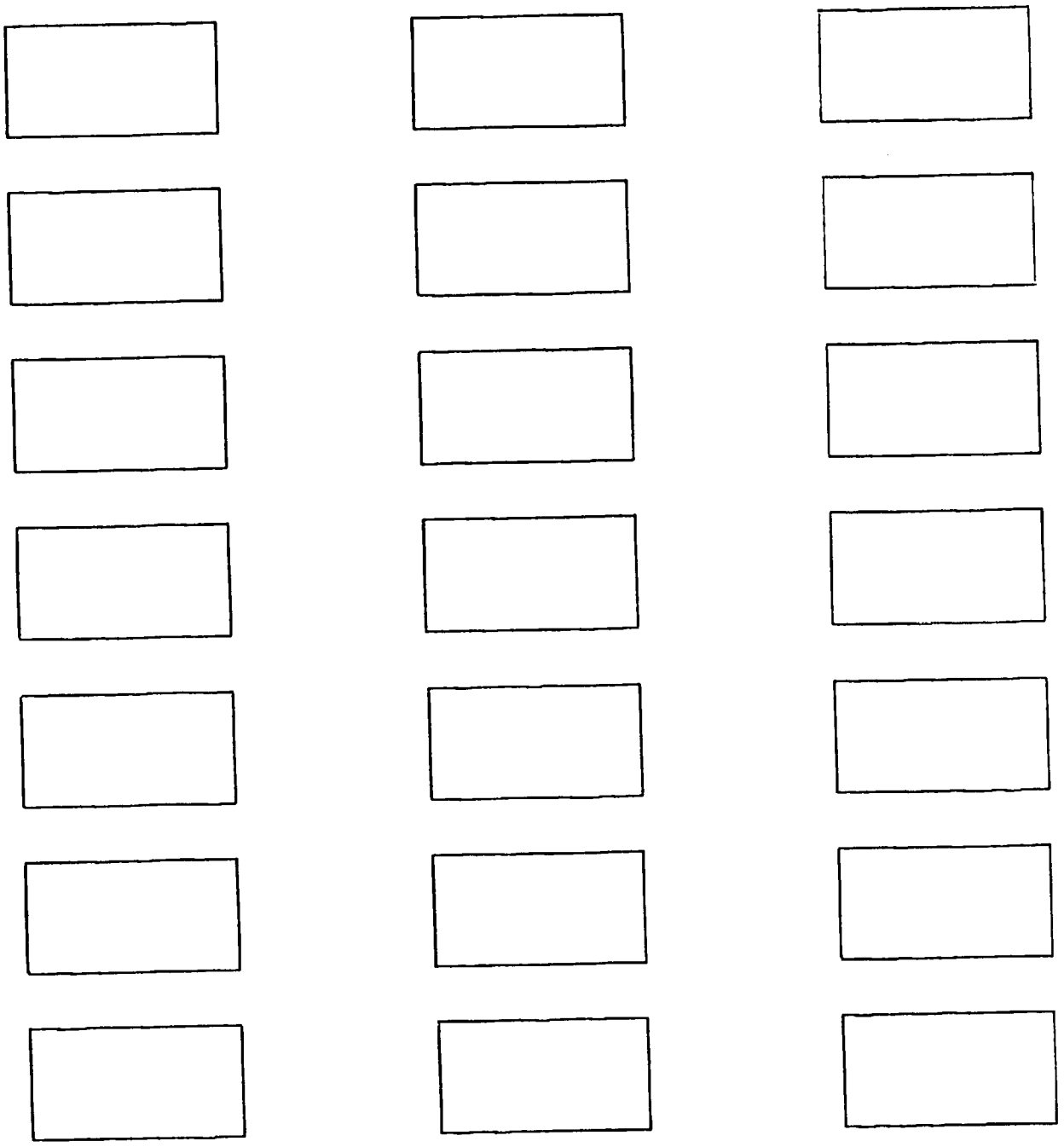
Other Remarks:

APPENDIX A.12

Dormitory Arrangement

Cottage _____

Room _____



_____

Door

WCTS - Daily ____ Weekly ____ Distribution of All ____ New ____ Respiratory Illness by Clinical Syndrome

Cottage	Study Population	Syndrome							
		Coryza	ARD	Pharyngeal	Laryngeal	Bronchitis	Pneumonitis	Other	Total
1	( )								
2	( )								
3	( )								
4	( )								
5	( )								
6	( )								
7	( )								
8	( )								
9	( )								
10	( )								
11	( )								
12	( )								
13	( )								
14	( )								
15	( )								
16	( )								
17	( )								
19	( )								
Total	( )								

APPENDIX B

Source Tables

APPENDIX B.1

PARTICIPANT MISSED MEDICATION DOSES, DISTRIBUTION BY NUMBER OF DOSES MISSED, TRIAL GROUP, AND TIME

Week of Trial	Percentage of Amantadine Population			Percentage of Placebo Population		
	Missing No Doses	Missing One Dose	Missing More Than One Dose	Missing No Doses	Missing One Dose	Missing More Than One Dose
1	79.6	15.6	4.8	71.8	23.7	4.5
2	80.1	17.5	2.4	88.8	9.0	2.2
3	86.6	8.7	4.7	90.4	7.4	2.2
4	86.0	10.0	4.0	98.5	1.5	0.0
5	91.3	8.0	0.7	87.0	7.9	4.1
6	94.0	5.3	0.7	93.4	5.1	1.5
7	91.5	7.9	0.6	95.7	2.9	1.4
8	98.0	0.7	1.2	97.1	1.5	1.4
9	92.1	7.2	0.7	89.7	8.1	2.2
10	85.0	10.4	4.6	88.4	8.7	2.9
11	75.7	14.5	9.8	69.3	15.6	15.1
12	90.2	8.5	1.3	87.5	9.6	2.9
13	90.2	5.3	4.5	83.6	11.9	4.5
14	92.7	4.6	2.7	95.5	2.2	2.3
15	92.1	3.3	4.6	93.2	6.0	0.8
16	83.3	9.7	7.0	88.0	6.8	5.2
17	91.7	2.1	6.2	94.2	1.5	4.3
18	94.5	0.7	4.8	88.2	6.1	5.7

APPENDIX B.2

CAPSULE RETURN RATE PER 100 DISPENSED
DISTRIBUTION BY TRIAL GROUP AND WEEK OF TRIAL

Week of Capsule Dispensing	Total Trial			Amantadine			Placebo		
	Number Dispensed	Number Returned	Return Rate/100 Dispensed	Number Dispensed	Number Returned	Return Rate/100 Dispensed	Number Dispensed	Number Returned	Return Rate/100 Dispensed
1	3,892	327	8.4	2,058	169	8.2	1,834	158	8.6
2	1,944	45	2.3	1,027	32	3.1	917	13	1.4
3	2,023	65	3.2	1,064	50	4.7	959	15	1.6
4	2,116	47	2.2	1,064	24	2.4	952	23	2.4
5	2,002	54	2.7	1,050	26	2.5	952	28	2.9
6	2,030	47	2.3	1,064	24	2.2	966	23	2.4
7	2,044	33	1.6	1,078	24	2.2	966	9	0.9
8	2,030	30	1.5	1,064	8	1.8	966	22	2.3
9	2,037	26	1.3	1,064	12	1.1	973	14	1.4
10	2,338	72	3.1	1,224	26	2.1	1,104	46	4.2
11	1,746	271	15.5	918	96	10.4	828	175	21.2
12	2,016	92	4.6	1,064	40	3.8	952	52	5.5
13	2,002	32	2.1	1,064	23	2.2	938	19	2.0
14	2,002	32	1.6	1,064	17	1.6	938	15	1.6
15	2,002	32	1.6	1,064	28	2.6	938	4	0.4
16	1,988	108	5.4	1,050	56	5.3	938	52	5.6
17	1,960	57	2.9	1,029	36	3.5	931	21	2.3
18	1,116	59	5.3	584	31	5.4	532	28	5.3
Total	37,178	1,439	3.9	19,594	722	3.7	17,584	717	4.1
Total Minus Correction*	36,725	986	2.7	19,366	494	2.6	17,359	492	2.8

*Corrected for intentional overdispensing during first week and for over dispensing occasioned by volunteer entrance into and exit from the trial.

APPENDIX B.3

PARTICIPANT WEEK END SLIPS, NUMBER ISSUED, NUMBER RETURNED AND NUMBER RETURNED INDICATING CAPSULE TAKEN DISTRIBUTION BY TRIAL GROUP AND TIME

Week of 1965	Total Capsules					Amantadine					Placebo				
	Number			% of Issued		Number			% of Issued		Number			% of Issued	
	Issued	Returned	Marked Taken	Returned	Marked Taken	Issued	Returned	Marked Taken	Returned	Marked Taken	Issued	Returned	Marked Taken	Returned	Marked Taken
7	45	27	27	60.0	60.0	27	14	14	51.8	51.8	18	13	13	72.2	72.2
8	16	13	11	81.3	69.8	10	8	7	80.0	70.0	6	5	4	83.3	66.7
9	1	1	1	100.0	100.0	1	1	1	100.0	100.0	0	0	0	0.0	0.0
10	19	9	9	47.4	47.4	11	3	2	27.3	18.2	8	7	7	87.5	87.5
11	22	7	6	31.8	27.3	13	4	3	30.8	23.1	9	3	3	33.3	33.3
12	48	34	33	70.8	68.8	27	18	17	66.7	63.0	21	16	16	76.2	76.2
13	28	21	20	75.0	71.4	13	9	8	69.2	61.5	15	12	12	80.0	80.0
14	11	10	10	90.9	90.9	6	5	5	83.3	83.3	5	5	5	100.0	100.0
15	4	4	4	100.0	100.0	4	4	4	100.0	100.0	0	0	0	0.0	0.0
16	201	121	117	60.2	58.2	110	67	64	60.9	58.2	91	57	53	62.6	58.2
17	1	1	1	100.0	100.0	0	0	0	0.0	0.0	1	1	1	100.0	100.0
18	5	3	3	60.0	60.0	4	3	3	75.0	75.0	1	0	0	0.0	0.0
19	95	43	42	45.3	44.2	48	23	23	50.0	47.9	47	19	19	40.4	40.4
20	9	4	4	44.4	44.4	3	1	1	33.3	33.3	6	3	3	50.0	50.0
21	14	8	8	57.1	57.1	12	7	7	58.3	58.3	2	1	1	50.0	50.0
22	85	48	38	56.5	44.7	50	23	23	46.0	46.0	35	15	15	42.8	42.8
23	12	6	6	50.0	50.0	9	4	4	44.4	44.4	3	2	2	66.7	66.7
Total	616	354	340	57.5	55.2	348	195	186	56.0	53.4	268	159	154	59.3	57.5

APPENDIX B.4

MEDICAL CLINIC VISITS BY ALL WCTS STUDENTS
DISTRIBUTION OF RATES BY SEX AND TIME

Week of 1965	Medical Clinic Visit Rate/100 of Population		
	Total	Male	Female
1	163.4	130.3	252.1
2	162.2	139.0	253.8
3	171.0	144.4	242.0
4	186.9	151.0	283.0
5	161.1	133.0	231.4
6	137.8	109.8	211.0
7	146.7	102.8	262.3
8	124.8 (208)*	94.6 (156.7)*	197.4 (329.0)*
9	187.8	147.6	295.0
10	188.9	153.9	280.5
11	156.6	126.1	237.4
12	153.2	127.1	222.8
13	146.9	116.2	229.0
14	154.1	133.3	209.0
15	133.5 (188.8)**	116.7 (166.9)**	177.0 (234.5)**
16	92.2 (164.5)**	74.6 (135.9)**	137.3 (227.2)**
17	187.0	166.7	242.4
18	141.0	131.3	190.9
19	149.5	123.7	217.0
20	153.8	126.4	222.0
21	132.0	111.1	184.2
22	145.6	120.4	209.4
23	173.4	147.4	261.5

*Rates in parentheses are adjusted to compensate for loss of two days of clinics during a blizzard.

**Rates in parentheses are adjusted to compensate for population changes caused by spring vacation.

APPENDIX B.5

WCTS INFIRMARY ADMISSIONS WITH RESPIRATORY ILLNESS
DISTRIBUTION BY GROUP AND TIME

Time Week of 1965	Total WCTS Population			Nontrial Population			Trial Population								
							Total			Amantadine*			Placebo*		
	Number	Admissions	Rate/1000/Week	Number	Admissions	Rate/1000/Week	Number	Admissions	Rate/1000/Week	Number	Admissions	Rate/1000/Week	Number	Admissions	Rate/1000/Week
3	516	4	7.8	302	2	6.6	214	2	9.3	113	2	17.7	101	0	0.0
4	525	7	13.3	259	4	15.4	266	3	11.3	141	1	7.1	125	2	16.0
5	524	3	5.7	247	2	8.1	277	1	3.6	146	1	6.8	131	0	0.0
6	521	3	5.8	243	2	8.2	278	1	3.6	147	0	0.0	131	1	7.6
7	522	5	9.6	243	4	16.5	279	1	3.6	147	0	0.0	132	1	7.6
8	526	5	9.5	240	2	8.4	286	3	10.5	150	0	0.0	136	3	22.1
9	525	11	21.0	239	4	16.7	286	7	24.5	150	1	6.7	136	6	44.1
10	527	5	9.5	241	3	12.4	286	2	7.0	150	1	6.7	136	1	7.4
11	531	11	20.7	241	3	12.4	290	8	27.6	151	2	13.2	139	6	43.2
12	528	1	1.9	237	1	4.2	291	0	0.0	153	0	0.0	138	0	0.0
13	525	6	11.4	235	3	12.8	290	3	10.3	152	3	19.7	138	0	0.0
14	530	4	7.5	240	2	8.3	290	2	6.9	152	1	6.6	138	1	7.2
15	531	7	13.2 (18.7)**	240	2	8.3 (11.2)**	291	5	17.2 (23.9)**	153	3	19.6 (27.6)**	138	2	14 5 (19.7)**
16	531	6	11.3 (20.2)**	240	2	8.3 (14.5)**	291	4	13.7 (23.6)**	153	2	13.1 (23.2)**	138	2	14.5 (24.0)**
17	522	3	5.7	234	1	4.3	288	2	6.9	152	0	0.0	136	2	14.7
18	520	4	7.7	234	1	4.3	286	3	10.5	152	0	0.0	134	3	22.4
19	518	3	5.8	232	2	8.5	286	1	3.5	152	0	0.0	134	1	7.5
20	523	2	3.8	237	0	0.0	286	2	7.0	152	1	6.6	134	1	7.5
21	516	4	7.8	233	3	13.0	283	1	3.5	149	1	6.7	134	0	0.0
22	514	2	0.0	234	0	0.0	280	2	7.1	147	2	13.6	133	0	0.0
23	520	0	0.0	241	0	0.0	279	0	0.0	146	0	0.0	133	0	0.0

*$p = .059$ (Sign Test)
**Rates in parentheses are adjusted to reflect population changes during spring vacation.

APPENDIX B.6

DAYS OF ABSENCE FROM ACADEMIC SCHOOL,
EXCLUDING ABSENCE OCCASIONED BY TRAUMA OR DISCIPLINE,
DISTRIBUTION BY TRIAL GROUP AND TIME

Week of 1965	Total School Population			Nontrial Population			Trial Population								
							Total			Amantadine*			Placebo*		
	Days of School	Days Absent	Rate/ 100 School Days	Days of School	Days Absent	Rate/ 100 School Days	Days of School	Days Absent	Rate/ 100 School Days	Days of School	Days Absent	Rate/ 100 School Days	Days of School	Days Absent	Rate/ 100 School Days
1	2080	214	10.3	1000	84	8.4	1080	130	12.0	605	75	12.4	475	55	11.6
2	2080	107	5.4	1000	45	4.5	1080	62	5.7	605	32	5.3	475	30	6.3
3	2095	97	4.6	1015	48	4.7	1080	49	4.5	605	24	4.0	475	25	5.3
4	1257	156	12.4	609	65	10.7	648	91	14.0	363	47	13.0	285	44	15.4
5	2130	326	15.3	995	115	11.6	1110	211	19.0	620	110	17.8	490	101	20.6
6	2130	65	3.5	1015	28	2.8	1115	37	5.9	625	19	3.0	490	18	3.6
7	2145	77	3.6	1005	38	3.8	1140	39	3.4	630	21	3.4	510	18	3.5
8	1290	110	8.5	597	55	9.2	693	55	7.9	384	32	8.3	309	23	7.4
9	2165	127	5.9	990	55	5.6	1175	72	6.1	640	29	4.5	535	43	8.0
10	1736	67	3.9	796	34	4.3	940	33	3.5	512	14	2.7	428	19	4.3
11	2200	87	4.0	1005	45	4.3	1195	42	3.5	650	26	3.5	545	16	2.9
12	2200	81	3.7	1005	42	4.2	1195	39	3.3	650	13	2.0	545	26	4.8
13	2200	46	2.1	1000	20	2.0	1200	26	2.2	655	18	2.8	545	8	1.5
14	2195	77	3.5	995	35	3.5	1200	42	3.5	655	25	3.8	545	17	3.1
15	2210	67	3.0	1010	30	3.0	1200	37	3.1	655	23	3.5	545	14	2.6
17**	2215	103	4.7	1020	58	5.7	1195	45	3.8	650	20	3.1	545	25	4.6
18	1740	93	5.4	760	50	6.6	980	43	4.4	532	25	4.7	448	18	4.0
19	2170	65	3.0	950	27	2.8	1220	38	3.1	660	14	2.1	560	24	4.3
20	2200	37	1.7	980	15	1.5	1220	22	1.8	660	6	0.9	560	16	2.9
21	2195	53	2.4	975	26	2.7	1220	27	2.2	660	13	2.0	560	14	2.5

*p = .398 (Sign Test)

**No school during week 16.

APPENDIX B.7

EPISODES OF ABSENCE FROM ACADEMIC SCHOOL
EXCLUDING ABSENCE OCCASIONED BY TRAUMA OR DISCIPLINE
DISTRIBUTION BY TRIAL GROUP AND TIME

Week of 1965	Total School Population			Nontrial Population			Trial Population								
							Total			Amantadine*			Placebo*		
	Number	Episodes of Absence	Rate/ 100 Population	Number	Episodes of Absence	Rate/ 100 Population	Number	Episodes of Absence	Rate/ 100 Population	Number	Episodes of Absence	Rate/ 100 Population	Number	Episodes of Absence	Rate/ 100 Population
1	416	78	18.8	200	35	17.5	216	43	19.9	121	25	20.7	95	18	18.9
2	416	67	16.1	200	32	16.0	216	35	16.2	121	18	14.9	95	17	17.9
3	419	97	23.2	203	48	23.6	216	49	22.7	121	24	19.8	95	25	25.8
4	419	78	18.6	203	36	17.7	216	42	19.4	121	23	19.0	95	19	20.0
5	426	104	24.4	204	40	19.6	222	64	28.8	124	34	27.4	98	30	30.6
6	426	47	11.0	203	22	10.8	223	25	11.2	125	13	10.4	98	12	12.2
7	429	42	9.8	201	23	11.4	226	19	8.4	126	11	8.7	102	8	7.8
8	430	43	10.0	199	20	10.0	231	23	10.0	128	12	9.4	103	11	10.7
9	433	61	14.1	198	30	15.2	235	31	13.2	128	12	9.4	107	19	17.8
10	434	40	9.2	199	20	10.0	235	20	8.5	128	10	7.8	107	10	9.3
11	440	44	10.0	201	24	11.9	239	20	8.4	130	9	6.9	109	11	10.1
12	440	47	10.7	201	23	11.4	239	24	10.0	130	11	8.5	109	13	11.9
13	440	26	5.9	200	12	6.0	240	14	5.8	131	10	7.6	109	4	3.7
14	439	39	8.9	199	17	8.5	240	22	9.2	131	12	9.2	109	10	9.2
15	442	40	9.0	202	21	10.4	240	19	7.9	131	11	8.4	109	8	7.3
17**	443	67	15.1	204	39	19.1	239	28	11.7	130	13	10.0	109	15	13.8
18	435	57	13.1	190	29	15.3	245	28	11.4	133	17	12.8	112	11	9.8
19	434	49	11.3	190	22	11.6	244	27	11.1	132	10	7.6	112	17	15.2
20	440	29	6.6	196	12	6.1	244	17	7.0	132	6	4.5	112	11	9.8
21	439	38	8.6	195	17	8.7	244	21	8.6	132	10	7.6	112	11	9.8

*$p = .046$ (Sign Test)

**No school during week 16.

APPENDIX B.8

WCTS EMPLOYEE ABSENTEE DAYS,
EXCLUDING LONG TERM ILLNESS,
DISTRIBUTION BY SELECTED GROUP AND TIME

Week of 1965	Total Employees			Cottage Employees			Academic School Employees		
	Days of Work	Days Absent	Absentee Rate/100 Days	Days of Work	Days Absent	Absentee Rate/100 Days	Days of Work	Days Absent	Absentee Rate/100 Days
1	1285	55	4.3	520	24	4.6	150	9	6.0
2	1285	35	2.7	520	18	3.5	150	1	0.7
3	1260	45	3.6	510	27	5.3	145	1	0.7
4	1260	35	2.8	510	21	4.1	145	0	0.0
5	1250	39	3.1	500	12	6.0	150	1	0.7
6	1250	22	1.8	500	10	5.0	150	1	0.7
7	1325	33	2.5	570	14	2.4	150	6	4.0
8	1325	42	3.2	570	25	4.4	150	1	0.7
9	1290	42	3.2	535	18	3.4	150	6	4.0
10	1295	32	2.5	540	22	4.1	150	0	0.0
11	1305	26	2.0	550	18	3.3	150	1	0.7
12	1300	37	2.8	550	25	4.5	150	2	1.3
13	1315	29	2.2	565	13	2.3	150	4	2.7
14	1315	25	1.9	565	10	1.8	150	6	4.0
15	1295	11	0.8	550	8	1.4	150	0	0.0
16	1300	26	2.0	550	17	3.1	150	0	0.0
17	1330	25	1.9	580	12	2.1	150	3	2.0
18	1345	26	1.9	590	12	2.0	150	7	4.7
19	1350	14	1.0	585	3	0.5	150	2	1.3
20	1350	11	0.8	585	10	1.7	150	0	0.0
21	1355	26	1.9	595	13	2.2	150	2	1.3
22	1360	18	1.3	600	17	2.8	150	1	0.7

APPENDIX B.9

WCTS EMPLOYEE ABSENTEE EPISODES EXCLUDING LONG TERM ILLNESS
DISTRIBUTION BY SELECTED GROUP AND TIME

Week of 1965	Total Employees			Cottage Employees			Academic School Employees		
	Number	Number of Episodes	Episode Rate/100	Number	Number of Episodes	Episode Rate/100	Number	Number of Episodes	Episode Rate/100
1	257	20	7.8	104	11	10.6	30	3	10.0
2	257	18	7.0	104	9	8.6	30	1	3.3
3	252	26	10.3	102	15	14.7	29	1	3.4
4	252	22	8.7	102	12	11.8	29	0	0.0
5	250	19	7.6	100	7	7.0	30	1	3.3
6	250	13	5.2	100	7	7.0	30	1	3.3
7	265	23	8.7	114	14	12.3	30	4	13.3
8	265	20	7.5	114	12	10.5	30	1	3.3
9	258	21	8.1	107	10	9.3	30	3	10.0
10	259	17	6.6	108	9	8.3	30	0	0.0
11	261	15	5.7	110	11	10.0	30	1	3.3
12	260	18	6.9	110	12	10.9	30	2	6.7
13	263	15	5.7	113	7	6.2	30	2	6.7
14	263	18	6.8	113	8	7.1	30	3	10.0
15	259	8	3.1	110	5	4.5	30	0	0.0
16	260	15	5.8	110	8	7.3	30	0	0.0
17	266	19	7.1	116	9	7.8	30	2	6.7
18	269	20	7.4	118	10	8.5	30	5	16.7
19	270	12	4.4	117	2	1.7	30	2	6.7
20	270	6	2.2	117	5	4.3	30	0	0.0
21	271	21	7.7	119	11	9.2	30	2	6.7
22	272	11	4.0	120	10	8.3	30	1	3.3

APPENDIX B.10

INCIDENCE OF ALL ILLNESS AMONG PARTICIPANTS
DISTRIBUTION BY TRIAL GROUP AND TIME

Time Week of 1965	Total			Amantadine*			Placebo*		
	Population	Number of Illnesses	Rate/100 Population	Population	Number of Illnesses	Rate/100 Population	Population	Number of Illnesses	Rate/100 Population
3**	214	31	14.5	113	15	13.3	101	16	15.8
4	266	26	9.8	141	14	9.9	125	12	9.6
5	277	17	6.5	146	6	4.1	131	12	9.2
6***	278	11	4.0	147	7	4.8	131	3	2.3
7	279	18	6.5	147	5	3.4	132	13	9.8
8	286	13	4.6	150	6	4.0	136	7	5.2
9	286	24	8.4	150	11	7.3	136	13	9.6
10	286	16	5.6	150	8	5.3	136	8	5.9
11	290	19	6.6	151	8	5.3	139	11	7.9
12	291	10	3.4	153	6	3.9	138	4	2.9
13	290	21	7.2	152	12	7.9	138	9	6.5
14	290	16	5.5	152	7	4.6	138	9	6.5
15	291	22	7.6	153	7	4.6	138	15	10.9
16	291	24	8.2	153	9	5.9	138	15	10.9
17	288	16	5.6	152	6	4.0	136	10	7.4
18	286	8	2.8	152	2	1.3	134	6	4.5
19	286	11	3.8	152	6	4.0	134	5	3.7
20	286	8	2.8	152	4	2.6	134	4	3.0
21	283	2	0.7	149	1	0.7	134	1	0.8
22	280	4	1.4	147	4	2.7	133	0	0.0
23	279	0	0.0	146	0	0.0	133	0	0.0
Total	---	317	---	---	144	---	---	173	---

*p = .038 (Sign Test)

**Week three figures are really prevalence because children with old illnesses were seen during the first week of the study.

***Trial began on Wednesday of this week.

APPENDIX B.11

INCIDENCE OF STREPTOCOCCAL ILLNESS AMONG PARTICIPANTS
DISTRIBUTION BY TRIAL GROUP AND TIME

Time Week of 1965	Total			Amantadine*			Placebo*		
	Population	Number of Illnesses	Rate/100 Population	Population	Number of Illnesses	Rate/100 Population	Population	Number of Illnesses	Rate/100 Population
3	214	6	2.8	113	2	1.8	101	4	4.0
4	266	5	1.9	141	2	1.4	125	3	2.4
5	277	6	2.2	146	3	2.0	131	3	2.3
6	278	1	0.4	147	1	0.7	131	0	0.0
7	279	3	1.1	147	2	1.4	132	1	0.8
8	286	7	2.4	150	2	1.3	136	5	3.7
9	286	11	3.8	150	7	4.7	136	4	2.9
10	286	4	1.4	150	3	2.0	136	1	0.7
11	290	6	2.1	151	4	2.7	139	2	1.4
12	291	2	0.7	153	2	1.3	138	0	0.0
13	290	6	2.1	152	5	3.3	138	1	0.7
14	290	5	1.7	152	3	2.0	138	2	1.4
15	291	6	2.1	153	2	1.3	138	4	2.9
16	291	2	0.7	153	2	1.3	138	0	0.0
17	288	4	1.4	152	3	2.0	136	1	0.7
18	286	0	0.0	152	0	0.0	134	0	0.0
19	286	5	1.8	152	0	0.0	134	5	3.7
20	286	1	0.4	152	1	0.7	134	0	0.0
21	283	1	0.4	149	1	0.7	134	0	0.0
22	280	1	0.4	147	1	0.7	133	0	0.0
23	279	0	0.0	146	0	0.0	133	0	0.0
Total	---	82	---	---	46	---	---	36	---

*p = .151 (Sign Test)

APPENDIX B.12

INCIDENCE OF ALL NONSTREPTOCOCCAL ILLNESS AMONG PARTICIPANTS
DISTRIBUTION BY TRIAL GROUP AND TIME

Time Week of 1965	Total			Amantadine*			Placebo*		
	Population	Number of Illnesses	Rate/100 Population	Population	Number of Illnesses	Rate/100 Population	Population	Number of Illnesses	Rate/100 Population
3	214	25	11.7	113	13	11.5	101	12	11.9
4	266	21	7.9	141	12	8.5	125	9	7.2
5	277	12	4.3	146	3	2.0	131	9	6.9
6	278	9	3.2	147	6	4.1	131	3	2.3
7	279	15	5.4	147	3	2.0	132	12	9.1
8	286	6	2.1	150	4	2.7	136	2	1.5
9	286	13	4.5	150	4	2.7	136	9	6.6
10	286	12	4.2	150	5	3.3	136	7	5.1
11	290	13	4.5	151	4	2.6	139	9	6.5
12	291	8	2.7	153	4	2.6	138	4	2.9
13	290	15	5.2	152	7	4.6	138	8	5.8
14	290	11	3.8	152	4	2.6	138	7	5.0
15	291	16	5.5	153	5	3.3	138	11	8.0
16	291	22	7.6	153	7	4.6	138	15	10.9
18	288	12	4.2	152	3	2.0	136	9	6.6
19	286	6	2.1	152	6	3.9	134	0	0.0
20	286	7	2.4	152	3	2.0	134	4	3.0
21	283	1	0.4	149	0	0.0	134	1	0.7
22	280	3	1.1	147	3	2.0	133	0	0.0
23	279	0	0.0	146	0	0.0	133	0	0.0
Total	---	235	---	---	98	---	---	137	---

*p = .011 (Sign Test)

APPENDIX B.13

INCIDENCE OF ILLNESS DIAGNOSED "OTHER" AMONG PARTICIPANTS
DISTRIBUTION BY TRIAL GROUP AND TIME

Time Week of 1965	Total			Amantadine*			Placebo*		
	Population	Number of Illnesses	Rate/100 Population	Population	Number of Illnesses	Rate/100 Population	Population	Number of Illnesses	Rate/100 Population
3	214	3	1.4	113	3	2.6	101	0	0.0
4	266	4	1.5	141	1	0.7	125	3	2.4
5	277	2	0.7	146	0	0.0	131	2	1.5
6	278	3	1.1	147	2	1.4	131	1	0.8
7	279	2	0.7	147	0	0.0	132	2	1.5
8	286	1	0.4	150	1	0.7	136	0	0.0
9	286	3	1.0	150	1	0.7	136	2	1.5
10	286	3	1.0	150	1	0.7	136	2	1.5
11	290	2	0.7	151	0	0.0	139	2	1.4
12	291	3	1.0	153	1	0.7	138	2	1.4
13	290	3	1.0	152	1	0.7	138	2	1.4
14	290	1	0.3	152	0	0.0	138	1	0.7
15	291	2	0.7	153	0	0.0	138	2	1.4
16	291	4	1.4	153	0	0.0	138	4	2.8
17	288	3	1.0	152	1	0.7	136	2	1.5
18	286	2	0.7	152	1	0.7	134	1	0.8
19	286	5	1.8	152	5	3.3	134	0	0.0
20	286	3	1.0	152	2	1.3	134	1	0.8
21	283	1	0.4	149	0	0.0	134	1	0.8
22	280	0	0.0	147	0	0.0	133	0	0.0
23	279	0	0.0	146	0	0.0	133	0	0.0
Total	---	50	---	---	20	---	---	30	---

*p = .011 (Sign Test)

APPENDIX B.14

INCIDENCE OF NONSTREPTOCOCCAL RESPIRATORY ILLNESS AMONG PARTICIPANTS
DISTRIBUTION BY TRIAL GROUP AND TIME

Time Week of 1965	Total			Amantadine*			Placebo*		
	Population	Number of Illnesses	Rate/100 Population	Population	Number of Illnesses	Rate/100 Population	Population	Number of Illnesses	Rate/100 Population
3	214	22	10.3	113	10	8.8	101	12	11.9
4	266	17	6.4	141	11	7.8	125	6	4.8
5	277	10	3.6	146	3	2.0	131	7	5.3
6	278	7	2.5	147	5	3.4	131	2	1.5
7	279	13	4.7	147	3	2.0	132	10	7.6
8	286	5	1.8	150	3	2.0	136	2	1.5
9	286	10	3.5	150	3	2.0	136	7	5.2
10	286	9	3.2	150	4	2.7	136	5	3.7
11	290	11	3.8	151	4	2.7	139	7	5.0
12	291	5	1.7	153	3	2.0	138	2	1.4
13	290	12	4.1	152	6	4.0	138	6	4.4
14	290	10	3.4	152	4	2.6	138	6	4.4
15	291	14	4.8	153	5	3.3	138	9	6.5
16	291	18	6.2	153	7	4.6	138	11	8.0
17	288	9	3.1	152	2	1.3	136	7	5.2
18	286	6	2.1	152	1	0.7	134	5	3.7
19	286	1	0.4	152	1	0.7	134	0	0.0
20	286	4	1.4	152	1	0.7	134	3	2.2
21	283	0	0.0	149	0	0.0	134	0	0.0
22	280	3	1.1	147	3	2.0	133	0	0.0
23	279	0	0.0	146	0	0.0	133	0	0.0
Total	---	185	---	---	78	---	---	107	---

*p = .059 (Sign Test)

APPENDIX B.15

LIST OF SEROLOGICALLY IDENTIFIED ILLNESSES

Identified As	Trial Group	Patient Number	Cottage Number	Method of* Identification	Clinical** Syndrome	Beta Hemolytic Streptococci Cultured
Influenza A_2	Amantadine	6230	7	HI	Pharyngeal	Yes
	Placebo	5297	6	HI, CF	AURD	No
	Placebo	4798	19	HI, CF	Pharyngeal	No
	Placebo	6204	2	HI, CF	AURD	No
	Placebo	6395	7	HI, CF	AURD	No
	Placebo	6188	16	HI, CF	Other, Non-respiratory	No
	Placebo	5860	9	HI, CF	Other, Non-respiratory	Yes
	Placebo	5405	13	HI, CF	AURD	Yes
	Placebo	5815	13	HI, CF	Pharyngeal	No
	Placebo	6265	9	HI, CF	Pneumonia	No
	Placebo	6362	15	HI, CF	AURD	No
	Placebo	5708	11	CF	Coryzal	No
Influenza B	Amantadine	6381	7	HI, CF	Coryzal	No
	Amantadine	6245	7	HI, CF	Pharyngeal	No
	Placebo	6105	7	HI, CF	Coryzal	No
Influenza C	Amantadine	5697	12	CF	AURD	No
	Amantadine	6258	14	CF	Bronchitis	No
Parainfluenza 1 or 2	Amantadine	5483	4	CF (1 and 2)	Coryzal	No
	Amantadine	6043	14	CF (2)	Other, Non-respiratory	No
	Placebo	6154	5	CF (2)	Coryzal	No

*HI = hemagglutination inhibition
CF = complement fixation

**AURD = acute undifferentiated respiratory disease

APPENDIX B.15, cont.

Identified As	Trial Group	Patient Number	Cottage Number	Method of* Identification	Clinical** Syndrome	Beta Hemolytic Streptococci Cultured
Parainfluenza 3	Placebo	5277	2	CF	Coryzal	No
	Placebo	6127	9	CF	Pharyngeal	No
Respiratory Syncitial Virus	Amantadine	6402	4	CF	Pharyngeal	No
	Amantadine	6002	2	CF	Coryzal	No
	Placebo	6267	5	CF	Pharyngeal	No
Adenovirus	Placebo	6135	6	CF	Other, Non-respiratory	No
	Placebo	6204	2	CF	Coryzal	No
	Placebo	5277	2	CF	Coryzal	No
	Placebo	6185	10	CF	Coryzal	No
Mycoplasma Pneumoniae	Amantadine	5290	13	CF	Coryzal	No
	Amantadine	5697	12	CF	AURD	No
	Amantadine	6250	7	CF	Pharyngeal	No
	Amantadine	6145	14	CF	Bronchitis	No
	Placebo	6365	7	CF	AURD	No
	Placebo	5708	11	CF	Pharyngeal	No
	Placebo	5277	2	CF	Coryzal	No

*HI = hemagglutination inhibition
CF = complement fixation

**AURD = acute undifferentiated respiratory disease

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