HISTORICAL ARTICLE

What Caused the Epidemic of *Pneumocystis* Pneumonia in European Premature Infants in the Mid-20th Century?

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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. *Pediatrics* 2005;115:e725–e736. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2157; *Africa, Europe, retrovirus, premature infants, T cells,* Pneumocystis *pneumonia.*

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 1940s[4–8] (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%.[2,9,13]

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 Jirovec[15,16] in Czechoslova-

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

Countries	1920–1929	1930–1939	1940–1949	1950–1954	1955–1959	1960–1966
Germany	4	5	8	36	79	2
Switzerland	0	0	3	4	2	1
Netherlands	0	0	1	0	1	0
Belgium	0	0	1	0	0	0
Sweden	0	0	1	2	3	0
Finland	0	0	0	8	5	0
Czechoslovakia	0	0	0	25	8	0
France	0	0	0	5	5	0
Austria	0	0	0	3	6	0
Hungary	0	0	0	5	1	2
Spain	0	0	0	1	2	0
Italy	0	0	0	3	18	0
Poland	0	0	0	0	5	0
Total reports	4	5	14	92	135	5

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

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 Vanek[1] (Table 1). A later report[2] 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 2. Numbers of Infants Who Survived or Died From Interstitial Pneumonia at the University of Würzburg From 1953 Through 1963

Year of Occurrence	Survivals	Deaths	Total Cases
1953	8	1	9
1954	13	7	20
1955	5	15	20
1956	8	10	18
1957	18	8	26
1958	70	22	92
1959	46	24	70
1960	44	16	60
1961	68	20	88
1962	9	1	10
1963	4	0	4

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[17] and small thymuses (A.S.G., unpublished observations). Approximately 27% of premature infants with interstitial pneumonia at the Würzburg University hospital died.[17] 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.[19] 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.[20–24] Each species of this ascomycetes fungus colonizes a different mammalian species.[21,23,25,26] 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.[15,16] 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.[27] The genetic strains of human Pneumocystis are stable and equally virulent.[23] Pneumocystis often causes brief, mild respiratory infections in normal infants and children.[28] Furthermore, most normal children experience undetected and perhaps asymptomatic Pneumocystis infections.[29,30]

Fatal Pneumocystis pneumonias occur in humans with severe defects in $CD4^+$ and $CD8^+$ T cells.[31–33] T-cell deficiencies are commonly due to congenital or genetic defects,[34] protein/energy malnutrition,[35,36] zinc deficiency,[37–42] and human immunodeficiency virus (HIV)[3,43–47] and in some patients with human T-cell leukemia virus type 1, also known as human T-cell lymphotropic virus type 1 (HTLV-1).[48,49] 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.[50]

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.[34] 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,[1,51,52] protein/energy malnutrition in affected 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,[17] University of Szeged,[11] and Heerlen[2] 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.[1,9,11,13] 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.[53] Consequently, zinc deficiency could have interfered with the development and function of T cell in the recipient infants.[37–42] However, certain aspects of zinc deficiency are less consistent with that possibility. (1) Zinc-deficient infants have poor growth.[53] (2) Zinc-deficient women have decreased growth, decreased fertility, and increased risk of infections.[40] (3) Feeding human milk to premature infants may have mitigated the development of a zinc deficiency, because the bioavailability of zinc is greater in human milk than in cow's milk.[54] Indeed, milk from zinc-sufficient women provides the zinc required for growth in the first 4 to 6 months of life.[55] (4) Severe zinc deficiency leads to B-cell deficiency and hence to a paucity of plasma cells,[56] 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[57]; and the development of certain T-cell subsets,[58] the T cell antigen-receptor repertoire,[59] and T-helper 1 responses.[60–62] 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.[63] Furthermore, some delays are more marked in premature infants.[64,65] In that respect, the production of another defense agent against *Pneumocystis*, surfactant protein A,[66] is particularly delayed in premature infants.[67] 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.[68] 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.[69,70] 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.[71]

Pneumonias Caused by Virulent Strains of Opportunistic Agents

The pattern of reports in European countries[1–3] (Table 1) 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[72] and environmental hospital studies[23,73] 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

genetic stability of human strains of *Pneumocystis*[23] and the rarity of severe *Pneumocystis* infections in other European populations including mature newborn infants and premature infants born in US Army hospitals during the epidemic are inconsistent with a more virulent *Pneumocystis*. Moreover, a recent molecular, epidemiologic study indicates that transmission of *Pneumocystis* from patients with *Pneumocystis* pneumonia to susceptible subjects is uncommon.[74]

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 syncytial viruses, *Candida*, *Nocardia*, and *Aspergillus* species[75–77] 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 caregivers or medications. Mothers admitted to the unaffected 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 involved 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[80] and T-cell responsiveness[81] and thus increases the risk for opportunistic infections. Trypanosomiasis was not a possibility in the premature 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 transfusions 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 *Pneumocystis* 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 intrauterine CMV infections, microcephaly, hepatosplenomegaly, and hematologic abnormalities,[82,88] were lacking in the affected premature infants. (3) CMV does not cause the lymphoid histopathology seen in the premature infants with fatal *Pneumocystis* pneumonia.[82,88]

Did a retrovirus cause the T-cell deficiency? A decade after the epidemic ceased, Gajdusek hypothesized 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 respect, 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[3,97] and HTLV[3,98–100] 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 thousands of colonists could have been infected from sexual contacts with native Africans, transfusions of contaminated blood, injections with contaminated nondisposable needles and syringes, or the ingestion of monkey meat and/or contact with monkeys contaminated with a retrovirus that was a precursor of the postulated human virus.

Given the scenario described above, some asymptomatic carriers of the virus from German colonies in Africa returned to Germany somewhat before, during, 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 second 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

T-cell retrovirus imported from German African colonies into Germany

⇩

Retrovirus spreads to European populations

⇩

Retrovirus contaminates blood supply, injection equipment

⇩

Retrovirus transmitted to premature infants in affected hospitals

⇩

T-cell deficiencies

⇩

Pneumocystis pneumonia

Fig 1. Possible sequence that led to the epidemic of interstitial pneumonia in European premature infants.

strains, some of which are closely related to HTLV-1 subtype B.[102] Those findings and other reports[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 (*Cercocebus torquatus*) in Cameroon,[103] 1 of the previous German colonies in Africa.[101] The 2 strains of the virus elicit cross-reactive antibodies to HTLV-2 in their hosts.[103] In that respect, human populations native to that region often hunt and eat monkeys infected with retroviruses.[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.[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 nonpathogenic simian immunodeficiency virus that naturally infects chimpanzees than to other strains of HIV.[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,[106] Germany,[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,[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.[90,91] Placental transmission was likely in the Heerlen outbreak,[2] because there was no difference in medical care between the affected and unaf-

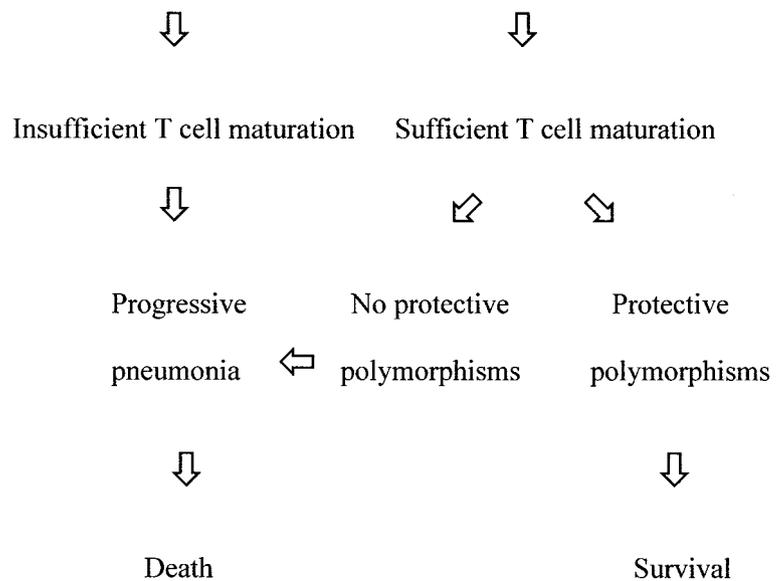Premature infants with *Pneumocystis* pneumonia

⇩   ⇩

Insufficient T cell maturation   Sufficient T cell maturation

⇩   ⬈   ⬂

Progressive   No protective   Protective

pneumonia ⇦ polymorphisms   polymorphisms

⇩   ⇩

Death   Survival

Fig 2. Possible immunologic events that led to recovery or death from *Pneumocystis* pneumonia in premature infants.

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.[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-1[108] and HIV?[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).[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 in-

volved. 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.[111,112] Blood transfusions were not commonly given to premature infants in the first few years after World War I.[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.[114]

In that respect, Lohr[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[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.[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,[116] which may have accounted for the paucity of reports of interstitial pneumonia in premature infants in that country.[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 K_1 (phylloquinone) 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 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 specific-

ities 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 death 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.

Perhaps the epidemic depended on a viral reservoir that existed only in west central Africa. If access to the reservoir disappeared or if some other vital link in the chain of transmission was broken, then the epidemic would have lessened and finally disappeared as chronic adult carriers in Europe died. In that respect, most infected German adults who returned from Africa just before World War II (1938) would have been between 50 and 60 years of age or
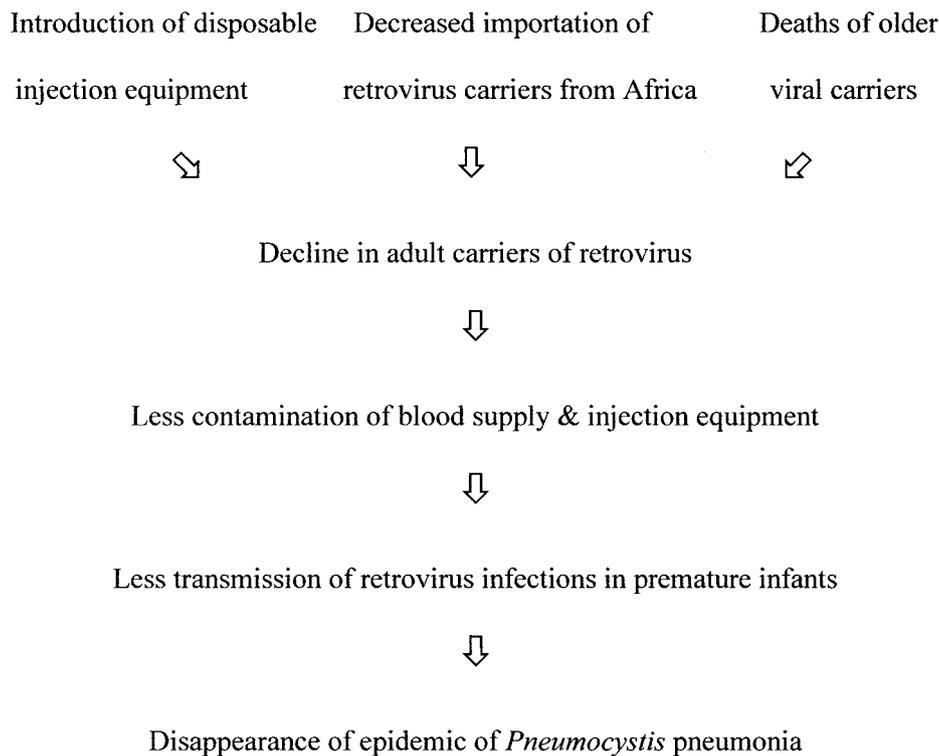
Introduction of disposable injection equipment	Decreased importation of retrovirus carriers from Africa	Deaths of older viral carriers
⇘	⇓	⇗

Decline in adult carriers of retrovirus

⇓

Less contamination of blood supply & injection equipment

⇓

Less transmission of retrovirus infections in premature infants

⇓

Disappearance of epidemic of *Pneumocystis* pneumonia

Fig 3. Possible sequence that led to the disappearance of the epidemic of interstitial pneumonia in European 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[3] 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[3] and briefly reiterated in a more recent book.[138] 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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