Changing Epidemiological and Clinical Aspects of Imported Malaria in Belgium

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Background: In the early nineties the increase of imported malaria in some European countries was temporarily halted, but it resumed in 1994. More Africans, more European travelers, and fewer long-term residents were counted amongst patients. A shift towards more subacute disease has been noted. This study intends to assess whether the same trends were observed in Belgium.

Methods: Clinical and epidemiological data of 128 patients treated for malaria in 1997 at the Institute of Tropical Medicine and the University Hospital of Antwerp were compared with 209 malaria patients treated in 1988/1989. Risk factors for clinical presentation and parasitemia were analysed.

Results: In Belgium the number of reported imported malaria cases remained almost stable between 1988 and 1997. In 1997, there were more African patients, less infections from Central Africa, and 50% less residents. Less patients reported prophylaxis use. The causative agent shifted from *Plasmodium falciparum* to other species. Subacute and atypical malaria became less frequent. In both years, there were no deaths, and severe malaria did not increase significantly. Mefloquine disappeared almost as a curative treatment, and was replaced by quinine, with or without a long acting agent, or by halofantrine.

The ethnic origin, nor the use of chemoprophylaxis, influenced disease characteristics. In 1988, malaria attacks in the previous months predisposed to subacute disease; longer residence, and attacks in the previous months, protected against high parasitemia; longer symptom duration correlated with absence of fever, and with splenomegaly. None of these risk factors was correlated with severe malaria.

Conclusion: The incidence of subacute malaria dropped significantly in the last decade. Although this presentation is almost limited to residents, the decline in malaria can not be explained by an overall shorter duration of stay, since the decline in this particular clinical presentation of malaria was also spectacular in residents. Apparently, insufficient treatment of malaria attacks in the previous months is the only independent risk factor.

In the eighties, increased travel, and increased transmission and resistance of the parasite against prophylactic regimens, provoked a considerable increase in imported malaria in Western countries.[1–5]

This trend was also observed in Belgium: the Institute of Tropical Medicine, the Belgian national reference center, received 7 positive thick films for malaria in 1957, 5 in 1967, 12 in 1977, 229 in 1987, and 267 in 1997. Together with an increase in the number of cases of imported malaria, a shift towards more subacute disease has been noted.[6–8] From 1990 to 1993 a decline has been reported in Germany, France, Italy, Sweden, and Great Britain, but from 1994 a recrudescence is evident[9–12] (Fig. 1). A shift from Caucasians to Africans was noted.[11–14] In Belgium however, the number of cases has remained relatively stable since 1986, if we exclude the malaria cases imported from a peace-keeping military action in 1994.[4] The evolution of cases treated at the Institute of Tropical Medicine and the Department of Tropical Medicine of the University Hospital Antwerp, of the cases refereed by the reference laboratory in Antwerp, and of the cases reported to the National Institute of Epidemiology and Hygiene between 1987 and 1997 is shown in Figure 2.

Since 1990, our clinicians noticed a dramatic and continuous decline in the number of cases of subacute and atypical malaria, while total numbers of malaria remained stable. In order to explain this phenomenon, we compare in this study the incidence of imported

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J Travel Med 2001; 8:19–25.

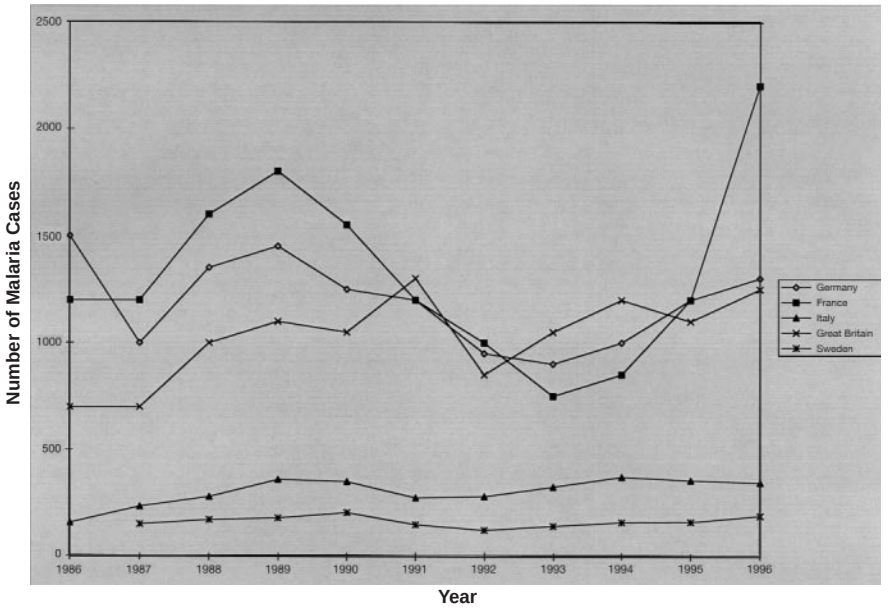

Figure 1 Evolution of the number of malaria cases in five European countries between 1986 and 1996.
For Italy, only Italian patients were counted, for Great Britain only falciparum cases. For Germany, numbers are given in cases/100,000 inhabitants, multiplied by 1000.
Data for Sweden were given by Dr. Johan Carlson from the Swedish Institute for Infectious Disease Control.

malaria, ethnic origin, visited countries, duration of stay, use of prophylaxis, symptom duration, relative frequency of species, parasitemia, and different treatment regimens between 1988 and 1997, and we analyse correlations between these possible risk factors and subacute, atypical, or severe presentation.

Material and Methods

We compared clinical data of all 128 patients with parasitologically proved imported malaria, who presented from January 1 to December 31, 1997 at the outpatient department of the Institute of Tropical Medicine, or at the ward of Tropical Medicine of the University Hospital of Antwerp, with an existing database of 209 consecutive malaria patients who presented from May 1, 1988 to December 1, 1989 (19 months). For 1988, two patients with concomitant acute hepatitis B were excluded, as their clinical features might have been biased.

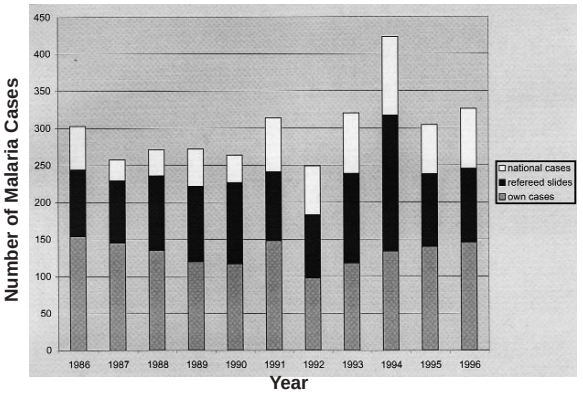

Figure 2 Evolution of the number of malaria patients at the Institute of Tropical Medicine, refereed slides (own cases and review for other centers) and all malaria cases reported to the National Institute of Hygiene and Epidemiology in Belgium 1986–1996.

For all patients suspected of malaria, at least 100 high power fields (10 × 100) of a thick film were examined. The diagnosis of malaria was made only if trophozoites were found. Cases with only gametocytes were excluded from the study.

Country and duration of residence, malaria chemoprophylaxis, previous malaria attacks and treatment, duration of symptoms at diagnosis, and disease characteristics were recorded.

Between 1988 and 1990, parasite resistance to chloroquine and other antimalarials was established or was emerging in most countries endemic for *P. falciparum*.[15] As adequate regimens for these countries (notwithstanding inherent toxicity) we considered mefloquine, chloroquine associated with proguanil, pyrimethamine with dapsone (Maloprim®) and pyrimethamine with sulfadoxine (Fansidar®). Chloroquine or pyrimethamine alone could not be considered as adequate prophylactic regimens. Regular prophylaxis was defined as taken regularly until 4 weeks after return.

Acute malaria was defined as malaria with symptoms for 7 days or less, subacute malaria when symptoms lasted more than 4 weeks. Atypical malaria was defined as symptomatic malaria without fever (but with nightsweats, headaches, fatigue, weight loss).

Anemia was defined as a hemoglobin level <10g/dL, thrombocytopenia as a thrombocyte count $<150x10^9$/L.

Splenomegaly was defined as a clinically palpable spleen, or a spleen with a maximal diameter of >14 cm

Table 1 Comparison between 1988 and 1997 of Epidemiology and Prophylaxis Intake of Patients Attending the Outpatient or the Emergency Department in Antwerp

	1988–89	*1997*	
General	*(%)*	*(%)*	*p Value*
Number of Cases	207	128	
Number of Cases/Year	130	128	NS
Sex Ratio M/F	2.1	2.4	NS
Median Age	34	34	NS
Ethnic Origin			
Caucasian	161/207 (78)	91/128 (71)	NS
African	35/207 (15)	33/128 (26)	.049
Other	11/207 (6)	4/128 (3)	NS
Country of Exposition			
Africa	196/203 (96)	116/128 (90)	NS
Central Africa	134/196 (68)	54/116 (46)	<.001
West Africa	53/196 (27)	44/116 (37)	NS
East Africa	7/196 (3)	16/116 (14)	.001
Southern Africa	2/196 (0.5)	2/116 (2)	NS
Asia	6/203 (3)	10/128 (8)	.04
Latin America	1/203 (0.5)	2/128 (1.6)	NS
Duration of Stay			
<1 Year	100/150 (66)	36/108 (33)	<.001
Prophylaxis			
Overall Prophylaxis Use	95/196 (48)	36/96 (37)	.01
Regular Prophylaxis / Prophylaxis Users	71/89 (79)	20/36 (55)	.005
Adequate Prophylaxis / Prophylaxis Users in Africa	42/91 (46)	29/35 (82)	.0001
Chloroquine (relative to overall intake)	38/87 (44)	4/36 (11)	
Chloroquine/Paludrin (relative to overall intake)	28/87 (32)	14/36 (39)	
Mefloquine (relative to overall intake)	5/87 (6)	15/36 (42)	

NS = not significant.

on abdominal ultrasound for adults. For children we relied on the interpretation of the radiologist.

Severe malaria was defined according to the WHO criteria.[16] For all patients, we recorded the results of the thick and the thin blood film, full blood cell count, lactate dehydrogenase, serum bilirubin and liver enzymes. For clinically suspected severe cases, all laboratory parameters for severe malaria were checked.

In 1988, the parasite load was determined as the number of trophozoites per high power field (10 × 100) in a thick film, the number of trophozoites per 100 fields in case of very low parasitemia, or the percentage of parasitised red blood cells in case of high parasitemia. In 1997, parasite load was given in parasites/μL, or in percentage of parasitised RBC for high parasitemias. For analysis, we first recalculated relative parasitemias to absolute. Further, with a conversion factor based on a sample of thick films read both per field and per μL, absolute parasitemias were recalculated to logarithmic classes corresponding to the 1988 reporting in parasites per field or per 100 fields.[17]

As dependent disease characteristics we consider a subacute or atypical presentation, the presence of splenomegaly, the disease severity, and hyperparasitemia. As risk factors we consider ethnic origin (Caucasian or other), duration of residence (less or more than 1 year), prophylaxis use (regular vs. irregular; regular and appropriate vs. irregular or inappropriate), history of presumed or proved malaria attacks in the months before presentation, and symptom duration (less or more than 8 days).

The chi-square test (EPI-INFO, WHO-CDC) was used for dichotomous variables, the Student's *t*-test for continuous variables, and the Kruskal-Wallis test for classes of parasitemia. Stepwise logistic regression (STATA, Stata corporation, Texas, USA) was used for risk factor analysis. Results of logistic regression are reported in odds ratios (OR) with confidence intervals (CI). We consider $p<.05$ as significant.

Results

Epidemiology

During the 19 month period in 1988/1989, 207 patients presented with a positive thick film, whereas during the 12 month period in 1997, 128 patients did (Table 1). The number of cases per year (130 vs. 128) and the sex ratio (2.1 vs. 2.4) did not differ significantly. The

Table 2 Comparison between 1988 and 1997 of Clinical Features of Patients Attending the Outpatient or the Emergency Department in Antwerp

	1988/89	*1997*	
Clinical Features	*(%)*	*(%)*	*p Value*
Symptoms > 1 week	76/181 (42)	30/118 (25)	.003
Subacute (> 4 weeks)	34/181 (19)	3/118 (2.5)	<.001
Atypical	34/202 (17)	12/126 (9)	.06
Splenomegaly	82/182 (45)	26/124 (21)	<.001
Hemoglobin <10 g/dL	17/206 (8)	8/125 (6)	NS
Thrombocyte count <150x10^9/L	124/187 (66)	75/120 (62)	NS
Hospitalization rate	105/207 (50)	42/128 (32)	.001
Severe cases	3/207 (1.5)	6/128 (5)	NS
Parasitology			
P. falciparum (vs. other species)	175/199 (87)	96/125 (76)	.03
Parasitemia< 1/ 100 fields	12/166 (7)	1/94 (1)	
Parasitemia 1-10/ 100 fields	23/166 (13)	6/94 (6)	
Parasitemia 10-100/ 100 fields	31/166 (18)	21/94 (22)	
Parasitemia 1-10/ field	51/166 (30)	30/94 (31)	.03
Parasitemia 10-100/ field	35/166 (21)	21/94 (22)	
Parasitemia > 100/field, <10%	10/166 (6)	14/94 (15)	
Parasitemia =or> 10%	4/166 (2)	1/94 (1)	
P. ovale	10/199 (5)	12/96 (10)	NS
P. vivax	13/199 (6)	10/96 (8)	NS
P.malariae	1/199 (0.5)	2/96 (1.6)	NS
Treatment of *P. falciparum*			
Chloroquine	1/172 (0.5)	0 (0)	
Mefloquine	106/172 (62)	1/95 (1)	<.001
Quinine (combined or not)	60/172 (35)	50/95 (53)	.004
Halofantrine	2/172 (1)	41/95 (43)	<.001
Artemether	0 (0)	2/95 (2)	

NS = not significant.

median age was the same (34 years). The study population remained predominantly Caucasian (78% vs. 71%), but there was a significant increase in Africans (15% to 26%).

The major part of the patients who presented in Antwerp with malaria returned from Africa, with a shift from Central Africa to West and East Africa. There were also more cases from Asia in 1997.

We noticed a significant drop in residents (stay>1year) vs. travelers: 66% of all patients stayed for more than 1 year in an endemic country in 1988/1989, only 33% did in 1997.

Chemoprophylaxis

Overall, fewer malaria patients took chemoprophylaxis in 1997, and of these, fewer reported regular use (see Table 1). This drop was due to significantly less use of prophylaxis in residents, while travelers remained on the same level. In 1988/1989, 40/88 residents used prophylaxis, in 1997, 3/29 (p<.001). In 1988/1989, 31/47 travelers used prophylaxis, in 1997, 30/57 (p=.16)

For exposition in Africa, adequate prophylaxis rose from 46% to 82%. As expected, the use of chloroquine dropped in 1997, compensated by a rise in the intake of mefloquine. Of mefloquine users in 1997, only two had *P. falciparum* infection with regular prophylaxis.

Considerably less Africans than Caucasians took prophylaxis in both study periods (1988/1989: 18% vs. 64%, p<.001; 1997: 7% vs. 51%, p<.001).

Disease Characteristics

Symptom duration before patients arrived at our outpatient or emergency department evolved significantly over time: in 1988/1989 many more patients had symptoms for more than 1 week than in 1997, and subacute malaria (> 4 weeks) was rather frequent in 1988/1989 but became rare in 1997 (19 vs. 2.5%, p<.001) (Table 2).

Atypical presentation decreased insignificantly from 17% in 1988/1989 to 9% in 1997 (p=.06).

Splenomegaly was twice as frequent in 1988/1989 than in 1997. It was more frequent in subacute disease

(p<.001). Frequency of anemia and thrombocytopenia remained at the same level, but anemia was more frequent in subacute malaria (p<.001).

There were no deaths, and cases that met the criteria for severe malaria remain rare.

Parasitology

P. falciparum remains the predominant species, but its relative frequency decreased significantly (87% vs. 75%) (see Table 2). All other species became more frequent, none of them presenting alone a significant increase. Within the *P. falciparum* parasitemias, there is a trend toward less very low parasitemias and more very high parasitemias. (Kruskal Wallis, p=.03).

Treatment

The hospitalization rate declined significantly (see Table 2). The use of halofantrine increased significantly, that of mefloquine dropped to almost zero. Only 2 patients were treated with artemether. Quinine alone or in combination again achieved first place.

In 1988/1989, 3 partial blood exchange transfusions were done, in 1997 only 1, although the number of severe cases increased from 3 (1.5%) to 6 (5%).

Risk Factors in *P. falciparum* Malaria

Subacute and atypical malaria were almost, and severe malaria completely, restricted to *P. falciparum* (32/36, 39/45, 9/9 respectively). Therefore, we limited the study of risk factors to *P. falciparum* malaria cases. As almost all *P. falciparum* cases came from Africa, the continent of infection could not be studied as a risk factor.

For 1997, no correlation could be found between risk factors and disease characteristics. For 1988/1989 multivariate analysis identified presumed or proved malaria crises in the last 6 months as the only independent risk factor for subacute malaria (OR 11.8, CI I2.9-47.4, p<.001). Symptom duration of more than 7 days was the only independent risk factor for symptomatic malaria without fever, and for splenomegaly (OR 11.08, CI 1.2-95.7, p=.029; OR 0.24, CI 0.09-0.53, p=.008). Residence of more than 1 year and previous attacks in the last 6 months were negatively correlated with high parasitemia (OR 0.22, CI 0.05-0.95, p=.043; OR computation impossible, given that no patients with a history of previous attacks had hyperparasitemia, p=.016). No correlation could be found between severe malaria and one of the risk factors.

Discussion

The Institute of Tropical Medicine and the department of Tropical Medicine of the University Hospital, Antwerp treated 44% of all reported malaria cases in Belgium for the 1986–1996 period (see Fig. 2). The laboratory of the Institute of Tropical Medicine refereed 79% of all cases in the same period. Notwithstanding underreporting, this study can be considered as fairly representative for imported malaria in Belgium.

Epidemiology

In Belgium, the temporary dip in malaria cases observed around 1992 in Germany, Italy, France, Sweden, and Great Britain was not observed (see Figs. 1 and 2). Up until now, there is no sound explanation for this temporary decrease. Perhaps, the introduction of mefloquine prophylaxis around 1990 had temporarily decreased imported malaria, whereas later the recognition of its toxicity favored other regimens.

The shift from Central Africa to other regions can be explained by political problems with Congo (ex-Zaire): Belgium suspended its aid and diplomatic relations after a bloody assault in Lubumbashi in 1990. This is in part responsible for the shift from residents to travelers, together with the world-wide decrease in long-term substitution.

Chemoprophylaxis

The drop in prophylaxis use in malaria patients might suggest that fewer travelers took prophylaxis: however, it is more probable that prophylaxis was more protective and that fewer travelers taking correct prophylaxis developed clinical malaria. It is evident that we lack the denominator.

It is remarkable that mefloquine use was so frequent in Belgian patients, comparing to French and British patients (42% vs. 6%, respectively 11%).[10,12] However, mefloquine use by travelers as measured on departure was 30% in a recent French study.[18] On the other hand, Belgian official prophylaxis counseling was almost not influenced by the negative reports about toxicity.[19] Do we face real mefloquine resistance, or might it be that break-through malaria in mefloquine users is frequently due to low serum concentration?[20]

Disease Characteristics

The three rather typical clinical features of malaria, splenomegaly, anemia, and thrombocytopenia have low sensitivity. Clinical diagnosis is almost impossible with such insensitive clinical features.[21] Only for subacute malaria are anemia and splenomegaly somewhat suggestive. Parasitology remains the cornerstone of diagnosis.

We hypothesised that the spectacular decline of subacute malaria could be explained by a lower proportion of residents, by a more frequent use of adequate prophylaxis, or by more correct treatment of malaria attacks. The proportion of residents declined, but the subacute presentation disappeared virtually also in residents. In

1997, the use of adequate prophylaxis was lower than in 1988/1989. Although details of treatment of malaria crises are too incomplete for analysis, the identification of malaria attacks in the previous 6 months as the only independent risk factor for subacute malaria suggests a predominant role of inappropriate treatment of presumed or proved malaria crises. In 1988/1989 the use of chloroquine alone as prophylaxis and as curative treatment was still widespread. Between the study periods, an intensive information campaign with oral and written instructions for malaria prophylaxis and treatment was set up for residents and travelers.

Splenomegaly became much less frequent. Only an association with symptom duration is present, and this might indeed explain the decrease of splenomegaly.

Lewis found more severe malaria, as defined by hyperparasitemia, cerebral malaria, or renal failure, in Caucasians as compared to patients of African origin.[22] Our study does not confirm this association, possibly because of the low number of severe cases, or because of the high proportion of residents in our study.

Steffen and Behrens found that delayed diagnosis was responsible for avoidable morbidity and mortality.[2] In the present study, symptom duration was not related to any of the severity parameters.

No association between overall, regular, or adequate chemoprophylaxis intake and duration, or presence of symptoms, or severity of disease, could be established, as described by Wetsteyn.[23] In our retrospective study only break-through malaria is recorded, whereas only prospective studies can assess accurately the efficacy of chemoprophylaxis. Further, patients might overreport chemoprophylaxis intake or regularity. Finally, symptoms could be attenuated by an incomplete effect of prophylactic medication, due to parasite resistance, causing a delay in disease manifestation, not affecting symptoms at presentation.

Parasitology

The shift from *P. falciparum* to other species can be explained by a shift in travel destination from Africa to Asia, and by more adequate prophylaxis, preventing *P. falciparum* malaria, but not affecting late attacks of other species.

The trend towards less very low *P. falciparum* parasitemias and more very high parasitemias could be correlated with the shift to less subacute malaria and less residents.

Treatment

Halofantrine and quinine took the place of mefloquine, which was abandoned as a curative treatment because of side effects. The hospitalization rate declined, but analysis of this phenomenon is biased by the fact that patients presenting at night at the emergency room are often hospitalized for convenience, not because of clinical severity.

In 1988/1989 the decision of exchange transfusion was often based on high parasitemia alone, whereas in 1997 clinical severity and parasite morphology was taken into account.[24]

Conclusion

In 1997 there were less residents, more Africans, and fewer patients taking prophylaxis than in 1988/1989. Subacute malaria was frequent and almost restricted to residents in 1988/1989 but virtually disappeared in 1997. We could not prove that it was provoked by inadequate prophylaxis, but we found a correlation with attacks in the previous months. The frequency of splenomegaly dropped considerably and was related to symptom duration. We saw less *P. falciparum*, with a shift towards more cases with high parasitemia. Our study could not show a prediction of disease severity or parasitemia by ethnic origin, or by prophylaxis intake. Mefloquine has replaced chloroquine as prophylaxis, halofantrine and quinine have replaced mefloquine as curative treatment.

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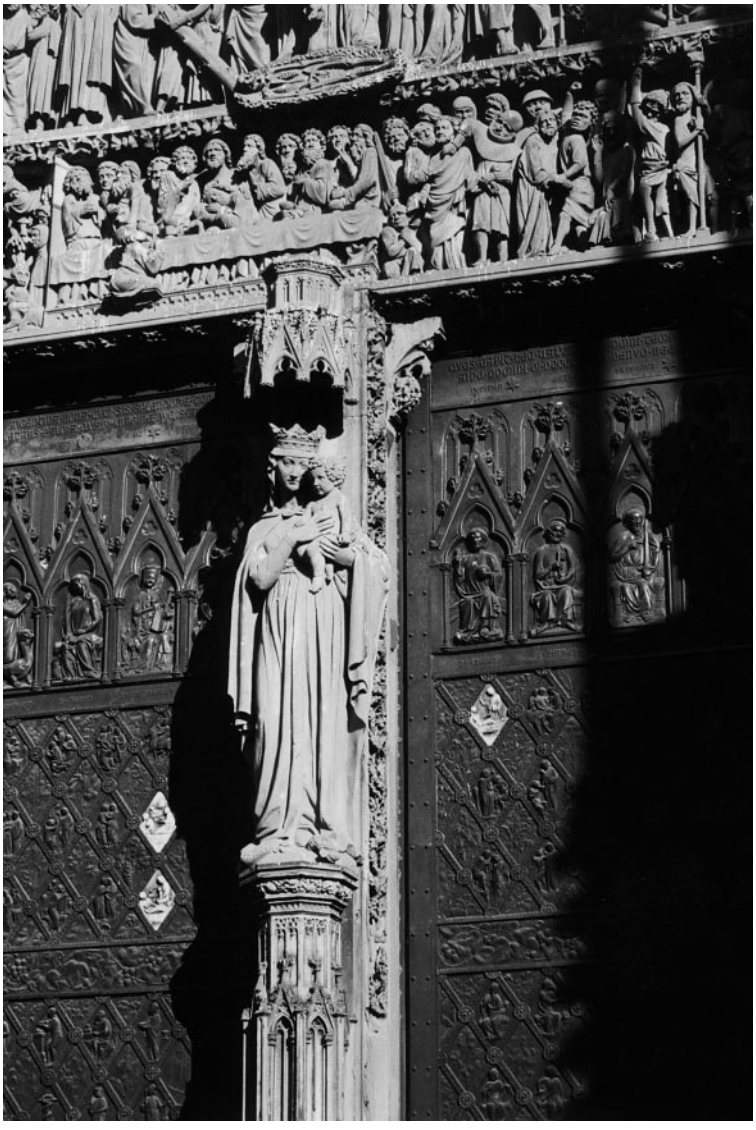

Details of cathedral, Strasbourg, France. Submitted by Charles D. Ericsson, MD.