Clinical Outcomes after Hepatitis C Infection from Contaminated Anti-D Immune Globulin

To the Editor: In the report by Kenny-Walsh and the Irish Hepatology Research Group (April 22 issue) on the outbreak of hepatitis C in Ireland in 1977 associated with the administration of anti-D immune globulin contaminated with hepatitis C virus (HCV), Table 1 lists the estimated number of recipients of anti-D immune globulin on the basis of the estimated number of vials issued and the number of recipients tested. We would like to supply more precise details.

Overall, 21,603 persons who indicated that they had received anti-D immune globulin between 1977 and 1979 have been screened for HCV by the Irish Blood Transfusion Service Board. Owing to the lack of complete records when the screening program began in 1994, the HCV-testing program was a self-referral one, which offered testing to all recipients of anti-D immune globulin. The total therefore includes persons who received contaminated anti-D immune globulin and those who received uncontaminated immune globulin as well as a considerable number who did not receive anti-D immune globulin, either because it was not required during that pregnancy or because they were, in fact, Rh-positive. A total of 795 have been found to be positive for HCV antibody, and 413 had positive results on polymerase-chain-reaction testing. Twelve batches, constituting 4062 vials, of contaminated or potentially contaminated anti-D immune globulin were in circulation in 1977 through 1979 (the batches had an expiration date of mid-1979). Since a small number of persons were known to have received multiple doses, the maximal number of possible recipients was 3951. To date, the formal process to identify those who received HCV-contaminated or potentially HCV-contaminated vials has resulted in the identification of 2592 such persons (66 percent of those exposed), of whom 2352 (91 percent) have been tested. It is therefore likely that the estimate of Kenny-Walsh and colleagues that 94 percent of those exposed will have been tested will be met.

We have analyzed in detail a subgroup of 1342 tested recipients using record cards that list the batch of anti-D immune globulin and information about the recipient, which were compiled at the time the immune globulin was administered. We found that the infectivity of the batches varied considerably, ranging from 60 percent to 0.7 percent, with an overall infectivity of 25 percent.²

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To the Editor: The Irish Hepatology Research Group found a relatively low prevalence of severe liver disease and HCV viremia among women who had been infected with contaminated anti-D immune globulin, as compared with other cohorts. After an average of 17 years of infection, cirrhosis had developed in only 2 percent. Furthermore, only 55 percent of those with antibodies against HCV tested positively for HCV RNA, in contrast to the much higher percentages in other reports. The authors speculate that the mode of infection may be an important variable in determining disease outcome. A similarly low rate of disease progression was reported in a study of 152 women who had been infected with HCV after receiving contaminated anti-D immune globulin.

Another possible explanation for these outcomes is that the immune globulin itself attenuated the acute infection. Attenuation of acute infection associated with polyclonal immunoglobulin has been reported in a number of viral infections, including hepatitis A and B. Unlike hepatitis B, hepatitis C has no effective immunoglobulin prophylaxis. However, it has been hypothesized that passive immunization with polyclonal immunoglobulins containing anti-HCV antibodies protected against recurrent HCV viremia and new HCV infection in liver-transplant recipients. Furthermore, the presence of high titers of antibodies that inhibit binding of the HCV envelope to human cells has been associated with natural resolution of chronic hepatitis C.

It is likely that anti-D immune globulin preparations used in the 1970s contained immunoglobulins against hepatitis C, some of which may have had these neutralizing properties.

The authors reply:

To the Editor: We welcome the very useful clarification data provided by Drs. Lawlor and Columb. The comparatively mild clinical course of the HCV RNA–positive women is consistent with the estimated infectivity of 25 percent for those exposed to anti-D immune globulin contaminated with HCV.

Dr. Bonis addresses the low prevalence of severe disease in our study population and raises the possibility of attenuation of the acute infection by the immune globulin preparation. Although his interesting hypothesis might be explored further, we again suggest that the relatively good outcome reported in our paper may have been the result of a single exposure (in the vast majority of cases) with a comparatively small infectious dose unaccompanied by the immunosuppressant effects of blood transfusion.

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Rapidly Fatal Infection with Ehrlichia chaffeensis

To the Editor: Human ehrlichial infections are increasingly being recognized as common tick-borne diseases in the United States. Clinical characteristics of ehrlichiosis include fever, headache, and malaise with leukopenia, thrombocytopenia, and elevated levels of hepatic aminotransferases. In rare instances, infection may result in multiple organ failure and death, particularly in immunosuppressed patients. Despite the potential severity of disease, death is uncommon in normal human hosts. We report two cases of rapidly fatal Ehrlichia chaffeensis infection in patients who presented to our institution in early June.

A 22-year-old man was hospitalized with hypotension after a one-week illness characterized by fever, headache, myalgias, and diarrhea following exposure to a tick during military exercises. Outpatient treatment had included ceftriaxone and erythromycin, with doxycycline added immediately before transfer to our institution because of progressive hypoxemia. Within 50 hours, generalized seizures, adrenal insufficiency, acute lung injury, disseminated intravascular coagulation, and multiple-organ failure resulted in death, despite aggressive resuscitation measures.

A 38-year-old man with AIDS, hepatitis B, and hepatitis C presented to our emergency department with fever, headache, diarrhea, and dysuria one week after exposure to a tick. Cephalexin had been prescribed for a suspected urinary tract infection. In the hospital, he had hypotension, generalized seizures, severe metabolic acidosis, acute lung injury, and multiple-organ failure and died within 24 hours, despite appropriate antimicrobial therapy.

Peripheral-blood specimens from both patients demonstrated intraehrlichocytic morulae (Fig. 1) and, as shown by polymerase chain reaction, were positive for E. chaffeensis 16S ribosomal DNA (methods described previously).

Human ehrlichial disease falls along a spectrum of severity, ranging from asymptomatic (in as many as 67 percent of patients) to fulminant and fatal. Normal hosts rarely succumb to ehrlichial infections, particularly when they are younger than 60 years and when appropriate antimicrobial therapy, such as doxycycline, is administered early. Because the symptoms are nonspecific, tick-borne infections may not be considered.

It is unclear whether our experience is a result of heightened recognition, increased exposure and environmental encroachment (e.g., through military training), infectious burden, or an unusually virulent infection. Regardless, for rapid initiation of appropriate empirical therapy — before diagnostic confirmation — it is imperative to recognize early the symptoms and laboratory abnor-
malities common to rickettsial infections in high-risk patients from endemic areas, to prevent the morbid cascade of organ failure.

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A Common B-Cell Precursor in Composite Lymphomas

To the Editor: Bräuninger et al. (April 22 issue) identified a common germinal-center B-cell precursor for both Reed–Sternberg cells and non-Hodgkin’s lymphoma cells in two patients with composite lymphoma. We studied five patients who had classic composite lymphoma with features of Hodgkin’s disease and non-Hodgkin’s lymphoma in the same lymph node to determine whether the two neoplasms were clonally related.

One patient presented with a combination of nodular-sclerosis Hodgkin’s disease and a high-grade B-cell lymphoma; the others had mixed-cellularity Hodgkin’s disease and low-grade B-cell lymphoma. Single cells were isolated from formalin-fixed, paraffin-embedded sections after immunohistochemical staining for CD20, CD15, CD30, and CD3. The cells of interest were isolated by destroying the surrounding tissue with an ultraviolet laser and removed with a computer-assisted micromanipulator. The isolated cells were then submitted to seminested polymerase-chain-reaction amplification of IgH gene rearrangement with primers LJH and FR3A for the first round, followed by a second reaction with primers VLJH and FR3A. The use of paraffin-embedded tissue allows better examination of morphologic features than does the use of frozen sections. Moreover, DNA amplification of single cells isolated from routinely embedded and stained sections has been shown to be comparable to that of fresh-frozen, microdissected cells in terms of sensitivity (unpublished data).

We amplified clonal IgH gene rearrangements in cells from four of the five patients (Table 1). In Patients 1 and 2, we obtained identical clones from the Reed–Sternberg cells and the non-Hodgkin’s lymphoma cells, suggesting that a single B cell was the precursor of both neoplastic components and supporting the hypothesis of a shared precursor that underwent neoplastic transformation. Patients 3 and 5 had different clonal rearrangements for the two neoplastic components, suggesting that they were clonally unrelated. We do not think that this result is due

Figure 1. Ehrlichia chaffeensis Morulae in Peripheral-Blood Specimens (Wright’s Stain, ×1250).
Panel A shows loosely packed morulae (arrow) within a vacuole of a monocyte from the 22-year-old patient. Panel B shows several morulae (arrow) within a monocyte from the 38-year-old patient with AIDS.
to therapy, as proposed by Bräuninger et al., because the Hodgkin’s disease and the non-Hodgkin’s lymphoma occurred simultaneously. Finally, in Patient 4, we could not detect a clonal amplification product of the Reed–Sternberg cells. This result could be due to a high number of somatic hypermutations in the primer binding sequences.

In conclusion, we believe it unlikely that composite B-cell lymphomas invariably have a single precursor, since other, even non–germinal-center B cells, may take part in the genesis of composite lymphomas.

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** Chronic Myeloid Leukemia **

*To the Editor:* The definition of “chronic myeloid leukemia” (CML) in Sawyers’s excellent review article (April 29 issue) describes the disease as “a malignant clonal disorder of hematopoietic stem cells that results in increases in not only myeloid cells but also erythroid cells and platelets in peripheral blood and marked myeloid hyperplasia in the bone marrow.” Although this definition accurately reflects the molecular and cellular pathophysiologic features of this condition, it is clinically misleading because patients with CML almost always present with an elevated granulocyte count, a variably increased platelet count (in 30 to 50 percent of patients), and anemia (in approximately 85 percent of patients). Only very, very rarely in CML is there thrombocytosis.

Indeed, in Table 1 of Sawyers’s review, the list of peripheral-blood findings appropriately does not include thrombocytosis. By counteracting the white cells’ effect on blood viscosity, the anemia associated with CML may actually be of some benefit to patients with marked leukocytosis. Thus, the usual presentation of CML is different from that of polycythemia vera. In the latter, there is commonly erythrocytosis, leukocytosis, and thrombocytosis and often the clinical effects of blood hyperviscosity. Measurement of leukocyte alkaline phosphatase, chromosomal studies (for the Philadelphia chromosome), and use of molecular probes for the BCR–ABL translocation can help distinguish the two conditions when necessary.

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Dr. Sawyers replies:

*To the Editor:* I concur with Dr. Nash’s comments and appreciate his clarification of this point.

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**TABLE 1. CHARACTERISTICS OF FIVE PATIENTS WITH COMPOSITE LYMPHOMA.**

<table>
<thead>
<tr>
<th>PATIENT No.</th>
<th>YEAR OF BIRTH</th>
<th>SITE</th>
<th>HISTOLOGIC FINDINGS</th>
<th>IMMUNOHistoCHEMICAL STAINING</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1916</td>
<td>Lymph node</td>
<td>Mixed-infiltrate</td>
<td>CD30 CD20 CD3 CD15</td>
</tr>
<tr>
<td>2</td>
<td>1962</td>
<td>Lymph node</td>
<td>Mixed-infiltrate</td>
<td>CD30 CD20 CD3 CD15</td>
</tr>
<tr>
<td>3†</td>
<td>1920</td>
<td>Lymph node</td>
<td>Chronic lymphocytic leukemia</td>
<td>CD30 CD20 CD3 CD15</td>
</tr>
<tr>
<td>4†</td>
<td>1920</td>
<td>Lymph node and spleen</td>
<td>Chronic lymphocytic leukemia</td>
<td>CD30 CD20 CD3 CD15</td>
</tr>
<tr>
<td>5</td>
<td>1923</td>
<td>Lung</td>
<td>Nodular sclerosis</td>
<td>CD30 CD20 CD3 CD15</td>
</tr>
</tbody>
</table>

*A plus sign denotes positive, a minus sign negative, and ND not done.†Patients 3 and 4 had chronic lymphocytic leukemia.*
The Pathogenesis of Melanoma Induced by Ultraviolet Radiation

To the Editor: In their otherwise admirable review of the pathogenesis of melanoma (April 29 issue),1 Gilchrest et al. misrepresent some of the epidemiologic evidence. The authors cite a paper I coauthored2 to indicate that incidence inversely related to latitude of residence. The point of the paper was that the stronger relation is with latitude of residence during the first 20 to 30 years of life, decades before the diagnosis of the tumor in most patients.

Although the authors correctly (in my view) interpret the evidence that melanomas result from intermittent intense exposure to reflect, in actuality, that melanomas result from exposure after a longish period of nonexposure, they go on to describe a strong positive association with sunburn and explain how protection is provided by tanning. There is little empirical evidence of a protective effect, however. Many analytic studies do show a link between the development of melanoma and the propensity to burn, but there is little evidence of protection conveyed by an ability to tan. Moreover, the protection associated with outdoor occupation is more likely to reflect educational status (and thus either an unknown behavioral factor or the constitutional skin color) than tanning in the workplace.3

In regard to sunburn, the consistent link is with childhood sunburn, which may reflect sunburn but alternatively may stand as a surrogate for skin color, pattern of solar exposure, or even biased recollection. The secular increase in the risk of melanoma in Sweden may be explained partly by sunny vacations, but that explanation would hardly be true for, say, Los Angeles or Sydney, Australia.4 This increase (which in many locales has diminished) probably represents a cohort effect in early sun-related behavior rather than an actual recent increase in intense exposure.

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To the Editor: The proposition of Gilchrest et al. that intermittent sun exposure is a more potent carcinogen for melanoma than total solar dose appears to be inconsistent with the available evidence. A systematic review of the results of 21 case-control studies did indeed reveal that a history of multiple sunburns through life is a predictor of melanoma.1 Although multiple sunburns can be interpreted as markers of intermittent sun exposure, their effects are cumulative, and a history of multiple sunburns also predicts the risk of actinic keratoses and squamous-cell carcinomas, lesions that are dependent on the dose of ultraviolet (UV) radiation. The predilection of melanoma for the face and, for men, the ears and its strong association with other skin cancers and actinic keratoses also point to a role for total solar dose. The observation that indoor workers have higher rates of melanoma than outdoor workers (offered as evidence for the selective carcinogenic effect of intermittent exposure) is tempered by the recognition that in outdoor workers, excess melanomas develop at habitually exposed sites, whereas in indoor workers, melanomas develop at sites of discretionary sun exposure.2

Furthermore, the model assumes that all melanomas share a single causal pathway, which is clearly at odds with accumulated evidence. There is strong evidence that the pathogenesis of lentigo maligna melanoma differs from that of other melanomas. Even when this histologic type is excluded, we and others have reported etiologic heterogeneity among cutaneous melanomas, as indicated by distinctive patterns of expression of the p53 tumor suppressor factor associated with the phenotypic attributes and anatomical sites of melanomas and the inverse association between the number of nevi and actinic keratoses among patients with melanoma.3 There is increasing evidence that melanomas that are histologically associated with nevus have different risk-factor profiles from melanomas that have arisen spontaneously. Together, these findings are consistent with the existence of multiple independent pathways of tumor development.

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The authors reply:

To the Editor: We agree with Dr. Mack that sun exposure during childhood rather than adulthood appears most critical in the pathogenesis of melanoma and that nevi—melanocytic proliferations that form primarily during childhood in sun-exposed areas—probably provide an expanded population of altered melanocytes from which melanomas may later arise.1 The greater risk conferred by childhood sun exposure may indeed reflect the greater proliferative capacity of melanocytes in children than in adults.2 He correctly states that there is less epidemiologic evi-
dence that tanning protects against melanoma than that sunburning predisposes one to it, although there is some evidence to this effect. More germane, the propensity to burn correlates inversely with the ability to tan, as reflected in the widely used classification of skin types that ranges from “always burns, never tans” to “rarely burns, always tans.” Our thesis, however, is only that the temporary increases in cutaneous melanin content and DNA repair capacity after a first UV exposure reduce the risk of mutations from subsequent UV exposures, as demonstrated experimentally.

Unlike Drs. Whitman and Green, we interpret the literature to state that childhood sunburns confer a greater statistical risk of melanoma than does fair complexion or sunny residence alone and that in patients with squamous-cell cancers, sunburns are indicative of fair skin and sufficient solar insult but confer no additional epidemiologic risk. The further statements by Drs. Whitman and Green also, to our reading, contradict the preponderance of the literature.

Our review presents hypothetical molecular mechanisms for melanomas induced by UV radiation, which (as we noted) are estimated to be two thirds of all melanomas, according to the epidemiologic evidence. Presumably the specific gene mutations produced in each melanoma then interact with host factors to influence the character of the melanoma.

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Disease Management

To the Editor: As Bodenheimer (April 15 issue) acknowledges, small health maintenance organizations (HMOs), medical groups, and community clinics lacking the resources to implement programs of chronic disease management may need to contract with a specialized vendor. Many of these vendors are for-profit entities. In Bodenheimer’s view, such partnerships may result in “a fragmented collection of specialized facilities centered on diseases rather than people” and failure to recognize that “people with chronic diseases often have multiple conditions plus acute problems that are unrelated to their chronic illnesses.” But, in fact, disease-management systems, however financed, can be structured to focus on the broader needs of patients, including the management of multiple conditions simultaneously.

For example, programs that rely on nurses as case managers and on other nonphysician health care professionals, including those that use telephone-based contact, have shown efficacy in the management of a variety of chronic medical conditions, risk factors for coronary artery disease, diabetes mellitus, and heart failure. Health care teams that include nonphysicians have worked closely with primary care physicians to ensure comprehensiveness and the continuity of care. Disease-management systems coordinated by telephone have already won the enthusiastic support of many physicians, who realize that skilled nonphysician health care professionals working under well-developed clinical protocols can often achieve excellent outcomes in the management of chronic disease.

Notwithstanding their effectiveness and general acceptance, health care teams are underused, largely because they are undercapitalized and underdeveloped. Because new programs are expected to be self-supporting, they generally focus on the conditions most likely to repay any investment in new technology (information-management systems) or personnel (case managers) over the short term. As Bodenheimer suggests, programs focused on heart failure, which lower short-term costs, are generally more likely to succeed from those focused on hypertension, which may lower long-term but not short-term costs. But, in fairness, this bias applies to nonprofit and for-profit health care providers alike.

The apocalyptic struggle between “carve-out” and “primary care” models of disease management posited by Bodenheimer will not be resolved completely or soon. In the meantime, there is a need to pursue a broad range of options for organizing and financing a more effective and affordable infrastructure for disease management.

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To the Editor: Bodenheimer’s restatements of the focused-factory approach I advocate in my book, Market-
Driven Health Care, are exactly opposite to my position. In my book I stated: “A focused [health care] factory is characterized by a multi-disciplinary team of people who work together.” For example, a focused factory for the treatment of diabetes is composed of endocrinologists; primary care physicians; ophthalmologists and other eye care professionals; vascular surgeons, cardiologists, and nephrologists; podiatrists and physical therapists; dermatologists; psychiatrists and other behavioral therapists; nurses; nutritionists; and home health care aides. They can treat all the problems diabetes are likely to encounter, including related diseases such as kidney and heart disease.

Furthermore, “A ‘team coordinator’ would support them in managing their disease.”

I compared the focused-factory model unfavorably with “carve-outs” composed of “a loose network of providers, who barely interact with each other,” and disease-management programs.

Contrast this with what Bodenheimer wrote: “Primary care physicians . . . would fall by the wayside. . . . Herzlinger and others who favor the carve-out model . . . downplay the fact that people with chronic diseases often have multiple conditions. . . . [Carved-out] disease management could represent the Balkanization of disease.”

Bodenheimer is also apparently unaware that his concern about the profitability of disease-management and carve-out firms is unconnected to financial reality; for example, two of the disease-management firms he discusses were sold at prices that caused multibillion-dollar losses for their pharmaceutical parents.2 Such organizations are unprofitable partially because they lack the customer focus and integrated team approach I advocated in Market-Driven Health Care.

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Geriatrics and the Limits of Medicine

To the Editor: In his Sounding Board article (April 22 issue),1 Goodwin wrote, “Modern medicine does not work well for old people.” Goodwin acknowledges that preventing diseases may be desirable but assails the treatment of “proto-illnesses,” such as hypertension, osteoporosis, high cholesterol levels, aortic aneurism, colonic polyps, and carotid-artery stenosis, which “do not cause symptoms and produce no suffering.” Is there a better way of providing relief from suffering than by preventing it? To view humane care of patients and scientific medicine as opposites is dangerous to good health. Care and cure are not mutually exclusive.

Too many geriatricians see themselves as protecting the elderly from modern medicine. In reality, older adults suffer from too little, not too much, modern medicine. Modern medicine relies on scientific study to determine which interventions benefit more people than they harm. A major problem is the application to the elderly of interventions tested only in younger populations. Past clinical studies have included too few older subjects. To remedy this shortcoming, more elderly people should be included in clinical trials. Goodwin believes that radical prostate surgery offers no proven benefit to many elderly men. He

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blames over-testing for prostate-specific antigen instead of the use of an inappropriate intervention.

Goodwin confuses the messenger and the message. He concludes that most older men, like the proverbial ostrich, would prefer to live “happily without knowing they had cancer [of the prostate].” The failures of geriatric care are rooted in too little, not too much, basic medical knowledge.

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Dr. Goodwin replies:

To the Editor: I thank Dr. Weksler for his thoughtful comments. Dr. Weksler appears to be equating science and “modern medicine.” I see science and medicine as being very different from one another. My criticisms concerned the current practice of medicine. A physician is a practitioner, not a scientist. Much of the knowledge base available to physicians comes from scientific investigation. Science provides information about the average behavior of groups — groups of molecules or kidneys or human beings. The practicing physician can use that information in making decisions about the care of individual patients.

As Dr. Weksler notes, medical practitioners should be highly motivated to prevent illness in their patients with actions based mostly on the results of scientific investigations. For example, there is no evidence from randomized, controlled trials that any treatment for local prostate cancer is better than no treatment at all, and there are valid scientific reasons for believing that any treatment of local prostate cancer in men 70 years of age or older might cause more harm than good. Thus, practicing physicians wishing to prevent disease in older men would tend to avoid prostate-specific–antigen testing.

In addition to knowledge of scientific investigation, there are also stores of personal, professional, and cultural wisdom that affect our decision making. Take, for example, an 82-year-old man obsessed with worries about prostate cancer. A wise medical practitioner might well order a prostate-specific–antigen test in the hope that a normal result would allay the patient’s anxiety. That decision would not be based on science, and it seems dismissive to call it “art.” It is based on knowledge from sources other than randomized, controlled trials.

I enthusiastically support further scientific investigation with respect to aging. Such investigation will doubtless result in better treatments, better preventive measures, and better health for older patients. This enthusiastic support is not inconsistent with my misgivings regarding modern medicine.

Much of modern medicine seems based not on science but on scientism, a belief system in which the trappings of science — the machines, the digital readouts, the P values — acquire a legitimacy independent of their utility in addressing the actual problems at hand. Scientific dogma can be invoked to justify either undertreatment or overtreatment. Wise, responsive clinical care is something else again.

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False Diagnosis of Maple Syrup Urine Disease Owing to Ingestion of Herbal Tea

To the Editor: Maple syrup urine disease is an inborn error of the metabolism of branched-chain amino acids named after the characteristic sweet aroma, reminiscent of maple syrup, present in the body fluids of affected patients. This aroma has been described variously as like that of burnt sugar, malt, curry, or Maggi (a widely available flavoring). We describe a case of “pseudo–maple syrup urine disease” caused by drinking fenugreek tea.

A five-week-old Egyptian infant had a 10-minute episode of unconsciousness while drinking bottled tea. He recovered spontaneously, but the parents nevertheless sought medical attention. On admission the child was in good clinical condition and alert, and the physical examination was unremarkable. The child exuded an aroma similar to that of Maggi, and a spontaneously voided urine sample had a similar aroma. This observation initiated emergency evaluations of metabolic amino acids and organic acids to rule out maple syrup urine disease; the results of all tests were normal. The parents mentioned that they had given their child an herbal tea (Helba tea) to reduce flatulence and prevent fever. This tea contains seeds of fenugreek (Trigonella foenum-graecum L.). Analysis of the infant’s urine by enantioselective multidimensional gas chromatography and mass spectrometry revealed the presence of sotolone, the compound responsible for the aroma in maple syrup urine disease. The tea prepared from fenugreek seeds was found to contain sotolone.

This report is similar to a previous report by Bartley et al., however, they did not identify the compound responsible for the aroma. Since herbal teas are very popular as home remedies, particularly in Middle Eastern countries, physicians should use caution when they are presented with young infants from such countries, to avoid unnecessary and costly investigations.

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