ABO Blood Groups and Cholera: An Investigation of an Infectious Disease as an Agent of Natural Selection.

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Abstract: In a 1949 landmark paper Haldane proposed that infectious diseases may act as agents of natural selection. Apart from the well-established link between sickle-cell anaemia and malaria, direct evidence for the selective effect of infectious disease is scarce. There is some evidence to suggest that blood group O individuals may be more susceptible than individuals from other blood groups to life-threatening cholera infections. Cholera is endemic to the Ganges River Delta in India, a region whose current population appears to represent the lowest global frequency of the O allele. Using a model proposed by Svanborg-Eden and Levin (1991) as the framework of investigation, this paper evaluates the evidence for cholera operating as an agent of natural selection in the Ganges River Delta. This model proposes a series of six conditions that must be met in order to accept an infectious disease-mediated selective effect. All six conditions could not be satisfied by the existing evidence, and it is therefore concluded that cholera cannot be accepted as further evidence of infectious diseases acting as agents of natural selection in human populations.

Introduction

One of the objectives of anthropological research is to seek explanations for human diversity through the investigation of evolutionary mechanisms such as genetic drift, founder effect, and natural selection. There is considerable controversy over which mechanism is the most important determinant of human variability. Random genetic drift and founder effect result when small populations grow and stabilize original, fortuitous genetic characters. Natural selection results when genetic variability leads to differences in reproductive fitness. This in turn is dependent upon locally determined features of the environment. These "locally determined features" are the agents of selection, however, their identification has been problematic (Weiss and Chakraborty 1982). Haldane, in his landmark 1949 paper, suggested that infectious diseases may act as powerful agents of selection. He argued first of all, that variability in host resistance to infection is inherited, and secondly, that pathogens adapt to the most common host genotype. The most common host genotype therefore becomes most susceptible to the pathogen. As a result, the rare host genotype is more resistant to pathogenic insult and more likely to survive and reproduce. Over time the rare genotype will become more common and the pathogen will then become adapted to the new common type. What is initially a common genotype eventually becomes the more resistant rare genotype. The net result of this negative frequency dependent natural selection is predicted to be a balance of diversity within a population (Jones and Harvey 1987). Diversity between

populations is explained as local adaptation of populations to different pathogens, which favour different host genotypes.

This argument for infectious diseases as agents of natural selection seems plausible enough, but what is the selective mechanism? Antigenic sharing between the host and the pathogen has been proposed (Damian 1964). In short, the pathogen mimics the most commonly occurring biochemical surface properties of cells in a host population. As a result, the host is unable to fully recognize the pathogen as non-self and therefore fails to mount an adequate immune response. This is the susceptible host. The resistant host is antigenically different from the susceptible host and therefore also the pathogen, and consequently is able to recognize the pathogen as non-self and mount an immune response. The advantage of individual variability in antigen type to members of the host population is apparent. Any new mutation in an individual host that allows it to mount a more effective immune response will favour its survival and reproduction. The resulting increase in frequency of the new mutation in the population will continue until it exerts selective pressure on the pathogen to circumvent the immune response. Conversely, any new mutation in a pathogen that allows it to circumvent the host immune response will rise in frequency in the pathogen population until the selective pressure becomes great enough to promote the spread of genes for new immune defenses in the host (Jones and Harvey 1987).

It is the purpose of this paper to evaluate the empirical evidence for ABO blood group-mediated resistance or susceptibility to cholera with the focus on the potential for cholera to act as an agent of natural selection.

Infectious Disease and Variability in ABO Blood Group Frequency

As early as 1914, it was recognized that there are inter- and intra-populational differences in the frequency of ABO blood types (Hirszfeld and Hirszfeld 1919). Since that time, a number of researchers have collected blood group frequency data from many populations. This data was first compiled in a single volume in 1954 (Mourant) and revised in 1976 (Mourant *et al.*). On the basis of this data, Mourant produced maps of the global distribution of ABO allele frequencies that illustrate their global variability. ABO blood group-mediated resistance or susceptibility to infectious disease has been posited as an explanation for this distribution (see for example: Mourant 1954; Springer and Wiener 1962; Pettenkofer *et al.* 1962). Apart from the well-worn sickle cell-malaria association, direct evidence for the selective effect of infectious disease is appallingly scarce (Livingstone 1980). It has been suggested, however, that cholera has acted as an agent of selection in India, producing what the Mourant compilation indicates is the lowest global frequency of the O allele.

Blood Group Activity in Bacteria

Studies have shown that bacteria react to human blood group antibodies A, B, and O(H) in a group-specific manner. Some bacteria, for example, react most strongly to antibody A, and others to either antibody B or O(H); but none react strongly to all three (Springer *et al.* 1961). This evidence suggests that they possess surface antigens similar in nature to those present on the surface of human blood cells. It is therefore con-

ceivable that natural antibody response may be variable among human ABO blood groups. It has been suggested that Vibrio cholerae carries an H-like antigen (Vogel *et al.* 1960), which is most common in human blood group O.

Cholera

Cholera is a dehydration disease that can be fatal within one or two days. The bacterial agent responsible, *Vibrio cholerae*, is transmitted through faecally-contaminated water or food. Once ingested the bacteria undergoes rapid reproduction in the lumen of the small intestine. It produces a toxin that binds to the epithelial cells of the small intestine, which regulate electrolyte balance and water absorption (Holmgren *et al.* 1975). The toxin causes tremendous and rapid water transfer from the cells of the body to the lumen of the small intestine, the result of which is protracted diarrhea and vomiting. In this manner the cholera bacteria are transmitted back into the environment where they are available to re-infect another host. In cases of severe fluid loss, the host will die without medical intervention. Since the pathogenesis of cholera involves interaction between intestinal cells, *V. cholerae*, and the enterotoxin it produces, it has been hypothesized that genetic differences expressed as surface antigens on intestinal cells may account for variability in host response to cholera infection (Levine *et al.* 1979).

Evaluating the Evidence: Cholera Case Study

The preceding discussion has been largely theoretical in nature. Mourant's compilation of ABO allele frequency data indicates global variability in the ABO blood system, with the lowest global frequency of the O allele occurring in India. Research has further suggested that the surface antigens present on human cells are also present in bacteria and, more specifically, that *V. cholerae* may possess surface antigen H. If resistance or susceptibility to cholera occurs as a result of antigenic mimicry, then the most susceptible hosts will be those with a high proportion of antigen H on their cells. These are the blood group O individuals. Are blood group O individuals more susceptible to cholera and, if so, is there evidence to suggest a selective effect? The significance of differential susceptibility to initial infection, to severity of the clinical disease, and most importantly, to mortality or fertility, must be considered in evaluating the potential for a selective pressure strong enough to account for the frequency of ABO alleles in India.

Svanborg-Eden and Levin (1990) have proposed a series of six conditions for the evaluation of disease-mediated natural selection. In the following section the evidence for cholera as an agent of natural selection is evaluated using these conditions as the framework of analysis.

Svanborg-Eden and Levin Criteria

1. The population encounters the infectious agent continuously or at frequent intervals.

In order for an infectious agent to exert the kind of selective pressure that is suggested by Haldane and others, it has to have been present long enough to affect many

reproductive generations. There have been seven global pandemics of cholera identified since 1817. The first of these is believed to have originated in India where it spread, as a result of British colonial activities to other parts of the world. There is, however, some debate as to the origin and antiquity of cholera (van Heyningen and Seal 1983). The term "cholera" has been in use since Hippocratic times (2400 years ago), however, it has been used to describe any number of gastrointestinal irritations of unknown origin (Howard-Jones 1974). It is, nevertheless, commonly believed to be endemic to India, and in particular to the delta of the Ganges River. The Ganges Valley is a region of dense population with poor sanitation and a large surface area of water. It has a warm climate with high humidity. These are all conditions that contribute to the maintenance of cholera as a major endemic disease (van Heyningen and Seal 1983). In a review of clinical descriptions of disease, Pollitzer (1959) has identified what he believes to be references to cholera in ancient Sanskrit writings. He also suggests that the religious rites invoked to ward off epidemics of the disease indicate long-term endemicity of cholera. The reality, as Howard-Jones suggests (1974), is that it is difficult to diagnose, particularly from incomplete references in ancient writings, exactly what the infectious agent responsible for the diarrheal illness described may have been.

Another question to consider is how long a disease must be endemic, or how often a population must encounter it, to cause an observable change in gene frequencies. The answer must be considered in terms of environmental context. In a hypothetical situation cholera can be considered as the sole selective factor operating and the answer may be easier to attain. In reality, there are a host of environmental factors that must be considered yet are impossible to control for in human populations. Any number of these may be selecting for blood group O, even as cholera may be exerting selective pressure against blood group O. It has been suggested, for example, that the blood group O infant is at an advantage in the maternal environment (several studies are cited in Mourant *et al.* 1978:24) or that individuals carrying the A allele are more susceptible to smallpox; which was also believed to be endemic to India (Vogel and Chakravaratti 1977). For cholera to exert a detectable selective influence it must be a more powerful selective agent than other factors and be endemic for a period of time longer than it is possible to demonstrate, even with vague references from historical records. Clearly, it is not possible to confidently satisfy this condition for the demonstration of cholera as an agent of natural selection.

2. There is inherited variation in susceptibility to disease within populations.

A considerable amount of research has been devoted to the investigation of a genetic component to resistance or susceptibility to cholera. In 1977 the first evidence of an association between blood type O and individuals with cholera and other cholera-type diarrheal diseases (where the causative agent could not be isolated) in hospital cases in the Philippines was published (Barua and Paguio 1977). At the same time another study in India reported similar results (Chaudhuri 1977). In both cases, the distribution of blood groups between affected individuals in a hospital setting were compared with the blood group distributions in ethnically comparable local populations. Sample sizes were too small to be significant (n=120 and n=200, respectively) and it was concluded that further studies were required to explore the possibility that individuals of blood type O are more susceptible to cholera and possibly other diarrheal diseases.

One problem with these earlier studies is the inability to control for the influence of environmental factors such as variability in colonization (i.e. dose of cholera each individual ingested in order to produce diarrheal response). To address this issue Levine and co-workers (1979) conducted a controlled study in which volunteers were given identical doses of *V. cholerae*. While the focus of their study was to examine the relationship between severity of cholera and HLA antigens, they also considered ABO blood type and severity of cholera. HLA antigens were found in similar frequency in all individuals, however, blood group O was found more frequently in individuals with severe cholera than in controls. In 1981, a study comparing blood type frequency in 210 hospital cases of cholera with 148 controls found a statistically significant higher percentage of blood type O in the cholera cases (Sircar *et al.* 1981). They cautiously concluded that individuals with blood type O are "probably more susceptible" to cholera attacks than other groups. The most definitive exploration of the association between blood type and severity of cholera was carried out by Glass and colleagues (1985). They assessed the relation of ABO blood type not only to cholera but also to other diarrheal infections. Previous studies suggested a possible link between blood type O and severity of diarrhea, but not strictly as a result of cholera infection. The Glass study examined the relationship between ABO blood groups and diarrheal illnesses associated with rotavirus, shigellae, pathogenic strains of *E. coli* and *V. cholerae* in Bangladesh. The ABO blood group was determined for 1346 patients, 682 of whom had a diarrheal illness that could be associated with a specific pathogen. The non-diarrheal patients served as controls. While patients with *V. cholerae* infection were twice as likely as the controls to belong to blood group O, there were no significant differences in the distribution of blood groups among patients infected with other enteric pathogens and their control group. This result is especially interesting for *E. coli*, since it has a similar pathogenic mechanism to cholera and might therefore be expected to show similar blood group variability.

The results of these studies do suggest a unique association between blood group and susceptibility to cholera. It is not possible to say with certainty, however, whether the identified association is really a direct result of biochemical differences inherited through the ABO blood system, or whether, as some studies have suggested, other inherited mechanisms play a role (see Chaudhuri and DasAdhikary 1978, for the possible role of other blood group substances; and Sack *et al.* 1972, for the effects of gastric acid secretion).

In order to properly understand this association it is necessary to determine the biochemical basis for it. One of the earliest studies, conducted by Finkelstein and colleagues (1965), found no significant differences in immune response to cholera, either artificially or naturally-induced, between individuals from blood types A, B, O, and AB. Their study, however, included a total of only 92 individuals. As such their results should be considered preliminary at best. More recent studies have attempted to address this issue. Results suggest that blood group O individuals are predisposed to severe cholera because they lack a compound (a mucous-like substance has been suggested) with the antigenic properties of blood groups A and/or B (Bennun *et al.* 1989; and Monferran *et al.* 1990). These antigenically characterized compounds are able to bind with cholera toxin, preventing it from binding to membrane receptors, consequently mediating the severity of the diarrheal response.

To conclude, there does not appear to be any inherited susceptibility to cholera infection *per se*, but there does appear to be inherited susceptibility to the severity of cholera. Further research is required on the biochemical basis for the differences in severity in order to state with certainty that the genetically inherited variation is based on ABO blood group.

3. This inherited variation is determined by one gene or a few major genes acting alone or collectively in a largely additive manner.

If, as the evidence suggests, the inherited variability of susceptibility to cholera is correlated to ABO blood groups, then this third condition is easily satisfied. ABO blood groups are inherited through multiple alleles at one gene locus. The A and B alleles are dominant to the O allele, but co-dominant to each other in a Mendelian mode of inheritance. These three allelomorphic genes, A, B, and O, are characterized by the presence of antigens on the surface of the red blood cell and other tissue cells such as intestinal epithelial cells (Race and Sanger 1975). This is significant since intestinal epithelial cells provide the binding site for *V. cholerae* and the enterotoxin responsible for producing fluid loss. Types A and B give rise to antigens A and B, respectively, on cell surfaces while type O does not give rise to any antigen unique to itself (Mourant *et al.* 1978). All three types produce an H substance precursor on the surface of the red blood cell, which in blood type O produces H antigen and in blood types A , B, or AB produces the respective antigen as well as antigen H. The H antigen is variable between the blood groups, with group O producing the strongest antigen-antibody response (Race and Sanger 1975). This is potentially significant support for the antigenic mimicry hypothesis since, as stated earlier, it has been suggested that *V. cholerae* also has an H-type antigen.

4. There is relatively little non-genetic (environmental) contribution to variation in the likelihood or magnitude of infection or the physiological response to it.

This condition is difficult to evaluate in human populations. Even if there have been no appreciable geographical or climatic changes to the Ganges Delta in thousands of years, "environmental variability" in human populations may be introduced by other factors. These may include, for example, age/sex related division of labour, or socioeconomic status, that may place one individual or group of individuals at higher risk of encountering a pathogen. Because cholera is transmitted through contaminated food and water, individuals at greater risk are those with limited access to sanitation. Most often these will be the individuals in lower socioeconomic strata (Chaudhuri and De 1977). In order to control for some of these variables in the investigation of inherited susceptibility to cholera, Glass and colleagues (1985) conducted a study of family contacts of cholera patients treated in hospital in Bangladesh. Of 2086 family members contacted, 565 family members became colonized with *V. cholerae*, 266 of whom developed diarrhea. There were no significant blood group differences between individuals who became infected and those who did not, however, more of those who developed severe diarrhea were blood group O. This of course provides further evidence that there is an inherited susceptibility to cholera, but there is no satisfactory resolution to the question of environmental contribution to variability in cholera infection.

What were the differences between the 565 contacts who did develop *V. cholerae* infection and the 1521 who did not? Since they were all family contacts it may be safe to assume there were few socioeconomic differences; however, age, sex, behaviour, occupation, and health must also be considered. Age- and sex-specific domestic activities may, for example, place some individuals at higher risk of exposure to *V. cholerae*. Further, individuals in a family may have differential access to nutritious food, potentially resulting in differences in health status between individuals. Differences in health status may result in variability in immune response to infection. The significance of these culturally-mediated factors must be carefully considered before suggesting a predominantly genetic component to cholera susceptibility.

5. Variation in susceptibility to disease is manifest prior to the termination of reproduction.

In order for a selective effect to be manifest, individuals must be affected prior to termination of reproduction, such that susceptible individuals are either less likely to reach reproductive age, or their reproductive output is decreased. By the age of 15, children in the Ganges Delta region of India have been calculated to be at a 6.0 percent risk of severe cholera and at a 3.0 percent risk of death from cholera (Glass *et al.* 1985). The Glass study further calculated that the risk for children of blood type O is twofold greater. Risks for other age groups were not reported. These numbers nonetheless suggest the potential for culling of individuals with blood type O from successive generations of children, prior to their reaching reproductive age. It is, however, important to note that the values derived for children at high risk for cholera morbidity and mortality in the Glass study were based on a sample of hospitalized children. It is problematic to infer that this sample is an accurate representation of the actual population at risk.

6. There are differences in the rate of mortality and/or fertility among susceptible and resistant individuals.

While data on differential fertility are not available, there do appear to be blood group-mediated differences in the morbidity rate of individuals with cholera. Although blood type O individuals are not believed to be any more susceptible to infection by *V. cholerae*, studies have suggested that they are more likely to suffer from severe diarrhea (e.g., Glass *et al.* 1985; Sircar *et al.* 1981; and Levine *et al.* 1979). As a result, in the absence of medical intervention. the mortality rate for cholera among individuals with blood type O may be higher than that for other blood groups. This certainly may have been the case in the past and it may still be apparent among cholera victims without access to medical care. The studies published to date are comprised of individuals who do have access to hospitals and it is difficult to assess how representative of the population as a whole such samples might be. As a result, even though an association between cholera morbidity and blood group is posited to occur, a direct link with differential mortality and/or fertility has not been established.

Discussion

The compilation of global ABO allele frequencies produced by Mourant and colleagues (1976) indicates that the lowest global frequency of the O allele occurs in India. There

is evidence to suggest that blood type O individuals are significantly more susceptible to severe diarrhea in response to cholera infection than all other blood types. It has been suggested that cholera is endemic to India. This apparent correlation between variability in susceptibility to cholera on the basis of ABO blood group with the low frequency of the O allele in India has been cited as possible evidence of natural selection.

On the basis of the criterion suggested by Svanborg-Eden and Levin (1990) it becomes clear that it is not yet possible to accept cholera as a potential agent of natural selection. While it appears that there may be a genetic component to resistance or susceptibility to cholera, it is not yet clear just what that component may be. It is true that a correlation appears to exist between ABO blood group and severity of cholera but, until the mechanism is understood, a causal relationship cannot be established. The recent results of Monferran and colleagues (1990) as well as Bennun and colleagues (1989) suggest that the mechanism may not be antigenic mimicry but, rather, differences in the biochemical behaviour of cells in the intestinal lumen based on the presence or absence of surface antigens. Blood type O individuals may be susceptible because they do not have the characteristic antigens that inhibit binding of the cholera toxin to the epithelial cells, not because the H antigen present on the cells of O individuals may also be present on *V. cholerae*.

It is also not yet possible to negate the environmental contribution to variation in susceptibility that may be introduced by cultural or behavioural elements. Further, it is not known how representative the hospital-based studies of the population of the Ganges Delta are. These are just a few of the difficulties encountered in establishing a genetic component to resistance or susceptibility to cholera.

What are the implications for natural selection? First of all, it cannot be stated definitively that cholera has been endemic to India for a long enough period of time to exert a detectable selective effect, especially when other potential agents of selection are considered. Smallpox is just one example of another disease believed to be endemic to India; individuals carrying the A allele are believed to be more susceptible to smallpox, rather than the O allele implicated in cholera susceptibility.

Secondly, even if it were possible to demonstrate without a doubt that there is a highly significant correlation between blood group O and cholera, it is important to consider that this represents the situation today. In order to detect natural selection, genotype and/or phenotype should be determined over several generations. The proposed global distribution of the ABO alleles must, first of all, be carefully scrutinized. How accurate a reflection are they of the populations they purport to represent? It is important to consider that the blood group data was collected by a large number of individuals over the course of this century. Differences in sampling procedures by data collectors, or small non-representative sample sizes, are just two factors that may have introduced significant bias. Even if the modern data could be considered representative, it is not possible to reconstruct past blood group frequencies of populations in the Ganges Delta in order to assess change in the frequency of blood group O. The temporal depth required to represent enough human generations to reflect selective pressures is inaccessible. More importantly, even if an association between ABO blood type and differential susceptibility to severity of cholera does exist, in order to actually argue for a selective effect, differential mortality and/or fertility must be demonstrated to occur as

a direct result. The sample sizes required to mathematically define even large selective differences is beyond the scope of most studies, as is so eloquently demonstrated by Barrett (1990). He suggests, for example, that to detect a relatively large difference in survival rate (on the order of 10%) requires sample sizes of between 2,500 and 10,000, depending upon the frequency of phenotypes!

Throughout this discussion the effect of possible changes in *V. cholerae* have not been considered. Since 1960 a new strain of *V. cholerae* has supplanted the Classical biotype. The El Tor strain is believed to be less virulent than the Classical strain responsible for the six previous pandemics. Rather than producing acute diarrhea, El Tor produces a more chronic condition in the host. It is also able to survive longer outside the human host (van Heyningen and Seal 1983). Studies have shown that the El Tor biotype has further evolved in recent years (Karaolis *et al.* 1994). Reduced morbidity will result in decreased mortality which, of course, has significant implications for the role of *V. cholerae* in natural selection. Infectious disease-mediated selection requires that no significant changes in virulence independent of genetic resistance or susceptibility of the host occurs. This is clearly not the case now and there is no reason to believe it was any different in the past.

Conclusions

At this time there is not enough evidence to suggest that the current frequency of O blood type in India is a result of the selective effect of endemic cholera. It is no easy task to demonstrate unequivocally a correlation between genetically inherited characteristics and resistance or susceptibility to infectious disease, especially in human populations. Even when such a correlation can be demonstrated, to associate this correlation with differential mortality and/or fertility and then prove that the selective effect is large enough to influence gene frequency distribution, requires sample sizes and control of environmental factors that may not be possible for human population studies.

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References

Barrett, J.A.
1990 The detection of selective differences in populations.
In: A.C. Swedlund and G.J. Armelagos (eds).
Disease in Populations in Transition. Anthropological and Epidemiological Perspectives: 47-53.
New York: Bergin and Garvey.

Barua, D., and A.S. Paguio
1977 ABO blood groups and cholera.
Annals of Human Biology. 4(5): 489-492.

Bennun, F.R., G.A. Roth, C.G. Monferran, and F.A. Cumar
1989 Binding of cholera toxin to pig intestinal mucosa glycosphingolipids: Relationship with the ABO blood group system.
Infection and Immunity. 57(3): 969-974.

Chaudhuri, A., and C.R. DasAdhikary
1978 Possible role of blood group secretory substances in the aetiology of cholera. *Transactions of the Royal Society of Tropical Medicine. 72(6)*: 664-665.

Chaudhuri, A., S. De
1977 Cholera and blood-groups. *Lancet. 2:* 404-405.

Damian, R.T.
1964 Molecular mimicry: Antigen sharing by parasite and host and its consequences. *American Naturalist. 98:* 129-149.

Finkelstein, R.A., C.J. Powell, J.C. Woodrow, J.R. Crevans, S. Stallings, J. Light-Orr
1965 Serological responses in man to a single small dose of cholera vaccine with special reference to the lack of influence of ABO blood group on natural antibody or immunological responsiveness. *Bulletin of the Johns Hopkins Hospital. 116*:152-160.

Glass, R.I., J. Holmgren, C.E Haley, M.R. Khan, A.-M. Svennerholm, B.J. Stoll, K.M. Belayet Hossain, R.E. Black, M. Yunus, and D. Barua.
1985 Predisposition for cholera of individuals with O blood group. Possible evolutionary significance. *American Journal of Epidemiology. 121(6)*:791-791.

Haldane, J.B.S.
1949 Disease and evolution. *La Ricerca Scientifica. (Suppl.)19*: 68-76.

Hirszfeld, L., and H. Hirszfeld
1919 Serological differences between the blood of different races. The results of researches on the Macedonian front. *Lancet. ii*: 675-679.

Holmgren, J., I. Lonnroth, J.-E. Mannson, and L. Svennerholm
1975 Interaction of cholera toxin and membrane GM1 ganglioside of small intestine. *Proceedings of the National Academy of Sciences USA. 72*: 2520-2524.

Howard-Jones, N.
1974 Cholera nomenclature and nosology: A historical note. *Bulletin of the World Health Organization. 51:* 317.

Jones, J.S., and P.H. Harvey
1987 It pays to be different. *Nature. 328:* 575-576.

Karaolis, D.K.R., R. Lan, and P.R. Reeves
1994 Molecular evolution of the seventh-pandemic clone of *Vibrio cholerae* and its relationship to other pandemic and epidemic *V. cholerae* isolates. *Journal of Bacteriology. 176(20):* 6199-6206.

Levine, M.M., D.R. Nalin, M.B. Rennels, R.B. Hornick, S. Sotman, G. VanBlerk, T.P. Hughes, and S. O'Donnell
1979 Genetic susceptibility to cholera. *Annals of Human Biology. 6(4):* 369-374.

Livingstone, F.B.
1980 Natural selection and the origin and maintenance of standard genetic marker systems.
Yearbook of Physical Anthropology. 23: 25-42.

Monferran, C.G., G.A. Rot, F.A. Cumar
1990 Inhibition of cholera toxin binding to membrane receptors by pig gastric mucin-derived glycopeptides: Differential effect depending on the ABO blood group antigenic determinants.
Infection and Immunity. 58(12): 3966-3972.

Mourant, A.E.
1983 ***Blood Relations. Blood Groups and Anthropology.***
London: Oxford University Press.

1954 ***The Distribution of Human Blood Groups.***
Oxford: Blackwell Scientific
Publishing.

Mourant, A.E., A.C. Kopec, K. Domaniewska-Sobczak
1976 ***The Distribution of the Human Blood Groups and Other Polymorphisms.***
London: Oxford University Press.

1978 ***Blood Groups and Disease. A study of associations of diseases with blood groups and other polymorphisms.***
London: Oxford University Press.

Pettenkoffer, H.J., B. Stoss, W. Helmbold, F. Vogel
1962 Reply to Springer and Wiener.
Nature. 193: 445-446.

Pollitzer, R.
1959 ***Cholera.***
Geneva: World Health Organization.

Race, R.R., R. Sanger
1975 ***Blood Groups in Man.*** Sixth Edition.
Oxford: Blackwell Scientific Publications.

Sack, G.H., N.F. Pierce, K.N. Hennessey, R.C. Mitra, R.B. Sack, D.N. Guha Mazumder
1972 Gastric acidity in cholera and non-cholera diarrhoea.
Bulletin of the World Health Organization. 47: 31-36.

Sircar, B.K., P. Dutta, S.P. De, S.N. Sikdar, B.C. Deb, S.C. Pal, S. Swarup Mitra
1981 ABO blood group distributions in diarrhoea cases including cholera in Calcutta.
Annals of Human Biology. 8(3): 289-291.

Springer, G.F., P. Williamson, W.C. Brandes
1961 Blood group activity of gram-negative bacteria.
Journal of Experimental Medicine. 113: 1077-1093.

Springer, G.F., A.S. Wiener
1962 Alleged causes of the present-day world distribution of the human ABO blood groups.
Nature. 193: 445-445.

Svanborg-Eden, C., B.R. Levin
1990 Infectious disease and natural selection in human populations: A critical evaluation. In A.C. Swedlund and G.J. Armelagos, (eds). *Disease in Populations in Transition. Anthropological and Epidemiological Perspectives:* 31-46. New York: Bergin and Garvey.

van Heyningen, W.E., J.R. Seal
1983 *Cholera. The American Scientific Research Experience.* Colorado: Westview Press.

Vogel, F., M.R. Chakravaratti
1977 ABO blood groups and smallpox in a rural population of West Bengal and Bihar (India). In C.J. Bajema (ed). *Natural Selection in Human Populations. The Measurement of Ongoing Genetic Evolution in Contemporary Societies:* 147-165. New York: Robert E. Krieger Publishing Company.

Vogel, F., H.J. Pettenkofer, W. Helmbold
1960 Über die Populationsgenetik der ABO Blutgruppen. *Acta Genetica Statistica Medicus (Basel). 10:* 267-294.

Weiss, K.M., R. Chakraborty
1982 Genes, populations, and disease, 1930-1980: A problem-oriented review. In F. Spencer (ed). *A History of American Physical Anthropology 1930-1980:* 371-404. New York: Academic Press.