Methylmercury Poisoning in Iraq

An interuniversity report.


(University of Baghdad)

T. W. Clarkson, J. C. Smith, and R. A. Doherty

(University of Rochester)

Methylmercury and its short-chain homolog elicit characteristic toxic effects in man that differ from the toxic effects of other mercury compounds (Ia, 2). The primary signs and symptoms of methylmercury poisoning result from damage to the nervous system and are characterized by loss of sensation at the extremities of the hands and feet and in areas around the mouth (paresthesia), loss of coordination in gait (ataxia), slurred speech (dysarthria), diminution of vision (concentric constriction of the visual field), and loss of hearing. Severe poisoning can cause blindness, coma, and death. There is a latent period of weeks or months between exposure to methylmercury and the development of poisoning symptoms. Ataxia may subsequently decrease but general recovery is poor. Prenatal exposure to methylmercury has resulted in mental retardation with cerebral palsy. Prior to the present outbreak in Iraq, between 200 and 300 cases of methylmercury poisoning had been reported in Iraq and in other parts of the world and more than 1000 cases had been ascribed to exposure to the ethylmercury homolog (Ia, 2). The earliest cases were due to occupational exposure following the introduction of methylmercury compounds as antifungal seed dressing agents. In the 1950's, reports of poisonings from nonoccupational sources appeared in the literature with increasing frequency. These included a few cases arising from the treatment of fungal skin infections as well as accidental and suicidal ingestion. Several large incidents of poisoning have occurred in Iraq, Pakistan, and Guatemala due to the ingestion of flour and wheat seed treated with methyl- and ethylmercury compounds. The fungicide ethylmercury-p-toluenesulfonamide was claimed to be responsible for two outbreaks in Iraq in 1956 and 1960.

In the 1960 outbreak, an estimated 1000 patients were affected by methylmercury poisoning and 370 were admitted to hospital. In Guatemala, cases that were originally thought to be viral encephalitis were reported during the wheat growing seasons of 1963, 1964, and 1965. Forty-five people were affected and 20 died. Methylmercury di-cyanamide, used to treat the seed wheat before distribution to farmers, was later established as the causal agent. A similar outbreak occurred in Pakistan in 1969.

Despite the large number of people...
affected, these incidents arising from the misuse and careless handling of alkyl mercury compounds have not constituted a threat to the general population. The first indication that methylmercury may present a threat to public health came from the epidemics of Minamata Bay and Niigata, Japan (1a). In what came to be referred to as "Minamata disease" a total of 121 people living in villages around Minamata Bay were poisoned during 1953 to 1960. Twenty-two infants were poisoned prenatally. Forty-six people died. A similar outbreak occurred in Niigata. As of 1970, 47 cases had been officially documented, and six deaths were recorded. Careful investigation revealed that the poisonings were due to the consumption of fish having high concentrations of methylmercury. The contamination of the waters of Minamata Bay and of the Agano River was traced to the release of methylmercury compounds from plastic industries in which inorganic mercury compounds were used as catalysts.

A more generalized threat to public health became apparent as a result of studies initiated in the 1960's in Sweden (1a). Increasing industrial and agricultural use and broad dissemination of mercury compounds resulted in increased amounts of mercury being found in birds and fish as well as in people consuming large quantities of fish caught in polluted waters. The mercury in fish was found to be entirely in the form of methylmercury, a surprising and disturbing discovery because the fish had been caught in lakes and rivers into which no discharge of methylmercury had occurred. Subsequent investigations revealed that microorganisms present in the sediments of rivers, lakes, and canals are capable of transforming various forms of mercury into methylmercury. Thus, discharge of phenylmercury compounds from the wood pulp industry, and metallic and inorganic mercury from chlorine-alkali plants where mercury electrodes are used, have contaminated large expanses of fresh water in many countries leading to high concentrations of methylmercury in fish. Evidence of steadily increasing amounts of mercury in the feathers of fish-eating birds in Scandinavia over the past 150 years points to general industrialization, including the burning of fossil fuels, as the source of a broad dissemination of mercury. High concentrations of methylmercury have now been found in certain carnivorous species of oceanic fish at the end of a long food chain (3).

There have been no documented cases of poisoning in human beings caused by the consumption of fish except during the epidemics in Japan where methylmercury itself was released from industry. Nevertheless, fishing has been restricted in large fresh water areas in Sweden and in the North American continent with consequent severe economic hardship to the fishing and tourist industries. Government agencies have set upper limits to the amounts of methylmercury permitted in fish and fish products used for consumption, usually in the range of 0.5 to 1.0 part per million (ppm). The limit of 0.5 ppm in Canada and the United States has virtually eliminated swordfish from the commercial market (3).

The introduction of guidelines for maximum safe concentrations of mercury in food is becoming of critical importance from various points of view—economic, nutritional, and health. The banning of certain species of fish is a serious consideration even in countries where alternative protein sources are available; it becomes critical in certain developing countries where fish may be the predominant source of protein in the diet. The present national and international guidelines for amounts of methylmercury that should be permitted in food depend heavily on epidemiological data from the two outbreaks in Japan. Substantial research programs to investigate the toxicity of methylmercury have been initiated in many countries. Necessarily, most of these programs involve studies on experimental animals and it is difficult to extrapolate the results to man. Thus, the study of the population exposed to methylmercury that we describe in this article is of great importance.

The Present Epidemic in Iraq

We describe herein an epidemic of methylmercury poisoning in farmers and their families in Iraq. Studies of the epidemic were initiated on an emergency basis in February 1972 and are still continuing. The period of the epidemic that we cover in this article extends from late February to the end of August 1972. This epidemic is the most catastrophic ever recorded in terms of its extent and the ensuing morbidity and mortality. A total of 6530 cases of poisoning were admitted to hospitals in provinces throughout the country, and there were 459 hospital deaths attributed to methylmercury poisoning (Table 1).

Human beings became exposed to
implications of methylmercury in Kirkuk, Ninevah, Arbil, Waset, Muthanna, Maysan, Dhok, Babylon, Anbar, Maysan, Kerbala, and Basra, Iraq, between 16 September and 15 October 1971. The rate of admissions to hospitals throughout the country increased in early January 1972, to several hundred cases each day. In late February, daily admissions had fallen to less than five and no new hospital admissions attributed to poisoning have been reported since 27 March 1972. Cases were reported from every province in the country (Fig. 1).

In this article we present new data on the toxicity of methylmercury compounds in man, on the metabolic fate of methylmercury in the human body, and on the effects of mercury-binding agents including a newly developed thiol resin. A description of the chain of events from the introduction of the mercury-treated grain to the widespread occurrence of poisoning and fatalities has a clear implication for future decisions concerning the use of methylmercury fungicides. It is also intended that the observations and conclusions herein will serve as useful information for any future studies of the affected population.

**Implication of Methylmercury**

Mercury-treated wheat was imported through, and distributed from, the southern seaport of Basra, Iraq, between 16 September and 15 October 1971. The corresponding dates for mercury-treated barley were 22 October and 24 November. The total amounts of treated wheat and barley distributed were 73,201 and 22,262 metric tons, respectively (Table 1). The grain was delivered to all provinces in the country, with over 50 percent of the total distribution going to the three northern provinces of Ninevah, Kirkuk, and Arbil. The amounts of treated grain delivered to each province did not exceed the normal requirements for seed grain. The grain was delivered to local granaries throughout the country, which, in turn, distributed it to the farmers. We do not have precise information on the times when the farmers first received the grain and when deliveries stopped. Interviews with victims of the epidemic indicate that consumption of bread made from the treated grain started as early as October in some families. Deliveries to some farmers may have continued into January 1972—the time when the authorities issued stringent warnings concerning the danger of consuming the grain.

Early in the outbreak it was thought that ethylmercury was responsible for the poisoning (4). This assessment was based on verbal assurances that the seed wheat involved had been treated with ethylmercury-p-toluene sulfonamide. However, at the same time, differences in clinical manifestations between this and earlier outbreaks of ethylmercury poisoning were noted. It was not until the end of March that the first samples of wheat and flour were analyzed by gas chromatography (5). No wheat samples in which the predominant compound of mercury was other than methylmercury were encountered. Wheat samples from a number of provinces were examined. Included were samples from unopened sacks of a shipment of over 60,000 metric tons of treated grain from Mexico. The methylmercury content varied from 3.7 to 14.9 μg of Hg per gram (mean 7.9 μg/g; N = 24), with one sample showing 30.6 μg/g. The ethylmercury content of these samples varied from 0.8 percent to 7.8 percent of the methylmercury content.

The mean methylmercury content of wheat flour samples was 9.1 μg/g with a range of 4.8 to 14.6 μg/g (N = 19). Ethylmercury could be detected in all these samples in small amounts, from 0.08 to 0.88 percent of the methylmercury content.

A relatively small amount of wheat (less than 5000 metric tons) may have been treated with phenylmercuric compounds according to official records. Also, wheat may have been treated locally with either ethylmercury-p-toluene sulfonamide or N-dimethylmercury-p-toluene sulfonamide. These compounds, however, have not been detected in the wheat and blood samples that we have analyzed.

The barley was reported to have been treated with a variety of compounds: phenylmercuric acetate, methylmercury dicyanamide, methylmercury-2,3-dihydroxypropylmercaptide and methylmercury acetate. At least 13,000 metric tons of barley were

### Table 1. Details of the epidemic of methylmercury poisoning in Iraq, shown by province (19).

<table>
<thead>
<tr>
<th>Province</th>
<th>Wheat Metric tons</th>
<th>Total seeds planted (%)</th>
<th>Barley Metric tons</th>
<th>Total seeds planted (%)</th>
<th>Rural population (thousands)</th>
<th>Cases admitted to hospitals</th>
<th>Cases dying in hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ninevah</td>
<td>31,766</td>
<td>46</td>
<td>9,102</td>
<td>41</td>
<td>584</td>
<td>592</td>
<td>9</td>
</tr>
<tr>
<td>Kirkuk</td>
<td>10,659</td>
<td>36</td>
<td>4,592</td>
<td>40</td>
<td>242</td>
<td>814</td>
<td>42</td>
</tr>
<tr>
<td>Arbil</td>
<td>10,105</td>
<td>46</td>
<td>1,538</td>
<td>23</td>
<td>222</td>
<td>242</td>
<td>10</td>
</tr>
<tr>
<td>Baghdad</td>
<td>3,784</td>
<td>26</td>
<td>377</td>
<td>8</td>
<td>449</td>
<td>107</td>
<td>34</td>
</tr>
<tr>
<td>Qadissiya</td>
<td>3,363</td>
<td>51</td>
<td>715</td>
<td>24</td>
<td>269</td>
<td>1,345</td>
<td>73</td>
</tr>
<tr>
<td>Waset</td>
<td>2,741</td>
<td>16</td>
<td>511</td>
<td>4</td>
<td>231</td>
<td>688</td>
<td>11</td>
</tr>
<tr>
<td>Muthanna</td>
<td>1,789</td>
<td>47</td>
<td>1,665</td>
<td>84</td>
<td>92</td>
<td>701</td>
<td>79</td>
</tr>
<tr>
<td>Diafa</td>
<td>1,627</td>
<td>31</td>
<td>962</td>
<td>21</td>
<td>262</td>
<td>675</td>
<td>12</td>
</tr>
<tr>
<td>Thi-Qar</td>
<td>1,456</td>
<td>21</td>
<td>382</td>
<td>5</td>
<td>366</td>
<td>191</td>
<td>30</td>
</tr>
<tr>
<td>Sulaimaniya</td>
<td>1,453</td>
<td>10</td>
<td>42</td>
<td>1</td>
<td>272</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Babylon</td>
<td>1,350</td>
<td>21</td>
<td>1,095</td>
<td>20</td>
<td>284</td>
<td>1,083</td>
<td>128</td>
</tr>
<tr>
<td>Dhiq</td>
<td>1,153</td>
<td>38</td>
<td>523</td>
<td>69</td>
<td>94</td>
<td>101</td>
<td>1</td>
</tr>
<tr>
<td>Anbar</td>
<td>831</td>
<td>16</td>
<td>224</td>
<td>18</td>
<td>184</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Maysan</td>
<td>693</td>
<td>24</td>
<td>699</td>
<td>22</td>
<td>241</td>
<td>106</td>
<td>8</td>
</tr>
<tr>
<td>Kerbala</td>
<td>276</td>
<td>56</td>
<td>25</td>
<td>7</td>
<td>89</td>
<td>141</td>
<td>5</td>
</tr>
<tr>
<td>Basra</td>
<td>155</td>
<td>24</td>
<td>10</td>
<td>19</td>
<td>127</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>73,201</td>
<td>22,262</td>
<td>35,000</td>
<td>6,000</td>
<td>500</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The percentage of all seeds planted, including those not treated with mercury.*
treated with methylmercury dicyandiamide. Of 13 barley samples examined, 10 showed predominately methylmercury and 3, phenylmercury.

Several hundred samples of human blood and hair and a few samples of tissues obtained at autopsy were examined. Most of these samples were from provinces near Baghdad but included a small series from more than half the provinces. In all these samples the predominant form of mercury was methylmercury. No other organic mercury compounds were detected. A small amount of inorganic mercury (up to 10 percent) was detected by selective atomic absorption (6).

The analysis of consecutive segments of samples of hair collected from female patients in May 1972 illustrated the dramatic increase in the mercury content during the epidemic (Fig. 2). Methylmercury was the predominant form of mercury in the hair samples. Other organic forms of mercury such as ethyl- or phenyl-mercury were not detected. The rate of growth of hair in the patients is not known, but a length of 40 cm of hair (Fig. 2) clearly allows study of mercury concentrations both during and prior to the epidemic. It is intended that by the analysis of such hair samples more detailed records can be obtained of the times at which exposure occurred, the duration of exposure, and the chemical forms of mercury involved. All the evidence now available points strongly to the conclusion that the epidemic was caused by methylmercury compounds.

Mercury in treated grain may enter the human body as a result of oral ingestion, inhalation, or skin contact. Oral ingestion would include the consumption of (i) homemade bread prepared from treated wheat and barley; (ii) meat and other animal products obtained from livestock given treated barley; (iii) vegetation grown from soil contaminated with mercury or stored in sacks that had contained the treated grain; (iv) game birds that had fed on the treated grain sown in the field; (v) fish caught in rivers, canals, and lakes into which treated grain had been dumped by the farmers; and (vi) maternal milk by suckling infants of exposed mothers. Inhalation and skin contact may have been important in instances where dusts were generated during the grinding of wheat into flour or were dispersed during the process of sowing the grain. For example, it was noted that farmers

had red salvia and phlegm when they were sowing the grain. This coloration probably came from the red dye that had been added to the wheat and barley to indicate that it had been treated with mercury.

The consumption of homemade bread prepared from treated grain appears to have been the predominant cause of mercury poisoning in this epidemic. Fifty-eight people gave sufficient information on their intake of contaminated bread to allow estimation of the total dose of mercury ingested.

The correlation coefficient between the amount of mercury ingested from bread and the concentration of mercury in the blood was 0.85 for people over 16 years of age and 0.89 for people aged 10 to 15 years. The concentration of mercury in treated wheat and in flour prepared from treated grain greatly exceeded concentrations of mercury found in other foodstuffs. The mercury concentration in samples of vegetables and dairy products was below 0.05 μg/g. Most meat samples contained around 0.2 μg/g (wet weight). For example, of 261 sheep killed at the end of February in the vicinity of Baghdad, 97 percent had mercury concentrations in the kidney tissue of less than 1 μg/g (wet weight), and 75 percent had concentrations of less than 0.2 μg/g (7). That homemade bread was the source of the mercury poisoning is supported by the finding that all recorded cases of poisoning occurred in the rural districts, in families who made their own bread. Not a single case of poisoning was recorded in major cities where bread is prepared commercially from government-inspected flour supplies.

Fig. 2. Concentrations of mercury (methylmercury, inorganic mercury, and total) in hair samples from two patients affected by methylmercury poisoning.

**Extent of the Epidemic Based on Hospital Admissions**

Epidemiologic estimations of the total number of individuals poisoned, as well as age-, sex- and pregnancy-specific case-fatality ratios, are not possible with the currently available data, which comprise numbers of patients admitted to regional hospitals. Approximately 90 percent of the cases that were hospitalized were admitted during January and February 1972. Methylmercury poisoning occurred widely throughout the country (Table 1 and Fig. 1) in all provinces that received mercury-treated grain. All poisonings occurred in rural districts, usually in household (extended family) groups. Within each province, local frequencies of hospitalization varied in villages and settlements, ranging as high as 10 percent of the population of some communities. The largest numbers of individuals admitted to hospitals were in the provinces of Babylon, Diala, and Waset, near Baghdad; Qadissiya and Muthanna, to the south; and Kirkuk and Nineveh, to the north (Table 1). The highest frequencies of hospital admissions (per 1000 rural population) were in the provinces of Muthanna, 7.6; Qadissiya, 5.0; Babylon, 3.8; Waset, 3.0; and Kirkuk, 3.4 (Fig. 1). The lowest frequency was in the northeastern province of Sulaimaniya, 0.015. There was no correlation between the total admissions per province or admissions per 1000 rural population and the amount of treated wheat and barley distributed in each province (Table 1).

Males and females of all ages were affected, from infants under 1 year of age to elderly people (Table 2). Of the hospitalized patients, 52 percent
were female and 48 percent were male. The largest subgroup consisted of individuals between 1 and 9 years of age—34 percent of all cases. When hospital admissions specific for age are plotted as number per 1000 rural population, frequency differences between age groups become much smaller (Fig. 3). The admissions frequency of the 0- to 1-year group is much lower than the other groups. Approximately one-half the children in this age group would have been born prior to the onset of the epidemic. Their chief, if not sole, source of methylmercury would have been maternal milk. The admissions frequency of affected pregnant females was remarkably low. One would expect to find approximately 150 pregnant females with diagnosable poisoning in the 6350 cases admitted to hospitals, yet only 31 such females were reported (Table 2; 8). The frequency of pregnant females was also low when computed on the basis of the rural population (Fig. 3).

The data on fatalities in patients should not be regarded as applicable to the general population—at least until the results of retrospective studies become available. The case fatality ratio in 31 hospitalized pregnant females was 45 percent. Hospitalized pregnant females in the 20- to 30-year age group experienced a much higher mortality (70 percent) than those above 30 years (10.7 percent). The implication of a high case fatality ratio among pregnant women may be incorrect because of the possibility that seriously ill pregnant females were selected for hospitalization. Hospital admission practices may also limit interpretation of the similar fatality ratios in males and nonpregnant females and of the finding that the fatality ratio in the 40- to 50-year-old males was lower than both the next older group and the 1- to 5- and 5- to 10-year age groups.

Unfortunately, death rates specific for age and sex are not available for the rural population and therefore cannot be compared with similar data for death rates due to methylmercury poisoning. Furthermore, members of the rural population do not know their ages precisely in years. The ages recorded in Table 2 represent the best estimates by attending physicians. The error in age estimation may account for the fact that no pregnant females were reported in the under-20 age group.

### Mercury in Plasma, Urine, Milk, and Other Body Fluids

All samples of whole blood were analyzed for their mercury content. Organic mercury is defined as the difference between the total amount of mercury and the amount of inorganic mercury, as determined by selective atomic absorption analysis (6). When samples of other biological fluids were collected, a sample of blood was also taken at the same time. The results (Table 3) show that most of the mercury in whole blood is in the organic form and is located in the red blood cells. Plasma, milk, urine, cerebrospinal fluid, and amniotic fluid differ from whole blood in that the concentration of total mercury was much lower and that the proportion of inorganic mercury was higher. The total amounts of mercury in plasma and milk correlated closely with the corresponding amounts in blood. The total amount of mercury in urine gives a poor indication of the amount in blood; the correlation coefficient between urine and blood was less than 0.1.

### Table 2. Distribution of cases of poisoning admitted to hospitals, and of deaths caused by poisoning, according to age and sex.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of cases admitted</th>
<th>Males</th>
<th>Nonpregnant females</th>
<th>Pregnant females</th>
<th>Total affected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Fatalities</td>
<td>Case* fatality</td>
<td>Cases</td>
<td>Fatalities</td>
</tr>
<tr>
<td>&lt;1</td>
<td>8</td>
<td>0</td>
<td>0.0</td>
<td>383</td>
<td>33</td>
</tr>
<tr>
<td>1-4</td>
<td>736</td>
<td>63</td>
<td>8.6</td>
<td>378</td>
<td>36</td>
</tr>
<tr>
<td>5-9</td>
<td>606</td>
<td>45</td>
<td>7.4</td>
<td>650</td>
<td>55</td>
</tr>
<tr>
<td>10-19</td>
<td>380</td>
<td>18</td>
<td>4.7</td>
<td>520</td>
<td>43</td>
</tr>
<tr>
<td>20-29</td>
<td>416</td>
<td>15</td>
<td>3.6</td>
<td>483</td>
<td>25</td>
</tr>
<tr>
<td>30-39</td>
<td>218</td>
<td>7</td>
<td>3.2</td>
<td>268</td>
<td>17</td>
</tr>
<tr>
<td>40-49</td>
<td>164</td>
<td>13</td>
<td>7.9</td>
<td>146</td>
<td>12</td>
</tr>
<tr>
<td>50-59</td>
<td>211</td>
<td>13</td>
<td>6.3</td>
<td>172</td>
<td>2</td>
</tr>
<tr>
<td>60+</td>
<td>3144</td>
<td>197</td>
<td>6.3</td>
<td>3353</td>
<td>248</td>
</tr>
</tbody>
</table>

* (Fatalities/cases) \(\times\) 100.
give a more accurate recapitulation of exposure and therefore will be of much greater importance in epidemiological studies. However, hair samples of adequate length are not always available from males.

The linear regression lines in Fig. 4A were drawn to give the best fit to all the points. However, the points in Fig. 4A suggest that the concentration of mercury decreased at a lower rate during the first 20 days than subsequently. These two cases were under observation from the beginning of March. The mercury concentrations in the blood of nine other cases sampled in March did not exhibit statistically significant changes during the first 20 days. A careful study will be made to see if these apparently steady concentrations of mercury in blood samples obtained in March represent a real phenomenon or an artifact of fluctuations in sampling or measurement.

Cases treated with mercury-binding agents. Several mercury-binding compounds were administered to patients in order to enhance the excretion of mercury. This was done in an effort to prevent any further deterioration of their condition and to improve their chances of recovery. The following compounds were administered: D-penicillamine, N-acetyl-DL-penicillamine, and a thiol resin (9). 2,3-Dimercaptopropanol (BAL), which is commonly administered in cases of inorganic mercury poisoning, was not used because previous reports indicated that BAL is ineffective in cases of methylmercury poisoning and increases the concentration of mercury in the brain of animals dosed with methylmercuric compounds (10).

The effects of the penicillamines and the thiol resin on the total amount of mercury in the blood are indicated in Fig. 4, B–D. There was considerable variation in the response of different individuals to mercury-binding compounds. For some individuals the mercury concentration was dramatically reduced during treatment (see Fig. 4); but for others the reduction was much less. More data must be obtained before the efficacy of the various compounds tested can be compared.

Data from the cases that responded to treatment with the penicillamines enable us to draw the following conclusions. First, a second series of doses was less effective in reducing the mercury concentration in the blood than the first series, when the daily dosage was the same. Second, in the initial 1 to 3 days following the start of a series of doses the mercury concentration increased before a significant decline was observed. This was probably due to the mobilization of mercury from tissues to the blood at a rate more rapid than that at which mercury was excreted in urine and feces. The peaks in mercury concentrations that occurred when N-acetyl-DL-penicillamine was administered are shown in Fig. 4D. When D-penicillamine was used (Fig. 4C) samples were not collected during the first few days after the start of the first series of doses. Third, the dose of penicillamines normally used in the treatment of inorganic mercury poisoning, 1 g/day, was either ineffective or elicited much smaller reductions in mercury concentrations than the dose of 2 g/day used in the cases described in Fig. 4, C and D.

This is the first study in which the thiol resin has been administered to human beings. Other studies had shown the resin to be highly effective in enhancing the elimination of methylmercury compounds from experimental animals (9). In view of the fact that the thiol resin is insoluble, it is not absorbed through the intestinal wall and can therefore be administered orally. The resin binds the methylmercury that is secreted into the gastrointestinal tract with the bile and other fluids and thus enhances the fecal excretion of methylmercury by preventing its reabsorption. Thus, the resin has two potential advantages over the diffusible complexing agents that are distributed systemically. First, when administered orally it does not result in redistribution of mercury in the body. Second, it is much less likely to have adverse (toxic) effects than the sulfhydryl agents that enter the bloodstream. In fact, no adverse effects were observed with any of the agents tested in this study. However, the maximum dose of D-penicillamine is limited by the risk of adverse side effects and for this reason neither of the penicillamines were administered at doses in excess of 2 g/day in the adult. The resin was given to adults at doses of up to 8 g/day, which is equivalent in sulfhydryl content to the penicillamine dose.

In treating patients with the complexing agents and the thiol resin we followed the procedures adopted for the treatment of inorganic mercury intoxication. Periods of treatment were interspersed with periods without treatment (Fig. 4, B–D). However, our results indicate that it might be preferable to treat continuously until the concentration of mercury in the blood has decreased to an acceptable level.
Clinical Manifestations

The predominant symptoms of poisoning in this epidemic closely resembled those previously described in other outbreaks of methylmercury poisoning (1a, 2). Because bread containing methylmercury was consumed for a relatively short period of time, the first symptoms, usually numbness in the extremities and in the perioral areas (paresthesia), did not usually appear until sometime after consumption of the bread had stopped. The mean latent periods (listed in Table 4 according to mercury concentrations in the blood) ranged from 16 to 38 days. In a few cases the cessation of consumption of the contaminated bread coincided with the onset of symptoms, whereas in others the latent period extended to 60 days.

The severity of the signs and symptoms was dose-dependent. Thus some people consuming contaminated bread over a short period of time exhibited only paresthesia. People consuming the bread for longer periods had other clinical manifestations. The severity of ataxia ranged from a slight unsteadiness in gait to such gross incoordination that the patient could not walk. Visual effects included blurred vision and constriction of the visual field, leading to blindness in the severe cases. Slurred speech and hearing difficulties became manifest in patients with higher mercury concentrations in the blood (Table 4). Fatalities resulted from apparent failure of the central nervous system. Involvement of the cardiovascular, gastrointestinal, and urinary systems was rare.

The severely poisoned patients died, irrespective of the medical treatment they received. Many of the surviving patients started to improve gradually 2 or 3 months after they stopped eating contaminated bread. Some patients that had become bedridden slowly recovered the ability to walk, but remained ataxic. One patient who was blind now responds to light. Paresthesia was the most persistent symptom. Although the blood of some of the patients treated with the penicillamines and thiol resin exhibited a significant decrease in mercury concentration, these patients did not show an accompanying dramatic improvement in other signs and symptoms. Careful follow-up comparisons of treated and untreated patients are now in progress. Since these observations were made on less than 200 patients and for only about 4 months, it is too early to draw positive conclusions about the ultimate extent of functional recovery.

Dose-Response Relationships

The most common symptoms of methylmercury poisoning reported at the time of the first clinical examination are shown in Table 4. Certain other symptoms, such as muscular pains and headache, did not correlate with the mercury concentrations in the blood. More details on this aspect of methylmercury poisoning will be provided in a later report. Some of the patients having mercury concentrations in excess of 4000 ng/ml were so severely affected that the recording of symptoms such as paresthesia, muscular pains, and headache was impossible. At mercury concentrations of 1 to 100 ng/ml the symptoms are probably caused by factors other than mercury.

The data reported in Table 4 give a cross-sectional view of the course of the epidemic. Ninety percent of the blood samples and case reports were obtained between the 1st week in March and the 3rd week in April. The concentrations of mercury in the blood must have increased sharply during ingestion of contaminated bread as shown by changes in the amount of mercury in hair (Fig. 2). The concentration in the blood attained a peak value at, or sometime after, the cessation of ingestion of methylmercury and then declined. The time at which the blood samples used to categorize the cases in Table 4 were collected corresponds approximately to an average of 65 days after cessation of ingestion of mercury.

If the first blood sample was taken more than 90 days after cessation of ingestion, the mercury concentration was corrected to an estimated value at 65 days, the half-time of clearance being assumed to be 70 days. Correction to times earlier than 65 days after cessation of ingestion was not attempted because the pattern of mercury clearance from blood was not established for this period. The sequential analysis of hair samples from these patients should help resolve this problem.

For the reason already discussed, the mercury concentrations listed in Table 4, because they apply to a time after exposure had ceased, cannot be compared to the concentrations associated with the onset of symptoms as reported for the Japanese epidemics of methylmercury poisoning (1a). However, comparison with previous epidemics is possible if we use the concentrations in Table 4 to estimate the total ingested dose of methylmercury, and from this calculate the amount of methylmercury in the body (the body burden) at the time of the onset of symptoms.

The total amount of mercury ingested by each individual would be determined by the number of homemade loaves consumed per day, the number of days the contaminated bread was consumed, and the concentration of

Table 4. The frequency of symptoms of methylmercury poisoning according to the concentration of mercury in the blood and the estimated total amounts of mercury ingested. The data were obtained from 93 cases admitted to hospitals and from additional individuals examined at home and living in the same rural districts as the normal residences of the hospital patients. The data in this table are only from individuals above 9 years of age. The clinicians were not aware of the mercury concentrations of the blood when they examined the patients. Numbers in parentheses represent numbers of patients in which particular symptoms could be examined.

<table>
<thead>
<tr>
<th>Concentration of mercury in blood (ng/ml)</th>
<th>Mean period of ingestion (days)</th>
<th>Mean latent period (days)</th>
<th>Mean time at which samples were obtained*</th>
<th>Cases with symptoms (%)</th>
<th>Cases (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–100</td>
<td>43</td>
<td>16</td>
<td>115</td>
<td>9.5</td>
<td>21</td>
</tr>
<tr>
<td>101–500</td>
<td>43</td>
<td>18</td>
<td>96</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>501–1000</td>
<td>43</td>
<td>26</td>
<td>33</td>
<td>60</td>
<td>17</td>
</tr>
<tr>
<td>1001–2000</td>
<td>43</td>
<td>32</td>
<td>58</td>
<td>79</td>
<td>25</td>
</tr>
<tr>
<td>2001–3000</td>
<td>58</td>
<td>30</td>
<td>82</td>
<td>100 (4)</td>
<td>17</td>
</tr>
<tr>
<td>3001–4000</td>
<td>68</td>
<td>20</td>
<td>100 (100)</td>
<td>83 (6)</td>
<td>28</td>
</tr>
<tr>
<td>4001–5000</td>
<td>38</td>
<td>20</td>
<td>85</td>
<td>66 (6)</td>
<td>7</td>
</tr>
</tbody>
</table>

* Days after onset of symptoms.
methylmercury compounds in the bread. Information on the first two points was obtained by questioning persons who consumed the contaminated bread. Unfortunately, samples of the contaminated bread were not available for analysis so that the amount of mercury that they contained had to be estimated from the mean concentration of methylmercury in samples of flour prepared from treated wheat. The loaves of unleavened bread are made in a similar fashion by all the farming families. The loaves average 200 g and contain 30 percent moisture (11). Thus, the average concentration of mercury in flour, 9 μg/g, would lead to a mercury content of 1.4 mg per loaf. Some families washed the treated wheat before preparation of the bread; others prepared bread from mixtures of treated and untreated wheat. However, 58 individuals from the group of patients described in Table 4 gave sufficiently detailed information to allow estimation of the total amount of mercury ingested. In Fig. 5 the estimated total intakes of mercury are plotted against the concentrations of mercury in the earliest blood samples collected—the same blood samples as were used in Table 4. The patients were divided into two groups according to age.

The slopes of the solid lines computed by least squares linear regression analysis for the two age groups differ significantly (P < .05), indicating that a given dose of methylmercury will lead to higher mercury concentrations in blood from the younger group. Differences in body weight between the two groups are presumed to be an important factor. For 1 mg of mercury ingested, the concentration of mercury in the blood was 17 ng/ml for the younger group and 9 ng/ml for the older group; the average body weights were 31 and 51 kilograms, respectively. The linear regressive lines may be compared in Fig. 5 with the broken lines computed from the relationship between the mercury concentration in the blood and the body burden of methylmercury based on experiments with a radioactive tracer as reported by Miettinen (12).

The slopes of the solid and broken lines do not differ significantly according to the r-statistic (P > .05). If this difference is real, it may be due either to differences in conditions of exposure between the Iraqi patients and the volunteers given labeled methylmercury or to underestimations of dose in Iraq, or to both causes. Underestimations of dose may also explain the positive intercepts on the ordinate made by the regression line: 140 ng of mercury per milliliter of blood in Fig. 5A, and 240 ng/ml in Fig. 5B. However, these intercepts are not significantly different from zero (P > .05).

A dose could be underestimated as a result of a patient's recollecting incorrectly the times of ingestion of contaminated bread. A recapitulation of exposure by sequential analysis of hair samples as illustrated in Fig. 1 should give an independent test. We have compared the reports of 14 patients with results of analyses of hair samples. The average duration of exposure, according to the patients' report, was 48 days and that computed from analysis of hair samples for the same patients was 66 days (13). Thus, we cannot exclude the possibility that the amounts of methylmercury consumed by the patients in Iraq have been underestimated. For example, the ingested dose of methylmercury was assumed to come entirely from the consumption of bread. The figure of 1.4 mg of mercury per loaf may be in error because this is based on mercury concentrations in flour and on assumed weights and water content of the loaves. Some individuals may have been exposed to other sources of methylmercury besides bread. Furthermore, patients visiting other households may have unwittingly consumed contaminated bread.

The true relationship between the concentration of mercury in the blood and the ingested dose may lie between the reported regression lines and the lines calculated from Miettinen's data. Consequently, we used both lines to estimate the cumulative dose of methylmercury from the mercury concentrations listed in Table 4 (14). From the information obtained from each patient on the period of consumption of contaminated bread and on the length of the latency period, it is possible to estimate the amount of methylmercury in the body at the time the patient stopped eating contaminated bread and at the time of the onset of symptoms (15). The logarithms of these values are plotted against the frequency of signs and symptoms in Fig. 6. Two scales are used on the abscissa corresponding to

---

Fig. 5 (left). The relationship between the concentration of the total amount of mercury in the blood and the estimated total amount of mercury ingested from contaminated bread. The solid line was drawn from linear regression analysis. The dotted line is the predicted concentration in the blood estimated from data published by Miettinen (12) on 15 volunteers given a single oral dose of labeled methylmercury. (A) Patients aged 10 to 15 years. (B) Patients more than 18 years of age. Fig. 6 (right). The relationship between frequency of signs and symptoms and the estimated body burden of methylmercury; (A) at the time of onset of symptoms; (B) at the time of cessation of ingestion of methylmercury in bread. Both scales on the abscissa are for body burdens of methylmercury calculated from the concentrations of mercury in the blood that are shown in Table 4 (see 15). For the top scale, use was made of the observed relationship between the mercury concentration in blood and the ingested dose as determined by linear regression analysis of the data in Fig. 5 (14). The bottom scale was estimated from the relationship between the mercury concentration in blood and the ingested dose as reported by Miettinen (12).
the two methods of estimation of the body burden of methylmercury. The upper scale refers to values of the body burden estimated from linear regression analysis of the data in Fig. 5, the lower scale to the values of the body burden estimated by use of Miettinen's relationship between the mercury concentration in the blood and the amount of mercury ingested.

The graph for each of the symptoms has the same general shape (Fig. 6). At the lower body burden of methylmercury, the line is horizontal. At the higher body burden, the points are related by a line of much steeper slope. The point at which the horizontal line intersects the sloping line represents the "threshold" body burden of methylmercury at which the sign or symptoms become detectable. Each symptom has a characteristic threshold body burden. These threshold values do not differ appreciably whether one plots the body burden at the time of onset of symptoms (Fig. 6A) or at the time of cessation of ingestion (Fig. 6B).

The lowest threshold body burden calculated from the linear regression line occurred when approximately 25 mg of mercury was present as methylmercury, and was associated with the onset of paresthesia. The thresholds for ataxia, dysarthria, deafness, and death were, respectively, 55, 90, 170, and 200 mg of mercury (Fig. 6A). When calculated from Miettinen's data the threshold body burden associated with the onset of paresthesia was approximately 40 mg of mercury present as methylmercury.

The validity of these estimated threshold values is limited by the fact that all the symptoms for which graphs were made (Fig. 6) occurred at a frequency between 0 and 10 percent, even when the concentrations of mercury in the blood were lowest. These background frequencies may represent the occurrence of such symptoms in the general rural population not exposed to mercury, or they may be due to error in diagnosis or, in the case of the reported symptoms, to inaccurate statements by the patient. It should be noted that many of the residents in the rural districts became aware of the symptoms of methylmercury poisoning, and the knowledge may have influenced their answers when describing symptoms to the clinician. Consequently, the calculated thresholds for body burdens refer to the onset of signs and symptoms over and above the background level of 5 to 10 percent. This is the limit of sensitivity of detection under the conditions of the study. Nevertheless, the threshold value of 25 to 40 mg of mercury as computed for paresthesia agrees remarkably well with the threshold figure of 30 mg of mercury computed by the Swedish Expert Committee from data on the Japanese epidemics (1a).

It is possible that, as the results of more neurological tests become available, effects of methylmercury poisoning may be detected at lower body burdens. However, electrophysiological investigations (16) conducted 7 to 8 months after cessation of methylmercury intake on patients with mercury concentrations of 800 ng/ml or more in the blood could not record any abnormalities in sensory thresholds, sensory latencies, sensory conduction velocities, H-reflex conduction times, motor conduction velocities, or the electrical activity of the biceps and triceps muscles during rest, passive stretch, or contraction. In two of the 14 patients examined, myoneural transmission failure similar to that recorded in myasthenia gravis was detected. This failure responded to prostigmine administration, but the significance of this observation in cases of methylmercury poisoning is uncertain.

**Methylmercury in the Fetus and Infant**

Our observations indicate that hazardous amounts of methylmercury can enter the fetus in utero, as well as the infant that consumes milk of a mother who has eaten contaminated bread. A total of 43 paired samples of maternal blood and milk were collected from 20 lactating mothers (17). The concentration of organic mercury in milk was proportional to the concentration of organic mercury in maternal blood up to concentrations of 2500 ng/ml (Fig. 7C). The concentrations in milk averaged 3 percent of the mean concentrations in blood. Only two lactating mothers had mercury concentrations in the blood that were above 2200 ng/ml. The concentration of organic mercury in milk was between 5 and 6 percent of the corresponding concentration in the maternal blood in these two cases. More samples will have to be analyzed to determine whether the ratio of the mercury concentration in milk to the concentration in blood changes significantly when the blood contains mercury in concentrations above 2000 ng/ml.

Paired maternal and infant blood samples were collected from 11 cases where the infant had been born prior to the epidemic and had thus been exposed only to methylmercury in maternal milk (Fig. 7B). The mercury concentration in the blood of each infant was either equal to or lower than that of its mother. The blood of eight infants had attained organic mercury concentrations above 500 ng/ml and three had concentrations above 1000 ng/ml. No signs of poisoning have yet been reported in these infants, but these concentrations must be regarded as hazardous in terms of the relationship between blood concentrations and symptoms as reported in Table 4. The ages of the infants exposed solely via
maternal milk range from 9 to 18 months.

Infants born during and after the period when the mother was consuming contaminated bread could have acquired methylmercury in utero or from maternal milk, or from both (Fig. 7A). This group differed from those whose only source of methylmercury was maternal milk in having organic mercury concentrations in the blood that were usually greater than the maternal concentrations. Only 1 infant in 11 had a lower mercury concentration, 4 had approximately the same concentration as the mother, and 6 had concentrations substantially higher. The blood of one newborn child had a mercury concentration approximately three times that of its mother (18). The mother had ingested contaminated bread during the first 2 months of pregnancy. The three infants with the highest mercury concentrations in the blood (all in excess of 2500 ng/ml) were only 2 months old, so that mercury from milk must have made a relatively small contribution to the mercury content of their blood. Several of these infants had signs of severe brain damage.

Our data are consistent with the conclusion that methylmercury readily crosses from mother to fetus, that the methylmercury concentration in the blood of the newborn is equal to, if not higher than, that in the mother, and that intake of contaminated maternal milk after exposure in utero counteracts the decline in concentration caused by excretion and growth. Undoubtedly, infants exposed to poisoning in the uterus face a greater hazard than those exposed only to contaminated milk. The latter group may face a significant hazard depending upon the concentration of mercury in the blood of the lactating mother.

Factors Contributing to the Epidemic

Many complex factors may have led to this outbreak of alkylmercury poisoning. Based on interviews with patients and other individuals involved in the outbreak, the following factors seem to have played a significant role.

1) Only a small fraction of the total amount of wheat distributed to the population was required to cause the reported 6000 cases of poisoning. The patients reviewed in Table 4 ingested between 50 and 400 mg of mercury as methylmercury present in homemade bread. This amount of mercury would correspond to the ingestion of 6 to 50 kg of wheat treated with mercury. Case reports from members of poisoned families support this calculation. These families used, on the average, about 100 kg of treated wheat to prepare bread. If one takes a median figure of five for the average size of the rural family (19), each individual would have consumed roughly 20 kg of wheat. Clearly, the distribution of 73,000 metric tons of wheat treated with methylmercury carries with it a great potential for human poisoning.

2) The precise time of delivery of the treated grain to farmers is not known. However, deliveries to the provinces took place just prior to and during the normal sowing season in Iraq. Some farmers may have received the treated grain after they had planted their own seed grain.

3) The latent period between dose and onset of symptoms, previously described for methylmercury intoxication, may have given the farmers a false sense of security. For example, some gave treated grain to their chickens for a period of a few days and observed no harmful effects. Human beings eating the contaminated bread did not have symptoms for weeks or months. By the time symptoms occurred a toxic dose had been ingested.

4) The grain was colored with a brownish-red dye. The dye, but not the methylmercury, could be largely removed by washing, giving the farmers the impression that the poison had been removed.

5) The effectiveness of labeling sacks with written and diagrammatic warnings is questionable if grain treated with alkylmercury compounds is to be distributed to a population unfamiliar with the language of the warning.

6) Mercury compounds other than the short-chain alkyl derivatives had been used in previous years.

A Perspective of Present and Future Studies

Data on dose-response relationships (Fig. 6) indicate that the effects of methylmercury become detectable in the population studied in Iraq when individuals have accumulated a body burden of approximately 25 to 40 mg of mercury. The accumulation of this amount of methylmercury leads to the probability that approximately 1 individual in 20 will experience symptoms of paresthesia. This threshold body burden is in agreement with the 30 mg of mercury (as methylmercury) estimated by the Swedish Expert Committee (14) but we must point out that an average body weight of 70 kg was assumed in the Swedish calculations whereas the threshold body burden estimated from Fig. 6 is based on a population with an average body weight of 51 kg. A reliable determination of this threshold figure is extremely important as it serves as a guide in judgments of hazardous intakes of methylmercury in human diet. Our result is subject to modification as our studies continue.

Our other main findings may be summarized as follows: (i) Methylmercury was identified as the causative agent of poisoning. The consumption of homemade bread prepared from wheat treated with a methylmercury fungicide was the chief, if not the sole, cause of the epidemic. (ii) The concentration of methylmercury (or all the mercury) in blood is the best indicator of the body burden in people exposed to methylmercury. Measurement of the mercury concentration in urine is of no value as a guide to the amount of mercury to which a person has been exposed. (iii) The measurement of the concentration of methylmercury in consecutive segments of hair samples is the best means of recapitulating the history of exposure. (iv) The rate at which mercury is cleared from blood varies among individuals. (v) The clearance of mercury from blood may be accelerated by oral administration of d-penicillamine, N-acetyl-d,l-penicillamine, or thiol resin. The efficacy of these agents differs between individuals. Presumably these mercury binding agents should be given as soon as possible after exposure to methylmercury, and it might be preferable to continue the treatment daily until mercury in the blood has decreased to nonhazardous levels. (vi) Methylmercury is transferred into milk at a concentration equal to 3 percent that of the blood. This amount may lead to a hazardous concentration in a suckling infant if the mercury concentration in the blood of the mother is high. (vii) The time at which the various symptoms of methylmercury poisoning appear is associated with differences in body burdens of mercury. In general, paresthesia appears first, followed by ataxia, dysarthria, and hearing defects at in-
creasing body burdens. (viii) Some functional recovery takes place, starting about 2 or 3 months after cessation of ingestion of mercury. (ix) Electrophysiological measurements do not offer an especially sensitive means of detecting the onset of methylmercury poisoning. Rather, their usefulness may be in identifying the nature and anatomical location of the lesions in the nervous system.

Our studies described herein have raised several important questions that are the subject of continuing investigations. These include the reported high mortality of affected pregnant females admitted to hospital, the degree and extent of functional recovery after methylmercury poisoning, the individual variation in the metabolic fate of mercury in human beings, and the response of human beings to this form of mercury. It is most important that studies of the individuals that we have already examined be continued.

Human beings are believed to be most sensitive to methylmercury during the early stages of the life cycle, including both the prenatal and the postnatal periods. Three categories of fetal and infant poisoning: can be studied in the Iraqi population: (i) those infants exposed solely to methylmercury in maternal milk; (ii) those exposed in utero and exposed to contaminated milk; and (iii) infants born approximately 1 year after the epidemic who may have been exposed to high concentrations of mercury during early intrauterine life.

One problem that should be given immediate priority is that of identifying the mothers that correspond to these three categories. In some cases, measurements of the mercury concentration in blood samples will still serve as a means of identification, but in most cases the analysis of sequential hair samples should serve as the best indication of exposure during pregnancy. Once identified, these infants and the mothers that have been exposed to methylmercury should be studied for many years for signs of effects of such poisoning. Information from such a study should help in determining the lowest concentrations of methylmercury that can have toxic effects when consumed by man.

References and Notes
1. This article was based on collaborative studies conducted by faculties at the Universities of Baghdad (Iraq) and Rochester, New York (U.S.A.). The study was organized under the auspices of a scientific committee (Chairman, Prof. F. Bakir) appointed to coordinate all studies of the methylmercury epidemic in Iraq. A clinical committee (Chairman, Prof. S. F. Damji) was responsible for studies on patients attending the administration of methylmercury-binding agents to patients. Faculty director of the Rochester program were Drs. T. W. Clarkson, J. C. Smith, and R. A. Doherty. The Mercury Investigation Committee, under the direction of Dr. H. I. Dahar, was responsible for programming the collection and analysis of all the biological samples obtained from patients under study. The observations on clinical symptoms were made by Drs. A. H. Al-Abbas, F. Bakir, S. F. Damji, T. Hamdi, S. Elhassani, K. Al-Jahant, M. A. Khalil, J. Kowaiti, M. Murtadha, F. Ode, and K. H. Al-Omar. Mrs. P. Dahir and Mr. M. Greenewald reviewed the cases for the analysis of mercury by atomic absorption spectrometry.

2. Gas chromatographic analysis of hair, blood, and other biological samples was conducted according to the method of R. Von Burg, F. Farrar, and J. Smith (in preparation).


4. In one assumption of a birthrate of 40 per 1000 population per year and assumed that pregnancy would not be detected in the first 2 months, one would expect to find approximately 144 pregnant females among the early cases admitted to hospital. This number would be subject to additional error if the population profile (with respect to age and sex) in the admitted cases were not the same as in the general population. Thus, the number of females exceeds the number of males in the admitted cases (Fig. 3) so that the figure 148 may be underestimated.

5. The thiol reagent, a synthetic organic ion exchange resin, was derived from a mass of the synthesis described by K. A. Kunitz (U.S. Patent 3,278,487 (1966)). The efficiency of the reagent in animal studies has been reported by T. W. Clarkson, H. Small, and T. Norseth [Arch. Environ. Health 18, 173 (1967)].


9. The relationships between the amount of mercury in blood samples obtained in Iraq, was calculated according to the method of R. Von Burg, F. Farrar, and J. Smith (in preparation).


12. The fraction, f, of the body burden of methylmercury that is excreted within 6 months has been reported by Miettinen in studies of volunteers given a single dose of methylmercury labeled with the 203Hg isotope (J. K. Miettinen, in Mercury, Mereurals and Merecupates, M. Miller, T. W. Clarkson, Eds. (Thomas, Springfield, Ill., 1972), pp. 233-243). The logarithm of the value of f declines linearly with time after exposure. The time required for the value of f to be reduced by one-half is 6 months. The value of f, as applied to mercury concentrations in blood samples obtained in Iraq, has been calculated from Miettinen's data, with the assumption of an exponential decline over the period extending from the middle of the exposure period to the time of collection of the blood sample. The value is then corrected for differences in body weights between Miettinen's volunteers (assumed to be 70 kg) and the Iraqi patients. The periods during which contaminated bread was consumed were calculated from the collection period to the point of the origin. The regression lines calculated in this way for the data in Fig. 5 are y = 17x for Fig. 5a; and y = 9x for Fig. 5b. The symbol y represents the total concentration of mercury in blood (expressed as nanograms) and the symbol x represents the total estimated dose of methylmercury expressed as milligrams.

13. The relationship between the amount of methylmercury ingested daily, W, and the amount accumulated in the body, B, is given by the expression:

\[ B = \frac{(m/k) \times (1 - e^{-kt})}{k} \]

where k is the elimination constant and t is time. On cessation of the body burden B will decline according to the relationship:

\[ B = B_{m} \times e^{-kt} \]

where B_{m} is the body burden at the time when ingestion of methylmercury stopped. The time taken for the body burden to decrease by one-half, T_{1/2}, is related to the elimination constant by the equation

\[ T_{1/2} = \frac{0.693}{k} \]
Support of New Principal Investigators by NIH: 1966 to 1972

Rate of entry of investigators into the NIH research project grant system is analyzed.

Carl D. Douglass and John C. James

In recent years, the growth of funds for the support of the National Institutes of Health (NIH) extramural research projects has slowed, and there was actually a slight decline in funds appropriated for research in fiscal year 1970. Increases in funding during fiscal years 1971 and 1972, up substantially from the 1970 level, indicated a resumption of the slower pace of growth extending approximately from 1966 to 1972. Such a situation has caused some concern in the biomedical community as to whether recently graduated but well-qualified scientists, not previously established as principal investigators, could compete successfully for new research grants. In view of this, the testing of the assumption that "new blood" is continually being infused into the population of investigators being supported becomes especially important. Consequently we have undertaken an analysis of the rate at which new investigators are gaining their research support from the NIH through the traditional research project grant mechanism. During periods of little or no growth, it is still possible for new investigators to receive support from NIH each year because of the turnover in the research grant system and the resulting availability of money to fund competing applications.

Each fiscal year there are three review cycles, in which new and competing renewal research grant applications are evaluated—first by the study sections, for scientific merit, and then by the National Advisory Councils, for policy consideration and relevance to the mission of a particular national institute. Approximately 70 percent of the grants awarded each year are noncompeting continuations, which are regarded as moral commitments since they represent the second, third, or further additional year of a project approved for a period of more than 1 year of grant support. These grants are classed as "noncompeting" and are funded without being resubmitted for competitive review because they fall within the approved project period. At the end of the project period, averaging about 3 years, the investigator may apply for a renewal of his research grant by submitting an application that will reenter the competition. Thus, both new and renewal applications are in competition for funds remaining from payment of noncompeting grant awards.

A detailed analysis (17) of NIH extramural programs from 1960 to 1970 provides background for understanding variations in the NIH growth pattern. Although the amount of support in dollars steadily increased, there was a decline in total number of projects supported during the latter half of the decade. The reason for the decline in the total number of research projects is related to such factors as inflation; increasing commitments to large biomedical research complexes, called "centers"; increasing technological complexity, which increases the cost of research; increased indirect costs; and increasing levels of personnel costs in research grant budgets. All of these factors influence the level at which NIH can support new projects in scientifically and programatically meritorious areas of research and, consequently, the rate at which well-trained scientists may enter the system and assume major responsibility for their own research. Moss (2) in a study of the applications presented to the June 1971 meeting of the National Advisory Heart and Lung Council, found that the applications of young scientists (under age 36) were approved at a higher rate than those of older, more established scientists.

The single largest NIH extramural grant program, that of investigator-initiated research projects, has been funded at levels ranging from $341 to $427 million annually since fiscal year 1966. Information on this program is shown in Table 1. The intent of our study was to measure the rate of entry of new principal investigators (PI's)

Dr. Douglass is deputy director of the Division of Research Grants and Dr. James is head of the Research Analysis and Evaluation Branch, Division of Research Grants, National Institutes of Health, Bethesda, Maryland 20014.