ABSTRACT. An epidemic of interstitial pneumonia principally involving premature infants occurred in Germany and nearby European countries between the 1920s and 1960s. Fatalities were due to Pneumocystis. Because the principal defenses against Pneumocystis are T cells, an acquired T-cell deficiency was postulated. A number of potential causes including malnutrition were considered. All were implausible except for a retrovirus that was benign in adults but virulent in premature infants. Furthermore, we suspect that the virus was imported into Germany from former German African colonies. Premature infants were vulnerable because of the developmental status of their T cells. Given the practices in that part of Europe at that time, the virus was most likely transmitted by contaminated blood transfusions and subsequent contamination of reusable needles and syringes used in injections. Although the epidemic ended 4 decades ago, a search for the postulated retrovirus can be conducted if tissues from affected infants are available.


ABBREVIATIONS. CMV, cytomegalovirus; HTLV-1, human T-cell lymphotropic virus type 1; Ig, immunoglobulin; STLV, simian T-cell leukemia virus; MHC, major histocompatibility complex; TcR, T-cell antigen receptor.

An epidemic of interstitial pneumonia struck premature (preterm) infants in Germany and surrounding countries during the mid-20th century.1–8 Fatalities were due to Pneumocystis.1,3 Pneumocystis pneumonia was also reported in malnourished, orphaned infants during that period.1 Many physicians assumed that the pneumonias in premature infants were also secondary to malnutrition. However, when the epidemic intensified and peaked in Europe during the 1950s, malnutrition was rare.

Since the epidemic ceased, much information emerged concerning Pneumocystis, the defense by T cells against Pneumocystis and other opportunistic agents, the causes of T-cell deficiencies including human retroviruses, and the developmental status of T cells in newborn infants. Furthermore, certain clinical practices common in premature nurseries in which the epidemic was centered and hitherto unpublished observations of the histopathology of the lymphoid system in some fatal cases were considered. This information permitted the formation of a hypothesis concerning the genesis of the epidemic that has not appeared in peer-reviewed articles. We propose that premature infants developed a T-cell deficiency because of a retrovirus imported from previous German African colonies.

PNEUMOCYSTIS EPIDEMIC IN EUROPEAN PREMATURE INFANTS

The epidemic was heralded by sporadic cases of fatal interstitial plasma cell pneumonia in German premature infants during the 1920s through the early 1940s8–9 (Table 1). Although epidemiologic methods were not sophisticated at that time, it is clear from the reports that although the epidemic progressively intensified and spread throughout Germany and into nearby European countries by the early 1950s,1,3,9–11 it continued to occur predominantly in Germany and nearby German-speaking countries or regions (Table 1). The epidemic peaked between 1955 and 1959 (Table 1) and quickly subsided during the early 1960s,3,9,10.

At the height of the epidemic in the 1940s and 1950s, numerous premature infants in many countries were affected. Many thousands of cases occurred in Germany.1,3,9,10 Some 2000 cases were reported in Czechoslovakia in 4 years.9 In 7 years, there were 200 cases in the University Children’s Hospital in Helsinki, Finland.12 During 1941–1949, 707 cases occurred in the German-speaking part of Switzerland, whereas no cases occurred in other sections of that country.13 Of 1104 premature infants born in 1959–1963 at the University of Szeged in Szeged, Hungary, 232 (21%) developed interstitial pneumonia.11 The frequency of interstitial pneumonia increased with decreasing birth weight (birth weight 2001–2500 g; 6%; birth weight 1501–2000 g; 21%; birth weight ≤1500 g; 41%).11 Males and females were affected equally. In most reports, the first signs of the pneumonia, rapid and labored respiration, began several weeks after discharge from the hospital nursery. The mortality rate was 20% to 30%.3,9,13

In 1942, Pneumocystis was identified in the lungs of 2 Dutch infants with fatal interstitial pneumonia, but no disease was attributed to the microorganism.14 Then in 1951, Vanek and Jirovec15,16 in Czechoslova-
kia reported that interstitial plasma cell pneumonia in some premature infants was due to *Pneumocystis*. Moreover, they recognized *Pneumocystis* in photomicrographs of lungs of premature infants with interstitial pneumonia published in 1938.6,7 Afterward, many cases of fatal *Pneumocystis* pneumonia in European premature infants were recognized.1–3,9,10 According to Gajdusek,1 there were at least 111 separate publications from Germany, 33 from Czechoslovakia, 21 from Italy, 13 from Finland, 10 from France, 9 from Austria, and 6 from Hungary during the decade after the report by Jirovec and Vanek1 (Table 1). A later report2 indicated that 81 cases of interstitial pneumonia occurred among 712 live births during 1955–1958 in 1 hospital in Heerlen, Netherlands. The overall mortality was 30%.2 To stem what was thought to be a hospital-acquired infection, some hospital nurseries closed.2,9 However, that did not seem to reduce the rates of infection, except possibly in the Heerlen outbreak.2 The abrupt cessation of the epidemic in the early 1960s was never explained.

### AUTHOR’S OBSERVATIONS 1955–1957

During 1955–1957, one of the authors (A.S.G.) was Chief of Pediatrics at the US Army Hospital in Würzburg, Germany. At that time, he visited the department of pediatrics at the University of Würzburg, where there were many cases of interstitial pneumonia in premature infants.17 His observations of the care of normal premature infants and clinical features of the affected infants and in that hospital are as follows.

Two aspects of clinical care of normal premature infants in the Würzburg University hospital were different from US Army hospitals in Europe and hospitals in the United States. The first was that donor human milk was the mainstay for newborn premature infants at Würzburg University and at many other European premature nurseries. Milk collected from lactating women in the surrounding countryside was brought to the hospital each day by a special train. The unprocessed milk was pooled and fed within 24 hours. After 4 weeks, feedings were switched to a mixture of donor human milk and acidified cow’s milk and then, shortly before discharge, just to acidified cow’s milk.17 In contrast, premature infants in the United States and in US Army hospitals in Europe at that time were principally fed cow’s-milk preparations.18

The contrast between the frequency of blood transfusions for premature infants in German civilian hospital nurseries and US Army hospital nurseries in Germany was also striking. At the University of Würzburg, otherwise healthy premature infants often received blood transfusions to prevent infections, whereas blood transfusions to premature infants in US Army hospitals in Germany were limited to the treatment of hemolytic disease of the newborn, blood loss, severe anemia, or shock.

A total of 417 cases of interstitial pneumonia in premature infants was treated at the University of Würzburg from 1953 to 1963 (Table 2).17 Males and females were affected equally.17 The number of cases in Würzburg peaked between 1958 and 1961, sharply decreased in 1962, and almost disappeared in 1963 (Table 2).17 Although interstitial pneumonia in premature infants was rampant in Europe during the 1950s,1–3,9,10 it was rare in infants born in the United States and at US Army hospitals in Germany, including those who received blood transfusions. Further-

### TABLE 1. Numbers of Publications of Plasma Cell Interstitial Pneumonia and *Pneumocystis* Pneumonia in Premature Infants in European Countries During the Mid-20th Century

<table>
<thead>
<tr>
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</tr>
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<td>3</td>
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<td>0</td>
<td>0</td>
<td>5</td>
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<td>Total reports</td>
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<td>5</td>
<td>14</td>
<td>92</td>
<td>135</td>
<td>5</td>
</tr>
</tbody>
</table>

Data are from reports of Gadjusek,1 Koop,2 and Goudsmit.3 Many affected premature infants were noted in each report.

### TABLE 2. Numbers of Infants Who Survived or Died From Interstitial Pneumonia at the University of Würzburg From 1953 Through 1963

<table>
<thead>
<tr>
<th>Year of Occurrence</th>
<th>Survivals</th>
<th>Deaths</th>
<th>Total Cases</th>
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<tbody>
<tr>
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<td>8</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>1954</td>
<td>13</td>
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<td>10</td>
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</tr>
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<td>8</td>
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</tr>
<tr>
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<td>70</td>
<td>22</td>
<td>92</td>
</tr>
<tr>
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<td>20</td>
<td>88</td>
</tr>
<tr>
<td>1962</td>
<td>9</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>1963</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Adapted from Figure 3 in *Folia Clin Int* (Barc). 1968;18:219.
more, the comparatively small number of premature infants born to women who were German nationals but married to American soldiers did not develop interstitial pneumonia if they were born in US Army hospitals during this time.

The experience at University of Würzburg was typical of other affected European centers. Signs of the pneumonia emerged 6 to 8 weeks after discharge from the hospital nursery (ie, at ~3 months of age). Chest radiographs revealed widespread interstitial pneumonias and small thymuses (A.S.G., unpublished observations). Approximately 27% of premature infants with interstitial pneumonia at the Würzburg University hospital died. The case-fatality rate resulting from Pneumocystis was not calculated, because the infection was diagnosed with certainty only when a lung biopsy or autopsy was performed and appropriate diagnostic methods for other opportunistic agents were not developed at that time.

Autopsies of 10 premature infants who died of interstitial pneumonia in Würzburg during 1955–1957 were reviewed by the author with the help of pathologists at the University of Würzburg (unpublished observations). Many plasma cells and cysts of Pneumocystis were seen in pulmonary alveoli. Plasma cells and germinal centers were abundant in peripheral lymphoid organs. However, lymphocytes were decreased in the thymic cortex, lymph nodes, spleen, and respiratory and intestinal tracts, and few Hassall’s corpuscles were detected in the thymus.

It was known at that time that plasma cells produced antibodies. Thus, it seemed likely that alveolar plasma cells were producing antibodies to Pneumocystis. However, the reason for the paucity of lymphocytes and Hassall’s corpuscles was unclear. If Pneumocystis was the primary pathogen, was it responsible for changes in the lymphoid system, or were the Pneumocystis infections caused by problems with the lymphoid system? Because little was known about the immune system and the defense against Pneumocystis at that time, an explanation was impossible.

ETIOLOGIES OF INTERSTITIAL PNEUMONIA

During the epidemic, Pneumocystis was responsible for the interstitial pneumonias in autopsied cases. However, the causes of nonfatal interstitial pneumonias were not identified because of the lack of definitive diagnostic methods. Pneumocystis, cytomegalovirus (CMV), toxoplasmosis, other opportunistic agents, or certain common respiratory viruses such as adenoviruses were possibilities. Although some intrauterine viral infections cause interstitial pneumonias, such infections would have emerged before discharge from the hospital nursery and not weeks later, as in this epidemic. Also, some features were inconsistent with common respiratory viruses. Indeed, such viruses should have spread to the general community in Germany and to populations in non-German-speaking regions of Europe during that period. Thus, opportunistic agents acquired after birth seemed to be the proximal causes of the interstitial pneumonias.

PNEUMOCYSTIS: TAXONOMY, BIOLOGY, AND DEFENSE

Pneumocystis is a genus in the fungus kingdom. Each species of this ascomycetes fungus colonizes a different mammalian species. The species that infects humans is designated as Pneumocystis jiroveci in recognition of Jirovec, the Czechoslovakian pathologist who, with Vanek, discovered that Pneumocystis was a pathogen in human infants. In this report, the species that infects humans will be referred to as Pneumocystis.

Human infections are contracted from other humans by airborne particles. Pneumocystis colonizes the lung, where it reproduces sexually and asexually. The genetic strains of human Pneumocystis are stable and equally virulent. Pneumocystis often causes brief, mild respiratory infections in normal infants and children. Furthermore, most normal children experience undetected and perhaps asymptomatic Pneumocystis infections.

Fatal Pneumocystis pneumonias occur in humans with severe defects in CD4+ and CD8+ T cells. T-cell deficiencies are commonly due to congenital or genetic defects, protein/energy malnutrition, zinc deficiency, and human immunodeficiency virus (HIV). In some patients with human T-cell leukemia virus type 1, also known as human T-cell lymphotropic virus type 1 (HTLV-1), such T-cell deficiencies also lead to other infections. In keeping with a T-cell defect, 63% of many hundreds of infants with interstitial pneumonia from several German clinics experienced prodromes of rhinitis, pharyngitis, or rhinopharyngitis.

OUR HYPOTHESIS

Based on a review of the epidemic, the biology of Pneumocystis, and the defense against it, we formulated a hypothesis concerning the cause of the epidemic among premature infants that addressed 4 features of the cases.

1. T cells but not plasma cells were deficient in affected premature infants.
2. The epidemic began in northern Germany and remained centered in Germany and surrounding countries and regions, where German was the dominant language. In contrast, few cases occurred in non-German-speaking regions and in premature infants born in US Army hospitals in Germany. This suggests an iatrogenic disease promulgated by certain clinical care practices prevalent in affected hospital nurseries and/or other lifestyle practices among German-language speakers at that time.
3. The epidemic began during adverse circumstances in Europe but continued and peaked when malnutrition was rare.
4. The pneumonias began several weeks after discharge from the newborn nursery.

Thus, the genesis of the epidemic is explored in the context of the biology of T cells in premature infants, the causes of T-cell deficiency, medical care given to normal premature infants in affected and nonaffected nurseries during the epidemic, and lifestyle
differences between the particular regions of Europe that were and were not affected.

T-Cell Deficiencies
The following T-cell deficiencies were considered.

Genetic and Congenital Defects
The epidemic nature of the disease is inconsistent with genetic defects in T cells because of their rarity. An intrauterine insult, other than an infection, seems implausible because of the requirement that the agent would have been prevalent in affected civilian hospitals in Germany but not in US Army hospitals in that country. Moreover, there was no evidence of the presence of an agent in German medical care facilities at that time that was toxic to the immune system.

Malnutrition
Because severe nutritional deficiencies caused Pneumocystis pneumonia in orphaned infants, protein/energy malnutrition in premature infants was considered but not found to be likely. (1) It was not stated in many reports whether many affected infants were small for gestational age. However, the patients at the University of Würzburg, University of Szeged, and Heerlen were principally normal size for gestational age. (2) Infants with intrauterine growth failure were born after the epidemic. (3) There were no reports that infants were malnourished when discharged from the newborn nursery. To be discharged, they had to be feeding and gaining weight well and have a body weight of at least 2500 g. (4) The infants were growing well until respiratory symptoms appeared. Thus, there was no evidence of a degree of protein/energy malnutrition that would have led to an immunodeficiency.

Zinc deficiency was considered also. Zinc is often limited in diets of deprived populations. Therefore, infants can be born with low body stores of zinc if maternal stores of zinc are low. If women who provided milk for the premature infants were zinc deficient, their milk would have been zinc deficient. Consequently, zinc deficiency could have interfered with the development and function of T cell in the recipient infants. However, certain aspects of zinc deficiency are less consistent with that possibility. (1) Zinc-deficient infants have poor growth. (2) Zinc-deficient women have decreased fertility, and increased risk of infections. (3) Severe zinc deficiency leads to B-cell deficiency and hence to a paucity of plasma cells, whereas the number of plasma cells in lymphoid tissues of infected infants was normal. (5) Given the greatly improved conditions in Western Europe by the 1950s, it was unlikely that zinc deficiency was a factor when the epidemic was at its peak. Thus, it is doubtful that zinc deficiency was responsible for the T-cell deficiencies.

Physiologic Developmental Delays of the Immune System
Physiologic developmental delays in the human immune system include the production of immunoglobulin (Ig)G, IgA, and secretory IgA antibodies; generation of antibody responses to polysaccharide antigens; synthesis of many cytokines; and the development of certain T-cell subsets. The T cell antigen-receptor repertoire, and T-helper 1 responses. T-helper 1 responses in the neonatal period are complex. They may be deficient, deviant, or normal depending on the type, timing, and degree of antigenic exposure. Furthermore, some delays are more marked in premature infants. In that respect, the production of another defense agent against Pneumocystis, surfactant protein A, is particularly delayed in premature infants. However, developmental delays are not a sufficient explanation for the Pneumocystis pneumonias, because premature infants born in the US Army hospitals in Germany did not develop interstitial pneumonia, and premature infants were born in previously affected regions after the epidemic.

Xenobiotics
Dioxins, which are wastes and byproducts from combustion and certain chemical and industrial processes, interfere with thymic generation of T cells in experimental animals. However, there are little data on the effect of dioxins during the human neonatal period. Recently, perinatal exposures to dioxins were reported to be associated with increased rather than decreased numbers of blood T cells in preschool age and school age children. Also, acquired T-cell defects caused by a xenobiotic seem unlikely, because such an environmental toxin most likely would have occurred across affected parts of Europe and yet did not affect US military dependents in the same regions.

Graft Versus Host Disease
Graft-versus-host disease from T cells in pooled donor human milk or from blood transfusions was considered as a cause of T-cell deficiency because engrafted T cells attack the thymus and other lymphoid tissues of the host. However, that was unlikely because of the absence of clinical or histopathologic evidence of that disease, including chronic dermatitis, hepatitis, or enteritis.

Pneumonias Caused by Virulent Strains of Opportunistic Agents
The pattern of reports in European countries strongly suggested the spread of an infectious agent. We first considered whether an unusually virulent strain of an opportunistic agent such as Pneumocystis directly caused the pneumonias. Experimental animal investigations and environmental hospital studies indicate that Pneumocystis is transmitted from human to human through airborne particles. It was assumed that infants in crowded nurseries were colonized in that way. However, the
migrations and T-cell responsiveness and thus in-
discovered that trypanosomiasis disrupts thymocyte
cells were.

For many of these same reasons, it is improbable that
virulent strains of other opportunistic agents such as CMVs, toxoplasmosis, parainfluenza virus, paramyxoviruses, adenoviruses, respiratory syncy-
tial viruses, Candida, Nocardia, and Aspergillus spe-
cies were prevalent during the epidemic. Such
organisms would have caused epidemics in term as
well as preterm infants and in US Army as well as
German civilian hospitals.

The outbreak in Heerlen also bears on this issue.2
Many cases of interstitial pneumonia occurred in 1 of
2 maternity hospitals in that community. The clinical
staff and care were identical in both nurseries so that
the infectious agents were not transmitted by care-
givers or medications. Mothers admitted to the un-
affected hospital were from a high socioeconomic
class and were married to men from the Netherlands.
Women admitted to the affected hospital were from a
low socioeconomic class, and many were married to
men from Eastern Europe who worked in nearby
coal mines. In this instance, it was likely that lifestyle
differences between these 2 populations were in-
volved in the transmission of the disease.

T-Cell Deficiency Caused by Infectious Agents

Stress resulting from severe infections in neonatal
infants is known to cause acute thymic involution.78
Although we cannot rule out some effect of stress on
the thymus, the totality of the evidence favors the
idea that a T-cell deficiency antedated the onset of
the Pneumocystis pneumonias and thus of the stress
secondary to that infection.

Were T cells in the affected infants attacked by an
infectious agent? Pneumocystis was first found in a
human with trypanosomiasis.79 Much later it was
discovered that trypanosomiasis disrupts thymocyte
migration and T-cell responsiveness and thus in-
creases the risk for opportunistic infections.

Trypanosomiasis was not a possibility in the prema-
ture infants, but other infectious agents that affect T
cells were.

CMV was considered for the following reasons.
1. CMV is common in human milk.82,83
2. Because donated human milk and blood transfu-
sions were given to the infants, if some infants did
not have protective maternal IgG antibodies to
CMV transferred via the placenta, they would
have been at greater risk for symptomatic CMV
infections.84
3. CMV disrupts functions of some dendritic cells
and subsequent T-cell activation.85
4. In some premature infants who died from Pneu-

cystis pneumonia, CMV was found in the
lungs.86

It is unlikely, however, that CMV was responsible for
the T-cell defect for the following reasons. (1) The
occurrence and subsequent cessation of the epidemic
is inconsistent with CMV because of its ubiquity.82,87
(2) The principal features of disseminated intrauter-
ine CMV infections, microcephaly, hepatospleno-

galy, and hematologic abnormalities, were
lacking in the affected premature infants. (3) CMV
does not cause the lymphoid histopathology seen in
the premature infants with fatal Pneumocystis pneu-
monia.82,88

Did a retrovirus cause the T-cell deficiency? A
decade after the epidemic ceased, Gajdusek hypoth-
esized that an occult viral infection that damaged the
immune system was incriminated in Pneumocystis
pneumonias in the premature infants.1 His idea was
prescient because it preceded the recognition of
HIV,45–47 which leads to deficiencies in CD4+ T cells,
and HTLV-1,49 which impairs the production of T
cells.48

The latent period of several weeks between hospital
discharge and the onset of interstitial pneumonia
is somewhat similar to the effects of HIV in certain
infants during the perinatal period.89–91 In that re-
spect, HIV attacks the thymus of young infants,92–94
and the thymic histopathology in HIV-infected
young infants is similar to that found in genetic
T-cell defects.34,95,96 Although this epidemic did not
involve currently recognized strains of HIV, a more
benign retrovirus that attacks T cells in premature
infants but spares the formation of plasma cells
would meet all criteria for the responsible agent.

ORIGIN AND FEATURES OF THE POSTULATED
RETROVIRUS

Where could such a retrovirus have originated and
how might it have been introduced into Europe? It
may have originated in west central Africa, from
which HIV-1,97 and HTLV-398–100 emerged (Fig 1). In
that respect, the epidemic began in Germany, which
had colonies in Cameroon and Togo from the late
19th century until World War I.101 Some of the thou-
sands of colonists could have been infected from
sexual contacts with native Africans, transfusions of
contaminated blood, injections with contaminated

non-disposable needles and syringes, or the ingestion
of monkey meat and/or contact with monkeys con-
taminated with a retrovirus that was a precursor of
the postulated human virus.

Given the scenario described above, some asymptom-
atic carriers of the virus from German colonies in
Africa returned to Germany somewhat before, dur-
ing, or directly after World War I. However, many
Germans repurchased their plantations in western
equatorial Africa in the mid-1920s and remained
there until just before World War II.3 They then
returned by boat to German Baltic ports.3 This sec-
ond group of returned expatriates could have been
the main transmitters of the retrovirus that caused the
epidemic.

Did the postulated retrovirus have some biological
properties similar to HTLVs or analogous simian
T-cell leukemia viruses (STLVs) found in equatorial
Africa? In that part of Africa, there are many STLV-1
strains, some of which are closely related to HTLV-1 subtype B.\textsuperscript{102} Those findings and other reports\textsuperscript{98,99} suggest that strains of STLV-1 were transmitted repeatedly over many years from monkeys to humans in equatorial Africa. In addition, STLV-3 was recently found in red-capped mangabeys (\textit{Cercocebus torquatus}) in Cameroon,\textsuperscript{103} 1 of the previous German colonies in Africa.\textsuperscript{101} The 2 strains of the virus elicit cross-reactive antibodies to HTLV-2 in their hosts.\textsuperscript{103} In that respect, human populations native to that region often hunt and eat monkeys infected with retroviruses.\textsuperscript{104}

Because HTLV-1 usually does not produce an immunodeficiency in infants, our attention turned to the possibility of a HIV-like virus. The clinical features of infected premature infants were not completely similar to HIV-1–infected infants, because many affected premature infants recovered, and those who recovered were not reported to have subsequent infections.\textsuperscript{12} It is more probable that the retrovirus was a more benign strain of HIV that nevertheless was virulent in very young infants. One reason for considering the possibility was the discovery in Cameroon of a less common strain of HIV (HIV-type 0) that is more closely related to non-pathogenic simian immunodeficiency virus that naturally infects chimpanzees than to other strains of HIV.\textsuperscript{105} Perhaps a variant of HIV-0 was the responsible agent. Thus, the postulated retrovirus may have arisen in equatorial Africa from simians, although the exact type of retrovirus remains to be demonstrated.

**SPREAD OF THE POSTULATED RETROVIRUS IN EUROPE**

World War II and its immediate aftermath led to malnutrition in the Netherlands,\textsuperscript{106} Germany,\textsuperscript{107} and many other European countries. Millions of Europeans were displaced during those periods. Moreover, there was an upsurge in blood transfusions because of the many thousands of trauma victims in Europe during the war. Such conditions may have facilitated the spread of asymptomatic carriers of the postulated retrovirus (Fig 2). By the 1950s, when the epidemic was at its peak, populations were stable and malnutrition was rare,\textsuperscript{101} but asymptomatic carriers of the postulated virus would have persisted.

**TRANSMISSION OF INFECTION TO PREMATURE INFANTS**

Possible routes of transmission of the retrovirus to European premature infants were the placenta, pooled donor human milk, blood transfusions, and/or nondisposable needles and syringes.

**Placenta**

The placental route is tenable for several reasons. Pregnant women could have been infected from sexual contacts with infected mates or through other previously described vectors. Such an intrauterine infection may not have been clinically manifest until some weeks after birth, as with intrauterine HIV infections.\textsuperscript{90,91} Placental transmission was likely in the Heerlen outbreak,\textsuperscript{2} because there was no difference in medical care between the affected and unaf-
fected hospitals in that city. However, placental transmission is not the sole explanation for all the outbreaks. It is of particular interest that most mature infants involved in the epidemic had neonatal complications that required intensive medical intervention.\textsuperscript{2,11} Those diseases may have further stressed the developing T-cell system of those infants. The consequent medical interventions (blood transfusions and reuse of needles and syringes) could have been the more likely transmitters of the virus (see below).

Human Milk

Could the virus have been transmitted to the premature infants by feedings of human milk from chronic female carriers as occurs with HTLV-I\textsuperscript{108} and HIV?\textsuperscript{109,110} The practice of feeding donor milk to premature infants was common in Germany and nearby countries during the epidemic. Feeding pooled human milk may have enhanced the likelihood of transmission, because comparatively few infected milk donors would have been needed to transmit the infection. A very large number of mature infants were breastfed during that same period but did not develop interstitial pneumonia. Although premature infants may have been more susceptible because of increased developmental delays in their immune system, those mature infants who developed interstitial pneumonia had neonatal complications and thus required medical interventions (see above).\textsuperscript{2,11} Also, pooled human donor milk was the routine method of feeding premature infants at the University of Würzburg throughout the decade of their epidemic of interstitial pneumonia in young infants, including the period in which the epidemic abruptly declined (Table 2). Human milk may have transmitted the virus, but the disappearance of the epidemic at the University of Würzburg while pooled human donor milk was still used suggests that other transmission routes were probably involved. Nevertheless, this mode of transmission could have been involved in some of the cases.

Blood Transfusions and Other Therapeutic Injections

Infants could have been exposed to the virus by contaminated blood transfusions. Blood transfusions were introduced into industrialized countries after World War I as a result of technical advances in blood typing, anticoagulants, blood storage, and donor recruitment.\textsuperscript{111,112} Blood transfusions were not commonly given to premature infants in the first few years after World War I.\textsuperscript{113} However, by the 1930s their use had increased in certain European countries, and by the 1950s, blood transfusions were commonly used in premature nurseries in many countries in continental Europe.\textsuperscript{114}

In that respect, Lohr\textsuperscript{115} emphasized that interstitial pneumonias in premature infants frequently followed blood transfusions. He also found that 4 of 11 patients with fatal cases of interstitial pneumonia from that same Berlin hospital that were reported in 1938\textsuperscript{4} received blood transfusions. Investigators from the University of Szeged also noted a strong relationship between blood transfusions and plasma cell interstitial pneumonia in premature infants.\textsuperscript{9}

It is pertinent that the frequency of blood transfusions to premature infants was much less in US Army hospitals than in civilian hospitals in Germany and that the blood supplies to the civilian and military hospitals in Europe were from different sources. Blood used in US Army hospitals came from US soldiers, whereas blood for German civilian hospitals came from adult civilians, some of whom may have been carriers of the postulated retrovirus. The use of blood transfusion was also uncommon in nurseries in Great Britain,\textsuperscript{116} which may have accounted for the paucity of reports of interstitial pneumonia in premature infants in that country.\textsuperscript{1–3,9}

Once the virus was introduced into hospitals by
contaminated blood used for transfusions, the effect would have been compounded by the use of the same nondisposable needles and syringes for other parenteral therapies. Indeed, disposable needles and syringes were not deployed for clinical use in industrialized countries until the late 1950s and early 1960s.117,118 During the epidemic, intramuscular injections of vitamin K₁ (phyllloquinone) were given routinely to newborn infants to prevent hemorrhagic disease of the newborn in Europe and the United States.119,120 Thus, it is likely that the postulated retrovirus was also transmitted by contaminated injection equipment (Fig 1).

SUSCEPTIBILITY OF T CELLS IN PREMATURE INFANTS TO THE POSTULATED RETROVIRUS INFECTION

If a retrovirus that attacked T cells was the proximal cause of the epidemic, why wasn’t the infection manifest in older children and adults in Europe? We assume that the agent was less virulent in adults and older children than in infants. The relatively short latent period before the onset of the interstitial pneumonias suggests that the unique features of T-cells in premature infants could have accounted for this increased susceptibility. Some possibilities are as follows. (1) Cytotoxic T-cell responses to cells infected with the postulated retrovirus may have been much less in young infants than adults as reported with HIV-1.121,122 (2) The virus could have invaded T cells from newborn infants more readily than those in adults. In that respect, under certain experimental conditions, newborn T cells display more receptors to 1 type of retrovirus after stimulation than adult T cells. In response to interleukin 7 in vitro, far more surface receptors to HTLV-1 are generated in newborn T cells than in adult T cells.123 If that occurred for receptors to the proposed retrovirus, then infected premature infants would have developed T-cell deficiencies, whereas older children and adults would have been spared.

RECOVERY FROM RETROVIRAL INFECTION AND INTERSTITIAL PNEUMONIA

The recovery of many premature infants from interstitial pneumonia may be explained by the normal ontogeny of T cells and common polymorphisms in the immune system (Fig 2). If infected premature infants survived long enough, protective T-cell responses may have developed that were equivalent to those found in mature individuals. Such responses would have first controlled and then eliminated the opportunistic agents, which is in keeping with a report that premature infants who survived the pneumonias were no longer at increased risk to common or opportunistic infections.12

Why did many affected infants recover and others did not? The question is compounded by the possibility that not all survivors had Pneumocystis pneumonia, because that diagnosis could only be made at autopsy during the epidemic. However, if one assumed that many of the infants survived, an immunologic explanation should be sought. Perhaps the difference was due to variations in binding specificities of major histocompatibility complex (MHC) class I and II molecules of the infants. For example, the activation of CD8⁺ cytotoxic T cells requires antigenic peptides to be presented to their surface T-cell antigen receptors (TCRs) in the context of MHC class I molecules (HLA-A, HLA-B, HLA-C) of suitable antigen-binding specificities.124 Because HLA-A, HLA-B, and HLA-C have many alleles each, a wide diversity of HLA antigen-binding sites occur in the general population.125 MHC class I molecules that efficiently bind a peptide fragment present it to TcRs on CD8⁺ T cells that recognize that same peptide. HLA alleles that less efficiently bind the peptide fragment from the pathogen fail to present the peptide fragment to the TcRs on cytotoxic T cells. In that case, cytotoxic T cells are not activated to destroy host cells that harbor the intracellular pathogen.124 Such differences in the recognition of retroviral and Pneumocystis peptides could account for which infants did or did not recover from the retrovirus and Pneumocystis infections (Fig 2). In that respect, allelic variation in MHC molecules may possibly influence the transmission of HIV-1 infections in breastfed infants or progression of HIV-1 infections.126–128

DISAPPEARANCE OF THE EPIDEMIC

Why did the epidemic disappear? Many plagues have receded spontaneously. They include the bubonic plague in the middle ages and thereafter,129,130 serious streptococcal infections in Great Britain in the 19th century,131 the influenza pandemic of 1918–1919,132 and widespread virulent, antibiotic-resistant staphylococcal infections during the 1950s.133 Epidemics may decline because of the deaths of carriers, survival of genetically resistant human populations,134 lessening of environmental circumstances that support the spread of the infection, and genetic changes in the infecting agent that render it less pathogenic. However, the HIV epidemic persists because of long-standing carrier states and ineffectual immune protection.135

Although the disappearance of the epidemic of Pneumocystis pneumonia in premature infants is unexplained, 4 possibilities may be considered (Fig 3). (1) Disposable needles and syringes began to be used in Europe in the 1960s,117,118 which is when the epidemic declined. (2) The population of chronic carriers may have decreased because of the deaths of older chronic carriers. (3) Donor selection for blood transfusions became more restrictive. Thus, over time, carriers among the aging population in Germany who had been African colonists would have been excluded. (4) Finally, genetic shifts in the virus may have decreased its ability to colonize adults or its virulence in premature infants.
older at the end of the epidemic in the 1960s. This scenario, however, has certain weaknesses. For instance, a nonpathogenic or weakly pathogenic retrovirus probably would have persisted in Europe if it were sexually transmitted. However, if negligible amounts of the virus were shed in seminal and cervical secretions, the infection would probably not have been maintained in European populations. In contrast, the virus may have continued to be reintroduced into human African populations from infected simians native to that region.

SUGGESTED RESEARCH

The epidemic of interstitial pneumonia caused by *Pneumocystis* and presumably other opportunistic agents in European premature infants disappeared ~40 years ago, but its cause may still be investigated if tissues or sera from fatal cases were preserved. If so, the following studies might be informative.

1. Lymphoid tissues could be examined to determine which T cells were deficient.
2. Zinc, essential for T-cell development, could be quantified in sera.
3. Dioxins that interfere with T-cell development could be measured in adipose tissues.
4. An analysis of *Pneumocystis* genes could test the possibility of an unusually virulent strain.
5. Genes for human retroviruses could be detected with primers derived from highly conserved motifs of reverse transcriptase genes\(^{136}\) or other common genetic markers found in human retroviruses or their simian precursors.\(^{3,97-100}\) These studies might also be performed on victims who survived the epidemic, because the DNA of many retroviruses integrates with human DNA and does not cause disease.

In addition, case-control or retrospective cohort studies could be conducted by examining clinical records of premature infants in the epidemic areas who did or did not develop interstitial pneumonia. Such virologic, immunologic, and epidemiologic studies might shed additional light on the cause of the epidemic and why the epidemic disappeared.

CODA

An epidemic of interstitial pneumonia in European premature infants often caused by *Pneumocystis* occurred during the mid-20th century. We hypothesize that the problem was caused by a retrovirus imported from Africa that attacked T cells from young infants but was less virulent than HIV-1, HIV-2, or HTLV-1. Contaminated blood transfusions from chronically infected carriers and consequent contamination of nondisposable injection equipment were the most likely vectors for the virus. Pathologic effects of the virus may have been more pronounced in young infants because of unique developmental features of their T cells.

As we were finishing this article, Lange and Klein's 1991 letter to *Lancet*\(^ {137}\) and Goudsmit's 1997 book\(^ 4\) that dealt in part with the epidemic of *Pneumocystis* pneumonia came to our attention. In each publication, it was proposed that the epidemic was due to HIV transmitted by blood transfusions, but the idea was not fully developed in those publications. Moreover, the idea that the retrovirus was imported into north Germany by former German colonists from Africa was proposed by Goudsmit in
his 1997 publication and briefly reiterated in a more recent book. We were heartened that those non-peer-reviewed reports provided a further impetus to test necropsy tissue from those victims for retroviruses closely related to HIV or other retroviruses that are tropic for T cells.

Finally, if the hypothesis is correct, the postulated retrovirus may still exist in west central Africa. It has only been in the last few decades that premature infants born in that region have had access to modern medical care and thus could have survived long enough past the immediate neonatal period to receive blood and other injection therapy and display infections secondary to T-cell deficiencies. Studies of T-cell–deficient premature infants in those regions who survive the immediate newborn period and are not malnourished or infected with HIV might therefore reveal the retrovirus that caused the epidemic of Pneumocystis pneumonia in European premature infants in the mid-20th century.

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REFERENCES

5. Fedor F. Über die pathologische anatomie der lungenveränderungen beim keuchhusten. Frank Z Pathol. 1927;35:213–255
15. Vanek J. Atipicka (intersicia) plura pneumonia, vyvolaná Pneumocystis carinii. Cas Lek Cesk. 1951;90:1121–1124
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