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FORMER AB0 SELECTION THROUGH MALARIA IN NORTHWESTERN GERMANY

ABSTRACT: The evaluation of the data recorded by Richter (1941) for AB0 and MN in the region of the rivers Elbe and Weser show marked differences between Marsch (marsh) and the Geest (higher, sandy uplands) on the northwest German coast. Particularly the Marsch between the Elbe and Weser deviates with a low frequency of AB0*A and a high frequency of AB0*0. This suggests selection through the malaria epidemics of earlier centuries. The other serogenetic differences in the Elbe-Weser region reflect the migrational and marital contacts along the Elbe and within the remote Geest and Heide (heath) regions further inland.

KEY WORDS: Selection through malaria – AB0 System – MN System – North West Germany – Marsh

Human biology has been familiar with associations between blood groups and infectious diseases since the sixties. Studies on India showing the relative immunity of blood group 0 and the stronger susceptibility of A and AB for smallpox may serve as the classical examples (Bernhard 1966, Walter *et al.* 1991). Consequently the particular regions in India which have been struck by smallpox repeatedly demonstrate especially low AB0*A and high AB0*0 and AB0*B-frequencies (Walter *et al.* 1991).

Such observations have also been made in the case of malaria. Gupta and Raichowdhury (1980) found for 476 malaria patients in Delhi that blood group A was more frequent (29.0 %) and blood group 0 less frequent (22.2 %) than the healthy control group (n = 1300, A 17.6 %, 0 32.9 %, there is no difference with B and AB, total P = 0.0000024 %). A metaanalysis of all regional studies, including those of Europe up to 1986, shows an increase of the A frequency in the malaria infected by a third as compared to healthy individuals (relative incidence in relation to blood group 0 of 1.330, Singh *et al.* 1986). An association between blood group A and malaria, however, has not been found in all of the examined populations. A causal physiological mechanism might be a receptor preference of *Plasmodium falciparum* to the blood group

specific substance glycoprotein A, be this a direct or indirect association via rosette formation of erythrocytes (Barragan *et al.* 2000). Thus, according to Walter *et al.* (1991) "Individuals with blood group A have a higher possibility of being infected by malaria (...) than those individuals with blood group 0." This means in population genetics, that AB0*A had a selective disadvantage and AB0*0 a selective advantage. So in the gene pool of that population during the course of generations the AB0*A allele decreased, particularly to be noticed in regions rich in A, and the AB0*0 allele increased.

MALARIA IN THE NORTHWEST GERMAN MARSCH

Widely unknown today, there have been vast regions in central Europe in which malaria has been endemic or even epidemic in the past. Particularly swampy valleys and plains welcomed *Anopheles*, practically irrespective of the unpleasantly low average and winter temperatures. An example for such a strong affection is the Marsh region (English: marsh, plural: Marschen) on the northwest coast of Germany. These are moist, low, flat and very fertile areas

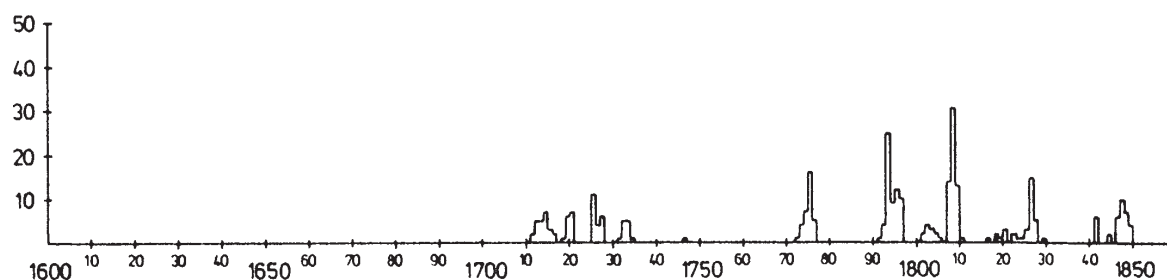


FIGURE 1. Death cause "high fever" in the parishes of Atens, Langwarden and Stollhamm on the western shore of the lower Weser river in the 18th and 19th centuries (in absolute numbers, from Norden 1984).

located directly at the coast, since a few centuries protected by dikes. The Marsh was known in the past for various epidemic and feverish diseases occurring especially during spring and late summer. In contrast, the Geest, the elevated and dry inland regions, had been spared from these haunting diseases. The "Marsh fever" was not recognized as a specific infection transferred by the *Anopheles* mosquito until the 1880s.

It is not known at which point of time malaria invaded the North Sea marshes, but we may assume at the moment that it was the middle of the 18th century. At least between 1770 and 1860 malaria led to a periodical considerable increase of mortality rates. Hinrichs (1992) termed them demographic "death crises". Solid references document malaria epidemics in 1806/07, 1825/26 and 1846/47 (Figure 1, Norden 1981). The disease appeared in its serious *Malaria tropica* form, as well as in the milder forms *M. tertiana* and *M. quartana*. This means in turn that the more important vector species (*Plasmodium falciparum*, *P. vivax*, *P. ovale* and *P. malaria*) were present (Martini 1938). The

milder forms often meant chronic health problems and subsequent diseases appearingly leading to death so that many malarial victims were registered under other ailments. During a hundred years, probably even much longer, there was no single generation living on the Marsh which was spared by human loss because of this fever epidemic. The affected Marschen were known as "fever marshes". However, since the second half of the 19th century better drainage techniques and hygiene measures effectively deteriorated the living conditions of the mosquito larvae (Hinrichs 1992), but the exact reasons for the extinction of *Anopheles* in the Marsh are still not clear (Knottnerus 1999).

Considering the impressive historical reports on malaria in the Marsh and the known associations between malaria and blood groups, this paper follows the question if among recent populations there are frequency deviations from the surrounding Geest and Heide (heath) which may be interpreted as serological traces of malaria induced selection. This is a contribution to historical epidemiology, a neighbour to recent and prehistoric epidemiologies.

TABLE 1. Frequencies of ABO and MN genotypes in the 16 regions of the Elbe-Weser-Area.

Region	AB0*A	AB0*B	AB0*0	MN*M	MN*N
Altes Land (Marsch)	0.27171	0.09032	0.63797	0.55140	0.44860
Kehdingen (Marsch)	0.25586	0.07781	0.66633	0.49554	0.50446
Hadeln (Marsch)	0.17362	0.06415	0.76223	0.47945	0.52055
Wesermünde (Marsch)	0.19625	0.06754	0.73621	0.43414	0.56586
Stade (Geest)	0.30269	0.08331	0.61400	0.56869	0.43131
Hadeln (Geest)	0.23062	0.03931	0.73007	0.68681	0.31319
Wesermünde (Geest)	0.31465	0.06810	0.61725	0.52977	0.47023
Cuxhaven (Geest)	0.30168	0.08026	0.61806	0.55810	0.44190
Bremervörde (Geest)	0.30258	0.06181	0.63561	0.57687	0.42313
Harburg (Geest)	0.34338	0.02893	0.62769	0.51225	0.48775
Rotenburg (Heide)	0.34066	0.07968	0.57966	0.59625	0.40375
Verden (Heide)	0.30500	0.06651	0.62849	0.53535	0.46465
Osterholz (Heide)	0.27183	0.06635	0.66182	0.60087	0.39913
Lüneburg (Heide)	0.26917	0.07432	0.65651	0.53253	0.46747
Dannenberg (Heide)	0.25669	0.10691	0.63640	0.55624	0.44376
Uelzen (Heide)	0.33730	0.06521	0.59749	0.57376	0.42624

MATERIAL AND METHOD

This objective demanded data from the region between the river mouths of Weser and Elbe. The materials of Richter (1941) are geographically well subdivided. He does not only include Marsh and Geest regions, but Heide regions as well. Heide (heath land), a sparsely forested grassland induced by intensively tending sheep, is located further inland; there is no essential geographical distinction to the Geest, but ecology and economy are different.

Richter's material includes frequencies for AB0 and MN for 3,662 patients and blood donors from 16 regions (political districts) of the Elbe-Weser coast region (Table 1). Richter did not pass on the individual numbers of the single regions. Their average is 229, so that even if a single number might be considerably smaller, it should be large enough for statistical and epidemiological assessment. In contrast to current surveys, the great advantage of this ancient material is the recording of data before 1945, it means that the population was largely autochthonous. After World War II and the large migrations of the immediate post-war years the established rural population received large contingents of refugees from the former eastern parts of Germany and from minority settlements in eastern Europe. Moreover, the increasing mobility of more recent decades again modified the anthropological and genetic characters of the population.

As a distance measure for the regions Hiernaux's (1965) method was used, which is based on the variable ranges as the dispersion measure, followed by a cluster analysis (average linkage). All five alleles of the two serological systems are weighted equally in this algorithm. The differences between the clusters are assessed for significance by the χ^2 test.

RESULTS

Essentially the dendrogram (Figure 2) shows two clusters. The much larger one is made up of two subclusters: The first subcluster (1a) includes the four districts (German: Kreise; singular Kreis) bordering the Elbe: Kehdingen, Altes Land, Lüneburg and Dannenberg. The former two belong to the Marsch and the latter two to the Heide. The larger second sub-cluster (1b) consists of almost all the Geest and Heide regions located in the interior. The Hamburg suburb of Harburg belongs to the first main cluster, but in isolation and with a great distance to both subclusters. The second main cluster (2) is clearly separated from the other one; it consists of only two districts, Hadeln and Wesermünde, located in the extreme northwest of the region studied. The city of Cuxhaven separates the two districts, it belongs to the interior cluster and is located on a Geest ridge that directly borders the coast. Finally, the

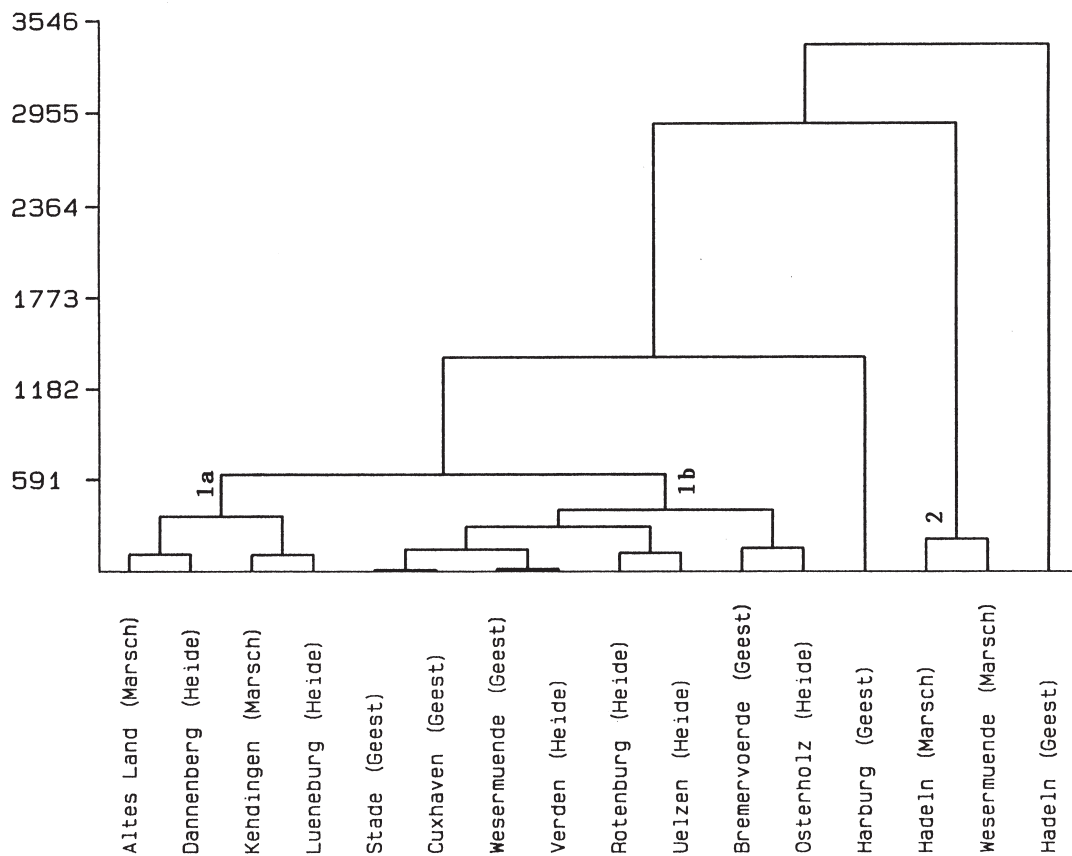


FIGURE 2. Dendrogram of the serogenetic distances in the Elbe-Weser region (AB0 and MN).

district Hadeln-Geest, also called Börde Lamstedt, a particular part of the Geest, is completely isolated. It does not have any similarity connections to other regions.

DISCUSSION

The historical population structure

The Elbe cluster (1a) comprises the regions which are connected by the traffic artery of the river (*Figure 3*). Obviously, traffic connections have also meant genealogical and marital relationships during the last centuries. Even though there is some relation to the neighbouring coastal Marschen (less AB0*A and MN*M in particular in Kehdingen), stronger ties exist to the regions of Lüneburg and Dannenberg located further upstream, the Marschen of the lower Elbe. The district of Dannenberg is also part of the Elbe cluster, although it differs from all other regions through a high AB0*B frequency. Dannenberg is part of the Hannoversche Wendland that was the farthest western extension of the Slavonic settlement in central Europe during the early Middle Ages. In this particular region Slavonic dialect was spoken up to the 18th century. The higher frequency of blood group B as in eastern Europe may be the consequence of this Slavonic history.

The Geest cluster (1b) is the consequence of common history and marital contacts of the more remote and poorer regions of the interior regions. There was also a social distance separating the poorer regions of the Geest from

the wealthier regions of the Marsh. The separate position of the Hamburg suburb of Harburg might have been caused by the influence of the close and large city which should have led to a less autochthonous population. The completely isolated position of the Börde Lamstedt (Hadeln-Geest) corresponds to its character of a Geest island enclosed by Marsh and moor; it might also turn out to be a genealogical isolate.

The findings mean a weaker historical depth of the simply inherited blood groups as compared to polygenic morphology, as has also been confirmed by the conclusions of the later survey of Westphalia. This is rooted in a susceptibility of blood markers to genetic drift and disease selection. The more recent population historic dynamics reflected by serology can be traced back to territorial boundaries and traffic relationships of the 16th to the 19th centuries (Schwidetzky *et al.* 1964, Schwidetzky, Walter 1967).

Finally the main cluster 2 comprises both coastal Marschen, Hadeln-Marsch as well as Wesermünde-Marsch; Kehdingen and Altes Land are river Marschen. Thus both main clusters mean a clear serologic difference between the (coastal) Marsh and the Geest.

Selection through malaria

The Marsh cluster is characterized by comparably very low AB0*A and high AB0*0 frequencies, moreover by a rare MN*M. The river Marschen Kehdingen and Altes Land belong to the Elbe cluster and occupy an intermediate

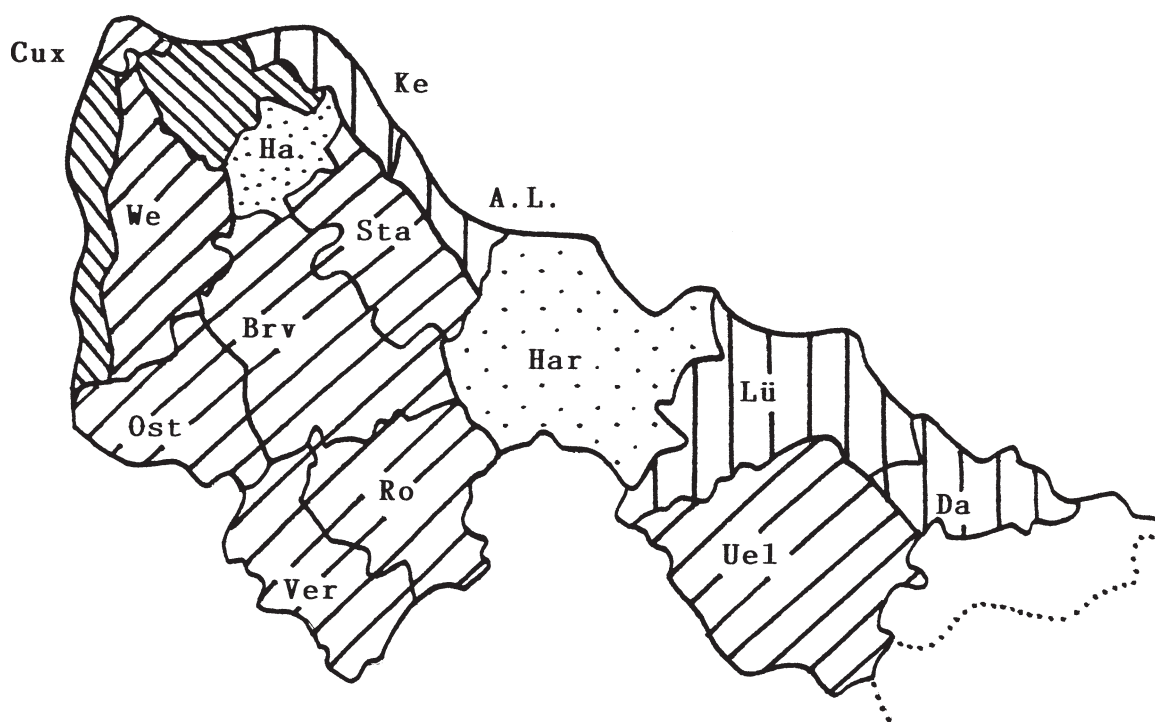


FIGURE 3. Map of the cluster structure of the dendrogram. Cux=Cuxhaven, We=Wesermünde, Ha=Hadeln, Ke=Kehdingen, A.L.=Altes Land, Sta=Stade, Brv=Bremervörde, Ost=Osterholz, Ro=Rotenburg, Ver=Verden, Har=Harburg, Lü=Lüneburg, Uel=Uelzen, Da=Danneberg. Wesermünde and Hadeln are divided into two regions (Marsh and Geest).

position between the coastal Marsh and the Geest clusters (Table 1). Between the coastal Marsh and the regions located further to the interior the differences of ABO* A and ABO* 0 can be as much as 15 percent. With the cautious assumption of 150 individuals per region the ABO system differences between the coastal Marsh cluster (2) and the Geest cluster (1b) are highly significant in the χ^2 test (P=0.0046%).

Consequently the Marsh shows the same serological characteristics as they are known in typical malaria infested regions. Thus it is suggested that selection through malaria against blood group A has taken place.

The order of magnitude of the selection acting upon this former population may be assessed using historical data. According to Hermann Allmers (1902), in the northern Marsh of the Elbe-Weser region "in some times (...) only one fifth of the population could be regarded to be healthy"; moreover, there was a high mortality rate (Norden 1981). This should mean a much higher selection rate than in Africa or for other diseases (maybe except for plague in the 14th century in central Europe). Around 4 to 5 generations were successively infected, which is a very short active time. Still it may have been sufficient to effect the recent population differences in ABO frequencies.

The historic sources also explain local differentiations. Allmers (1902) reports that particularly the northern Marsh or the Elbe-Weser region had been affected: "The river Marschen, e.g. Osterstade, the Land Wühdren, the Land Stedingen and the Stadland, the Alte Land and the Land Kehdingen are incomparably healthier and have been struck less frequently by the above mentioned diseases." So it was mostly the coastal Marsch which had been affected by high fever and which today displays the serological characteristics of malaria.

Thus the present distribution of ABO blood group alleles corresponds well to the 18th and 19th centuries differential distribution of malaria in the Elbe-Weser region. Even if a geographic and historic argument is by principle open to alternatives and thus is not an ultimate proof, it is in this case the most plausible explanation for the observed massive frequency differentiations within an otherwise rather small and open country. Now serological, immunological and molecular biological surveys of the Marschen would be desirable for a support of the malaria hypothesis. They might include further malaria relevant serological systems in the living population (Fy, Hp, Tf, CP, ACPI, G-6-PD, Walter 1998) and DNA systems in skeletons of the 18th and 19th centuries.

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