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The Great Potato Debate

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THE GREAT POTATO DEBATE

by

James D. Hudson

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I would like to thank Dr. Leo Vanderbeck, my principle advisor for his help and encouragement through the entire length of this research. Also Dr. Alan Russcher deserves my most sincere thanks for the hours of time devoted to my project particularly in seeing that the survey of mothers was conducted in a responsible manner. The statistical analysis of the Michigan data which I was able to gather would have been impossible without the help of Dr. Michael Stoline whose time and effort I truly appreciate.

In addition I would like to thank the entire staff of the Honors College including Dr. Clark, Mrs. Stein, Timm Rhinehart, and Michael Zeus whose friendly assistance and guidance have made my association with the Honors College a productive and memorable one.
INTRODUCTION

Anencephaly and spina bifida cystica are two of the most common severe congenital malformations consistently observed in human populations. Both represent defects in the neural tube and share a significant number of similar epidemiological associations, among them, occupational class, geography, sex ratio, maternal age, year and season of the year. In anencephaly, most of the brain and upper skull never form usually resulting in death within a few hours of birth. Spina bifida cystica is a malformation of the spinal cord often causing paralysis, vulnerability to infection, and early death.

In 1972 Dr. J. H. Renwick presented a controversial hypothesis which links epidemics of late blight of potato with epidemics of these two neural tube closure defects which he refers to collectively as ASB. According to Renwick's hypothesis, occurrence of ASB is "usually preventable by avoidance of a specific but unidentified substance present in certain potato tubers".(Renwick, #1 1972) A geographical correlation between high incidence rates for ASB and the distribution of potato blight epidemics throughout the world had led Renwick to the investigations which produced a considerable array of evidence supporting this hypothesized connection.

In October of the same year D. E. Poswillo et al. published the results of experiments performed on Colworth Wistar rats and cotton-eared marmosets (Callithrix jacchus). One group of each species were fed normal diets supplemented with
a blighted potato concentrate. This concentrate was made using Kerr's pink variety of potatoes infected with Phytophthora infestans, the causative organism of late blight of potatoes. Skins, sprouts, and discolored portions of the potatoes were included in the preparation which was boiled in deionized water, homogenized and freeze dried. None of the rats fed this preparation gave birth to any grossly abnormal offspring but of the eleven foetuses obtained from the six female marmosets fed the potato extract, four showed gross cranial osseous defects. The most severe defects were obtained from the females who had been receiving the potato supplement for the longest time before conception. (Poswillo, Sopher and Mitchell, 1972) Poswillo also hypothesized that these birth defects are no more common in marmosets than in humans, based on observations at the breeding colony of the Royal College of Surgeons of England. Poswillo, Hamilton and Sopher have also published results of teratogenic studies using marmosets exposed to thalidomide and irradiation which showed them to exhibit reactions highly similar to that of the human species. (Poswillo, Hamilton, and Sopher, 1972)

Most researchers who read Renwick's hypothesis seem to have dismissed it until Poswillo reported the striking results of his experiments. Newsweek magazine and a number of other popular magazines and newspapers then printed summaries of their work and cautioned expectant mothers to exercise care in choosing and preparing potatoes. This aroused considerable public concern especially among women who had already had children
affected by these defects. This publicity, which many people thought was too much, too early, did stimulate a more thorough investigation by numerous workers around the world. This paper will try to reexamine Renwick's hypothesis with respect to new evidence published by other workers and the information obtained by this author working in Michigan.
Renwick's indictment of blighted potatoes stemmed basically from the geographical correlation which he observed between ASB occurrence and blight occurrence. Dr. A. J. P. Martin (unpublished) had earlier conceived of the potato being responsible because he had found that another potato pathogen, *Synchytrium endobioticum* had a geographical distribution similar to that of ASB. This fungus causes potato wart disease and has been brought under control in recent years without a corresponding control of ASB. This inconsistency was resolved by Renwick's hypothesis that it is an antifungal compound that is produced by the potato in response to infection by a fungus or any other pathogen which is teratogenic. Then as Renwick stated, "the tendency for bad blight areas to be bad ASB areas perhaps reflects the fact that the potatoes that survive to be eaten in such areas are those that genetically or otherwise have a high level of antifungal compounds". Renwick covered a few of these compounds lightly in his paper but new evidence now enables us to take a closer look.

**Potatoes and Their Antifungal Agents**

Ever since the first potato blight epidemics in Europe in 1845-46 farmers and breeders have been trying to find potato varieties resistant to infection by the parasite. Indeed the introduction of such varieties has been the key factor in reducing blight throughout the world. In the last forty years the idea of breeding potatoes totally resistant to blight by crossing the domestic potato with *Solanum demissum* and other wild species
has been strenuously explored. The development of resistant varieties has led to the discovery that *Phytophthora infestans* is not a homogeneous species but is actually made up of an undetermined number of races. When varieties of potatoes were developed which were resistant to all known races of fungus another race soon appeared that was capable of attacking it. W. Black of Scotland has been responsible for much of the research on the genetics of blight resistance. His "major" gene theory of resistance has been most carefully studied. Black enumerated four major genes and named them R1, R2, R3 and R4. These genes acting alone or in combinations confer resistance to certain fungal races. The races of *P. infestans* have been named for the resistant varieties which they attack. Thus race 3 attacks potatoes with the R3 resistance gene and race 0 attacks none of the R-gene resistant varieties. So far no potato genotype known is resistant to the blight race 1,2,3,4. (Cox and Large, 1960)

In recent years potato breeders have come to regard field resistance which is a partial resistance as more valuable in the long run than R-gene resistance. Some of the common varieties of potatoes with field resistance are Champion, Kerr's pink, Alpha and Sebago. Even though field resistance is only a partial resistance it confers resistance to all known races which have been discovered so far. Another encouraging point in the potato breeding field was the discovery that *S. demissum*, the wild potato which has been used to breed R-gene hybrids also possesses field resistance to a high degree.
The relevance of these resistance mechanisms to this discussion lies in the antifungal compounds which they employ. In the R-gene mechanism the fungus is capable initially of attacking the tuber much as it would a susceptible tuber. In the R-gene resistant varieties however cells initially attacked die quickly and production of antifungal compounds called phytoalexins takes place almost immediately in and around the affected cells. In the susceptible tubers the infected cells do not die immediately and the fungus spreads rapidly to surrounding tissue. Only traces of the phytoalexins are found in these tissues. Byrd and Cutting (1971) give a good review of present understanding of this hypersensitive response to infection.

The antifungal terpenoids, rishitin and phytuberin are two of the phytoalexins so far extracted and identified from R-gene resistant tubers subjected to P. infestans. It is presently thought that these two compounds account for some of the resistance of these tubers but possibly more important are the steroid glycoalkaloids. These compounds vary with the variety of potato and the R-gene resistance which it possesses. This range of similar compounds have been characterized as accounting for 90% of the fungitoxicity of potato peel extracts to another fungus, Helminthosporum carbonum which is ineffective as a pathogen because it stimulates the hypersensitive reaction in the tubers. This hypersensitive response now appears to be a general, unspecific response to stress. Infection by a fungus or other incompatible pathogens represent an extreme stress
situation and results in the production and release of these phytoalexins.

Field resistance in potatoes has also been found to be imparted to certain varieties of potatoes through the constant production of similar and in some cases identical glycoalkaloids as those produced by the R-gene resistant varieties. Thus the field resistance is a constitutive property of the plants while the R-gene resistance is an induced response.

Renwick also identified several other toxic chemicals which are found in blighted potatoes but which are not antifungal compounds. The oxygenated coumarins—coumarin, scopoletin, aesculetin, and umbelliferone and their glucosides have been isolated from blight lesions of certain varieties of infected potato tubers. These compounds produce a characteristic fluorescence in the tissue around the blight lesions under ultraviolet light and have been shown to be produced both by P. infestans and the uninfected tuber itself in small amounts. (Austin and Clarke, 1966)

The apparent relationship of the synthetic mechanisms used by both organisms offer the possibility that they act together to produce the quantities observed in infected tubers.

There are also a few more compounds which have been suggested as possible teratogenic agents found in some potatoes. They are cinnamic acid derivatives isolated by D. D. Clarke (unpublished), alkaloids similar to cyclopamine, a chemical responsible for cyclops malformation in sheep (Keeler, 1973)
and cytochalasin B, a metabolite of *Helmintosporium dematioides*um which has been known to attack potatoes (Linville and Shepard, 1972).

We shall now consider the evidence which has been obtained in trying to implicate each of these groups of compounds as a possible teratogen found in potatoes. We must keep in mind however that the teratogen if one does exist may be an as yet unidentified compound.

**EVIDENCE FOR CHOOSING A TERATOGEN**

The results of Poswillo's preliminary experiments with rats and marmosets (Poswillo, Sopher and Mitchell, 1972) lent considerable credibility to Renwick's hypothesis but did little to help identify a possible teratogen in the potato. However, in August of 1973 he reported the results of more experiments with marmosets. In these further experiments marmosets were divided into three groups each with a different dietary potato supplement. The first group was fed normal domestic potatoes. The second group was fed potatoes rejected by the food--processing graders which were blighted, damaged and discolored in a ratio of 3:2:1. The last group of marmosets were fed tubers which were laboratory infected with *Erwinia carotovora*, a pathogen known to stimulate production of the antifungal toxins rishitin and phytuberin in potato tubers. All food preparation and feeding was done in the same way as in the earlier blighted potato trials.

None of the 35 offspring produced by these marmosets showed any gross anatomical defects however three sets of twins from the industry reject group showed similar behavioral abnormalities.
the significance of which has not been determined. Poswillo's only conclusion was that the cranial defects were not reproduced.

Of most interest is the results of the chemical analysis which Poswillo performed on the different potato extracts that he used in his experiments. Table 1 is a reproduction of those results which we will make use of in the course of this discussion.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Rishitin</th>
<th>Phytuberin</th>
<th>Total Glycoalkaloids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerr's Pink &quot;blighted&quot;</td>
<td>Trace</td>
<td>None</td>
<td>20</td>
</tr>
<tr>
<td>Erwinia-infected batch 1</td>
<td>89</td>
<td>69</td>
<td>1</td>
</tr>
<tr>
<td>Erwinia-infected batch 2</td>
<td>56</td>
<td>88</td>
<td>2</td>
</tr>
<tr>
<td>Industry-reject batch 1</td>
<td>8</td>
<td>Trace</td>
<td>38</td>
</tr>
<tr>
<td>Industry-reject batch 2</td>
<td>5</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Industry-reject batch 3</td>
<td>None</td>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>Domestic controls batch 1</td>
<td>Trace</td>
<td>None</td>
<td>10</td>
</tr>
<tr>
<td>Domestic controls batch 2</td>
<td>None</td>
<td>Trace</td>
<td>14</td>
</tr>
</tbody>
</table>

From Poswillo et al., 1973

THE GLYCOALKALOIDS Renwick, in his original paper cited evidence that in Scotland there is a higher risk of malformation for infants conceived in the spring and summer than for those conceived in the fall and winter. His hypothesis accounts for this by proposing that potatoes may become teratogenic as they age. It has been shown that the glycoalkaloid content of potatoes increases with age and exposure to light (Gull and Isenberg, 1960). Thus in the spring and summer when the last potatoes of previous year are being consumed the amount of glycoalkaloids
found in the tubers will be higher than in the fall and winter when the new crop is in. Renwick did in fact find considerable circumstantial evidence in his paper that the glycoalkaloids could possibly be teratogenic.

First of all solanidine which is a steroid alkaloid found in certain potatoes has already been shown to be toxic to the fungi and to man (Willimot, 1933). It is represented in the potato as a range of glycosides produced mainly by those potatoes with good field resistance to blight. Renwick thus realized that the tendency for a geographical area to be a bad blight area would increase the likelihood that field resistant varieties of potatoes would be grown in that area and thus result in a higher total solanidine content in the potatoes surviving to be eaten.

Another indictment of the glycoalkaloids in potatoes has come from Dr. Richard Keeler working with the steroidal alkaloid cyclopamine (Keeler, 1973). Cyclopamine was extracted from the Western range plant *Veratrum californicum* and found to be responsible for producing cyclops malformations in the offspring of sheep grazing on the weed. It was later discovered that cattle, goats and rabbits were also susceptible to insult by this teratogen. Of the alkaloids extracted from *V. californicum* three, cyclopamine (11-deoxyjervine), cycloposine (3-glycosyl-11-deoxyjervine) and jervine were all found to be teratogenic. In addition these teratogens produced defects in chick embryos some of which were certainly neural tube defects. A large number of other steroidal alkaloids were tested and found to be inactive and comparison
of the compounds suggested a specific structural requirement for teratogenicity. All three teratogenic substances share a common fused furanopiperidine ring structure. No alkaloids possessing this structure have yet been isolated from potatoes however many are known which have terminal furan and piperidine rings in which furan is fused to the steroidal portion rather than the piperidine ring. This type of an arrangement would still produce a planar structure which Keeler believes to be essential for teratogenicity. Keeler in a recent publication has established that rats are susceptible to cyclopamine at high dosage when administered with a buffer through a stomach tube. He has therefore hypothesized that if the teratogen in potatoes is similar to cyclopamine then rats should also be susceptible if given in the proper dosage and the proper time. Similar tests were carried out using solasodine and tomatodine which are alkaloids found in the potato and tomato respectively. No gross defects were observed in these tests although five resorptions were observed at high doses.

The analysis which Poswillo performed on his potato batches for glycoalkaloid content revealed that the original blighted Kerr's pink sample contained a higher total glycoalkaloid content than was found in all but one of the other potato samples. The remaining batch however was an industry-reject batch which had an even higher glycoalkaloid content and yet produced no gross anatomical defects in the offspring of the marmosets fed from that sample. Poswillo therefore concluded that it is not the
total glycoalkaloid content which is teratogenic but it was not
determined if the glycoalkaloid make up was the same for the two
batches. Since it has been shown that glycoalkaloid content is
variety dependent there could have been a specific glycoalkaloid
present in the Kerr's pink batch that was not present at all in
the industry-reject sample or was present in a much smaller
amount.

RISHITIN AND PHYTUBERIN Although much interest was given to these
two antifungal compounds early in this investigation, Poswillo's
results given in table 1 seem to indicate that neither of these
compounds were involved as the causative agent. The trace amounts
that Poswillo reported for the Kerr's pink sample was consistent
with findings that these compounds are found only in R-gene
resistant varieties (Katsui, Mural, Tanasugi, Imaizumi and Masamune,
1968). Since the Erwinia batches which were known to produce
rishitin and phytuberin showed high levels of these substances
and yet produced no observable defects it becomes doubtful that
these substances alone could have caused the birth defects observed
in the marmosets.

COUMARINS Little is known of the teratogenicity of this group
of compounds and the only work available has been with plants.
Coumarins have documented physiological effects on seed germin-
ation in lettuce which is of questionable value to this discussion.
We were not able to find data on varietal differences in coumarin
levels which could have been of value.
CYTOCHALASIN B  In April of 1972 George P. Linville and Thomas H. Shepard published an article entitled Neural Tube Closure Defects caused by Cytochalasin B. In their experiments Linville and Shepard cultured fertile chick embryos of 26 hour average development with thin egg albumin media where the only variable in the culture media was the presence or absence of a particular concentration of cytochalasin B.

Six of the thirty eight control embryos showed minimal delay in closure of the anterior neural pore while twenty seven from the thirty three treated embryos had obvious defects in the neural tube closure process. In addition an interesting dosage relationship was observed. With dose levels at 1.0 and 2.0 ug per explant a 51% and 88% mortality was observed respectively. Also both somite formation and embryonic stage in the survivors were retarded. However at the 0.5 ug dose level where 15 of 22 embryos showed abnormal neurulation there was only 12% mortality and survivors did not differ significantly from the controls in either somite number or stage of development (Linville and Shepard, 1972).

In other experiments it has been shown that cytochalasin B terminates certain morphogenetic processes which are mediated by contraction of microfilaments. Experiments have been done involving cleaving of marine eggs by cytokinesis and morphogenesis in salivary gland epithelium.

This earlier work as well as the discovery of a thin band of 40-50 µm microfilaments beneath the apical surface of the
neural plate cells and the association of these microfilaments with neurulation are what suggested the chick embryo experiments to Linville and Shepard. Shepard knew that cytochalasin B was also produced by the fungal pathogens Helminthosporium solani and Phoma exigua which are often found in mouldy seed potatoes. For this reason he suggested that cytochalasin B may be found in the blighted potatoes (Shepard, 1973). Carter (unpublished) analyzed all of the potato samples used by Poswillo and found that only the original Kerr's pink blighted potato concentrate showed any cytochalasin activity. This represented a total daily dose equivalent in activity to 3 µg of cytochalasin B per marmoset. Poswillo is now undertaking experiments to examine the effects of cytochalasin and solanine on marmoset morphogenisis.
Renwick has stated that up to 95% of the spina bifida and anencephaly in the U.K. can be prevented by avoidance of potatoes by women who are contemplating conception. His evidence comes mainly from the epidemiological data which he has gathered. This section of the discussion will review Renwick's interpretation of this data and consider other evidence submitted by other workers including some evidence I have found for Michigan.

The bulk of Renwick's potato data came from *Potato Blight Epidemics Throughout The World*, a U. S. Department of Agriculture handbook written by A. E. Cox and E. C. Large and published in 1960. This handbook consists of thorough studies of certain typical areas of certain countries around the world and fills in with comparisons of other areas to these. In the United States for instance Aroostock county in Maine, Long Island in New York and a potato growing area of Florida were chosen for study. These areas represented the different blight climates under which potatoes are grown in the U.S. Idaho was mentioned but not studied because dry hot conditions make late blight a very minor problem in that state. Maine presents the worst late blight problem in the U.S. because high humidity and lower temperatures are ideal for the fungal growth. Indeed as Renwick points out there is a general decreasing blight as you go from east to west across both the United States and Canada. More surprising however is that ASB incidence in the United States and
Canada follow similar patterns. Figures 1 and 2 are taken from Renwick (#1, 1972) and show this correlation more graphically.

Renwick has also shown that in Ireland where moist, cool weather is ideal for blight ASB rates are the highest in the world and in Belfast and Dublin the incidence averages almost 1% of all births. Similar types of high and low correlation were cited by Renwick for England, Europe and other parts of the world. The low incidence of about 1 case per thousand births that were reported for parts of Africa, Hong Kong, Manilla and Taiwan are considered by Renwick to be a 'background' incidence of unknown origin which is unaffected by the potato.

Renwick goes on to show how his hypothesis could fit other well substantiated data including occupational class (poorer people eat poorer quality potatoes), season of the year (older potatoes in spring and early summer), urbanization, twin data and race. Some questions have been raised on Renwick's interpretation of this data but more of the workers have attempted more thorough blight correlation studies in local regions and have reported varying results. These reports will be reviewed in chronological order as they were published.

In a follow up article in August of 1972 Renwick presented the data shown in Table 2. He reports a significance level, by an exact test of 0.001 (Renwick, #2, 1972). Figure 3 which Renwick published in January 1973 shows a striking graphic representation of a correlation found in England and Wales between 1961 and 1963. (Renwick, #1, 1973) Due to monthly variations in potato supply

Figure 1

Rank Order of States
- 1-12 (highest mortality)
- 13-24
- 25-36
- 37-48 (lowest mortality)

Mortality of white infants attributed to spina bifida and meningitis in each state of the United States, 1950-59. There is an evident correlation over the states between this mortality and the severity of potato blight as depicted in Fig. 1. Reproduced from Hewitt (1963).
TABLE 2

No. of stillbirths in Scotland with an anencephaly that was initiated in each of the years 1947-56 (in order of rank and adjusted to a constant 95,000 total births per year)  Blight score for the populous West of Scotland for preceding year

<table>
<thead>
<tr>
<th>Year</th>
<th>Stillbirths</th>
<th>Blight Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1947</td>
<td>292</td>
<td>2</td>
</tr>
<tr>
<td>1948</td>
<td>290</td>
<td>2</td>
</tr>
<tr>
<td>1949</td>
<td>289</td>
<td>1</td>
</tr>
<tr>
<td>1950</td>
<td>286</td>
<td>1</td>
</tr>
<tr>
<td>1951</td>
<td>264</td>
<td>0</td>
</tr>
<tr>
<td>1952</td>
<td>242</td>
<td>0</td>
</tr>
<tr>
<td>1953</td>
<td>241</td>
<td>1</td>
</tr>
<tr>
<td>1954</td>
<td>317</td>
<td>0</td>
</tr>
<tr>
<td>1955</td>
<td>209</td>
<td>0</td>
</tr>
<tr>
<td>1956</td>
<td>204</td>
<td>0</td>
</tr>
</tbody>
</table>

FIGURE 3

England and Wales

1.926/1000
1.860/1000
1.800/1000 corrected for trend of -0.06 cases per thousand per annum
1.730/1000
1.670/1000

Anencephaly incidence 1/1000 per year 1/1962 - 7/1968

Percentage of births without anencephaly contracted in calendar year.

and normal gestational length of anencephalic pregnancies (33 weeks)
Kenwick chose a twelve month period beginning and ending in mid-
February which is 1 1/3 years after the end of the relevant blight
year. Figure 3 was corrected for a trend of -0.06 cases per
thousand per year representing an unexplained downward linear
trend in anencephaly incidence. Kenwick observed a correlation
coefficient of 0.87 for this data.
In December of 1972 an editorial in the British Medical Journal noted that Professor E. G. Knox recently performed a computer survey testing the relationship of anencephalus with the consumption of over one hundred different foodstuffs. He found a negative correlation with potato consumption with his data from England and Wales. Renwick explains that potato consumption varies during the year with the quality of potatoes so that when potato consumption goes down it indicates poor quality potatoes are being sold and it is these potatoes which are teratogenic. Thus a negative correlation with potato consumption indicates a positive correlation with poor quality potatoes.

Knox did find some interesting positive correlations of his own, in particular with cured meats. "Thus those regions of England and Wales with the greatest intakes of cured meats had the highest anencephalus rates, while a drop in sales of corned beef after the Aberdeen typhoid outbreak was followed six months later by the lowest anencephalus rates on record." (Ed. British Medical Journal, 1972) Knox has been cautious in interpreting these and other results and suggests that certain foods and their additives deserve more careful study.

One of the first researchers to protest Renwick's theory in the literature was Irvin Emanuel. He had been working in Taiwan where in 1966 the average annual consumption of potatoes was 1 lb and the ASB rate was 1.15 per thousand births. This is not a high defect rate but in France during the same year
average potato consumption was 464 lb per person and the anencephaly rate was .54 cases per thousand births. (Emanuel, #1 1972)

Emanuel felt that the socioeconomic class distribution which he and other workers have consistently observed throughout the world is more significant than any potato affect. Renwick explained the class factor by saying that the poorer housewife prepares and eats more potatoes of poor quality than do women of higher class status. In Taiwan however it is the upper class that is more likely to eat potatoes at all and thus the class affect should not be seen there. In Renwick's reply (Renwick, #3 1972) he suggests that a staple food such as rice which also has many diseases may also produce the same teratogen as do potatoes but no evidence has been reported to substantiate this.

In February 1973 C. Smith et al. reported sets of data on ASB rates and haulm blight scores for the Edinburg area of Scotland for a seventeen year period from 1954 to 1971 (C. Smith, M. Wall, A. Boyd, J. C. Holmes, 1973). These workers used conception dates instead of birth dates and used the cases recorded conceived from July in one year (N) to June the next year to correspond with the blight from year N as this is the period during which these potatoes are consumed. A general downward trend was corrected for and the number of cases was adjusted to the mean number of 4300 births per year. No significant correlation was found between blight severity and cases of ASB recorded.
Shortly thereafter the results of teratogenic studies with rats were reported by S. Chaube et al. (S. Chaube, C. A. Swinyard, and R. H. Daines, 1973). These workers used pregnant Wistar strain rats gavaged with either raw or boiled homogenate of blighted Katahdin potatoes from the State of Maine. The animals were gavaged twice daily for seven consecutive days of pregnancy (days 5-11). Also two rats were treated identically with normal parts of blighted potatoes and three with normal marketable potatoes. No defects were recorded and this added to Poswillo's evidence that blighted potatoes are not teratogenic to rats.

P. S. Spiers then presented data comparing the northern and southern states of the United States with respect to potato blight and spina bifida rates (P. S. Spiers, 1973). Since there is more blight in the northern states than in the south it would be expected that this variation would also be observed for spina bifida incidence. This was not the case however and sometimes the opposite variation was observed. Spiers thus concludes that even if late blight is partly responsible it cannot account for the majority of cases that Renwick has hypothesized.

A study quite similar to the Edinburg study was reported for Boston in March of 1973 by MacMahon et al. (R. MacMahon, S. Yen and K. J. Rothman, 1973). Their study covered a thirty five year period from 1930 to 1964. They tried to correlate annual blight severity data for Maine, which supplies 60% of Boston's
potatoes, with the prevalence rate of neural tube defects in Boston conceived in the same crop year. The data was corrected to account for a curvilinear regression observed in the prevalence rates of neural tube defects. An insignificant correlation coefficient of 0.03 was observed for their data. A confirmed similarity between this data and Renwick's Scotland data make chance an unlikely explanation of the discrepancy of results. Also, during the months of July, August and September when Boston's potato supply comes from non-blight regions there has been no observed decrease in neural tube defect rates for the corresponding months.

No significant correlation was observed in another similar study done on anencephaly rates and blight data for eastern Canada (J. Mark Elwood, 1973).

Renwick has been working on setting up a potato avoidance trial in England to test his hypothesis directly but understandably has not yet published any results. In May of 1973 however, J. Lorber et al. reported an early diagnosis of anencephaly (J. Lorber, C.R. Stewart, and A. Milford Ward, 1973). The mother was one of 38 women under observation who had already delivered an ASB infant and one of several who had been on a potato-free diet organised by Lorber. She had not eaten any potatoes for six months before conception and all during pregnancy. The fetus was found to have anencephaly and a large spina bifida. Dr. Lorber feels one case is not enough to discount Dr. Renwick's
hypothesis and is continuing his potato avoidance trials.

Last August results from a different type of investigation were reported by C. A. Clark et al. (C. A. Clark, O. M. McKendrick, and P. M. Sheppard, 1973). They reported the results of a retrospective survey of certain dietary habits of mothers of 83 children with spina bifida and compared them with 85 matched controls. The main reason for the survey was to test Renwick's potato hypothesis as much as is possible by the survey method. The only significant relationship which was found which implicates potatoes in any way was the tendency for the mothers of affected children to eat more potatoes from a chip shop. These establishments do generally use poorer grade potatoes however these workers felt that this reflected a generally poorer diet and higher degree of ill health which was observed for this group rather than a direct causal relationship. In no other way did the survey support Renwick's hypothesis. These workers are presently preparing another survey limited to those factors which were found suggestive in the first survey along with a limited number of others such as preserved meats as was suggested by Knox (1972).

The next month another report was published which shall be the last one mentioned here. It related a study done in the state of New South Wales, Australia. Again it showed no significant correlation between blight score and corresponding ASB incidence rates (B. Field and C. Kerr, 1973).
THE MICHIGAN STUDY

There have been many unforeseen difficulties in trying to correlate late blight occurrence and ASB incidence in Michigan. Michigan is not a major potato producing state in the U.S. and usually hot weather in July and August keeps late blight at a minimum. The location of Michigan surrounded by the great lakes however keeps the humidity high and occasionally light rains combined with sustained temperatures below 70 °F result in ideal blight conditions. Even in these 'bad' blight years the blight is usually limited to a few farms in each potato growing area where for one reason or another spraying was not done or was ineffective because of rain or other weather conditions.

Accurate records like those kept in England and the rest of the U.K. are not kept in Michigan both because potatoes are not such an important crop here and blight is not so often severe as it is in Maine where late summer temperatures are generally lower. As a result the only blight information I was able to obtain for Michigan was from the memory of Dr. Howard Potter, a plant pathologist at Michigan State University. Dr. Potter's information dates back only to 1959 and only refers to certain years as 'bad' blight years. Table 3 gives this late blight data.

TABLE 3

<table>
<thead>
<tr>
<th>Year</th>
<th>Blight Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1959</td>
<td>severe(2)</td>
</tr>
<tr>
<td>1960</td>
<td>slight(1)</td>
</tr>
<tr>
<td>1961</td>
<td>slight(1)</td>
</tr>
<tr>
<td>1962</td>
<td>severe(2)</td>
</tr>
<tr>
<td>1963</td>
<td>severe(2)</td>
</tr>
<tr>
<td>1964</td>
<td>slight(1)</td>
</tr>
<tr>
<td>1965</td>
<td>slight(1)</td>
</tr>
<tr>
<td>1966</td>
<td>severe(2)</td>
</tr>
<tr>
<td>1967</td>
<td>severe(2)</td>
</tr>
<tr>
<td>1968</td>
<td>slight(1)</td>
</tr>
<tr>
<td>1969</td>
<td>slight(1)</td>
</tr>
<tr>
<td>1970</td>
<td>severe(2)</td>
</tr>
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</table>
From August through March 60% of the potatoes sold for consumption are Michigan grown potatoes. Idaho and Maine potatoes make up most of the 40% which are imported from other states during these months. From early April into August 40-50% of the potatoes are from Maine and 40-50% from Idaho with the rest coming mainly from California and Florida. Since Maine is the only other blight area which supplies substantial amounts of potatoes to Michigan it was the only other area for which a blight score was used. The Maine scores are those obtained by B. MacMahon for his Boston study and are shown in table 4.

<table>
<thead>
<tr>
<th>Year</th>
<th>Score</th>
<th>Year</th>
<th>Score</th>
<th>Year</th>
<th>Score</th>
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<tbody>
<tr>
<td>1950</td>
<td>severe(3)</td>
<td>1958</td>
<td>slight(1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1951</td>
<td>severe(3)</td>
<td>1959</td>
<td>severe(3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1952</td>
<td>slight(1)</td>
<td>1960</td>
<td>moderate(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1953</td>
<td>slight(1)</td>
<td>1961</td>
<td>none(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1954</td>
<td>severe(3)</td>
<td>1962</td>
<td>moderate(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1955</td>
<td>slight(1)</td>
<td>1963</td>
<td>severe(3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1956</td>
<td>slight(1)</td>
<td>1964</td>
<td>slight(1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1957</td>
<td>slight(1)</td>
<td></td>
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</tbody>
</table>

ASB rates in Michigan presented another problem. From 1950 to 1969 the only compiled death statistic for ASB was spina bifida with meningocele. From 1970 on, anencephaly was included as another category but these were only for live births as were the spina bifida data. Fetal deaths were only available for 1970, 1971 and 1972 and were located in another publication. In addition the deaths were grouped by age levels (i.e. less than 1 year, 1-4 years, 5-9 years, etc.). In order to have a reasonable sample size I was only able to consider the spina bifida.
deaths under one year of age and even this allowed for some overlapping in statistics from one year to the next. This data, given in cases per thousand live births is shown in table 5.

<table>
<thead>
<tr>
<th>Year</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>(.62)</td>
</tr>
<tr>
<td>1951</td>
<td>(.55)</td>
</tr>
<tr>
<td>1952</td>
<td>(.49)</td>
</tr>
<tr>
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<td>(.49)</td>
</tr>
<tr>
<td>1954</td>
<td>(.44)</td>
</tr>
<tr>
<td>1955</td>
<td>(.35)</td>
</tr>
<tr>
<td>1956</td>
<td>(.31)</td>
</tr>
<tr>
<td>1957</td>
<td>(.34)</td>
</tr>
<tr>
<td>1958</td>
<td>(.17)</td>
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<tr>
<td>1959</td>
<td>(.28)</td>
</tr>
<tr>
<td>1960</td>
<td>(.24)</td>
</tr>
<tr>
<td>1961</td>
<td>(.31)</td>
</tr>
</tbody>
</table>

Working with Dr. Michael Stoline we proceeded to run a computer analysis of this data. In order to eliminate the overall decline in incidence rates of spina bifida we first tried force the data into linear and quadratic regression models. The linear model accounted for 62\% of the variance while the quadratic model accounted for 66.5\% of the variance.

We then correlated the deviations from both the linear and quadratic models with the blight score of the same year from Maine. We obtained insignificant correlation coefficients of 0.41 and 0.37 respectively. This shows little correlation between the blight score in Maine for each year and the number of infant deaths due to spina bifida during the same year in Michigan.

We then ran the same correlation tests with the Michigan
blight data and obtained coefficients of 0.12 for the linear model and 0.06 for the quadratic model. Both were totally insignificant and so we then tried the correlation test for the blight score of the year previous with the incidence rate of a given year. For the Maine data the coefficients were 0.03 and -0.05 for the linear and quadratic models respectively. For the Michigan data the coefficients were -0.12 and 0.07. In addition we combined the blight data for both states for the years that they overlapped and weighted each set according to the percentage of potatoes obtained from that state. In other words the Michigan score was multiplied by 8/12 for the number of months and .60 for the percentage during those 3 months. The Maine score was the sum of 8/12 times .20 plus 4/12 times .45 both multiplied times the Maine score for that year. No significant correlation coefficients were obtained for the sum of these scores either.

In going back over these results we observed a non-random pattern of deviations from both the linear and the quadratic regression curves. The pattern suggested a quartic regression might be more appropriate. When this was completed it accounted for 81.5% of the variance. Again however we obtained an insignificant correlation coefficient of -0.25 for the Maine data which was our best data. We thus concluded that the potato blight occurring in both Maine and Michigan has no significant correlation with the incidence rates of spina bifida in Michigan for that same year and the following year.
CONCLUSION

Although there has been a considerable amount of evidence presented on both sides of this issue it is still impossible to draw any hard conclusions as to the validity of Renwick's potato hypothesis. Although the local studies generally dispute involvement of potato blight as a determining factor in ASB incidence rates these studies will not settle the question. Renwick is hoping that the potato avoidance trials being conducted separately by himself and Dr. Lorber will provide a definite answer. Certainly if ASB rates are at one extreme or the other during these trials they will provide an answer but it seems more likely that the results will lie somewhere in between and still allow different interpretations.

It would be most helpful if the marmoset experiments undertaken by Roswillo could be properly explained. Cytochalasin B now seems a likely culprit and indeed it may hold some of the responsibility for ASB occurrences in humans but more evidence is needed before anything can be said with certainty.

This author now has underway a survey of mothers of ASB infants in the Kalamazoo area. The sample size is small however and the results of the survey by C.A. Clark et al. throw doubt on the value of my smaller less detailed survey.

In any case I feel that research should be continued to try to assess the teratogenicity of blighted potatoes. The correlation studies reported here suggest that strict avoidance of potatoes by pregnant women is not called for although it is always
wise to discard diseased and badly damaged potatoes. Further correlation studies are not likely to extend our knowledge however and probably should not be encouraged. Experiments with rats fed blighted potatoes have not produced any positive results as yet. Keeler's experiments with cyclopamine suggest however that the rat's usefulness in this area may not have been realized yet.

Whether or not Renwick's hypothesis proves to have any validity at all, his article has stimulated research and added to our understanding in this very worthwhile area.
BIBLIOGRAPHY


