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We analyzed the data collected during a nationwide survey of cryptococcosis (1985–1993). We first checked the quality of the survey. The stability of its completeness (~50%) and its representativeness were assessed by the capture-recapture method after we cross-checked our data on cryptococcosis (as a presenting manifestation of AIDS) against those of the national registry of AIDS. Of the 1,057 cases of cryptococcosis (1,013 patients), 827 (86%) involved patients with AIDS. The increasing number of cases of human immunodeficiency virus (HIV)–related cryptococcosis over time paralleled the AIDS epidemic except for a higher male-to-female ratio. Malignancies (32%), organ transplantation (19%), and corticosteroid therapy (33%) were the main predisposing conditions in 163 patients without AIDS. Cryptococcal meningitis more frequently occurred in patients with AIDS than in HIV–negative patients ($P < 10^{-4}$). Among the 413 isolates available for serotyping, 410 were Cryptococcus neoformans variety neoformans (including 20.5% of serotype D). Three isolates of the variety gattii (serotype B) were recovered from patients without AIDS.

Cryptococcosis is caused by the encapsulated yeast Cryptococcus neoformans. Its main clinical feature is disseminated meningoencephalitis, which is still fatal in ~30% of cases despite antifungal therapy [1]. The major predisposing factors are cellular immune defects like those affecting patients with AIDS, with malignancies, or receiving corticosteroid or immunosuppressive therapy [2]. Important changes in the epidemiology of cryptococcosis have occurred since the beginning of the AIDS epidemic (as reviewed in [3]). Before the 1980s, only 300 cases were reported per year in the United States [2, 4]. Cryptococcosis is now the predominant cause of fatal fungal infection in patients with AIDS and ranks fourth among the CNS infections in these patients [5]. Extrapulmonary cryptococcosis is one of the AIDS-defining diseases [6].

The prevalence of cryptococcosis among patients infected with HIV varies from 2% to 10% in Western Europe [7, 8] and the United States [5, 9, 10] to >15% in some countries in Africa [11]. The percentage of cases of cryptococcosis attributable to coinfection with HIV is probably ~50%, but the precise figure is unknown [2]. Only a nationwide survey can provide data concerning the epidemiology of cryptococcosis, without the bias of a clinical trial.

In France, the National Reference Center for Mycoses (NRCM) has a role of expertise including the identification of unusual fungi, antifungal susceptibility testing, and therapeutic advice. In 1984 the increased number of cryptococcosis cases for which such testing or advice was sought (17 cases, vs. five in 1981) prompted the design of an epidemiologic survey of cryptococcosis. The cases collected from the beginning of 1985 to the end of 1993 were analyzed after the accuracy of the data collection was checked by the capture-recapture method (see the evaluation section).

Materials and Methods

Study Design

We retrospectively analyzed the cryptococcosis cases that were diagnosed in France from 1 January 1985 through 31 December 1993 and reported to the NRCM before 1 June 1994. The NRCM collected the data with the voluntary participation of clinicians and biologists. This passive system of collection was feasible because many of the participants were members of the French Society for Medical Mycology (Société Française de Mycologie Médicale) or members of the French Society for Infectious Diseases (Société de Pathologie Infectieuse de Langue Française). This allowed survey information to be disseminated at the annual meetings.

Requests for specific tests (cryptococcal antigen detection or antifungal susceptibility testing) or therapeutic advice provided an additional way for the NRCM to collect cases; questionnaires were sent to the biologists and treating physicians making such requests (semiactive system). Every year, each participant received a report on the cases recorded in the country during the previous year.

Case Definition

Only cases due to C. neoformans were analyzed. The yeast was identified as C. neoformans in each laboratory on the basis of a positive urease test, the absence of fermentation, appropriate carbon assimilations, and the presence of a capsule.
When identification was unclear, it was confirmed at the NRCM. Cases were considered to be cryptococcosis if they were diagnosed by culture of a specimen from any site, by antigen detection in CSF and/or serum, and/or by histology. Histologic examination was positive if encapsulated yeasts were observed in tissue sections after periodic acid–Schiff or Grocott-Gomori methenamine–silver nitrate staining. When a case was reported as a recurrence of cryptococcosis, it was not taken into account for the analysis unless it occurred >6 months after the previous episode or it was the first episode notified to the NRCM.

Serotyping of the Isolates

The participants were asked to mail each isolate together with the corresponding questionnaire. All the isolates were stored at 4°C in sterile distilled water. In 1992, a method combining diagnostic media and an immunofluorescence assay with a monoclonal antibody specific for cryptococcal polysaccharide [12] allowed the serotyping of the isolates on a routine basis [13]. Isolates stored at the NRCM before 1992 that were still viable were also serotyped. The individual results were sent back regularly to the laboratory of origin.

Questionnaire

Data were recorded by the treating physician and/or the biologist on the standard form and then mailed to the NRCM. The questionnaire was 1 page long and included administrative data (first three letters of the patient’s last name and first initial; patient’s sex and age; hospital ward; and city of diagnosis), epidemiologic data (ethnic origin, travel history, and risk factors for cryptococcosis), and clinical data (date of diagnosis, source(s) of culture-positive specimens, and positivity of antigen testing or histology). New variables were added in 1989 (exposure category for HIV infection, stage of the HIV disease, and initial antifungal therapy) and again in 1992 (CD4+ lymphocyte count at the time of the diagnosis of cryptococcosis).

Variables

For all the information specific to HIV-infected patients, we based our classifications on those established by the Centers for Disease Control and Prevention (CDC) in 1987 [6] and on variables used by the Réseau National de Santé Publique (RNSP), an organization responsible for collecting the AIDS case reports in France. Notification of the RNSP about AIDS cases has been mandatory in France since 1 June 1986.

Thus, five exposure categories were established: homosexuality/bisexuality, intravenous drug abuse, heterosexuality, contamination by blood or blood products (transfusion), and other (including combinations of the previous categories, mother-to-child contamination, and unknown risk factors).

Cryptococcosis was diagnosed in each case as an AIDS-defining illness (sometimes revealing the HIV infection) or later in the course of the HIV infection.

Ethnic origins were categorized as three groups, according to continents of origin: Europe, Africa (for North and Central Africa), and other (including North and South America, Caribbean Islands, and Asia).

Cases were classified as cryptococcal meningitis (with or without dissemination) or extrameningeal cryptococcosis. The cryptococcal meningitis cases involved culture- or antigen-positive CSF. Dissemination was defined by the culture-positivity of specimens from two or more sites.

Finally, France was divided into eight diagnostic regions, mainly on the basis of geographic and climatic differences. Since we did not know where the patients lived, we took into account the places where the diagnoses of cryptococcosis were made. These eight regions were the Mediterranean area, the Southwest, Paris and its suburbs (called Ile-de-France), the Center, the West, the North, the East, and Rhone-Alpes.

Evaluation of the Survey System by the Capture-Recapture Method

Because of the lack of other reference centers to evaluate the accuracy of the data obtained on cryptococcosis at the NRCM, we cross-checked our data on HIV-positive patients with those of the RNSP (where the national registry on AIDS—and thus on AIDS-defining illnesses—is kept). Extrapulmonary cryptococcosis can be reported to the RNSP if it is present at the time AIDS is diagnosed (within the first month). We used the capture-recapture method [14–16] to cross-check the data on patients diagnosed with AIDS and cryptococcosis between January 1989 and December 1992 (a delay in notifications to both systems prevented use of the data for 1993).

The capture-recapture method can be used (1) if the target population has an equal chance of being included in either of the systems, which means that the route of data collection should be different (a criterion fulfilled here) and the case definition should be identical (e.g., both cryptococcosis and AIDS-defining illness have the same definitions), and (2) if patients reported to both systems (doubly positive patients) can be unequivocally identified. Since the patients’ social security numbers were not available because of the confidentiality of the diagnosis of AIDS, we used the variables present in both questionnaires to identify the doubly positive patients (i.e., the initials of the last and first name, sex, age [±1 year], date of diagnosis [±1 month], and exposure category for HIV).

Knowing the number of patients notified to the NRCM \( R \) and to the RNSP \( S \), and identifying the number of doubly positive patients \( C \), we could calculate the number of patients notified only to the NRCM \( N1 \) or the RNSP \( N2 \) and use the following formulas to estimate

\[ N = \frac{(R + 1) \times (S + 1)}{(C + 1)} - 1; \]
by age or year of diagnosis) [14, 15].

...the independence of the survey systems (after stratification by age or year of diagnosis) [14, 15].

Statistical Analysis

Anonymity was preserved for the analysis, as requested by the Commission Nationale Informatique et Liberté. All the variables studied were entered, coded, and analyzed with Epi-Info software (version 5.0; CDC and World Health Organization, Geneva). In a small percentage of cases, no information was provided with regard to some variables. Unless this percentage exceeded 10%, the corresponding cases were excluded from analysis (this explains variations in the figures shown in the tables).

All cases were considered for the description of the disease itself, but only the first episode reported was taken into account for analysis of variables concerning the patients. Quantitative data were compared by means of analysis of variance, whereas qualitative data were compared with the Pearson’s χ² test or Fisher’s exact test. A difference was considered significant when the P value was < .05.

Results

Evaluation of the Quality of the Survey on Cryptococcosis

From 1989 to 1992, 384 cases of AIDS-defining extrapulmonary cryptococcosis were reported to the RNSP, whereas the NRCM collected 267 cases with the same definition. Identity (commonality) was found for 178 cases; when the cases were matched, a difference with regard to one variable was found for 14% of the cases (category of exposure [9 cases], age [8 cases], date of diagnosis [5 cases], or initials [2 cases]). Disagreement of two variables was noted for six patients.

By means of the capture-recapture method, the calculated number of cases of AIDS-defining cryptococcosis in HIV-infected patients in France was estimated to be 576 (95% CI, 558–594) (table 1). The overall completeness of the NRCM system was 46%, whereas that of the RNSP system reached 67%. Grouping of both databases allowed for identification of 82% of the estimated cases.

Stratification of the data according to the year of diagnosis or the age showed that the completeness of the NRCM system remained stable, although always less than that of the RNSP system. Concerning the representativity of the NRCM system, the observed distribution followed the expected distribution according to the year of diagnosis or the age of the patients. Independence of the systems was assessed by the lack of correlation between the notification rates per year of diagnosis, as calculated for both systems (data not shown).

Trends in the Occurrence of Cryptococcosis in France

Between 1985 and 1993, the NRCM recorded 1,057 cases of cryptococcosis from 119 different centers. More than 90% of the cases recorded in 1993 (compared to only 50% of the cases recorded in 1985) were reported through volunteer notifications; the remaining cases were collected through the semi-active system. The number of cases increased from 1985 until 1992 because of an increase in HIV-related cases (whereas the number of cases involving HIV-negative patients remained stable) (figure 1). In 1993, delayed reports accounted for the diminished number of cases. There was no marked seasonal change in the number of cases of cryptococcosis recorded (data not shown).

Cryptococcosis cases were recorded throughout the country but mostly in three regions: Île-de-France (56.7%), the Mediterranean area (13.4%), and the Southwest (10.8%). The other five regions accounted for ~15% of the AIDS cases and 18% of the overall cases of cryptococcosis in which the HIV status was known. The incidence of cryptococcosis varied around the country, from 0.03 to 0.94 per 100,000 people (figure 2).

Characteristics of the Patients with Cryptococcosis in France

The 1,057 cases of cryptococcosis involved 1,013 different patients (table 2). The factor predisposing to cryptococcosis was stated for 98% of the patients. The majority of the patients were young, white, HIV-infected males. The HIV-negative patients were significantly older than the patients with AIDS (mean age, 49 years vs. 36 years; P < .0001). There were only 8 cases involving children (<15 years old), of whom 5 were HIV-negative and 3 were HIV-positive.

There was a significant difference between HIV-positive and HIV-negative patients in terms of the number of females with cryptococcosis. The male-to-female ratio was more than four times higher for patients who had AIDS than for those who did not (8:1 vs. 1.7:1; P < .0001). It was still higher when only patients with AIDS who had been infected through heterosexual intercourse were considered (1:3.9), and among them the ratio was higher for white patients than for African patients (1:5.4 vs. 1:2.5). There was no difference in the percentage of patients from Europe and Africa who had AIDS (82% vs. 87%; NS).

Characteristics of the HIV-Infected Patients with Cryptococcosis

The majority (81.6%) of the patients with cryptococcosis had AIDS. The male-to-female ratios varied from 1:1 (for children and for adults >70 years of age) to a maximum of 11:1 (for adults aged 40–60 years). Five patients were receiving...
Table 1. Comparison of the data collected at the National Reference Center for Mycoses (NRCM) and the Réseau National de Santé Publique (RNSP, AIDS section) on cases of cryptococcosis occurring as AIDS-defining illnesses in HIV-infected patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>NRCM</th>
<th>RNSP</th>
<th>Common</th>
<th>Estimated no. of cases occurring</th>
<th>NRCM</th>
<th>RNSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>267</td>
<td>384</td>
<td>178</td>
<td>576</td>
<td>46</td>
<td>(43–49)</td>
</tr>
<tr>
<td>Per year of diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1989</td>
<td>37</td>
<td>70</td>
<td>29</td>
<td>89</td>
<td>42</td>
<td>(37–47)</td>
</tr>
<tr>
<td>1990</td>
<td>81</td>
<td>88</td>
<td>45</td>
<td>158</td>
<td>51</td>
<td>(45–59)</td>
</tr>
<tr>
<td>1991</td>
<td>78</td>
<td>109</td>
<td>53</td>
<td>160</td>
<td>49</td>
<td>(44–54)</td>
</tr>
<tr>
<td>1992</td>
<td>71</td>
<td>117</td>
<td>51</td>
<td>163</td>
<td>44</td>
<td>(39–49)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>570</td>
<td>47</td>
<td>(46–48)</td>
</tr>
<tr>
<td>Per patient’s age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–25</td>
<td>23</td>
<td>33</td>
<td>13</td>
<td>57</td>
<td>40</td>
<td>(32–54)</td>
</tr>
<tr>
<td>26–35</td>
<td>125</td>
<td>206</td>
<td>96</td>
<td>268</td>
<td>47</td>
<td>(43–50)</td>
</tr>
<tr>
<td>36–45</td>
<td>67</td>
<td>95</td>
<td>46</td>
<td>138</td>
<td>48</td>
<td>(44–55)</td>
</tr>
<tr>
<td>≧46</td>
<td>35</td>
<td>50</td>
<td>23</td>
<td>75</td>
<td>46</td>
<td>(39–56)</td>
</tr>
<tr>
<td>Unknown</td>
<td>27</td>
<td>0</td>
<td></td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>565</td>
<td>47</td>
<td>(44–50)</td>
</tr>
</tbody>
</table>

Corticosteroid therapy when cryptococcosis was diagnosed. The predominant categories for exposure to HIV infection were sexual orientation (55%) for men and iv drug abuse (27%) as well as sexual orientation (25%) for women (table 3). Heterosexual intercourse was the factor predisposing to HIV transmission for only 7% of the European patients, vs. 36% of the patients from Africa. Information on exposure was unavailable for almost one-fifth of the patients.

Cryptococcosis was diagnosed after the onset of AIDS for 52.3% of the patients and revealed the HIV infection for 14.3% of the patients. The CD4⁺ lymphocyte count at the time of diagnosis of cryptococcosis was available for 190 patients. The median CD4⁺ lymphocyte count was 26/mm³ (range, 0–230/mm³). Approximately 90% of the patients had <100 CD4⁺ lymphocytes/mm³.

Figure 1. Evolution of cryptococcosis during the 9-year survey in France (1985–1993). The total number of cases recorded at the National Reference Center for Mycoses and the numbers involving HIV-infected (HIV⁺) and HIV noninfected (HIV⁻) patients are shown.

Figure 2. Map of France showing the eight regions in which diagnoses of cryptococcosis were made during the survey (1985–1993): 1, Mediterranean area (population, 6.2 million); 2, Southwest (6.4 million); 3, Paris and suburbs, called Ille-de-France (10.6 million); 4, Center (5.4 million); 5, West (9.0 million); 6, North (6.1 million); 7, East (7.5 million); and 8, Rhônes-Alpes (5.9 million). The bold figures represent the number of AIDS/non-AIDS patients with cryptococcosis diagnosed in each region (for 23 patients, the HIV status was unknown); figures in parentheses show the incidence per 100,000 people in each region. We calculated the incidence rates by dividing the number of cases recorded in 1991 by the population of each region, estimated by the census in 1991 (an intermediate year in our survey).
Cryptococcosis was diagnosed by antigen detection alone in 2.4% of cases, and the liver in 1.3%. Rare sources of culture-positive specimens included bone (2 cases), feces (5 cases), and eyes (1 case).

Cryptococcal meningitis was more common in patients with AIDS than in HIV-negative patients (81% vs. 63%; \( P < 10^{-6} \)) (table 4). For patients with meningitis, the other culture-positive sites did not differ among HIV-positive and HIV-negative patients. Dissemination was noted in 16.5% of all patients. The extent of the workup (and thus of the extrameningeal involvement discovered) varied from one center of diagnosis to another (data not shown).

In cases of extrameningeal cryptococcosis, there was a significantly higher percentage of positive skin cultures for patients without AIDS than for patients with AIDS (30% vs. 5%; \( P < .0001 \)). Ten of the 18 patients with culture-positive skin lesions had no recognized predisposing conditions. Only 16 patients (7%) had a disseminated infection. Isolated cryptococcal pneumonia was noted in 14 patients without AIDS.

### Antifungal Treatment

Of the 787 cases recorded since 1989, data on the initial therapy prescribed were available for 727. Fewer than 5% of these cases (32 patients) were left untreated (mostly because of death at the time of diagnosis (21 of 24 patients with AIDS and 3 of 8 without AIDS)). Among the remaining 695 cases, the first antifungal agent prescribed was fluconazole for 63% of the patients with AIDS (vs. 52% for patients without AIDS; NS) (table 5). Amphotericin B plus flucytosine was more frequently administered to patients without AIDS than to patients with AIDS (56% vs. 37%; \( P < .04 \)). Antifungal therapy changed over time for patients with AIDS. Fluconazole was more prescribed as initial therapy in 1989 than in 1993 (84% vs. 54%). In parallel, use of amphotericin B increased from 16% in 1989 to 46% in 1993. Rarely prescribed were otherazole antifungal agents such as ketoconazole or itraconazole.

### Table 3. Exposure categories for HIV infection: distribution of HIV-infected patients with cryptococcosis diagnosed in France during the period of 1989–1993.

<table>
<thead>
<tr>
<th>Exposure category</th>
<th>Total (n = 642)</th>
<th>Males (n = 567)</th>
<th>Females (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homosexuality/bisexuality</td>
<td>41.7</td>
<td>47.3</td>
<td>...</td>
</tr>
<tr>
<td>Intravenous drug abuse</td>
<td>16.2</td>
<td>14.6</td>
<td>27.3</td>
</tr>
<tr>
<td>Heterosexuality</td>
<td>13.2</td>
<td>11.6</td>
<td>24.7</td>
</tr>
<tr>
<td>Transfusion</td>
<td>4.8</td>
<td>3.9</td>
<td>12.4</td>
</tr>
<tr>
<td>Other*</td>
<td>24.1</td>
<td>22.6</td>
<td>35.6</td>
</tr>
</tbody>
</table>

**NOTE.** The sex of some patients was not provided.

*Including combinations of the previous categories, mother-to-child contamination, and unknown risk factors.

*Calculated with use of \( n \) as denominator.

<table>
<thead>
<tr>
<th>Disease type</th>
<th>All cases of cryptococcosis (n = 1,057)</th>
<th>Patients with AIDS (n = 869)</th>
<th>Patients without AIDS (n = 165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptococcal meningitis</td>
<td>822 (78%)</td>
<td>704 (81%)</td>
<td>105 (63%)*</td>
</tr>
<tr>
<td>Percentage with involvement of RES1</td>
<td>29</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>Lung</td>
<td>15</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>16</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Skin</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Extrameningeal cryptococcosis</td>
<td>235 (22%)</td>
<td>165 (19%)</td>
<td>60 (37%)</td>
</tr>
<tr>
<td>Percentage with involvement of RES1</td>
<td>40</td>
<td>44</td>
<td>33</td>
</tr>
<tr>
<td>Lung</td>
<td>37</td>
<td>42</td>
<td>30</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>12</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Skin</td>
<td>11</td>
<td>5</td>
<td>30*</td>
</tr>
</tbody>
</table>

NOTE. Some cases had multiple sites of involvement, and some patients had more than one episode of cryptococcosis (thus, the number of cases is greater than the number of patients). RES = reticuloendothelial system.
* P < .0001, vs. patients with AIDS.
† As indicated by culture of specimens including blood (227), bone marrow (7), lymph nodes (14), and liver (10).
‡ As indicated by cultures of specimens including blood (81), bone marrow (4), lymph nodes (11), liver (4), and bone (2).

Serotypes of the Infecting Isolates

Isolates corresponding to 413 different patients were serotyped (the percentage of isolates serotyped increased over time, from 22% in 1990 to 87% in 1993). Three isolates were *C. neoformans* variety *gattii*, serotype B. All three were isolated from patients who did not have AIDS. Apart from the first patient, a man from Cambodia whose clinical history has been reported previously [20], the other two did not travel outside the country. The second patient sold exotic fruits [21]. The other one was a young girl who once owned a bird imported from Central Africa (Dr. C. Duhamel, Caen, personal communication).

The other 410 isolates were *C. neoformans* variety *neoformans*. The majority were of serotype A (79.5%), and the rest were of serotype D (20.5%). None of the isolates were of the A–D serotype and none were untypeable. A unique infecting serotype was detected when multiple isolates were serotyped for 47 different patients.

Table 5. Initial antifungal agent(s) used in the treatment of cryptococcosis in France since 1989.

<table>
<thead>
<tr>
<th>Agent(s) administered initially</th>
<th>All cases (n = 695)</th>
<th>Patients with AIDS (n = 619)</th>
<th>Patients without AIDS (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>135</td>
<td>123</td>
<td>12</td>
</tr>
<tr>
<td>Amphotericin B + fluconazole</td>
<td>88</td>
<td>73</td>
<td>15*</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>437</td>
<td>395</td>
<td>37</td>
</tr>
<tr>
<td>Miscellaneous†</td>
<td>35</td>
<td>28</td>
<td>7</td>
</tr>
</tbody>
</table>

* P < .04, vs. patients with AIDS.
† Including combinations (amphotericin B + fluconazole) or other azoles.

Discussion

Like cases of many other noncontagious diseases, cryptococcosis cases are not recorded unless a clinical trial is designed. To our knowledge, ours is the only country with an ongoing nationwide survey of cryptococcosis. Our survey is based mainly on a passive system of data collection (yielding ~90% of the cases), which could prevent some biases (e.g., overrepresentation of the most severe infections or of certain categories of patients) but have limited value for the description of cryptococcosis if the completeness or the representativity were unstable over time or too low. We thus decided to use the capture-recapture method [16] to assess the quality of our survey by cross-checking the data collected at the NRCM and in the national registry of AIDS with regard to cryptococcosis diagnosed as AIDS-defining illness. Both systems were independent, as suggested by different routes of data collection and as confirmed by the statistical analysis.

The completeness of the NRCM system was ~50%, a figure close to what has been associated with diseases recorded with mandatory notification systems [14]. The completeness of the RNSP system (67%) was surprisingly lower than what had been expected on the basis of the completeness of the AIDS survey itself (85% [22]). One explanation for this lower completeness value for the RNSP system could be that physicians may be more concerned about the notification of AIDS itself and may provide less accurate information on the AIDS-defining diseases. Relaxing the rules used to identify the patients notified to both systems increased the completeness values to 57% for the NRCM and 82% for the RNSP.

In any case, the representativity of the data collected at the NRCM was sufficient, since the observed distribution followed the expected distribution. The stability of the completeness
seemed also to warrant that the description of cryptococcosis will reflect the real trends, at least for HIV-infected patients with AIDS-defining cryptococcosis. There was no reason to think that cryptococcal infections occurring later during HIV infection would be reported differently. For HIV-negative patients, there was only indirect evidence that our data were reliable. The stability in the number of cases recorded each year at the NRCM has also been noted in Great Britain during the same period [7].

Between 1985 and 1993, 1,057 cases of cryptococcosis involving 1,013 different patients were recorded in France. The incidence of cryptococcosis per 100,000 people was higher in three regions (Paris and its suburbs, the Mediterranean area, and southwestern France), which follows the reported distribution of AIDS cases in the country [8]. There was no marked seasonal change in accordance with the proposed physiopathology of cryptococcosis [23].

The analysis of the risk factors clearly showed that HIV infection was the major underlying condition predisposing to cryptococcosis, accounting for >80% of the French cases. It was recently described as the predisposing illness for only 50% of 405 British cases diagnosed during the same period [7] and 53% of 171 Brazilian cases [24]. However, these studies differ in several respects. The Brazilian study describes the clinical features of cryptococcosis in that country and therefore used selected clinical records from a few centers [24]. In the British survey [7], the number of HIV-negative patients may be overestimated since the system of data collection is mainly semiautomatic.

However, differences in the number of patients coinfected with C. neoformans and HIV may also be explained by differences in the epidemiology of HIV infection. HIV infection has spread more in France than it has in the United Kingdom (30,000 AIDS cases in France vs. ~9,000 in the United Kingdom on 31 March 1994) [25].

Cryptococcosis was an AIDS-defining disease for almost half of the HIV-infected patients and revealed the HIV infection in 14% of them. Cryptococcosis also occurred in patients with advanced HIV infection (90% had <100 CD4+ lymphocytes/mm³). HIV-infected patients were mostly young, white, homosexual males, a profile reflecting the characteristics of patients with AIDS in France [8]. Although heterosexual intercourse is an increasing risk factor for HIV infection in Europe [25], it was a risk factor for only 7% of the European patients (as compared to more than a third of the African patients).

The frequency of cryptococcosis among patients with AIDS in France can be estimated on the basis of the number of cumulated cases of AIDS recorded at the RNSP and on the assumption that the calculated completeness is not dependent on the stage of HIV infection. It thus could reach 4.8% to 7.8% from 1989 to 1993, which would rank France at the same level as the United States [5, 26] but far below some regions of Africa [11] with regard to such a parameter.

We found that the male:female ratio was significantly higher among patients with cryptococcosis and AIDS than that reported for the total population of patients with AIDS (8:1 vs. 5:1) [8]. The predominance of cryptococcosis among males with AIDS has been emphasized in some reports [27, 28] but not others [29]. Among patients without AIDS, the number of males exceeded the number of females only by a factor of 2 [24, 30–32].

Cryptococcosis was rarely diagnosed in children and in the elderly. At these extreme ages, both sexes were equally infected. These findings could be explained by the influence of sex hormones in the development of cryptococcosis, although this has never been demonstrated for Cryptococcus species as it has been for other fungi [33].

The HIV-negative patients infected with C. neoformans were significantly older than the HIV-positive patients, as already noted [32]. The major risk factor for cryptococcosis was corticosteroid therapy (33% of patients). Some patients had no recognized underlying illness, but four patients had had contact with birds [34], and local traumas that could have favored cutaneous cryptococcosis affected nine patients. The factors predisposing to cryptococcosis in the HIV-negative French population were hematologic malignancies and solid cancers (32%), organ transplantation (19%), and other cellular immune defects (21%); 28% had no apparent predisposing factor. These data do not differ from those of previous reports on risk factors for cryptococcosis, dating from before the AIDS epidemic [30, 31, 35], except for the finding of idiopathic CD4 lymphocytopenia and a smaller percentage of patients without predisposing conditions.

The lack of well-defined procedures for diagnosis will limit our comments on the types of diseases recorded. There were indeed differences around the country in the number of positive cultures of specimens from body sites other than CSF and lung, but these were not apparently related to HIV status. Cryptococcal meningitis was significantly less frequent in HIV-negative patients than in patients with AIDS, a finding already noted in the aforementioned British report [7].

With regard to nonmeningeal cryptococcosis, the high incidence of skin lesions in HIV-negative patients (30%) has not been reported before (<10% in previous reports [2]). Although direct inoculation other than needlesticks [2, 36] has not been documented, we think that the relatively high number of reported injuries might explain this finding.

Fluconazole was given as primary treatment in 62% of the cases. However, prescription habits changed over time for patients with AIDS: there was a continuous decrease in fluconazole therapy from 1989 to 1993. The publication of guidelines for the treatment of cryptococcosis in patients with AIDS probably explains the trend [37, 38]. Since the study was not designed to compare the efficacy of regimens, we cannot comment on related modifications of clinical outcome for patients with AIDS; however, a comparison of the efficacy of amphotericin B and fluconazole for cryptococcosis in patients without AIDS in France has recently been undertaken [39].

Finally, the ability to serotype C. neoformans isolates on a routine basis at the NRCM proved helpful. Among the 413 clinical isolates of C. neoformans recovered from different
individuals, three were \textit{C. neoformans} variety \textit{gattii} and the remaining were of the variety \textit{neoformans}. Identification of serotype B isolates from patients living in Europe is uncommon. The clinical and travel history of the first patient, a native of Cambodia, might explain his infection with \textit{C. neoformans} variety \textit{gattii} [20], but the other two patients were French citizens who did not leave the country and for whom the most likely sources of contamination were exotic imports (fruits and a bird, respectively). For the \textit{C. neoformans} variety \textit{neoformans} isolates, we found that the majority (79.5%) were of serotype A and the remaining of serotype D, similar to earlier descriptions concerning a small number of isolates [40].

Our survey of cryptococcosis in France showed that HIV infection was the condition predisposing to cryptococcosis in >80% of the cases. However, it does not explain the higher susceptibility of male patients, especially those with AIDS, nor does it elucidate why the frequency of cryptococcosis varies so drastically around the world. Other studies should be designed to look for factors other than cellular immune defect that could explain the differences in susceptibility to cryptococcosis among HIV-infected and HIV-noninfected patients.

\section*{French Cryptococcosis Study Group}

This study group includes clinicians and microbiologists from various hospitals in France. The following members actively participated in data collection for our study: H. Chardon (Aix en Provence), H. Greze (Albi), M.-P. Hayette (Amiens), D. Chabasse (Angers), M. Martin (Angoulême), M. Pulik (Argenteuil), B. Hautefort (Arles), M. P. Le Pennec (Aulnay/Bois), J. Larfouilloux (Beaune), J.-P. Faller (Belfort), T. Barale (Besançon), C. Bouges-Michel (Bobigny), G. Delzang (Bondy), B. Couprie (Bordeaux), M.-E. Bougnoux (Boulogne/Billancourt), O. Masure (Brest), C. Lefort (Brive), C. Duhamel (Caen), C. Bidauld (Chalon/Saône), M. Zaegel (Chartres), C. Allard (Cherbourg), E. Laurens (Cholet), M. P. Le Pennec (Aulnay/Bois), I. Larfouilloux (Clichy), Y. Boussougant (Colombes), C. Chardon (Aix en Provence), A. Datry (Hopital de la Pitie-Salpetriere), V. Lavarde (Hopital Saint Louis), M. Arborio (Hopital du Val de Grâce), C. Demons (Hopital Lariboisière), P. Roux (Hopital Tenon), C. Chochillon (Hopital Bichat-Claude Bernard), A.-M. Deluol (Hopital Rotschild), J.-L. Poirat (Hopital Saint Antoine), J. Dupouy-Carnet (Hopital Cochin), and V. Blanc and D. Basset (Hôtel-Dieu).

\section*{References}


