In the mid-19th century, the German hygienist Max von Pettenkofer viewed cholera as resulting from the interaction between a postulated cholera germ and the characteristics of soils. In order to cause cholera, the cholera germ had to become a cholera miasma, but this transformation required prolonged contact of the germ with dry and porous soils when groundwater levels were low. This hypothetical germ-environment interaction explained more observations than did contagion alone. Despite its attraction, von Pettenkofer’s postulate also implied that cholera-patient quarantine or water filtration was useless to prevent and/or control cholera epidemics. The disastrous consequences of the lack of water filtration during the massive outbreak of cholera in the German town of Hamburg in 1892 tarnished von Pettenkofer’s reputation and marked thereafter the course of his life. von Pettenkofer’s complex mode of thinking sank into oblivion even though, in hindsight, germ-environment interactions are more appropriate than is bacteriology alone for explaining the occurrence of cholera epidemics in populations. Revisiting the fate of von Pettenkofer’s theory with modern lenses can benefit today’s quest for deciphering the causes of complex associations.
von Pettenkofer applied the knowledge he developed in all these different domains of public health to the prevention of epidemic diseases. His urban epidemiologic ideas contributed to the transformation of Munich from a once disease-ridden to a healthful city (2). von Pettenkofer was one of the most articulate voices in public health who, at the end of the 19th century, defended a multifactorial conception of disease causation. He insisted that it was an oversimplification to assert that germs were the sole causes of disease. In this paper, I show that von Pettenkofer’s attempts to comprehend the complexity of the mechanisms causing cholera engaged, maybe for the first time so explicitly in public health, the epidemiologic concept of the interaction of multiple factors or, synonymously, effect modification.

In 1854, during the cholera pandemic in which John Snow (1813–1858), in Great Britain, assembled key evidence in favor of polluted water’s being the principal mode of transmission of cholera (8), von Pettenkofer conceived a hypothesis that seemed to reconcile the two main alleged causes of cholera outbreaks at the time: environment and germ. The localist (or “environmentalist”) theory posited that cholera was caused by miasma, that is, particles emanating from rotten material polluting the air and contaminating people who inhaled them. For example, William Farr (1807–1883), the British compiler of vital statistics, was a localist. In contrast, the contagionist theory stated that cholera was caused by some still unidentified germ and was therefore an infectious disease. John Snow was a contagionist. At the time, no universally convincing evidence supported either of these two conflicting theories.

von Pettenkofer agreed that cholera followed the routes of human travel and that, in a given locality, it went from ship to harbor and markets before reaching more inland areas as a contagious disease would. He also argued, though, along with the localists, that cholera could not be purely contagious since doctors, nurses, and other hospital personnel treating cholera patients did not always get cholera (9, p. 298). Furthermore, contagionism could not explain why epidemics subsided spontaneously. von Pettenkofer knew that the removal of the Broad Street pump handle had no impact on the course of the cholera outbreak that John Snow had investigated, along with others, in 1854:

Again, in Broad Street, the pump handle was not taken off till September 8th. Now an examination of the facts will show that the cholera was already subsiding. In Broad Street on August 31st, there were 31 cases of cholera; on Sept 1st, 131 cases; on the 2nd, 125; on the 3rd, 58; on the 4th, 52; 8th, 14. Just as occurs in India and elsewhere, a violent epidemic generally subsides rapidly (10, p. 864).

von Pettenkofer therefore proposed a new theory, depicted in figure 1, that reconciled the localist and contagionist views. The cholera germ had to be transformed in the soil into a cholera miasma. This cholera miasma was released through putrefaction into the atmosphere. People who inhaled it fell sick with cholera. The quality of the soil played a crucial role. High, dry, rocky soils could not produce the cholera miasma in sufficient amounts to trigger an epidemic, but low, porous soils could. There needed, however, to be sufficient distance between the ground and the groundwater levels for the cholera germ to become miasma. Hence, cholera epidemics were more likely to occur in the summer, when groundwater levels were low, than in other seasons when groundwater levels grew higher. According to von Pettenkofer (11), evidence in favor of his hypothesis was in the inverse correlation between groundwater levels and the incidence of cholera in several European cities, as shown in Web figure 1 for Munich. (This supplementary figure referred to as “Web figure 1” is posted to the Journal’s website (http://aje.oxfordjournals.org/).)

In a paper intended as a response to a contemporaneous publication by Rudolph Virchow (1821–1902), the German cellular pathologist and social reformer, von Pettenkofer expressed his theory as a more general law according to which $x$ (the cholera germ) or $y$ (the quality of the soil) alone could not produce the disease, but $x$ and $y$ together produced $z$ (the cholera miasma), which caused the disease:

4. One may refer to the specific India cholera germ as $x$, its substrate, which must be provided by place and time.
as \( y \), and the product arising from these two, the true cholera poison as \( z \).

5. Neither \( x \) nor \( y \) alone can produce cases of Asiatic cholera, but only \( z \).

6. The specific nature (quality) of \( z \) is determined by the specific germ \( x \); its amount (quantity) by the amount of the substrate \( y \).

7. The nature of \( x \), \( y \) and \( z \) is so far unknown but one may assume, with a scientific probability bordering on certainty, that all three are of organic nature and that \( x \), at least, is an organized germ or body.

9. The facts support the assumption that \( x \) can feed itself and maybe considerably multiply in the human body, e.g., in the intestine, but the human body is in the case of cholera only the showplace of the effect of \( z \), and cannot produce \( z \) alone, if \( x \) does not enter in contact with \( y \) (12, pp. 294–296, translated by A. M.).

The groundwater level hypothesis united factors belonging to different domains, such as infection and geology, within a single causal mechanism. Ignorance of the causes of cholera made the hypothesis appealing: Postulating that the cholera germ was modified by soil explained more facts than did the localist and contagionist views alone. For example, it explained why cholera followed the routes of human travel but produced outbreaks only in certain localities. It supported preventing contact of cholera germ-bearing excrements with soil, using drainage, sewage systems, water supplies, and dwellings, which made sense because cholera outbreaks occurred preferentially in the poorest and filthiest neighborhoods.

von Pettenkofer’s hypothesis was consistent with the observation by William Farr that cholera incidence declined with geographic elevation because elevated localities are more likely to be on rocky soil (13, pp. 114–117). It appeared biologically plausible because the metamorphosis of the cholera germ into a cholera microbe was analogous to the process of fermentation discovered by Louis Pasteur (1822–1895) in France. Pasteur, a chemist as was von Pettenkofer, had demonstrated that fermentation required living organisms (yeast) and a medium (cider or sugar cane juice). In von Pettenkofer’s theory, the living organism was the cholera germ, and the medium was the suitable soil (12, p. 280).

However, the groundwater-level theory also had potentially deleterious implications for public health. von Pettenkofer was opposed to water filtration and quarantine, or *cordons sanitaires*, which stopped population migrations away from the epidemic because they were not aimed at preventing the cholera germ’s contact with cholera-susceptible soils. Unfortunately, these logical implications of the groundwater-level theory could dramatically amplify and disseminate a cholera epidemic. Indeed, a case in point occurred in the summer and fall of 1892 in Hamburg.

Two adjacent cities, the German Hamburg and the Prussian Altona, both pumped their water from the Elbe River. The two towns were part of the same conurbation, but they had different jurisdictions with regard to water treatment. Altona had a sand-filtered water supply, which efficiently eliminated cholera and typhoid germs. Hamburg’s water, in agreement with von Pettenkofer’s credo, was not filtered but allowed only to decant in large reservoirs. Between August and November of 1892, there were 8,606 deaths from cholera in Hamburg versus only a few in Altona. The streets that divided Hamburg from Altona neatly segregated the cholera deaths on Hamburg’s side (refer to maps in reference 2, p. 291). The medical authorities and the government of Hamburg, sympathetic to von Pettenkofer’s views, had first tried to conceal the facts. They bear a large responsibility for the unprecedented outbreak that killed 1.3 percent of the Hamburg inhabitants. They were therefore constrained by the Prussian government to surrender to Robert Koch (1843–1910), the leader of the contagionists who in 1883 had discovered the comma bacillus. Koch came to Hamburg and forced the application of mass disinfection and patient isolation. Later, the implementation of a sand-filtering water plant rapidly freed Hamburg from recurring cholera and typhoid epidemics.

Believers in the miasma theory were silenced (14, pp. 273–274). The reputation of von Pettenkofer, once “Europe’s leading sanitarian” (15), was greatly affected. Koch imposed his views in the proposal of the new Epidemics Law for the German Empire in October 1892, against von Pettenkofer, who stubbornly continued to negate the possibility of direct contagion.

Isolated and humiliated by Koch, von Pettenkofer had a single but extremely risky possibility for rescuing the situation to his advantage: Koch’s assertion that the “comma bacillus” (which von Pettenkofer admitted was the \( x \) factor) was the single cause of cholera had a major weakness; that is, the association did not satisfy Koch’s own causal postulates (16). One of the postulates required that cholera could be produced by the inoculation of the bacillus into a healthy host, but Koch’s attempts to infect guinea pigs, cattle, fowl, and rabbits all failed. For von Pettenkofer, the absence of “\( y \),” the soil factor, was the reason. Koch counterargued that humans were probably uniquely susceptible to the bacillus. Rebutter Koch’s defense required the unethical experimental contamination of human beings, so von Pettenkofer offered himself. On October 9, 1892, a week after his defeat against Koch in the epidemics law committee, at the age of 74 years, von Pettenkofer ingested a broth of cholera to prove that it alone was ineffective. To avoid all criticism, he had previously neutralized his gastric acidity by sodium bicarbonate (1, 17). The ingestion caused diarrhea and proliferation of cholera bacilli in his stools but was not fatal. Did anger and nervousness provoke an extra charge of stomach acid that sufficed to kill the bacilli he swallowed (14, p. 267)? Was von Pettenkofer partially immunized by previous exposures to the germ (1)? Or did Koch’s assistant send von Pettenkofer a diluted culture of the germ, suspecting that the old man was going to ingest it (2, p. 498)? I don’t know, but historians agree that this was a heroic but suicidal act, a last stand that only delayed the almost unanimous acceptance of the contagionist views. In 1894, at 76 years of age, von Pettenkofer retired from active work. In 1895, cholera was successfully inoculated into animals. On February 10, 1901, depressed, von Pettenkofer shot himself (1).
In the aftermath of the Hamburg 1892 epidemic, von Pettenkofer’s model was abandoned altogether without having been formally refuted, even though there was patently an environmental component underlying the sporadic and erratic occurrence of cholera epidemics. We know today that cholera epidemics result from interactions between the germ and environmental, biologic, and social factors (18). Intense episodes of warm precipitation, particularly on the Indian subcontinent, transform the temperature and salinity profiles of estuaries. The influx of large quantities of freshwater mobilizes stored nutrients in the bottom sediments and gives the dormant cholera bacterium a head start in its growth cycle. With the help of copepods, it reaches the gut tracts, first of crabs, clams, and oysters and ultimately of humans who ingest the contaminated seafood raw and disseminate it. The discovery of the comma bacillus could therefore not suffice to prevent cholera epidemics from recurring in communities. Since 1883, there have been at least two more cholera pandemics affecting Europe. The seventh pandemic lasted from 1961 to 1971. Von Pettenkofer rightly perceived that cholera etiology was complex and proposed a model that was plausible for his contemporaries.

GERM-ENVIRONMENT INTERACTION

Readers of the American Journal of Epidemiology have recognized in von Pettenkofer’s theory the concept of interaction that we use today in epidemiology to define a situation in which an association between an exposure and an outcome is modified by a third factor. Von Pettenkofer postulated that the quality of the soil modified the potential of the cholera germ to produce the cholera disease. Some soils transformed the inoffensive germ into a pathogenic miasma, while other soils did not. This model is not different from the interaction among fava bean consumption, hemolytic anemia, and glucose-6-phosphate dehydrogenase deficiency (G6PD): Fava beans produce hemolytic anemia only in people whose red blood cells cannot handle the fava-borne oxidative stress because of reduced activity of the G6PD enzyme. Fava beans and G6PD are causal partners, neither of which is capable of producing hemolytic anemia alone. In von Pettenkofer’s hypothesis, an analogous partnership between the cholera germ and porous soil was needed to cause the cholera disease.

In this context, isn’t it surprising that the scientific community did not isolate von Pettenkofer’s mode of thinking from the erroneous specifics of his groundwater-level hypothesis? No one found it necessary to demonstrate that the environmental component of the model was confounded by the greater consumption of potentially contaminated water and fruits during summer and dry seasons, when the bacillus reached high concentrations in empty wells and shallow rivers. No one was interested any longer in the kind of arguments that appealed to von Pettenkofer (19, p. 60) and, for almost half a century, Germany filled the chairs of hygiene with bacteriologists (5, p. 8).

ROLE OF INTERACTIONS TODAY

There is, to my knowledge, very little work on the emergence and relevance of the concept of interaction in public health, even though much thought has been invested in it since von Pettenkofer (20–22). Textbooks (23–27) provide a theory of how to assess, quantify, and test for interactions on multiplicative or additive scales. Moreover, interactions have become a growing concern in epidemiologic thinking.

Consider our current pursuit of the causes of cancer, atherosclerosis, psychiatric disorders, osteoporosis, and so on. We invoke the existence of interactions just as von Pettenkofer did, as a convenient way of reconciling apparently contradictory observations: Fast-evolving trends suggest that environmental factors are important, but neither every person nor every group exposed to these factors gets the disease. The real mechanisms remain elusive despite a wealth of research. No single scientific discipline seems to have the tools to solve the puzzle. Controversies persist between people who believe genes are crucial and those who believe the clout lies with the environment. In this context, gene-environment interactions are supposed to explain observations that neither nature nor nurture alone can (28).

A quick MEDLINE (National Library of Medicine, Bethesda, Maryland) search of the American Journal of Epidemiology (started in 1921) and the International Journal of Epidemiology (started in 1972) shows the growing popularity of the term “interaction.” It was practically never used other than to describe infectious processes before Rothman’s landmark 1974 paper (29). The number of article titles or abstracts that mentioned interaction or synergy, respectively, in the American Journal of Epidemiology and the International Journal of Epidemiology was one and zero in 1975, three and one in 1980, four and six in 1990, 17 and five in 2000, and 17 and 12 in 2006. However, this apparently growing reliance on the concept has had until now only a few clinical or public health consequences. How many examples can we list of etiologic discoveries that have helped us to 1) identify subgroups who would principally benefit from screening or prevention, 2) better understand the mechanisms of disease, or 3) provide individualized therapy? We know, for example, that smokers should stay away from trades exposed to asbestos (30) or from oral contraception (31), because they would be at very high risk of, respectively, lung cancer and coronary heart disease. However, the widely shared belief in the concept of gene-environmental interactions has yet to meet its public health expectations (32).

Recent work indicates that the reason for this failure (so far) is that our concepts, designs, and analytical methods are still too primitive to efficiently address the complexity of the phenomena we want to understand and control. Both Mayr (33) and McMichael (34, p. 319) note that interactions at all levels are probably the most pronounced characteristic of the determinants of population health. Inviting us to adopt a wider, ecologic perspective, McMichael vituperates, just as von Pettenkofer did before him, against the germ theory that persuades us to think in terms of unique causes. It is tempting, for example, to consider human immunodeficiency virus (HIV) as the cause of acquired immunodeficiency syndrome (AIDS) just as we consider the comma bacillus as the cause of cholera and to forget that the germ itself does not explain the dramatic differences in
infection prevalences across the world. Ecologic (or complex) causation requires that we simultaneously consider multiple causes and understand how human populations interact with and are modified by their natural and social environments. Similar ideas have been expressed under the concept of levels of organization and the metaphor of the Chinese boxes by Susser and Susser (35). In substance, epidemiology is evolving toward the study of causal relations more complex than those that have been explored and discovered in the last 50 years. The concept of interaction plays a central role in this process, but the discipline has not arrived there yet.

Is it really such a stretch to assume that von Pettenkofer originated the notions of interaction that we use today? Scientists such as Theobald Smith (1859–1934), Frank Macfarlane Burnet (1899–1985), Ronald Ross (1857–1932), and Rene Dubos (1901–1982) also were thinking in terms of multicausal models (36). They stressed the importance of interactions among agent, host, and environment, often referred to as ecologic models or as the “epidemiologic triad.” Yet, none of these, to my knowledge, brought the concept up to the level of formalization that von Pettenkofer did. The x, y, z theory is an early expression of two component causes or causal partners that are both necessary but not sufficient to produce an effect and, when united, constitute a cause of the disease. From this perspective, von Pettenkofer, more so than the other ecologic thinkers, pioneered a mode of thinking of etiology in terms of interaction with which we still struggle today.

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