Re-Discovering the Germ Theory of Disease: A Major Role for Proteomics

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In the 21st century we will re-discover the germ theory of disease [1-3]. The golden rule will be:

Germ theory causes disease.
Genes act in complex networks to prevent disease.

This concept will work for everything except trauma. Infection will be diagnosed by identifying its protein signature in urine using mass spectrometry; hence the major role for proteomics.

T lymphocytes identify the protein signature of microbes by recognition of a polypeptide fragment 8-12 amino acids long on the surface of macrophages in the groove of the MHC2 molecule. There are ten trillion ways of combining the twenty amino acids into a linear polypeptide sequence ten amino acids long. There aren’t many protein sequences in the bio-sphere so the polypeptide fragment recognized by the T lymphocyte receptor is specific for the protein from which it came and the organism that produced it. Bacterial toxins, secreted during episodes of bacteremia, are small enough to be filtered passively by the renal glomerulus. But all adults have antibodies to common toxins and thus immune complexes form in the circulation [4-6]. The complexes are too large to be filtered into the urine but they are found in the urine [7-9]. Thus they must be actively secreted. It is this observation that opens up the possibility of diagnosing recurrent low grade bacteremia.

There is increasing evidence that low grade chronic inflammation of unknown cause increases the risk of atherosclerosis [10,11]. The conventional risk factors of hypertension, hypercholesterolaemia, smoking and diabetes mellitus only account for part of the risk. Bacteria on the facial skin and in the upper airways are inhaled with each breath and transient bacteremia is common [12,13]. The bacteria are quickly cleared by neutrophils in the post-capillary venules of the lung and the toxins are neutralized by antibody but some damage might still occur particularly with pathogenic organisms such as *Staphylococcus aureus*. This is the hidden factor in the development of atherosclerosis and its complications. There is already some evidence to support this idea [9] and it is open to the proteomic community to prove it. Prevention will then depend on optimizing the skin microbial flora by displacing *S. aureus* and replacing it with *Staphylococcus epidermidis* and or *Corynebacterium* species.

The modern epidemic of senile dementia is a similar problem with a similar solution. Once again chronic low grade inflammation increases the risk of vascular dementia and Alzheimer’s disease [14]. The best bet for the hidden factor is chronic bacteremia and the main candidate organism is *S. aureus*. We must map the nasal flora in these patients, measure the level of IgG in the urine and then identify the protein in the urinary immune complexes. Prevention will be by optimizing the microbial flora as above.

The modern epidemic of obesity is stretching the resources of health services world wide. The word epidemic is a clue but deep in the psyche of the medical profession there is a much older idea [15]. An idea that emerges whenever we are faced with something we do not understand. An ancient concept which is never articulated but influences our thoughts:

Sin causes disease.
Piety is the basis of prevention.
Penance is required for cure.

These ideas are implicit in much of what is written about obesity. The presumed cause is gluttony and sloth. The proffered solution is punishing diet and punishing exercise. In fact obesity is a problem of physiological regulation and there is an obvious cause and an obvious solution. Bacteria of the gut flora produce a wide range of toxins and induce a wide range of antibodies in the host. Some of these proteins are orexigenic and some anorexigenic; they thereby interfere with the regulation of appetite [16,17]. Modern farming methods select for rapid weight gain in animals, this means they also select for the bacteria which disturb regulation and lead to weight gain. The candidate organism is *Escherichia coli* and the solution is to displace the orexigenic clones by organisms that do not have this effect. Once again the way is to optimize the microbial flora by controlled exposure.

The psychotics diseases schizophrenia and manic-depressive psychosis are caused by the synergistic interaction of heterozygous deleterious mutations in the genome [2,18,19]. This leads to a risk of failure in complex genetic systems leading to thought disorder and extreme mood disturbance. But psychosis is not inevitable even in those with the genetic predisposition. Something triggers the acute psychotic episodes and the likely cause is bacteremia [13,18,19]. Once again we must map the microbial flora, obtain specimens of urine during acute exacerbations, measure IgG, and identify the protein antigen in the complexes. Then optimize the flora and control exposure to prevent further episodes.

Functional disorders are another major part of psychiatric practice. Irritable bowel syndrome, anorexia nervosa, anxiety neurosis and chronic fatigue syndrome cause a great deal of human misery. These conditions are much more common in women than in men. The incidence, which appears to be on the increase, peaks in the 2nd, 3rd or 4th decades. There are no histological changes in tissues to give a clue to causation. A recent hypothesis is that they are caused by auto-antibodies to neuronal proteins induced by molecular mimicry with microbial antigens [17,20]. In which case the focus of research should

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be to identify the microbes which express the cross reacting proteins and remove them from the microbial flora.

The epidemic of diabetes mellitus is also causing concern. The conventional wisdom is that type 1 diabetes mellitus is an autoimmune disease of childhood due to too much hygiene [21,22]. Type 2 diabetes is a disease of adults associated with obesity and caused by glutony and sloth [23]. In the first case the sin is with the mother and in the second case with the patient. The islets of Langerhans in the pancreas contain several different types of endocrine cells only one of which (the beta cell) secretes insulin. It is the beta cells that are damaged in diabetes mellitus. There is an obvious evolutionary advantage to bacteria which interfere with insulin production or function because that will lead to hyperglycemia and boost the growth of bacteria in the blood. The likely candidate is our old enemy S. aureus and it should be possible to prove this hypothesis by examining urine specimens in these patients.

Cancer is another huge cause for concern. It is commonly regarded as an inevitable consequence of growing old. Stem cells acquire mutations by chance when they divide and it is only a matter of time before one stem cell acquires the specific set of mutations for malignancy leading to uncontrolled cell division [24-26]. Leading geneticists have argued this is pure chance [27]. However simple logic suggests otherwise. We produce 200 billion red cells, 100 billion white cells and 30 billion other cells each day [28]. There are more stem cell divisions in the red cell series than in all other cells put together. But cancer of the red cell stem cells (erythroleukaema) is very rare. Cancer is not an inevitable consequence of stem cell division. In fact consideration of stem cell kinetics leads to a different conclusion [29-31]: it is that each cancer has a cause. The causal factors damage stem cells and cause them to proliferate. These proliferating cells accumulate mutations and several malignant clones arise. One of the clones outgrows the others and becomes the malignant monoclonal tumour [32,33]. The cause of cancer, the factor that damages the stem cells in the first place, is infection or trauma [31]. Bacteria damage stem cells in the stomach and colon. But viruses are probably the culprits in many epithelial tissues. The stem cells of the red cell series are not a natural place for viruses as they cannot be passed on, but epithelia such as breast are a staging post in the virus life cycle. Once more controlling exposure to bacteria and viruses and optimizing the microbial flora will greatly reduce the incidence of cancer of all types.

In the future we will take an enteric coated pill every day of our life [1]. The pill will be precisely formulated to deliver a low dose of bacteria and viruses to our mucosal surface. This will ensure low dose, early mucosal exposure to all the bacteria and viruses that we are likely to meet in our lifetime. The pill will also be formulated to build up an optimum microbial flora in our gastro-intestinal tract. One cycle of exposure to most organisms will be complete by the end of the first year and then repeated throughout life. This will ensure that we develop immunity without suffering disease in infancy and then maintain that immunity throughout life. We will also need to apply various creams and lotions to our skin on a daily basis to optimize the flora. New viruses will emerge from time to time but they will be incorporated into the enteric pill and perhaps also delivered by nasal spray, again in a low dose to build up immunity and to prevent the virus spreading.

Disease will still occur but it will be rapidly diagnosed and prevented. Most people will lead healthy lives into their 11th or 12th decade. Death, however, is inevitable because our cells accumulate mutations and the rule still applies: germs cause disease, genes act in complex networks to prevent disease. The accumulation of mutations will gradually impair our response to infection and the germs will get in the end. Most people will die quietly in their sleep of sudden death in old age syndrome; due to common bacterial toxins interfering with cardio-respiratory control. The mode of death will be similar to that in sudden infant death syndrome [34-36].

The future is bright and it will be three cheers for proteomics, but only if the community of scientists gets on with proving this thesis.

**Conflict of Interest**

The author is the sole director of a newly formed company Lancastrian Microbial Ltd. The aim of the company is to develop commercial products for optimization of the microbial flora.

**References**