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Parkinson's: another look

L. Broxmeyer

Med-America Research, Whitestone, New York, USA

Summary Recent studies in the Parkinson's literature have cited a tuberculosis-like germ called *Nocardia* as being responsible for Parkinson's disease. Kohbata seemingly cemented a relationship between *Nocardia* and Parkinson's by finding serologic evidence in 20 of 20 Parkinson's patients, acknowledging that blood tests for *Nocardia* and the mycobacteria such as tuberculosis often cross-react, as they belong to the same order of bacteria, the *Actinomycetales*. Besides this difficulty in differentiation, a well-used medical school textbook of microbiology, Atlas, points out that even among experts, different observers may classify the same strain of bacteria as *Nocardia* or *Mycobacterium tuberculosis. Parkinson's: another look* is a theoretical article which presents compelling, well-documented evidence for an infectious cause for Parkinson's disease on historical, epidemiological, pharmacologic, microbiological, and biochemical levels. © 2002 Elsevier Science Ltd. All rights reserved.

BACKGROUND

Recent studies in the Parkinson's literature have cited a tuberculosis-like germ called *Nocardia* as being responsible for Parkinson's disease (1,2) on several occasions confirmed serologically in the blood. Kohbata seemingly cemented a relationship between *Nocardia* and Parkinson's by finding serologic evidence in 20 of 20 Parkinson's patients, acknowledging that blood tests for the *Nocardia* and the *Mycobacteia* such as tuberculosis often cross-react, as they belong to the same order – Actinomycetales (3). Besides this difficulty in differentiation, a well-used medical school text of microbiology points out that even among experts, different observers may classify the same strain as *Nocardia or Mycobacteium tuberculosis* (4). To add to existing difficulties, both organism's can be acid-fast, a property long used to identify *M. tuberculosis*. Atlas also mentions still another *Actinomycetales/corynebacteria* as equally hard to pick out from the others. Diptheria is a corynebacteia which Martyn found linked to Parkinson's (5). But even before this, diptheria's role in PD peppered the *Index Medicus* for decades. By 1994 Gao proved through the use of mycobacterial heat shock proteins against the blood of two Parkinson's patients that *mycobacteria* were somehow linked to Parkinson's (6). All of this has occurred in a setting in which not only do twin studies cast a doubtful aura regarding Parkinson's as hereditary (7,8) but other seemingly environmental causes are so diverse as to boggle the mind, unless it is recognized that many of these factors affect the disposition of the germ that actually causes Parkinson's to multiply, thrive and attack the dopaminergic nerve centers in the brain.

By 1934, Burn of Yale had identified a Gram-positive bacillus from the bloodstream of three infants that died from Parkinson causing Von Economo's encephalitis (9). This pathogen, in its sluggish motility and resemblance to *Listeria monocytogenes,* bore an eerie resemblance to an organism which with advanced stains was found to be acid-fast by a network of post-World War II female M.D.'s and PhD's (10), some of whom consistently found the germ in Wilson's disease, a primary cause of Parkinson's in the young (11). It had evolved as a cross between the *mycobacteria* and the *nocardia* as a result of viral phage transfer between the two species (10,12). Furthermore, the important Parkinson's DATATOP study (13) unwittingly settled upon an agent from a class originally designed to cure tuberculosis, an MAO inhibitor called Deprenyl (14). And recently Fuente-Aguado (15), Kurasawa (16), Mital and Sarkari (17), Otaki

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Correspondence to: **Lawrence Broxmeyer** MD, Med-America Research, 148-14A Eleventh Avenue, Whitestone, New York 11357, USA.

(18) and Solanki (19) all cured symptomatic Parkinson's using anti-tuberculous medications.

HISTORICAL AND OTHER PARALLELS

Parkinson's and tuberculosis share many common threads. Both came into force and were linked with the great Industrial Revolution. The *substantia nigra* was established as important to Parkinson's through a tuberculous attack on an autopsied patient (20). Both share a common preferential site of attack, the convexity or underside of the brain were the *substantia* and *basal ganglia* lie. Parkinson's last great epidemic, Von Economo's Encephalitis was, according to Hall, almost indistinguishable from T.B. (21). And Duvoisin all but ruled out any of the suspected viruses implicated at the time (22). Even in AIDS, often associated with Parkinson's, mycobacteria such as tuberculosis have been reported as the most common central nervous pathogen in HIV-infected people (23). Many of the patients with both Parkinson's and T.B. share the common denominator of a chronic wasting disease, a cachexic eating away of the flesh. Finally both are primarily diseases of older people with a male preference.

EPIDEMIOLOGICAL CONSIDERATIONS

Guam sits in the southernmost Marianas, within the Asian Pacific Rim. Regions in the world where T.B. is most prevalent lie within that rim. It soon became recognized that Guam had a relatively high number of neurodegenerative diseases in its midst – among them a Parkinson-dementia complex which melded classical Parkinson's often preceded by memory impairment (24). Parkinson's and ALS alone affect 10% of Guam's natives. This, in America would be equal to approximately 27 million Americans affected, a nightmarish scenario. Leprosy was once common in the Mariana's, but now is rare (25). To this day, there is no explanation as to why leprosy disappeared from the Mariana's, but T.B. meningitis, common, remained.

At first, investigators thought it was only Guam's indigenous natives, called the Chamorros that were affected by these neurodegenerative diseases. But since Magellan's Spanish claim to and discovery of the Mariana's, the Island's demographics where changing, rapidly. By the 18th century, Filipino immigration created a situation where approximately 1 out of 5 Chamorros were direct descendants from Filipino–Chamorro unions. Soon it was discerned that after a mean lapse of two decades, Filipino's were also contracting PD–Dementia on Guam. Or, were they importing it from the Philippines (26)? The question seemed impenetrable to Garruto until further epidemiologic studies were done back in the Philippines. A recent study published in *JAMA*lists Filipino immigrants to the U.S. as having the highest case rates for tuberculosis among foreign-born persons, second only to immigrants from Mexico (27). Mulder acknowledged that T.B. is a leading cause of death on Guam and that T.B. meningitis was not infrequently seen in its hospitals (28).

Lessell's study on the febrile seizures that accompany neurodegenerative disease concluded that the overwhelming majority of these occurred in the setting of upper respiratory tract infection (29). This does not support known viruses carried by insects. Hirano and Malamud's 17 post-mortems on Parkinson–Dementia Complex showed two that presented with pulmonary tuberculosis (30), while several others had 'pneumonia' which in turn could have been caused by cryptic tubercular disease. But even in this study of general pathologic findings, most of the 17 cases presented with neuropathic changes duplicated in the literature of tuberculous meningoencephalitis.

SMOKE SCREENS

Since James Parkinson wrote *Essays on the Shaking Palsy,* a mind-boggling number of causes and 'risk factors': infectious, pharmacologic, industrial and degenerative, have been implicated to cause the disease he first documented. In few cases has doctor/medical researcher James Young's warning been more applicable:

> Sixty years ago, to claim that the specific disease tuberculosis of the lungs had a multiplicity of direct causes was in keeping with the knowledge of the period. Thus it was believed that the inflammation of a bronchitis, the irritation of the inhaled fragments of stone with which this mason worked, etc. were each one a 'direct' cause of pulmonary tuberculosis, and that there were many other causes as well – for example heredity, unhealthy environment, etc. Time has shown that the greatly different direct irritants and the other indirect agencies operate in one common way – by increasing cell and tissue susceptibility to the one common factor, the *tubercle bacillus*. In many other cases the history of medical progress has shown that, where several causes have been advanced to account for a disease, these have proved to be nothing more than factors preceding, and predisposing to, the single common agent (31).
>
> James Young, 1924

As Jancovic relates, if Parkinson's was from a genetic cause, it would cluster primarily within at-risk gene lineage, but this, in general, has not been the case (32). In the meantime studies of twins, in which twins from a

single egg show no higher incidence of Parkinson's than those from two eggs, also argue against a genetic basis for Parkinson's (8).

Furthermore, most of the single-gene mutations found more commonly in Parkinson's code for metabolic enzymes. But Merrill, Geier and Petricciani induced human cells to initiate enzyme synthesis through infectious (bacterial) gene change (33). This validated Morse and Lederberg's earlier work which showed that the genetic code is universal and that genetic changes in human cells could come about by bacteria and their phage viruses within.

Inside disease-causing bacteria are viruses called 'phages'. It has long been known that not only do bacteria such as mycobacteria get infected with these phage viruses, but that there is an invisible war, called 'lysogeny' going on, in which bacteria use phages as viral weapons. Lysogeny is where one colony of bacteria sets out to destroy another by launching its tadpole-shaped phages towards its victim. If phages do not kill, they can genetically alter, creating new and dangerous germs for mankind to cope with. Furthermore, Mankiewicz, collaborating with Jackson established that phages inside mycobacteria such as tuberculosis could induce cytopathogenic changes in healthy mammalian tissue (12). Meanwhile, Lwoff and early phage workers showed how the phages inside Mankiewicz's mycobacteria could be activated by a host of chemical and other agents (34), some of them pesticide-like, explaining how the proliferation of different agents felt to cause Parkinson's could have occurred – by chasing phages with a cytopathogenic capability for human target tissue out of an existing bacterial infection.

In so far as those who would link the well-known risk factor of rural living to increased chemical exposure as a cause, Jancovic notes this could just as easily reflect exposure to an infectious agent (32). The *Actinomycetales* including the *nocardia* and *mycobacteria* are soil born worldwide and include *Mycobacteria kansii.*

Gorell documents that prolonged occupational exposure to copper, manganese and iron are all associated with Parkinson's (35). But David, an expert on mycobacteria, points out that mycobacterial cell mass can be greatly increased in the lab by adding any of these agents to existing culture medium (36).

On a biochemical level, oxidative stress has been mentioned as contributing to Parkinson's. The *substantia nigra* is under triple jeopardy from oxidant stress injury. In the body tyrosine is first converted to dopamine, itself highly toxic to catecholamine cells (37). Dopamine in turn is metabolized to hydrogen peroxide and free radical byproducts, which again can damage cell components of substantia (38). In addition, neuromelanin, found in the *substantia*'s pigmented neurons, contains large amounts of iron (39) which as has been mentioned is a significant growth factor for mycobacteria (36). Dopamine-derived hydrogen peroxide reacts with this iron, generating extremely neurotoxic free hydroxyl radicals. In 1991, Ben-Shacher and Youdin, by intranigral iron injections induced Parkinson's in rats (40).

Just how much of what's been documented in PD is secondary to mycobacterial intermediate metabolism is open to question. But mycobacteria are strict aerobes and oxygen must be available as the final electron acceptor. Three distinct respiratory chains have been described, one of which leads to the formation of hydrogen peroxide. The disposal of accumulated hydrogen peroxide is then accomplished by two iron–porphyrin enzymes, catalase and peroxidase, which occur in all mycobacteria and the products of which release their own free oxygen radicals (36).

In addition, mycobacteria synthesize their own tyrosine, precursor to dopamine in humans (36), and a possible source of 'oxidant stress overload' as individual generations of mycobacteria are replaced during an ensuing infection.

Also, how much dead mycobacteria, who's lipid content can amount to 40% of their dry weight (41), account for the higher levels of lipid peroxidation seen in the Parkinson's *substantia* (42), is open to interpretation, as is whether the increased level of iron found in Parkinson's *substantia* (43) couldn't at least be in part due to mycobacterial iron porphyrin release.

Pathologically in Parkinson's there is an accumulation of melanin-containing nerve cells brain the in stem, chiefly in the *substantia nigra* and the *locus coeruleus* (44). Melanin may be formed biologically *in vitro* by oxidation of tyrosine or tryptophan, both of which are aromatic amino acids manufactured by the mycobacteria (36).

CONCLUSION

It might have been coincidental that both *Mycobacteria tuberculosis* and Parkinson's came in to force and were linked with the great Industrial Revolution. Or fortuitous that Blocq and Marinesco established through tuberculoma attack that the *substantia* was important to Parkinson's (20). It could be considered incidental that the preferential site of attack of tuberculosis meningoencephalitis is the convexity of the brain, where it covers the *substantia*, the *basal ganglia* and has ready access to the cranial nerves. Perhaps even coincidental that Von Economo's encephalitis, which caused Parkinson's regularly, was, according to Hall and the ARNMD almost indistinguishable from CNS T.B. (21,45). It might be considered a fluke that Deprenyl (Eldopril) a Parkinson's

mainstay, comes from a class, the MAO inhibitors originally designed to cure tuberculosis (14). Or circumstantial that clinical and epidemiologic studies have peppered Parkinson's literature for decades linking tuberculosis-like germs: including *nocardia, corynebacteria* (diptheria) and the *mycobacteria* – not only easily confused by seasoned bacteriologists (4) but which also cross-react under serological identification (3). It might be considered adventitious that Burn isolated a germ (*9*) with an eerie resemblance to Jackson and Livingston's (10, 11) *mycobacteria/nocardia* cross in three Von Economo's infants at autopsy; or that Jackson found acid-fast forms in Burn's bacillus that she implicated as causing Wilson's disease (11), dominant cause of Parkinson's in the young. It might be considered insignificant that tuberculosis-like *Nocardia* has a specific affinity for *substantia nigral* neurons (1) and that the most convincing Parkinson's animal model to date happened when Beaman injected *nocardia* into mice (2). It might seem random that Kohbata & Shimokawa cemented a relationship by blood serology between *nocardia* and *mycobacteria* in 20 of 20 Parkinson's patients (3) or that Gao linked Parkinson's to *mycobacteria* in blood through diagnostic heat shock proteins (*6*). It could be considered anecdotal that Mital and Sarkari (17), Otaki (18), Fuente-Aguado (15), Solanki and Kurasawa (19) all independently cured Parkinson's with anti-tuberculosis therapy. It could be called inconsequential that in AIDS-related Parkinson's, sometimes listed as the most common cause of infectious Parkinson's, that Berenguer reported *mycobacteria* as the most common CNS pathogen in HIV infected people (23). It could be considered coincidental that Guam, where T.B. meningitis runs rampant, hosts an epidemic number of neurologic disorders, including Parkinson's–Dementia (24). It might seem that there is a lack of essential connection between the post-traumatic Parkinson's, say of an ex-boxer, and the fact that such trauma could also have caused a long-standing infection, such as tubercles in the brain, planted even decades before, to discharge bacilli into the meningeal spaces (46), reactivating a long quiescent disease from one punch too many. And it might seem unrelated that occupational exposure to copper, manganese and iron(35) are all not only associated with parkinsonism but the very substances which act as mycobacterial growth factors in the laboratory (*36*).

And it might seem chance that the triple jeopardy of oxidative stress under which the *substantia* sits, namely catecholamine toxic dopamine, derived from tyrosine; hydrogen peroxide and free radical byproducts: all of which can damage the *substantia* (38) are also manufactured by mycobacterial intermediary metabolism and cell-respiration (*36*).

It might be considered random that many Parkinson's victims show the same cachexic wasting away that has long typified consumption – or that the dopaminergic neuron loss McGear found as an active Parkinson's process, even after death (47), is just the sort of chronic process that so characterizes a disease like tuberculosis, which often begins in youth or childhood.

It could be considered incidental that tuberculosis and Parkinson's are presently considered diseases of the older population with more men than woman affected.

But in the end, and taken together, there are just too many coincidences in an ever-growing list to just casually dismiss.

In conclusion, the preponderance of convincing evidence, as we near the bicentennial of James Parkinson's original Essay points to a chronic infectious cause, not viral and most likely of the family *Actinomycetales* – either mycobacterial or a tuberculosis-like mycobacterial/nocardial cross. Clinical trials await.

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