A STUDY OF SEASONAL INCIDENCE OF CONGENITAL MALFORMATIONS IN THE UNITED STATES

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Seasonal cycles have long been analysed to study economic trends, but only within the past two decades has seasonal analysis been applied to congenital malformations. Since McKeown and Record (1951) carefully studied large numbers of anencephalic stillbirths and found a seasonal pattern of a winter excess and a summer trough, a steady output of articles dealing with the seasonality of malformations has appeared. The scope of malformations analysed for seasonal trend has been somewhat narrow, and the numbers of cases have been small. The malformations most often studied for seasonal trend include anencephaly, spina bifida, clefts of the lip and palate, congenital dislocation of the hip, Down's syndrome, hydrocephaly, and patent ductus arteriosus. Bailar and Gurian (1965) systematically reviewed past research on seasonal incidence of malformations.

The present study was undertaken to investigate seasonal variation in the incidence of clefts and other selected congenital malformations, taking advantage of the large number of cases identified through the National Cleft Lip and Palate Intelligence Service (NIS).

Materials

The NIS was established at the Dental Health Center in San Francisco for the collection and study of certificates of live birth on which congenital malformations were recorded in an attempt to identify epidemiologic variables related to the occurrence of clefts and other birth defects. Twenty-nine states and two cities of the United States were surveyed between 1962 and 1965. From these 31 reporting areas approximately 10,000 cases of cleft lip and/or cleft palate as well as about 86,000 cases of other congenital malformations were collected. A 1% systematic sample consisting of approximately 90,000 birth certificates was selected as a control group representing all live births from the same registration areas and the same years. Each malformation recorded on the birth certificates was coded according to a classification developed specifically for that purpose (Hay and Tonascia, 1968). Many demographic variables were abstracted from the birth certificates of both cases and controls and were coded, key punched, and transferred to magnetic tape. Among those variables that are relevant to this present study were month of birth, state and county of mother's usual residence, and type of congenital malformation. A more complete description of the NIS system has been published elsewhere (Greene, Vermillion, and Hay, 1965).

The following malformations were selected for seasonal analysis: isolated cleft lip, cleft lip and palate, isolated cleft palate, anencephaly, spina bifida, hydrocephaly, congenital heart disease, anorectal defects, hypospadias, positional foot defects, polydactyly, syndactyly, reduction deformities, and Down's syndrome. The criteria for selection of these malformations were homogeneity within malformation code category and adequacy of sample size. It should be noted, however, that some of the selected malformations fit the criteria better than others. If a child had multiple malformations, each malformation was counted in its appropriate category and hence the child was included more than once in the study. Isolated cleft lip and cleft lip with cleft palate were combined, as well as shown separately, because there is evidence that they may be a single disease entity distinct from isolated cleft palate (Fogh-Andersen, 1942). Occipital meningocele and ence-
phalocoele were grouped with spina bifida. Cases of imperforate anus accounted for over 80% of the ano-rectal defects.

**Methodology and Results**

Three types of analysis were used in the present study. In analysis I seasonal trends for the entire NIS reporting area were studied for the combined period 1962-65. The data were separated by climatic regions in analysis II in a search for seasonal trends within regions. In analysis III, the 1962-65 trends were broken down by individual years within climatic regions.

**Analysis I**

The initial analysis consisted first of arraying each selected malformation and the controls by month of birth for the combined years 1962-65. The monthly frequencies were adjusted for the different number of days in each month. The resulting monthly distribution of each malformation was then further adjusted for the seasonal variation in normal live births in the NIS areas.

These adjusted monthly frequencies formed the basis for the subsequent analysis. A statistical model for detecting cyclic trends, developed by Edwards (1961a), was applied to the monthly distribution of each malformation. For this model the NIS data represented a sample of all live births in the United States with congenital malformations. Very briefly, the Edwards' model uses chi-square to test for the presence of cyclic trend and fits a simple harmonic curve to the data. For a more detailed description of Edwards' model and its limitations see the Appendix (p. 31).

Table I shows the number of cases of each malformation, the incidence rate per 100,000 live births, and the Edwards' model chi-square values with probability levels. Cleft lip with or without cleft palate, hypospadias, and positional foot defects have probability levels of 0.05 or less. At a 5% probability level an average of 0.75 of the 15 tests would be significant by chance alone, if the tests were independent.

These 15 tests were not truly independent for two reasons. First, and most important, the cleft lip with or without cleft palate category was the sum of two other categories. Second, an individual may have had two or more malformations and may have been represented more than once in the analysis.

In order to portray cyclic trend and percentage variation in the monthly distributions, we plotted the ratio of frequency of malformation to average monthly frequency by month of birth. For convenience this ratio is called the *ratio of observed to expected* in Figures 1, 3, and 4.

For each of the three malformations that showed significant chi-squares, the first half-year represents above average incidence compared with the monthly average, and the second half-year represents below average incidence (Fig. 1). The simple harmonic curve fitted to the data in the Edwards' analysis gives a maximum incidence in March for cleft lip with or without cleft palate, for hypospadias, and for positional foot defects.

Most investigators of seasonality have studied the monthly or quarterly distributions of malformations by combining years, as in the present analysis. The significant seasonal trend that we found for cleft lip with or without cleft palate agrees with data published by Fujino, Tanaka, and Sanui (1963), which showed increased incidence in the March-May period as compared with expected numbers. Woolf, Woolf, and Broadbent (1963) found no statistically significant trend in cleft lip with or without cleft palate, but a greater number of cases than expected was observed in each month from December through April. The data presented by Gilmore and Hofman (1966) showed no trend for any type of cleft, but comparison with a control population was lacking. Edwards (1961b) found an increased incidence of cleft lip centered around March. Charlton (1966) noted a June increase in cleft lip and palate in one of his two sets of data. None of these authors observed any seasonal trend in the incidence of cleft palate. Although Fig. 1 indicates a monthly trend in cleft lip with or without cleft
palate, there is only a small variation above and below the monthly average incidence.

Published results on the seasonal incidence of hypospadias and positional foot defects are scarce. Slater, Watson, and McDonald (1964) found no seasonal pattern for either anomaly in their study of 84 malformations. The present analysis indicates a clear seasonal trend for hypospadias with a maximum of 11% above the average incidence in the January–June period and a minimum of 9% below in the last six months.

The test of positional foot defects yields an extremely high chi-square value. The graphic presentation of seasonal incidence is very similar to that for hypospadias, with maximum incidence 9% above average for the first six months and minimum incidence 12% below average for the last six months.

In this study the anomalies of the central nervous system which have been shown to demonstrate seasonal trend in British investigations (McKeown and Record, 1951; Edwards, 1958 and 1961b; Leck and Record, 1966; Record, 1961; Guthkelch, 1962) do not show any evidence of cyclic variation. The omission of fetal deaths from the present study may be the reason for this difference.

Analysis II

A more detailed method was designed to take into account the ambiguity of the term 'season', which is composed of two essential features, climate and time.

In the temperate zones of the earth the seasons usually refer to the four equal time periods into which the year is divided by the passage of the sun from solstice to equinox and equinox to solstice. These periods are marked by particular climatic characteristics of temperature, rainfall, humidity, etc. However, when a large geographical area such as the United States is considered, vastly different climatic conditions may occur in different regions in the same three-month time period. Alternatively, two different geographic regions may experience the same climatic pattern, but not during the same time periods, perhaps being out of phase by one or two months. It was not necessary to make this distinction in most of the present studies because they dealt with small geographical areas where the time factor and climate were closely related. The size of the United States makes this distinction appropriate in the present analysis.

In order to incorporate both time and climate in an analysis of season, it seemed reasonable to divide the United States into climatic regions and then within each region to analyse the time distribution of the selected malformations. The division was done on the basis of temperature. In a test sample of 69 cities, about 90% had their hottest and coldest readings in July and January, respectively, so these months were selected as the midpoints of summer and winter. Maps showing 'Normal Daily Average Temperature' for July and January, based on the years 1931–60 and with isotherms at 5°F. intervals, were obtained from the United States Department of Commerce. A 70°F. reading for July was arbitrarily selected to divide hot and moderate summer areas, and likewise a 40°F. reading for January was selected to divide moderate and cold winter areas. These divisions were made on the July and January maps along the 70°F. and 40°F. isotherm lines, respectively. The two maps were then combined so that the United States was divided into four summer-winter combinations: hot summers–cold winters, hot summers–moderate winters, moderate summers–cold winters, and moderate summers–moderate winters. Because the NIS data were classified by county, it was necessary to transfer the climatic map.
onto a county map of the United States. The resulting map is shown in Fig. 2.

Each malformation case was assigned to one of the four climatic regions according to county of mother's usual residence. The data for each region were adjusted for the number of days in the month and for seasonal variation in normal live births within each region, as described in analysis I. It is of passing interest that there are marked regional differences in the seasonal variation in the control sample of normal live births.

The Edwards' model was applied to each of the 15 malformation categories in each of the four climatic regions. Thus, 60 tests were performed, and at the 0.05 probability level three tests could be expected to be significant by chance alone if the tests were independent. If more than three tests should result in probability levels of 0.05 or less, there would be no way to determine which of the tests were those expected by chance and which might truly be significant. To avoid this dilemma we chose a 1% probability level, so that on the average only 0.6 tests would give false significance. The results of the application of Edwards' model to the regional data are shown in Table II.

Probability levels of 0.01 and lower occur four times. There is seasonal trend in each of the malformations showing cyclic activity in analysis I, but the trend is not present in each region. Cleft lip with or without cleft palate is significant only in the hot summer–moderate winter region (P <0.01); hypospadias is significant only in the moderate summer–moderate winter region (P <0.01); and the positional foot defect category is significant in the hot summer–moderate winter region (P <0.01) and highly significant in the hot summer–cold winter region (P <0.001). The fitted simple harmonic curves give maximum incidence in January, April, March, and April, respectively. Graphs for the malformations which give significant results are contained in Fig. 3.

The seasonal trend for cleft lip with or without cleft palate in the hot summer–moderate winter region is similar to the trend for the entire geographical area covered by NIS. However, the month of maximum incidence (January) precedes that of the national trend (March) by about two months, as calculated from the Edwards' fitted curves. A seasonally varying factor may be present in this region operating detrimentally on fetuses conceived in the spring. This hypothesis would explain why only one region showed cyclic activity, but would not account for the two-month difference between the regional and national trends.

The results for hypospadias are similar to those
for cleft lip with or without cleft palate. The significant trend present in the moderate summer-moderate winter region has a form like that of the national trend, and April is the month of maximum incidence for both fitted curves (compare Figs. 1 and 3). Because of this consistency, cases in this specific climatic region may be responsible to a large degree for the national trend.

For positional foot defects the two regions with the largest numbers of cases show significant trends similar to the national trend. The trend for the hot summer-cold winter region is extremely smooth, which might suggest the presence of a teratogenic factor which is especially regular in its behaviour. It is also possible that the significant results obtained for the two regions with hot summers, together with the high incidence in spring births, might indicate that some factor prevalent in hot summer areas was involved in the malformation process.

**Table II**

<table>
<thead>
<tr>
<th>Congenital Malformation</th>
<th>Hot Summer-Cold Winter</th>
<th>Hot Summer-Moderate Winter</th>
<th>Moderate Summer-Cold Winter</th>
<th>Moderate Summer-Moderate Winter</th>
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<tr>
<td>Controls</td>
<td>41,941</td>
<td>28,056</td>
<td>7,625</td>
<td>12,064</td>
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<tr>
<td>Isolated cleft lip</td>
<td>1,307</td>
<td>640</td>
<td>255</td>
<td>389</td>
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<tr>
<td>Cleft lip with palate</td>
<td>2,104</td>
<td>1,052</td>
<td>456</td>
<td>593</td>
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<tr>
<td>Isolated cleft palate</td>
<td></td>
<td>1,692</td>
<td>711</td>
<td>982</td>
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<tr>
<td>Rhizomelicism</td>
<td></td>
<td>773</td>
<td>317</td>
<td>460</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>2,826</td>
<td>1,661</td>
<td>506</td>
<td>600</td>
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<tr>
<td>Congenital heart disease</td>
<td></td>
<td>814</td>
<td>266</td>
<td>302</td>
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<tr>
<td>Polydactyly</td>
<td></td>
<td>1,201</td>
<td>584</td>
<td>798</td>
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<tr>
<td>Syndactyly</td>
<td>985</td>
<td>494</td>
<td>218</td>
<td>300</td>
</tr>
<tr>
<td>Reduction</td>
<td>2,733</td>
<td>1,069</td>
<td>478</td>
<td>885</td>
</tr>
<tr>
<td>Down's syndrome</td>
<td>5,736</td>
<td>2,597</td>
<td>1,115</td>
<td>1,770</td>
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<tr>
<td>Polydactyly</td>
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<td>2,330</td>
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<td>1,405</td>
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<tr>
<td>Syndactyly</td>
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<td>462</td>
<td>226</td>
<td>336</td>
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<tr>
<td>Reduction</td>
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<td>668</td>
<td>226</td>
<td>459</td>
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<tr>
<td>Polydactyly</td>
<td>1,968</td>
<td>785</td>
<td>411</td>
<td>646</td>
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</table>

**Analysis III**

In the previously described analyses the years 1962 through 1965 have been combined. A disadvantage of combining years is that even though there may be cyclic trend in some or all of the individual years, an overall cyclic trend may not be detected because the month of maximum incidence may not be the same in each year. Therefore, the individual years were examined for the presence of seasonal trend. In order to accommodate this procedure we restricted the scope of malformations considered to cleft lip with or without cleft palate, hypospadias, and positional foot defects.

The appropriate adjustments to the data were made for the different number of days in each month and the seasonal variation in normal live births. Their Edwards' model was applied individually to the selected malformations for each year from 1962 through 1965 in each climatic region. At a 1% probability level an average of 0.96 of the 96 tests would be significant by chance alone. As shown in Table III, four tests are significant, three of which are associated with positional foot defects. These statistical results are difficult to interpret on anything but a year-by-year basis inasmuch as there is only one recurrence of a single year's trend. In this case the cyclic trend in 1962 and 1964 in the hot
seasonal incidence of congenital malformations

summer–cold winter region for positional foot defects supports the corresponding 1962–1965 trend from analysis II. Because a graphic analysis of the data seemed more promising than the Edwards' statistical analysis, it was used in the remainder of analysis III.

The Edwards' model assumes that if a cyclic trend exists, it is in the form of a simple harmonic curve having a peak and a trough within a single 12-month period. Although this is the way seasonal variations frequently occur, it need not necessarily be so for congenital malformations. To allow for the possibility of alternate-year cycles or other types of variation, the data were arrayed on a single continuum from January 1962 to December 1965. For each of the individual years 1962–65, the graphs showing ratio of observed to expected monthly frequencies were constructed and placed side by side in sequence. A three-month moving average was applied to the composite graph to remove some of the variation that results from placing all births for a month at a single point. This procedure was carried out for the three selected malformation categories in each of the climatic regions. A visual inspection of the 12 resulting graphs suggested cyclic activity in at least four of them, and they are reproduced in Fig. 4.

Cleft lip with or without cleft palate in the hot summer–moderate winter region consistently shows above average incidence from November through March. This trend verifies the seasonal recurrence suggested in analysis II.

The pronounced seasonal trend for hypospadias is almost identical in 1962 and 1963 for the moderate summer–moderate winter region. In these two years a large peak exists in the February–June period with a trough in the remainder of the year. This trend
DISCUSSION

The prevention of congenital malformations depends upon the detection of controllable causes. Infectious diseases, like rubella, are potentially preventable, and the intake of teratogenic drugs, such as thalidomide, can be restricted during pregnancy. In this context, the study of seasonal incidence of congenital malformations is of more than academic interest. If a seasonal trend can be demonstrated for a malformation, then we can look for concomitant trends in other factors, such as infectious diseases, availability of certain nutrients, use of chemical pesticides, ingestion of drugs, amount of fluid intake, cosmic or other radiation, *ad infinitum*.

In the present study no attempt was made to identify or even to speculate on environmental factors that might possibly be related to the three malformations that demonstrated significant seasonal trend—cleft lip with or without cleft palate, hypospadias, and positional foot defects. Nevertheless, all three of these malformations show periods of maximum incidence in the early part of the year, suggesting that one or more teratogenic factors may be acting detrimentally on mid-year (summer) conceptions. The analysis by climatic region suggests that if a teratogenic factor is influencing the incidence of congenital malformations it may be restricted to, or be more potent in, certain climatic regions.

Generally speaking, teratogenic agents produce a spectrum of malformations and more than one organ system is usually affected. Therefore, an attempt should be made to detect seasonal trend separately for multiple malformation cases and single malformation cases. Of particular interest would be the analysis of individuals having at least two of the three congenital malformations discussed at length in this paper because of the similarities in their trends in analysis I. While beyond the scope of the present study, we may undertake these additional analyses in the future.

LIMITATIONS

There are several possible sources for error in this study which deserve mention:

1. Clefts and other malformations are underreported on birth certificates, although at least one study (Hay, 1967) has suggested that underreporting of clefts does not occur differentially according to month of birth.

2. The selection of the 31 reporting areas of the NIS was not made randomly. Therefore, in order to generalize the results of this study to all malformed livebirths in the United States, it must be assumed that there is no correlation between the selection and the reported trends of malformations.

3. The method for dividing the United States into climatic regions has some potential flaws. Precipitation, humidity, prevailing winds, and many other factors combine with temperature to make a climate, and the four regions were defined only on the basis of temperature.

4. Some of the malformation categories are not entirely homogenous, especially positional foot defects which, paradoxically, demonstrated the clearest seasonal trend of all the categories studied.

5. As mentioned earlier, the omission of fetal deaths from this study limits the usefulness of the results obtained for malformations of the central nervous system.

6. The month of conception rather than the month of birth would have been preferable as a starting point for testing seasonal trend, but uncertainty regarding the length of gestation for many cases made it infeasible.

SUMMARY

Utilizing birth certificates from the National Cleft Lip and Palate Intelligence Service (NIS), a study of seasonal variation in the incidence of congenital malformations was conducted. Approximately 60,000 malformations in babies born between 1962 and 1965 were included in three types of analysis.

In analysis I seasonal trends for the entire NIS...
areas were studied for the combined period, 1962–65. The data were separated by climatic region in analysis II in a search for seasonal trends within region. In analysis III the 1962–65 trends were broken down by individual years within climatic region.

Of the 15 malformation categories tested, only cleft lip with or without cleft palate, hypospadias, and positional foot defects demonstrated a statistically significant seasonal trend. Cleft lip with or without cleft palate showed a seasonal trend for the entire NIS area, but only the hot summer–moderate winter region displayed a significant seasonal trend. The peak of the curve for this region occurred in January, two months earlier than the March peak for the national trend. When individual years were analysed the trend in this region was evident in each year.

Hypospadias demonstrated a seasonal trend for the entire NIS area with April as the month of maximum incidence. The only significant trend within climatic region occurred in the moderate summer–moderate winter region and it was similar to the national trend and had the same peak. This trend was present in 1962 and 1963 but disappeared in 1964 and 1965 when the data for this region were analysed by individual years.

The seasonal trend for positional foot defects showed a March maximum for the entire NIS area. A similar trend was found in the hot summer–moderate winter region for the combined period 1962–65, and especially in 1964 and 1965. A striking seasonal trend, also similar to the national trend, was present in the hot summer–cold winter region where the incidence rose to a spring peak and fell to an autumn trough in each year separately as well as in the combined period.

**APPENDIX**

Briefly, the Edwards' model divides a circle into 12 equal sectors, each centred at angle

$$\theta_i = \frac{2\pi i}{12} - \frac{1}{2} \left( \frac{2\pi}{12} \right) \left( i = 1, 2, \ldots, 12 \right)$$

from a fixed starting line as in Figure 5. The months of the year are assigned consecutively to these sectors starting with January in sector 1. A weight consisting of a square root transformation of the observed frequency of a malformation, \( N_i \), for month \( i \) is then placed on the rim of the circle at angle \( \theta_i \). At this point it is assumed that the expected monthly frequencies, \( E(N_i) \), are proportional to the simple harmonic curve, \( 1 + \alpha \sin (\theta_i + \phi) \), where \( 0 \leq \phi \leq 1 \) allows a variable amplitude and \( 0 \leq \phi \leq 2\pi \) is the angle corresponding to the date of maximum incidence on the fitted curve. Both \( \alpha \) and \( \phi \) are to be estimated in this procedure.

Under the null hypothesis, \( \alpha = 0 \) and the expected monthly frequencies are equal. Intuitively this would place the centre of mass of the above weighted circle at the origin. A significant deviation of the computed centre of mass from the origin would then give reason for rejecting the null hypothesis and accepting an alternative hypothesis that \( \alpha > 0 \). The square of this deviation can be shown to have a chi-square distribution with two degrees of freedom under the null hypothesis and this is the basis for testing the null hypothesis versus the alternative hypothesis.

Empirically the Edwards' model has been successful in detecting cyclic trend of the simple harmonic type. Unfortunately, the model also detects by means of its chi-square test other types of trend which are neither in the simple harmonic category nor in the more general cyclic category. A hypothetical example illustrates this point.

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</tr>
</tbody>
</table>

\[
\chi^2 = 7.41 \text{ (probability level 0.025)}
\]

\[
\phi = 195^\circ \text{ (July)}
\]

**REFERENCES**


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