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Review Article

Infectious Diseases And Traditional Medical Ideas About Inheritance. II. Tuberculosis, Syphilis, And Rheumatic Fever As Models.

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Running head: Infection and Heredity

Abstract

Infections largely defined medical practice well into the 20th century. Tuberculosis, syphilis, and rheumatic fever, common diseases with chronic components, and a major part of medicine in the pre-antibiotic era, are used here to examine traditional relationships between infections and inheritance. Experience with these conditions supported doctrines of heredity, degeneration, diatheses, and polymorphism that also applied to inherited disorders, and emphasized variability that opposed the distinct unit traits of Mendelism.

Keywords : *Infection, Heredity, Rheumatic fever, Syphilis, Tuberculosis, Degeneration, Diathesis, Polymorphism.*

INTRODUCTION

Tuberculosis, syphilis, and rheumatic fever, common diseases with chronic components, are used here to examine traditional relationships between infections and heredity. Their impact before antibiotics is almost unimaginable: Once, "sooner or later everyone has pulmonary tuberculosis" (Woodcock 1910), nearly universal in cities (Lister 1920), causing as much as a third of mortality in industrialized countries in 1900 (Baldwin 1907). By 1900, about 1 in every 22 people in the United States had syphilis (Amstey 1994); by 1942, draftees had a 4.5% prevalence, with an 11.3% regional peak (Rasnake et al. 2005)! Rheumatic fever, once the most common cause of acquired heart disease, was still a top childhood killer in 1950 (Stollerman 2003).

Infections largely defined medical practice well into the 20th century. They supported diseases as variable entities, with multiple causes, and shared doctrines of heredity, degeneration, diatheses, and polymorphism with models of inheritance. With this, they reinforced medical interest in, and ideas about, heredity, but fit poorly into single gene models, delaying the integration of genetics into medicine (Lubinsky 2024).

TUBERCULOSIS (TB)

TB had a strong hold on popular and medical thought (Sontag 1978). It usually begins in the lungs, but can start elsewhere- e.g., in the gut from infected milk. It may be limited to one site, or spread widely, with acute and chronic problems, and very different courses- confusion remained even after *Mycobacterium tuberculosis* was identified as the causative organism in 1882 (Sakula 1982).

Like the blind men and the elephant, physicians saw different aspects as separate. One form, scrofula (swollen and often ulcerated lymph glands of the neck) was well known by the 11th century (Garrison 1929: 288). Consumption, (*phthisis* in Greek), specific for TB in the early 20th century, started as a wasting away, a literal consumption of flesh known for centuries- the Hippocratic School recognized pulmonary phthisis, and saw it as hereditary, a common belief at the time (Herzog 1998). When Richard Morton wrote the first book on this in 1685, he felt that it was inherited (1935), but saw scrofula as a different disease that also caused wasting (King 1982: 25).

Recognition of a lung disease began around mid 17th century as autopsies became common. Sylvius saw lung swellings reminiscent of scrofula, and suggested a hereditary disposition causing both (Baldwin 1907). In 1733, Desault

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divided causes of phthisis into antecedent and conjoint: Victims generally had contracted chests, phthisical parentage, and hereditary predisposition, or exposure to contagion, the conjoint cause, while tubercules and concretions in the lung set up the disease, with elimination resulting in a cure (Kidd 1918).

Bayle, in the early 19th century, rejected inflammation in favor of a constitutional disease dependent upon a tuberculous *degenerescence*. His *Phthisis tuberculosa* also included pulmonary gangrene and lung cancer, and was only one of several possible expressions (Baldwin 1907). Soon after, Laennec (who invented the stethoscope) narrowed this considerably, making phthisis essentially pulmonary tuberculosis (King 1982: 35), with other manifestations still seen as separate. By 1819 he saw the tubercle as the key to all forms of the disease, and it was named tuberculosis by Schonlein in 1839 (Sakula 1982). Laennec also rejected contagion in favor of heredity (1826).

In 1835, Sir James Clark (soon physician to Queen Victoria) cited an inherited diathesis as the cause. In 1844, Stokes, also influential, noted "a strumous diathesis or hereditary predisposition" in some but not all cases, and Cotton in 1858 spoke of both a hereditary taint and an acquired tuberculous diathesis (Waller 2003). In mid 19th century, Virchow, a founder of modern pathology, saw scrofula as a constitutional (and inherited) weakness of badly developed glands and lymphatics, different from TB (Kidd 1918), and enlarged lymph nodes continued to be seen as predispositions to TB, instead of sequelae (Baldwin 1907).

For Huth (1875), "rickets, together with phthisis, tabes mesenterica [mesenteric lymphatic TB], tubercular meningitis, hydrocephalus, spina bifida, and a few others, with their consequent mental and nervous diseases, are at present considered merely different members of the great scrofula family of disease." This could be transmitted prenatally, with "infants born with both large and miliary tubercles in their lungs."

But, for phthisis, "the influence of inheritance has been much over-rated… probably, the average is only [!] about 12 per cent. for direct inheritance, and for family predisposition 48 per cent." And, of course, "all causes which tend to a diminution of vital power are causes of phthisis" (pp. 255-7). Here, a "family of disease" is polymorphism's variability and transformation, "consequent mental and nervous diseases" a neuropathic diathesis with "diminution of vital power" and degeneration, all of this hereditary.

Even after Koch found the bacillus, contagion was questioned (Cornet 1907: 20-27), and other organisms suggested, e.g., for Shaw (1920), TB sputum also contained "saprophytes [microbes living on dead material], several other pathogenic organisms, and even putrefactive organisms," suggesting that interactions had a role in creating the clinical disease.

By 1900, doctors generally saw a specific organism with "classic" lung lesions and other findings. But there were different manifestations- it still wasn't today's view of one disease caused by a single bacillus. First, there were functionally different diseases: Lung involvement, consumption, Pott's disease of the spine, intestinal TB, scrofula, and so on, all with different problems and needs. They were the same only in the sense that everybody in a car accident has trauma!

Second, the bacillus was far from sufficient- "90 per cent of a population infected by tubercule do not succumb to it" (Lister 1920), and "only a small minority die from it" (Woodcock 1910), so other factors had to be involved. And here, many continued to take an inherited component for granted- "if the disease itself be not inherited, a particular temperament which renders the constitution liable to be attacked by it, is capable of hereditary transmission (Turner 1889: 548). Even Koch accepted an inherited predisposition (Kidd 1918). Indeed, "doubt has been thrown upon the belief that contagion is the major determinant in the distribution of the disease" (Solis-Cohen 1894: 718).

There were physical signs of susceptibility- constitutions indicating diatheses, an inherited "habitus phthisicus, characterized by a narrow chest, with long vertical diameter and thin neck" (Cornet 1907: 327). Lenz had "no doubt that the asthenic constitution entails an enhanced susceptibility to pulmonary tuberculosis. The experience of life-assurance companies has shown that persons who were accepted as free from tuberculosis but ultimately died of the disease had had a comparatively small chest measurement at the time of acceptance; and G. Florschütz… believes that the low-grade constitution is to be regarded as a contributory cause of tuberculosis rather than as a consequence of that disease" (1931: 389).

With this were signs of degeneration. Rivers, in "The Atavistic-Degenerative Diathesis of Tuberculosis," noted "the old observation [of Laennec, almost a century before] that the heart and arteries of consumptives are exceptionally small" with evidence of "an autochthonous constitutional anomaly," suggesting a weak or asthenic constitution. There was a general hypervariability, and stigmata of degeneration-throwbacks to more primitive structures- with a relationship between nervous system abnormalities and TB, and "the especial vulnerability of idiots and the subjects of dementia praecox [schizophrenia] and primary dementia" (1923).

Kallmann, studying the inheritance of schizophrenia, had a chapter on a genetic relationship with TB (1938). He found a greater direct vulnerability that extended to the normal siblings of the insane, pointing to "a genetically non-specific constitutional defense mechanism" (1953: 152-3).

Scrofulosis was "not a disease, but a condition predisposing to certain disease processes, and particularly to hyperplasia, tuberculous inflammation, caseation of lymph glands…

any peripheral inflammation, however slight, is prone to be prolonged" (Chrystie 1894). And different constitutions favored different forms of TB, "that pulmonary tubercule favoured brunettes, and that in bone or glandular disease fair traits predominated, and that red heads were especially predisposed to tuberculous peritonitis" (Rivers 1923).

On another level, the primarily affected lung (right or left) "is in about 80% of the cases identical in parents and children or in brothers and sisters... Brehmer has also observed that in members of a particular family tuberculosis tends to originate at the same age... [T]uberculosis of other organs than the lungs tends in the members of any one family to attack some particular organ or group of organs (the bones, the kidneys, the cerebral membranes)" (Lenz 1931: 388). For Vogt, a noted ophthalmologist, "in many cases the lowered immunity to tuberculosis handed down from generation to generation affects, not the lungs, but the bones or joints, or the kidneys, or the eyes, while in the last named it affects now the cornea, now the iris or the choroid, now the retina and its vessels, or again the whole globe... [W]e shall have to consider not only the hereditary low immunity of the system as a whole to tuberculosis, but also that of individual organs and parts of organs, and hence of circumscribed cellular groups" (1941: 857).

TB was popularly believed to have a propensity for the passionate, who were deficient in vitality (Sontag 1978)- what "is wanting... is the life-force, the vital energy — an energy which we know to exist because of its manifestations as fully as we know electric energy to exist" (Solis-Cohen 1894a). "An irritable nervous system is so frequently associated with pulmonary tuberculosis that neurasthenia, hysteria, or nervous instability in general have long been considered predisposing factors... those persons who possess by inheritance or otherwise a delicate nervous organization frequently fall victim to this disease... In the true psychoses there is an undoubted predisposition, especially with imbecile melancholics... Epileptic families are also prone to tuberculosis" (Baldwin 1907: 179).

Warthin, in a classic paper (1913), saw certain familial cancers "frequently associated with a marked susceptibility to tuberculosis..., also with reduced fertility [with] the running out of a family line through the gradual development of an inferior stock, particularly as far as resistance to tuberculosis and cancer goes."

Hutchinson linked tuberculosis, cancer, and insanity to consanguinity (1900). For Arner, for scrofula "almost universally recognized as hereditary... we should therefore expect to find intensified by double heredity [consanguinity]." And, indeed, US Census data showed that consanguinity "seems appreciably to intensify scrofula, but there is no indication that scrofula is ever caused by parental consanguinity" (1908). Early authors cited 10 to 85% of cases of TB as hereditary (Cornet 1907), and a hereditary diathesis or constitution continued to find support (Pearson 1912; Pearl 1920). Family histories showed important connections between individual and family issues- "morbid heredity should be as a breviary always open in front of us to instruct us with all possible certainty as to the prospects of a given case as regards its evolution, its termination, its possible consequences for the individual or for his descendants" (Raymond 1908). Surgeons included heredity in case series- a family history could be an important guide to diagnoses of non-specific complaints, but I saw no indication of common concerns that outcomes were worse in familial cases. Familial susceptibility and resistance to tuberculosis continued to be an active field of medical research at least through the mid 1940s (Puffer 1944).

Racial proclivities included greater resistance among Jews (Rakower 1953), and less in Blacks (Pinner, Kasper 1932).

For animals, Sewall Wright, a famous geneticist, and Lewis found marked genetic differences in resistance among inbred strains of guinea pig (1921). One animal breeding text emphasized inherited predispositions to TB, and a particular "faulty conformation" (Shaw 1901: 78-9, 85), with a wonderful photo of a "Yearling Grade Heifer (Illustrating predisposition to tuberculosis)" (p. 81)! Interestingly, current work supports genetic resistance to TB in cattle (Yuan et al. 2021).

Finally, heredity in development interacted with infection. For "mongolism," Down linked "ethnic features" with "degeneration... for the most part... arising from tuberculosis in the parents... the hereditary origin of the degeneracy" (1862). For Ballantyne, dean of fetal pathologists, "malformations and structural peculiarities in the children of phthisical parents has been known for years, and V. Hanot has called it heteromorphic tubercular heredity. Various dystophias have been noted, such as minor malformations and structural peculiarities of the cranium, hernias, ectopia of the testicle, malformations of the heart and great vessels, lobulation of the liver, congenital dilatation of the oesophagus, infantilism, congenital dislocation of the hip, hare-lip and palatal defects, deaf mutism, and even actual monstrosities (pseudencephaly, anencephaly). In these cases it would seem almost as if the malformation or anomaly had taken the place of the truly tubercular lesion" (1902: 215-6).

Syphilis

We see similar considerations with syphilis, a sexually transmitted disease caused by *Treponema pallidum*, a spiral shaped bacterium. Infection occurs in stages. Primary cases show skin lesions at the site of infection. Secondary findings begin about two months later, with a flu-like illness and general rash, plus effects on areas that include brain, kidney, liver, and joints. A tertiary form can follow, usually 3 to 30 years later, with a slowly progressive inflammation that can strike anywhere, and incapacitate or kill. The aorta can

balloon out, and leak or burst. Brain involvement is typically a general paresis (paralysis of the insane), and spinal cord *tabes dorsalis* has a variety of findings, although an unusual gait is typically the most obvious.

Probably only about a third of untreated cases go beyond the secondary stage, a little less than half with severe problems (Centers for Disease Control and Prevention 2022). Both secondary and tertiary findings can be exceedingly diverse: "Know syphilis in all its manifestations and relations and all other things clinical will be added unto you" (Osler 1897). And, when the fetus was infected from the mother, there could be complicated effects, again, with a high degree of variability.

It took some time to connect late findings with syphilis. Tabes dorsalis represented an ongoing controversy for half a century (Lubinsky, 2024a). The pathological picture of general paralysis was first delineated in 1822, but wasn't associated with syphilis until 1857 and, for some time, both were labeled "para-syphilitic-" not true manifestations of the disease. Aortic issues weren't really linked until 1876 and, even in 1930, it was "only very recently that all opposition to the idea that general paralysis is a true syphilitic manifestation disappeared" (Faber: 105; 107).

Syphilis was certainly less romantic (figuratively, that is) than tuberculosis. Degeneration rather than sensitivity was its hallmark, supported by added findings in congenital cases acquired from the mother. With this came a host of possible interacting and predisposing factors, and much confusion. Overall, "the story of the search for the cause of syphilis is a tale to make the judicious grieve. 'One hundred and twenty-five causes of syphilis,' said Lassar, speaking in 1905, 'have been established during the last twenty-five years'"(Osler 1907: 440).

Fleck described divisions into different forms, and links with humors, constitutions, and various other factors (1935). Other venereal diseases were a particular problem, especially gonorrhea and chancroid. In the late 15th century, "all three diseases probably flourished luxuriantly, things became hopelessly mixed; and then for over three hundred years the theory of the unity of the virus… held sway. It was developed by Astruc into the theory that, the virus being the same, differences in the lesion depended on whether a non-secreting or a secreting surface were affected" (Osler 1907: 439). It wasn't until the 1850s that a true differentiation was made and accepted (p. 440), but, still, in 1884, one view of syphilis was "a specific contagious, noninfectious disease; communicable by contact of the poison with a breach of surface, or by hereditary transmission" (Cochran et al., 2000)

The bacterium was identified in 1905, although some saw "a biological difference between the spirochaetes of general paralysis and tabes and those of primary syphilis" (Routh 1918). But, as with TB, a predisposition seemed to determine the organs affected and to what degree. Tabes dorsalis only occurs in a few percent of cases, and Erb found it more often with predisposing causes, among them cold exposure, sexual excess and overwork, and that old standby, a neuropathic tendency (Osler 1907: 488). Bing (1939: 310-11) noted that it was "widely agreed that hereditary neuropathic predisposition contributes to the development of tabes: Erb has found evidence of this in 28 per cent of his patients with tabes… If one very carefully examines tabetic patients for signs of degeneration (malformations of the skull, palate, lobes of the ears, fissural angiomas, etc.), one will find that these stigmas are much more frequent than in normal individuals. The implication is that there is also a defective anlage [embryonic precursor] of the spinal cord which predisposes the patient who has contracted syphilis to the development of tabes. This supposition is supported by the finding that the majority of spinal cord heterotopies and abnormal coursing of fibers within the cord are found in tabetics."

And, as suggested for TB, syphilis interacted with heredity in development. Multiple genetic disorders were ascribed to congential syphilis, e.g., congenital night blindness (Hulke 1866), Friedreich ataxia (Friedreich 1877), and Wilson's disease (Noone 1916: 364) [all recessives]. For cleidocranial dysostosis, a dominant affecting skull and collar bones, alcoholism, TB, syphilis, and rickets were suggested (Fitzwilliams 1910: 1475), and, for multiple exostoses, a dominant with bone growths and deformities, TB had been proposed, and syphilis "suggested as a cause in this, as in most obscure conditions" (Stocks 1925: 48).

While syphilis in pregnancy can cause losses, infants appear normal, only to show a variety of problems over time (Cooper and Sánchez 2018). As far back as 1616, Licetus suggested that, just as syphilis might cause deformations by destroying tissues in adults, so might inflammations and corroding humors affect the more tender fetus (Ballantyne 1904: 159). In 1839, JY Simpson, an influential obstetrician, proposed that fetal inflammation might produce the developmental arrests that Harvey had suggested in 1651 (Ballantyne 1904: 163).

Diday asked, skeptically, "*Can hereditary syphilis manifest its action by morbid effects other than the characteristic symptoms of venereal disease*? This question… might be done in reference to almost all the diseases of infancy; for there are very few in the etiology of which syphilis has not been accused of playing a more or less direct part-" he then cited induration of cellular tissue, rickets, tabes, some kinds of tetter [a skin disease], obstinate sleepiness, convulsions, hemicrania and hydrocephalus, imperforate anus, hypospadias, and pemphigus (a skin blistering). He rejected this, but added "that the venereal dyscrasis never attacks… an infant, without imparting to its constitution a debility which predisposes it to all kinds of organic or functional affection. Acute diseases occur more readily in it and are more severe… diathesis more deeply rooted" (1858: 119). So, if syphilis didn't necessarily

cause abnormalities, it could intensify the effects of whatever did.

Rheumatic Fever (RF)

Rheumatic fever arises from a streptococcal infection (only proven in 1931), usually in the throat, but sometimes unrecognized. In a few cases, two to three weeks later, *after the organism is gone*, a variety of problems, isolated or combined, appear, as the body's response affects its own organs.

There can be heart inflammation, joint pain and swelling (rheumatism in the older literature, but actually an arthritis), and involuntary muscle movements (Sydenham's chorea). Fever, abdominal pain, a rash, and nodules under the skin may also occur. Once this response occurs, recurrences become more likely (National Center for Immunization 2022). The heart can show immediate damage but, more often, problems develop years or decades later, and can be fatal. Long term heart problems from RF may have affected more than 2% of the 19th century urban European population (Wilkinson 1935). Around 1950, rheumatic fever "killed more school-age children than all other diseases combined" (Stollerman 2003).

Difficulties with diagnosis and long term follow up make incidence and effects hard to assess, but they certainly were significant. Rantz (1963) found a 6.1% yearly rate of acute rheumatism in the U.S. Army during the civil war. Not all of this was rheumatic fever, but records suggested a "substantial number."

There were all sorts of theories about the rheumatism, "for no disease has provided a greater diversity of opinion:" Lactic acid, sweating, a nervous system disease that affected joint nutrition, and others were suggested. Maclagan, who discovered the use of aspirin here, thought it "allied to malaria- a miasmatic disease, liable to appear in low lying, damp localities at certain seasons" (Wilkinson 1935).

Sydenham, a great 17th century physicians, separated the joint issues from gout, to which it shows some resemblance. He also gave a superb description of the chorea, which was named for him, but failed to recognize any connection with the arthritis. Similarly, despite reports of heart problems associated with acute rheumatism, there was still no general recognition of the relationship as late as 1832. And even then, "acute rheumatism was considered merely a disease of joints, with the occasional involvement of the heart, brain or lungs by a kind of metastatic spread" (Wilkinson 1935).

Huntington's disease, a dominant genetic disorder with movement problems and neurological deterioration, added to the confusion. This is probably what Ellison saw in 1832 when he noted that chorea in adults "is frequently connected with paralysis or idiotism and will perhaps never be cured. It appears to arise for the most part from something in the original constitution of the body, for I have often seen it hereditary." However, for childhood chorea, most likely Sydenham's, there were also suggestions of heredity in 1783, 1810 and 1815 (Hayden 1981: 6).

For AE Garrod, "the tendency towards chorea is far more conspicuous in some rheumatic families than in others... probably due to some peculiarity of the nervous organisation of their members" (1890: 125). Cheadle, in a classic work on childhood rheumatism, saw, for the chorea, "a physiological basis in that greater mobility of the nervous system and motor readiness of expression... and in the more excitable temperament of quick, intelligent children, and of girls as compared with boys" (1889: 52-3). He also suggested a family relationship of the rheumatic taint and anemia and "growing pains" (pp. 41, 64). In 1935, Wilkinson noted "a definite family incidence," and added that "many experienced clinicians have believed in a rheumatic type of patient- a child who from appearance, colour, and build may be recognized as predisposed to rheumatic disease. These children are possessed of a low resistance to many infections, they take disease severely, and develop rheumatism even in good circumstances."

Bing, in his classic neurology text, felt that "both an inherited rheumatic and neuropathic predisposition play an important etiological role in this disease. In not a few cases a familial tendency to chorea has been traced... It has been ascertained quite frequently that many of the forebears of choreic patients had rheumatic disorders. Also that in a few of the antecedents there were epilepsy, hysteria, and other neuropathic tendencies" (1939:155-6). Gates noted occasional epidemics, "but it is also hereditary in a large proportion of cases, like epilepsy and schizophrenia... generally considered part of the syndrome of rheumatic fever, but it may occur without the latter" (1946: 1020).

It appeared that "the tendency to rheumatism [in RF] is transmitted as strongly as the tendency to gout." Of 592 children in a general hospital, for 173 with a clear history of acute rheumatism in immediate relatives, 22% had developed "unmistakable rheumatic affection;" for others, only 4.5% (Cheadle 1889: 26-8). Garrod found corresponding frequencies of 35% and 21% in a similar study of adults (1890: 52). Both also cited uncontrolled studies showing a high frequency of the disorder in close relatives of affected patients.

Garrod noted that proportions of affected parents seemed to decrease the older the children were, not surprising, since "those who inherit a tendency to rheumatism would suffer from the disease at an earlier age than those who have no such hereditary predisposition, and Fuller's observations agree perfectly with what is observed in other hereditary diseases, such as gout and tubercule" (1890: 51).

Malformations of the heart were attributed to fetal inflammation with RF in pregnancy (Lubinsky 1991), and

Virchow added multiple small kidney cysts (Senator 1905: 369, 372).

Once a specific disorder was delineated, other conditions were soon added as parts of rheumatic fever (if there was fever) or rheumatic heart disease (if there was not), including specific bacterial and viral infections, and other causes of arthritis, such as lupus, as yet undifferentiated, or difficult to diagnose (Taranta, Markowitz 1989: 3).

Inherited factors were still cited, "that the hereditary constitution may be a factor in determining predisposition to this disease" (Gauld et al., 1939) or, a probability "that heredity plays a definite role in the etiology of the disease" (Gauld and Read 1940). Wilson also found susceptibility controlled by a single recessive gene (1940: 20-58).

CONCLUSIONS

Tuberculosis, syphilis, and rheumatic fever, common diseases with chronic and variable findings, were powerful models for medical practice until the middle of the 20th century. An inherited component was considered central to all three during that time, with infection and heredity as causal factors that could act together. Doctrines that dominated medical views of inheritance at the time- heredity, degeneration, diatheses, and polymorphism- were also applied to these disorders. They were part of a model for diseases as diffuse and variable entities with multiple causes and for theories of inheritance that fit poorly with the distinct causal entities of Mendelism, delaying the integration of genetics into medicine for decades.

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