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### Key passages

*Brit. J. prev. soc. Med.* (1953), 7, 163-179

## THE SELF-CONTROLLED AND SELF-RECORDED CLINICAL TRIAL FOR LOW-GRADE MORBIDITY

BY

LANCELOT HOGBEN and M. SIM

*Birmingham*

### 3. THE INTENTION

What began as an academic discussion of the psychological difficulties which may confront the thyroidectomized subject, if previously accustomed to long hours of intense intellectual work and with little capacity for relaxation of mental activity, thus encompassed both the possibility that the subject's condition might be in large measure attributable to involuntal phenomena not directly connected with surgical treatment and the possibility that the subject (H) had a myopathy which might respond to prostigmine. It was the former consideration which led the investigator (S) to include in the treatment schedule both a *placebo* and *d*-amphetamine, but without the subject's knowledge before the completion of the trial.

It would be untrue to say that the writers were fully alert to all the issues stated in the foregoing introductory remarks when they undertook the experiment which follows. Nor would it be true to say that their intention was exclusively directed to evaluate a treatment, to throw light on a pathological condition, or (still less) to explore the usefulness of a particular method of inquiry. The truth is that the motives of each were mixed. In different measure each had some concern for the subject's health and some for the possibility of refining the type of procedure best described as *treatment under investigation*. The fact that one of the participants, the subject, had a special interest in the design of medical records and that each of them recognized at the outset the pitfalls which beset interpretation of a

trial when the yardstick of efficacy is, in part, the affective testimony of the subject did, however, lead at the outset to the adoption of a regimen from the outcome of which they believe it to be possible to infer some useful indications concerning the proper conduct of the self-controlled and self-recorded trial.

Indeed, initial lack of premeditation with that end in view and inadequacy of preliminary planning as seen in retrospect have made them more alert to appropriate safeguards. Thus it goes without saying that the experiment recorded is not a model for others to follow. On the contrary, defects of design, as they came into focus *pari passu*, are the raw materials from which, as the writers hope, it is now possible to prescribe a more exacting regimen which may prove to be of great value.

#### 4. PROCEDURE

In so far as the undertaking had an aim, its aim was to ascertain whether physical fatigue and muscular weakness of which the subject complained was attributable to myasthenia *sensu stricto*. Thus

the subject was aware that the experiment would entail the administration of prostigmine and a control substance, not necessarily inert. He was not aware that his colleague had included in the schedule of treatment courses both a placebo (*lactose*) and an active reagent (*d-amphetamine*). The self-record of his reaction to the latter is therefore an internal check on the reliability of the subject's testimony. To keep him wholly in ignorance both of the expected outcome of the treatment administered on any particular day and of the identity of the treatment administered on consecutive days, his colleague prescribed the channel of transmission as follows:

- (1) The *investigator* (S) specified the daily regimen of dosage in conformity with a key identifying that of three consecutive days by a letter of the alphabet.
- (2) The *liaison officer*, a colleague (C), transmitted the daily dosage to the patient in accordance with instructions referable to the code signs only, having therefore no means of inferring whether treatments on successive 3-day periods of a 26-fold sequence were identical, or of identifying the treatment on any single day.
- (3) The *subject* (H) received the dosage from (C) without access to the code sign referable thereto.

Each dose (3 times daily) was a tablet of the same size to be swallowed with water. Thus the subject's only means of associating the experience of particular days with a particular treatment was the taste and/or

texture of the tablet, if noticed. The subject reported no impression of such differences; and we may here discount this source of leakage. Ideally, it is easy to forestall in a comparable situation by recourse to a standard gelatine capsule.

As stated, the temporal unit of treatment by any one of the three substances administered was 3 days, on each of which the subject received three doses at 4-hourly intervals, the single doses being 5 mg. for amphetamine and 15 mg. for prostigmine. The experiment went on for 78 ( $=32 \times 6$ ) days covering the complete alphabetic code, the actual sequence of 3-day courses being: L. A. L. P. L. A. P. A. L. P. A. L. P. L. L. A. P. L. P. A. P. A. P. A. L. L. Thus the patient received the control agent ten times, prostigmine eight times, and amphetamine eight times. The intercalation of the control in parts of the cycle once or twice between the other two in succession or between successive administration of either is one safeguard against the danger of misinterpreting delayed action. In addition, the comparison of response on the first and third day of each 3-day course allows for a check which would not be applicable in an experiment involving 1-day courses only.

At the start the subject wrote a summary of normal daily routine of diet, motions, sleep, work, and other particulars referable to the immediate period antecedent to the beginning of the experiment and deemed to be relevant to the definition of the baseline reaction to L. Thereafter for each day, he completed a report recording his experience relative to the same and his affective reactions on rising, etc. He followed a consistent plan, though without a *pro forma* schedule, more by habit than by premeditation. Even so, the outcome illustrates forcibly the loss of information entailed by record-keeping in diary form.

The prescribed times for the three daily doses were 8.30 a.m., noon, and 5.30 p.m. The reader will note that the last dose of the day was not administered immediately before retiring. This was intentional on the part of the colleague (S) responsible for the treatment schedule. Late administration might have led the subject to infer that one of the agents was a soporific or the converse; but the diary discloses no comments on the subject's sleep experience other than times of retiring and rising.