Epidemiology of Aplastic Anemia in France: A Prospective Multicentric Study

By J.Y. Mary, E. Baumelou, M. Guiguet, and the French Cooperative Group for Epidemiological Study of Aplastic Anemia

Incidence rates of aplastic anemia (AA) are rare among defined populations. Since June, 1984, a cooperative group, including 83 University medical centers throughout metropolitan France, prospectively recorded new cases of AA and followed them up. Inclusion criteria were: at least two depressed blood cell lineages (hemoglobin \( \leq 10 \) g/100 mL and reticulocytes \( \leq 50 \times 10^9/L \), granulocytes \( \leq 1.5 \times 10^9/L \), platelets \( \leq 100 \times 10^9/L \)) and a bone marrow biopsy compatible with the disease. Between May, 1984, and April, 1987, 292 cases were recorded. After exclusion of constitutional disease, 27 patients did not satisfy the inclusion criteria with relation to either bone marrow or blood evaluations and seven patients were initially misdiagnosed (shown in the follow-up), leaving 250 confirmed AA cases in the register. The annual incidence in France appeared to be about 1.5 per million inhabitants. The sex ratio of AA cases was similar to that of the population. In men, two peaks of incidence were observed: one between 15 and 30 years and one after 60 years. In women, the only peak was observed after 60 years. An excess of cases was observed in small towns but not in rural areas. About two of every three cases had severe AA, with a possible excess in younger cases. Based on a minimum follow-up of 1 year for 238 patients, the fatality rate was estimated at 17% at 3 months after diagnosis and at 34% at 1 year. Among 243 suspected etiologies reported by the physicians, 74% were declared idiopathic. 13% presumably associated to drug toxicity, and 5% related to hepatitis. AA appears to be a rare and severe disease in metropolitan France, often of unknown origin, a fact that emphasizes the necessity of controlled etiologic studies.

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MATERIALS AND METHODS

Case ascertainment and follow-up. This study is a population-based study situated in all French metropolitan areas. Eighty-three medical centers covering the whole of France contributed to the survey for this cooperative study. These centers consisted of hematology, internal medicine, and pediatric units and hematology laboratories. Recruitment of cases, according to the time of diagnosis, began prospectively in May, 1984, and was performed in two steps. First, new cases were recorded by the responsible clinician in each center using a standardized registration form. At this step, the only criterion for the inclusion of a new case was the clinician’s diagnosis. Patients with neoplastic or granulomatous disease involving the bone marrow, cases presenting after chemotherapy or radiotherapy, and patients with splenomegaly, systemic lupus erythematosus, or other conditions masquerading as AA were not included by the clinicians at this step.

As soon as the registration form was received at the coordinating center, the information was verified. Apparently erroneous, suspicious, or missing data were returned to the clinic for confirmation or completion. At this step, particular attention was given by one of the study team members, a trained hematologist, to data that allowed further confirmation of the diagnosis. A follow-up form was sent by the coordinating center to the clinician 1 month after the diagnosis, and then every 6 months, in order to update patient status; ie, death, lost to follow-up, misdiagnosis, follow-up in the same center, transfer to another medical center. Information was collected about treatments, complications, and clinical status; ie, worsening, stabilization, improvement, or free of disease without any transfusion need. Finally, when the case interview had been performed by a trained interviewer or when the case had been withdrawn from the case-control study according to inclusion and exclusion criteria, information about suspected etiology of the disease was requested of the clinician, who was not aware of any interview results. A list of possible AA cases was provided by hematology laboratories, allowing the coordinating center to check for possible unregistered cases and to request information on those cases from clinicians.

In a second step, patients coming from abroad for disease treatment and those with constitutional disease were excluded. Registered cases were then identified for analysis according to the

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following criteria: at least two depressed blood cell lineages at the
time of diagnosis at distance of blood product transfusion; ie, (1)
hemoglobin value ≤10 g/100 mL with a reticulocyte count ≤50 ×
10^9/L, (2) polymorphonuclear count ≤1.5 × 10^9/L, (3) platelet
count ≤100 × 10^9/L, and a bone marrow biopsy specimen with
decreased cellularity compatible with the disease, showing no
significant fibrosis or neoplastic infiltration. By the end of this
process, the diagnosis had been confirmed. In the absence of a biopsy,
five cases were selected according to the course of the disease at
follow-up, that is, cases dying quickly after diagnosis. Two of these
cases were confirmed by postmortem examination of the bone
marrow. Severity of the disease at diagnosis was assessed using the
criteria of Camitta et al.1

Data presentation. The population under study was drawn from
the French national census of 1982 performed by the Institut
National des Statistiques et Etudes Economiques (INSEE). To
adjust for the increase of the population during the study period,
INSEE projections were used.20 Crude and stratum specific incidence
rates were calculated from these projections by age, sex, place
of residence (rural, ie, less than 2,000 inhabitants; 2,000 to 20,000;
20,000 to 100,000; more than 100,000 excluding Paris; and Paris and
its suburbs). The number of inhabitants in residence for each case
was determined using the INSEE dictionary of French cities.20 Data
were first presented as the number of cases distributed across the
different population strata under study, and specific incidence rates
were given to allow for direct standardization of these rates to any
given reference population. Second, they were expressed according
to sex, age, or place of residence through the ratio of the observed
number of cases to the corresponding expected number, assuming no
influence of the stratum on the incidence. This ratio of observed to
expected numbers, a method already used by other authors for
internal standardization of mortality rates,21 will be referred to as
stratum specific incidence ratio (stratum SIR) in this article.
Consequently, a stratum SIR of 1.5 indicates 50% more cases than
would be expected from the crude incidence rate and the French
census. Third, data were standardized either by age and sex on the
total French population19 or by age on the world standard population22
by using the direct method.23 Survival rates were calculated by
actuarial method24 using the 1-month period after diagnosis. The
minimum follow-up time was 1 year for all cases.

Statistical methods. Calculation of the confidence interval of
incidence rates was performed by using a normal approximation to a
Poisson distribution.25 Comparison between distributions within a
given strata was done through the χ^2 method, conceptually grouping
categories, when necessary due to the low expected frequencies (less
than 5). When the χ^2 test was significant for heterogeneity of the
specific incidence rates across a given stratum, a particular SIR at a
given level of the strata was tested by comparing the expected and
observed numbers of cases using a normal approximation to a
Poisson distribution.25

RESULTS

In April, 1988, there were 417 patients initially diagnosed
as AA cases in one of the participating centers and reported
to our registry. Among these patients, 324 were
diagnosed between May, 1984, and April, 1987. Of these, 74 were
excluded for the reasons indicated in Table 1. Notably, 10% were
patients coming from abroad for treatment of their
disease. Eight patients had a constitutional disease. Only one
patient had insufficient information to allow the confirmation
of the diagnosis, and 26 patients did not fulfill the inclusion
criteria at the second step. Seven were misdiagnosed, as
demonstrated during follow-up. Finally, 250 cases of AA
were confirmed.

Hematological presentation of AA cases at diagnosis,
before blood transfusion, is shown in Table 2. Most patients
were thrombocytopenic or neutropenic. When the presence
of both erythroid criteria were necessary for a case to be
declared erythropenic, 79% of the 235 evaluable cases were
erythropenic. Two thirds of these patients displayed an
impairment of the three medullary lineages.

The number of cases, according to the month of diagnosis,
is shown in Fig 1. The overall annual incidence of AA, based
on 250 confirmed cases, was estimated to be 1.51 per million
inhabitants (1.42 standardized on the age distribution of the
world standard population), allowing for a 95% confidence
interval (range of 1.32 to 1.70). This incidence appeared to
be relatively constant over time as crude incidence rates
(stANDARDIZED INCIDENCE RATES ON THE WORLD STANDARD POPULA-
TION) of 1.43 (1.38), 1.57 (1.47), and 1.51 (1.43) were ob-
erved during the first, second, and third year, respectively, of
the present study.

Table 3 shows the specific incidence rates according to age
and sex. The sex ratio was close to unity, overall and during
each year. The sex SIRs were 1.03 and 0.97 for males and
females, respectively (χ^2 = 0.272, P > .50). The age distribu-
tion of cases was clearly different from that of the French
census in males (χ^2 = 19.877, P < .001) and in females

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
<th>Criterium</th>
<th>Percentage of Cases Fulfilling Criterium (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/100 mL)</td>
<td>2.4-14.5</td>
<td>≥10</td>
<td>87 (250)</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>0-2.1</td>
<td>≤50</td>
<td>90 (233)</td>
</tr>
<tr>
<td>Polymorphonuclear count</td>
<td>0-2.1</td>
<td>≤50</td>
<td>94 (244)</td>
</tr>
<tr>
<td>Platelet count</td>
<td>0.3-4.0</td>
<td>≤100</td>
<td>99 (250)</td>
</tr>
</tbody>
</table>

Abbreviation: Hb, hemoglobin.
Among females, there was a sharp incidence peak above the age of 60, with twice as many cases as expected ($P < .001$, age SIRs of 1.98 over 60 and 2.30 over 70) and an antimode between 30 years and 44 years ($P < .01$, age SIR of 0.36). In males, two incidence peaks were observed: in the 15 years to 29 years and in the above 60-year-old age groups. There were about 50% more cases than expected ($P < .01$, age SIR of 1.53 and $P < .05$, age SIR of 1.40, respectively). The antimode was observed in the 30-year- to 59-year-old age group ($P < .01$, age SIR of 0.60). Globally, the age distribution by sex was stable over the 3-year period: in females ($x^2 = 3.082$, $P > .05$) and in males ($x^2 = 9.063$, $P = .003$). Nevertheless, this distribution appeared to be extremely variable in males, whereas the excess of cases was almost constant for females above the age of 60 (age SIRs of 1.98, 2.08, and 1.90 for each respective year). A trend was observed that restricted the peak in young adult males to the first year of the study (age SIRS of 2.30, 1.27, and 1.10 for each respective year).

The number of cases according to the number of inhabitants at their place of residence, shown in Table 4, did not follow the census distribution ($x^2 = 13.911$, $P < .01$). No excess was observed in rural areas (less than 2,000 inhabitants) that had an SIR of 0.81, but it was noted in small cities (2,000 to 20,000 inhabitants) that had an SIR of 1.52 ($P < .001$), a fact which was constant throughout the observation period (SIRs of 1.57, 1.50, and 1.48 for each respective year).

In the registry, about two thirds of the confirmed cases (163 of the 238 evaluable cases) were diagnosed as severe AA according to Camitta's criteria. Table 5 shows the relationship between age and severity of the disease. In males, there was an excess of severe cases (87%) in young patients (less than 15 years of age), while 44% of the cases were severe in the patients aged 30 to 44 years ($x^2 = 10.199$, $P < .05$). In females, although the same trend was observed, the relationship was not significant ($x^2 = 3.583$, $P > .40$).

The time elapsed since the evidence of the first symptoms until diagnosis varied from less than 1 month to several months. Almost half of the cases were diagnosed during the same month, and 86% within less than 3 months of the appearance of their initial symptoms. This delay was significantly shorter for younger patients (0 to 15 years, $P < .02$) and for severe cases ($P < .02$) when defined according to Camitta's criteria. A higher proportion of cases had a delay of less than 1 month in younger and severe patients.

All cases should have been followed-up for at least 1 year. Only one case was lost to follow-up just after diagnosis, and only five patients were followed for less than 1 year. Actuarial Age at Diagnosis (yrs) 0-14 15-29 30-44 45-59 60+ Total Males No. cases 24 46 16 13 27 126 Specific incidence rate ($\times 10^6$/yr) 1.34 2.38 0.91 0.96 2.18 1.56 Females No. cases 17 23 9 23 52 124 Specific incidence rate ($\times 10^6$/yr) 1.00 1.21 0.52 1.67 2.89 1.46

Table 4. Standardized Specific Incidence Rates of AA According to Size of Geographic Area of Residence

<table>
<thead>
<tr>
<th>No. Inhabitants of Place of Residence</th>
<th>Paris Area</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2,000 (Rural)</td>
<td>2,000-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20,000-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100,000-</td>
<td></td>
</tr>
<tr>
<td>2,000,000</td>
<td>40</td>
<td>250</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. cases</td>
<td>54</td>
<td>61</td>
</tr>
<tr>
<td>Specific incidence rate ($\times 10^6$/yr)</td>
<td>1.22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.35</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.45</td>
<td></td>
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<tr>
<td></td>
<td>1.56</td>
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</tbody>
</table>

Standardization by age and sex on the total French population.
Table 5. Distribution of New Cases of AA by Severity and Age per Sex

<table>
<thead>
<tr>
<th>Age at Diagnosis (yrs)</th>
<th>0-14</th>
<th>15-29</th>
<th>30-44</th>
<th>45-59</th>
<th>60+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>87 (23)</td>
<td>67 (43)</td>
<td>44 (16)</td>
<td>77 (13)</td>
<td>80 (25)</td>
<td>72 (120)</td>
</tr>
<tr>
<td>Females</td>
<td>73 (15)</td>
<td>56 (23)</td>
<td>44 (9)</td>
<td>65 (23)</td>
<td>71 (48)</td>
<td>65 (118)</td>
</tr>
</tbody>
</table>

Values are percent of severe cases; values in parentheses show number of evaluable cases according to criteria defined by Camitta et al.18

Fig 2. Actuarial survival rates after diagnosis are shown in Fig 2. Almost all deaths occurred during the first year after diagnosis, with a fatality rate of 17% during the first 3 months, 29% during the first 6 months, and 34% during the year after diagnosis.

The suspected etiology of the disease was reported by the clinicians in 243 cases (97% of the registered confirmed cases). About 74% of these cases of AA were declared idiopathic, and 13 cases (5%) were associated with hepatitis. Among the 32 cases in which a drug association was suspected, 6 were attributed to gold compounds and 1 to chloramphenicol. Twelve cases were declared to be related to a possible toxic exposure. Among the suspected miscellaneous etiologies, there were two cases associated with pregnancy. Interestingly, in one case, the disease regressed after delivery, but reappeared during the course of a new pregnancy.

DISCUSSION

During the first part of the survey in 1984 several meetings concerning the survey were organized by Professor Y. Najean and Dr E. Baumelou in the different French administrative regions with the participation of medical authorities and clinicians. The purpose of these meetings was not to register new cases of AA but to ensure widespread knowledge of the existence of the protocol throughout metropolitan France. Primarily for that reason, several cases were recorded by physicians who were not initially associated with the protocol. During the 3-year study period, the number of cooperative centers increased from 55 (from May to December, 1984) to 78 (from January, 1985, to July, 1986) and to 83 by the end of the study. Moreover, a few cases were reported to the coordinating center by clinicians who, while not participating in the protocol, were aware of it. Increasing the number of centers during the course of the study might affect the degree of completeness of the register over time. Indeed it might explain the lower incidence rate observed in the first year. The differences between the 3-year incidence rates were not significant, however, and were most likely due to random fluctuations.

The present study demonstrates several advantages over previous studies of the descriptive epidemiology of AA, as incidence rates were prospectively available for a well-defined population. Prospective identification of cases, with confirmation by follow-up of registered cases, is clearly more accurate than a retrospective search of cases through medical records and/or death certificates. The population under study was well-defined. Indeed, the probability that patients with AA had been referred to hospitals in other countries would appear minimal for two reasons. First, management of AA cases is standard and effective in France, particularly in the case of bone marrow transplant, where several units are available. Second, patient treatment in a foreign country would cause serious financial problems, due to the cost of the medical care in the absence of the French social insurance. Finally, as a consequence of the size of the population under study, many cases were accumulated, allowing derivation of accurate incidence rates according to age, sex, and size of place of residence.

Table 6 summarizes the previously published results for incidence rates of AA. Although these rates are not strictly
comparable due to the absence of age and sex standardization in most studies, a rough examination of incidence levels could be envisioned due to the absence of large differences in the age/sex structure of the populations studied. The crude incidence rate of AA in France is of the same order of magnitude of those published by the IAAAS for different European areas and Israel (0.6 to 2.8)\(^2\) and for the United Kingdom,\(^4\) but much lower than those previously published for the Uppsala area,\(^9\) Israel,\(^10\) the Baltimore area,\(^1\) three counties in South Carolina,\(^11\) the northern region of England,\(^12\) and the southern region of Buenos Aires.\(^13\) Some of these discrepancies could be accounted for by differences in diagnostic criteria. Most studies used similar criteria to define pancytopenia, some of these using leukopenia\(^10,13\) instead of neutropenia, but pancytopenia occasionally was not defined.\(^6,14\) In the older studies,\(^6,10\) no bone marrow cellularity was required for case definition, AA being solely defined as pancytopenia. In a recent study, a retrospective examination of 213 consecutive cases of pancytopenia observed in a hematology laboratory of a large hospital that includes most of the medical and surgical specialties (Hospital Henri Mondor, Créteil, France), was conducted. Only 10% of these pancytopenias could be ascribed to AA,\(^15\) whereas numerous pancytopenias were observed in patients with myelodysplastic syndromes, acute myeloid leukemia, acute myeloid disorders with myelofibrosis, acute lymphoblastic leukemia, lymphoproliferative disorders, or vitamin deficiencies. This rough estimate of 10% applied to data where the sole diagnostic criterium was pancytopenia\(^6,10\) results in an incidence rate of 1.3 and 2.5 for Sweden and of 0.8 for Israel, values of the same order of magnitude as our own incidence rate (1.5) and the incidence published by the IAAAS for Israel (1.6).\(^17\)

Clearly, some methodological problems arise from using retrospective studies,\(^6,9,11-13,15\) which lead to much higher incidence rates than prospective ones (references 14 and 17, this study). The high mortality rates published for AA in Japan\(^2\) and in the United States and Canada\(^1\) raise the problem of the proportion of those deaths attributed to AA that were actually due to AA. This problem has already been pointed out by the IAAAS.\(^17\) Wallerstein et al\(^6\) reported that only 60 cases could be confirmed among the 290 cases with death certificates. In the study conducted in the Baltimore area,\(^11\) incidence rates of 7.0 and 6.1 in men and women, respectively, decreased to 4.8 and 3.8 when cases reported by death certificate only were excluded. As demonstrated in this study, among 111 death certificates designated as aplastic anemia or pancytopenia, only 55% met the criteria of AA when case notes were examined. Uncontrolled mortality statistics could give only a very rough estimate of the true incidence of AA. A study is projected in France to assess the validity of AA death certificates in parallel with our registry.

Finally, these differences should be interpreted with caution, taking into account the number of registered cases in the different studies, which varied from 27\(^12\) to up to 250 (this study). For instance, data published by Seklo et al for males\(^11\) led to a 95% confidence interval of 5.0 to 9.0 for cases identified by medical records and/or death certificates and to 3.2 to 6.5 for cases identified by medical records. These large intervals stressed the importance of sample size on the accuracy of estimates.

We applied different criteria for diagnosis of aplastic anemia recently published in the literature\(^12,26\) to our data. Among the evaluable cases identified in our registry as AA, 98% and 94% were selected according to Camitta’s and IAAAS criteria, respectively. Among our rejected patients, those who did not fulfill our criteria or whose diagnosis was changed during the follow-up, 10 and 4 of the 28 were selected using the same criteria, respectively. This indicates that rather similar results would have been obtained when using these different criteria.

The sex ratio is close to unity, as already observed in all large studies for incidence\(^9,11,17\) and mortality\(^2,27\) rates. The excess of cases in elderly people has also been observed in numerous studies.\(^9,14,17\) For these cases, a greater excess in females than in males was also noted in Europe and Israel,\(^10,17\) contrary to the results noted in the American studies.\(^11,13\) Whether or not this discrepancy uncovers an actual difference between the United States and Europe remains unknown. A possible explanation could be random fluctuations, at least in small sample size studies.\(^12\) A peak incidence in young adult males was suggested by mortality rates\(^2\) and observed by the IAAAS,\(^17\) but this was at least partly explained by a cluster of cases in a military brigade in one area. This could well be the case in our study, since this
excess of cases in young males was not consistently observed throughout the 3-year period. Careful examination of these cases will be performed during the case control study, although no direct evidence of a cluster can be currently detected.

AA cases were not more frequent in rural areas than was expected from the French population distribution by place of residence. This is in contradiction with previous results obtained in France. Differences between the two studies are mainly methodological. The previous study was a retrospective study from a selected number of centers throughout France, which could well have led to a selection bias, whereas the present study is a prospective study on a well-defined population.

Two thirds of our cases were diagnosed as severe AA, according to Camitta's criteria. This proportion appears to be relatively high, although no comparison could be made on the basis of the literature. Nevertheless, it is entirely possible that some moderate or borderline cases were not reported to the coordinating center, due to a good prognosis and a low fatality rate. On the other hand, it is quite unlikely that severe cases could have escaped the registration procedure, especially young cases for whom bone marrow transplant is the first treatment of choice. Indeed, all French bone marrow transplant teams were associated with the study. No obvious difference in the severity of the disease was observed between males and females. Young patients appeared to be severely ill more frequently, with males possibly inclined to be more severely ill when compared with females. In a recent retrospective study of severe AA in young people (less than 15 years of age), an excess of males was observed. The corresponding crude incidence rate was 2.0 per 10^6 inhabitants per year in Denmark, when constitutional disease was excluded. The corresponding figure in our study was 1.0 per 10^6 inhabitants per year, taking into account the observed incidence and the proportions of severe cases in young people. These two estimates do not differ according to corresponding sample sizes (36 and 41, respectively).

Two indices of severity were compared, one used in the results section and a quantitative index proposed by Najean and Pecking. Using only two categories for the latter, as suggested by the authors (index lower than 50 for severe cases), we checked for the degree of agreement between these two ways of assessing severity of the disease. Surprisingly, a low agreement was observed (κ = .395, n = 197), while approximately the same proportion of severe cases was observed. Clearly, these differences stress the necessity of revising the definition of the severity of this disease. A recent attempt to define this severity has opened the problem for discussion, and our database will be used to address this issue in a future paper.

The fatality rate was estimated to be 34% and 39% at 1 year and 2 years, respectively; proportions lower than those recently published by IAAAS (49% at 2 years), by Davies (62% at 2 years), by Clausen for severe cases in Denmark (74% at 4 years), and by Gale et al (80% between 1 and 2 years after diagnosis). Clearly, in this last review, severe cases of AA were selected. The high fatality rate in the few months after diagnosis has already been quoted by different authors. No statistics were projected to study fatality rate according to age, due to the small sample size. Nevertheless, we observed a trend towards lower fatality rates for younger cases (less than 15 years old), as compared with the others. This could reflect the efficacy of bone marrow transplant in these patients.

As to the etiology of the disease, the proportion of declared idiopathic diseases in our registry is higher than some of those previously published and similar to others. It is clearly possible that the case control study in progress at the time of patient selection could have influenced the clinician's judgment in stating only rather obvious etiologies, even if both studies were carefully separated. No attempt was made to analyze the suspected etiology according to age, since it resulted in sample sizes that were too small.

In conclusion, aplastic anemia appears to be a rare disease in France, as compared with results noted in recent American studies. The importance of a biopsy to diagnose cases is, again, reinforced by this study, as is follow-up of identified cases to avoid misdiagnosis. In spite of the efforts in patient management, AA often remains a fatal disease, underlying the importance of epidemiologic studies of risk factors to diminish the occurrence of the disease.

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APPENDIX

Participants in the study (number of registered cases). Professor E. Glauckman, Hôpital Saint Louis, Paris (35); Professor F. Bauters, Hôpital Huriel, Lille (31); Dr E. Baumelou, Dr J. Rio, Hôtel Dieu, Paris (21); Professor H. Rochant, Dr M. Imbert, Hôpital Henri Mondor, Créteil (20); Professor A. Broustet, Dr J. L. Lenain, Hôpital du Haut Levêque, Pessac (19); Dr J. P. Pris, Hôpital Purpan, Toulouse (17); Professor J. L. Harousseau, Hôpital St. Jacques, Nantes (16); Professor J. P. Lamagnere, Centre Hospitalo-Universitaire Bretonneau, Tours (16); Professor J. J. Viaila, Hôpital E. Herriot, Lyon (15); Professor M. Navarro, Hôpital Lapeyronie, Montpellier (14); Professor F. Oberling, Dr B. Duclos, Dr P. Lutz, Hôpital de Hautepiere, Strasbourg (13); Professor O. Guerci, Dr A. Guerci, Hôpital de Brabois, Vandoeuvre (13); Professor J. Briere, Dr P. Jeffredo, Hôpital Augustin Morvan, Brest (12); Professor J. Bonhomme, Dr T. Petrella, Hôpital du Bocage, Dijon (10); Professor D. Holland, Dr M. F. Sotto, Centre Hospitalo-Universitaire Grenoble, La Tronche (10); Professor B. Varet, Dr F. Dreyfus, Hôpital Cochin, Paris (10); Professor P. Y. Le Prise, Hôpital de Pontchaillou, Rennes (9); Professor A. Najman, Dr J. P. Laporte, Dr M. P. Lemonnier, Hôpital Saint Antoine, Paris (7); Professor M. Leporrier, Centre Hospitalo-Universitaire Clémenceau, Caen (7); Dr B. Audhuy, Hôpital Louis Pasteur, Colmar (7); Dr G. Dine, Hôpital des Hauts-Côtes, Troyes (7); Professor Y. Carcassi, Professor J. A. Gauthier, Dr N. Tubiana, Institut Paoli Calmettes, Marseille (6); Dr A. Pesce, Hôpital de Cimiez, Nice (6); Professor J. L. Binet, Hôpital La Salpêtrière, Paris (6); Professor B. Desablens, Hôpital Amiens (5); Professor R. Leconte des Floris, Professor P. Hervé, Dr M. F. Leconte, Centre Hospitalier, Besançon (5); Dr J. M. Guillot, Hôpital des Enfants, Bordeaux (5); Professor G. Tchernia, Dr G. Tertian, Hôpital Antoine Beclère, Clamart (5); Professor F. Turpin, Dr M. Janvier, Centre René Huguenin, St. Cloud (5); Dr M. Bonnet,
Hôpital Trousseau, Paris (4); Professor H. Piquet, Centre Henri Becquerel, Rouen (4); Professor J. Delobel, Dr B. Pautard, Hôpital Nord, Amiens (3); Professor G. Malinvaud, Centre Hospitalier Régional, Limoges (4); Dr P. Travade, Dr A. Cavarz, Hôpital Dieu, Clermont Ferrand (4); Dr J.F. Schved, Centre Hospitalier-Universitaire, Nîmes (3); Dr P. Pasquier, Hôpital de la Croix St Simon, Paris (3); Professor C. Griselli, Hôpital Necker, Paris (3); Dr C. Gandhour, Centre Eugène Marquis, Rennes (3); Professor G. Schaison, Hôpital Saint Louis, Paris (3); Dr E. Baumelou, Hôpital Foch, Suresnes (3); Professor F. Freycon, Dr D. Frappaz, Hôpital Nord, St Priets en Jarez (3); Dr J. Jaubert, Hôpital Nord, St Priets en Jarez (2); Dr C. Martin, Centre Hospitalier, Annecy (2); Dr F. Lejeune, Dr G. Delzant, Dr M. Nathanhon, Hôpital Jean Verdier, Bondy (2); Professor J. Tanzer, Dr F. Guhilot, Dr B. Benz-Lemoine, Centre Hospitalier-Universitaire, Poitiers (2); Professor J.P. Dommeguez, Dr P. Danel, Hôpital de Bièvre, Kremlin Bièvre (2); Dr C. Allard, Hôpital de Meaux, Meaux (2); Dr J. Gardais, Centre Transfusion Sanguine, Angers (1); Professor A. Goguel, Professor B. Lagardère, Hôpital Ambroise Paré, Boulogne (1); Dr P. Solal, Hôpital Beaujon, Clichy (1); Professor F. de Pailleres, Hôpital Louis Mourier, Colombes (1); Dr M. Mougeot-Martín, Centre Hospitalier, Creil (1); Professor L. Degos, Hôpital Saint Louis, Paris (1); Dr P. Beauvais, Hôpital Trousseau, Paris (1); Dr Jolly, Centre Hospitalier, Reims (1); Dr A.M. Blaise, Hôpital Robert Debé, Reims (1); Dr E. Le Gall, Hôpital Soud, Rennes (1); Dr P. Morice, Centre Hospitalier, St Brieuc (1); Dr F. Beauvais, Centre Hospitalier Général, St Germain en Laye (1), Dr R. Gire, Centre Hospitalier Intercommunal, Villeneuve St Georges (1); Dr Guibe, Centre Hospitalier Médocal, St Lo (1); Dr M. Parat, Centre Hospitalier, Blois (0); Dr P. Cas assault, Hôpital Avicenne, Bobigny (0); Dr C. Debauchez, Hôpital Ste Camille, Bry sur Marne (0); Dr G. Hoerni-Simon, Fondation Bergonie, Bordeaux (0); Professor F. Teillet, Hôpital Louis Mourier, Colombes (0); Dr P. Veyssier, Dr D. Zyliberait, Centre Hospitalier, Compiègne (0); Dr J.L. Dutel, Centre Hospitalier, Dinan (0); Professor R. Moulias, Centre Hospitalier Charles Foix, Ivry (0); Dr P. Gruyer, Centre Hospitalier de Versailles, Le Chesnay (0); Dr J. Furoli, Centre Hospitalier, Mantes la Jolie (0); Dr F. Rumilly, Hôpital de Bonsecours, Metz (0); Dr A. Kessler, Centre Hospitalier Intercommunal, Montfermeil (0); Professor C. Lejeune, Dr J.C. Ropert, Centre Hospitalier, Neuilly sur Seine (0); Professor A. Bernadou, Hôpital Dieu, Paris (0); Professor M.M. Samama, Hôpital Dieu, Paris (0); Dr G. Boissinot, Hôpital International Université de Paris, Paris (0); Professor Y. Najean, Hôpital Saint Louis, Paris (0); Dr C. Audrion, Hôpital Laennec, Paris (0); Dr J.F. Bocara, Hôpital Saint Vincent de Paul, Paris (0); Dr M.J. Grange, Hôpital Lariboisière, Paris (0); Dr Laurens, Hôpital du Val de Grâce, Paris (0); Dr E. Neveux, Centre Hospitalier, Sèvre (0); Dr J.L. Ricome, Centre Hospitalier, St Germain en Laye (0).

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