Koch is Dead:
Why We Should Discard Traditional Views of Infectious Processes?

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More than a century after the birth of the first germ theories, 19th century notions of infectious disease causality continue to haunt our efforts to develop effective investigational and intervention strategies. This is due not only to the distorted view of the relationship between infection and disease they encourage, but, more importantly, to the almost mystical power that notions such as Koch's postulates have had to deflect our attention away from the development of utilitarian problem-solving skills.

In paraphrase, Koch's postulates were as follows:

1. The agent must be found to be present in every case of the disease it putatively causes. (Causal necessity)
2. The agent, when isolated in pure form and inoculated into a susceptible host, must be able to reliably produce a disease syndrome indistinguishable from that for which it is the putative cause. (Causal sufficiency under controlled conditions)
3. The agent must not be found in healthy animals or in animals with diseases other than the one for which it is the putative cause. (Casual sufficiency under field conditions)

In graphic form, Koch's postulates view can be illustrated as in Figure 1. All the non-infected animals (unshaded) are healthy as denoted by smile faces. All the infected animals have the disease putatively caused by the agent as denoted by the frowns. Thus, we find the agent in every case of the specified disease because it is *necessary* for disease to occur; and we never find the agent in a healthy animal or one with another disease because infection with the agent is *sufficient* to cause the target disease.

In contrast to Koch's world view, modern visions of infectious disease causality have had to recognize overwhelming evidence that infection alone is not sufficient to cause disease. Based on serological studies, longitudinal agent-sampling studies, and controlled inoculations, many infected animals remain healthy. This

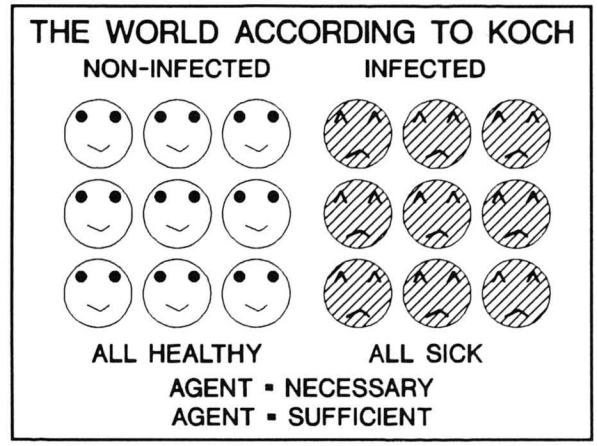

Figure 1. Robert Koch's classic, 19th century model of the relationship between infection and disease.

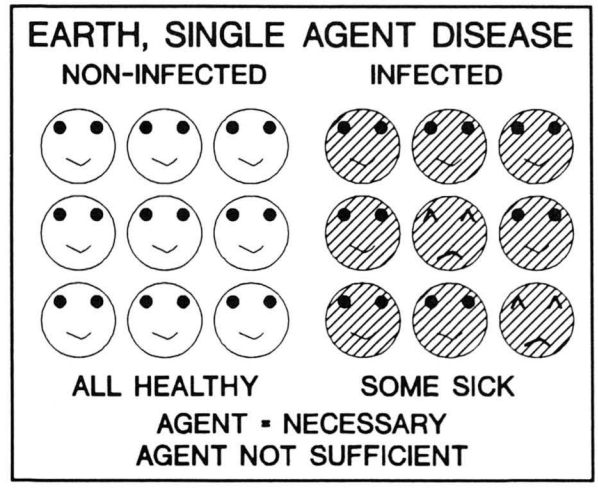

Figure 2. Most infectious agents are relatively host adapted, and infection is associated with disease only under unfavorable environmental or nutritional circumstances.

is illustrated in Figure 2 by the shaded (infected) smile faces. Causal necessity is preserved in modern theories of single agent diseases (e.g., infection with *Anaplasma*

spp. is necessary for anaplasmosis as symbolized by the lack of frown faces among non-infected). In multi-agent diseases such as diarrhea or respiratory disease, however, more than one agent can be involved in an indistinguishable disease syndrome; thus, cases can be found of the syndrome which lack a particular agent (frown faces among non-infected as shown in Figure 3).

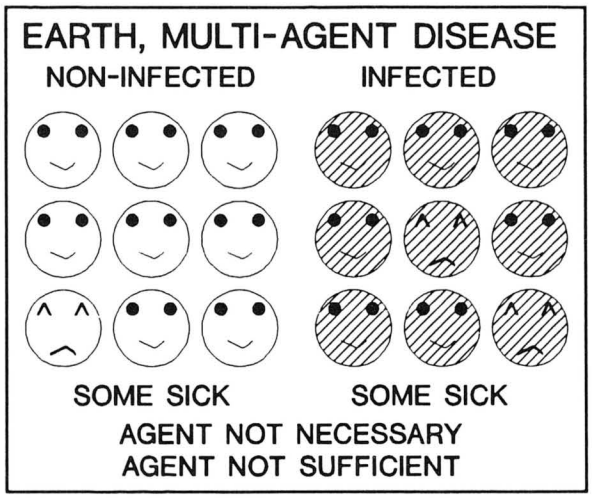

Figure 3. In multi-agent disease complexes, no single agent is associated with all cases; thus infection with a particular agent is neither necessary nor sufficient.

Whatever its failings, the notion of causal sufficiency of infectious agents has been persistent in the minds of medical professionals, and this has resulted in a distorted, often ineffectual problem solving strategies. Language has created something of a barrier to change in that textbooks and lectures still refer to an infectious agent as "the cause" of its associated disease. But, beyond linguistic inertia, the notion of causal sufficiency of infectious agents continues to have influential defenders who have muddied the waters with specious arguments. The most common argument, in this regard, is that the mere finding of the agent or antibodies to it in an animal does not constitute "infection." The animal must have the disease putatively caused by the agent in order to be deemed "truly infected." A little thought will reveal the circular futility of this reasoning. If we set out to test the hypothesis that infection with agent A is sufficient to cause disease X, and if we require for our definition of infection that the animals in which the agent is found must also have disease X to be deemed "truly infected," then we should not be surprised to find that every A-infected animal--without exception--has disease X. For example, if we require animals to have clinical anaplasmosis--in addition to the presence of *Anaplasma* in their red blood cells--to judge them as having *Anaplasma* infection, we should not be surprised in finding that all *Anaplasma*-infected animals have anaplasmosis. Tautologies* aside, the evidence seems overwhelming that most *Anaplasma*-infected animals never develop anaplasmosis, and so on with most other infectious agents and their associated diseases. (*A tautology is a statement in which the conclusion is a restatement of the premise, as in the above example which reduces to "all cattle with anaplasmosis have anaplasmosis").

From a diagnostic viewpoint, continued adherence to the notion of causal sufficiency has fostered an overly taxonomic approach to problem solving which lacks utility for livestock disease problems. In the taxonomic approach, naming the "cause" (agent) of the infectious disease problem places the solution at hand, or at least closer at hand.

Consider a diarrheal problem in a cow/calf herd. The traditional approach is to find out "What is causing the problem," meaning, in this context, "What infectious organism has entered this herd, infected these calves, and is causing them to be sick with diarrhea?" In an effort to obtain this answer, we submit fecal samples and gut segments from diarrheic calves and get a "diagnosis" of rotavirus and cryptosporidia. Have we found what is causing the problem? Are we any closer to an answer?

Arguably, we have not even diagnosed what is causing the disease suffered by the particular calves from which samples were submitted, and this information is of only a peripheral interest, in any case. Since rotavirus and cryptosporidia are commonly occurring neonatal agents, present in all herds, and to which infection is near-universal during some part of the first 3 months of life, we would not be surprised to find agents such as cryptosporidia or rotavirus in calves which were, say, struck by lightening and were otherwise perfectly healthy. Likewise, even if diarrhea associated with another agent were occurring, we would still expect to commonly find rotavirus and cryptosporidia in some of the submitted cases. Though it is frequently claimed that one can somehow "gain insights" based on the frequency of particular findings or the numbers of agents present in individual fecals, such "insights" are more in the nature of "feelings" that are impossible to support with logic or science.

Once we accept that mere infection is not sufficient to cause infectious disease, a number of similar conundra arise in diagnosing individual cases. The taxonomy of diagnosis becomes muddled as do the minds of those seeking to solve herd problems using taxonomy. But this is not the main diagnostic dilemma faced by the food animal practitioner since taxonomy is not an effective problem solving strategy. If our goal is to help solve a herd's disease problem, our diagnosis needs to tell us how the herd in question is different from herds which aren't having the problem. We need to look at the relationship between infection and disease at the herd level rather than at the individual level.

Consider Figure 4 which shows the relationship between infection and disease for an endemic agent. Endemic agents are those which are always present in

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cattle populations. Note that there are no non-infected herds in Figure 4 since many bovine agents (e.g., most of the diarrheal and respiratory agents) have ubiquitous or nearubiquitous distributions. Notice also that there are many herds without disease which are infected with the agent in question (flags at full staff). This, too is characteristic of endemic agents. Just because rotavirus and cryptosporidia are present on a farm does not mean that the farm will have excessive diarrheal morbidity or mortality--otherwise all farms would be so afflicted.

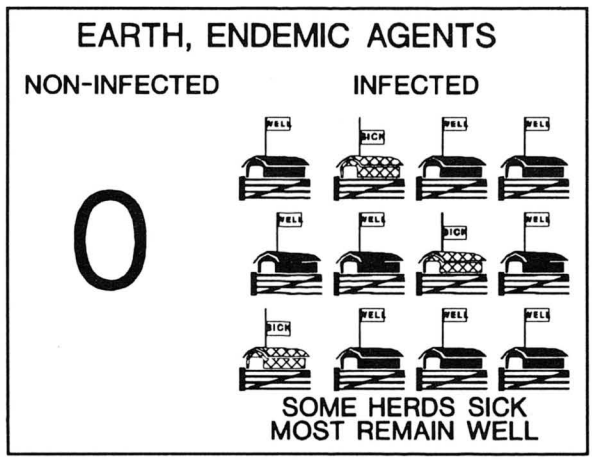

Figure 4. Many infectious agents of bovines are ubiquitous, or nearly so; existing on farms with excess disease as well as those without disease problems.

Is it legitimate to diagnose an endemic agent as the cause a disease outbreak? The role of endemic agents in disease outbreaks seems similar to that played by gravity in bridge failures or oxygen in barns fires. Surely gravity is a necessary element in bridge failures and oxygen in barn fires, but submitting samples for gravity or oxygen would hardly be considered legitimate activities in diagnosing the reasons for a bridge failing or a barn burning. Efforts are instead directed toward those factors which are **not** universally characteristic of all bridges or barns, **and** over which one has control. Similarly, in outbreaks of disease in cattle herds which are associated with endemic agents, we focus our attention on those factors which are not common to all herds and over which we have direct control. Making a herd diagnosis based on a finding of an endemic agent is the moral equivalent of telling a producer his barn burned down because he's got oxygen on his place.

As shown in Figure 5, some agents have an epidemic distribution. They are normally not present in herds of cattle. For example, *Salmonella typhimurium* and *S. dublin* seem to conform well to the epidemic pattern with respect to cow-calf herds. Most herds lack the agent and thus do not have the associated disease; biosecurity is maintained (if only by accident). In another group of herds, the agent is introduced but either does not spread or does not produce disease in most infected animals. In other herds in which the agent is introduced, it spreads and produces an outbreak of disease.

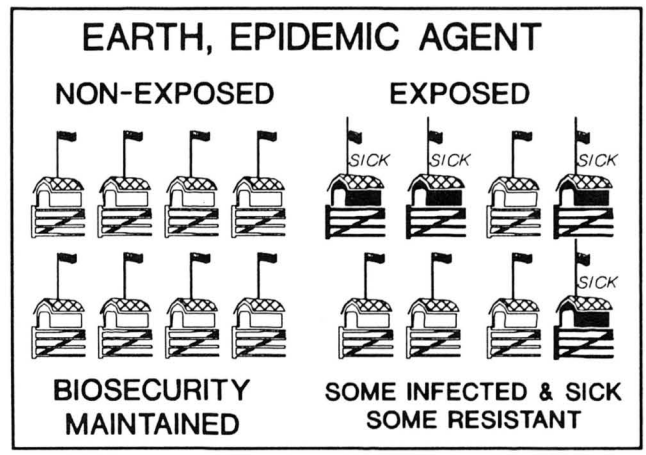

Figure 5. Epidemic agents exist in only a fraction of herds. Herds in which biosecurity is maintained avoid disease problems associated with the agent as do some herds where the agent is introduced.

What is the value of taxonomic diagnosis (agent naming) for epidemic agents? Clearly, identifying epidemic agents associated with a compatible disease syndrome is very important in solving herd disease problems. Yet, even here, the importance is sometimes overstated since identifying the agent doesn't really give us the "cause"-- at least not from a utilitarian viewpoint. We can't just say "No more Salmonella around here!" For herds which are currently experiencing outbreaks, solutions will involve identification of those specific management factors which enhance transmission and/or increase the susceptibility of cattle to the disease-producing effects of the agent. For herds wishing to establish or maintain biosecurity, we must identify those factors which are critical to this (e.g., what role does feed play and what specific actions, if any, need to be taken with respect to feed). Thus, even in the case of epidemic agents, we are still faced with identifying differences between affected and non-affected herds beyond mere microbiological ones.

The main failing of lingering notions of infectious disease causality such as those embodied in Koch's postulates is that they lead adherents to place too much emphasis on laboratory submissions. It would be incorrect, however, to interpret this as an argument that diagnostic laboratories are useless anachronisms. Strategic sampling--that aimed at testing management level hypotheses--can play a critical role in effective problem solving; but, if we can't explicitly describe how a set of laboratory samples will help us identify the underlying system failures which must be present for disease outbreaks to occur, then we are just frittering away the client's money in order to put a name to his or her misery.

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