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Chronic Granulomatous Disease

Report on a National Registry of 368 Patients

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Introduction

Chronic granulomatous disease (CGD) is a genetically determined primary immunodeficiency disease in which phagocytic cells are unable to kill certain bacteria and fungi after ingesting them (8, 9, 11, 17, 20, 28, 42). The underlying defect is an inability of phagocytic cells to reduce molecular oxygen and create the reactive oxygen metabolites that are necessary for efficient intracellular microbicidal activity (11, 17). However, the increased susceptibility to infection in patients with CGD is limited to a specific class of microorganisms. Many bacteria and fungi are catalase positive and do not themselves have a net production of reduced oxygen metabolites, such as hydrogen peroxide. A subset of these catalase-positive organisms is not killed efficiently by the phagocytic cells of patients with CGD and is responsible for the overwhelming majority of serious infections in these patients (11, 17, 20, 28, 32, 39). In contrast, microorganisms that are catalase negative, and do have a net production of hydrogen peroxide, are thought to supply the missing reactive oxygen metabolites when they are ingested, correct the metabolic defect and, thereby, contribute to their own death. Thus, these organisms are infrequent causes of infection in patients with CGD.

In addition to their increased susceptibility to infection, patients with CGD also are prone to develop a variety of inflammatory and/or rheumatic diseases, such as inflammatory bowel disease and a lupus-like syndrome (11, 17, 20).

Although there are a number of different molecular defects that can cause CGD, they all affect 1 or another component of the NADPH oxidase of the phagocytic cell (4, 11, 17, 20). (See the **Review in Molecular Medicine** on CGD by Segal and colleagues in this issue [43a].) The most common form of the disease is due to an X-linked recessive defect in gp91^{phox}, an integral membrane protein of the NADPH oxidase encoded on the short arm of the X-chromosome (17). Three other forms of the disease are due to autosomal recessive defects in other major components of the oxidase, p22^{phox}, p47^{phox}, and p67^{phox}, each of which is encoded on a different autosomal chromosome (17).

Because CGD is relatively uncommon, it has been difficult to develop a detailed and comprehensive clinical picture of the disorder. Accordingly, a national registry of patients with CGD was established in 1993 in order to provide a minimal estimate of the incidence of the disorder, characterize some of its epidemiologic features, and define its clinical characteristics in a large cohort of patients.

Materials and Methods

Ascertainment of patients

The Immune Deficiency Foundation received a contract from the National Institute of Allergy and Infectious Diseases on October 1, 1992, to establish and maintain a registry of United States residents with chronic granulomatous disease. A total of 8,001 physicians who were members of 7 academic societies (American Academy of Allergy and Immunology, Clinical Immunology Society, Society for Pediatric Research, American Pediatric Society, American Society for Clinical Investigation, Infectious Disease Society, and American Society of Hematology) and were also faculty members of United States medical schools and/or were on the mailing list of the Foundation were contacted. Each was sent a 1-

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page questionnaire in the spring of 1993 inquiring if they had patients with CGD, or had had patients in the past, and if they would be willing to enter their patients in the registry. In addition, the chairpersons of all departments of pediatrics and internal medicine that had residency training programs were sent the same questionnaire and requested to pass it on to the members of their faculties who might see patients with CGD. A total of 1,044 physicians responded to this initial mailing; 223 physicians reported that they followed patients with CGD and were willing to enter them in the registry. In November 1993, the physicians who reported that they had patients with CGD and were willing to enter them in the registry were then sent a 4-page clinical data entry form requesting detailed information on the demographic characteristics of the patient, laboratory findings relating to the diagnosis of CGD, the clinical characteristics of the patient's disease, and the patient's latest status. They were requested to register both living and deceased patients. As a result of this initial mailing, 80 physicians registered 303 patients. The first patient was registered in November 1993.

In November 1996, a second request was mailed to all 17,000 members of the above academic medical societies asking them if they treated patients with CGD who had not been entered in the registry and if they would be willing to enter them. Of the 1,108 physicians who responded, 125 who had not previously registered patients reported that they followed patients with CGD, and they were sent the clinical data entry form. As a result of this mailing, 65 more patients were registered by 14 additional physicians.

Between January 1996 and February 1997, a 1-page follow-up form was sent at approximately 6-month intervals to the physicians who had previously registered living patients. By October 1997, follow-up data were received on 205 of the 320 patients who were alive when they were initially registered.

A total of 368 patients with CGD were entered in the registry between November 5, 1993, and September 30, 1997, by 94 physicians (see Appendix). The demographic and clinical data on these patients form the basis of this report.

Construction of registry

In order to maintain patient anonymity, the only identifying data collected on individual patients were their birth date, initials, gender, and race; the patient's name, address, phone number, social security and/or hospital number were not obtained. Duplicate entries from different physicians were avoided by cross-checking individual patients' birth dates, gender, and race.

Patients were considered to have CGD if they had at least 1 test indicating abnormal function of the phagocytic NADPH oxidase system or abnormal intracellular bactericidal activity of their phagocytic cells (11, 17, 20, 28, 42). Of the 368 patients entered in the registry, 327 had an abnormal nitroblue tetrazolium test, 158 had abnormal production of superoxide, 96 had abnormal chemiluminescence, 51 had an abnormal oxidant-dependent fluorescence, 35 had abnormal hydrogen peroxide production, 33 had abnormal oxygen consumption, 10 had abnormal iodination of bacteria, and 131 had abnormal phagocytic killing; 257 of the 368 (69.8%) patients had more than 1 abnormal test.

Patients were considered to have the X-linked recessive form of the disease if they had 1 or more of the following: 1) a positive family history of a lateral male relative (for example, maternal uncle, maternal male first cousin, etc.) with the disease, 2) their mother showed 2 distinct populations of phagocytic cells with respect to the ability to reduce nitroblue tetrazolium, 3) reduced activity of cytochrome b, 4) absence of $gp91^{phox}$ by immunoblotting, 5) a mutation in the gene for $gp91^{phox}$. Patients were considered to have 1 of the autosomal recessive forms of the disease if they had 1 or more of the following: 1) they were female or they were male with a female relative with documented CGD, 2) absence of $p22^{phox}$, $p47^{phox}$, or $p67^{phox}$ by immunoblotting, 3) a mutation in the gene for $p22^{phox}$, $p47^{phox}$, or $p67^{phox}$.

Results

Estimated incidence of CGD in United States residents

The estimated incidence of CGD in the United States by year of birth from 1980 to 1989 is presented in Table 1. This decade was selected for use in estimating the incidence of CGD in order to minimize underestimating its prevalence. For example, patients born decades ago might have been more likely to have died before being diagnosed, and therefore would be unknown to physicians in the registry sampling frame. Thus, they might be underrepresented in the registry. Similarly, patients born after 1990 may not yet have been diagnosed because of their young age (see below) and also, therefore, would be underrepresented in the registry.

As can be seen in Table 1, for the decade of 1980–1989, the average annual incidence was 1/255,000 live births. In 5 of those years (1982, 1983, 1984, 1987, and 1988) the incidence was relatively constant at approximately 1 CGD birth per 200,000 live births, suggesting that the best estimate of the *minimum* incidence of CGD is between 1/200,000 live births and 1/250,000 live births.

Demographics

The demographic characteristics of the patients with CGD are presented in Table 2. The 368 patients were members of 318 different kindreds; 259 patients (70%) had the X-linked recessive form of the disease, 81 (22%) had an autosomal recessive form of the disease, and in the remaining 28 (8%) there was in-

TABLE 1. Estimated incidence of CGD

Year	Total Births*	CGD Births†	Births/Case of CGD
1980	3,612,000	15	240,800
1981	3,629,000	15	241,933
1982	3,681,000	17	216,529
1983	3,639,000	18	202,167
1984	3,669,000	19	193,105
1985	3,761,000	12	313,417
1986	3,757,000	9	417,444
1987	3,809,000	18	211,611
1988	3,910,000	17	230,000
1989	4,041,000	14	288,643

Abbreviations: CGD = chronic granulomatous disease.

*Total Births, US National Center for Health Statistics, Vital Statistics of the United States.

†Number of births of patients with CGD entered in the Registry.

TABLE 2. Demographic characteristics of patients with CGD

Demographic	XLR	AR	Unknown	Total
Total patients	259	81	28	368
Male	257	31	28	316
Female	2*	50	0	52
Kindreds	219	71	28	318
Race				
Caucasian	216	64	24	304
Black	29	7	3	39
Asian	3	3	0	6
Mixed	2	3	0	5
Native American	0	1	0	1
Unknown	9	3	1	13

Abbreviations: XLR = X-linked recessive; AR = Autosomal recessive.

*Two female carriers of X-linked CGD who had markedly skewed X-chromosome inactivation and clinical symptoms consistent with CGD.

sufficient information to establish the genetic form of the disease. Two of the patients with the X-linked form of the disease were adult women whose sons had documented X-linked recessive disease. These women were reported to have skewed X-chromosome inactivation of their phagocytic cells resulting in 5% or less normal activity of the NADPH oxidase system in their phagocytic cells and clinical signs of CGD.

Of the 81 patients with an autosomal recessive form of the disease, 56% (45/81) had a deficiency of $p47^{phox}$, 12% (10/81) had a deficiency of $p67^{phox}$, and 8% (7/81) had a deficiency of $p22^{phox}$ (Table 3). In 24% (19/81) of the patients there was insufficient information to allow identification of the genetic subtype.

Age at diagnosis

The ages at which patients were diagnosed with CGD are displayed in Figure 1. Although the majority of patients with CGD (76%) were diagnosed before the age of 5 years, a significant number (10%) were not diagnosed until the second decade of life and on rare occasions (4%) in the third decade or later. Delayed diagnosis was especially evident in the autosomal recessive forms of the disease where 24% of the patients were diagnosed in the second decade of life and 9% in the third decade or later, in contrast to 5% and 1%, respectively, for the X-linked recessive form. The oldest patient diagnosed with the X-linked recessive form of the disease was 69 years of age (44) and the oldest patient diagnosed with an autosomal recessive form of the disease was 30 years of age.

TABLE 3. Genetic subtypes of autosomal recessive CGD

Deficiency	No. of Patients
$p47^{phox}$	45/81 (56%)
$p67^{phox}$	10/81 (12%)
$p22^{phox}$	7/81 (8%)
Unknown	19/81 (24%)

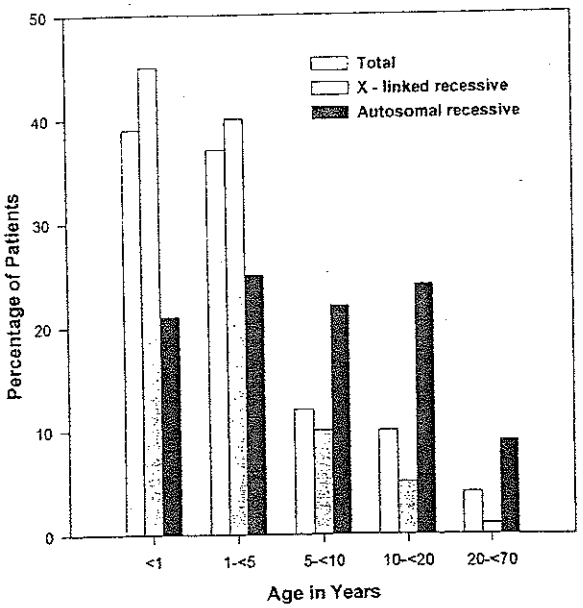

FIG. 1. The age at diagnosis of patients with chronic granulomatous disease.

As can be seen in Table 4, patients with the X-linked recessive form of the disease were significantly younger at the time of diagnosis than patients with autosomal recessive forms of the disease. Since the majority of cases of CGD are inherited in an X-linked recessive fashion, and therefore the majority of patients are male, there might have been a bias in favor of testing for CGD in males and therefore a bias toward earlier diagnosis in males. However, when the average age at diagnosis of the patients (males) with the X-linked form of the disease was compared with the average age at diagnosis in males with the autosomal recessive form of the disease in order to control for gender bias, the patients with the X-linked recessive form were still diagnosed significantly earlier in life than their male

TABLE 4. Age at diagnosis of CGD

Genetic Type	Mean Age at Diagnosis (yr)
X-linked recessive	3.01*
Autosomal recessive	
All	7.81
Male	7.35
Female	8.13

*$p < 0.05$ comparing patients with X-linked recessive CGD to all patients with autosomal recessive CGD or to either male or female patients with autosomal recessive CGD.

TABLE 5. Prevalence of infection by site in CGD

Type of Infection	XLR (n=259) No. (%)*	AR (n=81) No. (%)*	Unknown (n=28) No. (%)*	Total (n=368) No. (%)*
Pneumonia	207 (80%)	62 (77%)	21 (75%)	290 (79%)
Abscess (any kind)	175 (68%)	57 (70%)	18 (64%)	250 (68%)
Subcutaneous	112 (43%)	34 (42%)	10 (36%)	156 (42%)
Liver	67 (26%)	27 (33%)	4 (14%)	98 (27%)
Lung	41 (16%)	11 (14%)	8 (29%)	60 (16%)
Perirectal	45 (17%)†	6 (7%)	6 (21%)	57 (15%)
Brain	8 (3%)	4 (5%)	0	12 (3%)
Other‡	23 (9%)	3 (4%)	2 (7%)	28 (8%)
Suppurative adenitis	153 (59%)§	26 (32%)	15 (56%)	194 (53%)
Osteomyelitis	69 (27%)	17 (21%)	4 (14%)	90 (25%)
Bacteremia/fungemia	54 (21%)†	8 (10%)	3 (11%)	65 (18%)
Cellulitis	14 (7%)	4 (5%)	0	18 (5%)
Meningitis	10 (4%)	4 (5%)	1 (4%)	15 (4%)
Other¶	70 (27%)	33 (41%)	9 (32%)	112 (30%)

Abbreviations: XLR = X-linked recessive; AR = autosomal recessive.

*The number (%) of patients within each genetic category who had at least 1 episode of the specific infection.

†$p < 0.05$ comparing XLR and AR.

‡Includes 4 patients each with dental and/or chest wall abscesses, 3 patients each with abdominal abscess, 2 patients each with gall bladder, kidney, splenic, and/or peritonsillar abscesses, and 1 patient each with myocardial, oral, perihepatic, perinephric, psoas, prostatic, scrotal, testicular, and/or umbilical abscesses.

§$p < 0.02$ comparing XLR and AR.

¶Includes 20 patients reported with impetigo, 16 with sinusitis, 13 with otitis media, 11 with septic arthritis, 10 with urinary tract infection/pyelonephritis, 9 with gingivitis/peridontitis, 8 with chorioretinitis, 6 with gastroenteritis, 5 with paronychia, 3 each with conjunctivitis, hepatitis, and/or epididimytis, and/or 1 each with empyema, epiglottitis, cardiac empyema, mastoiditis, and/or suppurative phlebitis.

counterparts with the autosomal recessive disorder (see Table 4).

Prevalence of infections

Information was also obtained regarding the types of infections diagnosed in patients with CGD. As shown in Table 5, pneumonia occurred at least once in nearly 80% of the patients. Abscesses and suppurative adenitis also occurred in more than 50% of the patients, with significant numbers of patients also experiencing osteomyelitis, sepsis, cellulitis, and meningitis. Among those patients who had had at least 1 abscess, subcutaneous abscesses occurred in the largest number of patients, followed by abscesses in the liver, lung, perirectum, and brain.

Significantly more patients with the X-linked recessive form of the disease had at least 1 episode of suppurative adenitis ($p < 0.02$), perirectal abscess ($p < 0.05$) or bacteremia/fungemia ($p < 0.05$) than did patients with the autosomal recessive forms of the disease (see Table 5).

TABLE 6. Isolation of microorganisms from CGD patients with pneumonia

Organism	XLR (n=207) No. (%)*	AR (n=62) No. (%)*	Unknown (n=21) No. (%)*	Total (n=290) No. (%)*
Aspergillus spp.	85 (41%)	29 (47%)	6 (29%)	120 (41%)
Staphylococcus spp.	23 (11%)	8 (13%)	3 (14%)	34 (12%)
Burkholderia cepacia	15 (7%)	7 (11%)	2 (10%)	24 (8%)
Nocardia spp.	13 (6%)	8 (13%)	0	21 (7%)
Mycobacterial spp.	7 (3%)	2 (3%)	3 (14%)	12 (4%)
Atypical mycobacteria	4 (2%)	0	1 (5%)	5 (2%)
Serratia spp.	9 (4%)	3 (5%)	2 (10%)	14 (5%)
Klebsiella spp.	7 (3%)	0	0	7 (3%)
Pseudomonas spp.	5 (3%)	1 (2%)	1 (5%)	7 (3%)
Candida spp.	5 (2%)	0	0	5 (2%)
Paecilomyces spp.	2 (1%)	2 (3%)	0	4 (1%)
Other†	35 (17%)	10 (16%)	2 (10%)	47 (17%)

Abbreviations: See previous tables. spp. = species.

*Number (%) of patients within each genetic category with pneumonia who had at least 1 episode caused by the specific organism.

†Includes 6 patients reported who had at least 1 episode of pneumonia caused by a "fungal" organism, 4 each with pneumonia caused by *H. parainfluenzae* and/or *Mycoplasma* spp., 3 each with pneumonia caused by *Fusarium* and/or *Legionella* spp., 2 each with pneumonia caused by respiratory syncitial virus, *Rhizopus*, *Acinetobacter*, *Enterobacter*, and/or *Salmonella* spp., and 1 each with pneumonia caused by adenovirus, *Aerococcus*, *Exophiala*, *Moraxella*, *Streptomyces*, and/or *Chryseomonas* spp.

Etiology of infections

The most common etiologic agents of the different infections are listed in Tables 6–11. It should be noted that the relative frequencies of the different etiologic agents listed in Tables 6–11 represent the absolute number and proportion of patients in a given genetic category who had at least 1 episode of the infection caused by that specific organism. As can be seen in the tables, the prevalence of the microorganisms responsible for infection differed based on the location of the infection.

Nearly half of the patients (41%) who had experienced pneumonia had at least 1 episode caused by *Aspergillus* (Table 6). In fact, about one-third of the total 368 patients had had *Aspergillus* pneumonia. In addition, a significant number of patients experienced at least 1 episode of pneumonia caused by staphylococcal species, *Burkholderia cepacia*, and/or *Nocardia* species. It should be noted that since *Burkholderia cepacia* was previously known as *Pseudomonas cepacia*, some of the infections caused by *Burkholderia cepacia* may have been reported as caused by *Pseudomonas* without a species designation, thereby underestimating the true prevalence of *Burkholderia cepacia* infections in these patients.

The organisms causing abscesses differed depending on the location of the abscess (Table 7). For ex-

TABLE 7. Isolation of organisms from CGD patients with abscesses

Abscess	XLR (n=175) No. (%)*	AR (n=57) No. (%)*	Unknown (n=18) No. (%)*	Total (n=250) No. (%)*
Subcutaneous				
Total	112	34	10	156
Staphylococcus spp.	31 (28%)	7 (21%)	4 (40%)	42 (27%)
Serratia spp.	20 (19%)	3 (9%)	0	23 (15%)
Aspergillus spp.	8 (7%)	0	0	8 (5%)
Klebsiella spp.	5 (4%)	2 (6%)	0	7 (5%)
Candida spp.	5 (4%)	0	1 (10%)	6 (4%)
Other†	23 (24%)	4 (4%)	1 (10%)	28 (18%)
Liver				
Total	67	27	4	98
Staphylococcus spp.	35 (52%)	14 (52%)	1 (25%)	50 (50%)
Serratia spp.	4 (6%)	1 (4%)	0	5 (5%)
Streptococcus spp.	5 (7%)	0	0	5 (5%)
Nocardia spp.	3 (4%)	0	0	3 (3%)
Aspergillus spp.	2 (3%)	1 (4%)	0	3 (3%)
Candida spp.	2 (3%)	0	0	2 (2%)
Other‡	8 (12%)	0	0	8 (8%)
Lung				
Total	41	11	8	60
Aspergillus spp.	11 (27%)	2 (18%)	1 (13%)	14 (23%)
Nocardia spp.	2 (5%)	1 (9%)	1 (13%)	4 (7%)
Staphylococcus spp.	4 (8%)	0	1 (13%)	5 (8%)
Burkholderia cepacia	1 (2%)	2 (18%)	1 (13%)	4 (7%)
Other§	6 (13%)	2 (18%)	1 (13%)	9 (15%)
Perirectal				
Total	45	6	6	57
Staphylococcus spp.	4 (9%)	1 (15%)	0	5 (9%)
Klebsiella spp.	2 (4%)	0	0	2 (2%)
E. coli	2 (4%)	0	0	2 (2%)
Other¶	4 (9%)	0	1 (15%)	5 (9%)
Brain				
Total	8	4	0	12
Aspergillus spp.	6 (75%)	1 (25%)	0	7 (58%)
Staphylococcus spp.	0	1 (25%)	0	1 (8%)
Exophiala spp.	0	1 (25%)	0	1 (8%)

Abbreviations: See previous tables.

*Number (%) of patients with specific abscess who had at least 1 episode caused by the specific organism.

†Includes 3 patients each who had a subcutaneous abscess caused by *E. coli*, *Pseudomonas* and/or *Enterococcus* spp., 2 each who had a subcutaneous abscess caused by a "fungus", *Chromobacterium*, *Enterobacter*, *Nocardia*, and/or *Salmonella* spp., and 1 each who had a subcutaneous abscess caused by *Acetinobacter*, *Diphtheroids*, *Exophiala*, *Fusarium*, *Microascus*, *Paecilomyces*, *Penicillium*, and/or *Providencia* spp.

‡Includes 1 patient each who had a liver abscess caused by *Coccidiomycosis*, *Enterococcus*, *Klebsiella*, *Lactobacillus*, *Pediococcus*, *Peptostreptococcus*, *Pseudomonas*, and *Streptococcus milleri*.

§Includes 1 patient each who had a lung abscess caused by *Candida*, *Coccidiodomycosis*, *Fusobacterium*, *Klebsiella*, *Zygomycosis* (mucormycosis), *M. tuberculosis*, *Paecilomyces*, and/or *Serratia* spp.

¶Includes 1 patient each who had a perirectal abscess caused by *Edwardsiella*, *Enterococcus*, *Nocardia*, and/or *Proteus* spp.

ample, in the case of subcutaneous, perirectal, or liver abscesses, more patients had at least 1 episode of a staphylococcal abscess than they did with any other organism. In contrast, in the case of lung or brain abscesses, more patients had at least 1 episode of an *Aspergillus* abscess than they did with any other organism.

Staphylococcal species were also the most prominent cause of suppurative adenitis, with over 25% of the patients with adenitis having at least 1 episode caused by this organism (Table 8). Suppurative adenitis caused by *Serratia*, *Candida*, or *Klebsiella* was less frequent, but still relatively common.

More patients with osteomyelitis had infections caused by *Serratia* species than any other organism, although osteomyelitis caused by *Aspergillus* was nearly as common (Table 9). Osteomyelitis caused by *Paecelomyces*, *Staphylococcus*, or *Nocardia* also occurred in a smaller, but significant, fraction of patients.

There was a more even distribution of organisms reported as a cause of bacteremia/fungemia than with any other specific infection (Table 10). For example, although *Salmonella* was reported in more patients than any other organism, bacteremia or fungemia caused by *Burkholderia*, *Candida*, *Staphylococcus*, and/or *Pseudomonas* was found in nearly as many patients.

Meningitis was very uncommon. Only fifteen patients were reported to have had meningitis, and there was no predominant organism apparent (Table 11).

Finally, although a substantial minority of patients had at least 1 episode of cellulitis (see Table 5), only 2 of the 18 patients had an organism identified, both unusual pathogens, *Chromobacterium violaceum* in 1 and *Serratia marcescens* in the other.

TABLE 8. Isolation of organisms from CGD patients with suppurative adenitis

Organism	XLR (n=153) No. (%)*	AR (n=26) No. (%)*	Unknown (n=15) No. (%)*	Total (n=194) No. (%)*
Staphylococcus spp.	44 (29%)	3 (12%)	3 (20%)	50 (26%)
Serratia spp.	14 (9%)	4 (15%)	0	18 (9%)
Candida spp.	10 (7%)	1 (4%)	3 (20%)	14 (7%)
Klebsiella spp.	9 (6%)	1 (4%)	0	10 (6%)
Nocardia spp.	3 (2%)	1 (4%)	0	4 (2%)
E. coli	3 (2%)	0	1 (6%)	4 (2%)
Other†	11 (8%)	4 (15%)	1 (6%)	16 (8%)

Abbreviations: See previous tables.

*Number (%) of patients with suppurative adenitis who had at least 1 episode caused by the specific organism.

†Includes 3 patients each with suppurative adenitis caused by *B. cepacia*, 2 patients each who had suppurative adenitis caused by *Pseudomonas* spp., and 1 patient each with suppurative adenitis caused by *Acinetobacter*, *Aerococcus*, *Aspergillus*, *Bacillus subtilis*, *Enterobacter*, *Streptococcus*, and/or *Candida (Torulopsis) glabrata*.

TABLE 9. Isolation of organisms from CGD patients with osteomyelitis

Organism	XLR (n=69) No. (%)*	AR (n=17) No. (%)*	Unknown (n=4) No. (%)*	Total (n=90) No. (%)*
Serratia spp.	22 (32%)	2 (12%)	2 (50%)	26 (29%)
Aspergillus spp.	17 (25%)	3 (18%)	0	20 (22%)
Paecilomyces spp.	3 (4%)	3 (18%)	1 (25%)	7 (8%)
Staphylococcus spp.	2 (3%)	2 (12%)	1 (25%)	5 (6%)
Nocardia spp.	1 (1%)	2 (12%)	0	3 (3%)
Burkholderia cepacia	2 (3%)	0	0	2 (2%)
Klebsiella spp.	2 (3%)	0	0	2 (2%)
Pseudomonas spp.	1 (1%)	1 (6%)	0	2 (2%)
Enterobacteriaceae spp.	2 (3%)	0	0	2 (2%)
Other†	4 (6%)	1 (6%)	0	5 (6%)

Abbreviations: See previous tables.

*Number (%) of patients with osteomyelitis who had at least 1 episode caused by the specific organism.

†Includes 1 patient each who had osteomyelitis caused by a "fungus," *E. coli*, *Penicillium*, *Proteus*, and/or *Salmonella* spp.

Miscellaneous disorders

A variety of disorders has been described in patients with CGD for which no infectious etiology has been identified. As can be seen in Table 12, obstructive lesions of the gastrointestinal and urinary tract and colitis/enteritis were seen in a substantial number of CGD patients entered in the registry. However, both gastric outlet obstruction and urinary outlet obstruction were seen significantly more commonly in the X-linked recessive form of the disease than in the autosomal recessive forms ($p < 0.01$).

A number of patients and their first-degree female relatives were reported to have systemic lupus erythematosus or discoid lupus erythematosus (see Table 12). Lupus was not more common in patients

TABLE 10. Isolation of organisms from CGD patients with bacteremia or fungemia

Organism	XLR (n=54) No. (%)*	AR (n=8) No. (%)*	Unknown (n=3) No. (%)*	Total (n=65) No. (%)*
Salmonella spp.	11 (20%)	1 (13%)	0	12 (18%)
Burkholderia cepacia	7 (13%)	0	1 (33%)	8 (12%)
Candida spp.	5 (9%)	2 (25%)	0	7 (11%)
Staphylococcus spp.	6 (11%)	0	0	6 (9%)
Pseudomonas spp.	5 (9%)	1 (13%)	0	6 (9%)
Serratia spp.	4 (7%)	0	0	4 (6%)
Acinetobacter spp.	2 (4%)	1 (13%)	0	3 (5%)
Klebsiella spp.	2 (4%)	1 (13%)	0	3 (5%)
Other†	9 (17%)	3 (38%)	0	12 (18%)

Abbreviations: See previous tables.

*Number (%) of patients with bacteremia or fungemia who had at least 1 episode caused by the specific organism.

†Includes 2 patients each who were reported to have bacteremia/fungemia caused by *Arizona himanshi*, *Aspergillus*, and/or *Enterobacter* spp. and 1 patient each reported to have bacteremia/fungemia caused by *Aerococcus*, *Corynebacterium*, *E. coli*, *Nocardia*, *Penicillium*, and/or *Rhodococcus* spp.

TABLE 11. Isolation of organisms from CGD patients with meningitis

Organism	XLR (n=10) No. (%)*	AR (n=4) No. (%)*	Unknown (n=1) No. (%)*	Total (n=15) No. (%)*
Candida spp.	2 (20%)	0	1 (100%)	3 (20%)
H. influenzae	2 (20%)	0	0	2 (13%)
Burkholderia cepacia	1 (10%)	0	0	1 (7%)
Enterovirus	1 (10%)	0	0	1 (7%)

Abbreviations: See previous tables.
*Number (%) of patients with meningitis who had at least 1 episode caused by the specific organism.

with the X-linked recessive form of the disease than in patients with the autosomal recessive forms. However, lupus was significantly more common in the mothers, maternal grandmothers, and/or maternal aunts of patients with the X-linked recessive form of the disease than it was in their counterparts in families of patients with the autosomal recessive forms ($p < 0.01$). Although direct evidence was not provided on the survey instrument to confirm that each of the female relatives of the patients with the X-linked recessive form of the disease who had lupus were carriers, in 20 of the 21 kindreds, at least 1 of the females with lupus was the mother of the patient, suggesting that they were, in fact, carriers. It is noteworthy that the mothers of 5 of the 6 X-linked recessive patients who had lupus also had lupus themselves.

Four patients were reported to have idiopathic/immune thrombocytopenia (ITP), 1 had myasthenia gravis, and 7 had chorioretinitis. None of the patients developed a malignancy.

Treatment

Of the 368 patients, 269 (73%) patients were currently being treated, or had been treated in the past, with interferon-gamma. Fifty-five patients (15%) had received granulocyte transfusions at least once in their course. Three hundred twenty-nine patients (89%) were being treated, or had been treated at some point in their course, with prophylactic trimethoprim/sulfamethoxasole or dicloxacillin. Two patients, both with the X-linked recessive form of the disease, had had a bone marrow transplant; in 1 there was no engraftment, and the other patient died of gastrointestinal hemorrhage soon after the transplant.

TABLE 12. Miscellaneous illnesses in CGD

Illness	XLR (n=259)	AR (n=81)	Unknown (n=28)	Total (n=368)
Lupus syndromes				
DLE in patient	6	4	0	10
SLE in patient	0	2	0	2
Kindreds with DLE	19/219†	1/71	0	20
Kindreds with SLE	2/219	1/71	0	3
Obstructive lesions				
Gastric outlet	49†	4	4	57
Esophageal outlet	3	0	0	3
Urinary outlet	29†	3	5	37
Colitis/enteritis	49	11	4	64
ITP	4	1	0	5
Myasthenia gravis	0	1	0	1
Chorioretinitis	7	0	1	8

Abbreviations: See previous tables.
DLE = discoid lupus erythematosus; SLE = systemic lupus erythematosus; ITP = idiopathic/immune thrombocytopenia.
†$p < 0.01$ comparing XLR to AR.

Survival

Most patients were alive when they were entered in the registry, and, as can be seen in Figure 2, most of the living patients were in their first or second decade of life when entered in the registry. However, a significant number of patients had survived into their third and fourth decades, and there were isolated patients surviving into the fifth and sixth decades. It is noteworthy that a greater proportion of patients with an autosomal recessive form of the disease had survived past the second decade of life (42%) than had patients with the X-linked recessive form (22%) ($p < 0.01$).

There was an overall mortality of 17.6% (Table 13), including patients who were deceased at the time they were entered in the registry and patients who died subsequent to their entry into the registry. Mortality was significantly higher in patients with the X-linked recessive form of the disorder (21.2%) than in patients

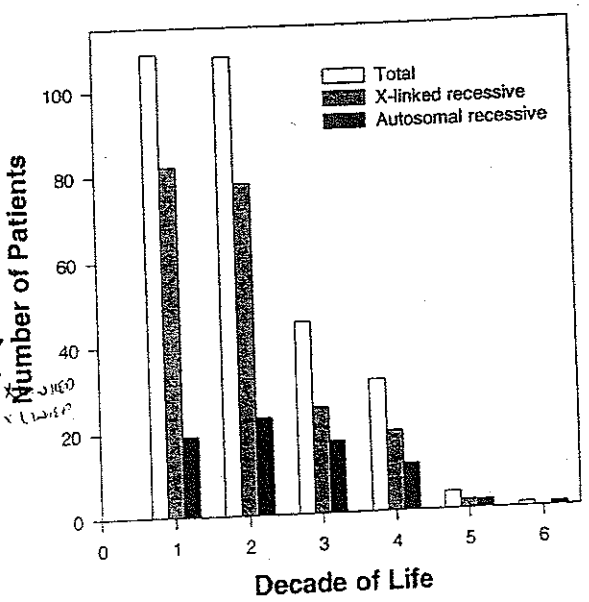

FIG. 2. The age of living patients with chronic granulomatous disease. The age at latest entry of information into the registry is shown.

TABLE 13. Mortality in CGD

Genetic Type	Mortality
X-linked recessive	21.2% (54/259)*
Autosomal recessive	8.6% (7/81)
Unknown genotype	16.7% (4/28)
Total	17.6% (65/368)

*$p < 0.02$ comparing XLR to AR.

with the autosomal recessive forms of the disorder (8.6%) ($p < 0.02$). The distribution of patients' ages at the time of death is displayed in Figure 3.

There may have been some bias with respect to either overreporting or underreporting of patients who were deceased at the time they were entered in the registry. Therefore, follow-up information on survival was requested on the cohort of 320 patients who were alive at the time of their initial entry into the registry in order to assess survival prospectively; follow-up information was available on 205 of the 320 (65%) patients. During the follow-up period, 14/149 (9.4%) of the patients with the X-linked recessive form of the disease died, 3/46 (6.5%) of the patients with an autosomal recessive form of the disease died, and 1/10 (10%) of the patients with an unidentified genetic form of the disease died. Survival was also estimated using a Kaplan-Meier plot (Figure 4). Although the estimated survival was greater in patients with the autosomal recessive forms of the disease (88% at 5 years of follow-up) than in patients with the X-linked recessive form of the disease (76% at 5 years of follow-up), the difference was not statistically significant.

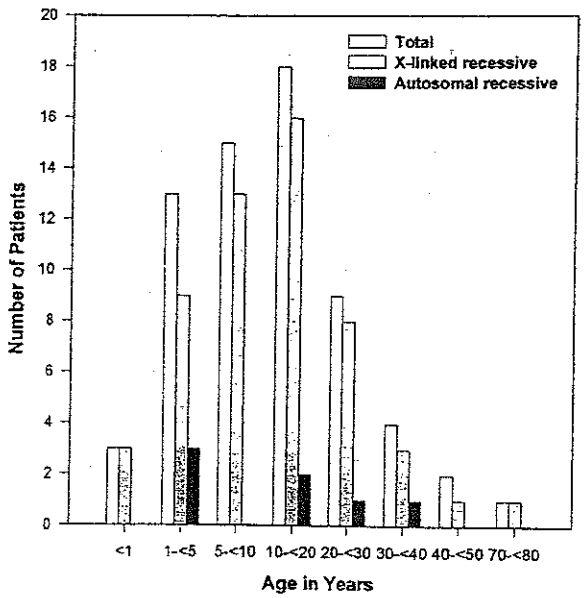

FIG. 3. The age at death of patients with chronic granulomatous disease.

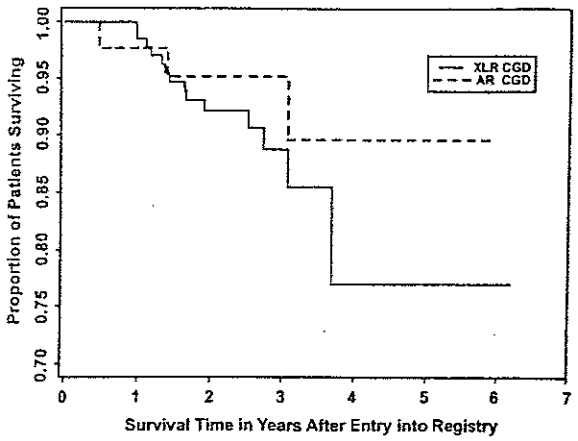

FIG. 4. Kaplan-Meier analysis of survival of patients with chronic granulomatous disease who were alive at the time of initial entry into the registry. (XLR CGD = X-linked recessive chronic granulomatous disease; AR CGD = autosomal recessive chronic granulomatous disease.)

Infections caused by *Aspergillus* were the most common cause of death, accounting for over one-third of all deaths (Table 14). Infections caused by *Burkholderia* were also a relatively common cause of death, with death caused by *Pseudomonas* and *Candida* infections occurring less commonly. In

TABLE 14. Causes of death in CGD

Cause of Death	XLR (n=54)	AR (n=7)	Unknown (n=4)	Total (n=65)
Aspergillus spp.	18	3*	2*	23
Pneumonia alone	9	2	2	
Pneumonia with extension/ dissemination	9	1		
Burkholderia cepacia	9	2*	1*	12
Sepsis	7	1	1	
Pneumonia	4	1		
Pseudomonas spp.	3			3
Pneumonia	2			
Sepsis	3			
Candida spp.	3		1	4
Meningitis	1		1	
Pneumonia				
Sepsis	2			
Pneumonia/sepsis/ meningitis (unknown etiology)	6	1		7
Miscellaneous†	8	2	1	11

Abbreviations: See previous tables.

*1 patient in each of these 2 categories (AR and unknown) died of combined *Aspergillus* and *Burkholderia cepacia* infections.

†One patient each died of *Nocardia* pneumonia, *Mycobacterial* pneumonia, disseminated histoplasmosis, *Zygomycosis* (mucormycosis) infection of the lung and osteomyelitis, *Zygomycosis* (mucormycosis) infection of the lung, *Phialophora parasitica* pneumonia, *Penicillium* pneumonia, gastrointestinal hemorrhage, aortic aneurysm, seizures and aspiration, and auto accident.

some instances the infections were not confined to a single site. For example, although *Aspergillus* pneumonia was a common cause of death, it was often accompanied by extension/dissemination to the ribs, chest wall, and/or spine. Similarly, fatal infections with *Burkholderia* or *Pseudomonas* species often involved concurrent pneumonia and sepsis.

Discussion

Since the initial clinical description of CGD in 1957 (8) and the delineation of its underlying defect in intracellular phagocytic microbicidal activity in 1967 (42), a large number of clinical reports have been published on the disorder. However, most of these have focused on specific clinical issues, such as the occurrence of unusual or rare infections, non-infectious complications, or therapy, and have involved limited numbers of patients. There have been relatively few original reports involving comprehensive clinical studies in large series of patients. The first of these involved an analysis of the first 88 patients published in the literature for which adequate clinical data were available and focused on the clinical signs and symptoms of the disorder and the kinds of organisms responsible for infections (27); this report was subsequently updated to include 168 patients (28). Soon thereafter, a second series, focusing on the organisms responsible for infections in these patients, analyzed 70 patients previously reported in the literature and 9 patients of the authors' (32). A series published in 1988 examined factors influencing mortality in 52 patients collected from 17 institutions in the United States (29). Another series published in 1989 reviewed the frequency and nature of infections in 48 patients seen in a single institution in Europe (39). Finally, the experience in the medical management of over 100 patients with CGD in several European institutions was published in 1993 (15).

The construction of a registry of United States residents with CGD has provided a unique opportunity to estimate the minimal incidence of the disorder, characterize some of its epidemiologic features, and define a broad range of its clinical characteristics in a large cohort of patients. The registry contains information on 368 patients from 94 physicians in 77 different medical institutions.

Molecular basis of CGD

The functional NADPH oxidase is composed of several structural and regulator proteins (4). Two of these ($gp91^{phox}$ and $p22^{phox}$) are membrane bound, initially in the membrane of the secondary granules, and make up the cytochrome b558. This complex binds heme and FAD, both of which are necessary for electron transport. With ingestion of a pathogen and subsequent fusion of secondary granules with the phagocytic vacuole, the cytochrome becomes lodged in the membrane of the phagocytic vacuole. In the event of large extracellular pathogens like fungal hyphae, secondary granules fuse with the plasma membrane and deposit the cytochrome on the cell surface.

The structural cytosolic proteins, $p67^{phox}$ and $p47^{phox}$, and the regulator $p40^{phox}$ exist pre-associated with each other in the cytosol. With cellular activation, they are phosphorylated and bind en bloc to the cytochrome. This assembly also requires 1 or 2 small G-proteins. When all these requirements are fulfilled the assembled NADPH oxidase transfers an electron from NADPH to molecular oxygen, leading to the formation of superoxide. This in turn is converted into hydrogen peroxide and hypochlorite that have potent antimicrobial properties.

Mutations have been identified in each of the 4 major structural components of the NADPH oxidase (11, 17). In this registry 70% of patients had the X-linked recessive form of the disease. Mutations may occur anywhere in the $gp91^{phox}$ gene. About one-third appear to arise from new mutations, occurring in either egg or sperm. In contrast to the case with the $gp91^{phox}$ mutations, almost all $p47^{phox}$ mutations occur at the same site in the beginning of exon 2 and are due to an apparent recombination event involving a near highly homologous pseudogene for $p47^{phox}$. Mutations in $p67^{phox}$ and $p22^{phox}$ are less common and have no apparent predilection for specific parts of the gene. So far, no mutations have been identified in $p40^{phox}$ or rac. Since $p40^{phox}$ is thought to play a down-regulatory role, a CGD phenotype would not be expected from a deficiency of $p40^{phox}$. A mouse model suggests that a rac mutation should lead to increased susceptibility to infection and may resemble CGD.

Construction of the registry and its limitations

Although the construction of a registry of United States residents with CGD has provided a great deal of information on a large series of patients, there are certain limitations inherent in this type of registry.

For example, although this is the largest series of patients with CGD, it is likely that many patients in the United States with CGD were not registered. Survey instruments were sent to more than 17,000 members of professional societies who might have been expected to care for patients with CGD. In addition, survey instruments were sent to the chairpersons of departments of pediatrics and medicine that have residency programs with a request to pass them on to the individuals in their departments who care for CGD patients. However, not all physicians contacted

through these mechanisms responded to the request to participate in the registry. In addition, physicians who were not members of the above professional societies or who were not members of academic departments of pediatrics or medicine might not have been aware of the registry and, therefore, might not have registered their patients. Finally, a number of patients might have died before the diagnosis was made and therefore might have been unavailable to the registry.

There also was no way to insure that all available information was supplied on each patient. For example, certain clinical information, such as the details of a specific infection, the existence of an affected relative, or the long-term course of the patient, might not have been available to the reporting physician. Similarly, it is possible that deceased patients were underreported, relative to living patients, since they would no longer be active patients and might have been unknown to the physicians who were currently at the institution.

Another limitation relates to the degree to which details were reported on the patients. For example, detailed information on the species of each organism was not provided in every instance. Therefore, it was not always possible to determine whether the patient had an infection with *Aspergillus fumigatus* or *Aspergillus nidulans* or with *Staphylococcus aureus* or *Staphylococcus epidermidis*. In addition, since *Burkholderia cepacia* was previously known as *Pseudomonas cepacia* (40), some of the infections caused by *Burkholderia cepacia* may have been reported as caused by *Pseudomonas* without a species designation, thereby underestimating the true prevalence of *Burkholderia cepacia* infections in these patients.

Finally, some of the information obtained from the reporting physician was in response to an open-ended question requesting "other" infections and "other" illnesses. Under these circumstances there may have been inconsistent reporting of certain illnesses that the clinical data entry form did not specifically request, such as myasthenia gravis or ITP.

Incidence

It has been difficult to obtain a reliable estimate of the incidence or prevalence of CGD in a population. It is not a reportable disease in the United States and it is too uncommon for a single locality or medical center to estimate its prevalence reliably. A number of reports have examined the distribution of the different primary immunodeficiency diseases within populations. In fact, surveys of primary immunodeficiency diseases that have included CGD have been performed in Sweden (14), Italy (34), Brazil (22), and Spain (38). However, most of these surveys have reported the prevalence of CGD as a percentage (1.5%-10.9%) of all primary immunodeficiency diseases, rather than as a prevalence or incidence within the population at large. Three series have attempted to determine its *prevalence* within different populations and have estimated it as approximately 1/1,300,000 individuals in Japan (25), 1/1,375,000 individuals in Australia (7), and 1/450,000 individuals in Sweden (1).

The results of the current study suggest that the minimal *incidence* of CGD among residents of the United States is between 1/200,000 and 1/250,000 live births. Although we attempted to register as many patients as possible, this is clearly an underestimate of its incidence. As discussed, not every physician in the United States was contacted, not all of the physicians surveyed who had patients registered their patients, and not all patients may have been diagnosed. Nevertheless, even though the minimal incidence derived from this registry is likely to be an underestimate, it is higher than previous estimates.

Clinical differences between X-linked recessive and autosomal recessive forms of the disorder

Three previous studies have examined whether the X-linked recessive form of CGD has a different, or more severe, clinical phenotype than the autosomal recessive forms. In 1 series of 12 patients, the 7 patients with the X-linked recessive form had a significantly earlier age of onset of symptoms and age at diagnosis than did the 5 patients with autosomal recessive forms (51). In another series of 21 patients, the 12 patients with the X-linked recessive form of the disease also had a significantly earlier age of onset of symptoms and age at diagnosis, and significantly more infections per year, than did the 9 patients with the autosomal recessive form of the disease (1). Finally, a third series of 48 patients examined survival rates of patients in the 2 groups, but was unable to demonstrate a difference (39).

Results from the present series of patients suggest that, in addition to the age of onset of symptoms and age at diagnosis, there are other significant differences in the clinical features of CGD between patients with the X-linked and autosomal recessive forms of the disease. As in the previous studies, the patients in the present series with the X-linked form of the disorder were diagnosed significantly earlier than those with the autosomal recessive forms of the disorder, even when controlling for gender. In addition, the patients in the present series with the X-linked recessive form of the disorder had a higher prevalence of certain infections such as perirectal abscess, suppurative adenitis, and bacteremia/fungemia. They also had a higher prevalence of chronic inflammatory manifestations of the disease, such as gastric outlet and urinary outlet obstruction. And finally, mortality was significantly

higher in patients with the X-linked recessive form of the disease. The additional differences in clinical severity found in the present series of 368 patients may not have been apparent in the previous studies because of their limited numbers of patients.

Thus, based on a number of different clinical parameters, patients with the X-linked recessive form of the disease appear to have a more severe clinical phenotype than those with the autosomal recessive forms. The basis for the more severe clinical phenotype in the X-linked recessive form of the disease is unknown. Differences in gender distribution between the X-linked and autosomal recessive forms would not appear to be responsible for the more severe clinical phenotype in the X-linked recessive form, since in the present series, when the age of onset was compared between males with the X-linked recessive form and *males* with the autosomal recessive form, there was still a significant difference. Unfortunately, we could not control for gender in the other clinical outcomes since they occurred too infrequently in the autosomal recessive form of the disorder to allow for meaningful comparisons.

There are cases of defects in the gp91^{phox} that result in the production of a hypofunctional protein possessing small amounts of residual superoxide production (17). These cases seem to have milder clinical phenotypes, suggesting that the production of small amounts of superoxide and hydrogen peroxide, even if very little, is clinically significant. By dihydrorhodamine 123 oxidation there is some small amount of residual hydrogen peroxide production in p47^{phox}- deficient patients when compared to gp91^{phox}-deficient patients. Whether this small amount of hydrogen peroxide accounts entirely for the phenotypic differences between X-linked recessive and autosomal recessive forms of CGD is not certain, but it is consistent with the data available. There appears to be an absolute need for the cytochrome for electron transfer, whereas the above observations suggest that the cytosolic factors are important but not absolutely required for minimal activity.

Prevalence and etiology of infections

More patients had at least 1 episode of pneumonia than any other kind of infection, followed by abscesses, suppurative adenitis, osteomyelitis, bacteremia/fungemia, cellulitis, and meningitis. Pneumonia was also the most prevalent infection in 3 other series of patients with CGD (20, 27, 39), while in 1 series skin infections were the most prevalent (1). However, in each of those series, suppurative adenitis, rather than abscesses, was the second most prevalent infection. The differences in the relative prevalence of infections between the present and previous series may relate to a variety of factors, including the number of patients reported, the changing clinical expression of the disorder over time, and the way in which information on specific infections was requested and/or reported.

The organisms most frequently reported as responsible for a specific infection varied from infection to infection. For example, more patients with pneumonia, pulmonary abscesses, and brain abscesses had *Aspergillus* species isolated than any other organism. In contrast, *Staphylococcus* species were the most common microorganisms isolated from subcutaneous, liver, and perirectal abscesses as well as from patients with suppurative adenitis. More patients with osteomyelitis had at least 1 episode caused by *Serratia* species than any other organism, although *Aspergillus* osteomyelitis was nearly as common. Finally, *Salmonella* species were the most common microorganisms isolated from patients with hematogenous infections. Other organisms, uncommon in normal hosts, such as *Burkholderia cepacia*, *Nocardia*, *Paecilomyces* species, and *Serratia*, were also seen regularly in these patients.

It should be mentioned that the organisms that were isolated from certain specific infections might not represent the true distribution of organisms for that infection, but rather may reflect a bias in sampling. For example, in the case of pneumonia, empiric antibiotic therapy without the isolation of an organism may have resolved infections caused by bacteria, such as staphylococci, leading to an underestimate of the prevalence of certain bacteria as a cause. In contrast, those patients with *Aspergillus* pneumonia would not have responded to empiric antibiotic therapy and therefore would have been more likely to have had the organism isolated by invasive diagnostic procedures, which in turn would lead to a more accurate estimate of its prevalence.

Since the original series of patients with CGD, the relative prevalence of different bacteria and fungi has changed. For example, in the original series of patients (27), *Aspergillus* was reported to have been isolated from only 6 of 92 (7%) patients. Similarly, in another early series, which combined patients from the literature with first-hand experience from a single institution, *Aspergillus* was responsible for slightly more than 10% of the fatal infections (32). However, in a more recent series from a single institution in Europe, 40% of the patients had at least 1 infection caused by *Aspergillus* (39). In the current series, *Aspergillus* was the most commonly isolated organism from those patients with pneumonia in whom an organism was identified, with over 40% of patients with pneumonia (and one-third of the total 368 patients) having had *Aspergillus* at least once. Similarly, *Burkholderia cepacia* has emerged as a significant pathogen in CGD since the original clinical series (27, 32, 39, 40). In the present series it was

the second most prevalent organism isolated from patients with pneumonia, the second most prevalent organism isolated from patients with bacteremia, and accounted for nearly 20% of the deaths.

Miscellaneous disorders

In addition to infections, patients with CGD have been reported to have a variety of inflammatory and/or rheumatic conditions. These have included obstructive lesions of the esophagus, gastrointestinal tract, and urinary tract (2, 10, 12, 13, 26, 50), inflammatory bowel disease (3, 16, 24, 45, 52), discoid and systemic lupus erythematosus (5, 35, 41, 46, 47), chorioretinitis (21, 33, 36, 48), ITP (38), and Behçet syndrome (30). In fact, in some instances, these inflammatory disorders have been the first clinical manifestation of CGD and have led to diagnosis (13, 49). Histologically, there is usually significant localized inflammation, which can reflect granuloma formation (24, 43, 45, 48), although nonspecific inflammatory responses containing histiocytes or eosinophils have also been described (6, 13, 21, 31).

The current series is large enough to provide the opportunity to examine the prevalence of these disorders in patients with CGD and determine whether they are more likely to occur in 1 genetic form of the disease than in the other. For example, obstructive lesions of the esophagus, gastric outlet, and/or urinary tract occurred in 1%, 16%, and 10% of patients, respectively. We note that the 2 most common of these, gastric outlet obstruction and urinary tract outlet obstruction, were significantly more common among patients with the X-linked recessive form than patients with autosomal recessive forms. In a previous study that examined all the urologic manifestations of CGD, obstructive lesions of the urinary tract were also significantly more common in patients with the X-linked form of the disease (50).

Colitis and enteritis were also relatively common in the present series, occurring in 17% of patients. Although colitis and enteritis were more prevalent in patients with the X-linked recessive form of the disease (49/259; 19%) than in patients with the autosomal recessive form (11/81; 13%), the difference was not significant.

The etiology and pathogenesis of the inflammatory and/or rheumatic diseases in CGD are unclear. In a recent study, several polymorphic variants of genes encoding molecules important in innate immunity and inflammatory responses (for example, mannose binding lectin and Fc gamma receptors) were found to be associated with the development of inflammatory and/or autoimmune disorders in patients with CGD (19). These data suggest that common variations in other genes involved in the generation of an inflammatory response can contribute to the development of clinical complications of CGD.

Outcome

The original designation of CGD was "fatal granulomatous disease of childhood" (8, 9). In fact, in a survey of the first 92 patients reported in the literature, 45 had died, and 34 of the 45 deaths had occurred before the age of 7 years (27). Fortunately, the prognosis of patients with CGD appears to have improved significantly since its original description (1, 39, 51). In the present series, 17.6% of patients were either dead at the time they were registered or died during follow-up. Although the different mortality figures reported initially and those reported in the present series probably reflect improvements in therapy of infections (15, 18, 20, 39) and the diagnosis of milder cases, the differences may also reflect the different ways in which the patients were ascertained. For example, in the years immediately following the description of the disease, there may have been a bias in favor of reporting the more seriously affected patients and therefore an overestimate of mortality. Conversely, in the current survey, physicians may have been biased in favor of registering living patients and therefore underestimated mortality. Because of these qualifications, we attempted to obtain follow-up information on the cohort of patients who were alive when they were registered. Over a 5-year period of follow-up, a Kaplan-Meier analysis estimated mortality at approximately 5% per year for the patients with the X-linked recessive form of the disease and 2% per year for the patients with the autosomal recessive forms of the disease.

Although the infectious causes varied, 2 organisms, *Aspergillus* and *Burkholderia cepacia*, accounted for just over half of the deaths. Most commonly, fatal *Aspergillus* infections were characterized by pneumonia, with direct extension to the chest wall and vertebrae and dissemination to the central nervous system occurring commonly. In contrast, fatal *Burkholderia cepacia* infections most often were characterized by sepsis and/or pneumonia.

In spite of its relatively high mortality rate, most patients with CGD were alive when entered in the registry and were alive at follow-up. Importantly, more than one-quarter of all the living patients, and 42% of the living patients with the autosomal recessive forms of the disease, were 20 years of age or older. Thus, the prognosis for patients with CGD appears to be better than envisioned when the disorder was originally described. The use of prophylactic antibiotics, prophylactic interferon gamma, and early diagnosis and aggressive management of infections has converted CGD from "fatal granulomatous disease of childhood" to a chronic illness of children *and* adults. The data presented here provide clear evidence that although CGD still claims the lives of children and young adults at unacceptable rates, it is a disease with a finite spectrum of clinical presentations that can be anticipated and managed. With this

clearer picture of CGD, new prophylactic and therapeutic approaches that address the ongoing infectious and inflammatory complications of this disease can be pursued.

Summary

A registry of United States residents with chronic granulomatous disease (CGD) was established in 1993 in order to estimate the minimum incidence of this uncommon primary immunodeficiency disease and characterize its epidemiologic and clinical features. To date, 368 patients have been registered; 259 have the X-linked recessive form of CGD, 81 have 1 of the autosomal recessive forms, and in 28 the mode of inheritance is unknown. The minimum estimate of birth rate is between 1/200,000 and 1/250,000 live births for the period 1980–1989. Pneumonia was the most prevalent infection (79% of patients; *Aspergillus* most prevalent cause), followed by suppurative adenitis (53% of patients; *Staphylococcus* most prevalent cause), subcutaneous abscess (42% of patients; *Staphylococcus* most prevalent cause), liver abscess (27% of patients; *Staphylococcus* most prevalent cause), osteomyelitis (25% of patients; *Serratia* most prevalent cause), and sepsis (18% of patients; *Salmonella* most prevalent cause). Fifteen percent of patients had gastric outlet obstruction, 10% urinary tract obstruction, and 17% colitis/enteritis. Ten percent of X-linked recessive kindreds and 3% of autosomal recessive kindreds had family members with lupus. Eighteen percent of patients either were deceased when registered or died after being registered. The most common causes of death were pneumonia and/or sepsis due to *Aspergillus* (23 patients) or *Burkholderia cepacia* (12 patients). Patients with the X-linked recessive form of the disease appear to have a more serious clinical phenotype than patients with the autosomal recessive forms of the disease, based on the fact that they are diagnosed significantly earlier (mean, 3.01 years of age versus 7.81 years of age, respectively), have a significantly higher prevalence of perirectal abscess (17% versus 7%), suppurative adenitis (59% versus 32%), bacteremia/fungemia (21% versus 10%), gastric obstruction (19% versus 5%), and urinary tract obstruction (11% versus 3%), and a higher mortality (21.2% versus 8.6%).

Appendix

The following physicians entered patients in the registry: Stuart L. Abramson, MD, PhD, Texas Children's Hospital, Houston, TX; Garrett Adams, MD, PhD, Kosair Children's Hospital, Louisville, KY; William L. Albritton, MD, Children's Hospital at Sacred Heart, Pensacola, FL; Burton R. Anderson, MD, University of Illinois at Chicago, Chicago, IL; Robert Anolik, MD, Allergy & Asthma Specialists PC, Norristown, PA; Ann M. Arvin, MD, Stanford University Medical Center, Palo Alto, CA; Amal H. Assa'ad, MD, Children's Hospital Medical Center, Cincinnati, OH; Parvin H. Azimi, MD, Children's Hospital Oakland, Oakland, CA; William J. Barson, MD, Children's Hospital, San Diego, CA; John F. Bastian, MD, Children's Medical Group, San Diego, CA; Kiran K. Belani, MD, Park Nicollet Medical Center, Minneapolis, MN; Roger L. Berkow, MD, University of Alabama at Birmingham, Birmingham, AL; Laurence A. Boxer, MD, University of Michigan Medical Center, Ann Arbor, MI; Jeff Brand, MD, Anchorage, AK; E. Stephen Buescher, MD, Eastern Virginia Medical School Center for Pediatric Research, Norfolk, VA; Joseph A. Church, MD, Children's Hospital Los Angeles, Los Angeles, CA; Michael J. Chusid, MD, Medical College of Wisconsin, Milwaukee, WI; Robert A. Clark, MD, The University of Iowa, Iowa City, IA; Mary Ellen Conley, MD, University of Tennessee, Memphis, TN; M. Cooperstock, MD, University Hospital, Columbia, MO; C. Cunningham-Rundles, MD, PhD, The Mount Sinai Medical Center, New York, NY; John T. Curnutte, MD, Genentech, Inc., South San Francisco, CA; A. Todd Davis, MD, Children's Memorial Hospital, Chicago, IL; Joseph D. Dickerman, MD, University of Vermont College of Medicine, Burlington, VT; Mary C. Dinauer, MD, James Whitcomb Riley Hospital for Children, Indianapolis, IN; Jale Dolen, MD, New Braunfels, TX; Steven D. Douglas, MD, Children's Hospital of Philadelphia, Philadelphia, PA; Kathryn M. Edwards, MD, Vanderbilt University Medical Center, Nashville, TN; James Clifford Fagin, MD, North Shore University Hospital, Great Neck, NY; Senih Fikrig, MD, SUNY Health Science Center, Brooklyn, NY; Barry M. Friedman, MD, Ohio State University, Columbus, OH; John I. Gallin, MD, National Institutes of Health, Bethesda, MD; Armond S. Goldman, MD, University of Texas Medical Branch at Galveston, Galveston, TX; Robert A. Good, MD, PhD, All Children's Hospital, St. Petersburg, FL; Jed B. Gorlin, MD, Boston Children's Hospital, Boston, MA; Stephen Grandgeorge, MD, The Hitchcock Clinic, Bedford, NH; Frank Gruskay, MD, Yale University School of Medicine, New Haven, CT; Patricia Harkins, MD, Pediatric South, Pittsburgh, PA; Richard E. Harris, MD, Children's Hospital Research Foundation, Cincinnati, OH; Duane D. Harrison, MD, Children's Hospital of Michigan, Detroit, MI; Lee Hilliard, MD, University of Alabama at Birmingham, Birmingham, AL; Mary Beth Hogan, MD, West Virginia University, Morgantown, WV; Michelle Hulse, MD, Wayzata Children's Clinic, Wayzata, MN; Jack H. Hutto, MD, All Children's Hospital, St. Petersburg, FL; Anthony J. Infante, MD, PhD, University of Texas Health Science Center, San Antonio, TX; Richard Fuller Jacobs, MD, Arkansas Children's Hospital, Little Rock, AR; Jerri Ann Jenista, MD, Ann Arbor, MI; Lawrence K. Jung, MD, Creighton University Medical Center, Omaha, NE; Mary Ann Kish, MD, Health Partners Riverside Clinic, Minneapolis, MN; Mark Steven Klempner, MD, New England Medical Center, Boston, MA; Alan P. Knutsen, MD, St. Louis University Medical Center, St. Louis, MO; John Knutson, MD, Kaiser-Permanente, Dallas, TX; Lisa J. Kobrynski, MD, Emory Egleston Pediatric Care Foundation, Atlanta, GA; Thomas L. Kuhls, MD, University of Oklahoma, Oklahoma City, OK; Lawrence E. Kurlandsky, MD, Grand Rapids, MI; Richard M. Lampe, MD, Texas Tech University, Lubbock, TX; Howard M. Lederman, MD, PhD, Johns Hopkins Hospital, Baltimore, MD; J. Douglas Lee, MD, Marshfield Clinic, Marshfield, WI; Myron I. Liebhaeber, MD, Santa Barbara Medical Foundation Clinic, Santa Barbara, CA; Richard M. Locksley, MD, University of California San Francisco, San Francisco, CA; Bennett Lorber, MD, Temple University School of Medicine, Philadelphia, PA; Harry L. Malech, MD, National Institutes of Health, Bethesda, MD; Robert J. Mamlok, MD, Lubbock, TX; Sharon A. Nachman, MD, SUNY at Stony Brook School of Medicine, Stony Brook, NY; Peter E. Newburger, MD, University of Massachusetts Medical Center, Worcester, MA;

Hans D. Ochs, MD, University of Washington School of Medicine, Seattle, WA; Kathleen M. O'Neil, MD, The Children's Hospital of Buffalo, Buffalo, NY; Robert L. Pinsky, MD, Bangor, ME; Keith R. Powell, MD, University of Rochester School of Medicine, Rochester, NY; Alice S. Prince, MD, Columbia University, New York, NY; Paul G. Quie, MD, University of Minnesota Medical School, Minneapolis, MN; Robert L. Roberts, MD, PhD, UCLA Medical Center, Los Angeles, CA; Henry Rosen, MD, University of Washington Medical Center, Seattle, WA; Frank T. Saulsbury, MD, University of Virginia Medical Center, Charlottesville, VA; Michael J. Schumacher, MD, University of Arizona Health Science Center, Tucson, AZ; Penelope G. Shackelford, MD, Childrens Hospital of Washington University, St. Louis, MO; Ziad M. Shehab, MD, University of Arizona Health Sciences Center, Tucson, AZ; Ann O'Neill Shigeoka, MD, University of Utah Medical School, Salt Lake City, UT; Stanford Taylor Shulman, MD, Children's Memorial Hospital, Chicago, IL; Susan B. Shurin, MD, Rainbow Babies and Children's Hospital, Cleveland, OH; Lawrence J. Sindel, MD, Pulmonary Associates of Mobile, Mobile, AL; John W. Sleasman, MD, University of Florida College of Medicine, Gainesville, FL; Paul M. Southern, MD, University of Texas Southwestern Medical Center, Dallas, TX; Philip J. Spagnuolo, MD, Metrohealth Medical Center, Cleveland, OH; E. Richard Stiehm, MD, UCLA Medical Center, Los Angeles, CA; James M. Tracy, DO, Omaha, NE; Dale T. Umetsu, MD, PhD, Stanford University Medical Center, Palo Alto, CA; Andrew H. Urbach, MD, Children's Hospital of Pittsburgh, Pittsburgh, PA; Richard L. Wasserman, MD, PhD, Dallas, TX; Leonard B. Weiner, MD, SUNY Health Science Center, Syracuse, NY; J. Gary Wheeler, MD, Arkansas Children's Hospital, Little Rock, AR; Jerry A. Winkelstein, MD, Johns Hopkins Hospital, Baltimore, MD; Betty B. Wray, MD, Medical College of Georgia, Augusta, GA; Anne B. Yates, MD, University of Mississippi Medical Center, Jackson, MS.

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