PLASTIC ANEMIA is thought to have multiple causes, with exposure to drugs and other chemicals being the most prominent. At the end of the 19th century, Santesson described benzene-induced marrow failure in Swedish bicycle tire workers, and in the early 20th century a strong link was established between dipyrone and the related dyscrasia, agranulocytosis. Subsequent case reports have documented an association between a large variety of pharmaceutical agents and aplastic anemia. In published case series, drugs have been the most commonly identified causes of aplastic anemia, chloramphenicol has been mentioned especially frequently. Drug-associated aplastic anemia has important implications for the prescribing practice of physicians, drug development, governmental regulation and the wording of warning labels, and expensive tort actions.

For decades, aplastic anemia has appeared to be more common in Asia than in the West. In a population-based study, we recently documented the incidence of the disease in Bangkok as approximately twice that in Europe and Israel. There is little evidence for ethnic variability in the rates of aplastic anemia, and one of the suggested explanations for the higher incidence in the Far East has been drug use. For example, chloramphenicol is believed to be widely used in developing countries as compared with its infrequent use in the West. A recent publication suggested that the use of pyrazolone derivatives might be partly responsible for the higher incidence. In general drugs are more freely available in Asia, usually without prescription, and may be components of folk or herbal remedies.

In 1989 we instituted a population-based case-control study of aplastic anemia, with the specific intent of addressing drug and chemical exposures. The study was conducted with the proven methods of the International Agranulocytosis and Aplastic Anemia Study (IAAAS), which quantified the relative risks associated with a large number of drugs and the two blood dyscrasias in Europe and Israel. Both investigations used standardized interviews of patients, and controls were matched by trained personnel using carefully designed questionnaires. Considerable efforts were made to identify all drug use in the period preceding the clinical symptoms of the disease. We now present our analysis of the data from Thailand.

MATERIALS AND METHODS

The study began in greater Bangkok (including the city of Bangkok and the suburbs Nonthaburi, Nakornpathom, Pathumthani, Samutprakarn, and Samutsakorn—total population about 8.75 million) in January 1989. In November 1991 it was expanded to the Khonkaen region in northeastern Thailand (Khonkaen, Kalasin, Mahasarakam, Loei, Nongkai, Udonthani, and Royed—population 7.64 million) and to the Songkla region in the south (Songkla, Yala, Pattani, Satoon, Nakornrithammarat, and Trang—population 4.99 million). Potential cases were identified by regular contact with hematologists or other physicians either by telephone or visit at least every other week. Eligible subjects were required to meet at least two of the following criteria: white blood cell count $\leq 3.5 \times 10^9/L$, platelet count $\leq 50 \times 10^9/L$, and hemoglobin concentration $\leq 100$ g/L or hematocrit $\leq 30\%$. If the latter criterion was one of the two fulfilled, a reticulocyte count $\leq 30 \times 10^9/L$ was also required. Patients who had received chemotherapy or radiotherapy were excluded. The de-
DRUGS AND APLASTIC ANEMIA IN THAILAND

Two hundred and seventy subjects and 737 controls were interviewed. The information obtained included demographic data, relevant medical history, a detailed history of drug use, and data on exposure to radiation and chemicals. Diagnostic and final acceptance of cases also required a characteristic bone marrow biopsy showing hypocellularity without fibrosis or infiltration by leukemic, lymphomatous, or carcinoma cells. Acceptable diagnoses included trauma, acute infections (e.g., pneumonia), acute abdominal emergencies (e.g., appendicitis), and other conditions (e.g., cataract). Acceptable diagnoses or final acceptance of cases also required a characteristic bone marrow biopsy showing hypocellularity without fibrosis or infiltration by leukemic, lymphomatous, or carcinoma cells. 

Controls were selected from among other hospital patients of the same sex and age range (<2, 2-5, 6-14, 15-24, 25-44, 45-64, and ≥65 years) as the subjects according to a list of admission diagnoses judged to be independent of antecedent drug use or occupational exposure. Acceptable diagnoses included trauma, acute infections (e.g., pneumonia), acute abdominal emergencies (e.g., appendicitis), and other conditions (e.g., cataract). Acceptable diagnoses or final acceptance of cases also required a characteristic bone marrow biopsy showing hypocellularity without fibrosis or infiltration by leukemic, lymphomatous, or carcinoma cells.

Subjects and controls were interviewed by trained monitors who were physicians or nurses. The information obtained included demographic data, relevant medical history, a detailed history of drug and pesticide use, and data on exposure to radiation and chemicals. The method described for the IAAAS was used. Excess risks are expressed as the number of cases per million users in a 5-month period (equivalent to the interval used in the estimation of the relative risks).

RESULTS

The use of antibiotics among subjects and controls is shown in Table 1. Chloramphenicol was used by 2% of the subjects and 1% of the controls; there was no statistically significant association, although the multivariate relative-risk estimate was elevated, at 2.7 (95% confidence interval, 0.7 to 10). With too few exposed controls for multivariate analysis, the crude relative-risk estimate for sulfonamide exposure was significantly increased, at 7.9 (P = .004). There was a modest, nonsignificant elevation in the multivariate point estimate for tetracyclines (1.8). The estimates for penicillins and ampicillin/amoxicillin were at or close to 1.0, and the upper 95% confidence limits were below 3.0. Unspecified antibiotic use was reported by 9% of the subjects and 6% of the controls.

The results for analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) are shown in Table 2. Salicylates and paracetamol were commonly used. There was no evidence of association for either drug group, with multivariate relative-risk estimates at or close to 1.0, even for regular use (at least 4 days in at least 1 week). In the latter category (regular use), the upper 95% confidence limit was 2.4 for salicylates and 2.5 for paracetamol; it was below 2.0 for less frequent use of both drugs. There was also no evidence of association for pyrazolone derivatives (relative-risk estimate, 0.5). As a group, NSAIDs were used more commonly by subjects (2%) than controls (1%), but none of the individual drugs were taken by sufficient subjects or controls for formal risk evaluation.

To control confounding by the concomitant use of more than one potentially causal drug and by other factors, multiple logistic regression was used. The factors included in the model were age, sex, region, year of hospital admission, total household income (adjusted for inflation to 1989), years of education, history of hookworm and tuberculosis, farming, and occupational exposure to solvents and pesticides, use of household pesticides, and exposure to various drugs in days 29-180. Multivariate relative-risk estimates are shown only for drugs with at least four exposed subjects and four exposed controls.

The etiologic fraction (the proportion of cases attributable to an exposure) was estimated for each drug showing a statistically significant association with aplastic anemia (based on multivariate analysis where numbers permitted). It was also used together with the relative risk and overall incidence (4.1 per million in all regions combined) to estimate the excess risk or absolute risk, according to the method described for the IAAAS.12 Excess risks are expressed as the number of cases per million users in a 5-month period (equivalent to the interval used in the estimation of the relative risks).

Data analysis. Relative risks were estimated for all systemic drugs used by at least four subjects in a 5-month period ending 1 month before admission (ie, 2 to 6 months before admission, henceforth referred to as days 29-180), with the exception of categories of drugs that are not of interest as potential risk factors for aplastic anemia (eg, vitamins, iron preparations, antacids, laxatives, drugs used to treat aplastic anemia, such as anabolic steroids). For completeness, numbers of exposed subjects and controls are shown in the Results without relative risk estimates for drugs used by fewer than four subjects. Topical drugs were considered unlikely to be etiologically relevant and were not evaluated.

To control confounding by the concomitant use of more than one potentially causal drug and by other factors, multiple logistic regression was used. The factors included in the model were age, sex, region, year of hospital admission, total household income (adjusted for inflation to 1989), years of education, history of hookworm and tuberculosis, farming, occupational exposure to solvents and pesticides, use of household pesticides, and exposure to various drugs in days 29-180. Multivariate relative-risk estimates are shown only for drugs with at least four exposed subjects and four exposed controls.

The etiologic fraction (the proportion of cases attributable to an exposure) was estimated for each drug showing a statistically significant association with aplastic anemia (based on multivariate analysis where numbers permitted). It was also used together with the relative risk and overall incidence (4.1 per million in all regions combined) to estimate the excess risk or absolute risk, according to the method described for the IAAAS.12 Excess risks are expressed as the number of cases per million users in a 5-month period (equivalent to the interval used in the estimation of the relative risks).
Table 1. Exposure to Systemic Antibiotics in Days 29-180 Before Admission Among 253 Subjects With Aplastic Anemia and 1,174 Controls

<table>
<thead>
<tr>
<th>Drug</th>
<th>Subjects: No. (%)</th>
<th>Controls: No. (%)</th>
<th>Crude Relative Risk (95% confidence interval)</th>
<th>Multivariate Relative Risk (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol</td>
<td>4 (2)</td>
<td>8 (1)</td>
<td>2.3 (2.7 (0.7-10))</td>
<td></td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>5 (2)</td>
<td>3 (0.3)</td>
<td>7.9* (0.6-5.6)</td>
<td></td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>5 (2)</td>
<td>13 (1)</td>
<td>1.8 (1.0 (0.4-2.7))</td>
<td></td>
</tr>
<tr>
<td>Penicillins</td>
<td>6 (2)</td>
<td>12 (2)</td>
<td>1.1 (1.0 (0.4-2.7))</td>
<td></td>
</tr>
<tr>
<td>Ampicillin/amoxicillin</td>
<td>13 (6)</td>
<td>48 (4)</td>
<td>1.3 (1.0 (0.4-2.7))</td>
<td></td>
</tr>
<tr>
<td>Other named antibiotics†</td>
<td>2 (1)</td>
<td>9 (1)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Unspecified antibiotic</td>
<td>23 (9)</td>
<td>71 (6)</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

* P = .004.
† Includes cloxacillin (1 subject, 3 controls), norfloxacin and metronidazole (1, 0), norfloxacin (0, 2), dicloxacillin (0, 2), erythromycin (0, 2).

drugs are to be expected; there are numerous limitations to the documentation of associations with case reports, including nonstandardized disease definitions, no comparison series to allow for the quantification of risks, and the tendency to selectively report exposure to drugs that are already suspected.

The results of the present case-control study in Thailand, the largest epidemiologic study of aplastic anemia conducted to date, identified only a few drugs that were associated with the development of the dyscrasia. There were significantly elevated relative risks for sulfonamides and thiazide diuretics, which are chemically related, and for mebendazole. Excess risk estimates ranged between 9 and 12 cases per million users in a 5-month period. No significant association was observed with chloramphenicol use. The etiologic fraction for all associated drugs combined was far lower at 5% than in the IAAAS.

Chloramphenicol deserves special comment. This drug has been considered to be among the most common causes of aplastic anemia in the past. After its introduction into clinical practice in the late 1940s, chloramphenicol was blamed for a seeming epidemic of aplastic anemia; however, almost half of cases collected between 1949 and 1952 in the United States were ascribed to prior use of this antibiotic, and chloramphenicol was usually associated with 20% to 30% of the aplastic anemia occurrences in case report series.

Table 2. Exposure to Analgesics and NSAIDs in Days 29-180 Before Admission Among 253 Subjects With Aplastic Anemia and 1,174 Controls

<table>
<thead>
<tr>
<th>Drug</th>
<th>Subjects: No. (%)</th>
<th>Controls: No. (%)</th>
<th>Crude Relative Risk (95% confidence interval)</th>
<th>Multivariate Relative Risk (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4 d/wk</td>
<td>47 (19)</td>
<td>193 (16)</td>
<td>1.2 (0.9 (0.6-1.4))</td>
<td></td>
</tr>
<tr>
<td>≥4 d/wk</td>
<td>7 (3)</td>
<td>32 (3)</td>
<td>1.0 (1.0 (0.4-2.4))</td>
<td></td>
</tr>
<tr>
<td>Paracetamol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4 d/wk</td>
<td>97 (38)</td>
<td>455 (39)</td>
<td>1.0 (1.2 (0.8-1.7))</td>
<td></td>
</tr>
<tr>
<td>≥4 d/wk</td>
<td>18 (7)</td>
<td>66 (6)</td>
<td>1.3 (1.3 (0.7-2.5))</td>
<td></td>
</tr>
<tr>
<td>Pyrazolones*</td>
<td>5 (2)</td>
<td>32 (3)</td>
<td>0.7 (0.5 (0.2-1.6))</td>
<td></td>
</tr>
<tr>
<td>NSAIDs†</td>
<td>5 (2)</td>
<td>12 (1)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Unspecified pain medication</td>
<td>21 (8)</td>
<td>105 (9)</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

* Includes dipyrone (3 subjects, 25 controls); propyphenazone (2, 2); aminopyrine (0, 2); dipyrone and aminopyrine (0, 1); dipyrone and propyphenazone (0, 1); antipyrine (0, 1).
† Includes diclofenac (1 subject, 3 controls), piroxicam (1, 3), mefanamic acid (1, 2), naproxen (1, 1), indomethacin (1, 1), phenylbutazone (0, 2).
Table 3. Exposure to Miscellaneous Drugs in Days 29-180 Before Admission Among 253 Subjects With Aplastic Anemia and 1,174 Controls

<table>
<thead>
<tr>
<th>Drug</th>
<th>Subjects: No. (%)</th>
<th>Controls: No. (%)</th>
<th>Crude Relative Risk</th>
<th>Multivariate Relative Risk (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazides</td>
<td>6 (2)</td>
<td>5 (0.4)</td>
<td>5.7</td>
<td>7.7 (1.5-40)</td>
</tr>
<tr>
<td>Mebendazole</td>
<td>4 (2)</td>
<td>3 (0.3)</td>
<td>6.3*</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>9 (4)</td>
<td>18 (2)</td>
<td>2.4</td>
<td>1.3 (0.5-3.5)</td>
</tr>
<tr>
<td>Other psychoactive drug†</td>
<td>8 (3)</td>
<td>25 (2)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>50 (20)</td>
<td>265 (23)</td>
<td>0.8</td>
<td>0.5 (0.2-1.2)</td>
</tr>
<tr>
<td>Other antihistamines†</td>
<td>6 (2)</td>
<td>42 (4)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Phenylpropanolamine</td>
<td>43 (17)</td>
<td>221 (19)</td>
<td>0.9</td>
<td>1.8 (0.7-4.7)</td>
</tr>
<tr>
<td>Unspecified cold/fever drug</td>
<td>42 (17)</td>
<td>162 (14)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Diphenoxylate/atropine</td>
<td>15 (6)</td>
<td>41 (3)</td>
<td>1.7</td>
<td>1.7 (0.9-3.4)</td>
</tr>
<tr>
<td>Loperamide</td>
<td>3 (1)</td>
<td>6 (0.5)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Unspecified antidiarrheal</td>
<td>10 (4)</td>
<td>27 (2)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>6 (2)</td>
<td>31 (3)</td>
<td>0.9</td>
<td>0.6 (0.2-1.7)</td>
</tr>
<tr>
<td>Herbal preparations§</td>
<td>58 (23)</td>
<td>218 (19)</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

* P = .03.
† Includes amitriptyline (1 subject, 1 control), amitriptyline and unspecified tranquilizer (1, 0), mianserin (1, 0), haloperidol (1, 0), metoclopramide (0, 2), unspecified sedative/tranquilizer (4, 22).
‡ Includes triprolidine (2 subjects, 6 controls), clemizole (1, 10), diphenhydramine (1, 1), doxylamine (1, 0), cinarrazin (0, 5), hydroxyzine (0, 5), dimenhydrinate (0, 4), cinarrazin and dimenhydrinate (0, 1), astemizol (0, 1), flunarsazine (0, 1), mebhydrolin (0, 1), unspecified antihistamine (1, 7).
§ The preparations taken by 14 subjects (6%) and 76 controls (6%) included both herbal ingredients and drugs.

Estimates of risk in more formal studies ranged from 1 in 800,000 to 1 in 6,000. However, these studies did not use rigorous diagnostic criteria, and conditions other than aplastic anemia, such as myelodysplastic syndrome, were not excluded. Moreover, in some cases exposure to chloramphenicol could have occurred after the onset of the disease but before diagnosis. These problems could have led to overestimation of the incidence of aplastic anemia among chloramphenicol users.

With narrowing indications the use of chloramphenicol has decreased; despite its efficacy, low cost, and lack of common side effects, however, its withdrawal from several national markets was not followed by a decline in aplastic anemia incidence. Chloramphenicol was not commonly used in the present study population in Thailand (1% of the controls). Thus, although we did not observe a significant association, the upper 95% confidence interval of 10 does not allow the rigorous exclusion of the possibility of an elevation in risk. However, should there have been a major increase, such as the relative risk of 30 reported from California, our study should have detected it.

Sulfa compounds have been frequently linked to aplastic anemia but are more commonly linked to agranulocytosis and modest levels of neutropenia. The use of sulfa drugs in the treatment of infections, a possible first sign of marrow failure, and in “autoimmune” diseases that may be independently associated with immune suppression of hematopoiesis are potentially confounding of a true etiologic relationship. The present study was designed to avoid these potential complications; the finding of a significant risk associated with both sulfonamide antibiotics and the chemically related thiadizide diuretics confirms an association of these agents with aplastic anemia, although with the proviso that there were too few subjects and controls exposed to sulfonamide antibiotics for rigorous multivariate analysis. In comparison the IAAAS data showed elevated relative-risk estimates for the trimethoprim combination and other sulfonamides, but these were not significant on multivariate analysis (by contrast, these drugs were strongly associated with agranulocytosis). Curiously, Asians might be expected to be less susceptible to sulfa toxicity, as fast acetylation is far more common than among Whites, and there is a strong association of sulfonamide toxic reactions with the slow acetylation phenotype.

The association with mebendazole was not previously reported and was based on small numbers, without control of confounding. Thus, it must be considered tentative pending confirmation. Other major groups of drugs that were significantly associated with aplastic anemia in the IAAAS were not shown to be related to the disease in Thailand in the current study. These pharmaceutical classes include the NSAIDs, thyrostatics, psychoactive medications, and single agents such as gold, penicillamine, and allopurinol. Although differences in susceptibility between the two populations cannot be excluded, a more detailed explanation is simply much lower rates of use of the relevant drugs among Thais. For example, 8% of European controls in the IAAAS reported use of an NSAID in the preceding 6 months compared with only 1% of Thai controls.

Among other drugs, it was recently suggested that pyrazolone derivatives, such as aminopyrine, might be at least partly responsible for the higher incidence of aplastic anemia in the Far East. The present results provide evidence to refute this claim: The relative risk for pyrazolones was below one, and the upper confidence limit was sufficiently low to rule out an increase of 1.7. A similar lack of association was observed in the IAAAS.

Herbal preparations were used by about 20% of subjects and controls. These preparations may have been contaminated with known or unknown drugs or chemicals that may
be associated with aplastic anemia. In Thailand, herbal remedies are regarded as agents that can be used freely because they might be beneficial and will not be harmful. There were some identified combinations of herbal preparations with drugs, none of which have been implicated in marrow failure syndromes; however, most had unidentified ingredients. In any event, there was no overall association between herbal preparation usage and aplastic anemia in this study.

The possibility that the present findings could be biased must be considered. The identification and enrollment of subjects was actively pursued by study personnel. It did not rely on voluntary reporting by hospital staff, which could be selectively related to drug use or prior beliefs about drug risk. Virtually all subjects were identified in this study. No subjects or controls refused the interview. Selection bias is therefore unlikely.

Information bias is possible because physicians would undoubtedly have questioned the subjects about medication use before the study interview. Controls would not have been subjected to this same questioning. However, we used a highly structured questionnaire, including systematic questions about indications for drug use followed by a list of trade names to minimize information bias. In addition, if anything, information bias would most likely have led to overestimation of associations, not the relative lack of associations observed here.

General underreporting of drug use could have resulted in associations being missed, and as noted, the reported use of many previously attributed drugs was low. It is reassuring in this context that in a small (31 cases), parallel case-control study of agranulocytosis in Thailand, the overall etiologic fraction for suspected drugs was substantial, at 70%, and comparable to the etiologic fraction of 65% in the IAAAS. These remarkably similar results for agranulocytosis imply that underascertainment of drug use is an unlikely explanation for the small etiologic fraction seen for aplastic anemia.

A limitation to the present findings stems from the wide, and hence imprecise, exposure period of 2 to 6 months before hospital admission. This was necessitated by the impossibility of systematically defining the clinical onset of the disease because of the vagueness of many of the presenting symptoms (e.g., weakness, fatigue). In particular, it may be that some of the use of certain drugs, such as antibiotics, was initiated after the disease began for early, nonspecific manifestations such as infections. Again, however, this would probably have led to spurious associations being identified, rather than a lack of associations.

Aplastic anemia is more common in Thailand than in Western countries. After the first year of data collection in the present study, we reported an incidence in Bangkok of 3.7 cases per million population per year, which has been consistent in subsequent years, and is about double the overall incidence from the IAAAS. Contrary to what might have been expected, the current findings suggest that only a small proportion of Thai cases can be accounted for by drugs. It is thus especially important to explore the etiologic role of other factors, including occupational and environmental exposures. The present study has documented an inverse association between aplastic anemia and socioeconomic status and an increased risk among grain farmers. Causal agents that might explain the findings have not been identified. An independent modest association with agricultural pesticides was also observed. Data on household pesticides, which are commonly used in Thailand, and on hepatitis serology will be the subject of future reports.

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APPENDIX

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Low Drug Attributability of Aplastic Anemia in Thailand

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