Epidemiological Study of an Illness in the Guatemala Highlands Believed to Be Encephalitis

Drs. José Víctor Ordóñez, Juan Alfredo Carrillo, Mario Miranda C., James L. Gale

A periodic, irregularly distributed illness of unknown etiology that affected certain families in an agricultural area in Guatemala was shown epidemiologically to be caused by eating seeding wheat impregnated with a mercury solution.

For three years an unusual illness had been occurring sporadically in the Guatemala Highlands. It appeared in the summer months and affected a small number of persons. From the nature of the symptoms, which involved the central nervous system, it was thought to be an encephalitis of undetermined etiology.

Because of the small number of cases reported, the illness did not warrant detailed study at that time. It was classified as probably infectious encephalitis, since it could not be distinguished from other sporadic encephalitic diseases.

An investigation carried out in 1965 resulted in defining the clinical and epidemiological characteristics of the illness and identifying its causative agent.

Background

Beginning in July 1965 reports were received of a considerable number of cases with alarming symptoms—mainly functional impotence of the extremities, blindness, deafness, and loss of consciousness.

The cases occurred mainly in the vicinity of Sibilia, Panorama, and Huitán in the Department of Quezaltenango, and by the end of August there had been 16 cases with eight deaths.

Because of the increased incidence of the disease, the seriousness of the symptoms, and the high case-fatality rate, a complete study of the problem was undertaken. The opinion of physicians—that it was a seasonal outbreak of infectious encephalitis of unknown origin—was based on the fact that at the same season in 1963 and 1964 similar cases, some of them fatal, had occurred in Panorama.

Method of Work

In order that all the factors that might be involved in the occurrence of the disease could be studied and its etiology determined, the following activities were undertaken:

1. Study of the ecological characteristics of the region, including the socioeconomic status of the population.
2. Entomological investigation of the affected area.
3. Epidemiological investigation of each case.

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6 This investigation was carried out chiefly by Dr. Romeo de León of the School of Medical Sciences, University of San Carlos, Guatemala.
4. Clinical examination of all patients.
5. Investigation of other etiological agents, in particular toxic agents. Insecticides, paints, foods, and other substances that might have affected these households were examined.
6. Collection of blood specimens from patients, contacts, and the general population for virological examination.
7. Collection of post-mortem material for other laboratory investigations.

Main Features of the Region

The area affected was part of the rural mountainous area of the Departments of Quetzaltenango, Totonicapán, and San Marcos. The altitude in this area ranges from 8,000 to 9,800 feet. The climate is dry and rather cold, and there is a marked difference in temperature between day and night. At that time of the year the temperature at night was about 32°F. There is a well-defined rainy season extending from May until October; 1965 was relatively dry. The population comprises mainly Indians who subsist by cultivating maize and wheat; part of the crop is sold and the rest is eaten by the farmers and their families.

The living habits are simple and uniform—especially the diet, which consists primarily of wheat and maize. Most of the land is cultivated except for small wooded areas, mainly under conifers. Some of the houses are grouped to form hamlets, but most are widely scattered in the mountains.

The drinking water does not come from a single source; the families use small mountain springs. There is no system for the disposal of human or other waste.

Insects are few, and there are almost no arthropods except fleas and, very rarely, lice.

Cases of the Illness in 1965

Between July and October 1965 there were 45 cases, with 20 deaths; the distribution of cases according to place of origin is shown in Table 1.

The table also shows the high incidence and case-fatality rate in the villages of Panorama and Centro. The fatality rate was always more than 25 per cent, and in Centro it reached 88 per cent.

Although only 12 families were affected, many of their members fell sick and died. This made the attack rate very high in comparison to that for the general population, and pointed up a special characteristic of the illness.

| TABLE 1 — Distribution of the Illness by Locality, Number and Rates of Cases and Deaths, and Case-Fatality Rates. |
|---|---|---|---|---|
| Locality | Population | Cases | Deaths | Case-fatality rate |
| | | Number | Rate % | Number | Rate % | |
| Siguilá | 500 | 1 | 0.2 | 1 | 0.2 | 100 |
| Panorama | 400 | 15 | 3.8 | 4 | 1.0 | 26 |
| Centro | 269 | 8 | 3.0 | 7 | 2.6 | 88 |
| La Unión | 200 | 2 | 1.0 | — | — | — |
| Palomora | ... | 4 | ... | 2 | ... | 50 |
| San José Chisalqui | 1,722 | 15 | 0.9 | 6 | 0.3 | 40 |
| Total | 3,091 | 45 | 1.5 | 20 | 0.6 | 44 |

... Data not available.
— None.
TABLE 2 — Cases and Deaths by Locality and Sex of Patients.

<table>
<thead>
<tr>
<th>Locality</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Sigilá</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Panorama</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Centro</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>La Unión</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Palomora</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>San José Chicalquix</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>26</strong></td>
<td><strong>19</strong></td>
</tr>
</tbody>
</table>

— None.

Following are some data on the families affected:

- Number of families: 12
- Number of members: 74
- Cases: 45
- Percentage: 61
- Deaths: 20
- Percentage: 27
- Case-fatality rate (per cent): 44

Figure 1 shows 43 cases arranged according to the week in which the symptoms began to appear. No information about the onset of the disease could be obtained about the two cases that died. The histogram covers patients from all the affected localities, since the number observed in some of them was so small that separate analysis was not justified. It can be seen that the first cases appeared in the week beginning 11 July and that the number then began to drop, reaching zero two weeks later. At the beginning of August new cases occurred, rising to seven in each of the next three weeks. In the last week of August the number of cases began to fall. By the middle of September there were none, but in the week beginning 19 September three final cases occurred.

Table 2 shows the distribution of patients and the deaths by sex. It will be seen that there were more cases and more deaths among males.

TABLE 3 — Cases and Deaths by Age Group and Sex.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>0 to 1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2 to 9</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>10 to 19</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>20 and over</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>24</strong></td>
<td><strong>21</strong></td>
</tr>
</tbody>
</table>

— None.

Table 3 shows the distribution of cases by age group. The first fact that stands out is that more than 50 per cent of the cases occurred in persons under 10 years of age, and 75 per cent in persons under 20. It is also notable that there were no cases in the first
year of life. The case-fatality rate was rather similar in all the age groups.

Tables 4 and 5 summarize the clinical signs and the laboratory findings in patients, most of whom were hospitalized. Fever and the other symptoms that usually accompany it (headache, muscular pain, weakness, and so on) hardly ever appeared, either at the onset of the disease or during its course. This fact was confirmed by careful questioning of relatives and, sometimes, of the patients themselves. But functional impotence of the extremities, especially the legs, appeared more or less suddenly and in a few hours led to inability to walk. It continued throughout the course of the disease and was observed to persist to a certain extent in convalescents of the previous year. It appeared to be associated with muscular atrophy accompanied by spasticity (in some cases flexure contractures) and loss of coordination. In most of the cases this was the major disturbance at the beginning of the disease.

In addition to the symptoms and signs mentioned, the tendon reflexes were heightened in most patients and myoclonic movements were observed in others.

Blindness followed functional impotence of the extremities and was the other symptom that was almost universal. It rapidly grew worse until it became total, and was the most serious sequela of the disease.

Deafness was also frequent, though less so than blindness. There may have been more cases than were noted, since it could not be detected in some patients owing to coma or extreme youth.

Coma, which was observed in most of the hospitalized patients, appeared late in the course of the disease, developed gradually, and was often succeeded by death.

It is interesting to note that the patients rarely had convulsions.

Two laboratory findings were noteworthy for their frequency. One was negative: an absence of changes in the spinal fluid, except in five cases in which the level of proteins and cells rose slightly. The second was positive: the frequency with which chemical and cytological examinations revealed changes in the urine, which consisted in an elevated albumin level (between 0.5 g and 2 g per liter) and the presence of granular and leukocyte cylinders.

### Search for Other Etiological Agents

The possible involvement of other etiological factors was carefully investigated. For this purpose the dwellings of the families affected were inspected to see whether they contained insecticides, paints, rodent poisons, and other toxic substances. Members of the patients' families, neighbors, and, in the case of families living in organized communities, the authorities were questioned. This investigation proved fruitless.

Next, possible toxic elements in food, such as edible mushrooms, were investigated. In the course of this investigation it was noted that during the period of the year in
which the illness occurred, many families, and especially the poorest, ate part of the wheat given them for seed, which had been treated with a fungicide known commercially as Panogen—an organic mercury compound. All the families affected sowed the treated grain during the period concerned, and many of them admitted having eaten some of it, sometimes mixed with maize, sometimes unhusked, and more or less carefully washed to remove its chemical coating.

Some patients and members of their families denied that they had eaten the wheat. However, the impression was that the denial was caused by fear, since neighbors and local authorities stated categorically that they had indeed done so.

An additional item of information was the absence of cases among the poorest families, which often found it difficult to get enough to eat.

It was learned that the treatment of the wheat seed with Panogen was begun on 15 April each year. This product is a solution of methyl mercury cyanhydric diamide, containing the equivalent of 1.5 per cent mercury in an organic compound. It is added to the seed in a proportion of 3 cm$^3$ per 10 pounds; the seed is then immediately bagged and is ready for distribution and sowing. The bags bear a warning to the effect that the seed contained in them is for agricultural use only and is not to be eaten.

The sowing period for wheat runs from May to July in that area. This, then, is the period during which the people have access to the seed.

**Laboratory Data**

**Serological.** Hemagglutination inhibition tests for Venezuela, St. Louis, and Eastern Equine encephalitis were carried out on 21 blood specimens obtained from patients, family contacts, and the general population of the affected communities. In all but three cases the titer was under 10 (in the highest of the exceptions it was only 40). These titers were without significance for the diagnosis, and the results were therefore considered negative.

**Toxicological.** Specimens obtained from two patients on whom an autopsy was performed immediately after death were examined toxicologically.

From one of them specimens of brain, spleen, kidney, and liver were obtained; part was examined in the country and part abroad. Examination of a mixture of 340 g of these organs revealed the presence of 15 µg mercury. It was subsequently learned that the examination made abroad of the same specimens, and also of a quantity of the wheat seeds, had given the following results:

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Methyl mercury cyanhydric diamide (ppm)</th>
<th>Mercury (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Spleen</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Kidney</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Liver</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Wheat seed</td>
<td>26</td>
<td>17</td>
</tr>
</tbody>
</table>

As for the other case, an analysis of 40 grams of liver showed it to contain 8 µg mercury.

**Discussion and Conclusions**

The disease in question affected the central nervous system. At the onset there were apparently no prodromal symptoms and no symptoms compatible with infection. The course of the illness and its symptoms were serious and surprisingly uniform. The case-fatality rate was high and there were disabling sequelae.

These characteristics, together with the laboratory findings, were not those normally...
observed in infectious encephalitis. The negative results of the serological tests excluded the possibility of viral encephalitis, the initial diagnosis. The irregular geographic distribution of the disease and the proved absence of likely vector insects also suggested another etiological agent. The fact that since 1963 similar cases had been observed only during a certain period of the year, and in the same area of the country, indicated that the causative factor also had seasonal and geographic limitations.

The intensity and nature of the signs pointed rather to a pathological disorder caused by toxic substances.

The epidemiological study showed plainly that wheat treated with Panogen must have been the toxic cause of the disease. All the characteristics noted, including the high attack rate in certain families, the significant age distribution, the absence of cases during the first year of life, and the seasonal and geographic distribution, were clearly explained if this wheat was taken as the cause. This conclusion was supported by the laboratory findings, which showed obvious signs of attack on the kidney parenchyma.

Furthermore, the clinical picture observed in the patients was compatible with poisoning by an organic mercury compound (1, 2). These compounds are absorbed through the skin and the gastrointestinal and respiratory tracts and are stored mainly in the liver, the kidneys, and the brain. Organic compounds that have alkyl radicals may be even more toxic: not only is more absorbed but less is excreted, and thus more is stored. Brain damage caused by mercury compounds with methyl or ethyl radicals may be irreversible. There are seldom the acute symptoms caused by gastrointestinal irritation and renal failure that are frequent in inorganic mercury poisoning.

In cases of organic mercury poisoning the nerve symptoms appear first, sometimes after repeated small doses, with months of latency. This may explain what happened to the persons who ate the seed but showed no symptoms.

The clinical signs vary greatly and include tremor, visual disturbances that may go so far as varying degrees of blindness, progressive loss of coordination, generalized myoclonic movements, mental deterioration, and coma. The clinical picture frequently worsens even after exposure to the poison has stopped. The duration of the illness in fatal cases is from 1 month to 15 years.

In the series of cases in question, besides the characteristic clinical picture observed, toxicological examinations of material obtained from the two post-mortem examinations conclusively proved the presence of mercury. The amounts found are similar to those found by other authors in cases of poisoning caused by organic mercury compounds with alkyl radicals (3, 4).

In conclusion, the epidemiological investigation, the clinical picture, and the serological and toxicological findings confirmed that the illness was caused by poisoning with an organic mercury compound—that used for preserving grain intended for planting but eaten by the affected families.

Summary

In 1965 an epidemiological study was made in an agricultural area of Guatemala to establish the etiology of an illness affecting certain families. The involvement of the central nervous system gave the impression that the disease was an encephalitis of undetermined etiology.

A study was made of the characteristics of the area, and of the economic and social situation of the inhabitants, and an entomological survey was undertaken to identify vectors. An epidemiological investigation was made of each case, as was a clinical examination of each patient. A search was made also for other etiological agents, especially toxic agents. Blood samples from patients, contacts, and the general population, as
well as post-mortem material from those who had died from the illness, were examined.

The persons afflicted were Indians living in the mountains and cultivating corn and wheat. Except for small wooded areas, most of the land is cultivated; part of the crop is sold and the remainder is kept for food. The water they drink comes from mountain springs, and there is no system of excreta or garbage disposal. Insects are not plentiful in the area.

Between July and October 45 cases of the disease occurred and of these 20 died. Only 12 families were affected, but many members fell ill and died.

More than 50 per cent of the cases occurred among children under 10 years of age, and 75 per cent among those under 20 years of age. There was no case among children under one year of age. The case-fatality rate was similar for all age groups.

The predominant symptoms of the disease were: loss of the use of extremities, blindness, deafness, and loss of consciousness. Among significant laboratory findings mention should be made of the absence of changes in the spinal fluid and high levels of albumin (0.5 g to 2 g per liter) in the urine.

It was discovered that the solution with which the wheat used for sowing had been treated had a high mercury content, and investigation showed that the families in which the disease occurred had used part of this seeding wheat for food, despite the clear warning printed on the wrappings.

A toxicological examination of a mixture of organs taken from a dead patient revealed the presence of 15 μg of mercury. An examination of other samples of post-mortem material, as well as wheat seeds, was also positive for mercury.

The conclusion reached was that the cause of the disease was mercury poisoning resulting from the ingestion of wheat treated with that substance.

REFERENCES


