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Park's story and Winters' tale: alternate allocation clinical trials in turn of the century America

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Introduction

In 1898, Johannes Fibiger of Copenhagen, in the setting of scepticism about the efficacy of diphtheria antitoxin, famously allocated 484 patients admitted to his hospital on alternate days to either receive or not receive antitoxin in order to test its utility.^{1–3} Over the subsequent half-century before the Medical Research Council's randomized control study of streptomycin for pulmonary tuberculosis, alternate allocation would emerge as an increasingly utilized and respected methodological tool for determining therapeutic efficacy.^{4–6} Yet the advent and early dissemination of this methodology – and the resistance to its wider application – is only now beginning to be seriously researched.

William H Park (1863–1939), the longstanding director of the laboratories of the New York Board of Health, has been justifiably honoured for having saved countless lives through the use of diphtheria antitoxin and immunization in New York City at the end of the 19th century and beginning of the 20th century.⁷ During those same years, Park was closely associated with some of the most sophisticated and visible therapeutic trials in America (and the world). In addition to using alternate allocation of patients to treatment comparison groups, they used double-blinding,⁸ multisite collaboration, and statistically compared treatment groups, including the use of statistical synthesis (meta-analysis).⁹

Park would claim, like Fibiger, to have first conducted such an alternate allocation study in the 1890s in the setting of scepticism regarding the utility of diphtheria antitoxin. Yet a deeper investigation of the context of Park's apparent study

reveals not only a surprise twist, but important insights into the advent of, and resistance to, the alternate allocation method in the United States, and possibly further afield.

Park's story

In September 1894, Émile Roux reported before the Eighth International Congress of Hygiene and Demography in Budapest his dramatic case series of diphtheria patients treated at the Hôpital des Enfants Malades in Paris with antitoxin, noting an approximately 50% reduction in mortality when compared to prior years or to the contemporary cases at the Hôpital Trousseau.^{10–12} In New York City, Park led the successful efforts of the Board of Health laboratories to produce such horse-derived antitoxin. He was also, by this time, the Diphtheria Diagnostician at New York City's Willard Parker Hospital, one of three hospitals run by the city Board of Health for the treatment of patients with contagious diseases.⁷ At the same hospital, attending physician Joseph E Winters (1848–1922) had become a very prominent and vocal opponent of antitoxin, first engaging with Park in public debate before the New York Academy of Medicine on 5 April 1895,¹³ four days after the well-publicized death of Bertha Valentine in Brooklyn from an apparent complication of antitoxin administration.¹¹ There, based upon the experiences of the first three months of antitoxin use at the Willard Parker Hospital, from January to March 1895, Winters claimed that antitoxin could cause both haemolysis and 'antitoxin septicaemia,' opposing it not only on account of its apparent (to him) inefficacy,

but 'on account of its immediate danger to life.'¹³ By May 1896, Winters concluded a long paper read before the New York Academy of Medicine by continuing to declare that if he had 'found that antitoxin did not do any harm, even though it was valueless in the treatment of diphtheria – even though it did not reduce the mortality – I would never had said anything against it. It is because I believe it is dangerous that my convictions compel me to speak. The time will come, gentlemen, when every member of this academy will feel with reference to it as I do tonight.'¹⁴

Describing this background 35 years later, Park would glibly recollect:

*An interesting experience developed in the Willard Parker Hospital during the winter of 1896. One of the leading paediatricians of the city and an attending physician at the hospital was violently opposed to the use of antitoxin, and so I arranged that alternate patients should receive the antitoxin, and the remainder should not receive it. The test lasted six weeks; several of the patients who were given the antitoxin early did surprisingly well, while several with similar cases who did not receive antitoxin did badly. The difference in the outcome of the cases was so great that we decided to discontinue the observations. We believed that although we had lost a few lives by it, we had gained a certainty as to the value of antitoxin which we would not otherwise have obtained, and this enabled us to persuade the members of the medical profession much more rapidly than if we had not carried out the experiment.'*¹⁵

Yet the actual sequence of Park's reporting of the study throws light on the perceived value and acceptance of such alternation of patients in America at the time it was purportedly conducted. Despite contributing frequent reports to the *Medical Record* and *Medical News* during the latter half of the 1890s, Park never reported the study in those journals; nor did he report the study in his reviews of the treatment of diphtheria in Alfred L Loomis' and William Gilman Thompson's *System of Practical Medicine*¹⁶ or Hobart Hare's *System of Practical Therapeutics*,¹⁷ despite his inclusion of 'statistics' for the year 1896 in the latter report. Indeed, it seems that the most influential clinical investigation in favour of antitoxin in America during the latter half of the 1890s was the 1896 collective

investigation by the American Pediatric Society concerning the use of antitoxin in private practice, gathering and collating mortality data from case series provided by 613 different physicians.^{11,18,19}

Park seems to have first publicly described his alternate allocation study at a 'symposium on serum therapy' before the New York County Medical Association in what appears to have been early 1900, where he related:

A very interesting test of the value of antitoxin in diphtheria ... was tried a year ago last summer. For 6 weeks only every alternate case received antitoxin. Dr. Winters looked after the treatment of those not receiving it, and Dr. Berg, I believe, those receiving it. I carefully watched both series of cases, and the difference was very marked in favour of the antitoxin series. Even Dr. Winters did not ask to have the test prolonged.'^{20,21}

Such a recounting would seem to place the trial in the summer of 1898. Park did not cite Fibiger in his 1900 report, but by the time he delivered his 1906 Harvey Lecture, he stated: 'An absolutely ideal method to show the influence of antitoxin is one made by Fibiger [sic]. ... In this, at the same time every other case [sic] was treated with antitoxin. ... This method, however, for obvious reasons is not available at this time. We once made a similar test at the Willard Parker Hospital.'²² Park cited a 1904 German review paper²³ as his source for the Fibiger information; and by 1912, in a paper justifying the use of animal experimentation, Park reported his own study as having taken place in 1895.²⁴

From such self-reporting, it remains unclear when Park conducted his original alternate allocation study – whether in 1895, 1896, 1898, or (as will be discussed later) 1899 – or whether the multiple dates cited stemmed from simple misattribution or from an attempt to establish priority over Fibiger. And Park's apparent reluctance to report the study before 1900 perhaps reveals that the calculus concerning the merits and drawbacks to the methodology was not as unequivocally favourable as it would become in retrospect, perhaps offering insights into contemporary ethical and epistemological concerns regarding alternate allocation studies when such other methods as 'collective investigation' were at hand. Important enough, but the story gets still more interesting.

Winters' tale, Part I: public statements and published literature

In the conventional telling, Joseph Winters has been handed down to history as 'consistently on the wrong side of every important question,'²⁵ the epitome of the recalcitrant old guard pathetically holding out before the advance of science. As noted by the biographers of fellow New York diphtheria expert, L Emmett Holt: '[Winters] was a forceful person and in consequence had something of a following, but he happened to be neither intelligent nor well read. Quite unable to keep abreast of the newer developments in medicine, he took refuge in opposing them.'²⁵ Not surprisingly, the biographers of Hermann Biggs – who would serve above Park as the influential General Officer of the New York City Department of Health and later as Commissioner of the New York State Department of Health²⁶ – and Park offer similar characterizations. They offered the backdrop against which, for example, the heroic Park had been 'determined to fight this thing [proving the utility of diphtheria antitoxin] through until his less perceiving contemporaries agreed with him'.⁷

Evelynn Hammonds, in her authoritative account of diphtheria in New York City from 1880–1930, first challenged this view, revealing the manner by which Winters' arguments at the 1895 and 1896 meetings were both convincing to many at the time, and grounded in Winters' wariness regarding the reductionist bacteriological redefinition of the disease itself.¹¹ In speaking before the New York Academy of Medicine a decade previously – when mercury, rather than antitoxin, had represented the 'specific' proposed for diphtheria – Winters had articulated a competing 'rational therapeutics' through which to contest such glib support of specifics.²⁷ As John Harley Warner has related, throughout much of the 19th century, principles of individualization of treatment to the many characteristics of patients had rendered the empiric use of universal specifics seemingly untenable.²⁸ And as Winters had stated regarding the many variables for the individual diphtheria patient:

Each and all of these conditions should be our chief guides, as in every case much depends on the

precision with which the exact nature of the case, and the state of the vital powers are ascertained. The mode of treatment in vogue has for its object (according to its exponents) to attack the poison germ of the disease, as an entity, and destroy it, leaving out of view every other consideration. Physicians in search for such a specific are distracted from a rational treatment. These experiments have doubtless killed more patients than germs.²⁷

At the level of general therapeutic advancement there was a broader affront to the profession in relying upon individual cases seemingly 'cured' by such specifics:

It is easy to be deceived in regard to the usefulness of a remedy employed against diphtheria, for some cases will do well with very little treatment, provided they receive good care.²⁷

By 1896, in his nearly three-hour report before the same Academy,²⁵ Winters had explicitly moved from such general theoretical concern with 'specifics' to a more particular attack upon antitoxin itself. As he defended himself:

With reference to a prejudice, it is monstrous to speak of it – a prejudice against anything which could do any good in such a disease as diphtheria! A man who would have a prejudice against a specific for diphtheria should not be allowed to practice medicine. If there is a specific for diphtheria, I want it.¹⁴

Yet Winters had maintained his general therapeutic scepticism for such 'specifics'. And such scepticism, in the published literature, would find form in the occasional use of alternate allocation of patients to treatment comparison groups. In his 1896 presentation,¹⁴ Winters first reported on the limited use of patient alternation, to determine the ideal dosage of antitoxin. Having divided the patients into a 'mild' series of 49 patients who would receive either 1000 or 2000 units, and a 'severe' series of 45 patients who would receive either 2000 or 3000 units, Winters could report on the improved survival (30.4% versus 50%) among the 'severe' patients who received 2000 units (thus striking an oblique blow at the apparent efficacy of antitoxin) while conveniently failing to elaborate upon the

apparently improved survival (8.3% versus 16%) among the 'mild' cases who received 2000 units instead of 1000 units.

The next published hint of alternation at the Willard Parker Hospital appeared three years later in the *Echoes and News* section of the 1 April 1899 issue of *Medical News*:

The chlorin treatment of diphtheria has been submitted to a test experiment at the Willard Parker Hospital, New York City, during the past six weeks. Every alternate patient ill with diphtheria received the chlorin treatment and every alternate one the antitoxin treatment. In connection with the chlorin treatment tonics and general sustaining remedies were used. Dr. Winters supervised the chlorin treatment, and Dr. Berg the antitoxin. The mortality was higher, and the patients generally seemed to be decidedly worse with the chlorin treatment than those with the antitoxin. It is the opinion of those who witnessed the results that the chlorin solution seemed harmless, but useless. It produced neither good nor bad results. The course of the disease presented the picture so familiar previous to the discovery of antitoxin.²⁹

It remains unclear whether this 'chlorin' experiment was in fact the alternate allocation experiment later retrospectively reported by Park. It does contain the elements of a six-week trial, alternate groups cared for by Winters and Henry Berg, and the alternation, in some respects, of patients to antitoxin versus no-antitoxin groups. And in a 1912 talk given at Harvard, reflecting upon alternate allocation diphtheria antitoxin 'experiments worthy of record,' Park reported that in one such experiment, 'in order to test a new remedy, no antitoxin was given to one-half of the patients for six weeks. The results were so bad in a considerable number of those not receiving antitoxin that all were put back on the antitoxin treatment.³⁰ It was in fact this published talk to which Sir Frederick William Andrewes referred, a decade later, in his own account of alternate allocation diphtheria antitoxin treatments.³¹ Alternatively, the study may well have been a follow-up to a previous antitoxin study entailing alternate allocation. Sadly, the minutes of the Medical Board of the Willard Parker and Riverside Hospitals, preserved at the New York Academy of Medicine, make no mention of such a trial. But that is

not to state that they fail to shed further light upon alternate allocation studies at the Willard Parker Hospital.

Winters' tale, Part II: the archival evidence

The Medical Board of the Willard Parker and Riverside Hospitals was first convened on 3 February 1894, with members serving as attending physicians at both hospitals. Its first members included John Winters Brannan (elected President of the Board), Joseph Winters, JT Armstrong, Albert T Swan, WP Northrup, and Henry W Berg, with Brannan and Winters the first appointed (all references in this section, unless otherwise stated, are to the Minutes of the Willard Parker and Riverside Hospitals, Volume I³²). In June 1894, 'Dr. Northrup made some extended remarks on the advisability of collective investigation by the medical board of methods that will bolster convalescence from the communicable diseases, especially diphtheria and the method of most rapidly getting rid of the Loeffler bacillus.' Within months, of course, Roux presented the Paris results of treatment with diphtheria antitoxin before the International Congress in Budapest, and the Willard Parker Hospital prepared to use serum developed by Park at the Board of Health to treat its patients in the forthcoming calendar year.^{7,11,33}

It was in this setting, at the 11 December 1894 meeting initially attended by Brannan, Winters, Swan and Armstrong, that the following entry was placed in the minutes:

Dr. Winters suggested that in view of the probable introduction of antitoxine treatment of diphtheria, and of the uncertainty of the mortality from diphtheria, it would be unscientific for this board to unqualifiedly indorse [sic] the value of this treatment, and he would suggest that the antitoxine be administered to every other case, the alternate cases being treated as has been customary in the past until the value of the remedy is established beyond peradventure. This was moved, seconded and adopted by a majority vote.

Dr. Berg entered just before the preceding vote. Dr. Winters moved that the resolution be reconsidered, it was adopted. The resolution was then again put and lost.

In other words, it appears to have been *Joseph Winters*, months before the death of Bertha Valentine, and skeptical regarding the universal use of the new specific before its utility had been determined, who felt comfortable enough withholding antitoxin from alternate patients in a test of its utility. In making such a suggestion, he was admittedly in the ironic position of having subordinated his prior emphasis upon individualized treatment to his concern to test the emerging 'specific' itself. And it appears to have been Berg – reported as being the administrator of antitoxin in the supposed alternate study – who turned the discussion against conducting such a trial, though the recorded description of events is admittedly terse and confusing.

So how, then, was Winters' skepticism allayed, or his concerns disproved? Not, it appears, through such a proposed alternate allocation study. On 14 May 1895, Park and Biggs were appointed, as members of the Board of Health, as *ex officio* members of the Medical Board. Park and Winters served together on the board well into the 20th century, working, it seems amicably, on such small subcommittees as those convened 'to consider the matter and form of histories and reports that should be kept of the cases treated in the hospital,' and to consider how to procure more autopsies. Yet at the same time, Winters' fellow members of the Medical Board would publicly excoriate him, and privately outmaneuver him, with respect to the use of antitoxin. In January of 1896, at a Medical Board meeting at which Winters was not present, it was 'unanimously carried' that:

[N]o changes shall be made in the customary general or local treatment of diphtheria in Health Department Hospitals by any member or members of the medical board without previous consideration and consult of this board. The method of treatment shall consist in the systematic use of antitoxic serum, irrigations of the nose and throat as shall be required and the use of all other customary therapeutic and operative measures and drugs such as tonics, stimulants, [etc.] as may be indicated in each individual case.

In May of that year, Winters delivered his epic presentation before the New York Academy of Medicine. This prompted John Winters

Brannan – President of the Medical Board, for whom Winters at times substituted as acting President at board meetings when Brannan was absent – to publicly rebuke his fellow Medical Board member at the subsequent Academy meeting on 4 June 1896:

All of us [at the hospital], with the single exception of Dr. Winters, have from the beginning been in favor of the thorough trial of the serum treatment, which is still going on in the Willard Parker Hospital. ... As long ago as December 1894, it was evident to the other members of our board that [Dr. Winters] had strong doubts of the curative power of antitoxin and was prepared to find it of no value.

All the members of the medical board have the greatest friendliness for Dr. Winters, but we believe that he has made a grave mistake, and that he has done great wrong to the hospital of which he is one of the attending physicians, and that his words have caused widespread harm among the people of New York and of the whole country.³⁴

Privately, that same week, a 'special meeting' of the Medical Board was convened, though not attended by Winters. There, as Secretary Berg reported:

[It was] unanimously carried that whereas the statistics and conclusions of Dr. Winters a member of this board as to the results obtained in this hospital with the use of antitoxin in the treatment of Diphtheria are at variance with the hospital records and with the opinions [and] conclusions of the other members of the Board and whereas in the opinion of the Board their wide publication would be detrimental to the best interests of this hospital and the public health, Resolved that it is the opinion of the Board that said statistics and conclusions of Dr. Winters should not be published.

Publicly censured and privately censored, Winters would be present at the following Board meeting, on 9 June 1896, at which one assumes that the minutes of the previous meeting were approved, in accordance with the bylaws of the Board. No alternate allocation trials were mentioned in the minutes from those meetings. In fact, no mention or consideration of alternate allocation – not even regarding the 'chlorin' trial described in the

Medical News – would appear again in the minutes until June 1900, when it was reported by Dr Berg:

[D]uring the past month at the Willard Parker Hospital, every alternate case was treated with small doses of antitoxin (1000–2000 units not repeated) with the view of determining which method is more desirable in the treatment of diphtheria. Both methods having equally competent advocates in the profession at large.

It is not surprising that such a trial would be permitted in the setting of apparent equipoise; and Park himself would publicly report on the trial, stating that 'antitoxin is a powerful remedy and its exact dosage would be an important therapeutic advance.'³⁵ What is surprising, in retrospect, is that the 'chlorin' trial was permitted to proceed in 1899 with a treatment group of patients who did not receive anti-diphtheritic serum. The Board members may have been convinced of the potential efficacy of the 'chlorin' treatment (the speaker who followed Brannan at the New York Academy of Medicine debate in 1896 had noted a 5.6% mortality rate in a small series of treated cases,^{36,37} while in November of 1898 a series of articles on the chlorine treatment of diphtheria and the challenges of its proponents to have it tested by the Board of Health was reported in the *New York Times*^{38–40}). Alternatively, they may have thought, to paraphrase Park's later assessment, that although they might lose a few lives by it, they would gain a certainty as to the value of the remedy which they would not otherwise be able to obtain. The former rationale, in view of the telling behaviour of the Board otherwise, seems more likely.

Conclusion

The purpose of this article is not to exonerate Joseph Winters, who indeed appears to have picked the wrong horse (literally) in the diphtheria antitoxin story. Rather, it is to situate the advent of the alternate allocation trial in America in the 1890s as one method among many for those who sought a basis for a 'rational therapeutics.' The 1890s rise of serotherapy – used for relatively reducible disease categories, often in institutional settings, with hard endpoints such as mortality rates – appears to have provided

an important stimulus to its use, which would increase substantially over the ensuing half-century. But important stumbling-blocks remained to its wider application, perhaps none so large as ethical qualms concerning the withholding of a remedy that already appeared promising based on other forms of evidence. It is thus not surprising that Winters, rather than Park, appears to have first suggested an alternate allocation study of diphtheria antitoxin at the Willard Parker Hospital. And Park's utilitarian bravado in his 1931 recollection thus obscures the apparent fact that for clinical researchers at the turn of the 20th century – including Park himself – alternate allocation represented a potentially powerful, but equally problematic, tool, one whose use would require ongoing justification and promotion in the decades that followed.

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