Metabolic theories of Whipple disease (draft of Feb 2012)

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Abstract

Whipple disease is a rare, infectious, disease first described from a single case by Whipple in 1907. As well as characterising the clinical and pathological features of the condition, Whipple made two suggestions regarding its aetiology. These were either than the disease was caused by an infectious agent, or that it was of metabolic origin. As the disease is now thought to be caused by infection with the bacterium *Tropheryma whipplei*, historical reviews of the history of the disease typically mention only the first of these suggestions. In this paper, we therefore revisit Whipple's other theory. We argue that a diverse and often successful research programme was developed around this mechanism of disease causation which gave rise to many useful findings on the condition. In the later parts of this article, we then turn to discuss the surprising neglect of this period of Whipple disease research in the current literature, and conclude by offering a brief reconstruction of this early history suitable for use in a technical context.

Keywords

Whipple disease – Causation - Metabolic disease - Infectious disease - Theory choice

1: Introduction

Whipple Disease (WD) is a rare, infectious, disease causing a complex constellation of symptoms:

> Whipple's disease is primarily a gastrointestinal disease manifesting as a malabsorption syndrome, and is detected through endoscopy and intestinal biopsy. Nongastrointestinal manifestations of the disease, although less common, are reported and have aided in its recognition as a multiorgan disease entity.
>
> (Afshar, Redfield and Higginbottom, 2010: 263)

About 1000 cases have been reported worldwide since its discovery in 1907 (Fenollar, Puechal and Raoult, 2007) Whilst this disease is not without clinical interest, our focus here is historical. In particular, we wish to extract a moral here about how scientific practitioners do (and, more ambitiously, should) understand the history of their own disciplines.

The writing of this paper was motivated by a study of histories of WD found in technical articles on the condition.[i] These short historical vignettes typically present the development of our current understanding of WD arising from a process of gradual accumulation of facts from the earliest and most rudimentary clinical description, via the discovery of a (possibly causal) bacteria, to our detailed, contemporary knowledge. These authors suggest that each new publication on WD simply presented a further piece of the puzzle, with the implication that the intellectual history of the disease is one of simple compilation of pathological evidence.

As we will go on to argue, the history of WD is much more rich and controversial than this. In particular, disputes regarding the aetiology of the disease led to many complexities, confusions, wrong-turnings, arguments and - yes, occasionally - substantive developments in understanding. While it is a truism to argue that there is more to the history of medicine than simple progression to the point of current knowledge, we wish to argue that the story that we tell here - and that is omitted in reviews produced in the usual manner - is valuable to scientific practitioners. As such theoretical oscillations are often a feature of newly discovered diseases, we think that an awareness of this historical issue is enlightening for our current understanding of medicine in general.

We will use this rich motif of disputes between competing theories to construct this paper. In section two, we outline the first description of the disease. Here, we suggest that two different aetiological theories were in place from the outset. We then go on to show that a choice between competing theories was rapidly made, even in the absence of decisive evidence one way or another. In section three, we then go on to demonstrate the consequences of this decision in shaping the manner in which the disease as a whole became understood. This description will be underwritten by our argument that difficulties in understanding and treating WD were the direct consequence of theoretical claims about WD causation. More specifically, the loss of one of the two aetiological theories suggested by Whipple (1907) led to adverse outcomes for researchers and patients. In section four, we then discuss how - and why - Whipple's other aetiological theory began to be taken seriously once again.

We conclude this paper by arguing that this kind of historical concern does not necessarily lead to verbosity. In section five, we suggest a short reconstruction of the history of WD which could potentially be used in the introduction to a technical medical paper, while still admitting the difficulties and uncertainties of this historical episode. We certainly agree that, for reasons of priority and of concision, historical introductions to current technical reviews should not be expected to deal with every complication, quirk and contingency possible. However, we think that the kind of historical presentation currently prevalent in the literature makes these reviews misleading, rather than succinct. We therefore present an example of a short historical introduction to WD, such that might be used in a technical context, in our conclusion.

2: The early history of Whipple's disease

The conventional account of the discovery of Whipple disease goes something like this: in 1907, Dr George Hoyt Whipple described the ante- and post-mortem examinations of a 36 year old physician who had recently returned from a period of medical missionary work in Turkey. He had been suffering, with increasing severity, for five years with steatorrhoea, bronchitis, arthritis, and abdominal pain. While this progressive clinical presentation suggested peritoneal tuberculosis or some kind of intra-abdominal malignancy, both were soon ruled out at autopsy. Instead of the caseous nodules or malignant deposits characteristic of either of these suspected diagnoses, extensive deposits of fat were found to surround the abdominal organs. One particular sample of an intrabdominal lymph node, when Levaditi stained and examined under light microscopy, revealed “great numbers of a rod-shaped organism (?)...about the diameter of the spirochaete of syphilis but not of spiral shape...[which] closely resemble in form the tubercle bacillus...its distribution in the glands is very suggestive.” (Whipple, 1907: 388) These organism-like structures were found primarily within macrophages, which themselves were of an abnormal foamy appearance, but were also found within the peri-visceral extracellular regions of the gut. Given the close resemblance of these organism-like structures to the aetiological agents of other diseases, this strongly suggested that some kind of novel infectious process was responsible for this unknown disease. Indeed, these structures were later identified as bacteria and are now known to cause the disease. Perhaps because of this, this aetiological suggestion is widely known.

What is much less widely known is that Whipple also described another aetiological mechanism capable of accounting for the symptoms present in this case. In fact, not only was this alternative mechanism suggested as a possibility, but was suggested to be by far the most likely cause of the disease. Apart from the bacteria-like structures, most of the pathological changes found seemed to instead indicate that this patient was suffering from an “obscure disease of fat metabolism” (Whipple, 1907: 390). This explanation offered an harmonious unification of the diverse pathological features: the presence of abnormal fat in the stools; extensive deposition of fat in the abdomen; loss of normal subcutaneous fat stores; the development of an inflammatory tissue reaction to the abnormal intra-abdominal fat deposits; disturbed architecture of the intestinal villi; and the presence of fatty droplets in macrophages (hence their distinctive foamy appearance), in a way that an infectious cause did not:

> Several facts indicate that this fat is in itself in some way abnormal or holds in suspension some abnormal or toxic substance...the pathological changes are limited to the apparatus to do with the absorption of fat, while the lymphatic tissue of the marrow, spleen and bronchial glands

> etc., is normal...all this suggests very strongly that here we are dealing with some obscure disease of fat metabolism.
>
> (Whipple, 1907: 390)

For Whipple, the fat theory of WD offered a superior explanation of the clinical features of the disease, while the bacterial theory did not. The evidence for an infectious cause - the puzzling "peculiar structures" and their very suggestive "distribution in the glands" (Whipple, 1907: 390) - were insufficient: "it is not claimed that this is the etiological factor in this disease".

In conclusion, Whipple suggested two very different aetiological theories - metabolic or infectious – in this paper.[ii] However, as the metabolic version appeared to more strongly unify the clinical features of the condition, and offered greater explanatory power in terms of accounting for their mechanism of development, it was quickly accepted as the key aetiological change in this individual, to the detriment of the bacterial theory. These concerns regarding potential explanatory power and consilience of this suggested mechanism were also instrumental in Whipple's introduction of the term 'intestinal lipodystrophy' to describe the disease.[iii]

WD was therefore understood to be a kind of metabolic diseases until the 1950s.[iv] So it is a surprise to find historical reviews which suggest that researchers in this period simply employed different words for the same condition; for instance, "[f]irst diagnosis of the disease (postmortem), referred to as 'intestinal lipodystrophy'" (Afshar, Redfield and Higginbottom, 2010: 264). This is not just a matter of terminology. Whipple's conception of intestinal lipodystrophy was completely different from the modern sense of WD, relying as it did on a metabolic cause of the condition. In the next section, we will explore the consequences of conceptualising this disease as a metabolic one.

3: Whipple disease as a metabolic disease

Following Whipple, an early period of research which we characterise as case-based, is apparent. We adopt this terminology because the prevailing mode of reasoning found here involved the examination of specific features of individual cases. This kind of reasoning is rather different to that found in the second group of papers discussed in this section (Ziegler, 1928; Jarcho, 1936; Reinhart and Wilson, 1939). Rather than dealing with specific features of cases, these works attempted a more general synthesis of the features and causes of the disease. Here, researchers begin to describe WD as an abstracted clinical entity, capable of acting as the focus of more general diagnostic and causal claims. This change - from individual features of individual cases, to general features of the disease - is conceptually significant. For one, it reified WD into a condition which could be a legitimate target of further clinicopathological inquiry. For another, it demonstrated the negotiation of clinical features for either inclusion or exclusion from WD. For a third, it permitted researchers to simply exclude alternative diagnoses in a less laborious way than was possible in the era of case-based thinking.

In section 3.1, we therefore discuss three example of this early, case-based approach to WD. In section 3.2, we then contrast these reports with three later examples in which WD was understood much more generally. In section 3.3, we characterise the metabolic era of WD in overview, while in section 3.4 we describe the way in which treatment was approached during this period.

3.1: Case-based research

3.1.1: Blumgart 1923

The first post-Whipple cases were reported in 1923, by Blumgart. He reported ante- and post-mortem studies on three individuals with a range of symptoms similar to those of Whipple's case. The symptoms were distinctive in that they were both unusual, yet shared by the three cases. The summary of these findings is worth repeating at some length:

> The disease tended to occur in early middle life, with insidious onset, gradual downward progression over a period of one and a half to two years, finally terminating in death. The presenting symptoms were weakness, emaciation, on the average of three soft, semisolid, yellow bowel movements daily, with an excess of fat. Acidosis and tetany were noted in two cases.
>
> (Blumgart, 1923: 128)

After a note to the effect that the only significant abnormal investigation findings were an unusually high gastric pH, and normochromic anaemia, the description continues:

> Pathologically, the significant changes were confined to the intestines and to the mesenteric lymph nodes. In all three necropsies, only incidental changes were found elsewhere. The small intestine showed small granular elevations of the mucosa, usually gray in appearance. Microscopically, these elevations were found to consist of

> phagocytes containing ingested fat. The phagocytes were large and mononuclear, and contained a foamy reticulated cytoplasm. The mesenteric lymph nodes were noticeably enlarged and hyperplastic, and contained similar phagocytes, with ingested fat.
>
> (Blumgart, 1923: 128)

However, the cause of these symptoms remained obscure:

> It would seem that a definite clinical and pathological syndrome with such an intangible etiologic background must have been previously recognized. Nevertheless, search of the literature has uncovered only one analogous case, reported by G.H. Whipple.
>
> (Blumgart, 1923: 126)

These case studies were therefore reported as examples of *intestinal lipodystrophy*. A wide range of alternative diagnoses were considered, including Addison's disease, bacillary dysentery and sprue. However, the symptoms and pathological results found in the cases appeared at odds with any of these established disease entities, as summarised in table 1. A diagnosis of Addison's disease - typically caused by destruction of the adrenal glands by tuberculosis - was supported by two features common to all three patients: profound muscle weakness and disturbances in nutrient absorption (producing cachexia and anaemia). However, post-mortem investigation failed to reveal the characteristic signs of active or prior TB infection that would usually be expected, with the appearance of the adrenal glands being, in all cases, approximately normal. Similarly, a diagnosis of sprue could offer explanation of the steatorrhoea, cachexia, anaemia and the remitting course of the illness, but the patients lacked the characteristic history of travel to the tropics, inflammation of the tongue, characteristic stools (they were not "enormous, fermented, whitish or grayish pultaceous stools, very acid in reaction, and often yeasty in odor, and foamy" (Blumgart, 1923: 125)). In addition, the individuals had several distinctive features that were not characteristic of sprue, including anomalous gastrointestinal histopathology, which was characterised by strange, gray "small granular elevations of the mucosa" (Blumgart, 1923: 128). A diagnosis of pernicious anaemia, while neatly explaining the "the gastro-intestinal symptoms, the pallor, the gastric anacidity and the asthenia" (Blumgart, 1923: 125) could not account for many other details, including the precise pattern of the anaemia, the loss of subcutaneous fat, and the various histopathological findings described above. Finally, while the duration and character of the gastrointestinal symptoms supported a diagnosis of dysentery, this was excluded by the histopathological finding in the small intestine, the "character of the stools...and the postmortem distribution of the lesions in the small intestine rather than in the large bowel" (Blumgart, 1923: 125).

Table 1: Blumgart's (1923) findings with respect to likely differential diagnoses

	Addison's disease	*Sprue*	*Pernicious Anaemia*	*Bacillary Dysentary*
Pigmentation	**Yes (case one only)**	**-**	**-**	**-**
High colour index	**-**	**-**	**Yes**	**-**
Asthenia	**Yes**	**-**	**Yes**	**-**
GI disturbance	**Yes**	**-**	**Yes**	**-**
Diarrhoea	**-**	**Yes**	**-**	**Yes**
Fatty Stool		**Yes**		**No**
Lesions in small intestine	**-**	**-**	**-**	**No**
Gastric anacidity	**-**	**-**	**Yes**	**-**
Cachexia	**-**	**Yes**	**No**	**-**
Anaemia	**-**	**Yes**	**No**	**-**
Vitiligo	**No**	**-**	**-**	**-**
Pallor	**-**	**-**	**Yes**	**-**
Tongue ulcer	**-**	**Yes, but atypical**	**-**	**-**
Tendency to remission	**-**	**Yes (case three only)**	**-**	**-**

Summary table of Blumgart's (1923) findings with respect to likely differential diagnoses. Yes = found, presence required for particular diagnosis; no = absent, presence required for particular; - = absent, presence not required for particular diagnosis.

First, these cases seemed to represent instances of the same disease entity. This was suggested by the characteristic clinical features. "In all essential characteristics, these all seem to belong definitely to one disease group." (Blumgart, 1923: 126) This conjunction of clinical features further suggested that these cases were caused by a novel disease by a process of exclusion. The symptoms of the three cases were "not in accord with any hitherto recognized diagnosis", yet the "similar signs, symptoms, course and postmortem findings, strongly suggested a definite disease entity." (Blumgart, 1923: 113) However, Blumgart made no particular suggestions about the mechanisms by which these symptoms arose. In

fact, the findings "yielded little knowledge of the underlying etiologic factors" (Blumgart, 1923: 113). And while many of the features: fatty stools; weight loss; weakness; abnormal mesenteric lymph nodes containing accumulations of fatty material; acidosis and tetany; otherwise essentially normal postmortem examinations, were similar to those described by Whipple, there were numerous points of divergence: "none of the cases here described here was characterized by arthritis, eosinophilia, fever, purpura or enlarged intestinal villa, as found in Whipples' case." (Blumgart, 1923: 126).

3.1.2: Tucker 1924

Tucker's case report is of an individual with a constellation of strange symptoms in the absence of a well-understood cause. He reported an antemortem diagnosis of "progressive lipodystrophy" in an otherwise well 18 year old man with profound cachexia, who had lost some 40% of his total body weight over a period of three years. This rapid decline, in the absence of other symptoms, suggested that this individual was suffering from a condition of impaired absorption of nutrients. Two possible mechanisms of this were suggested. Perhaps this patient had some kind of global impairment of uptake of nutrition from the gut (Tucker, 1924: 1092). Alternatively, and perhaps more plausibly given the earlier work of Whipple and Blumgart, some kind of problem with fat absorption was responsible. However, a defect affecting fat absorption alone did not appear capable of explaining the striking loss of fat deposits throughout the body. Tucker therefore concluded that this disease arose from "…a profound disturbance in fat metabolism" (Tucker, 1924: 1092). Once again, though, the aetiology of this abnormal fat metabolism was obscure: "…we are dealing with a lipodystrophy resulting from a disturbance in the metabolism of fat, the cause of which we have not determined" ((Tucker, 1924: 1092). This was therefore claimed to be the fifth case reported of "progressive or so-called intestinal lipodystrophy" (Tucker, 1924: 1092). One notable novelty was the discussion of the utility of treating the disease with insulin. This reduced the rate of weight loss, reduced the quantity of fat lost in the faeces, and improved the patient's endurance. We will discuss this in context in section 3.4.

3.1.3: Holmes and Starr 1929

Holmes and Starr reported the case histories of five individuals suffering from cachexia, malabsorption, hypercalcaemia and tetany. These bore clinical and pathological similarities to the case reported by Whipple:

> Whipple reported as a hitherto undescribed disease the case of a medical missionary suffering from arthritis, who, on returning from Turkey, developed a condition characterized by progressive emaciation, abdominal swelling and tenderness, and stools which indicated permanent interference with fat absorption without deficiency in fat splitting. The symptoms were attributed to mesenteric tuberculosis but the necropsy did not reveal any signs of tuberculosis. The most striking finding was an unusual deposition of fat and fatty acids in the intestinal and lymphatic tissues. Sprue was not considered.
>
> (Holmes and Starr, 1929: 975)

They also showed similarities to the cases reported by Blumgart:

> Blumgart has reported three fatal cases of malabsorption of fat, with emaciation and anemia, and in two acidosis and tetany....The other physical and laboratory observations were also similar to those observed by us. In the three necropsies in Blumgart's cases, the significant pathologic changes were confined to the intestine and to the mesenteric

> lymph nodes. The small intestine showed small granular elevations of the mucosa, usually gray in appearance. On microscopic examination these elevations were found to consist of phagocytes containing ingested fat. The mesenteric lymph nodes were enlarged and contained similar phagocytes.
>
> (Holmes and Starr, 1929: 975)

Again, the process by which possible diagnoses were excluded by particular clinical findings was emphasised:

> The condition described resembles celiac disease and sprue but may easily be mistaken for other diseases. The most characteristic symptoms are emaciation, fatty diarrhea and calcium imbalance.
>
> (Holmes and Starr, 1929: 980)

The details of this case, and the conclusions drawn, were very similar to those of Whipple and Blumgart. The presentation was also similar. The details of the particular case: the symptoms and signs; the course of the illness; the response of the individual to therapy, are discussed at length, not the general features of the underlying disease. This approach, looking at particular features of specified instances of the condition, represents an example of what we might term *case-based reasoning* (see, for example, Forrester, 1996). It was not the features of the disease in general that were of interest. While a characterisation of the condition as some kind of metabolic disorder was shared between these three authors, no particular characterisation of the general aetiology of the disease was given. Similarly, no agreement over which symptoms should be considered part of the condition was in place (see, for example, the differences identified by Blumgart between the three cases he reported and that of Whipple). These early investigations thus represented a deeply individualistic exploration of the condition, without drawing conclusions about the disease in general.

3.2 A more general description of WD

3.2.1: Ziegler 1928

Zeigler's 1928 article treats the condition in a different way. While it still presents the details of a single case with similarities to those previously described,[v] this clinical description is allied to a broader attempt to understand the underlying pathogenesis of the condition in general terms. The clinical description is similar to those earlier cases. Briefly, the reported history is that of an emaciated 50 year old man with diabetes, and without significant other clinical findings. The disease was fatal, and no post-mortem examination was performed. Again, he had "a symmetrical and progressive loss of subcutaneous fat over the face, neck, arms, thorax and abdomen, with relative abundance of subcutaneous fat over the hips and lower extremities" (Ziegler, 1928: 147). Likewise, "fat-ingesting phagocytes" (Ziegler, 1928: 164), similar to those found in Whipple's and Blumgart's cases, were found in the tissue between the intestinal lymph nodes. And once again, some kind of defect in fat metabolism was thought to be responsible: "Such cases favour the hypothesis that a disorder of fat metabolism may play a part in progressive lipodystrophy." (Ziegler, 1928: 161)

In itself, this case description is of a kind with the earlier examples. However, a novel kind of synthesis is also present, marking the beginnings of attempts to try and understand this disease in general terms. This is apparent in the other six cases described in this paper, which were instances of cutaneous lipodystrophy, a distinct disorder of fat metabolism. While the authors do not claim that WD is just the same thing as cutaneous lipodystrophy, they do seem to suggest that intestinal lipodystrophy is perhaps a related variant of the cutaneous disease. For example, they write that: "The observations in this group tend to support the general opinion that there are a variety of lipodystrophic disturbances which cannot be classified under one heading." (Ziegler, 1928: 161).

This attempt to suggest that WD might be a variant of another, rather better described, condition is important. WD was not an easy disease to investigate - it was very rare, rapidly fatal, and associated with a confusing constellation of symptoms. The use of other pathological states, particularly if they provided circumstances that were more tractable to clinical investigation, might well permit the resolution of disputes regarding particular features of WD by analogy. For example, Ziegler suggested that the nature of the granule-containing phagocytes found in intestinal lipodystrophy might be usefully investigated by reference to very similar cells found in cutaneous lipodystropies.[vi] In this way, various features found in the cases of WD might fruitfully be probed in more conducive circumstances.

3.2.2: Jarcho 1936

This paper describes the case of an individual with steatorrhoea associated with unusual intestinal lesions. While the details of the case, in particular the list of excluded differential diagnoses (sprue, "lipoid storage" disorder and congenital lymphatic abnormality), have much in common with earlier work in the case-based era, this research was characterised by a new approach to the aetiology of the disease. Despite the small number of cases considered (three - this one, and one each from Whipple and from Blumgart), the author is much more direct concerning the nature of the aetiology of the disorder. It is the dilatation of lymphatic vessels seen - either owing to obstruction or to congenital malformation - that appeared responsible (Jarcho, 1936: 283). This obstruction led to an impaired ability of the gut to absorb fat, and thus to the symptoms of the disease. While "the cause and genesis of the lesions remains unknown" (Jarcho, 1936: 284), this mechanism did suggest that WD was aetiologically distinct from other known diseases:

> Thus it is evident that the three cases under discussion present lesions distinctly different from anything previously described and do not fall into existing categories...Since the entire series of cases is so small it would be unwise to venture an opinion with regard to a possible relation between the intestinal and the extra-intestinal lesions. In this matter judgment may well wait.
>
> (Jarcho, 1936: 283-4)

As well as this novel contribution to the question of aetiology, an interesting footnote to this case lies in the discussion regarding histological techniques for detecting fats in lymphatic tissues. A range of confusing and apparently contradictory results had occurred when fat-specific stains were used.[vii] The authors claimed that these strange results were a consequence of poorly understood staining techniques:

> Since the critical studies of Hueck and of Kaufmann and Lehmann, it is evident that the fat stains employed do not possess the specificity formerly claimed for them. In the present instances, therefore, the results of staining merely support the supposition that the deposited material is a mixture of cholesterol, neutral fat, and fatty acids.
>
> (Jarcho, 1936, 281)

However, the non-fatty nature of these deposits in lymphoid tissue would later play a central role in supporting alternative models of WD causation.

3.2.3: Reinhart and Wilson 1939

A further case of WD was presented by Reinhart and Wilson. While many details of this case are rather atypical, with the patient suffering from both extensive chylous ascites and blood dyscrasia, the authors conducted a direct histological comparison between this case and those of Whipple and Jarcho, showing similarities in histopathological appearance. Again, the abdominal lymph nodes "…contained a large amount of hyaline appearing material which takes a minimal fat stain, but is apparently lipoid substance" (Reinhart and Wilson, 1939: 489). This is therefore argued to be a case of intestinal lipodystrophy rather than any other disease of lipid metabolism.

Two aetiological mechanisms were suggested. First, the extensive deposits of fat in the mesenteric and retroperitoneal lymph nodes could perhaps be due to primary lymphatic obstruction, producing a secondary deposition of lipids around the intestines. In general, though, this appeared a poor choice of mechanism, as notably there was no evidence of such obstruction in the cases reported by Whipple and Blumgart. The second mechanism suggested was more plausible. A metabolic increase in the rate of fat excretion into the intestinal lumen, followed by increased reabsorption into the intestinal wall, could explain the emaciation and decrease in total body fat seen in all cases.

3.3: Characterising the metabolic era

Between the years of 1907 and 1950 WD was understood to be a disease of abnormal fat metabolism. This was, considering the tiny number of cases reported, a flourishing research programme, in which many features of the condition were examined, reported and debated. As a consequence, WD became legitimate: it had particular symptoms and signs associated with it; it could be diagnosed (or excluded), and its pathology could be described and compared to that found in other diseases. This was a period of building the disease from, first, the features of individuals, and later, sets of characteristic clinical findings, such that it became possible to describe a typical case. This process of building up a picture of the clinical features of the disease was substantively completed by 1950.[viii]

A change in styles of inquiry instrumental to this process of legitimisation can be found between the case-based and later synthetic periods. While a range of investigations about similarities and analogies were performed throughout the metabolic era, in the earliest publications, these predominantly explored negative analogies between purported cases of WD and other, similar conditions. Here, the essential question was not what the disease *was*, but what it *was not*. This is apparent in the painstaking investigation of possible differential diagnoses - and their exclusion - that is so characteristic of this early research. Later, however, a move towards positive analogy - for example, the similarities noted between

intestinal lipodystrophy and cutaneous lipodystrophy (Ziegler, 1928) - became more typical of WD research.

While all the explanations of WD aetiology during this period were based around the idea that this was firmly a disease of abnormal fat metabolism, what remained in doubt was the precise nature of this defect. As we review in table two, competing theories of WD aetiology during this period fell into three broad groups: chemical, hyperfunctional or mechanical causes.[ix]

Table 2: Examples of different aetiological theories in WD, 1907—1950.

	Aetiological mechanism
Chemical	
Whipple (1907)	Fat is chemically abnormal, or contains toxic substances
Hass (1938)	Fatty acids with high melting point serve as a source of irritation to produce an inflammatory reaction
Korsch (1939)	Functional alteration of pancreatic lipase results in abnormally split interstitial fat, causing inflammation
Sailer and McGann (1942)	Local necrosis of fat tissue results in lipolytic ferments
Hyperfunctional	
Reinhart and Wilson (1939)	Increased intestinal excretion and reabsorption of fat
Mechanical	
Jarcho (1936)	Obstructive chylangiectasis, possibly with a congenital cause
Hill (1937)	Possible bacterial lymphangitis causes fibrotic obstruction, leading to dilation of the bile duct
Rosen and Rosen (1947)	Partial obstruction of the thoracic duct
Newman and Pope (1948)	Obstruction of the lymph node due to chronic inflammatory process

3.4: Treatment in the metabolic era

The evolution of the treatment regimens from 1907 up to the 1970s can be divided into three periods: empirical, steroids, and antibiotics.

3.4.1: Empirical approach

In this era, WD was typically a postmortem diagnosis: “Of the 22 acceptable cases of Whipple’s disease which have been reported, only 2 have had an antemortem diagnosis” (Kampmeier and Peterson, 1949: 248). Clinicians therefore attempted to relieve the symptoms, characterized by weight loss, arthralgia,

diarrhea and abdominal pain. For instance, intravenous glucose (Whipple, 1907), sodium bicarbonate, intravenous protein hydrosylate, neostigmine bromide, bile salts, sodium taurocholate, or tomato juice were unsuccessfully used to treat cachexia. As for abdominal pains, palliation via paracentesis (Reinhart and Wilson 1939), cholecystectomy (Kampmeier and Peterson, 1949), or camphorated opium and codeine (Hendrix and Black-Schaffer, 1950) were the only therapeutic options available.

3.4.2: Steroids

Plummer wrote an influential report in which he suggested that Whipple's disease might be acquired, rather than a congenital metabolic defect (Plummer et al., 1950). This was motivated by the similarities that WD had to a range of acquired endocrine disorders, including Addison's disease. This analogical argument, in which it was postulated that WD was associated with an impaired adrenocortical response, and disturbed phospholipid metabolism, suggested that patients might benefit from treatment with either corticosteroids or adrenocorticotropic hormone (ACTH). Studies had shown the effect of steroids on fat absorption and mobilization; mesenchymal lesions, similar to those seen with Whipple's disease, went into remission as a result of such therapy.

3.4.3: Antibiotics

In 1952, Paulley et al. published a report describing the remission of a patient following chloramphenicol administration (Paulley, 1952). Indeed, in an attempt to resolve the persistent diarrhea and steatorrhoea caused by the disease, the newly-developed and potent antibiotic was prescribed. This led to a startlingly prompt resolution of all the symptoms in this case. While this was a telling piece of evidence against metabolic theories of the disease, it remained insufficient to persuade all researchers that the disease might have a microbiological cause: "I must again emphasize that this is a psychosomatic disorder." (Paulley, 1964).

4: Whipple's disease as an infectious disease

During the early 1950s, metabolic theories of the aetiology of WD became untenable. This conceptual change arose from two discoveries made during this period. The first of these was the discovery that the foamy material found in the macrophages of WD sufferers was not fat, but instead was comprised of insoluble aggregates of glycoprotein. The second was the successful treatment of a WD sufferer with antibiotics, as discussed in section 3.4.3, and the realisation that this supported an alternate interpretation of the aetiology of the condition. Together, these two developments seriously weakened the theoretical authority of all the metabolic theories, and it is this weakening that we will discuss in the first two sub-sections below. In the final sub-section, we will briefly outline the eventual (re-)discovery of bacteria in WD, and discuss how metabolic theories of WD were replaced by an infectious one.

4.1: PAS-positive granules

As mentioned above, researchers since Whipple had remarked on the unusual macrophages found in the intestinal tissues of sufferers. These cells had a characteristically 'foamy' appearance, which was thought to be due to the presence of fat droplets in them. However, researchers had noted a variety of anomalous effects while attempting to demonstrate the fatty nature of these deposits (see, for instance,

note 45 above). In 1949, Black Schaffer noted that when sections of intestinal mucosa and mesenteric lymph nodes were stained using Periodic-Acid Schiff (PAS), it became apparent that these droplets were not, in fact, fat. Instead, they comprised insoluble aggregates of glycoprotein. As the claim that these deposits were fat was a vital piece of pathological evidence in favour of metabolic theories in general, the finding that they were, in fact, something else, strongly suggested that metabolic theories of the cause of WD were in need of revision:

> ...the presence of this readily demonstrated glycoprotein in the intestinal mucosa and mesenteric lymph nodes, indicates that Whipple's disease is more than an obscure defect in fat metabolism and is certainly not the result as is commonly suggested, of a block of the mesenteric lymphatic. Thus the name *lipodystrophy intestinalis*, first proposed by Whipple and currently in use, would seem to be inappropriate.
>
> (Black-Schaffer, 1949: 227)

This meant that some metabolic theories were immediately crushed, particularly those that claimed that mechanical obstruction of the lymphatic system was aetiologically important. However, it was still somewhat plausible that these non-fatty granules could have resulted from an unknown defect in fat metabolism. This acted as a spur to further research on the precise microstructure of these granules and the macrophages that contained them.[x] In turn, this would lead fairly directly to the unequivocal identification of bacterial structures in WD material. Together, the direct effect of undermining the primacy of a defect in fat metabolism and the indirect effect of stimulating particular, focused, microstructural investigations in WD, seriously damaged the metabolic theories, and later played a crucial role in making the infectious theory of the disease viable.

4.2: Finding an organism

In 1960, Cohen et al. reported the discovery of "dense round, oval and rod shaped bodies", surrounding the cell membranes of macrophages, in a jejunal biopsy specimen from an individual with WD (Cohen et al., 1960: 412). Under both light and electron microscopy, these particles had a "virus-like character" (Cohen et al., 1960: 413) suggesting the presence of some kind of infectious agent. However, they did not draw any firm conclusions about either the kind of agent that these dense bodies might represent, nor about any possible means by which these particles might participate in the development of the disease.

In a similar study in 1961, Yardley and Hendrix reported "extracellular bacillary bodies" in the PAS-positive granule-containing macrophages of a jejunal sample (Yardley and Hendrix, 1961: 83).[xi] Although the authors did not unequivocally label these structures as bacteria, they noted that they shared "many of the[ir] morphological characteristics" (Yardley and Hendrix, 1961: 83). The suggestion that these structures were of viral origin was discarded: they were both too large and too internally structured for that to be the case (Yardley and Hendrix, 1961: 91). The detection of these probable organisms

suggested both a means of explaining PAS-positive granules, and a possible route to a new aetiological theory of WD:

> Our findings suggest that Whipple's disease may either be a peculiar infection due to a micro-organism most closely resembling a bacterium, or, even if the organisms are not the *primary* causative factor, that they may play a role in genesis of the PAS-positive granules.
>
> (Yardley and Hendrix, 1961: 81)

One speculative suggestion was that the bacillary bodies were phagocytosed by macrophages. This, in turn, might produce the PAS-positive granules. Several possible mechanisms for this were suggested: the granules might be produced by a normal or abnormal cellular response to the bacteria or they might arise from accumulations of incompletely digested bacterial cell walls (Yardley and Hendrix, 1961: 85). Understanding the genesis of the granules had assumed particular importance for the aetiological programme due to the realisation that the granules were not confined to the gut, but were widely distributed throughout the tissues (Sieracki and Fine, 1959):

> Whipple's disease, therefore, is considered a systemic disease by pathologists and clinicians, and it is believed that the PAS-positive substance is of major significance in its pathogenesis.
>
> (Yardley and Hendrix, 1961: 80)

5: Conclusion

The detection of bacteria, in combination with the other discoveries identified above, marked the end of the metabolic era of WD. This had, for the three decades between Blumgart in 1923, to the scepticism of the early 1950s, a flourishing research programme. Much of importance about the disease had been discovered: clinical features, pathology and possible treatment strategies had all been investigated, and a wide range of cases had been reported. This was a rich and successful project in many ways. Therefore it seems strange that arguably the most successful period of research on this condition is not noted in historical reviews.

We think that taking account of this episode, and others like it, is important for the practitioner. We should expect new research to be difficult and subject to revision. If past research is presented in a way that paints an inappropriately congruent picture of the way things came about, it may lead to inappropriate expectations for future research. This motivates our call for a thoughtful revision of the current methodology of historical reviews in medical journals, to reflect the claim that histories of diseases are usually more turbulent than the smooth processes of accretion that we find here might suggest. These must acknowledge the doubts, conceptual changes, constraints and uncertainties that characterise research practices. As an important special case of this, we should acknowledge the importance of terminology. That what is now known as Whipple disease (and previously as Whipple's disease, with the deprecation of the possessive form in disease nomenclature reflecting changing attitudes much more broadly) is distinct from lipodystrophy intestinalis. It should not be described as an alternate name for the same thing. Reference of this kind matters.

We think these issues can be admitted succinctly. Not every complication, quirk or contingency is important. But the kinds of difficulties associated with finding things out that we highlight are not odd, or unusual, but are the stuff of medical research itself.

5.1: A reconstruction of the early history of WD

From a single case, the clinical features of Whipple disease were first described in 1907 by Whipple.
While he drew no firm conclusions regarding aetiology, two means were suggested by which these symptoms could be explained: as the consequences of a disorder of fat metabolism, or of an infectious disease. While both were plausible, the case for WD being a metabolic disease was more so, particularly given the extensive deposition of fatty material in the lymphatic nodes of the abdomen. Thus, the disease appeared to result from a defect in fat metabolism, as the contemporary terminology of *lipodystrophy intestinalis* might suggest.

A consensus that the disease was a metabolic one persisted until about 1950. During this period, much was done to map the clinical and pathological features of the condition. Additionally, a range of more

specific aetiological theories were suggested which were all variants on the concept that the disease resulted from abnormal fat metabolism. However, this consensus about the metabolic origin of Whipple disease was gradually broken down by three findings. First, that the fatty deposits seen in the disease were not fat, but were instead glycoprotein aggregates. Second, that treatment with antibiotics was beneficial to some patients, and third, that bacteria were detectable in affected tissues.

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Endnotes

[i] See, for example, Afshar, Redfield and Higginbottom (2010); Fenollar, Puechal and Raoult (2007); Fenollar et al. (2010). Note that we will use the term 'Whipple disease' (WD) throughout this article. Despite the anachronism, and our call for sensitivity in using historical terminology in section five, the use of the multifarious technical terms for the condition in a previous draft made this piece unmanageably complicated.

[ii] In the interest of clarity, we will currently leave aside the heterogeneity within these broad groups. There were actually a great many different metabolic theories in play during the first half of the twentieth century. This is by no means unusual during the early stages of disease investigation. See, for example, Worboys (2000) for many similar examples.

[iii] Whipple carefully noted the importance of selecting a name for this condition, especially given the doubt over the aetiology: '…no suitable name can be applied to it until the etiological factor is determined. The term *Intestinal Lipodystrophy* is suggested as this seems to offer less objections and to have more points in favor than any one word or combination of words which have been considered.' (Whipple, 1907: 391) This hesitancy, regrettably, was not followed by later authors.

[iv] WD was successfully treated in 1951 using antibiotics (Paulley, 1952), but it was not until 1961 that bacteria were unequivocally identified (Chears and Ashworth, 1961; Yardley and Hendrix 1961). However, as we will later go on to assert, the (re)discovery of bacteria was not the only piece of evidence to count against the metabolic theories.

[v] The paper gives clinical details of seven individuals. However, only one (case number seven) was said to have intestinal lipodystrophy.

[vi] As described in, for example, Gilchrist and Ketron (1916).

[vii] 'The Scarlach R and Sudan III stains showed that the large spaces in the intestine and lymph nodes contained masses of fat. For the most part this fat was not lost during the staining procedures. Fat was likewise demonstrated within many mononuclear cells and within giant cells. With the nile-blue sulphate stain most of the material in the lymphatics stained blue; a few areas were stained pink. With the Smith-Dietrich stain these areas stained gray-blue to black; much of the lipoid was removed. With the Ciaccio method followed by Sudan III a few small areas were stained red. In sections tested by the Schultz cholesterol method a few areas gave the blue color indicative of cholesterol. This was confirmed by the polariscopic examination, which likewise showed a few small areas of double refractility.' (Jarcho, 1936: 280).

[viii] See, in particular, the reviews of Hendrix and Black-Schaffer (1950) and Plummer et al. (1950).

[ix] See also Plummer et al. (1950).

[x] Although technological factors also played a role in this. Two examples are the availability of the transmission electron microscope in the early 1950s (Ruska, 1991), and the development of peroral biopsy techniques, permitting analysis of intestinal tissues from the living subject. See, for this, Cohen et al. (1960). Detection of PAS-positive granules has subsequently been utilised as a diagnostic test for WD (Fenollar, Puechal and Raoult, 2007).

[xi] Similar findings of apparently bacterial structures in WD were also made at about the same time by Chears and Ashworth (1961).