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LAKEHEAD UNIVERSITY

DOES MATERNAL INFLUENZA CAUSE SCHIZOPHRENIA?
A NORTHWESTERN ONTARIO STUDY

BY: GILLIAN GRAHAM ©

A THESIS SUBMITTED IN PARTIAL FULFILLMENT

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ABSTRACT

It has long been noted that schizophrenics have a significantly greater chance of being born in the late winter or early spring. Climatic fluctuations and procreational habits have been studied as possible triggers for this effect, with no significant results. A relatively new idea is that mothers who are exposed to influenza during the second trimester of their pregnancy, may somehow transmit the virus or its antibodies to the developing fetus, leading to subtle brain damage which later manifests itself as schizophrenia. This theory fits well with premorbid studies which show that schizophrenics do show some degree of impairment during childhood. It is also supported by numerous neuroanatomical findings of early developmental damage in schizophrenics' brains.

This study attempted to replicate the findings of researchers who have looked at the incidence of schizophrenia subsequent to major influenza outbreaks. Two significant pandemics were in 1918 and 1957. Neither Chi-Squared nor visual analysis showed a peak in schizophrenic births following the 1918 or 1957 epidemic, using information gathered from files of Northwestern Ontario Psychiatric patients. However, when the methodology used in a recent Japanese study is duplicated, a significant elevation is seen following the 1918 epidemic, but not following the 1957 epidemic. There is also evidence of a significant increase in the birthrate of male schizophrenics and of schizophrenia situated at the chronic end of the spectrum. These results are only detectable using the latter methodology however, leading to the conclusion that maternal influenza does not appear to lead to schizophrenia in the offspring, and that research methodologies in this field are in need of clarification and standardization.

INTRODUCTION

A remarkably diverse range of causal agents and environments have been proposed for adult-onset schizophrenia. Given that it is a disease which has long defied any rigid categorization, the absence of a specific, known etiology only adds to its mysterious and baffling aura.

Over the years, specialists have attributed demonic possession, cold, aloof mothers, and aberrant genes to the formation of schizophrenic individuals. However, studies have failed to demonstrate any differences in the parenting styles of schizophrenics' mothers, and if it were simply a matter of one or more heritable alleles, then the disease, with its accompanying 30% reduction in reproductive fitness would have died out in the human gene pool long ago. (Huxley et al., 1964)

A recent hypothesis that makes room for a wide range of differing influences (genetic, environmental, and social) is that fetuses that are exposed to influenza while in the second trimester of development, have an increased risk of developing schizophrenia later in life. This is not the first time a viral etiology has been proposed. Early in this century, an outbreak of influenza led to post-encephalitic psychoses in some adults, and researchers began looking for influenza antibodies in the serum of

schizophrenics and other psychotic patients. Since no significantly elevated antibody levels have ever been detected, the direct viral infection hypothesis was abandoned.

EVIDENCE FOR A DEVELOPMENTAL ORIGIN

More recent research also throws doubt on the theory that adult-onset schizophrenia is caused by sudden, structural damage to a previously intact and healthy brain. A growing body of anatomical and cytological research cites significant, bilateral deformities in the architecture of schizophrenic brains. (Jakob & Beckmann, 1986; Falkai et al., 1988; Roberts, 1991). Decreases of up to 6% in brain length and mass, dramatically enlarged ventricles, and deficits in hippocampal cortical tissue, are some of the most common findings. (Bruton et al., 1990: Pakkenberg, 1987)

No evidence of inflammatory cell gliosis has been detected in the damaged areas. The lack of gliosis is of utmost significance, for it indicates that these abnormalities are not a reaction to an infectious or environmental agent occurring immediately before the symptoms appear. Rather, these neuroanatomical faults can be seen as originating in the early, fetal stages of brain development. Further evidence lies in findings of cytoarchitectonic deviancies in cortical cell migration and

neuronal pattern formation. These events take place only in a brain that is less than two years of age. (Kovelmann & Scheibel, 1984)

There is also a current trend in research which indicates that, contrary to previous beliefs, schizophrenic individuals display some degree of pre-morbid symptomatology. As children they are subtly different from their siblings and peers, showing both excesses and deficits in their behaviour. There have been studies of genetically at-risk, adopted children (De Lisi et al., 1991), follow-back studies which have examined scholastic and psychological records of adult patients (Aylward et al., 1984), and longitudinal studies of children with deviant behaviours and personalities (Mednick & Schulsinger, 1968). Some of the longitudinal studies have been in progress for up to thirty years, and most are finding some degree of pre-morbid symptomatology in the pre-schizophrenic child. (Venables, 1987)

SEASONALITY OF BIRTH STUDIES

Psychiatric researchers have long been aware of a strong season of birth effect for schizophrenia. Statistics show that from five to fifteen percent more schizophrenics are born in the late winter and spring. (Hare, 1978; Bradbury and Millar, 1985) Procreational habits and temperature extremes (Watson et al., 1984) have been investigated as

possible reasons for this excess, with no significant relationship detected. It has also been proposed that this seasonality effect is a statistical artifact, caused by the fact that a person born early in the calendar year is chronologically older and has had more time to develop schizophrenic symptoms and be admitted for them (Lewis, 1989). As a result of this criticism, more recent studies have been tabulating admission years from July to June, rather than the usual January to December. These studies still show an excess of late-winter/early-spring births, which weakens the artifactual hypothesis. It is also noteworthy that twenty out of twenty-five Northern Hemisphere studies have detected a seasonality effect, with more births from January to April. Only one out of six Southern Hemisphere studies have detected similar peaks during their winter months. Because of the moderating influence of the Pacific Ocean, Southerns Hemisphere winters tend to be far milder than their northern counterparts. This indicates that there is something about the cold Northern Hemisphere winters that is predisposing the neonate's brain to future schizophrenic symptomatology. Various infectious diseases have been implicated as targets of focus, with influenza being the most popular.

INFLUENZA PANDEMICS AS A POINT OF REFERENCE

The last two hundred years of civilization have been characterized by radical social changes. The industrial revolution, coupled with a global population explosion brought previously rural clusters of humanity together into crowded and often unsanitary urban centers. These swarms of dirty, often malnourished humans provided a fertile breeding ground for low-grade, fast spreading viral infections like influenza. It is noteworthy that the rates of schizophrenia in the general population have increased proportionally to this demographic shift. (Hare, 1988) It is even more telling that a higher proportion of schizophrenics are found in urban areas, especially in the cramped, unhealthy ghetto sections. Whereas this finding was previously attributed to downward socio-economic drifting of mentally unstable people, recent research shows that more schizophrenics are actually being born in dense urban centres, rather than just gravitating towards them. (Lewis et al., 1992; Takei et al., 1992) It is possible that this effect can be partially explained by the increased likelihood of influenza exposure for urban rather than rural dwellers. Flu spreads much more easily in cities.

A popular method of investigating this hypothesis has been to look for correlations between the major influenza epidemics of this century, and subsequent increases in schizophrenic births. (Torrey et al., 1988; Barr et al.,

1990; O'Callaghan, 1991; Cooper, 1992) There is some indication that the second trimester is when the developing brain is most vulnerable, since those fetuses that were in their fourth through sixth months of gestation during these pandemics are most likely to become schizophrenic in adulthood. (Murray et al., 1992)

GENDER AND MARITAL STATUS AS VARIABLES

It is also worth noting that some studies have found that the gender of the at-risk individuals, as well as their marital status can have an impact on their susceptibility. A recent Japanese study found that more female schizophrenics were born after the peak of the 1957 A-2 influenza epidemic than were born in "non-risk" periods. This finding did not apply to males. (Kunugi et al, 1995)

Other researchers have suggested that female schizophrenia is under greater genetic influence than male schizophrenia, and that an environmental factor such as influenza would have more of an impact on male fetuses. (Murray et al, 1992). Overall there appears to be mixed results with respect to gender, with some studies finding statistically significant results for men only, and others finding a link between influenza exposure and schizophrenia only for females. (Cooper, 1992).

Some researchers have suggested that acute and chronic schizophrenia are two distinct subtypes, and that the

marital status of the patient is a good indicator of the severity of illness. Single subjects are more likely to present with the chronic subtype, which is more likely to result from subtle brain damage. Married (including divorced, separated, widowed, and common-law subjects) are more likely to present with symptoms that place them towards the acute end of the spectrum. Some studies have found disparities between single and married schizophrenics, with respect to birth seasonality and disease patterns. This suggests that disease-related factors play a role in process schizophrenia, but not the acute form. (Watson et al, 1984)

Q: WHY THE SECOND TRIMESTER VULNERABILITY?

While the influenza hypothesis is appealing, providing a plausible explanation for both demographic, anatomical, and seasonality evidence, there are some obvious questions that spring to mind. First, why the second trimester vulnerability? What is it about maternal influenza at this point in pregnancy that can have such an impact? One hypothesis is that this is when the blood-brain barrier is still weak; an infectious agent in an older fetus would not be able to cross this barrier, and a first trimester fetus may be more severely affected and end in spontaneous abortion. (Wright et al., 1993) There is considerable neurodevelopmental evidence which indicates that during the second trimester, a process of cell migration and neuronal

pattern formation takes place which is highly vulnerable to any disruptive force. (Roberts, 1991) Cytoarchitectonic abnormalities in schizophrenic brains indicate a disrupted pattern of neuronal migration and disorganization in cortical areas that would have been forming throughout this critical developmental period. (Benes, Davison, and Bird, 1986)

THE MECHANISM OF FETAL DAMAGE

The first route of potential damage is through actual infection of the fetus by the influenza virus (viraemia). Since influenza has been shown numerous times to be incapable of crossing the placenta (O'Callaghan et al., 1991), this explanation is unlikely. Another source of fetal disruption could be hypoxia, fever, electrolytic imbalance, or malnutrition in the mother as a result of her being infected. This is harder to test since it is rarely known for certain whether or not a schizophrenic's mother actually had influenza, or any of the above accompanying symptoms. However, a wide variety of maternal states which are antithetic to the "normal" homeostasis of pregnancy, have been shown to cause subtle or severe teratogenic effects. (Kerwin & Murray, 1992)

New literature in this field suggests a more indirect route for fetal damage: While the virus itself is unable to cross the placenta, maternal antibodies are able to enter

the fetus's system. It has been proposed that these antibodies come into contact with the developing fetal brain and disrupt the migration of cortical cells from the ventricular area, causing neurodevelopmental damage. (Wright et al., 1993) This hypothesis is attractive because it is compatible with schizophrenia's well-known genetic component, which will be discussed next.

THE GENETIC COMPONENT OF SCHIZOPHRENIA

One of the most persistent findings in the search for an etiology of schizophrenia, is that there is a genetic component to the disease. Twin studies, adoption studies, and research into the family pedigree of schizophrenics, all point to some degree of heritability. The question is this; how can schizophrenia persist in the human population with its drastic fertility disadvantage? Eliot Slater suggested thirty years ago that the heritable component is not a schizophrenia gene per se, rather it is a mother's genetic tendency towards elevated immune response; she is more efficient at fighting off deadly diseases (Slater, 1971). This may be a mixed blessing for the mother. She has less chance of succumbing to infections and thus an increased reproductive potential, however, the excess of antibodies she produces are proposed to have a teratogenic effect on her offspring, with a specific tendency towards minor fetal brain damage. While Slater originally thought in terms of

smallpox and bubonic plague, the current focus is on polio, diphtheria, rubella, and especially influenza. Since influenza is more common in the cold winter months, this is when a mother's immune system would be most prone to producing large quantities of antibodies, which would lead to season of birth effects for schizophrenia.

HYPOTHESES

Ho 1A: There will be a peak in schizophrenic births in the five to eight months subsequent to the 1918 influenza epidemic, compared to those same months in control years.

Ho 1B: There will be a peak in schizophrenic births in the five to eight months subsequent to the 1957 influenza epidemic, compared to those same months in control years.

Ho 2A: Average birthrate for schizophrenia will be greater in the four year period following the 1918 influenza epidemic than during the four year pre-epidemic period.

Ho 2B: Average birthrate for schizophrenia will be greater in the four year period following the 1957 influenza epidemic than during the four year pre-epidemic period.

Ho 3: There will be a greater increase for male schizophrenic births than for female schizophrenic births subsequent to each epidemic.

Ho 4: There will be a greater increase for individuals who have never married than for individuals who married at some point in their life (including common-law). This is based on the premise that individuals who never marry are more likely to present with the chronic form of schizophrenia.

RATIONALE

Ho 1A, Ho 2A: Influenza infection during the second trimester of pregnancy will lead to an increased immune response in the mother, which will have teratogenic effect on the fetus, leading to an increased likelihood of adult-onset schizophrenia.

Ho 1B, Ho 2B: Immune response following exposure to influenza, may be elevated for up to two years, thus pregnancies which occur during this extended time frame, may result in an increased risk of schizophrenia in the offspring.

Ho 3: The teratogenic effects of influenza lead to a more chronic form of schizophrenia, which is the sub-type that males are most likely to present with. Also, females are more susceptible to the genetic factor, and less prone to fetal environmental disruptions.

Ho 4: Studies have shown that individuals who never marry are more likely to present with a chronic form of schizophrenia. It is hypothesized that exposure to the influenza virus results in this type of schizophrenia, rather than in the acute subtype.

METHOD

GENERAL PROCEDURE

Sample Selection

The subjects used in the study were individuals who were admitted to the Lakehead Psychiatric Hospital for major mental illness. Data from the hospital card and microfiche files of these patients were collected and analyzed using a variety of measures. The criterion for inclusion in the sample group was a diagnosis of schizophrenia. For subjects with more than one admission, a schizophrenia diagnosis at any time during their psychiatric history qualified that subject for inclusion in the sample group. Two sets of sample subjects were focused on; the subjects born in the time surrounding the 1918 influenza epidemic (189 cases), and the subjects born in the time surrounding the 1957 influenza epidemic (182 cases). Date of birth was the primary variable recorded.

Since the birthplace of the subjects was of importance, this was noted when possible. However, the records of the 1957 patients did not contain any information on place of birth so this variable was not included in the 1957 analyses. Other variables that were examined were; marital status and gender. Marital Status was divided into 6 categories for the 1918 study, and 7 categories for the 1957 study. These categories were condensed and dichotomized to

form 2 groups; single subjects (meaning subjects who never married during their lifetime) and married subjects, (subjects who at some time during their lifetime were married). This category included patients who were classified as married, separated, widowed, divorced, or common-law. The 1918 group had a total of 94 single subjects, and 95 married subjects. The 1957 group had a total of 135 single subjects and 47 married subjects. There were a total of 241 males; 123 in 1957 and 118 in 1918. There were fewer female subjects; 59 in 1957 and 71 in 1918, for a total of 130 females.

For the 1918 Sample Group, 38 subjects were born in Thunder Bay, 39 were born elsewhere in Northwestern Ontario, 42 were born elsewhere in Canada, and 69 were born in Europe or Asia.

Due to the absence of a stable hospital record-keeping format, it was not possible to record the age at first diagnosis for sample or control subjects.

Diagnostic criterion for sample

Patients who were diagnosed with schizophrenia at some point during their L.P.H. history were included in the sample group. The diagnoses differed somewhat between the 1918 and the 1957 birthdate groups. Those born around the time of the 1918 epidemic would have been admitted and diagnosed from the late 1920's onwards, with schizophrenia

admissions for this group falling off in the 1950's. Table 8 in the appendix gives a list of which diagnoses were accepted as meeting the criteria for schizophrenia for the 1918 group. So as to maintain a fairly well-defined sample group, diagnoses that are situated close to affective disorders on the schizo-affective spectrum, were not included in the sample group. Table 9 lists the accepted diagnoses for those born during and around the 1957 epidemic, subjects who were first displaying schizophrenic symptomatology from the early 1970's onwards. Once again, the sample group was defined by a fairly stringent diagnostic criterion, with schizo-affective diagnoses not included in the sample group. This was to ensure that the sample group was categorically separate from the control group.

Control Disorder

The control subjects were matched with respect to date of birth to the sample subjects, however, instead of schizophrenia, they had a diagnosis of depression. Control subjects were selected for each epidemic, and they were pooled from the same records as the sample subjects. There were a total of 80 control subjects for the 1918 epidemic, and 94 control subjects for the 1957 epidemic. Birthplace, Gender, and Marital Status were also noted, although birthplace was not available for the 1957 controls.

In 1918, 33 of the control subjects were born in Thunder Bay, 25 were born elsewhere in Northwestern Ontario, 7 were born in other parts of Canada, and 9 were born in Europe, Asia, or the United States. Birthplace was unknown for 6 of the 1918 control subjects.

52 of the control subjects were single, 12 in the 1918 epidemic group and 40 in the 1957 group. The same dichotomization of marital status was used for the controls as was used for the sample group. There were a total of 74 males; 30 in the 1918 group, and 44 in the 1957 group. In contrast to the sample subjects, there were more female controls than males; 50 in the 1918 group, and 50 in the 1957 group, for a total of 100 females.

Diagnostic criterion for controls

Tables 1 and 2 list the diagnostic criteria that were used for the control subjects from the 1918 group and the 1957 group. As with the sample subjects, diagnoses that did not tend towards schizo-affective disorder on the schizo-affective spectrum were used to define the control group. This was to maintain a strong qualitative difference between control and sample subjects.

Reliability

A check of the reliability of data collection was run by having an independent researcher (a checker) go through the

archival material which was the source of all data. Once he was proficient in identifying both sample subjects and control subjects, using the same selection criteria used by the researcher, the checker went through five percent of the patient files, selecting both sample and control subjects, and making note of their birthplace, gender, marital status, and date of birth.

Inclusion reliability is defined as the percentage of cases chosen which are identical for both data collectors. For the diagnostic group of schizophrenia, inclusion reliability was 96.8 %. For the control group, reliability was 98 %.

Reliability of subject information was also calculated. This is defined as the percentage of information in the 5 separate fields (gender, marital status, etc.) that was agreed upon. For the diagnostic group, 95.7% of the information matched, and for the control group, 99.3% of the information was in agreement.

These reliability ratings were obtained by dividing the total number of agreed diagnoses, or agreed pieces of information, by the total number of cases checked and multiplying by 100 to achieve a percentage.

Historical Research

Records from the Thunder Bay Historical Society, the City Archives, Statistics Canada, and literary sources were used

to pinpoint the course of the epidemics, as well as the influenza virus's maximal impact on the Northwestern Ontario Region. The 1918 epidemic took more time to move across Canada, arriving in major centres like Toronto in September of 1918, and reaching more isolated centres in December. There is far more historical documentation for this epidemic than for the 1957 epidemic, due to its extreme lethality, and high mortality rates. Local Health reports and newspaper accounts pinpoint the epidemic's arrival in Thunder Bay, on Oct. 7, 1918, brought from Montreal by Canadian Car employees. The epidemic peaked on November 9, with seventy-three cases reported on that day, and was subsiding by February of 1919. Figure 1 illustrates the mortality curve of the epidemic as it struck Thunder Bay. Since the time period from October through April was the period of potential exposure to the virus in Thunder Bay, infants born from early 1919 onwards are considered at risk. It is estimated that approximately four thousand of (then) Thunder-Bay's thirty-three thousand residents developed full-blown influenza. The window of potential exposure for subjects born elsewhere in Canada is wider, ranging from late summer of 1918, to late spring of 1919. Subjects born in Europe or Asia may have been exposed as early as March of 1918. Overall, approximately 20% of the Canadian populace caught the virus; a total of 1.6 million people. Of these, between thirty and fifty thousand died. The worldwide death

toll from the epidemic is placed at between twenty and thirty million.

The spread of the 1957 epidemic was dramatically quicker, and less documentation exists. Due to technologies such as jet travel, the window of exposure to influenza during this epidemic was similar on all parts of the globe, with Stats' Canada Health reports pinpointing its impact in September, October, November, and December of 1957. For this reason, birthplace of the subjects born in this time period was of no great significance, and the analysis was not hampered by its absence.

Normalization of Data

It was important to control for the effects of population fluctuations on rates of birth for both sample and control subjects. These fluctuations would have resulted from immigration, emigration, changes in reproductive rates, or historical events such as the final stages of World War I in the case of the 1918 subject group. To achieve this, the data were normalized using demographic information obtained from Statistics Canada publications and Thunder Bay archival material. Statistics Canada provided population stats for Canada from 1914 to 1922, and 1953 to 1963. The Thunder Bay Archives provided population statistics for the cities of Port Arthur and Fort William (collectively known as Thunder Bay) for the corresponding time periods. Reliable

population statistics could not be obtained for Europe, Asia, and the United States, therefore the data for this segment of the sample group were not normalized. Normalized data are presented in the form of births /100,000. The overall population trend for the 1914-1922 and 1953-1963 time periods was one of slight general increase with some degree of fluctuation.

Power Analysis

A power analysis was done on the control and sample groups from 1918 and 1957. This was to determine if our N allowed for a statistically valid analysis of the data. The results, as recorded in table 3, show that our subject pools were large enough to detect a medium or large-sized effect, but not a small effect.

DATA ANALYSIS

Chi Squared Analyses

Using non-normalized, raw data, chi squared analyses were performed on the sample group, as well as the controls. The time periods of interest were divided into a yearly format, and a tri-monthly format, with each year being divided into four equal segments of three months each.

As well, the two separate epidemics were combined in such a way that the peaks of each epidemic were overlayed on each other. This approximately doubled the number of subjects,

creating a separate, artificial study group labelled the "combined" group. Analyses were performed on the combined group to elucidate the effect of gender and marital status, since N became too small when isolating these variables in the separate epidemic groups. Normalized data were not used since these groups included foreign-born subjects.

Replication of Japanese Study

A recent Japanese Study examined the correlation between the 1957 influenza-A and influenza-B epidemics and subsequent risk for schizophrenia. (Kunugi et al, 1995) Their analysis was simple and yielded significant elevations of schizophrenic births following the epidemics. They also found that a greater number of female schizophrenics were born during the risk exposure months following the epidemic than in corresponding months of the four years before and after the epidemic. For comparison purposes, we replicated their methodology. Using our 1918 and 1957 sample and control groups, and including subjects born worldwide for the 1918 group, we compared schizophrenic births from six to twelve months after the worldwide epidemic peak (April - September, 1919 and April - September, 1958) to the mean number of schizophrenic births in corresponding months of the 2 years before and after the influenza epidemic peak (April - September, 1917, 1918, 1920, & 1921 and April - September, 1956, 1957, 1959, & 1960).

Chi-squares were applied to compare the observed rates of schizophrenic and depressive births in the risk months, with the mean number of schizophrenic and depressive births in the corresponding control months.

RESULTS

CHI-SQUARED ANALYSIS OF THE 1918 EPIDEMIC

When the sample and control subjects are classified according to year of birth and chi squared analyses are applied to test for significant deviations from expected numbers, none of the chi squares reach significance at $p<0.05$. The incidence of schizophrenia appears to be unaffected by the influenza epidemic of 1918. (See Tables 4 & 5)

To test the possibility that the impact of the epidemic on schizophrenic births would be cumulative and seen over several years because of high post-infection maternal antibodies, the sample was divided into two halves; pre and post epidemic. Pre epidemic includes subjects born from 1915 through 1918. Post epidemic births are from 1919 through 1922. The chi square failed to reach significance at $p<0.05$ for any of the four birthplace categories. (Table 4)

Chi squared analyses were not applied to the trimester data, because the expected value in each cell was frequently less than five, making analysis difficult.

Even when examining only those subjects born in and around Thunder Bay, where we could accurately pinpoint the time of maximal risk for foetal exposure, the result does not support the hypothesis of increased schizophrenic births resulting from the epidemic. (Table 4)

VISUAL ANALYSIS OF BIRTHRATE TRENDS

Birthplace: Canada (Figure 5)

The sample and control groups were classified by date of birth into 3-month segments to maximize the number of data points. Normalized data offer the clearest picture by eliminating variability due to population fluctuations, and are used whenever possible.

As shown in Figure 5, the schizophrenia birthrate fluctuated noticeably. Any trends that may be present subsequent to the Fall of 1918, could easily be overshadowed by seemingly random birthrate fluctuations. Schizophrenic births peaked in the second and fourth quarters of 1917, (with 8.69 and 7.45 births/100,000 respectively). There was another peak in the summer of 1922, and a peak six months after the epidemic with 7.20 births/100,000.

The birthrate for the control group of depressed patients also fluctuated, but with generally less variation. A

visual inspection of Figure 5 reveals a peak in depressive births in the spring of 1918, with 4.92 births/100,000.

Birthplace: Thunder Bay (Fig. 6)

Figure 6 illustrates the birth trends for schizophrenics and controls born in Thunder Bay and Northwestern Ontario in tri-monthly segments, using normalized data.

The epidemic peaked in November of 1918, therefore viral infection during the second trimester of pregnancy would result in increased schizophrenic births during the late spring of 1919. No such peak occurred, which does not add support to the direct viral infection hypothesis.

The birthrate for depression controls peaked in the spring of 1918.

Birthplace: Canada, Europe, Asia, U.S.A. (Fig. 7)

When subjects born in Europe and other parts of the world were added to the Canadian data, sample size increases but normalization of the data could not be accomplished because population trends were unknown for other countries. As shown in Figure 7, the maximum number of schizophrenic births occurred in the winter of 1919, approximately six months after the epidemic. This is consistent with hypothesis 1A. There were lesser peaks in the summers of 1917 and 1922. The control group displayed minor peaks in the spring of 1918 and the winter of 1921, but overall, the

rate of birth for control subjects fluctuated much less over time and did not peak following the epidemic.

JAPANESE STUDY REPLICATION (Table 6)

There were 19 subjects born during the 6 risk-exposure months directly following the 1918 epidemic. A total of 45 subjects were born in the corresponding months of the 4 comparison years. Table 6 shows the number of schizophrenics born during the risk-exposure period following the epidemic, and the mean number born during the corresponding months of 1917, 1918, 1920, and 1921. Gender and marital status were analyzed separately. A Chi Square test revealed significantly fewer schizophrenic births in control years than in the at-risk period for the sample group as a whole. ($X2 = 5.34$, $df=1$, $p<0.05$)

A significantly larger number of male schizophrenics were born during the risk exposure months of 1919 ($X2=7.79$, $df=1$, $p<0.05$). It should be noted that this test was also significant at $p<0.01$. The number of female schizophrenics born during the risk-exposure period was not significantly higher than the number born in the comparison years.

A significantly larger number of single subjects were born in the risk exposure months. ($X2=4.17$, $df=1$, $p<0.05$). Births of married schizophrenics however, were not significantly elevated during the risk-exposure months.

There were no significant findings for the control subject births in 1919 (Table 7). For the 1958 at-risk period, there were no significant elevations for sample or control subjects, using the Japanese methodology (Tables 8 & 9).

Since our Japanese replication methodology frequently involved chi squared tables with less than five subjects in one or more of the cells, it was necessary to do a Fisher Exact Probability Test in these instances. As illustrated in Table 10, the chance of achieving the same distribution of data (as occurred in our tables) by chance alone, was always quite high. This calls into question the validity of the chi square probabilities we obtained.

ANALYSIS OF THE 1957 EPIDEMIC (TABLE 5)

For the 1957 data, place of birth was not known for the sample or control subjects, which limited the analysis. Whereas the 1918 subjects were classed according to place of birth, this was not possible with the 1957 subjects. Also, reliable global population figures do not exist on a yearly basis for this time period so 1957 data are not normalized.

Chi squared analysis performed on cases grouped according to year of birth was not significant. As shown in table 2, dichotomized pre and post epidemic groups (1953-1957 vs. 1958-1962) also yielded non-significant results under chi squared analysis.

Visual analysis of the 1957 data (figure 8), revealed no yearly peaks following the epidemic for either schizophrenia of depression. For the trimester data, figure 9 revealed peaks of schizophrenic births in 1954, 1956, as well as lesser peaks in late 1958 and early 1959.

For depression, a small peak occurred in the fall of 1957.

ANALYSIS OF COMBINED DATA (TABLE 11)

In this analysis, the 1918 and 1957 data are combined into one file, with a total N of 344 experimental subjects and 141 controls. Place of birth was no longer a variable for this file, since only the 1914-1922 subject files contained this information. Examination of table 3 reveals that none of the chi squared analyses were significant. Year A was defined as the combination of 1915 and 1954, year D the combination of the two epidemic years, so on up to year H, which was 1922 and 1961 combined. We would expect to see a peak in schizophrenic births during the combined years of 1919 and 1958 (year "E"). No effect of epidemic was detected in this analysis and visual inspection of Figure 10 confirms no peaks in either experimental or control group births following the epidemic.

GENDER AND MARITAL STATUS (Table 11)

Gender and Marital Status were available for both epidemic groups and are analyzed subsequently. There were a total of 322 male subjects and 163 female subjects. When the combined group of sample subjects (N=344) was analyzed with respect to gender (see table 3), chi squared analysis of rates of schizophrenia by year of birth was not significant for either males or females.

For control subjects diagnosed with depression (N=141), the same analyses failed to reach significance for males or females by year of birth.

The combined group of subjects was divided into subjects who never married during their lifetime (single), and subjects who were, at some point, married or living common-law (married). There were a total of 234 single subjects and 251 married subjects. Chi squared analysis of marital status by year of birth was not significant. ($p < 0.146$ for the sample group and $p<0.388$ for the control group).

Visual analysis of Fig. 14 reveals a trend of higher rates of depression for married subjects born following the influenza epidemics. No such trend is visible for schizophrenia. (figure 13)

DISCUSSION

LIMITATIONS OF THE STUDY

The most prominent difficulty with this study, was the variation in birthrate over time for the schizophrenia group. This fluctuation was not nearly as obvious for the control group, however, this may have been due in part to a floor effect, with the lower birthrate numbers limiting downward fluctuation of the control disorder. Identifying a control group with more equivalent incidence rates to the experimental group may produce a better comparison in future studies. Unfortunately, it is difficult to find a disorder not linked to schizophrenia which has similar incidence or ascertainment rates. The noise inherent in the data can be partially controlled by:

(1.) Normalizing the data for demographic shifts in population. (However, one can not control for or discern all of the potentially teratogenic environmental factors in existence seven decades ago.)

(2.) Maximizing N by combining data points and;

(3.) Spectral analysis, a specific technique to filter out noise due to random background events and identify key characteristics of the "signal", the true epidemic-related peaks in schizophrenic births. Spectral analysis was attempted for this study, however it was not applicable to these data due to an inability to effectively construct a

noise-filter, since there was no evidence of regularity in the fluctuation of birthrates for 1918 or 1957.

There are some noteworthy peaks in schizophrenic births at points other than post-epidemic, especially in the 1918 data. These peaks may be linked to other factors such as climate changes, increased stress levels due to WW1, or viruses other than influenza. The greater fluctuation in the schizophrenia birthrates may be indicative of greater environmental sensitivity of the foetus to teratogenic effects resulting in later-onset schizophrenia rather than depression.

Another difficulty was determining whether or not the 1918 and 1957 data were comparable. It was difficult to compare the 1918 data with the 1957 data, due to;

(1.) The difference in record keeping methods of the two eras. - Having access to information about place of birth for the 1957 subjects would have made direct comparisons easier. It would have also made normalization of the data more accurate. Since the schizophrenic patients born outside of Canada were more likely to be born directly following the 1918 epidemic, it would have been beneficial to analyze corresponding birthplace effects for the 1957 sample group.

(2.) Diagnostic trends or propensities may differ significantly between the two time periods studied. Over the course of this century, there has been a gradual drift

away from a narrow Kraeplinian diagnostic style, towards a broader spectrum diagnosis such as the Bleulerian style.

Another difficulty was the size of the sample and control groups. Although the numbers appear large at first glance, with N=269 for the 1918 group and N= 276 for the 1957 group, further analysis at the tri-monthly level produced groups with numbers as low as three and four, sometimes as low as zero subjects per time-frame. This made chi squared analysis impossible at this level, and all other analytic tools lost significant power. Future studies should expand the sample and control groups, in order to allow powerful analysis at the trimester level. Spectral analysis works best when the researcher divides the data into as many separate time frames as possible and only very large numbers will permit this.

When performing analyses within a tri-monthly time-frame, the possibility exists that we have made a type 2 error due to lack of power. We may have failed to detect a statistically significant effect when in fact it was there. The complementary argument to this is that if it can not be seen visually then the effect size is not large and the resulting variance accounted for could only be trivial.

While diagnostic criteria were well defined for both eras, there are qualitative differences between a 1918 schizophrenia or depression diagnosis and a 1957 diagnosis. Also, there is the error resulting from different

clinicians' idiosyncratic diagnostic styles. Since subjects in this study were diagnosed by a variety of different practitioners, diagnostic inconsistencies are unavoidable. To control for this, future researchers should diagnose sample and control patients themselves, using a strict template of symptoms and behaviours, with information coming from the files of patients. This would be much more time-consuming however, and would still be subject to a certain degree of diagnostic error due to the incomplete or selective recording of information in the clinical record.

Another complicating factor involves the control years following the epidemics. If damage occurs as a result of maternal influenza antibodies, rather than through direct infection by the virus itself, then theoretically, subjects born two, three, even up to four years after an epidemic may still be exposed to these antibodies, and may still evidence increased risk for schizophrenia. There is some indication that rates remain elevated past 1919 into 1922. There is no way of accurately controlling for subjects' time of exposure to the virus.

A major drawback is that we can't know if our subjects' mothers were actually infected with influenza. All we have to work with is the increased likelihood of maternal infection in times of epidemic resulting in an increased risk of schizophrenia in the offspring. There are other diseases that accompany influenza pandemics and prey on

already weakened immune systems. Measles, mumps, polio, diphtheria, rubella, and varicella-zoster (chicken pox) have all been studied as possible infectious agents for fetal brain damage and later schizophrenia, with significant results for measles, polio, and varicella-zoster. (Torrey et al., 1988)

There are several questions that need to be addressed, both in this study, and in future studies which examine the viral hypothesis:

If influenza is a factor, then how important is it? How does it combine with heritable factors to produce adult-onset schizophrenia? What is the actual mechanism of damage? Also, why is there a delay in the onset of florid symptoms until the late teens or early twenties? What happens in the life of an individual to bring the disease out of its relatively dormant state, and what, if anything, can be done to prevent onset in people who are at risk?

DISCUSSION OF RESULTS

The 1918 Epidemic: This influenza epidemic did not appear to lead to an increased rate of schizophrenia in the offspring of mothers who would have been at maximal risk for exposure to the virus. It is interesting, however, that while there was no peak in schizophrenic births in Thunder Bay, Northwestern Ontario, or in the rest of Canada, when

Foreign-born subjects are included (mostly immigrants from Europe), a noteworthy peak during the post-epidemic "at-risk" period is visible in the graph.

This finding could be interpreted in two different ways; (1) as a real effect, or (2) as a random fluctuation in schizophrenic births. If this peak, is, in fact due to the 1918 influenza epidemic, we must ask ourselves why it occurs in Europe only, and not in Canada where the flu was equally rampant. The virus may have mutated by the time it spread through Canada, Canadian mothers may have been more resistant, or may have developed a different, less damaging antibody response. European mothers, already weakened by wartime malnutrition, and subjected to enormous post-war stress, may have been more vulnerable to the effects of the virus. This is all speculation based on hindsight however, and adds no real clarification to the questions asked at the onset of this study.

Whatever the reason for the post-epidemic European peak, the absence of a similar peak for Canadian-born subjects significantly weakens the viral hypothesis.

The 1957 Epidemic: The complete absence of a post-influenza peak in schizophrenic births following the 1957 epidemic further weakens the viral hypothesis. If influenza is a significant risk factor, then **any** large epidemic should be followed by an elevation in schizophrenic births. Chi

squared analyses revealed no such trend, and visual inspection of the graphs shows no evidence of an elevation during the at-risk period. Since the epidemic spread more quickly during the late 1950's, the at-risk period would have been more or less the same in all geographic locations. This would have increased the likelihood of seeing a peak in the six months post-epidemic, as opposed to after the slower-spreading 1918 epidemic, when the window of exposure would have varied according to locale. Therefore, the absence of any statistical or visual evidence strongly bolsters the null hypothesis.

1918 and 1957 Combined: The combined sample group was twice as large as the individual epidemic groups. This added statistical power was to have helped eliminate noise and random fluctuations in the data. Statistical and Visual analysis shows no peak during the six-month at-risk period. This is a serious blow to the viral hypothesis, since the formation of a combined sample group should have magnified any small but significant effect that may have been present but undetectable in the 1918 and 1957 groups alone.

Gender and Marital Status: The absence of an effect for gender or marital status, is inconsistent with other studies in this area. The graphs do not reveal any peaks for male or female, single or married schizophrenic births following

the at-risk period. It is conceivable that the effect was only present for male subjects, or for single subjects, and by examining the sample group as a whole we had previously masked this effect. This may have contributed to the lack of any significant findings for the previous sections. However, the absence of significant findings for gender or marital status when examined separately, rules out the possibility of a masked but significant viral effect. Since the sample groups we worked with for gender and marital status analyses were a combination of the 1918 and 1957 epidemics, any viral effect should have been enhanced (for reasons explained above). The absence of an effect for gender or marital status, does not add support for hypotheses 3 or 4, and weakens the viral hypothesis as a whole.

The Japanese Methodology: In light of the previous findings, none of which add support to the influenza-schizophrenia link (with the exception of the foreign births anomaly), it is initially puzzling to find significant results when we turn to a different analytical methodology. There were statistically significant elevations in schizophrenia for the sample group as a whole, for male schizophrenics but not females, and for single but not married subjects.

Results were significant at the $p<0.05$ level for the sample group as a whole, and for single subjects. For male schizophrenics, the elevation in birthrate following the at-risk period was significant at $p<0.01$. This was statistically impressive at first glance. Why then, did this supposedly strong effect disappear when alternate methodologies were used? The Fisher Exact Probability results must be considered in this case. The subject groups were small in all of the Japanese methodology chi squared tests, and the probability of achieving similar results by chance was always large. It is possible that the 1918 result is a chance phenomenon as well. This clarifies the need for a universally accepted analytic method, and casts doubt on analytic tools currently used by other researchers.

CONCLUSIONS

PRIMARY CONCLUSIONS

In summary, the findings of this project do not lend support to the viral hypothesis of schizophrenia. Neither the 1918, nor the 1957 influenza epidemics were followed by significant elevations in schizophrenic births. There is no strong evidence that maternal influenza exposure in Northwestern Ontario resulted in an increased risk of schizophrenia for the offspring in either time period. If influenza was, in fact, a teratogenic factor, then its effects were minor and undetected by the statistical

procedures we employed.

There is some limited evidence for an increase in schizophrenic births worldwide, following the 1918 epidemic, but not the 1957 epidemic. The elevation is a result of the inclusion of European-born sample subjects, and the limitations of this finding must be noted. First, the socio-economic climate in Europe in 1918 and 1919 was such that a number of other factors may have added stress to a pregnant woman's system. Second, the population growth rate is not known for Europe during the 1914-1922 time period, so the peak in 1919 may simply be part of a larger general birthrate peak. Third, if influenza is proposed as a teratogenic factor, then any effect should be noted in all populations, not just European-born schizophrenics. A noteworthy effect would manifest peaks in all of the Canadian-born subjects as well.

A third conclusion is that there is strong overall variability in rates of births for schizophrenics, and less variability in rates of birth for the control group. This created difficulties in interpreting the data, and it is something that future researchers will need to anticipate and hopefully resolve.

METHODOLOGICAL CONCLUSIONS

There are a number of observations and insights with respect to the methodology of this project and others like it. These are important for the future of viral-hypothesis research, and are perhaps as important as the actual scientific findings.

Paralleling the variability in schizophrenic birthrates themselves is extreme diversity in how the data are analyzed from study to study. While an effect may appear strong in one study, it can easily be made to disappear by simply switching to a different method of analysis. This was aptly demonstrated when we replicated the Japanese study. Apparantly strong, robust findings that were significant at $p<0.01$ dissolved when a different analytic method was used. This violates the concept of reliability, and we cannot conclude that a correlation is actually there. A truly robust finding would emerge regardless of analytic method. This complaint has been echoed by the researcher T.J. Crow, who initially concluded that his research supported the viral hypothesis, but upon re-evaluation, using different statistical analyses, decided that the effect was an artifact (Crow, 1990).

While my research began with a hypothesis-testing approach, the absence of significant peaks following both epidemics led me to proceed with a more exploratory style of research. This is why I replicated the Japanese study.

After a re-evaluation of my choice of statistical tools, I concluded that my approach may have been too conservative, and the way I used the chi-square tests may have been insensitive to possible effects of the epidemic. After replicating the Japanese study, and analyzing the results, I suspected that their approach was too liberal. They applied the chi-square test in a way that may have falsely magnified insignificant findings, distorting the data and producing exaggerated peaks in the expected direction. It would appear that an appropriate statistical approach lies somewhere between the two, or perhaps with a different statistical device altogether. A test that takes into account more of the variance might be considered for future studies, for example, a more parametric test such as a t-test or a one-way anova.

One of the main difficulties I encountered in my research, stemmed from the confusing array of methodologies available in the field. There is no clear approach to this research, and comparison of the different methods used by researchers is hampered by these stylistic idiosyncracies.

While there were some significant findings in this study, they are overshadowed by the lack of consistency of findings, both within this project and among other similar projects. Rather than focus on the findings that supported the viral hypothesis, I chose to focus on the lack of methodological consistency that weakens any supporting

evidence that may have emerged. It is of utmost importance to highlight the methodological disarray that permeates this field. Therefore, a further conclusion is that common standards for methodological rigour need to be developed for future projects investigating the viral hypothesis of schizophrenia. This is a necessary first step, which must precede any further research efforts.

In the process of this project, I collaborated with an engineer, who orchestrated the spectral analysis segment of this project, as well as an economist, who explained the logic of cause and effect statistics and trends across time. I also met with a statistician, numerous psychologists and psychiatrists in an attempt to set up a rigid sample and control group. Other medical specialists helped to clarify the importance of teratogenesis, embryology, immunology, virology, epidemiology, genetics, cytoarchitectonics, and the history of medicine. The staff at the Thunder Bay Archives helped with details of the two influenza epidemics, and also provided much information on the probable impact of these epidemics. Without the input of this knowledgeable group, this research would have been impossible. Future studies might consider a team or a "think-tank" approach, as this is a field that clearly benefits from having people with diverse academic backgrounds working on a single problem.

Overall, what contribution did this research make to the viral-hypothesis field, the field of psychology, and society in general?

First and foremost, we failed to demonstrate an effect, that is, we failed to reject the null hypothesis. This can be interpreted as evidence against the idea that maternal influenza infection causes schizophrenia, or it can be taken as evidence that a proper and rigorous methodology is not yet in place.

T.J. Crow opposes the idea that influenza and schizophrenia are linked. He believes that "viral theories are flawed because they provide no explanation for the ubiquitous and approximately constant occurrence of the illness." He also stresses that viral theories are difficult to refute (Crow and Done, 1992). Since we can't ever know if mother was infected, we will never be able to make a strong case for causal attribution. Because researchers in this field are dealing with probabilities, retrospective reasoning, and error-prone historical data, there may never be strong support and general agreement over the viral hypothesis, and a hypothesis that cannot be refuted, does not make for good science.

Another contribution, is that this study failed to replicate the findings of other studies, despite well-designed methodology, including a control diagnosis.

This study has numerous obvious limitations, a variety of confounding variables, as well as the many unknown factors that could distort the results. Despite these drawbacks, it is an exciting area of research that is attracting a growing number of projects. Findings of a significant correlation, and analyses which fail to detect a significant effect can both contribute to our understanding of schizophrenia and its etiology.

REFERENCES

Aylward E, Walker E, Bettes B. (1984) Intelligence in schizophrenia. Schizophrenia Bulletin, 10, 430-459.

Barr CE, Mednick SA, Munk Jorgensen P. (1990) Exposure to influenza Epidemics During Gestation and Adult Schizophrenia. Archives of General Psychiatry, 47, 869-874.

Benes FM, Davison J, Bird ED. (1986) Quantitative cyto-architectural studies of the cerebral cortex in schizophrenics. Archives of General Psychiatry, 43, 31-35.

Bradbury TN, Miller GA. (1985) Season of birth in schizophrenia: A review of evidence, methodology, and etiology. Psychology Bulletin, 98:569-594.

Bruton CJ, Crow TJ, Frith CD, Johnstone EC, Owens DG, Roberts, GW. (1990) Schizophrenia and the brain. Psychological Medicine, 20:285-304.

Cooper SJ. (1992) Schizophrenia after Prenatal Exposure to 1957 A2 Influenza Epidemic. British Journal of Psychiatry, 161: 394-396.

Crow TJ. (1990) The continuum of psychosis and its genetic origins. British Journal of Psychiatry, 156:788-797.

Crow TJ. (1991) A single Locus for psychosis and intelligence in the exchange region of the sex chromosomes? Ethical Issues of Molecular genetics in Psychiatry, Spring-Verlag Berlin Heidelberg.

Crow TJ, Done DJ. (1992) Prenatal exposure to Influenza does not cause schizophrenia. British Journal of Psychiatry, 161:390-393.

De Lisi L, Boccio AM, Riordan H, Hoff AL, Dorfman A, McLelland J. (1991) Familial thyroid disease and delayed language development in schizophrenia. Psychiatry Research, 38:39-50.

Falkai P, Bogerts B, Roberts GW. (1988) Measurement of the alpha-cell-migration in the entorhinal region: A marker for the developmental disturbances in schizophrenia? Schizophrenia Research, 1:157-158.

Faustman WO, Bono MA, Moses JR, Csernansky JG. (1992) Season of birth and neuropsychological impairment in schizophrenia. The Journal of Nervous and Mental Disease, 180(10):644-648.

Hare EH. (1978) Variations in the seasonal distribution of births of psychotic patients in England and Wales. British Journal of Psychiatry, 132:155-158.

Hare EH. (1988) Temporal factors and trends, including birth seasonality and the viral hypothesis. In H.A. Nasrallah (Ed.), Handbook of Schizophrenia, 3:345-377.

Huxley J, Mayr E, Osmond H, Hoffer A. (1964) Schizophrenia as a genetic morphism. Nature 204, No.4955:220-221.

Jakob H, Beckmann H. (1986): Prenatal developmental disturbances in the limbic allocortex in schizophrenics. Journal of Neurological Transcripts, 65:303-326.

Kendell RE, Kemp IW. (1989) Maternal influenza in the etiology of schizophrenia. Archives of General Psychiatry, 46:878-882.

Kerwin R, Murray RM. (1992) A developmental perspective on the pathology and neurochemistry of the temporal lobe in schizophrenia. Schizophrenia Research, 7:1-12.

Knight J. (1991) Correspondence: Schizophrenia and influenza. The Lancet, 338:390.

Kovelman JA, Scheibel AB. (1984) A neurohistological correlate of schizophrenia. Biological Psychiatry, 19:1601-1621.

Kunugi H, Shinichiro N, Takei, N (1995) Schizophrenia Following in Utero Exposure to the 1957 Influenza Epidemics in Japan. American Journal of Psychiatry, 152:450-452.

Lewis MS, Griffin TA. (1981) An explanation for the season of birth effect in schizophrenia and certain other diseases. Psychology Bulletin, 89:589-596.

Lewis MS. (1989) Age incidence and schizophrenia: Part 1. The season of birth controversy. Schizophrenia Bulletin, 15(1):59-72.

Lewis MS. (1989) Age incidence and schizophrenia: Part 2. Beyond age incidence. Schizophrenia Bulletin, 15(1):75-80.

Lewis G, David A, Allgudandlt G. (1992) City birth and schizophrenia. The Lancet, 340:137-140.

Livingson R, Balkozar S. (1993) Season of birth and Neurodevelopmental disorders: Summer birth is associated with dyslexia. Journal of the American Academy of Child and Adolescent Psychiatry, 32(3):612-616.

Maurizi CP. (1984) Influenza and schizophrenia: a possible connection with the substantia nigra. Medical Hypotheses, 15:163-167.

Maurizi CP. (1985) Why was the 1918 influenza pandemic so lethal? The possible role of a neurovirulent neuraminidase. Medical Hypotheses, 16:1-5.

Mednick SA, Schulsinger F. (1978) some premorbid characteristics related to breakdown in children with schizophrenic mothers.

Mednick SA, Machon RA, Huttunen MO. (1988) Adult schizophrenia following prenatal exposure to an influenza epidemic. Archives of General Psychiatry, 45:189-192.

Mednick SA. (1990) Correspondence: Influenza and schizophrenia: Helsinki vs Edinburgh. Archives of General Psychiatry, 47:875.

Mednick SA, Machon, RA, Huttunen MO. (1990) Correspondence: An update on the Helsinki Influenza project. Archives of General Psychiatry, 47:292.

Murray RM, Jones P, O'Callaghan E, Takei N, Sham P. (1992) Genes, viruses and neurodevelopmental schizophrenia. Journal of Psychiatric Results, 26(4):225-235.

O'Callaghan E, Sham P, Takei N, Glover G, Murray RM. (1991) Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic. The Lancet, 337:1248-1250.

Pakkenberg B. (1987) Post-mortem study of chronic schizophrenic brains. British Journal of Psychiatry, 151:744-752.

Pulver AE, Kund-Lee, Y, Wolyniec PS. (1992) Season of birth of siblings of schizophrenic patients. British Journal of Psychiatry, 160:71-75.

Roberts GW. (1991) Schizophrenia: A neuropathological perspective. British Journal of Psychiatry, 158:8-17.

Sham PC, O'Callaghan E, Takei N, Murray GK, Hare EH, Murray RM. (1992) Schizophrenia following pre-natal exposure to influenza epidemics between 1939 and 1960. British Journal of Psychiatry, 160:461-466.

Sham PC, Takei N, Murray RM. (1992) Correspondence: Schizophrenia following pre-natal exposure to influenza epidemics between 1939 and 1960. British Journal of Psychiatry, 161:712-714.

Slater E & Cowie V. (1971) The genetics of mental disorders. London: Oxford University Press.

Takei N, O'Callaghan E, Sham P, Glover G, Murray RM. (1992) Winter birth excess in schizophrenia. Schizophrenia Research, 6:102.

Torrey EF, Rawlings R, Waldman IN. (1988) Schizophrenic births and viral diseases in two states. Schizophrenia Research, 1:73-77.

Torrey EF. (1991) A Viral-Anatomical Explanation of Schizophrenia. Schizophrenia Bulletin, 17(1):15-18.

Venables P. (1987) The Emanuel Miller Memorial Lecture, Childhood markers for adult disorders. Journal of Child Psychology and Psychiatry, 30(3): 347-364.

Watson CG, Kucala T, Angulski G, Brunn C. (1982) Season of Birth and Schizophrenia: A response to the Lewis and Griffin critique. Journal of Abnormal Psychology, 91:120-125.

Watson CG, Kucala T, Tilleskjor C, Jacobs L. (1984) Schizophrenic birth seasonality in relation to the incidence of infectious diseases and temperature extremes. Archives of General Psychiatry, 41:85-90.

Wright P, Gill M, Murray RM. (1993) Schizophrenia: Genetics and the maternal immune response to viral infection. American Journal of Medical Genetics (Neuropsychiatric Genetics), 48:40-46.

APPENDIX

TABLES 1-11

FIGURES 1-22

Table 1

Diagnostic Criterion for 1918 Subjects	ICD-Code
<u>Sample Group</u>	
Schizophrenia; catatonic type	300.2
Schizophrenia; paranoid type	300.3
Acute Schizophrenic Reaction	300.4
Schizophrenia; other and unspecified	300.7
<u>Control Group</u>	
Depression	311.0
Neurotic Depression	301.1

Table 2

Diagnostic Criteria for 1957 Subjects	ICD-Code
Sample Group	
Schizophrenia; Hebephrenic type	295.1
Schizophrenia; Catatonic type	295.2
Schizophrenia; Paranoid type	295.3
Schizophrenia; Acute Schizophrenic Episode	295.4
Schizophrenia; Borderline or Latent	295.5
Schizophrenia; Residual	295.6
Schizophrenia; Unspecified	295.9
Not Included	
Schizophrenia; Schizo-Affective type	295.8
Schizophrenia; Through Prolonged Drug Use	295.9
Control Group	
Depression	311
Neurotic Depression	300.4

Table 3

Power Analysis

Chi-Squared Results, 1918 & 1957

1918 Group, Birthplace=N.W.Ontario (N=135)

small effect	p=15%
medium effect	p=95%
large effect	p=100% (approx.)

1918 Group, Birthplace=Canada (N=184)

small effect	p=22%
medium effect	p=97%
large effect	p=100% (approx.)

1918 Group, Birthplace=Worldwide (N=269)

small effect	p=35%
medium effect	p=100% (approx.)
large effect	p=100% (approx.)

1957 Group (N=276)

small effect	p=36%
medium effect	p=100% (approx.)
large effect	p=100% (approx.)

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* p = the probability of detecting an effect, given N.

small effect:	1% of variance explained.
medium effect:	6% of variance explained.
large effect:	15% of variance explained.

Table 4

Chi Squared Results - 1918

	Chi Sq.	d.f.	Sig.
DIAG X YEAR OF BIRTH			
1. Northwestern Ontario	4.064	7	0.557
2. Canada	6.817	7	0.851
3. All	7.708	7	0.463
DIAG X PRE/POST EPIDEMIC			
1. Northwestern Ontario	0.008	1	0.996
2. Canada	0.302	1	0.860
3. All	0.163	1	0.922

Table 5

Chi Squared Results - 1957

	Chi Sq.	d.f.	Sig.
1. Diag x Year of Birth	8.718	9	0.559
2. Diag x Pre/Post-Epidemic yrbirth.	3.136	1	0.209

Table 6

Chi-Squared Results: 1918, Sample Group

Japanese Replication Methodology

	Schizophrenics Born During:		Analysis	
	N:Risk-Exposure Months (1919)	Mean N:Comp. Yrs (1917-1918 & 1920-1921)	X2	P
TOTAL	**19**	**11.25**	**5.34**	**+**
Males	14	6.75	7.79	*
Females	5	4.5	0.06	n.s.
Single	11	6.0	4.17	+
Married	8	5.25	1.44	n.s.

* Significant at $p<0.01$
\+ Significant at $p<0.05$

Table 7

Chi-Squared Results: 1918, Control Group

Japanese Replication Methodology

	Depressed Pts Born During:		Analysis	
	N:Risk Exposure Months (1919)	Mean N:Comp. Yrs (1917-1918 & 1920-1921)	X2	P
Total	**4**	**5.25**	**0.3**	**n.s.**
Males	1	1.75	0.32	n.s.
Females	3	3.50	0.07	n.s.
Single	0	0.50	0.5	n.s.
Married	4	4.75	0.19	n.s.

Table 8

Chi-Squared Results: 1957, Sample Group

Japanese Replication Methodology

	Schizophrenics Born During:		Analysis	
	N:Risk-Exposure Months (1958)	Mean N:Comp. Yrs (1956-1957 & 1959-1960)	X2	P
Total	**8**	**10**	**0.40**	**n.s.**
Males	7	7.5	0.03	n.s.
Females	1	2.5	1.13	n.s.
Single	5	7.5	0.83	n.s.
Married	3	2.5	0.10	n.s.

Table 9

Chi-Squared Results: 1957, Control Group

Japanese Replication Methodology

Depressed Patients Born During			Analysis	
	N:Risk-Exposure Months (1958)	Mean N:Comp. Yrs (1956-1957 & 1959-1960)	X2	P
Total	**5**	**5.75**	**0.09**	**n.s.**
Males	3	3.00	0.00	n.s.
Females	2	2.75	0.20	n.s.
Single	2	3.00	0.33	n.s.
Married	3	2.75	0.02	n.s.

Table 10

Fisher Exact Probability Tests: Japanese Methodology

1918

Sample Group; gender variable:	p=0.21
Sample Group; marital status variable:	p=0.29
Control Group; gender variable:	p=0.57
Control Group; marital status variable:	p=0.99

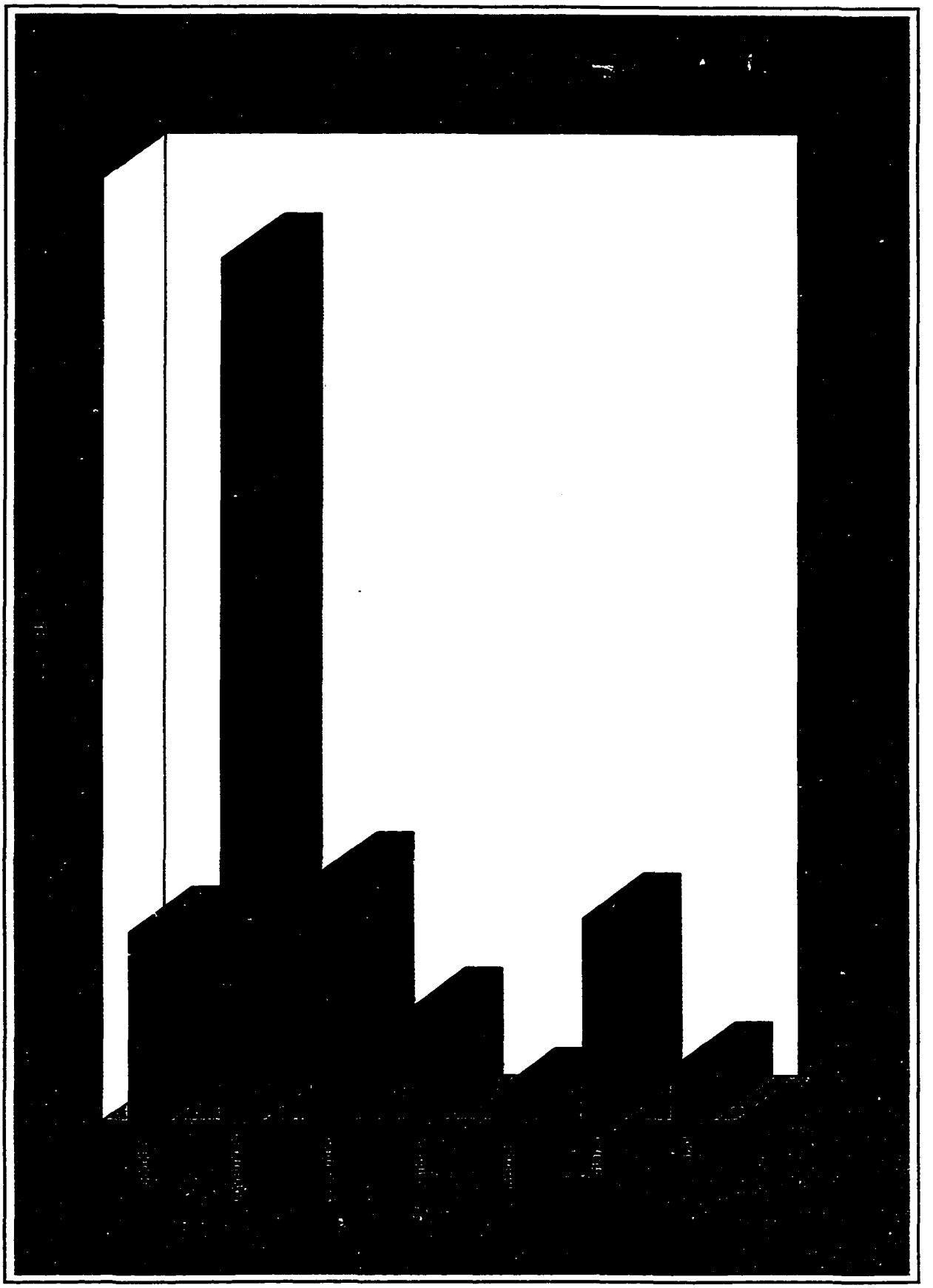
1957

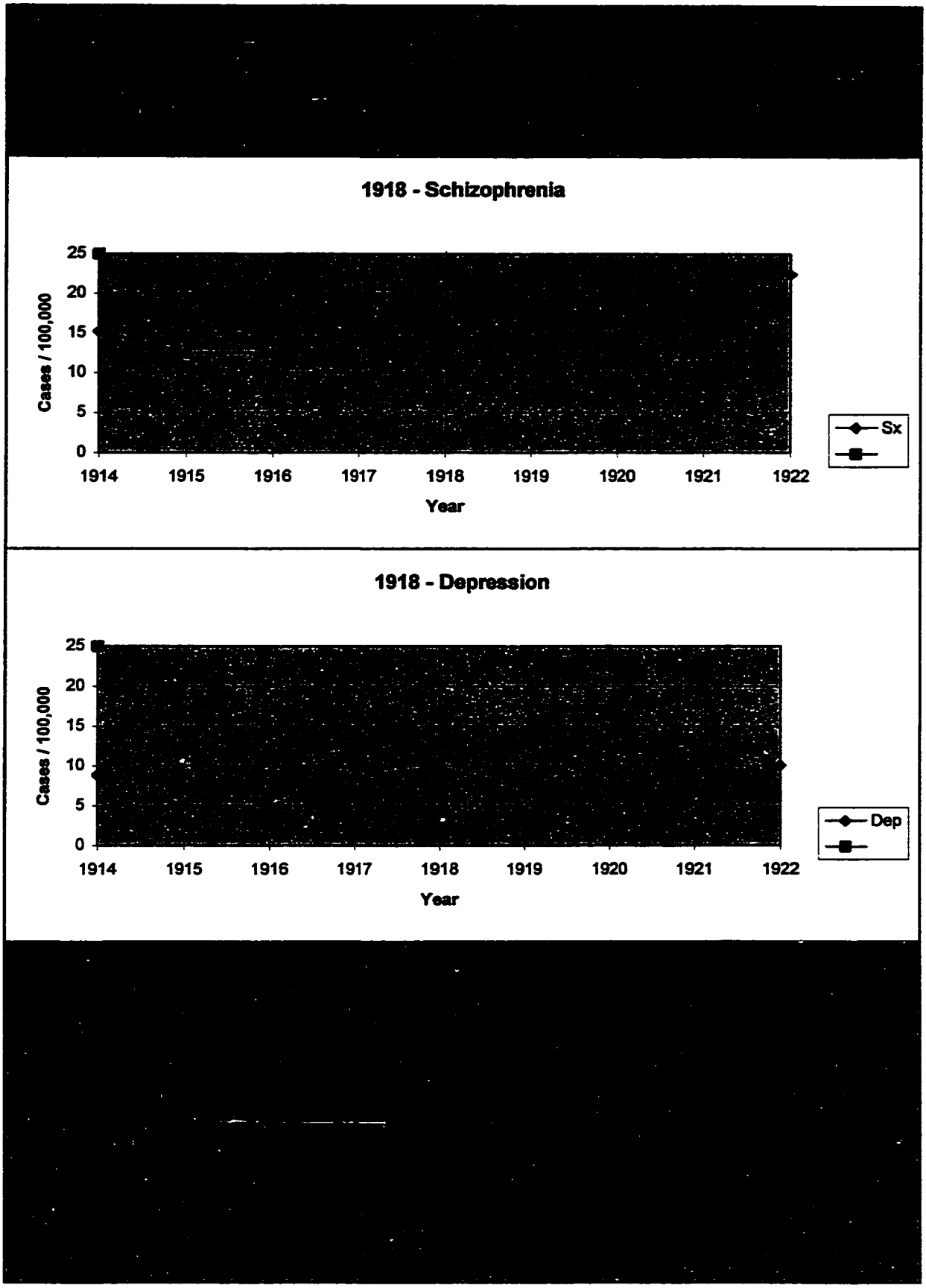
Sample Group; gender variable:	p=0.42
Sample Group; marital status variable:	p=0.33
Control Group; gender variable:	p=0.48
Control Group; marital status variable:	p=0.39

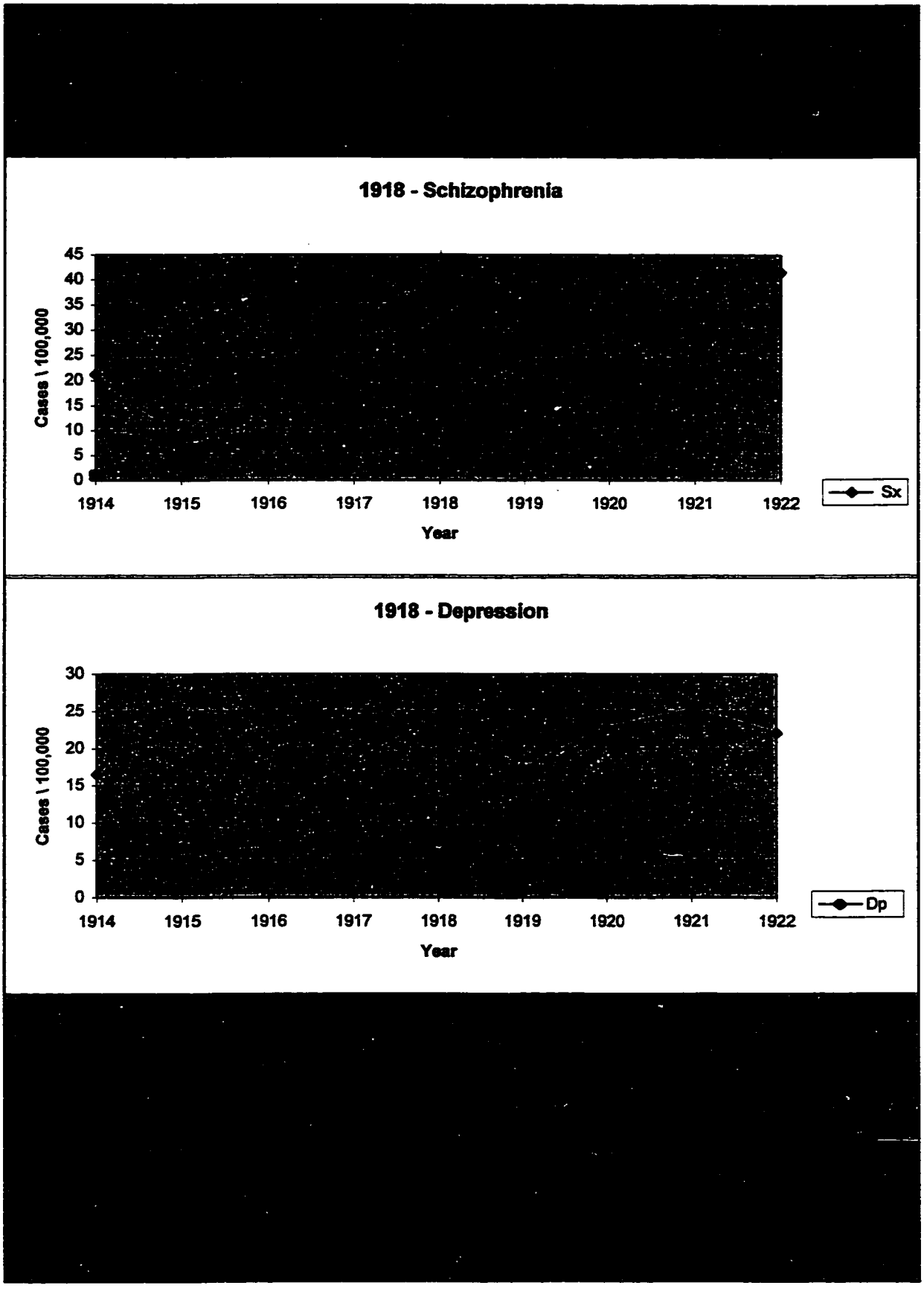
Table 11

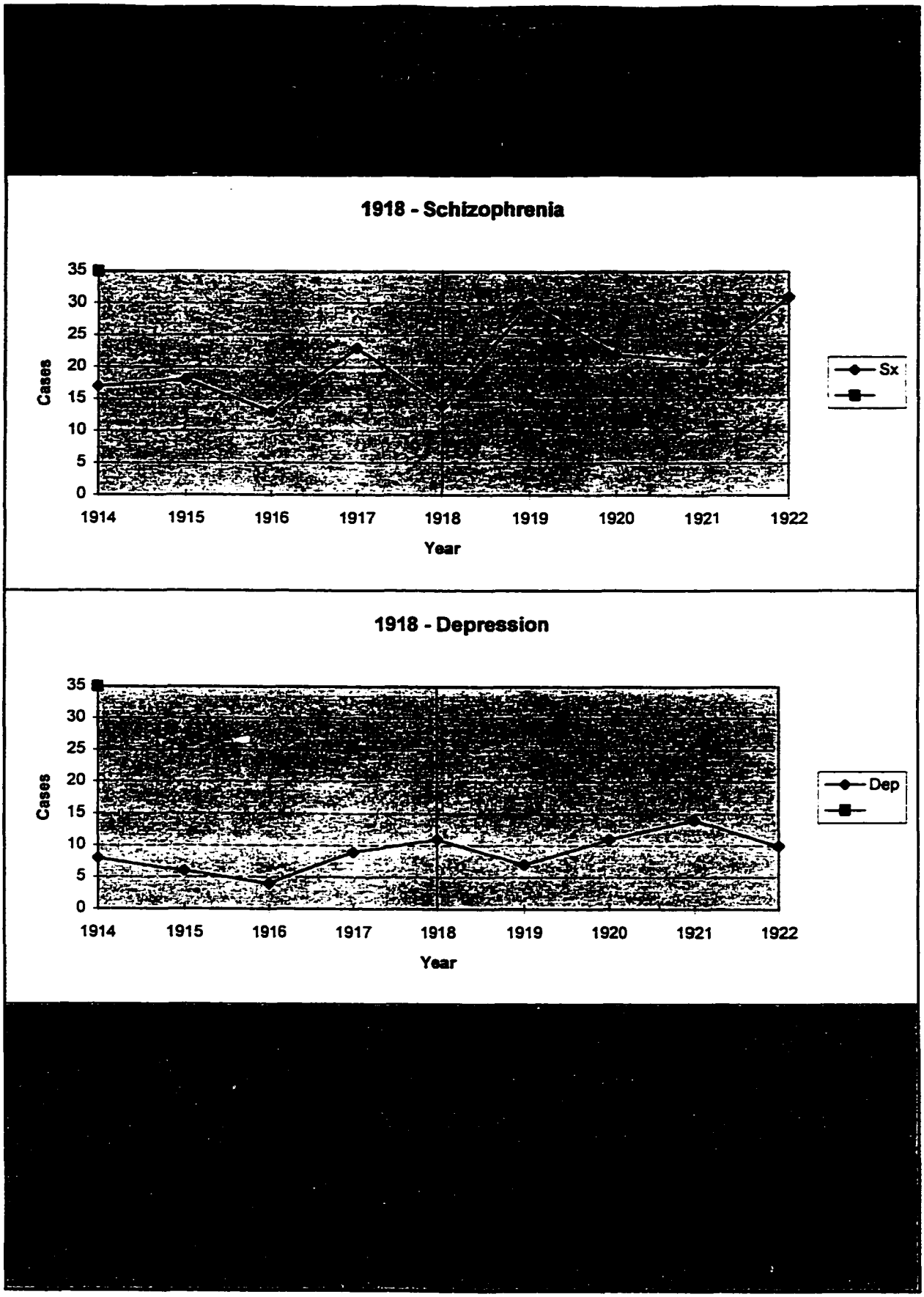
Chi Squared Results - Combined Epidemic Groups

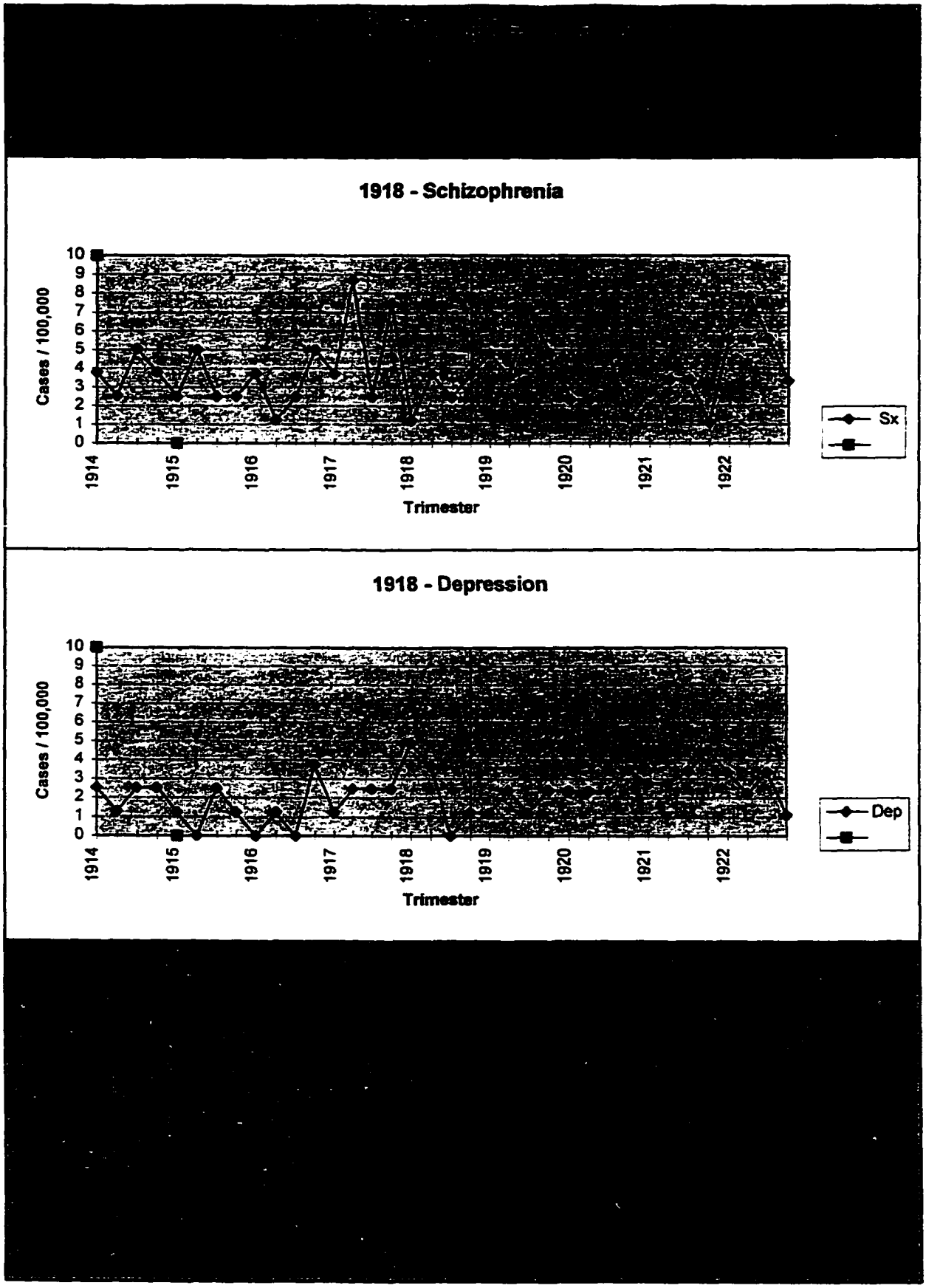
	Chi Sq.	d.f.	Sig.
1. Diag. x Yr. of Birth	11.833	7	0.106
2. Diag. x Pre/Post Epidemic Yrbirth	0.035	1	0.851
Schizophrenia Group			
3. Gender x Yr. of Birth	5.836	7	0.559
4. Marital Status x Yr of Birth	10.834	7	0.146
Depression Group			
5. Gender x Yr. of Birth	2.453	7	0.931
6. Marital Status x Yr of Birth	7.407	7	0.388

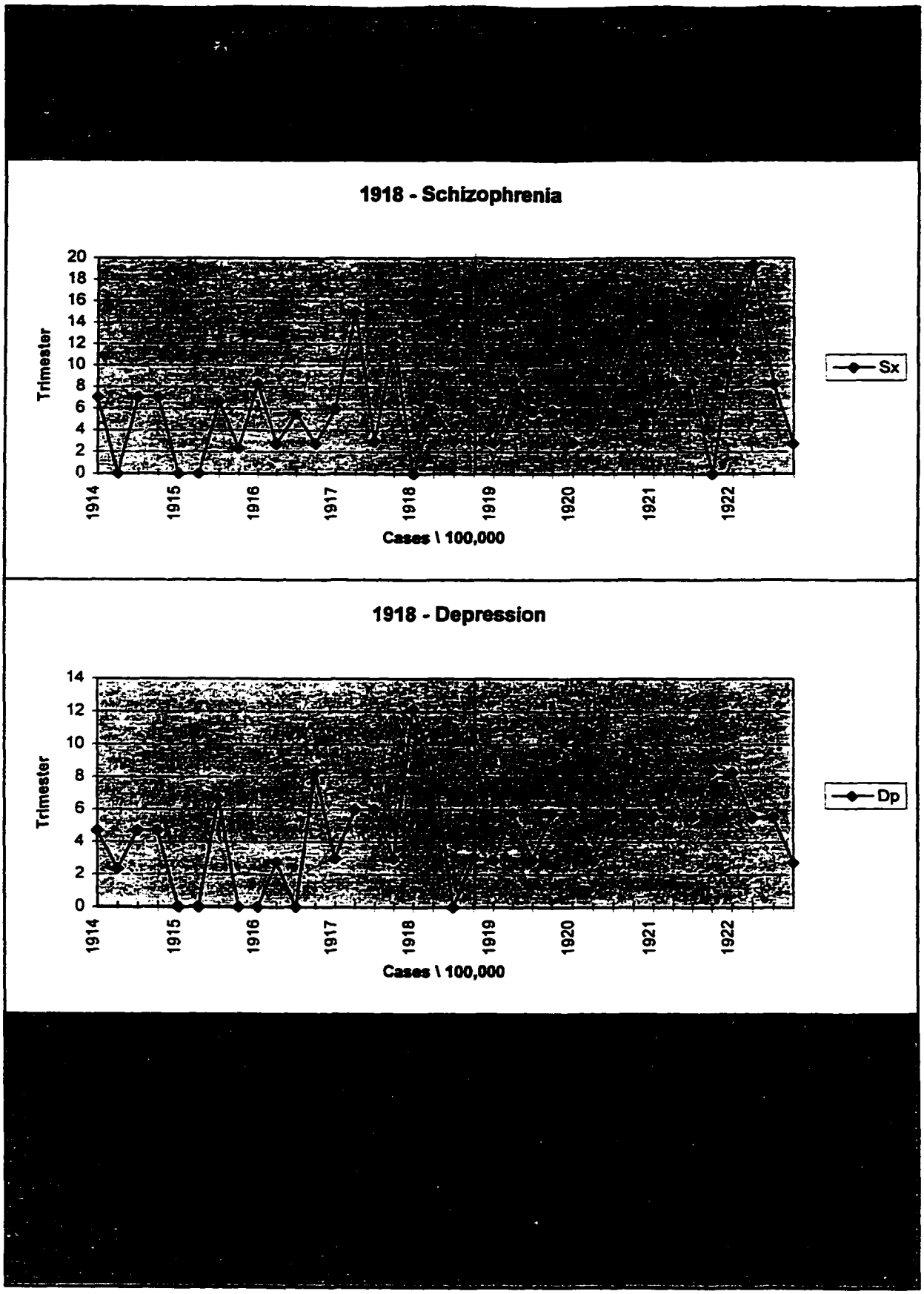


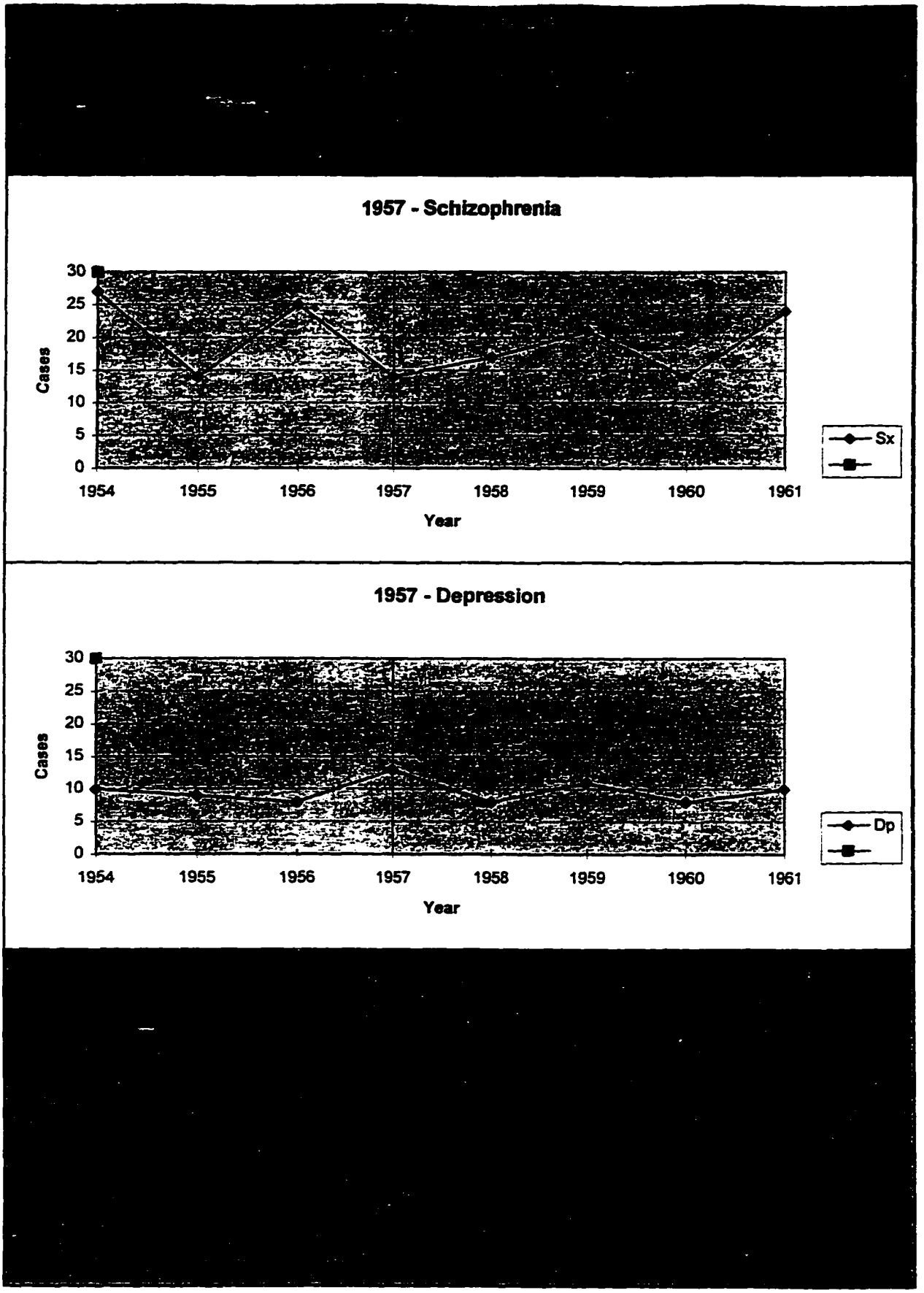


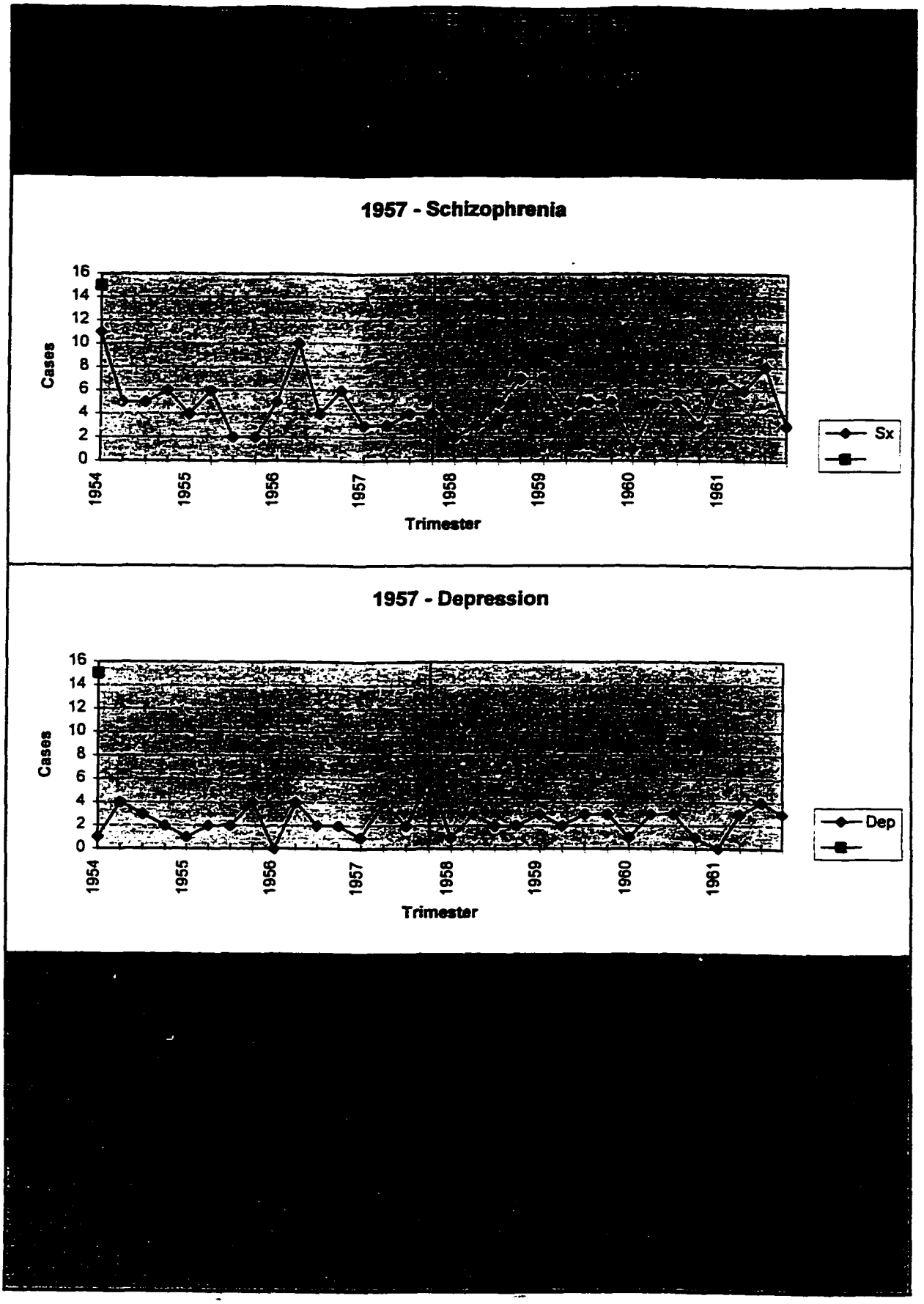


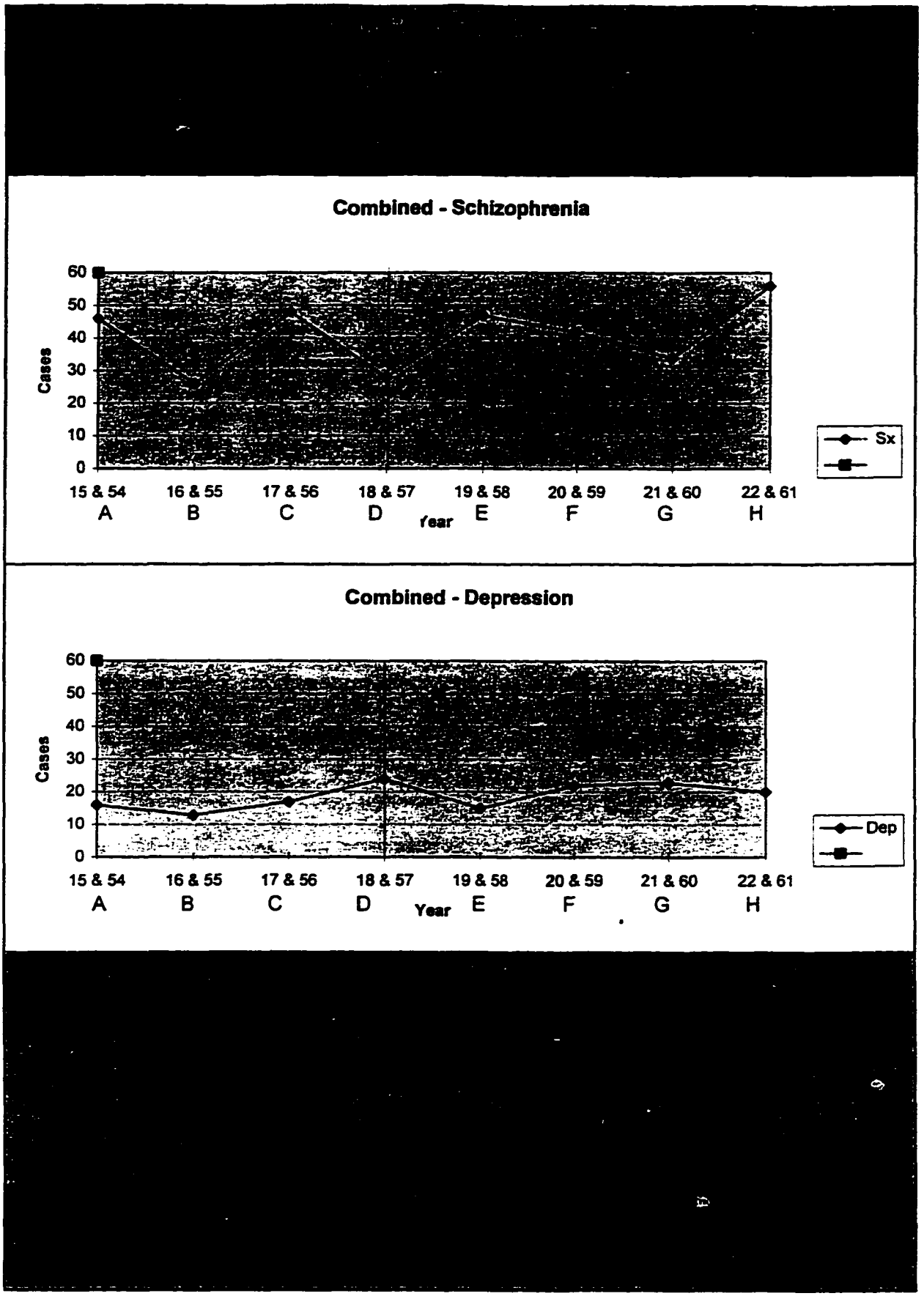


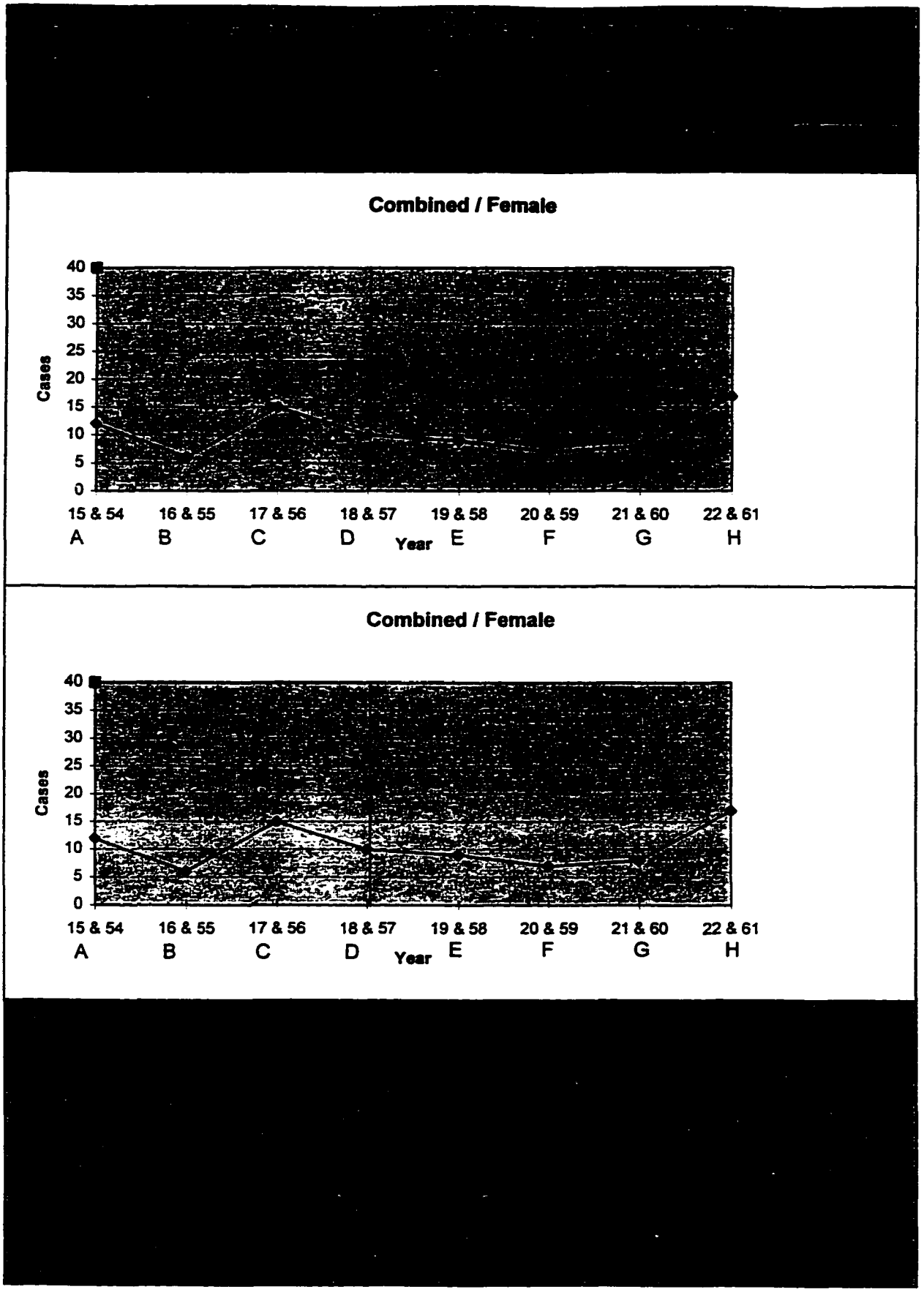


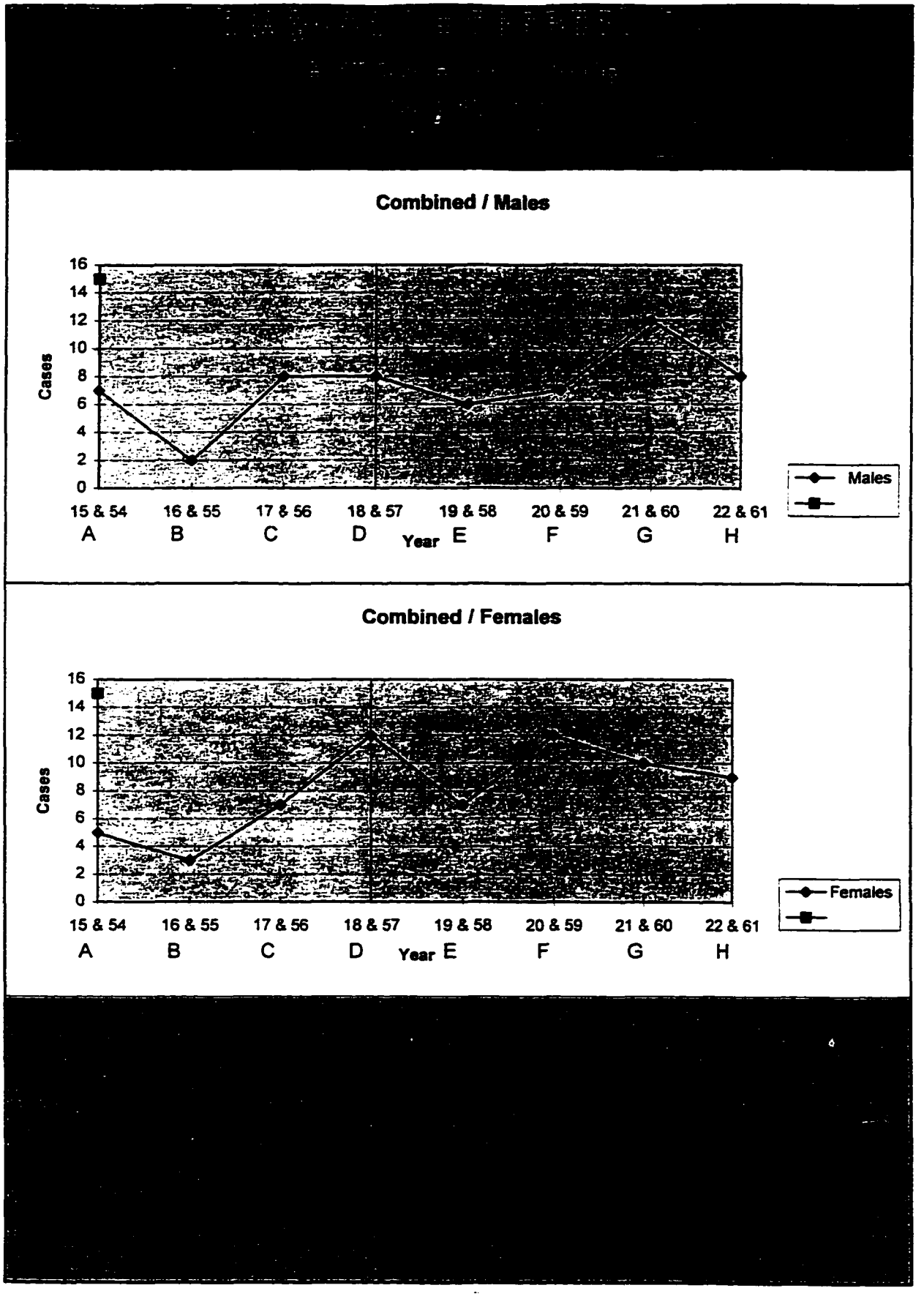


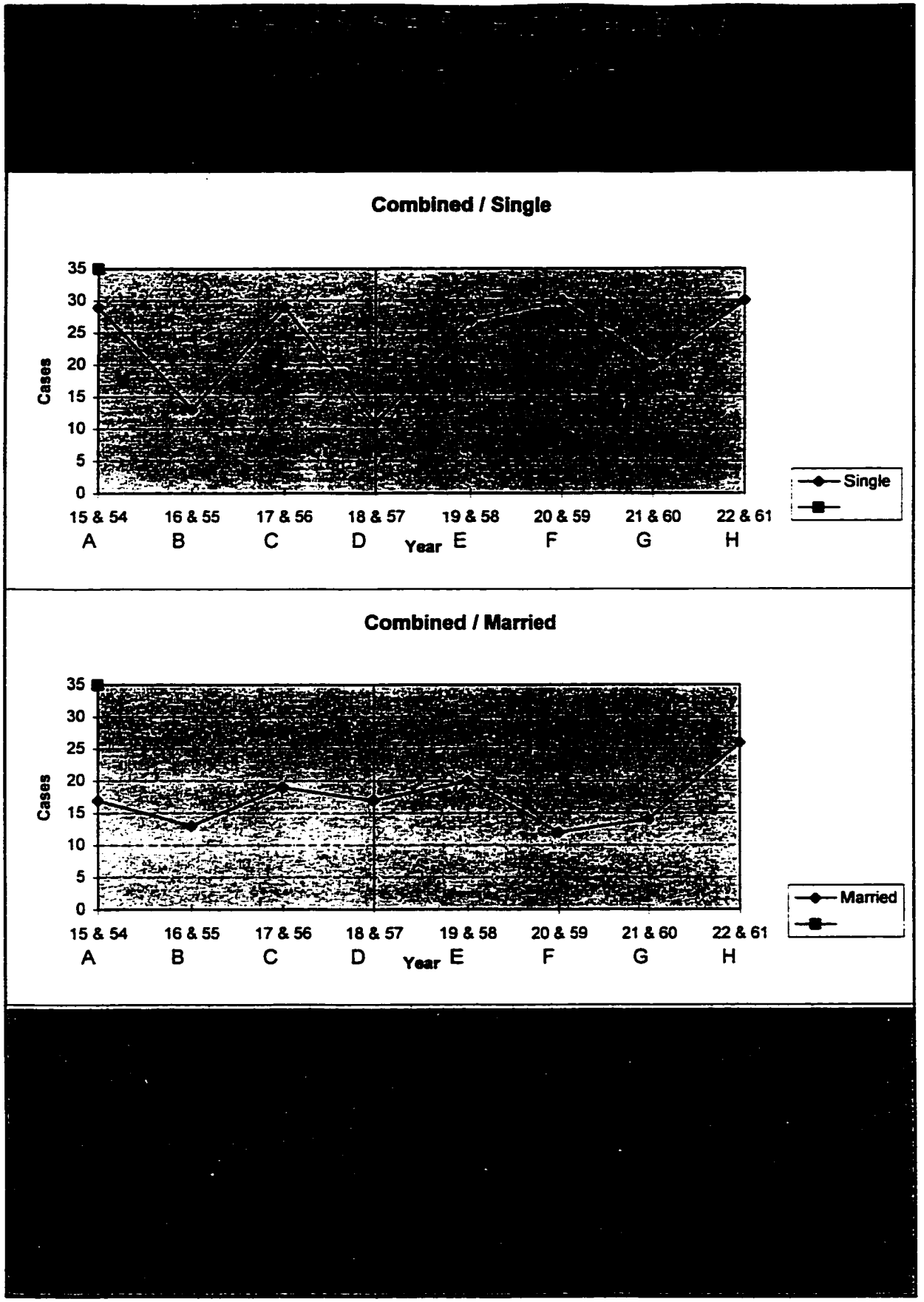


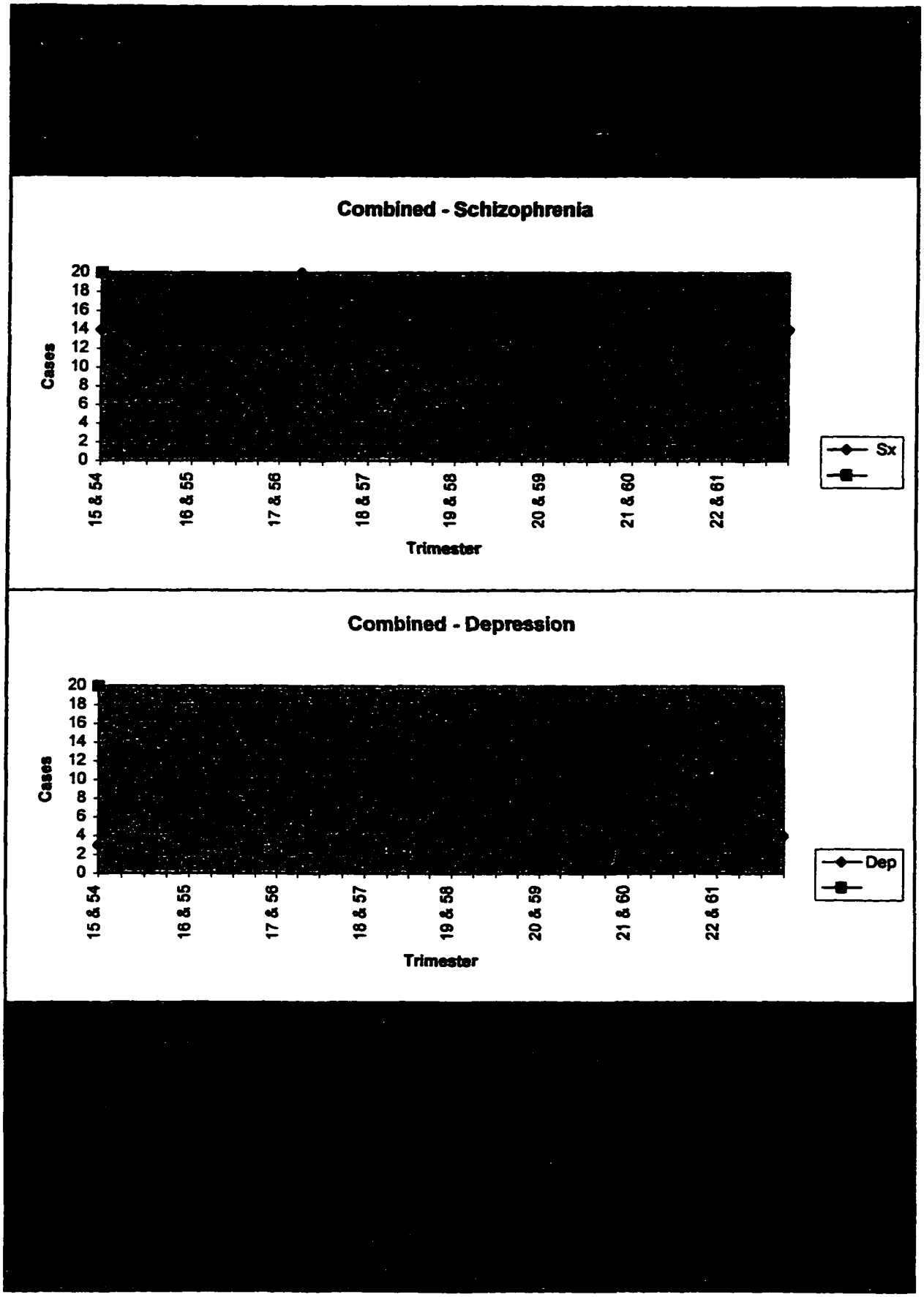


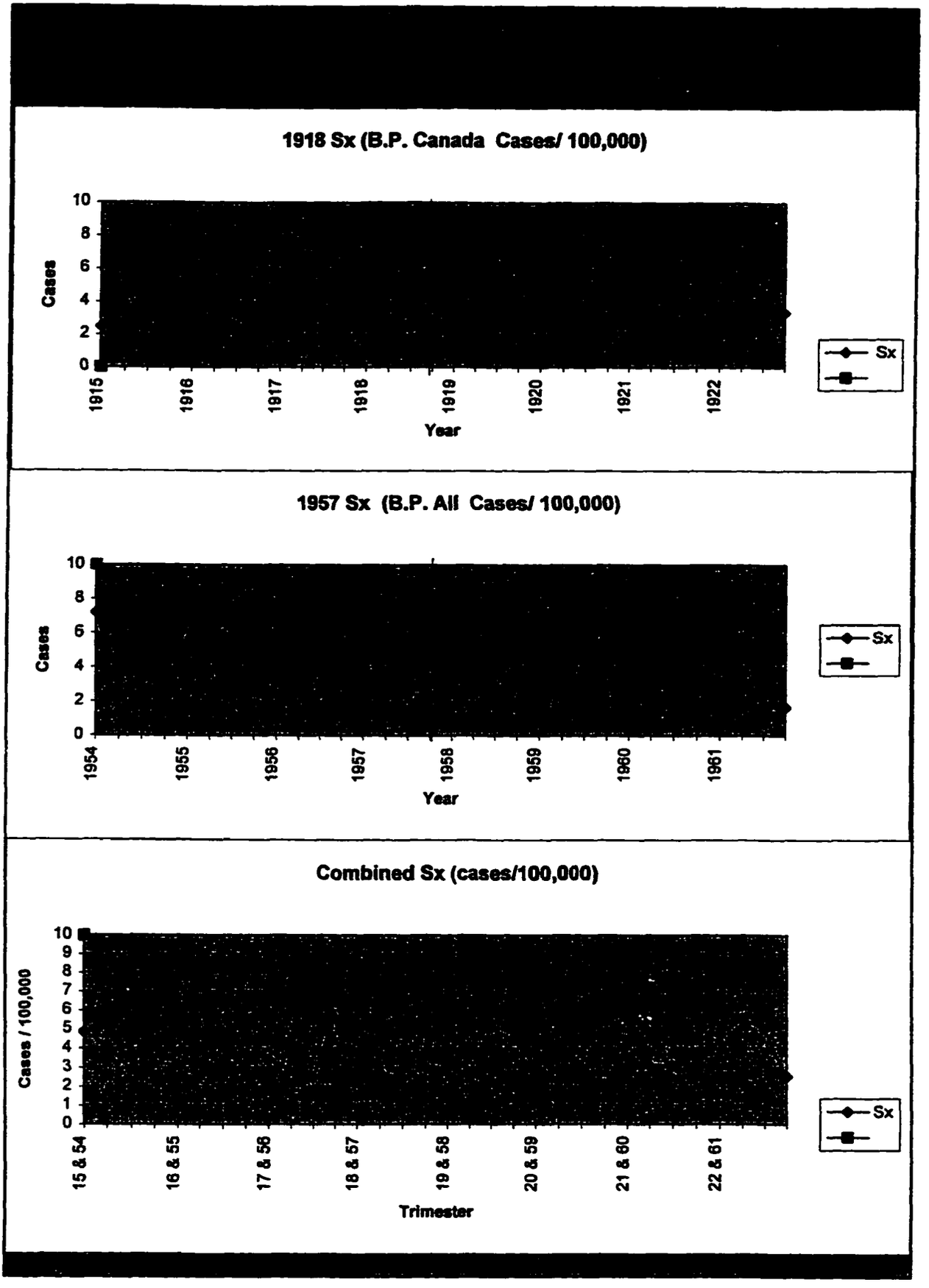


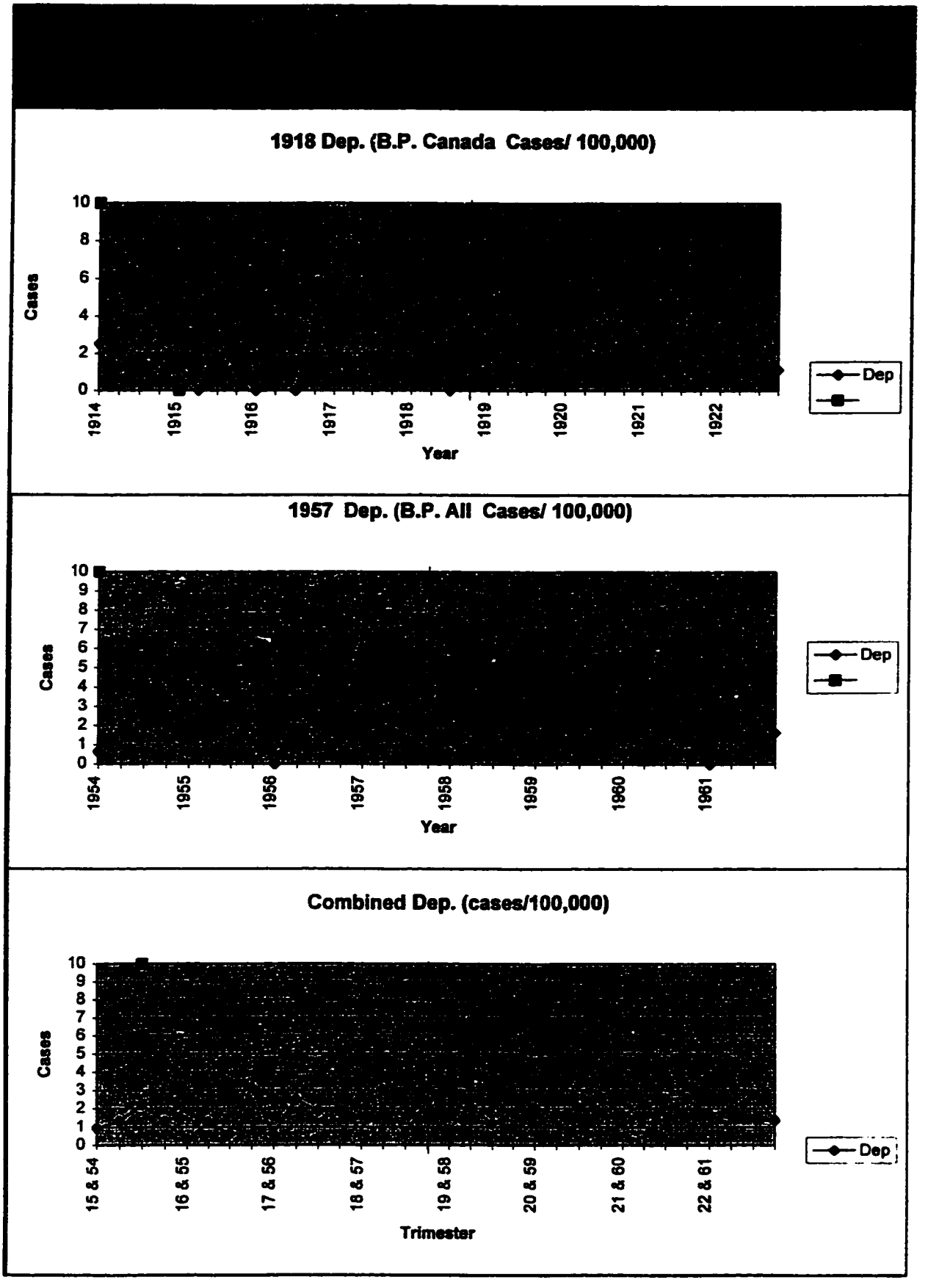


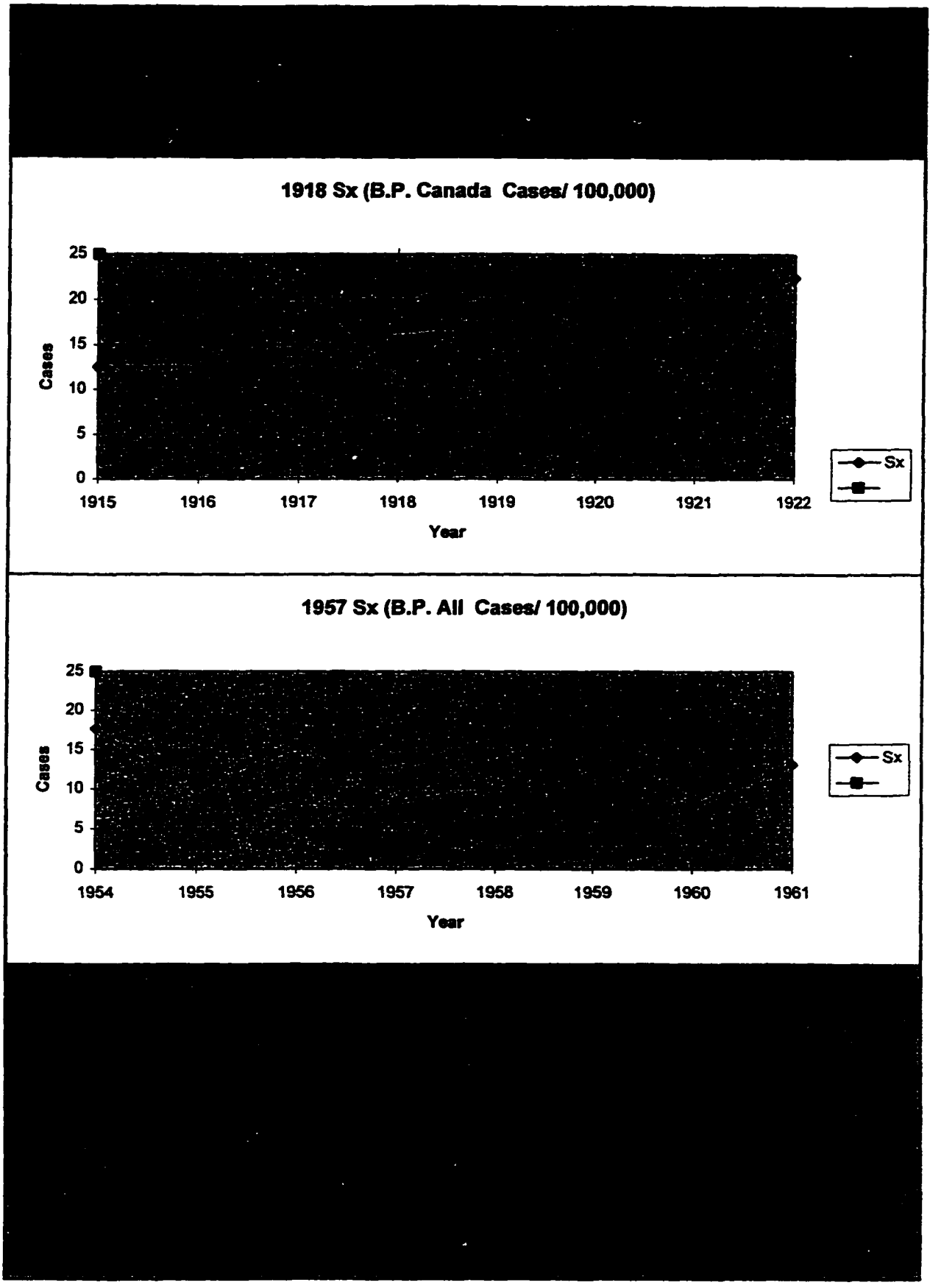


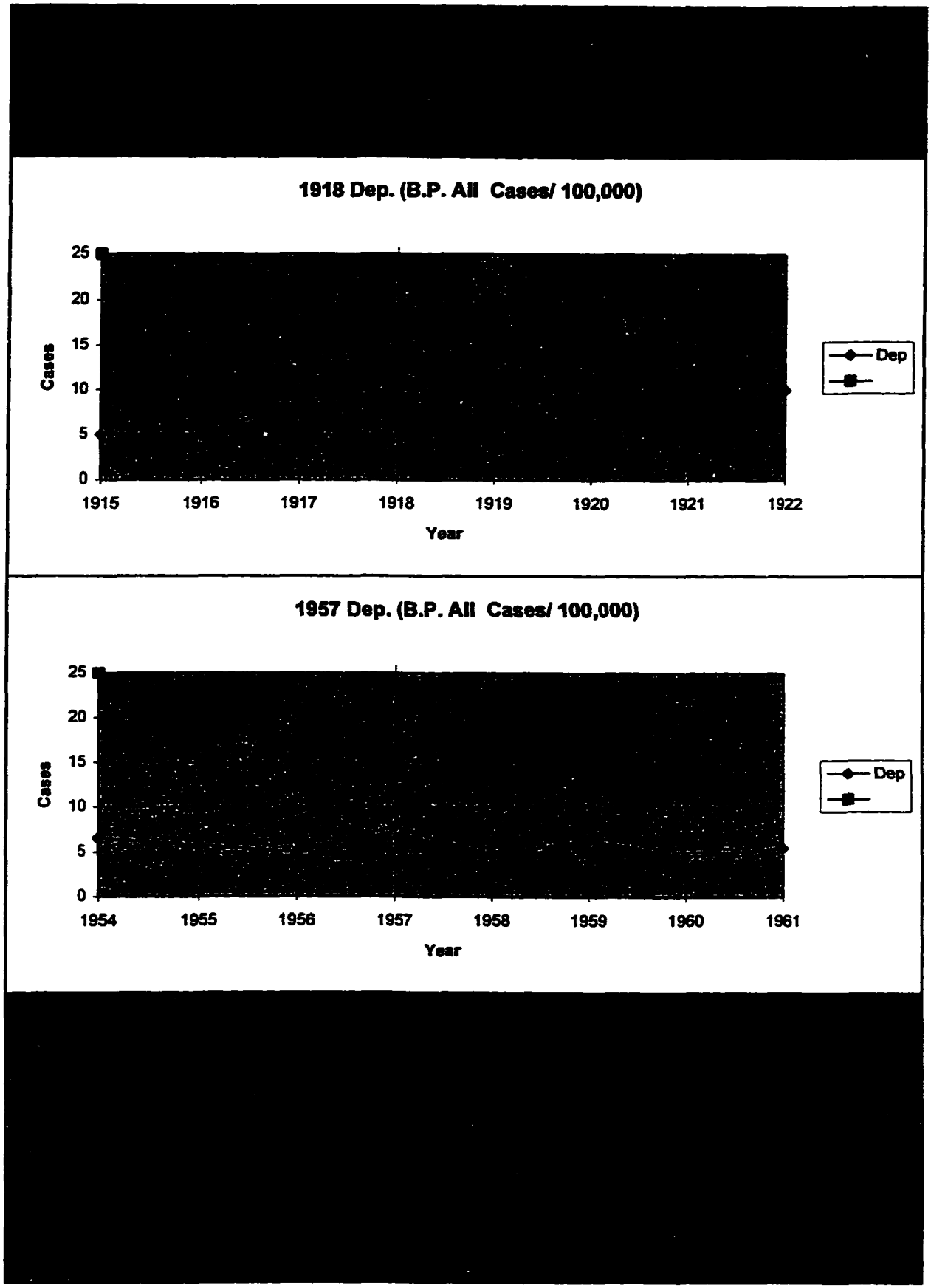


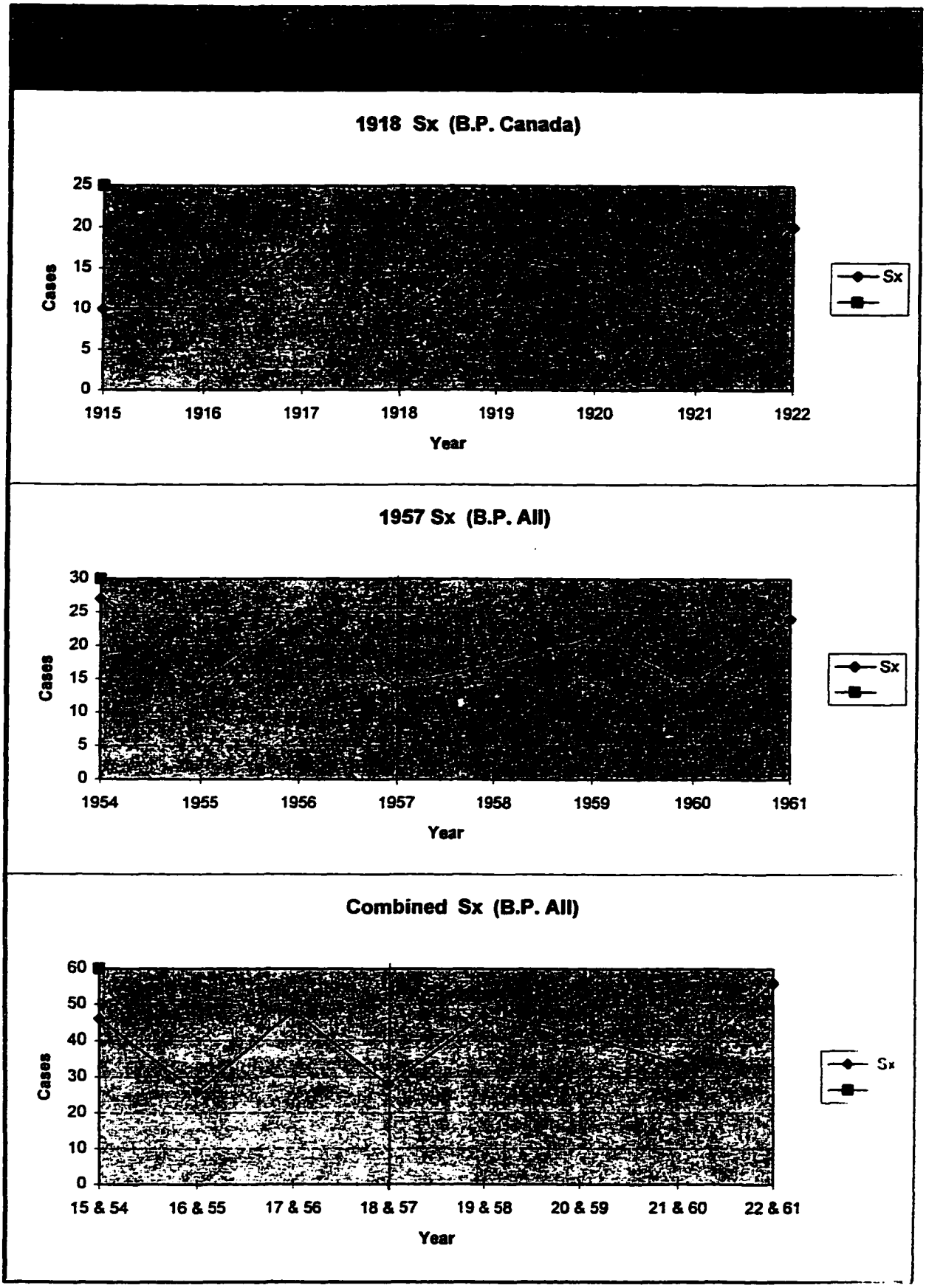


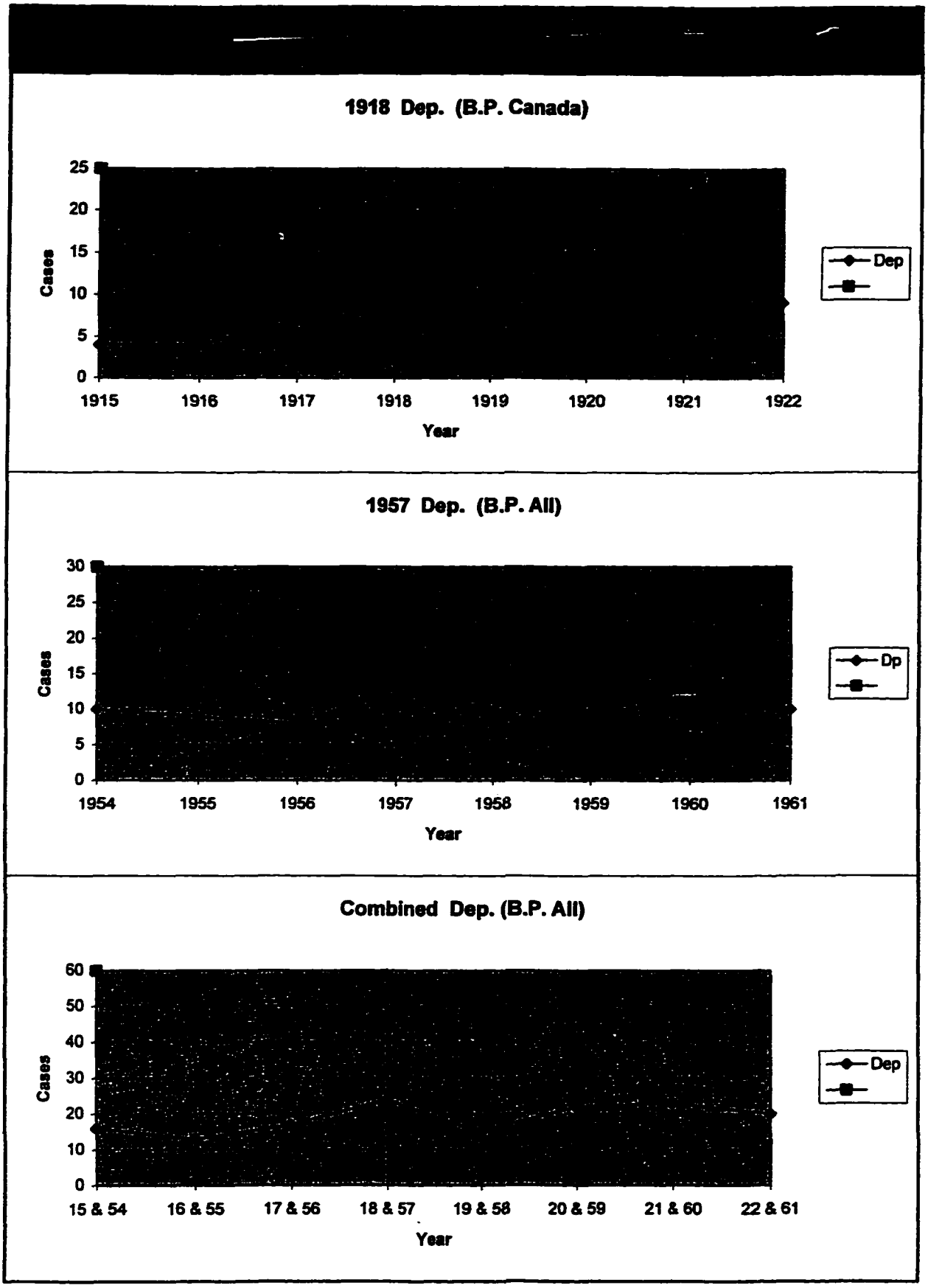


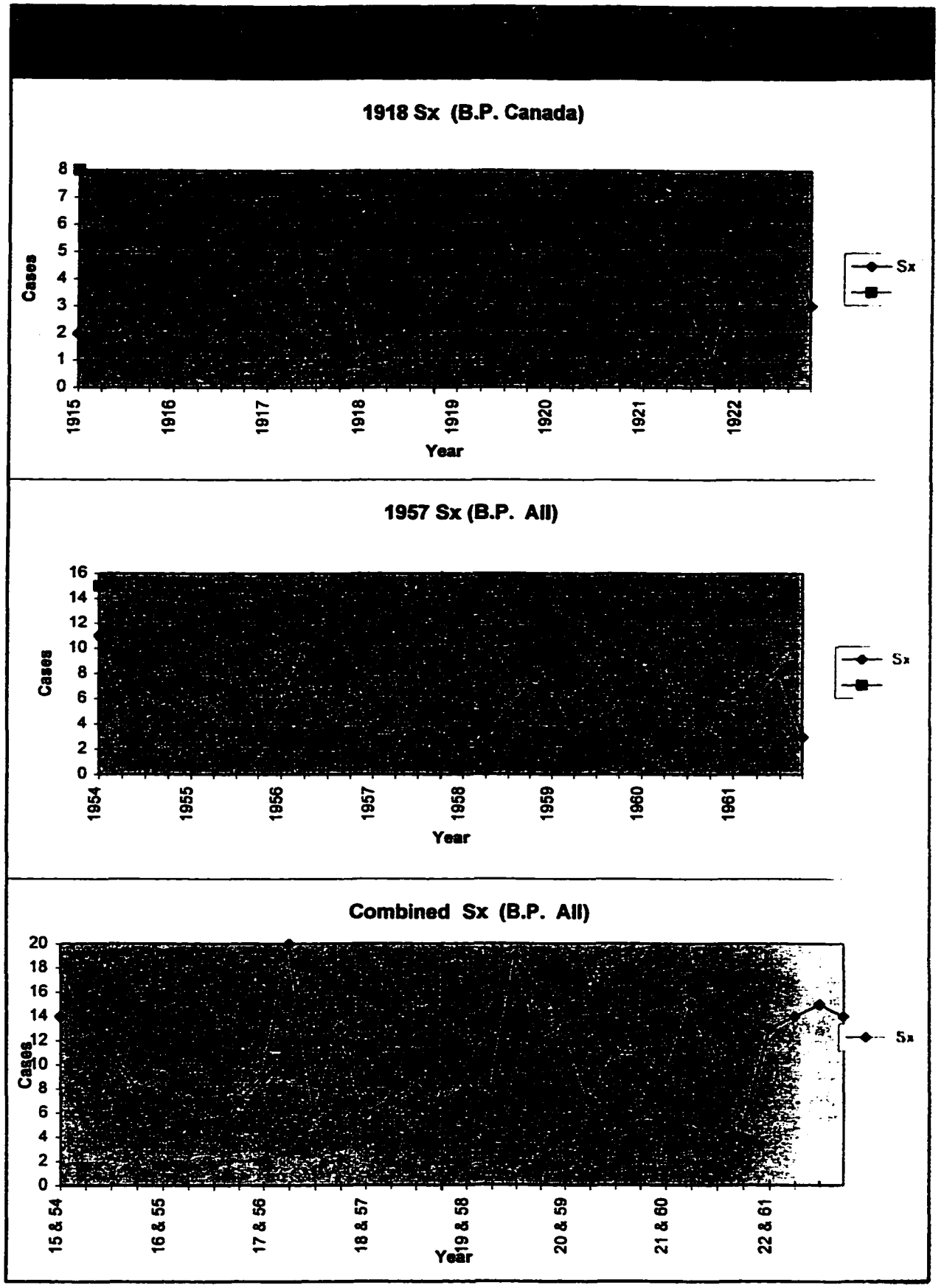












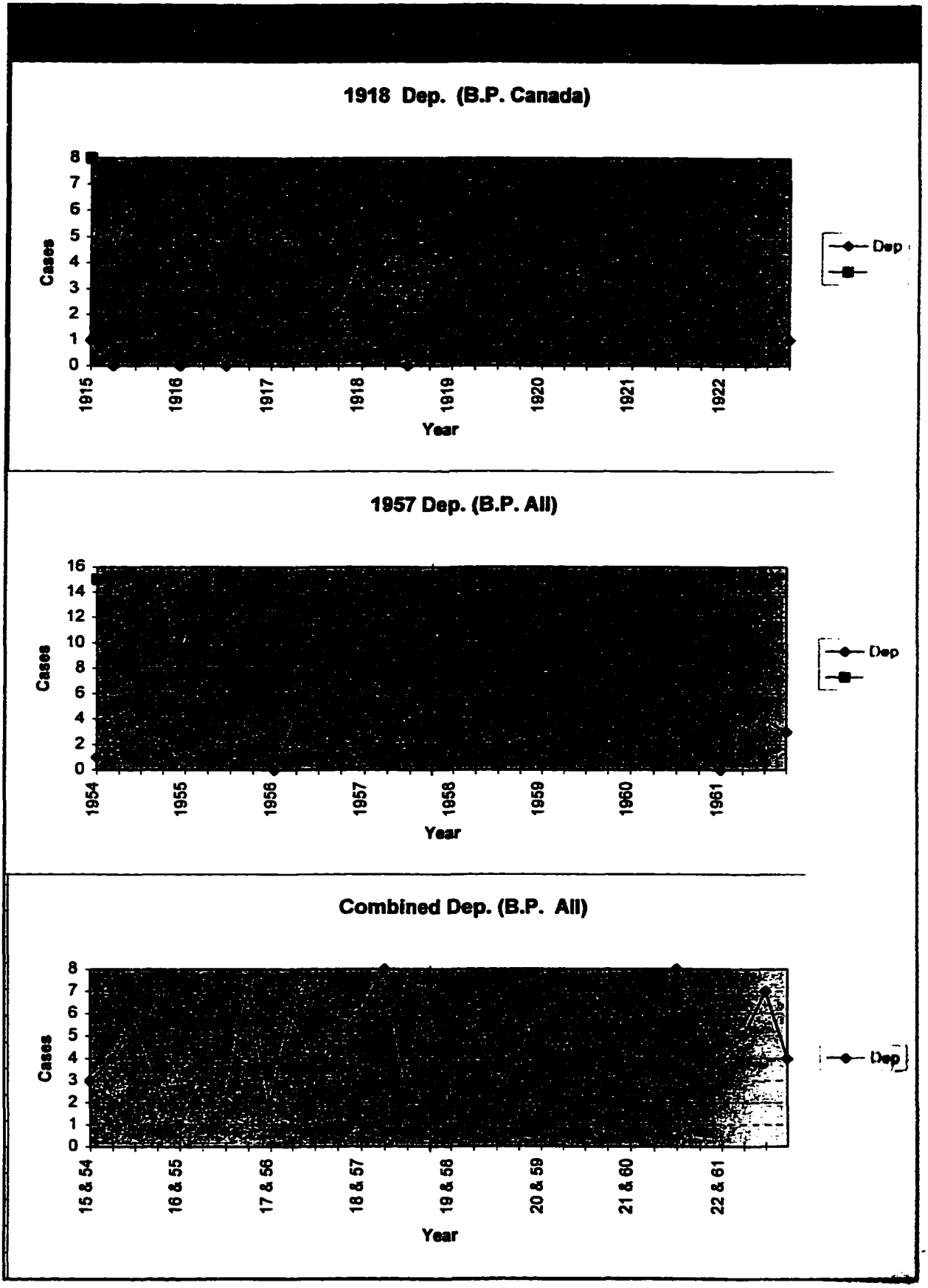
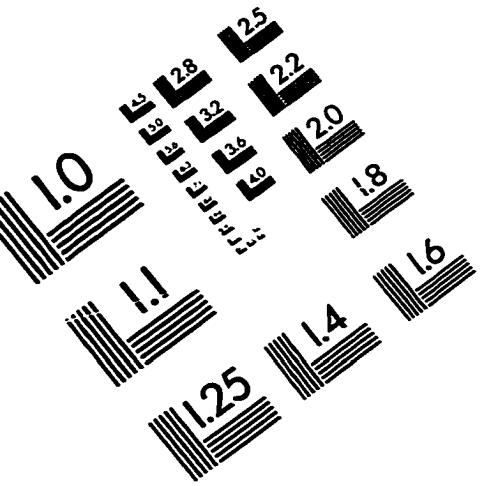
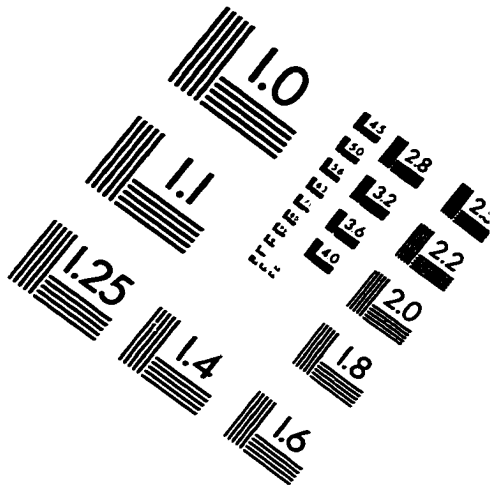
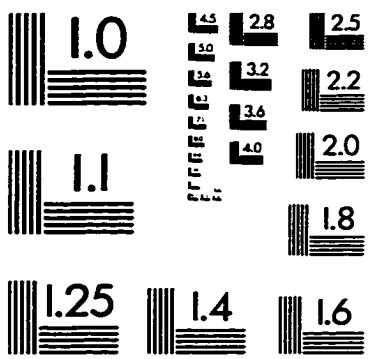
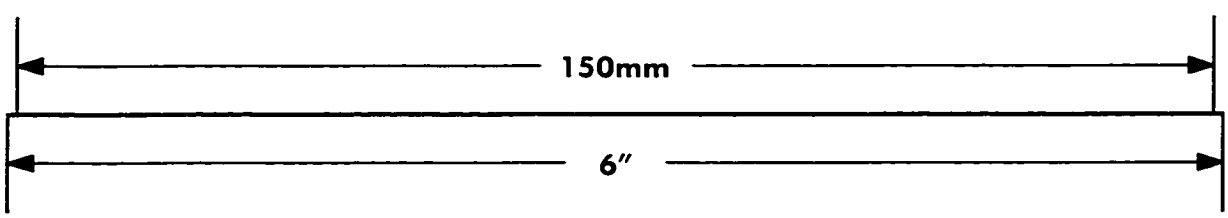


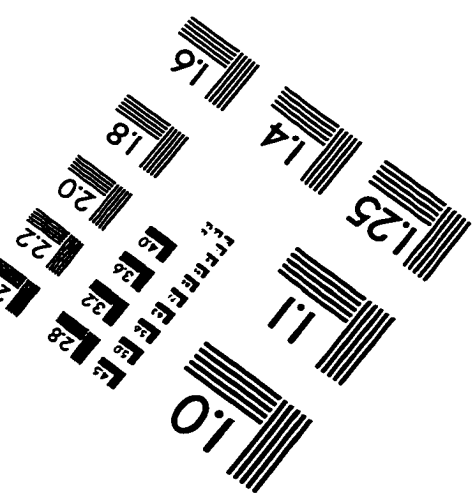
IMAGE EVALUATION
TEST TARGET (QA-3)

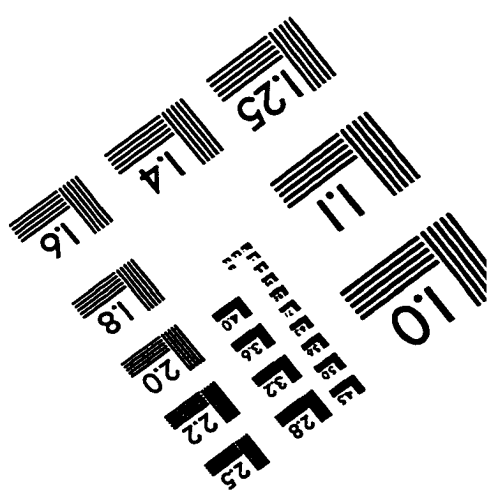












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